

Carbohydrates and Related Compounds

Carbohydrates are aldehyde or ketone alcohols containing carbon, hydrogen, and oxygen in which the hydrogen and oxygen are generally in the same ratio as in water. Because carbohydrates are the first products formed in photosynthesis, they are a convenient starting point for any discussion of constituents of vegetable drugs. Moreover, carbohydrates are the products from which, by subsequent organic reactions, the plant synthesizes a greater number of other constituents.

Carbohydrates may be classified into 2 broad groups: sugars and polysaccharides. Sugars are monosaccharides, i.e., compounds that cannot be hydrolyzed to simpler sugars; disaccharides, which yield 2 monosaccharide molecules on hydrolysis; trisaccharides, which yield 3; tetrasaccharides, which yield 4; and so forth. Monosaccharides are classified by the number of carbon atoms in the molecule. Those with 3 carbon atoms are trioses; 4 carbon atoms, tetroses; 5 carbon atoms, pentoses; 6 carbon atoms, hexoses; and others. Sugars are crystalline, soluble in water, and sweet tasting.

The more complex, high-molecular-weight polysaccharides are represented by starch (page 39), inulin (page 42), and the celluloses (page 43). These polysaccharides can usually be hydrolyzed to a component

hexose and are therefore called hexosans; starch, which yields glucose, is known as a glucosan; and inulin, which yields fructose, is known as a fructosan. Sugars and starch are important products in the economy of mankind. They are extensively used as foods and pharmaceuticals.

The plant also builds its structural skeleton from carbohydrate material. Cellulose, a polysaccharide composed of glucose units joined by β -1,4 linkages, forms the primary cell walls in plants. Other substances also occur with cellulose, for example, the hemicelluloses. These are also high-molecular-weight polysaccharides but are considerably more soluble and more easily hydrolyzed than cellulose. Closely related to the hemicelluloses are the gums and mucilages (page 45) which constitute an important group of drugs both from the pharmaceutical and the therapeutic viewpoint. Also associated with cellulose are the pectins (page 54), which have some pharmaceutical application.

No summary of the carbohydrates is complete without mentioning the pentoses and pentosans. The name pentose is applied to a group of sugars that has the general formula $C_5H_{10}O_5$ (arabinose, xylose, ribose). The pentoses are products resulting from the hydrolysis of the pentosans. Xylan, which occurs in the wood of decid-

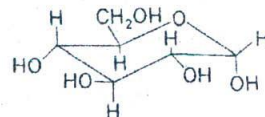
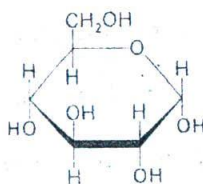
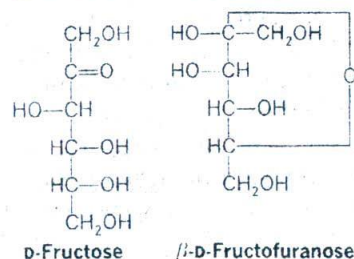
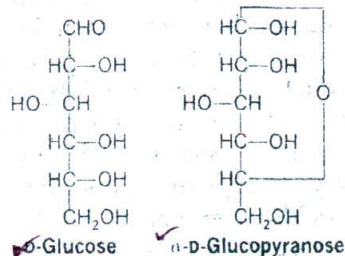
uous trees, is an example of a pentosan. Pentoses also result from the hydrolysis of gums and mucilages.

MONOSACCHARIDES. A simple sugar is chemically defined as a substance belonging to the carbohydrate group that is a ketonic or aldehydic substitution product of a polyhydroxy alcohol. The simplest of these is a diose $\text{HO}-\text{CH}_2-\text{CHO}$ (hydroxyacetaldehyde), which does not occur free in nature. An aldehydic and a ketonic triose do exist (glyceraldehyde and dihydroxyacetone), usually in the form of phosphate esters. Moreover, certain organisms can oxidize glycerin to dihydroxyacetone. The tetroses also are not found in the free state. Pentoses, however, occur commonly in nature, usually as products of hydrolysis of hemicelluloses, gums, and mucilages.

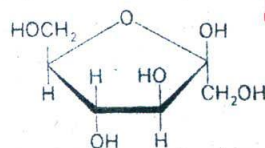
Hexoses are by far the most important monosaccharides found in plants. They are the first detectable sugars synthesized by plants and form the units from which most of the polysaccharides are constructed. There are 16 possible aldohexoses and 8 ketohexoses which, if we consider both the *alpha* and *beta* forms, permit 48 isomers. Of these, only 2 occur in the free state in plants: they are D-fructose (levulose) and D-glucose (dextrose). Both are found in sweet fruits, honey, and invert sugar. When starch is hydrolyzed, it yields glucose, whereas inulin yields fructose.

Glucose is an aldohexose, that is, a polyhydroxy alcohol having an aldehyde group, whereas fructose, which has a ketone group, is a ketohexose. These groups explain the reducing properties of the monosaccharides and account for the commonly applied term "reducing sugars." The hexoses may be considered as 6-membered, open-chain compounds. Five of the carbon atoms have alcohol substituents, and the sixth carbon is part of an aldehyde or ketone group. Such an aliphatic formula readily illustrates and explains stereoisomerism, but many of the other properties of the hexoses can only be explained on the basis of a ring structure.

Evidence indicates that glucose and other hexoses often exist in cyclic forms as well as in straight chain structures. Glucose generally forms a 6-membered pyranose ring that may be written in either of 2 ways. (See diagram that follows.)



α -D-Glucopyranose



β -D-Fructofuranose

Fructose is more complex because it can exist in 2 cyclic forms. Fructopyranose is the structure of the crystalline sugar, and the furanose structure (5-membered ring) seems to occur when fructose is present in oligosaccharides and polysaccharides.

Phosphate esters of certain heptoses (7-carbon sugars) are of vital importance in the glucose metabolism of animals and in the photosynthetic process of plants. A few years ago, an 8-carbon sugar was isolated

from crushed avocado pulp. This unusual sugar was named D-glycero-D-manno-octulose; it has also been isolated from species of the rock-garden plant, *Sedum*.

DISACCHARIDES. Sucrose (α -D-glucopyranosyl- β -D-fructofuranoside) is the only disaccharide that occurs abundantly in the free state in plants, although maltose has occasionally been reported in the cell sap. Sucrose occurs in fruit juices, sugar cane, sugar beet, the sap of certain maples, and in many other plants. Upon hydrolysis sucrose yields **invert sugar**, which consists of equimolecular quantities of glucose and fructose. Sucrose is a nonreducing sugar.

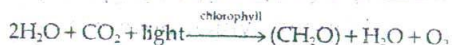
Maltose (4-O- α -D-glucopyranosyl-D-glucopyranose), although seldomly occurring in the free state in nature, is produced in large quantities by the hydrolysis of starch during the germination of barley and other grains (diastatic fermentation). It is a reducing sugar and, upon hydrolysis, yields 2 molecules of glucose.

Glucose, fructose, sucrose, and maltose are the sugars most commonly occurring in vegetable drugs. Certain other sugars, however, occur to a limited extent in nature, either in the free state or in glycosidal combination. Among these are the monosaccharides: mannose (occurring in mannosans) and galactose (a constituent of lactose and raffinose), and the disaccharides: trehalose (widely distributed in the fungi) and lactose (milk sugar). Lactose possesses a functional aldehyde group and is a reducing sugar. Trehalose is a nonreducing sugar.

BIOSYNTHESIS OF CARBOHYDRATES

PRODUCTION OF MONOSACCHARIDES BY PHOTOSYNTHESIS. Carbohydrates are products of photosynthesis, a biologic process that converts electromagnetic energy into chemical energy. In the green plant, photosynthesis consists of 2 classes of reactions. One class consists of the so-called light reactions that actually convert electromagnetic energy into chemical poten-

tial. The other class consists of the enzymatic reactions that utilize the energy from the light reactions to fix carbon dioxide into sugar. These are referred to as the dark reactions. The results of both of these types of reactions are most simply summarized in the following equation:



Although this equation summarizes the overall relationships of the reactants and products, it gives no clue as to the nature of the chemical intermediates involved in the process. The elucidation of the reactions by which carbon dioxide is accepted into an organic compound and ultimately into sugars with regeneration of the carbon dioxide acceptor was a major achievement in biosynthetic research. The pathway of carbon in photosynthesis, as worked out primarily by Calvin and co-workers, is presented in Figure 2-1.

PRODUCTION OF SUCROSE. Sucrose is of considerable metabolic importance in higher plants. Studies have shown that sucrose is not only the first sugar formed in photosynthesis but also the main transport material. Newly formed sucrose is, therefore, probably the usual precursor for polysaccharide synthesis. Although an alternative pathway consisting of a reaction between glucose 1-phosphate and fructose is responsible for sucrose production in certain microorganisms, the biosynthesis of this important metabolite in higher plants apparently occurs as shown in Figure 2-2.

Fructose 6-phosphate, derived from the photosynthetic cycle, is converted to glucose 1-phosphate which, in turn, reacts with UTP to form UDP-glucose. UDP-glucose either reacts with fructose 6-phosphate to form first sucrose phosphate and ultimately sucrose, or with fructose to form sucrose directly. Once formed, the free sucrose may either remain in situ or be translocated via the sieve tubes to various parts of the plants. A number of reactions, e.g.,

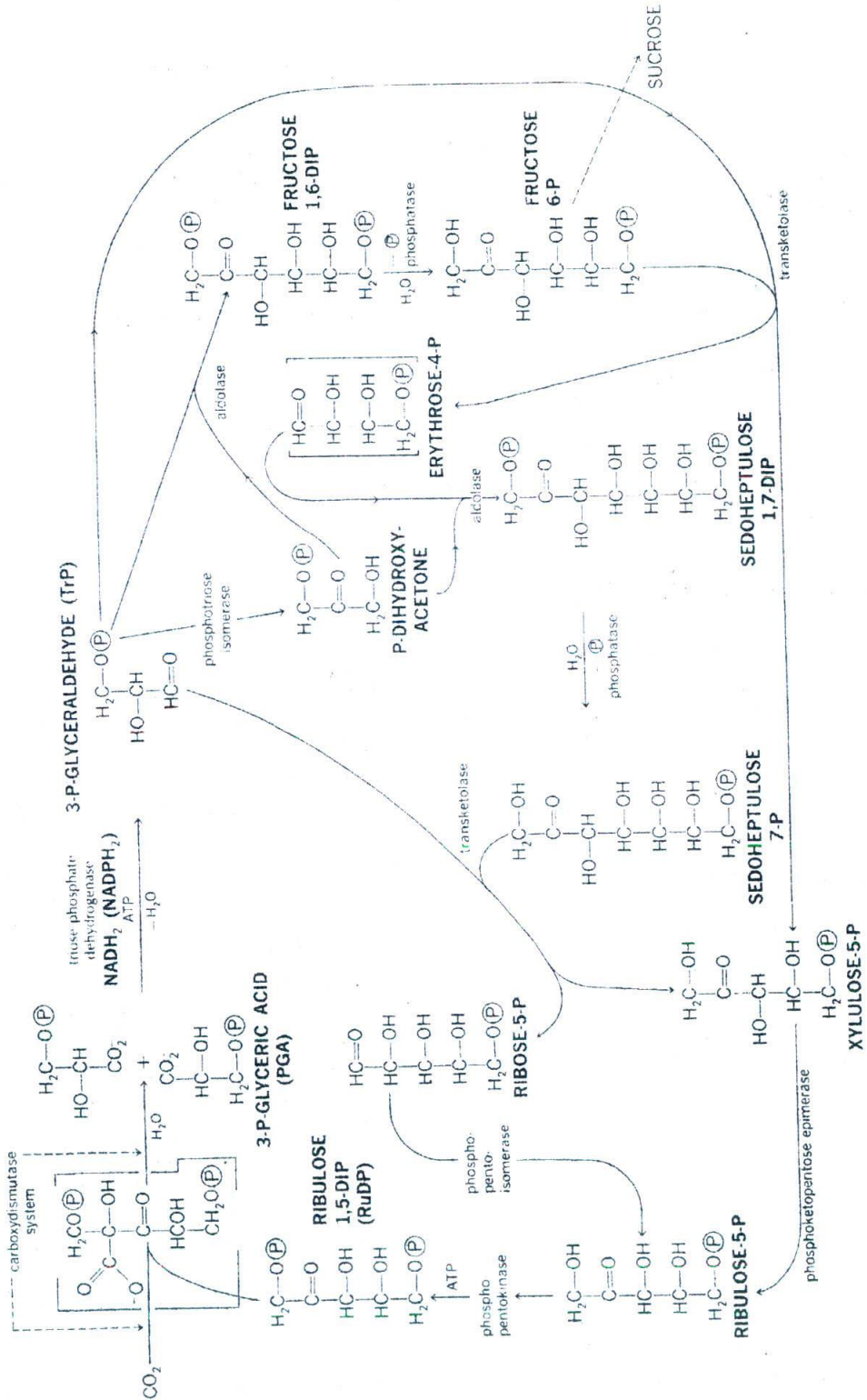


Fig. 2-1. The path of carbon dioxide fixation in photosynthesis.

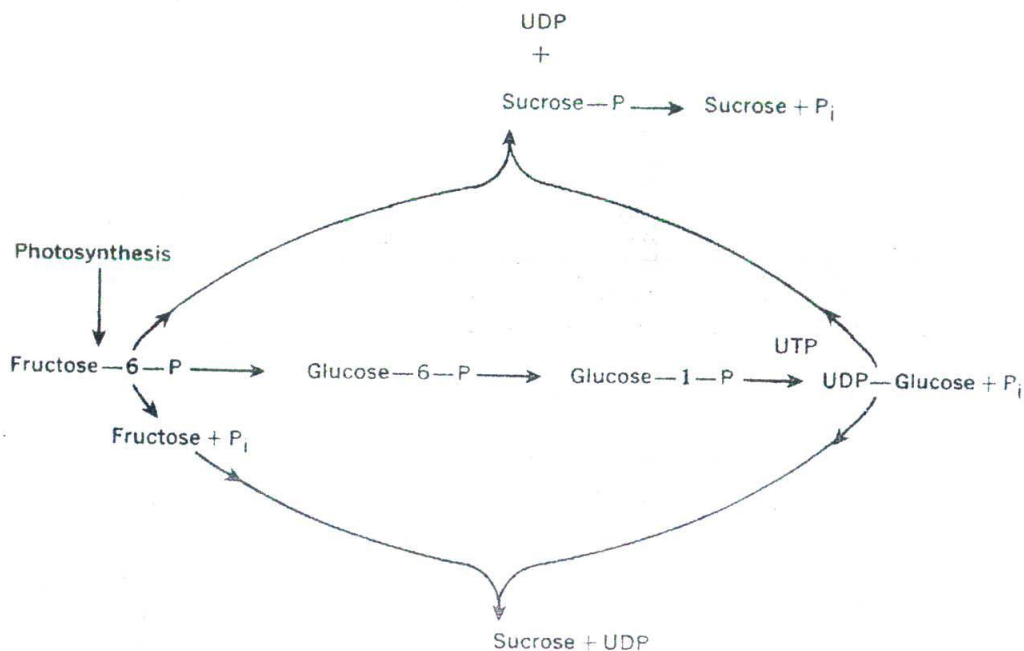


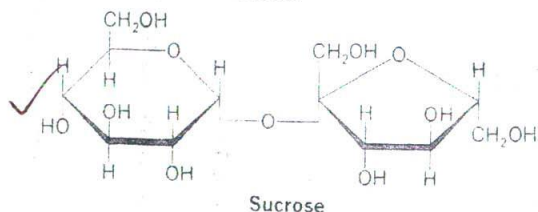
Fig. 2-2. Pathways of sucrose biosynthesis.

hydrolysis by invertase or reversal of the synthetic sequence, convert sucrose to monosaccharides from which other oligosaccharides or polysaccharides may be derived.

SUGARS AND SUGAR-CONTAINING DRUGS

Sucrose

Sucrose is a sugar obtained from *Saccharum officinarum* Linné (Fam. Gramineae), *Beta vulgaris* Linné (Fam. Chenopodiaceae), and other sources. It contains no added substances.



Sucrose is also known as **saccharum** or **sugar** and is widely distributed in plants. It is obtained commercially from sugar cane

and sugar beets, but it can be obtained from the sugar maple (*Acer saccharum*, Fam. Aceraceae), from various palms, and other sources. Cane sugar is produced in Cuba, Puerto Rico, Louisiana, the Philippines, Hawaii, Indonesia, and India, while beet sugar is largely produced in Germany, Austria, Russia, France, and the United States. The enormous total world production is about equally divided between cane sugar and beet sugar.

Sugar cane is native to India and was introduced into Europe by the Venetians during the Crusades. In the fifteenth and sixteenth centuries, sugar cane found its way into most European colonies in the tropics.

Sugar beets are grown in places other than tropical and semitropical countries. In Michigan, California, and other states, the cultivation and harvesting of sugar beets represent an important industry (Fig. 2-3).

PRODUCTION. The juice is obtained from sugar cane by crushing the stems between a series of heavy iron rollers. It is boiled with lime to neutralize the plant acids,

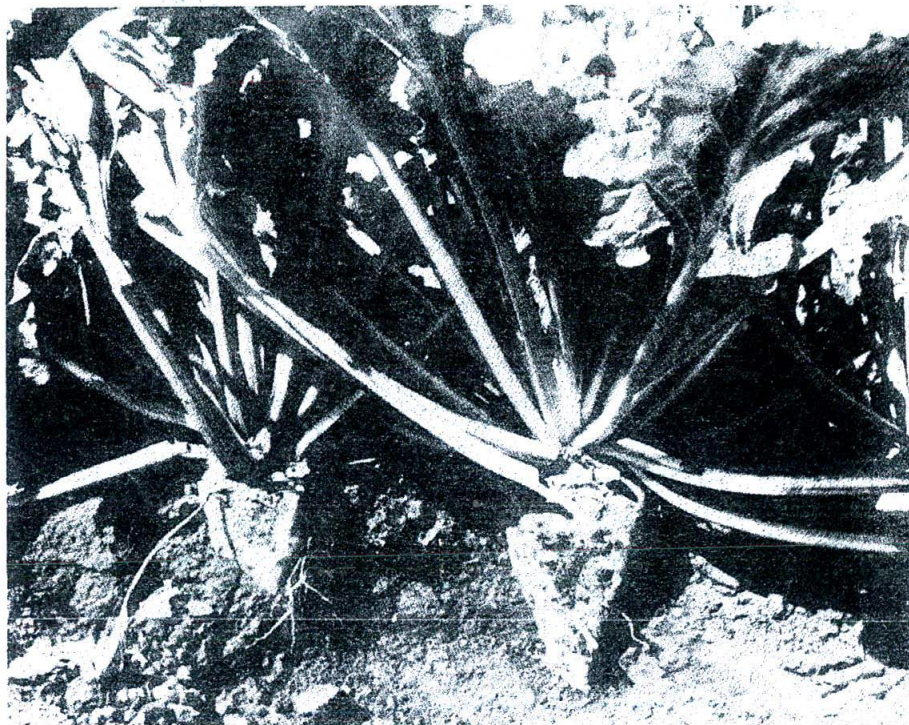


Fig. 2-3. Sugar beets with stems and leaves attached. (Courtesy of Farmers and Manufacturers Beet Sugar Association, Saginaw, Michigan.)

which would otherwise change the sucrose to invert sugar, and to coagulate albumins. The latter rise to the top as a scum and are removed. The juice is filtered, sometimes decolorized with sulfur dioxide, concentrated, and crystallized. When crystals of sugar are no longer obtainable, the residual, dark-colored syrup is **molasses**, which is extensively used in foods, prepared animal foods, and in the manufacture of ethyl alcohol.

Sucrose is obtained from sugar beets in a somewhat different manner. The beets are dug, washed, and sliced into small, limp slivers known as "cosettes" (Fig. 2-4). Sucrose and other soluble constituents are extracted from the plant material with hot water. The crude sugar-containing solution is then subjected to the purification process.

USES. Sugar is a pharmaceutical necessity for syrups; it is also a demulcent and a

nutrient. In sufficient concentration in aqueous solution, sugar is bacteriostatic and preservative. Sugar masks disagreeable tastes in troches and tablets and retards oxidation in certain preparations.

Dextrose

Dextrose, α -D(+)-glucopyranose or D-glucose is a sugar that occurs naturally in grapes and other fruits. It is usually obtained by controlled enzymatic hydrolysis of starch. High-conversion hydrolysates are subjected to rigorous purification procedures to yield crystalline dextrose that is 99.5 to 100% pure and suitable for parenteral use.

USES. Dextrose is a nutrient and may be given by mouth, by enema, by subcutaneous injection, or by intravenous injection, as required. It is an ingredient in dextrose injection, alcohol and dextrose injection, dextrose and sodium chloride in-

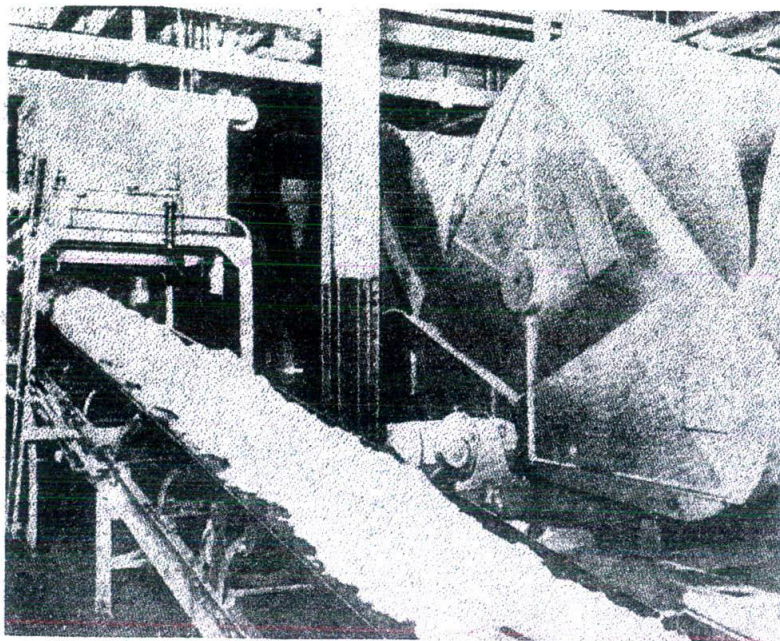


Fig. 2-4. Sugar beet cossettes being conducted by conveyor belt to diffusion battery. (Courtesy of Farmers and Manufacturers Beet Sugar Association, Saginaw, Michigan.)

jection, dextrose and sodium chloride tablets, dopamine hydrochloride and dextrose injection, lidocaine hydrochloride and dextrose injection, and potassium chloride in dextrose injection. It also is present in anticoagulant citrate dextrose solution and in anticoagulant citrate phosphate dextrose solution, each of which is an anticoagulant for the storage of whole blood.

Dextrose Excipient

Dextrose excipient is a crystalline dextrose monohydrate that has undergone less rigorous purification; it is intended for use as an agent of pharmaceutical necessity. A purified mixture of saccharides (not less than 93% dextrose), also prepared by controlled enzymatic hydrolysis of starch, is known as **dextrates** and is used industrially as an agent of pharmaceutical necessity. These solid products are used as sweetening agents, as substitutes for sucrose in syrups, and as tablet binders and coating agents. They have replaced liquid glucose for many pharmaceutical purposes.

It should be noted that the term dextrose is widely used in pharmacy, medicine, and various commercial channels. However, glucose, the accepted scientific name, is employed in the chemical and biochemical literature. Dextrose, frequently in the form of liquid glucose, is used commercially in the manufacture of candy, carbonated beverages, ice cream, bakery products, and in the canning industry.

Liquid glucose is a product obtained by the incomplete hydrolysis of starch. It is a colorless or yellowish, thick, syrupy liquid that is nearly odorless and tastes sweet. It contains primarily dextrose, but dextrans, maltose, and water are also present. It is used as an agent of pharmaceutical necessity.

In the United States, liquid glucose is usually prepared by controlled acid hydrolysis of corn starch. The washed starch is mixed with diluted hydrochloric acid and heated for 22 minutes at about 30 lb pressure, the acid is neutralized, and the neutral liquid is centrifuged and filtered until

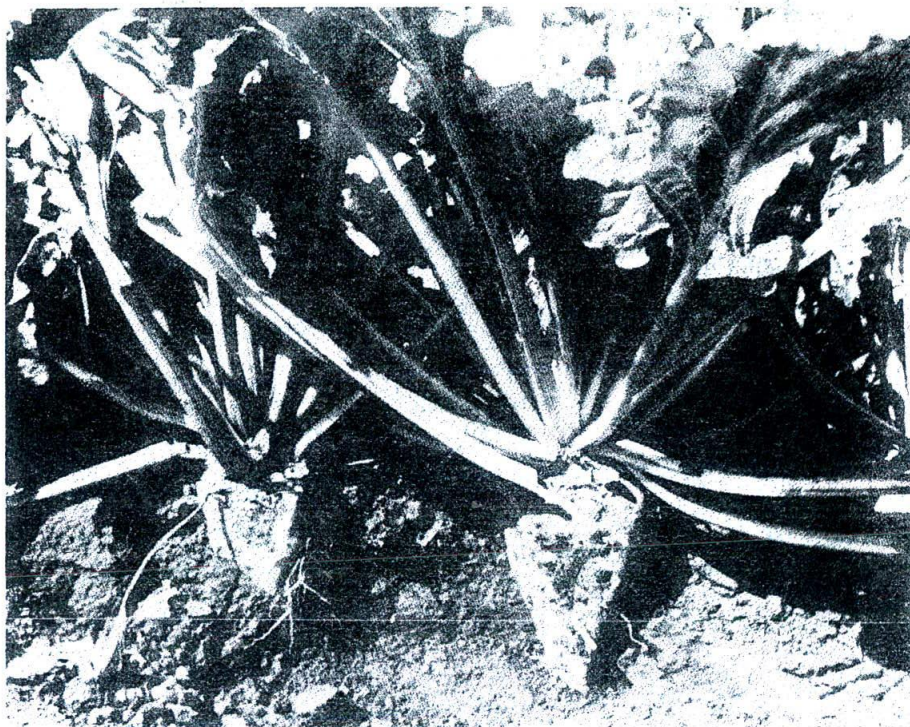


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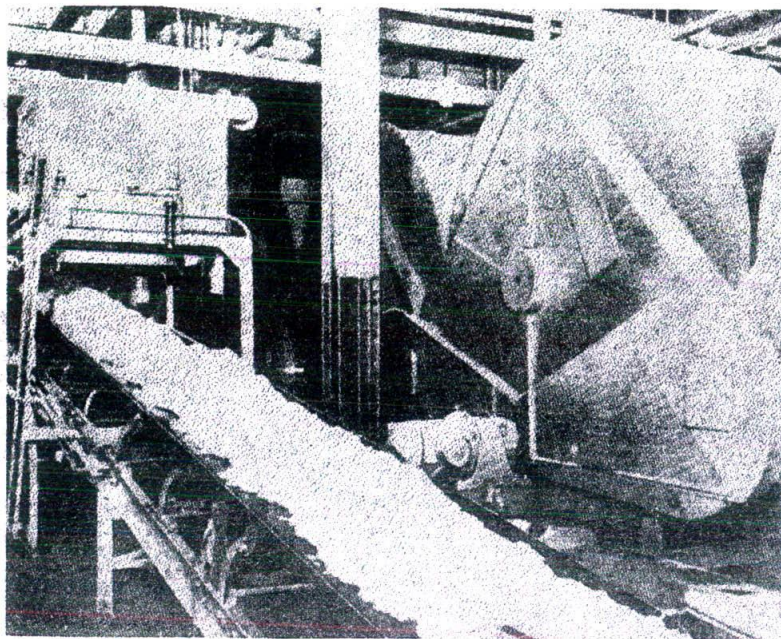


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clear. This clear liquid is then evaporated to the syrupy condition. ✓

Calcium gluconate is the calcium salt of gluconic acid. Gluconic acid is obtained by the oxidation of dextrose, either with chlorine or electrolytically in the presence of a bromide. It can also be obtained by fermentation. Calcium gluconate is soluble in cold water and less irritating for parenteral use than calcium chloride. An electrolyte replenisher, calcium gluconate is used to obtain the therapeutic effects of calcium. The usual dose is 1 g orally 3 or more times a day or by intravenous infusion at intervals of 1 to 3 days.

Calcium gluceptate and calcium levulinate are calcium salts of 7- and 5-carbon acids that are prepared semisynthetically from readily available carbohydrates. Glucoheptonic acid is prepared from glucose via a cyanohydrin intermediate, and levulinic acid can be prepared from starch or cane sugar by boiling with hydrochloric acid. The salts are calcemic and are used parenterally to obtain the therapeutic effects of calcium.

Ferrous gluconate is the ferrous salt of gluconic acid. It is classed as a hematinic and is employed in iron deficiency anemia. The usual prophylactic dose is 325 mg a day, and the usual therapeutic dose is 325 mg 4 times a day. It causes less gastric distress than inorganic ferrous salts.

PROPRIETARY PRODUCTS. Fergon®, Feralet®, and Simron®.

Fructose

Fructose, D-fructose, levulose, β -D (-)-fructopyranose, β -D (-)-fructofuranose, or fruit sugar is a sugar usually obtained by the inversion of aqueous solutions of sucrose and the subsequent separation of fructose from glucose. When sucrose is hydrolyzed, fructose and dextrose are formed in equal quantities. Fructose is a ketone sugar that occurs naturally in most sweet fruits (hence, the name fruit sugar) and in honey. It is usually obtained from an enzymatically prepared high-fructose syrup,

but it may also be obtained by the hydrolysis of inulin.

DESCRIPTION AND PHYSICAL PROPERTIES. Fructose occurs as colorless crystals or as a white, crystalline or granular, odorless powder that has a sweet taste. It is freely soluble in water.

USES. Fructose is used as a food for diabetic people and may be of particular benefit in diabetic acidosis. Infant feeding formulas often contain fructose. When given parenterally, it produces less urinary secretion than glucose.

Fructose is an ingredient in fructose injection and fructose and sodium chloride injection. These preparations are fluid, nutrient, and electrolyte replenishers and are administered either intravenously or subcutaneously, as required.

Fructose is about half again as sweet to the taste as glucose. This is of interest to calorie-conscious individuals, and the use of high-fructose sweeteners is expanding. **High-fructose sweeteners** are prepared by controlled enzymatic isomerization of glucose. Glucose isomerase from a *Streptomyces* species is immobilized, and a glucose-containing solution (derived from starch) is exposed to the enzyme. High-fructose corn syrups containing up to 90% fructose are available commercially.

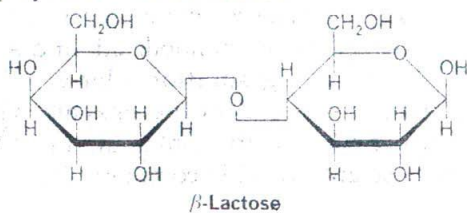
Lactose

Cow's milk is the fresh, unpasteurized, or pasteurized milk of *Bos taurus* Linné (Fam. Bovidae), without modification. It complies with the legal standards of the state or community in which it is sold.

Cow's milk is a white, opaque liquid that is an emulsion of minute fat globules suspended in a solution of casein, albumin, lactose, and inorganic salts. It has a slight but pleasant odor and an agreeable sweet taste. Cow's milk has a specific gravity between 1.029 and 1.034 and contains from 80 to 90% of water, in which are dissolved about 3% of casein, about 5% of lactose, and from 0.1 to 1% of mineral salts. Milk contains from 2.5 to 5% of fat (butter) and

is rich in vitamins. When milk is allowed to stand a few hours, the fat globules (cream) rise to the top. Each is surrounded by an albuminous layer. When churned, the fat globules unite to form **butter**, leaving a liquid known as **buttermilk**. The milk left after separation of the cream is known as **skimmed milk** which, if treated with rennin, forms a coagulum. Upon proper treatment, this coagulum is made into **cheese**. The liquid separated from the coagulum is known as **whey** and contains lactose and inorganic salts. **Condensed milk** is prepared by partial evaporation of milk in a vacuum and consequent sterilization in hermetically sealed containers by autoclaving. **Malted milk** is prepared by evaporating milk with an extract of malt. Low heat and vacuum are used to prevent the destruction of enzymes.

Milk is a nutrient. It is the source of lactose, yogurt, and kumyss (fermented milk). Casein and sodium caseinate are employed in culture media.



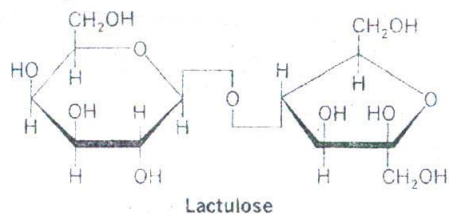
Lactose or milk sugar is a sugar obtained from milk. The sugar is crystallized from the whey obtained in the manufacture of cheese. These impure crystals are redissolved in water, decolorized with charcoal, and recrystallized.

DESCRIPTION. Lactose is a nutrient and a **pharmaceutical necessity**. It is odorless and has a faintly sweet taste. Lactose is stable in air but readily absorbs odors. Upon hydrolysis, lactose yields D-glucose and D-galactose. It reduces Fehling's solution, undergoes mutarotation, and forms an osazone. Lactose is hydrolyzed by the specific enzyme lactase. It is not hydrolyzed by maltase, sucrase, or diastase and differs markedly from the other sugars because it

easily undergoes lactic and butyric acid fermentations.

USES. Lactose is a tablet diluent. It is less sweet than sucrose and is more easily hydrolyzed. It is used, therefore, as a nutrient in infants' food; it also has a minor role in establishing the intestinal microflora because it provides the preferred substrate for lactobacilli. Its principal pharmaceutical use is as an inert diluent for other drugs.

Lactulose is a semisynthetic sugar prepared by alkaline rearrangement of lactose. It yields fructose and galactose upon hydrolysis. Lactulose is poorly absorbed, and most orally ingested lactulose reaches the colon unchanged. Bacteria in the colon metabolize the disaccharide to acetic and lactic acids, and sufficient accumulation of these irritating acids causes a laxative effect.



Although a daily dosage of 10 to 20 g of lactulose is effective in chronic constipation, the most significant therapeutic use of this sugar is to decrease the blood ammonia concentration in portal-systemic encephalopathy. The acidified stools trap ammonia as the ammonium ion; reabsorption is thus prevented, and blood ammonia levels may be decreased by 25 to 50%. The usual dosage is 20 to 30 g of lactulose as a syrup 3 or 4 times a day.

PRESCRIPTION PRODUCTS. Cephulac® and Chronulac®.

Xylose

Xylose, D-xylose, or wood sugar is a pentose obtained by boiling corn cobs, straw, or similar materials with dilute acid to hydrolyze the xylan polymer. Xylose has a sweet taste and is normally absorbed from the small intestine, but it is not metabolized to a significant extent by mammalian en-

zymes. The latter properties have led to its approval by the FDA for use as a diagnostic agent to evaluate intestinal absorption. The relative excretion of xylose in the urine is indicative of intestinal malabsorption states that may accompany such conditions as celiac disease, sprue, Crohn's disease (regional ileitis), pellagra, radiation enteritis, and surgical resection.

PRESCRIPTION PRODUCT. Xylo-Pfan®.

DRUGS CONTAINING COMPOUNDS METABOLICALLY RELATED TO SUGARS

Products of Glycolytic and Oxidative Metabolism

Because the catabolism of carbohydrates provides the basic metabolic framework upon which all of the cell's activities depend, these reactions are usually examined in great detail in textbooks of biochemistry. For this reason, only a brief summary is presented here.

Certain important pharmaceutical products, such as ethanol and citric acid, are produced by the cellular respiration of carbohydrates, especially glucose. Ordinarily the reactions involved are considered to compose several consecutive systems. The first reactions involve the anaerobic conversion of glucose to pyruvic acid by glycolysis (Embden-Meyerhof pathway, Fig. 2-5). Subsequently, in the absence of air, the pyruvic acid may be converted to lactic acid or to ethanol, depending on the identity of the biologic system involved. In the second series of reactions, pyruvic acid undergoes oxidative decarboxylation to yield acetyl coenzyme A (acetyl-CoA or "active acetate," Fig. 2-6), which can be utilized in a variety of reactions, including the acetylation of aromatic amines and alkaloids or the biosynthesis of fatty acids or steroids. However, most of the acetyl-CoA undergoes condensation with oxaloacetate to form citrate, thereby entering the tricarboxylic acid cycle, where it is ultimately

oxidized to carbon dioxide and water with the liberation of energy (Fig. 2-7).

Although some alternative mechanisms for glucose dissimilation are known, e.g., the hexose monophosphate shunt, the aforementioned are the principal reaction sequences. They are summarized in Figures 2-5, 2-6, and 2-7, starting with glucose 6-phosphate, which may derive directly from the photosynthetic cycle or from the phosphorolysis of polysaccharide.

Cherry Juice

Cherry juice, or *succus cerasi*, is the liquid expressed from the fresh, ripe fruit of *Prunus cerasus* Linné (Fam. Rosaceae).

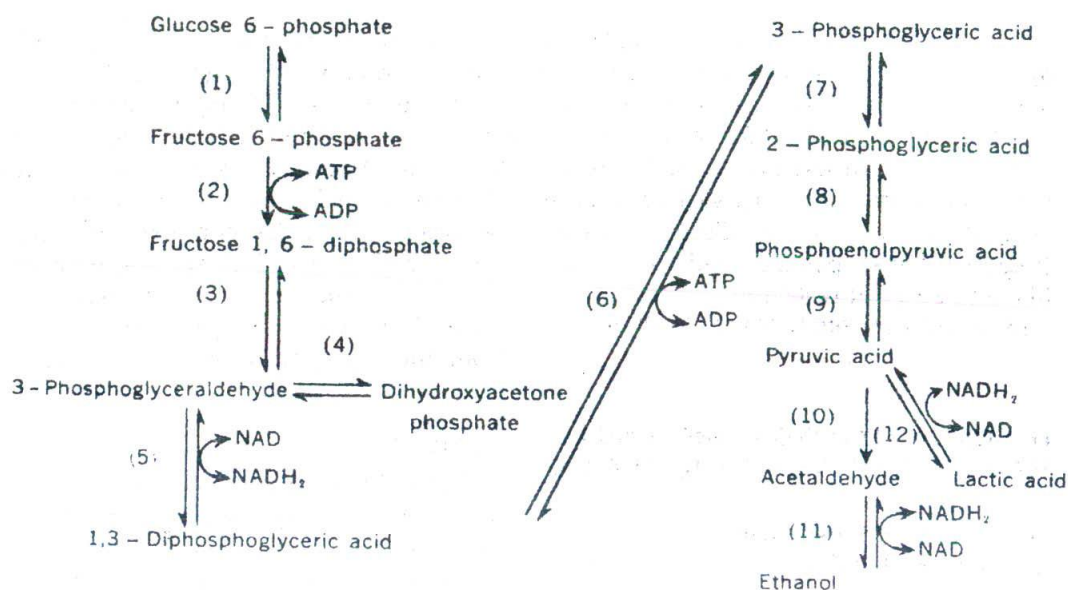
The cherries are washed, stemmed but not pitted, and coarsely ground to break the pits without mashing the kernels. The mixture is preserved with 0.1% benzoic acid and allowed to stand at room temperature (possibly for several days) until the addition of one half its volume of alcohol to a small portion of the juice produces a clear solution that does not become cloudy within 30 minutes. This test indicates that the pectin in the juice has been destroyed by enzymatic action and that the juice or the syrup made from the juice can be used in medicinal preparations without causing cloudiness owing to the presence of alcohol. The pectin-free juice is pressed from the mixture and filtered to a clear liquid.

Cherry juice contains not less than 1% of malic acid.

Cherry juice is used in the preparation of **cherry syrup**, a flavored vehicle that serves as a pleasant disguising agent in pharmaceutical mixtures, especially those of an acidulous nature.

Acids

Plant acids, such as citric, lactic, and tartaric acids, find wide application in the formulation of foods and medicines. These acids function as acidulants or components of buffer systems to control acidity. They



Reaction	Enzyme	Reaction	Enzyme
(1)	Phosphohexose isomerase	(7)	Phosphoglyceromutase (Mg ⁺⁺ , 2, 3-diphosphoglycerate)
(2)	Phosphofructokinase (Mg ⁺⁺)	(8)	Enolase (Mg ⁺⁺ , Mn ⁺⁺)
(3)	Aldolase	(9)	Pyruvic acid kinase (Mg ⁺⁺ , K ⁺)
(4)	Phosphotriose isomerase	(10)	Pyruvic acid decarboxylase (Mg ⁺⁺ , thiamine pyrophosphate = TPP)
(5)	Phosphoglyceraldehyde dehydrogenase	(11)	Alcohol dehydrogenase
(6)	Phosphoglyceric acid kinase (Mg ⁺⁺)	(12)	Lactic acid dehydrogenase

Fig. 2-5. Reactions of glycolysis.

are nearly ideal substances for such purposes. The organic acids cause less irritation than do comparable quantities of inorganic acids. They are also nontoxic, a property that would be anticipated for a primary biologic metabolite such as citric acid.

Citric acid was first isolated in crystal form from lemon juice by Scheele in 1784. It is present in many fruits and plants and

is obtained commercially from lemons, limes, or pineapples, but mostly by fermentation of sucrose. Citric acid appears as colorless, odorless, translucent crystals and is readily soluble in water and alcohol.

This tricarboxylic acid is particularly useful in buffering systems. Citric acid is used as an acidulant in effervescent formulations and in a variety of other products. It is an ingredient in potassium citrate and

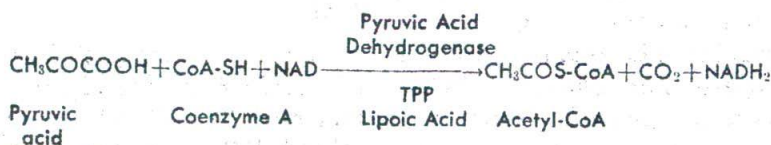


Fig. 2-6. Oxidative decarboxylation of pyruvic acid.

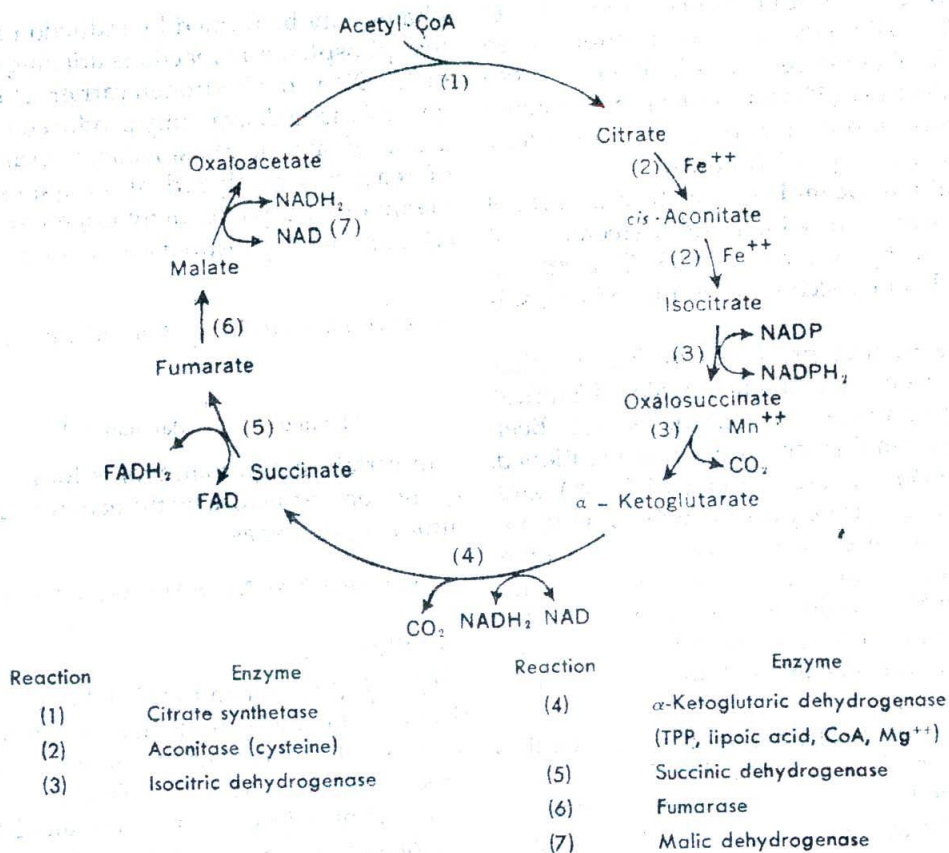


Fig. 2-7. Tricarboxylic acid cycle.

citric acid solution and sodium citrate and citric acid solution, systemic alkalinizers, and in anticoagulant citrate dextrose solution and anticoagulant citrate phosphate dextrose solution.

Lactic acid is available as a colorless or yellowish, nearly odorless, syrupy liquid. It is miscible with water, alcohol, and ether and consists of a mixture of lactic acid and lactic acid lactate equivalent to a total of not less than 85% and not more than 90% by weight of lactic acid. It is obtained by the lactic fermentation of sugars or is prepared synthetically.

Lactic acid is used as an acidulant, especially in infant feeding formulas. Sodium lactate injection is an electrolyte replenisher and is used in the treatment of metabolic acidosis. Calcium lactate is a calcium

replenisher; the usual oral dose is 1 to 5 g 3 times a day.

Tartaric acid is a dicarboxylic acid obtained as a by-product of the wine industry. It is soluble in water and freely soluble in alcohol. Tartaric acid is used as a substitute for citric acid in buffer systems and in effervescent formulations.

Ferrous fumarate is a hematinic agent that is comparable to ferrous gluconate. The usual therapeutic dose is 200 mg 3 or 4 times a day.

PROPRIETARY PRODUCTS. Feco-T®, Feostat®, Fumasorb®, Fumerin®, Hemocyte®, Iron®, and Palmiron®.

Alcohol

Alcohol or ethanol is a liquid containing not less than 92.3% by weight, correspond-

ing to 94.9% by volume, of ethanol at 15.56° C. As a 70% w/v solution, alcohol is used as a local anti-infective. Alcohol (5 or 10%) and dextrose (5%) injection is administered by intravenous infusion to increase caloric intake and replenish fluids.

Diluted alcohol is a mixture of alcohol and water in which the percentage of ethanol, by volume at 15.56° C, is 48.4 to 49.5. Diluted alcohol is employed as a solvent.

The natural processes of fermentation have been utilized since earliest historical times to make alcoholic beverages. Beer made from fermented grain is mentioned in the *Papyrus Ebers* (about 1500 B.C.), and fermented grape juice or wine was probably known earlier. Natural fermentation produces a concentration of alcohol in the fermenting liquid that rarely exceeds 14% by volume because the fermentative organisms are usually inhibited at such a concentration.

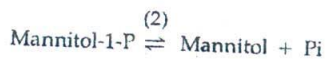
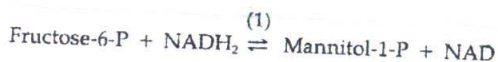
The process of distillation, by which the alcohol in the fermented liquid can be concentrated in the distillate, was not known until the eighth century A.D. Only in modern times has the process been so perfected that pure alcohol results. By distillation, brandy (from wine), whiskey (from fermented malted grain), and rum (from fermented molasses) are produced on a commercial basis. Each usually contains from 40 to 55% of alcohol. Wine is sometimes used medicinally as a mild stimulant and tonic, and brandy and whiskey are properly classed as central nervous system depressants.

Products of Reductive Metabolism

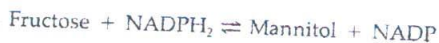
Dulcitol, mannitol, sorbitol, and other sugar alcohols are widely distributed in plants, but enzymes or enzyme systems capable of reducing a sugar to a sugar alcohol have never been isolated from a higher plant source.

However, evidence gained from studies conducted with microbial enzymes indicates that sugar alcohol (glycitol) phos-

phates may be formed by reduction of ketose phosphates in reactions utilizing NAD or NADP as the hydrogen carrier. The free glycitols are subsequently produced by the action of specific phosphatases. Examples of reactions catalyzed by enzymes, (1) mannitol phosphate dehydrogenase and (2) mannitol 1-phosphatase, follow:



In certain fungi, mannitol is formed directly from D-fructose by the action of mannitol dehydrogenase:



Mannitol

Mannitol or D-mannitol is a hexahydric alcohol obtained by reduction of mannose or by isolation from manna. Manna is the dried saccharine exudate of *Fraxinus ornus* Linné (Fam. Oleaceae) and contains 50 to 60% of mannitol; manna has also been used for its laxative properties.

Mannitol is a white, crystalline powder that is odorless and sweet-tasting. It crystallizes in orthorhombic prisms or in aggregates of fine needles and is freely soluble in water and boiling alcohol but almost insoluble in cold alcohol.

Mannitol is not absorbed from the gastrointestinal tract. When it is administered parenterally, it is not metabolized and is eliminated readily by glomerular filtration (approximately 80% of a 100 g dose appears in the urine in 3 hours). These properties have led to the use of mannitol as a diagnostic aid and as an osmotic diuretic. Some tubular reabsorption of mannitol (less than 10%) introduces an uncontrolled variable when this substance is used for diagnostic purposes.

The usual diagnostic dose of mannitol injection is 200 mg per kg of body weight in a 15 to 25% solution administered intra-

venously in 3 to 5 minutes. The usual diuretic dose is 50 to 100 g daily in a 5 to 25% solution by intravenous infusion at a rate adjusted to maintain a urine flow of at least 30 to 50 ml per hour; either mannitol injection or mannitol and sodium chloride injection is used for diuretic purposes.

PRESCRIPTION PRODUCT. Osmitol®.

Sorbitol

Sorbitol or D-glucitol is a hexitol that was originally obtained from the ripe berries of the mountain ash, *Sorbus aucuparia* Linné (Fam. Rosaceae). It also occurs in many fruits but is generally prepared from glucose by hydrogenation or by electrolytic reduction. It is also known as **D-sorbitol**.

Sorbitol is a well-known hexahydric sugar alcohol that has received wide acceptance in pharmaceutical and commercial fields. This compound was developed during World War I when mannitol hexanitate was introduced as a substitute for mercury fulminate, which was in short supply. Mannitol was obtained from glucose, and substantial quantities of sorbitol remained as a by-product. At that time there were few known markets for sorbitol. At present, sorbitol is widely used in both crystalline and soluble forms. It is readily soluble and compatible with syrup, alcohol, and other polyols.

Sorbitol tastes approximately half as sweet as sucrose, has humectant properties, is not absorbed on oral ingestion, and is not metabolized readily. These properties make sorbitol a particularly useful ingredient in toothpastes, chewing gums, and various dietetic products. Sorbitol must be used in conjunction with saccharin or some other noncaloric sweetener in dietetic beverages because it acts as an osmotic laxative when taken in large amounts. Solutions of this hexitol, sometimes in combination with mannitol, are also used for urologic irrigation.

POLYSACCHARIDES AND POLYSACCHARIDE-CONTAINING DRUGS

Starch

Probably no other single organic compound is as widely distributed in plants as starch. It is produced in large quantities in green leaves as the temporary storage form of photosynthetic products. As a permanent reserve food material for the plant, starch occurs in seeds and in the pith, medullary rays, and cortex of the stems and roots of perennials and other plants. It constitutes from 50 to 65% of the dry weight of cereal seeds and as much as 80% of the dry matter of potato tubers.

In the United States alone, more than 6 billion lb of pure starch are marketed annually; of this amount, more than 95% is made from corn. Although starch is widely distributed in the plant kingdom, relatively few plants provide starch on a large scale. Corn and other cereals, such as rice, sorghum, and wheat, contribute to the world's supply. Commercial starch is also obtained from potato tubers, maranta rhizomes, and cassava roots. Starch occurs in granules (or grains) that have characteristic striations. These striations and the size and shape of the granules are more or less characteristic in many species of plants and may be used as a microscopic means of identifying the botanic origin of the starch. In this manner, the identity of many food and drug products of vegetable origin may be established.

CHEMISTRY AND PROPERTIES OF STARCH.

Starch is generally a mixture of two structurally different polysaccharides. One component, termed **amylose**, is a linear molecule composed of 250 to 300 D-glucopyranose units uniformly linked by α -1,4 glucosidic bonds, which tend to cause the molecule to assume a helixlike shape. The second component, **amylopectin**, consists of 1000 or more glucose units that are also connected with α -1,4 linkages. However, a number of α -1,6 links also occur at branch

points. These links amount to about 4% of the total linkages, or 1 for approximately every 25 glucose units.

Because of these structural differences, amylose is more soluble in water than is amylopectin, and this characteristic may be used to separate the two components. More efficient separations are effected by complexing and precipitating the amylose with suitable agents, including various alcohols or nitroparaffins. Amylose reacts with iodine to form a deep blue complex; amylopectin gives a blue-violet or purple color.

Most starches have a similar ratio of amylose to amylopectin, averaging about 25% of the former to 75% of the latter. Certain waxy or glutinous starches contain either no amylose or small amounts (less than 6%).

α -Amylase (α -1,4-glucan 4-glucano-hydrolase), an enzyme present in pancreatic juice and saliva, hydrolyzes starch by a random splitting of α -1,4-glycosidic linkages. Amylose thus gives rise to a mixture of glucose, maltose, and amylopectin, a mixture of branched and unbranched oligosaccharides containing α -1,6 bonds.

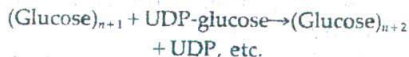
β -Amylase (α -1,4-glucan maltohydrolase) produces its effect by removing maltose units from the nonreducing ends of polysaccharide molecules. The end-product in the case of amylose is nearly pure maltose. The hydrolytic action of β -amylase on the α -1,4 linkages of amylopectin continues until a branch point is approached. Because the enzyme lacks the capacity to hydrolyze α -1,6 bonds, the reaction stops, leaving polysaccharide fragments known as dextrans as the product of incomplete hydrolysis.

Hydrolysis of starch by mineral acids ultimately produces glucose in nearly quantitative yields. The course of hydrolysis may be conveniently followed by the iodine reaction, which changes successively from blue-black to purple to red to no reaction.

Starches generally form colloidal sols

rather than true solutions. If a suspension of starch in cold water is added to boiling water while stirring, the opaque granules swell and finally rupture to give a translucent sol. If this sol is somewhat concentrated, it sets to a firm jelly when cooled. Cold, concentrated aqueous solutions of the caustic alkalis, of chloral hydrate, of ammonium thiocyanate, or of hydrochloric acid also cause the swelling and ultimate rupture of the starch granules to form pastes.

BIOSYNTHESIS OF STARCH. Synthesis of the amylose fraction of starch is effected by enzymes known as transglycosylases. The reaction involves the lengthening of priming chains of identical composition by the addition of single glucose residues. In certain microorganisms, glucose 1-phosphate is the glucose donor, and the enzyme that catalyzes the transfer is phosphorylase. Various sugar nucleotides, such as UDP-glucose and ADP-glucose, function as glycosyl donors in higher plants. Primer is essential to the reaction and must be a chain of at least 3 α -1,4-linked glucose units. The following equations illustrating this reaction show UDP-glucose as the source of the glucose residues:



Amylopectin, the branched component of starch, is formed from amylose by the action of a transglycosylase designated Q-enzyme. This enzyme effects the splitting of a monosaccharide chain containing at least 40 glucose units into 2 fragments. The fragment that carries the newly exposed reducing end first forms an enzyme-substrate complex and, in this form, is transferred to an appropriate acceptor chain, establishing an α -1,6 branch. This is illustrated diagrammatically in Figure 2-8.

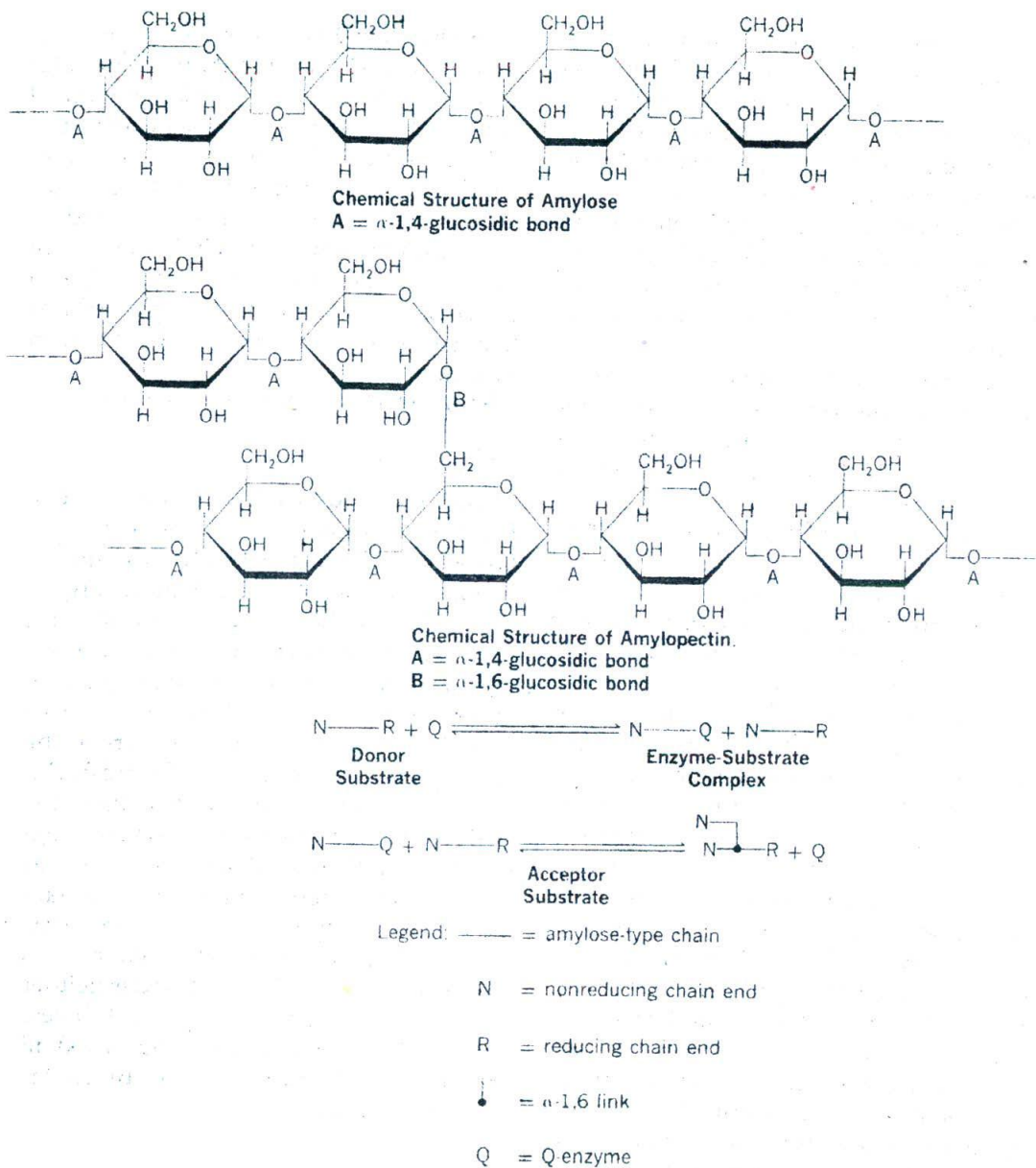


Fig. 2-8. Formation of α -1,6 branch in amylopectin (diagrammatic).

Corn, Wheat, and Potato Starches

Starch, as the term is used in pharmaceutical circles, consists of granules separated from the mature grain of corn, *Zea mays* Linné (Fam. Gramineae), the mature grain of wheat, *Triticum aestivum* Linné (Fam. Gramineae), or from tubers of the

potato, *Solanum tuberosum* Linné (Fam. Solanaceae). Granules of corn starch are polygonal, rounded, or spheroidal and are about 35 μm in diameter. Wheat and potato starches are less uniform in composition, each containing 2 distinct types of granules. Wheat starch contains large lenticular granules 20 to 50 μm in diameter and small

spheric granules 5 to 10 μm in diameter; potato starch consists of irregularly ovoid or spheric granules 30 to 100 μm in diameter and subspheric granules 10 to 35 μm in diameter. Starches obtained from different botanic sources may not exhibit identical properties for specific pharmaceutical purposes, such as tablet disintegration, and they should not be interchanged unless performance equivalency has been ascertained.

Preparation of starch involves disruption of the plant cells to release the starch granules, and appropriate manipulations are necessary in the case of corn and wheat to eliminate tacky proteins (glutens), which impede free flow of the starch and lipids from the embryo (germ), causing the embryo to become rancid. The separated embryos contain vitamin E (see page 293) and can be processed to yield useful oils.

Starch is used as an ingredient in dusting powders and as a pharmaceutical aid. The latter applications include use as a tablet filler, binder, and disintegrant. Purified starch **amylose** is also particularly useful for such purposes. A starch suspension may be swallowed as an antidote for iodine poisoning. Starch has many commercial uses, such as paper sizing, cloth sizing, and laundry starching. It is the starting material from which liquid glucose (corn syrup), dextrose, dextrans, and high-fructose sweeteners are made.

Pregelatinized starch is starch that has been chemically or mechanically processed to rupture all or part of the granules in the presence of water. It is subsequently dried. The material may be modified further to enhance compressibility and flow characteristics. Pregelatinized starch is slightly soluble to soluble in cold water and is used as a tablet excipient.

Sodium starch glycolate, a semisynthetic material, is the sodium salt of a carboxymethyl ether of starch. It is used as a disintegrating agent in tablet formulations.

Hetastarch is a semisynthetic material that is prepared in such a manner that it is

approximately 90% amylopectin, and 7 or 8 hydroxyethyl substituents are present for each 10 glucose units. A 6% solution of hetastarch is used as a plasma expander.

It is adjunct therapy in treatment of shock caused by hemorrhage, burns, surgery, sepsis, or other trauma. The duration of the improved hemodynamic status is 24 to 36 hours. The polymer is degraded, and molecules with molecular weights of less than 50,000 are eliminated rapidly by renal excretion.

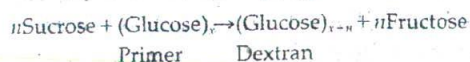
PRESCRIPTION PRODUCT. Hespan®.

Inulin

Inulin or hydrous inulin is a D-fructofuranose polymer whose residues are linked in linear fashion by β -2,1 bonds. It is obtained from the subterranean organs of members of the family Compositae. It is particularly abundant in taraxacum, inula (elecampane), lappa (burdock root) echinacea (cone flower), and chicory (succory or blue dandelion root). Inulin occurs in the cell sap and, by immersing the fresh rhizome or root in alcohol for some time, the inulin usually crystallizes in sphaerite aggregates. Inulin is used in culture media as a fermentative identifying agent for certain bacteria and in special laboratory methods for the evaluation of renal function. It is filtered only by the glomeruli and is neither excreted nor reabsorbed by the tubules. The usual dose is 10 g dissolved in 100 ml of sodium chloride injection by intravenous infusion.

Dextran

Dextran is an α -1,6-linked polyglucan that is formed from sucrose by the action of a transglucosylase enzyme system (dextran sucrose) present in *Leuconostoc mesenteroides*. This reaction can be summarized in the following equation:



Dextrans of the desired size are prepared

by controlled depolymerization (acid hydrolysis, fungal dextranase, or ultrasonic vibration) of native dextrans or by controlled fermentation, including use of a cell-free enzyme system. At present, dextrans with clinical utility have average molecular weights of 40,000, 70,000, and 75,000. The two large dextrans are used in 6% solutions as plasma expanders in cases of shock or pending shock caused by hemorrhage, trauma, or severe burns; dextran is not a substitute for whole blood when the latter is indicated. These dextran preparations are well-suited for their intended uses because their osmolarity and viscosity resemble those of plasma, they are serologically indifferent and relatively non-toxic, and their effectiveness is prolonged by the slow metabolic cleavage of the 1,6-glucosidic linkage.

The low-molecular-weight dextran crosses extravascular space and is excreted readily, but a 10% solution can be used as an adjunct in the treatment of shock. It is also employed to reduce blood viscosity and to improve microcirculation at low flow states. Dextrans interfere with some laboratory tests and may significantly increase clotting time.

PRESCRIPTION SPECIALTIES. Gentran[®], LMD[®], Macrodex[®], and Rheomacrodex[®].

Iron dextran injection is a sterile, colloidal solution of ferric hydroxide in complex with partially hydrolyzed dextran of low molecular weight in water for injection. It is a hematinic preparation that is administered by intramuscular or intravenous injection. Iron dextran injection is particularly useful when oral iron preparations are not well tolerated.

PRESCRIPTION PRODUCTS. Feostat[®], Feronim[®], Hematran[®], Hydextran[®], Imferon[®], Irodex[®], K-Feron[®], Nor-Feran[®], Proferdex[®], and Rocyte[®].

CELLULOSE

Purified Cotton

Purified cotton is the hair of the seed of cultivated varieties of *Gossypium hirsutum*

Linné or of other species of *Gossypium* (Fam. Malvaceae) that is freed from adhering impurities, deprived of fatty matter, bleached, and sterilized in its final container. Purified cotton is also referred to as **absorbent cotton**. *Gossypium*, the ancient name for the cotton plant, is from the Arabic *gos*, meaning a soft silky substance; *hirsutum* is from the Latin, meaning rough or hairy.

G. hirsutum, as cultivated in the southern United States, is an annual herb that attains a maximum height of about 4 feet and yields most of the commercial cotton known as American Upland Cotton; *G. barbadense* Linné, a somewhat larger plant, is cultivated in South Carolina and Georgia along the sea coast and yields Sea Island Cotton.

The plants produce capsules (bolls) that open along longitudinal sutures when ripe and reveal a mass of white hairs attached to the brownish seeds. The mass of hairs (cotton fibers) and seeds is collected and "ginned," a machine process for removing the seeds. To render cotton absorbent and suitable for surgical use, it is first carded (combed) to remove gross impurities and short hairs (linters). The cotton is then washed with a weak alkali solution to remove fatty materials, bleached with chlorinated soda, washed with weak acid, washed with water, and finally dried and recarded into flat sheets. After the absorbent cotton is packaged, it is usually sterilized.

Cotton for textiles is spun into thread and then woven; or, it may be treated with various chemicals, thereby yielding such fabrics as mercerized cotton, rayons, and others. The United States produces about half the world's supply of cotton. Cotton is also produced in Egypt and other tropical parts of Africa, India, the West and East Indies, and South America.

Cotton has been known since remotest antiquity. It has been cultivated in India for more than 3000 years. Egypt had a well-developed cotton industry 4000 years ago.

Cotton has been found in the mounds of the Aztecs in Mexico.

DESCRIPTION. Purified cotton occurs as white, soft, fine, filamentlike hairs that appear under the microscope as hollow, flattened, and twisted bands that are striate and slightly thickened at the edges. The hairs are unicellular and nonglandular, ranging from 2.5 to 4.5 cm in length and from 25 to 35 μ in diameter. Cotton is nearly odorless and practically tasteless.

Purified cotton should be free from alkali, acid, fatty matter, dyes, and water-soluble substances. Such cotton consists almost exclusively of cellulose, a β -linked linear glucopyranosyl polymer. The β -linkage is not hydrolyzed by mammalian enzyme systems, an important consideration in the application of many cellulose derivatives, but is hydrolyzed by cellulase, which is produced by many microorganisms, including the rumen microflora of herbivorous animals.

USES. Purified cotton is employed as a surgical dressing; it serves as a mechanical protection to absorb blood, mucus, or pus and to keep bacteria from infecting wounds. Commercially, cotton is employed for textiles and is a source of pure cellulose in the manufacture of explosives, cellulose acetate, and other materials. Absorbent gauze, microcrystalline cellulose, purified rayon, and such cellulose derivatives as carboxymethylcellulose, cellulose acetate phthalate, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, methylcellulose, oxidized cellulose, and pyroxylin find special applications in pharmacy and medicine.

Powdered cellulose is purified, mechanically disintegrated cellulose prepared by processing α -cellulose obtained as a pulp from fibrous plant materials. It exists in various grades and exhibits degrees of fineness ranging from a free-flowing dense powder to a coarse, fluffy, nonflowing material. It is used as a self-binding tablet diluent and disintegrating agent.

Microcrystalline cellulose is a purified, partially depolymerized cellulose prepared by treating α -cellulose, obtained as a pulp from fibrous plant material, with mineral acids. It is used as a diluent in the production of tablets.

Purified rayon is a fibrous form of bleached, regenerated cellulose. It is used as a surgical aid and may not contain more than 1.25% of titanium dioxide.

Cellulose Derivatives

Methylcellulose is a methyl ether of cellulose containing not less than 27.5% and not more than 31.5% of methoxy groups. It is obtained by the reaction of cellulose with caustic soda and methyl chloride and consists of a white, fibrous powder or granules. In water, methylcellulose swells to produce a clear to opalescent, viscous, colloidal suspension. Methylcellulose is a bulk laxative and a suspending agent. The usual cathartic dose is 1 to 1.5 g with water 2 to 4 times a day. Ophthalmic solutions (0.5 and 1.0%; Methopto Forte[®] and Murocel[®]) of methylcellulose are used as topical protectants; these products are marketed as "artificial tears" or contact lens solutions.

PROPRIETARY PRODUCTS. Cologel[®] and Hydrolase[®].

Ethylcellulose is an ethyl ether of cellulose containing not less than 44% and not more than 51% of ethoxy groups. It is a free-flowing white powder. Ethylcellulose is a tablet binder and film coating.

Hydroxyethylcellulose is a hydroxyethyl ether of cellulose. It is available in varying degrees of substitution and is used as a thickening agent and as an ingredient in some formulations for artificial tears (Adsorbotear[®], Lyteers[®], and Neo-Tears[®]).

Hydroxypropylcellulose is a hydroxypropyl ether of cellulose. It contains not more than 80.5% of the hydroxypropyl groups. It is used as a stabilizer and thickener in liquid preparations and as a binder and film coating in tablet formulations.

Hydroxypropyl methylcellulose is the propylene glycol ether of methylcellulose in which both hydroxypropyl and methyl groups are attached to the anhydroglucose rings of cellulose by ether linkages. A number of commercial products are available that differ somewhat in the composition of their ether substituents. The ether components of the products used medicinally and pharmaceutically fall in the following ranges: not less than 19% and not more than 30% of methoxy groups and not less than 4% and not more than 12% of hydroxypropyl groups. Hydroxypropyl methylcellulose occurs as a white, fibrous or granular powder. It is used as a suspending agent, a thickening agent, and a tablet excipient. Ophthalmic solutions (0.3 to 1.0%; Isopto[®], Lacril[®], Muro[®], Tearisol[®], Tears Naturele[®], and Ultra Tears[®]) of this hydrophilic polymer are used as topical protectants or artificial tears for contact lenses.

Pyroxylin or soluble guncotton is a product obtained by the action of a mixture of nitric and sulfuric acids on cotton. It is a mixture of cellulose nitrates. Pyroxylin is a pharmaceutical aid used in the preparation of collodion and flexible collodion, topical protectants.

Oxidized cellulose and oxidized regenerated cellulose are similar products that contain not more than 24% of carboxyl groups; they differ in that they contain not less than 16 or 18%, respectively, of carboxyl groups. They are usually available in the form of sterile pads, pledgets, and strips and are used as local hemostatics.

SPECIALTY PRODUCTS. Novocel[®], Oxycel[®], Surgicel[®].

Cellulose acetate phthalate is a reaction product of phthalic anhydride and a partial acetate ester of cellulose. It contains not less than 19% and not more than 23.5% of acetyl groups and not less than 30% and not more than 36% of phthalyl groups. It is a free-flowing, white powder and is used for enteric coating of tablets. Various forms

of **hydroxypropyl methylcellulose phthalate** are also used as tablet-coating agents.

Sodium carboxymethylcellulose is the sodium salt of a polycarboxymethyl ether of cellulose. It is a hygroscopic powder that is used as a suspending agent, a thickening agent, a tablet excipient, and a bulk laxative. It is also used in varying proportions with microcrystalline cellulose to give suspending agents with different viscosities. The usual cathartic dose of sodium carboxymethylcellulose is 1.5 g with water 3 times a day.

PROPRIETARY PRODUCTS. Disolan Forte[®] and Disoplex[®].

Carboxymethylcellulose and its sodium salt are used as bulking agents, usually combined with other drug substances, in products intended for appetite suppression. Representative products include Caltrim[®], Diet-Aid[®], Diet-Trim[®], Pretts[®], and Spantrol[®].

GUMS AND MUCILAGES

Gums are natural plant hydrocolloids that may be classified as anionic or nonionic polysaccharides or salts of polysaccharides. They are translucent, amorphous substances that are frequently produced in higher plants as a protective after injury. Useful hydrocolloids are also contained in some seed embryos or other plant parts (in the case of pectins), are extracted from various marine algae, and are produced by selected microorganisms. A number of semisynthetic cellulose derivatives (see page 44) are used for their hydrophilic properties, and they can be considered as specialized hydrocolloid gums.

Gums are typically heterogeneous in composition. Upon hydrolysis, arabinose, galactose, glucose, mannose, xylose, and various uronic acids are the most frequently observed components. The uronic acids may form salts with calcium, magnesium, and other cations; methyl ether and sulfate ester substituents further mod-

ify the hydrophilic properties of some natural polysaccharides.

Gums find diverse applications in pharmacy. They are ingredients in dental and other adhesives and in bulk laxatives. But their most frequent contribution is as agents of pharmaceutical necessity. These hydrophilic polymers are useful as tablet binders, emulsifiers, gelating agents, suspending agents, stabilizers, and thickeners. When problems are encountered in the utilization of hydrocolloids, some alteration in the hydration of the polymer is usually involved; for example, gums are precipitated from solution by alcohol and by lead subacetate solution.

An effort has been made to distinguish between mucilages and gums on the basis that gums readily dissolve in water, whereas mucilages form slimy masses. Other investigators have tried to distinguish between them on the basis that mucilages are physiologic products and gums are pathologic products. However, these classifications have not been successful. Knowledge of the nature of the polysaccharide polymers is increasing, and it now seems advantageous to abandon extensive use of such designations and to focus on those features that are associated with useful physical properties. The hydrocolloids may be linear or branched, and they may have acidic, basic, or neutral characteristics. Basic polymers have limited commercial importance; acidic and neutral hydrocolloids are widely used, and some generalizations can be made about their properties.

Gums consisting of linear polymers are less soluble than those with branched constituents, and linear hydrocolloids yield solutions with greater viscosity. These features are related to the increased possibility for good alignment and considerable intermolecular hydrogen bonding among linear molecules. This tendency for intermolecular associations also explains why solutions of linear polysaccharides are less stable (tend to precipitate), especially with

reductions in temperature, than solutions of branched molecules. This observation could significantly influence the shelf life of product formulations. When linear polymers contain uronic acid residues, coulombic repulsion reduces intermolecular associations and gives more stability to solutions. However, hydrocolloids with acid groups also have the potential for anionic-cationic interaction to give precipitation or to alter the hydrophilic properties in another manner.

Branched hydrocolloids form gels rather than viscous solutions at higher concentrations. They tend to be tacky when moist, a feature that is advantageous for adhesive purposes, and to rehydrate more readily than linear hydrocolloids, a property of importance in drug formulations that must be reconstituted immediately before use.

The sources of commercially useful gums or hydrocolloids can be summarized as follows:

1. Shrub or tree exudates—acacia, karaya, tragacanth
2. Marine gums—agar, algin, carrageenan
3. Seed gums—guar, locust bean, psyllium
4. Plant extracts—pectins
5. Starch and cellulose derivatives—hetastarch (see page 42), carboxymethylcellulose, ethylcellulose, hydroxypropyl methylcellulose, methylcellulose, oxidized cellulose (page 44)
6. Microbial gums—dextrans (page 42), xanthan

Plant exudates have been the traditional gums for pharmaceutical purposes, and they still find significant application; however, preparation of these gums is labor-intensive and carries a premium price, and their use will probably continue to decline. Marine gums are widely used as utility gums at the present time, and their competitive position appears stable. Guar gum is obtained from an annual legume that is adaptable to modern agricultural practices

and will likely join various cellulose derivatives and the microbial gums as those hydrocolloids whose applications are expanding.

Tragacanth

Tragacanth is the dried, gummy exudate from *Astragalus gummifer* Labillardière, or other Asiatic species of *Astragalus* (Fam. Leguminosae). It is commonly known as **gum tragacanth**. The name tragacanth is from the Greek *tragos* (goat) and *akantha* (horn) and probably refers to the curved shape of the drug; *astragalus* means milkbone and refers to the exuding and subsequent hardening of the drug; *gummifer* is from the Latin and means gum-bearing. The plants are thorny branching shrubs about 1 meter in height and are abundant in the highlands of Asia Minor, Iran, Syria, the Soviet Union, and Greece. When the plant is injured, the cell walls of the pith and then of the medullary rays are gradually transformed into gum. The gum absorbs water and creates internal pressure within the stem, thus forcing it to the surface through the incision that caused the injury. When the gum strikes the air, it gradually hardens owing to the evaporation of the water. The nature of the incision governs the shape of the final product. The gum exuding from natural injuries is more or less wormlike and is twisted into coils (formerly known as **vermiform tragacanth**) or is shaped like irregular tears (formerly known as **tragacanth sorts**) of a yellowish or brownish color. The better grade comes from transverse incisions made with a knife in the main stem and older branches. The gum from such incisions is known as **ribbon gum** and **flake gum**, depending on the shape of the solidified exudate. The gum usually shows longitudinal striations caused by small irregularities in the incision. The metamorphosis occurs only at night, and the tragacanth ribbons exhibit transverse striations that show the amount that exudes each night. The shorter the drying time, the whiter and more trans-

lucent the ribbons. This form of tragacanth is graded commercially by numbers: No. 1 is almost colorless (white) and nearly translucent, No. 2 and No. 3 have more color and opacity. Tragacanth was known to Theophrastus (300 B.C.) and Dioscorides and seems to have been used during the Middle Ages. It was not until recent times, however, that the natives learned to clean the bases of the bushes and incise the bark with a knife, thus producing the clean, white, semitransparent product of present-day commerce.

Tragacanth contains 60 to 70% of bassorin, a complex of polymethoxylated acids, which swells in water but does not dissolve. Bassorin has an elongated molecular shape and forms a viscous solution. Tragacanthin, which is probably demethoxylated bassorin, composes about 30% of the gum and is the more water-soluble component. *Uses*—

Tragacanth is employed pharmaceutically as a suspending agent for insoluble powders in mixtures, as an emulsifying agent for oils and resins, and as an adhesive. Tragacanth is the most resistant of the hydrocolloids to acid hydrolysis and thus is preferred for use in highly acidic conditions. It is employed in cosmetics (hand lotions) as a demulcent and an emollient and in cloth printing, confectionery, and other processes.

Acacia

Acacia is the dried, gummy exudate from the stems and branches of *Acacia senegal* (Linné) Willdenow or of other related African species of *Acacia* (Fam. Leguminosae). It is commonly known as **gum arabic**. *Acacia* is from the Greek *akakia*, coming from *ake*, meaning pointed and referring to the thorny nature of the plant; *senegal* refers to its habitat. The name "gum arabic" seems to be a misnomer because little acacia is produced on the Arabian peninsula and none is exported. The name may reflect the drug's extensive use by the early Arabian physicians.



Fig. 2-9. Bark is peeled from the stems of *Acacia senegal* growing in the Sudan. (Photo courtesy of Boxall and Company, Ltd., Khartoum and P.S. Buschaert Company, Inc., New York.)

Acacia plants are thorny trees about 6 meters in height that grow in the Sudan and in Senegal. Most of the official drug comes from cultivated trees in Kordofan. The trees are tapped by making a transverse incision in the bark and peeling it both above and below the cut (Fig. 2-9), thus exposing an area of cambium 2 to 3 feet in length and 2 to 3 inches in breadth. In 2 or 3 weeks, the tears of gum formed on this exposed surface are collected; the average annual yield of gum per tree is 900 to 2000 g. The formation of the gum may be caused by bacterial action or by the action of a ferment. No trace of metamor-

phosed cell walls is found in the gum; therefore, the gum must be formed from cell contents. The gum is occasionally exposed to and bleached by the sun. Numerous minute cracks often form in the outer portion of the tears during the bleaching process, thus giving them a semiopaque appearance. The tears are garbled and graded by hand, then packed and shipped via Port Sudan.

Acacia has been an article of commerce since remote times. The tree and heaps of gum are pictured during the reign of Ramses III and in later inscriptions. It was exported from the Gulf of Aden 1700 years before Christ. Theophrastus mentioned it in the third century B.C. under the name of "Egyptian gum." During the Middle Ages, acacia was obtained from Egypt and Turkey. The West African gum (Senegal) was imported by the Portuguese during the fifteenth century.

Acacia consists principally of arabin, which is a complex mixture of calcium, magnesium, and potassium salts of arabic acid. Arabic acid is a branched polysaccharide that yields L-arabinose, D-galactose, D-glucuronic acid, and L-rhamnose on hydrolysis. 1,3-Linked D-galactopyranose units form the backbone chain of the molecule, and the terminal residues of the 1,6-linked side chains are primarily uronic acids. Acacia contains 12 to 15% of water and several occluded enzymes (oxidases, peroxidases, and pectinases) that can cause problems in some formulations.

Acacia is unusually soluble for a hydrocolloid and can form solutions over a wide range of concentrations. It remains in solution at alcohol concentrations below 60%, a property that is useful in some drug formulations. Solutions of acacia have low viscosity and good stability over the pH range of 2 to 10; these properties contribute to the gum's use as an excellent emulsifying agent.

Acacia is also used as a suspending agent. It possesses useful demulcent and emollient properties and finds application

as an adhesive and binder in tablet granulations.

Ghatti gum or Indian gum is a product that is sometimes used as a substitute for acacia. It is an exudate from *Anogeissus latifolia* (Fam. Combretaceae), a tree indigenous to India and Sri Lanka. It is a branched hydrocolloid and readily forms dispersions with cold water; the dispersions are more viscous than those of acacia.

Karaya Gum

Karaya gum or sterculia gum is the dried, gummy exudate from *Sterculia urens* Roxburgh, *S. villosa* Roxburgh, *S. tragacantha* Lindley, or other species of *Sterculia* Linné (Fam. Sterculiaceae), or from *Cochlospermum gossypium* DeCandolle or other species of *Cochlospermum* Kunth (Fam. Bixaceae). These trees are native to India and are widely scattered in the Indian forests. They may attain a height of 10 meters, but the trunks are large, soft, and corky. *Sterculia* is from the Latin *Sterculius*, the deity that presided over manuring, and refers to the fetid odor of the trees.

The gum exudes naturally or from incisions made to the heartwood and is collected throughout the year, mostly from March to June. The incisions produce knoblike masses of gum that are collected frequently for 9 months. The tree should then be allowed to rest for 2 to 3 years. Three commercial grades are collected in the central provinces of India and exported from Bombay; the various meshes of granular and powdered karaya are produced in the United States.

Karaya gum consists of an acetylated, branched heteropolysaccharide with a high component of D-galacturonic acid and D-glucuronic acid residues. Varying amounts of pigmented impurities are also present in commercial grades of this gum; its color ranges from pale yellowish to pinkish brown. Karaya gum is one of the least soluble of the exuded plant gums. It absorbs water, swells to several times its

original bulk, and forms a discontinuous type of mucilage.

Karaya gum is used as a bulk laxative, as an agent for forming emulsions and suspensions, and as a dental adhesive. It is used extensively in wave set solutions and in skin lotions, in the textile and printing industries, in the preparation of food products, and in the preparation of composite building materials.

SPECIALTY PRODUCT. Karaya gum is an ingredient in Movicol®.

Sodium Alginate

Sodium alginate or algin is the purified carbohydrate product extracted from brown seaweeds by the use of dilute alkali. It is chiefly obtained from *Macrocystis pyrifera* (Turn.) Ag. (Fam. Lessoniaceae). Algin is found in all species of brown seaweeds (Class Phaeophyceae), and some commercial algin has been obtained from, among other sources, species of *Ascophyllum*, *Ecklonia*, *Laminaria*, and *Nereocystis*. *Macrocystis pyrifera* is harvested from several temperate zones of the Pacific Ocean; the area off Southern California is a major producing site.

Algin consists chiefly of the sodium salt of alginic acid, a linear polymer of L-guluronic acid and D-mannuronic acid. Mannuronic acid is the major component, but there is some variation with the algal source. The alginic acid molecule appears to be a copolymer of 1,4-linked manno-pyranosyluronic acid units, of 1,4-linked gulopyranosyluronic acid units, and of segments where these uronic acids alternate with 1,4-linkages.

Sodium alginate occurs as a nearly odorless and tasteless coarse or fine powder and is yellowish white in color. It is readily soluble in water, forming a viscous, colloidal solution. It is insoluble in alcohol, ether, chloroform, and strong acid.

Sodium alginate is a suspending agent. It is also used in the food industry (ice cream, chocolate milk, salad dressings, icings, confectionery), for suspending cos-

metic preparations, as a sizing, and for other industrial purposes. Algin is metabolized by the body and has a caloric value of approximately 1.4 calories per g. The caloric value of the small amount used in most manufactured products is insignificant.

Alginic acid is relatively insoluble in water, but it is used as a tablet binder and thickening agent. Useful gel-forming properties are associated with salts of various polyvalent cations and alginic acid. Calcium alginate has found application for a number of gelation purposes, including the formation of a firm gel for preparing dental impressions. The propylene glycol ester of algin has been prepared and is especially useful in formulations that require greater acid stability than that possessed by the parent hydrocolloid.

Agar

Agar is the dried, hydrophilic, colloidal substance extracted from *Gelidium cartilagineum* (Linné) Gaillon (Fam. Gelidiaceae), *Gracilaria confervoides* (Linné) Greville (Fam. Sphaerococcaceae), and related red algae (Class Rhodophyceae). Agar is sometimes referred to as **Japanese isinglas**.

These algae grow along the eastern coast of Asia and the coasts of North America and Europe. Most of the commercial supply comes from Japan, Spain, Portugal, and Morocco. Mexico, New Zealand, South Africa, and the United States are also significant producers.

Agar is prepared in California as follows: the fresh seaweed is washed for 24 hours in running water, extracted in steam-heated digesters with dilute acid solution and then with water for a total period of about 30 hours. The hot aqueous extract is cooled and then congealed in ice machines. The water from the agar almost completely separates as ice. The 300 lb agar ice block (containing about 5 lb of dry agar) is crushed, melted, and filtered through a rotary vacuum filter. The moist agar flakes are dried by currents of dry air in tall cyl-

inders. The fully dried product can be reduced to a fine powder.

Agar usually occurs as bundles consisting of thin, membranous, agglutinated strips or in cut, flaked, or granulated forms. It may be weak yellowish orange, yellowish gray to pale yellow, or colorless. It is tough when damp, brittle when dry, odorless or slightly odorous, and has a mucilaginous taste. Agar is insoluble in cold water, but if one part of agar is boiled for 10 minutes with 65 times its weight of water, it yields a firm gel when cooled.

Agar is predominantly the calcium salt of strongly ionized, acidic polysaccharides. It can be resolved into 2 major fractions, agarose and agarpectin. The structures of these constituents have not been fully established, and they are probably variable. The primary carbohydrate component appears to consist of alternating, 1,3-linked D-galactopyranosyl and 3,6-anhydro-L-galactopyranosyl units. Most of the anhydrogalactose residues in agarpectin have a sulfate ester substituent, but agarose is characterized by a low sulfate content.

Agar hydrates to form a smooth, non-irritating bulk that favors normal peristalsis and is used as a laxative. Agar is also used as a suspending agent, an emulsifier, a gelating agent for suppositories and surgical lubricants, and a tablet excipient and disintegrant. It is extensively used as a gel in bacteriologic culture media and as an aid in food processing and other industrial processes.

PROPRIETARY PRODUCTS. Agoral[®] and Petrogalar[®].

Agarose also finds special application in clinical diagnostics. It is used as a matrix for immunodiffusion, for **electrophoretic** separation of globulin and other proteins, and for techniques involving gel filtration and gel chromatography.

Carrageenan

Carrageenan is a term referring to closely related hydrocolloids that are obtained from various red algae or seaweeds. *Chlon-*

drus crispus (Linné) Stackhouse and *Gigartina mamillosa* (Goodenough and Woodward) J. Agardh (Fam. Gigartinaceae) are major sources of carrageenan; these algae are commonly known as chondrus or Irish moss.

These plants are common along the northwestern coast of France, the British Isles, and the coast of Nova Scotia (Fig. 2-10). The plants are collected chiefly during June and July, spread out on the beach and bleached by the action of the sun and dew, then treated with salt water, and finally dried and stored. The chief points of collection in the United States are located 15 to 25 miles south of Boston, where *Chondrus crispus* is gathered and used in the manufacture of carrageenan. *Gigartina mamillosa* is most abundant north of the *Chondrus crispus* region; thus, it rarely oc-

curs in the drug collected in the United States, though it is not unusual in the imported chondrus.

Chondrus is an allusion to the cartilage-like character of the dry thallus; *Gigartina* is an allusion to the fruit bodies that appear as elevated tubercles on the thallus. The specific name, *crispus*, pertains to the curled fronds; *mamillosa* to the small, breastlike, stalked fruit bodies or cystocarps.

The carrageenan hydrocolloids are galactans with sulfate esters and physically resemble agar. The carrageenans differ chemically from agar because they have a higher sulfate ester content. Carrageenans can be separated into several components, including *k*-carrageenan, *i*-carrageenan, and λ -carrageenan.

There are some differences in the specific

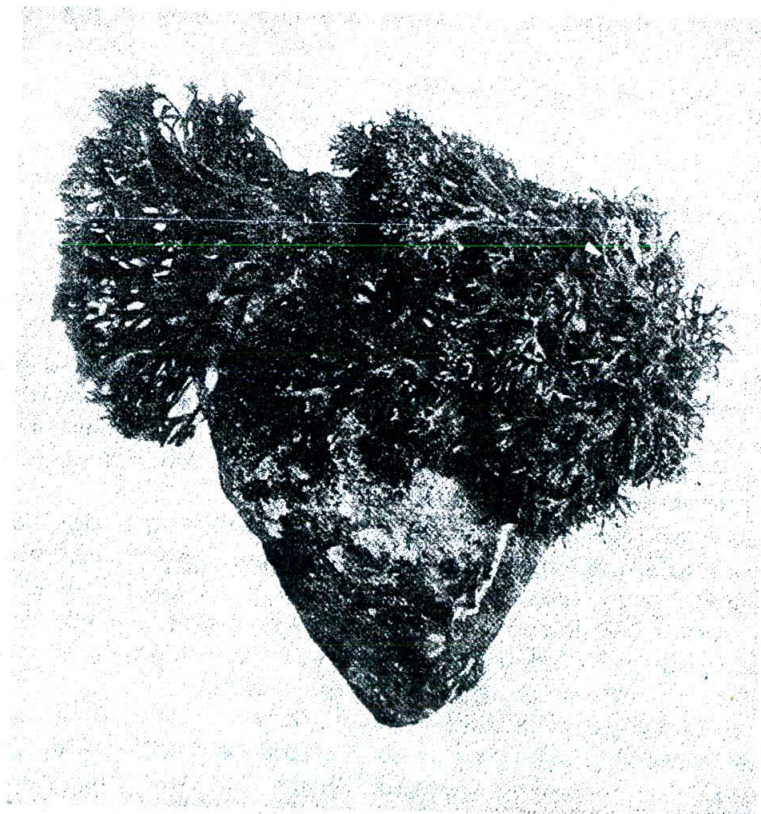


Fig. 2-10. Specimen of *Chondrus crispus* attached to the rock where it was found growing along the Massachusetts coast.

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properties and applications of the individual carrageenans. For example, *k*- and *i*-carrageenans tend to orient in stable helices when in solution, but λ -carrageenan does not. Consistent with these properties, *k*- and *i*-carrageenans are good gelating agents, and the nongelling λ -carrageenan is a more useful thickener.

Carrageenans are widely used to form gels and to give stability to emulsions and suspensions. The firm texture and good rinsability of these hydrocolloids are particularly desirable in toothpaste formulations. They are also used as a demulcent, a bulk laxative, and an ingredient in many food preparations.

PROPRIETARY PRODUCT. Chondrus is an ingredient in the laxative preparation, Kondremul®.

Furcellaria fastigiata (Huds.) Lamour., a red alga, yields an extract called furcellaran or Danish agar. This hydrocolloid is similar to *k*-carrageenan, and it finds some use, especially in Europe, as a gelating and suspending agent.

Plantago Seed

Plantago seed, psyllium seed, or plantain seed is the cleaned, dried, ripe seed of *Plantago psyllium* Linné or of *P. indica* Linné (*P. arenaria* Waldstein et Kitaibel), known in commerce as Spanish or French psyllium seed; or of *P. ovata* Forskal, known in commerce as blonde psyllium or Indian plantago seed (Fam. Plantaginaceae) (Fig. 2-11). *Plantago* is from the Latin and means sole of the foot, referring to the shape of the leaf; *psyllium* is from the Greek and means flea, referring to the color, size, and shape of the seed (fleeseed); *arenaria* is from the Latin *arena* and means sand, referring to the sandy habitat of the plant. *Ovata* refers to the ovate shape of the leaf.

P. psyllium is an annual, caulescent, glandular, pubescent herb native to the Mediterranean countries and extensively cultivated in France, which yields the bulk of the American imported psyllium seed.

P. ovata is an annual, acaulescent herb

native to Asia and the Mediterranean countries. The plant is cultivated extensively in Pakistan.

In France, the seeds are planted in March and harvested in August, when they are about three quarters mature. The fields are mowed about dawn, when the dew is heaviest, to prevent scattering of the seed. The plants, partially dried in the sun, are threshed, and the seeds are cleaned and bagged and allowed to dry fully. In Europe, the seeds have been a domestic remedy since the 16th century, but only since 1930 have they been extensively used in America as a popular remedy for constipation.

Commercially, the most important plantago product is the husk of the seed of *P. ovata*. It is produced in Pakistan and further purified and processed in the United States. However, **psyllium husk** may be prepared from any of the three commercial *Plantago* species. A physicochemical process is used to separate the mucilaginous layer of the seed coat.

Plantago seeds contain 10 to 30% of hydrocolloid, which is localized in the outer seed coat. The hydrocolloid material can be separated into acidic and neutral polysaccharide fractions, and, upon hydrolysis, L-arabinose, D-galactose, D-galacturonic acid, L-rhamnose, and D-xylose are obtained. The exact compositions of the polymers have not been determined. Solutions of the purified gum are thixotropic; the viscosity decreases as shear rate increases, a property that is of potential value.

STANDARDS AND TESTS. When psyllium seed is placed in water, the radial and outer walls of the epidermal cells swell to form layers of mucilage about the seed (Fig. 2-12). The following test for quality has been devised:

Place 1 g of plantago seed in a 25-ml graduated cylinder, add water to the 20-ml mark, and shake the cylinder at intervals during 24 hours; allow the seeds to settle for 12 hours, and note the total volume occupied by the swollen seeds: the seeds

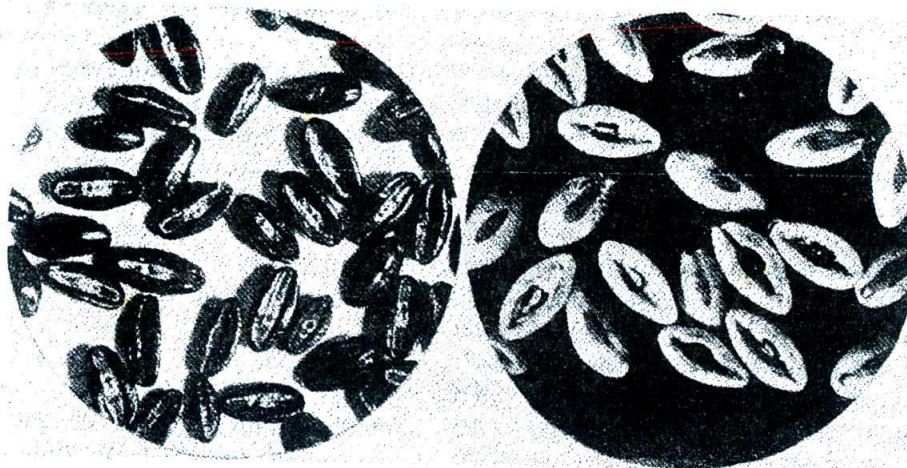


Fig. 2-11. Psyllium seed: A, French psyllium seed (*Plantago psyllium*). B, Indian plantago seed (*Plantago ovata*).

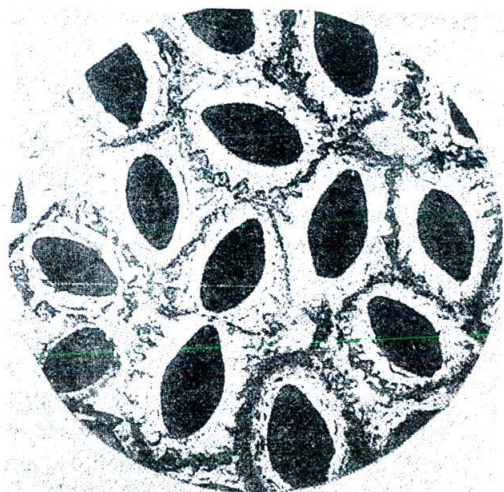


Fig. 2-12. Seeds of *Plantago psyllium* placed in water show the swelling of the mucilage.

of *P. psyllium* occupy a volume of not less than 14 ml, those of *P. ovata* not less than 10 ml, and those of *P. indica* not less than 8 ml.

USE AND DOSE. Plantago seed is a cathartic. Its action is caused by the swelling of the mucilaginous seed coat, thus giving bulk and lubrication. The seeds should be taken with a considerable amount of water. The usual dose is 7.5 g.

Combined with various chemicals such

as powdered anhydrous dextrose, sodium bicarbonate, monobasic potassium phosphate, citric acid, and others, psyllium husk (psyllium hydrophilic mucilloid) is used as an ingredient in preparations for the treatment of constipation.

PROPRIETARY PRODUCTS. Casyllium[®], Cillium[®], Effersyllium[®], Fiberall[®], Hydrocil[®], Konsyl[®], Metamucil[®], Modane[®], Mucilose[®], Naturacil[®], Perdiem[®], Pro-Lax[®], Prompt[®], Regacillium[®], Reguloid[®], Saraka[®], Serutan[®], Siblin[®], Syllact[®], Syllamalt[®], and V-Lax[®].

Cydonium or quince seed is the ripe seed of *Cydonia vulgaris* Persoon (Fam. Rosaceae). These seeds possess a mucilaginous epithelium equivalent to approximately 20% of their weight. This mucilage is composed of cellulose suspended in a more soluble polysaccharide that yields L-arabinose and a mixture of aldobiouronic acids. The hydrocolloid forms viscous solutions with thixotropic properties, and it is used as an ingredient in some wave setting lotions. Economic considerations preclude many other potential uses of this hydrocolloid.

Guar Gum

Guar gum or guaran is the powdered endosperm of the seed of *Cyamopsis tetra-*

gonolobus (Linné) Taubert (Fam. Leguminosae), an annual plant that is readily cultivated in dry climates. Texas is a major producing area. Use of this gum is expanding rapidly, and there is no practical limit on the amount of gum that can be produced by modern agricultural practices to meet the demand.

The hydrocolloid is a galactomannan. 1,4-Linked D-mannopyranosyl units form a linear chain; single 1,6-linked D-galactopyranosyl residues are attached to alternate mannose moieties. This molecular structure gives properties that are intermediate between those typically associated with branched and linear hydrocolloids. The gum hydrates in cold water and is stable in acidic formulations.

Guar gum is used as a bulk-forming laxative and as a thickening agent, a tablet binder, and a disintegrator in pharmaceuticals. The food processing and paper industries are large users of this gum.

PROPRIETARY PRODUCTS. Gentlax B® and Guarsol®.

Locust Bean Gum

Locust bean gum is the hydrocolloid-containing powdered endosperm of the seed of *Ceratonia siliqua* Linné (Fam. Leguminosae) (Fig. 2-13), a tree native to the Mediterranean region. The slow development of the tree (approximately 15 years for initial seed production) restricts the prospects for increasing the supply of the gum to meet expanding demands for hydrocolloids.

A "flour" or powder made from the flesh of the mature seed pods of the tree is the carob, which is currently popular with natural food advocates. This material resembles chocolate and can be used in a variety of food products. It is also known as carob pulp or St. John's bread, the latter name from its legendary use as the food of St. John the Baptist.

Locust bean gum is a galactomannan and is similar to guar gum. The structural distinction is locust bean gum's lesser fre-

quency of galactose substituents on the linear mannose chain of the locust bean polymer; every fourth or fifth mannose residue is substituted. Locust bean gum has properties slightly more typical of linear hydrocolloids; it is incompletely dispersed in cold water.

Locust bean gum can be used in pharmaceuticals as a thickener and stabilizer and in other manufacturing processes where a hydrocolloid is indicated.

Xanthan Gum

Xanthan gum is a high-molecular-weight microbial gum prepared by the action of *Xanthomonas campestris* on suitable carbohydrates. The exocellular gum is recovered from the fermentation broth by precipitation with isopropyl alcohol. Commercial gums with various genetically controlled compositions and molecular weights are available. Xanthan gum is marketed as the sodium, potassium, or calcium salt.

The main component of xanthan gum is a branched, partially acetylated polysaccharide containing D-glucose, D-glucuronic acid, and D-mannose. The polymer tends to consist of repeating units of 16 sugar residues; 13 units form a linear chain, and 3 sugar residues are single-sugar side-chain substituents. The gum dissolves in hot and cold water to give high viscosity solutions, and it has good compatibility with a wide range of salts. The viscosity is independent of temperature between 10 and 70° C.

Xanthan gum is used in pharmaceuticals for its excellent emulsifying and suspending properties. The pseudoplastic properties of this gum enable toothpastes and ointments both to hold their shape and to spread readily.

PECTIN

Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. Pectin is from the

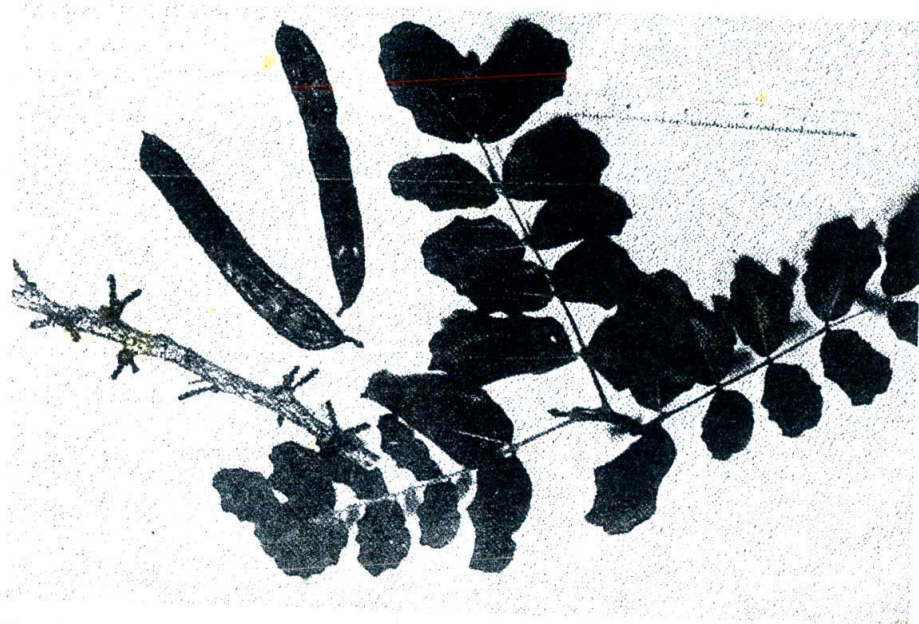


Fig. 2-13. Carob (*Ceratonia siliqua*) showing the compound leaves, also the pods containing seeds from which locust bean gum is obtained. (Photo, courtesy of Dr. Julia F. Morton, Director, Morton Collectanea, University of Miami.)

Greek and means congealed or curdled. It is a natural hydrophilic colloid consisting chiefly of partially methoxylated polygalacturonic acids; the main carbohydrate component is a linear, 1,4-linked D-galacturonan. The molecular weight of pectin ranges from 100,000 to 250,000. Pectin yields not less than 6.7% of methoxyl groups and not less than 74% of galacturonic acid. The gelling power and viscosity of solutions depend on the number of galacturonic acid units in the molecule.

Pharmaceutical pectin differs from "commercial" pectin because it does not contain sugars or organic acids. Pharmaceutical pectin is pure pectin to which no additions have been made.

Pectin may be standardized to the convenient "150 jelly grade" by the addition of dextrose or other sugars. It sometimes contains sodium citrate or other buffer salts. Much of the commercial pectin is obtained as a by-product of the citrus canning industry. Citrus peel is a rich source of pectin, the amount varying with the season

and the variety. Approximately half of the pectin made in the United States is derived from lemon peel.

Pectin in fruit is found in an insoluble form known as protopectin; it is converted to the soluble form by heating the fruit with dilute acid. This solution of pectin can be precipitated by alcohol or by "salting out." It is then washed and dried.

Pectin is a coarse or fine powder, yellowish white in color, almost odorless, and has a mucilaginous taste. It is completely soluble in 20 parts of water, and the solution is viscous, opalescent, colloidal, and acidic to litmus paper. One part of pectin heated in nine parts of water forms a stiff gel.

Pectin is classified as a protectant and a suspending agent and is an ingredient in many antidiarrheal formulations. As a colloidal solution, it has the property of conjugating toxins and enhancing the physiologic functions of the digestive tract through its physical and chemical properties. In the upper intestinal tract, pectin possesses a surface area composed of ul-

tramicoscopic particles (micelles) that have the property of colloidal absorption of toxins. The efficacy of pectin in the gastrointestinal tract is largely owing to this colloidal action.

PROPRIETARY PRODUCTS. Pectin is an ingredient in the following preparations: Amogel[®], Diabismul[®], DIA-quel[®], Diar-Aid[®], Diarkote[®], Diatrol[®], Donnagel[®], Infantol[®], Kaodene[®], Kaodonna[®], Kaopectate[®], Kaypectol[®], K-Pek[®], Parellixir[®], Parepectolin[®], Pecto Kay[®], Pektamalt[®], Polymagma[®], and Quiagel[®].

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