Sugars: their origin in photosynthesis and subsequent biological interconversions[1-3]

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ABSTRACT   Sugar has been valued as a commodity for thousands of years. Despite its long history in commerce, the biological mechanisms accounting for the production of sugar are rather recent discoveries. The reactions are remarkable. Sugar is produced by all green plants and photosynthetic bacteria in a reaction sequence capable of forming carbon-carbon bonds. The very first steps occur independently of solar energy input, but to sustain the reaction, the products of initial fixation are phosphorylated and undergo a reduction in oxidation state. These steps responsible for phosphorylation and reduction are driven by products generated in the chloroplast upon the absorption of light. At this point, after just a few reactions, the products of photosynthesis have already acquired the attributes characteristic of sugars. Once carbon is stabilized as simple sugars in the chloroplast, the products undergo a sequence of rearrangements to sustain a cycle leading to new carbon dioxide acceptor molecules, and with each turn of the cycle a new carbon atom is introduced into the pool. As the process continues some of the carbon is diverted to synthesize starch within the chloroplast. Sucrose is synthesized in the cytoplasm adjacent to the chloroplast from exported carbohydrate as a diversion from the formation of starch. Sucrose represents the principal transport substance in most plants. Storage starch, cellulose, and other complex cell wall polysaccharides are typically derived from the sugar monomers found in sucrose. Sugars supply all the fixed carbon for synthesis of biological compounds and are fundamental for sustaining the energy flow to all food systems.   *Am J Clin Nutr* 1995;61(suppl): 915S–21S.

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Introduction

Carbohydrates have served as the fundamental source of energy needed to drive metabolism and to assemble structures since biological systems first evolved. To most people, the word sugar connotes the sensation of sweetness. It was undoubtedly the quest for sweetness by early people and by many animals that led to honey being taken from the nests of bees and to the selection of certain ripe fruits and berries. It was honey collected by bees as nectar from flowers that was probably the universal source of "refined" sugar until a few thousand years ago (1). However there is also evidence that the northeastern Native Americans were tapping maple trees to extract syrup, a form of concentrated sugar, long before the Europeans arrived.

The cultivation of plants for sweetness apparently began in Asia. Sugar cane is believed to be native to the islands of the South Pacific but as long as 3000 y ago it was taken to India and grown as a crop. The stalks were typically cut and chewed directly for their sweetness but they were also transported and traded through the markets. Somewhat later the stems were crushed and the expressed sap concentrated by boiling to form a brown solid. Over time sugar cane was brought west through the Near East and eventually to Africa and the export of sugar products to Europe increased. By the early 1400s the Venetians had devised a procedure to refine brown sugar concentrates to produce white sugar. The Venetian monopoly on white sugar kept prices high and fostered an increasing demand among the European aristocracy. Another component of the European refined sugar cartel emerged in Spain and was controlled by the Moors. With the growing demand for sugar the local sugar monopolies continued to make attractive profits. It is not surprising therefore that sugar cane was introduced into the new world by the third voyage of Columbus (1). Both the Spanish and the Portuguese quickly established huge sugar plantations in tropical America. The British joined in somewhat later in their tropical Western world colonies. The scale of sugar operations in the new world was such that labor requirements grew and growers turned to slavery. By the mid 16th century the sugar industry had become dependent on this form of labor. Sugar cane was apparently introduced into Hawaii by Polynesians during their voyages from the South Pacific. The commercial production of sugar from cane began in Hawaii in the early 1800s and labor requirements were met mostly through migration of Asians.

Currently more than one-half of the commercial sugar supply is derived from sugar cane with most of the rest supplied by sugar beets. The development of sugar beets as a source of sucrose actually occurred much later than that of sugar cane. Certain beet roots were known to yield a sweet syrup, even in ancient times, but it was not until the mid 18th century that beet syrup was first used for sugar production in Germany. The advantage of sugar beets was their ability to thrive in temperate

climates. As a result, Germany became a major producer along with France, Austria, and Imperial Russia. Political leverage led to the encouragement of beet production in Europe to reduce the dependency on tropical countries for sugar. The United States became a major producer of beet sugar just within this century.

Sucrose is a main product in sweetener commerce and because it is such a highly purified product it fosters a tendency to think of sugar as a product of sugar factories. We need to be reminded that the chemical synthesis of any sugar is exceedingly complicated. Despite this complexity all living systems are absolutely dependent on the formation and utilization of sugar. In addition to sucrose, sweeteners are now derived from corn starch, and corn syrup constitutes a major component of the sugar industry to meet the demand for soft drinks. The multifaceted starch industry is also an integral part of our nutritional infrastructure. There is increasing evidence for important roles of even more complex carbohydrates. Some of the key elements of photosynthesis are examined here to gain an appreciation of the processes leading to the formation of the entire spectrum of sugars in nutrition.

Photosynthesis

Photosynthesis is an operational term, one that is in such common use that we often do not think of its significance nor do we appreciate fully its biological implications. In plants, photosynthesis is initiated by the absorption of light by the chlorophyll of chloroplasts in leaves. A variety of pigments in addition to chlorophyll are arrayed on the chloroplast membranes as complexes for efficient collection of incoming photons. These pigment aggregates, described as antenna complexes, offer a collection surface rather than a molecular target point and are organized to deliver captured energy to a reactive center. At that center the electron from chlorophyll is transferred from the pigment (2). Through chlorophyll, the photosynthetic pigment complex captures solar energy delivered by photons in the visible region of the spectrum. The energy of the photons is assimilated as a consequence of electron transport coupled with charge separation because of the unique membrane structure of the chloroplast. Electron gradients establish potentials across membrane-bound vesicles to drive the formation of ATP (2) and at the same time electrons are retained by the reduction of NADP$^+$ in its conversion to NADPH. Because these two substances, ATP and NADPH, are directly coupled to light absorption, they represent the light-dependent links to the transfer of energy. As the fixation of carbon dioxide occurs, the transformed solar energy is embodied in the newly formed carbon bonds and the accumulated mass and energy are conserved through the development of increasingly complex molecular structures.

In photosynthesis the remarkable convergence of mass and energy not only serves in the nutrition of contemporary nonphotosynthetic organisms but the products of photosynthesis of ancient plants now yield coal, oil, and natural gas. Fuel for cars, heat for homes, and energy for industry were all originally derived from sugars that were synthesized eons ago and converted to fossil fuels. In addition to the formation of sugars and their derivatives for food, fiber, and shelter, the light reaction in photosynthesis is responsible for the dissociation of water to

yield electrons to replace those depleted from chlorophyll. As a consequence, chlorophyll is restored to its initial state for further photoexcitation. Electrons to restore chlorophyll are extracted from water and oxygen is released. It is believed that virtually all the oxygen in the atmosphere is derived from photosynthetic activity by plants and that oxygen escaping into the upper atmosphere sustains the formation of the ozone layer, a filter that protects all terrestrial life from ultraviolet radiation damage. Life has many direct and indirect links to the photosynthetic process.

In this discussion we have focused on the molecular mechanisms embodied in plants for the capture of solar energy, but the efficiency in solar conversion is dependent on other essential adaptations. The energy flux to the surface of the earth occurs at a relatively moderate rate, affording organisms some protection from what otherwise might be damaging radiation. Nevertheless it is clear that exposure to solar radiation for any extended period is dangerous for humans. We know, for example, that there is a high risk of skin cancer associated with sunbathing. Plants, however, function continuously with full solar exposure. In part they are protected by pigments such as carotene, which suppresses otherwise damaging radiation by moderating aberrant oxidation damage. Despite the damage and the need for protection even in plants, on a total energy basis, the relatively low solar influx to the surface of the earth means that the photosynthetic system is operating at a relatively low energy input even in exposed fields. To compensate, plants not only organize molecular aggregates for photon collection within the chloroplast, as described before, they also deploy leaves with a high surface area to mass ratio to maximize the surface for exposure. The overall effectiveness of energy capture in a crop is based on how effectively the ground surface is covered to capitalize on the incoming sunlight.

Interesting questions arise about how the chloroplast became the organelle for photosynthesis. It is generally believed that the earliest photosynthetic organisms were primitive cyanobacteria (2). Although these organisms continue to exist independently in the world today, during evolution some appear to have been adopted within the cells of nonphotosynthetic organisms and to have been nurtured in an environment where, in exchange for some sugars produced in photosynthesis, the host provided a degree of protection and a favorable environment. Eventually the relationship became so specialized that an interdependency was established. It is now generally believed that the chloroplast organelle in plants is the remnant of what was once long ago an independent photosynthetic organism. Because of their common ancestry, photosynthetic plants and photosynthetic bacteria share fundamental mechanisms with a few important distinctions.

Fixation of carbon and the origin of sugar

Once the photosynthetic system is charged with electrons and energized with ATP the next step is to coordinate these events with the fixation of carbon. Carbon is the exclusive element for photosynthesis because it has the unique properties that impart to biological molecules the capacity for diverse functions. No other element can replace carbon in this role. But the use of carbon creates a dilemma. At least from the perspective of the plant, the sources of carbon in the biosphere offer

serious disadvantages for efficient incorporation. If, for example, carbonate were to be used directly as the form of carbon, plants would be restricted to aquatic systems to absorb soluble carbonate or to terrestrial carbonate deposits, where they would have to extract carbonate as a mineral presumably through some solvent process. In either case the distribution of plants on the earth's surface would be greatly restricted. The alternative to direct uptake of carbonate is carbon dioxide. We know that carbon dioxide is used in photosynthesis but it is interesting to consider the formidable constraints this gas imposes on the system. An engineering study of the system would probably conclude that the incorporation of carbon dioxide by photosynthesis is simply not feasible. The gas is so unreactive that it is used for fire extinguishers; it is also highly oxidized and cannot burn and its atmospheric concentration (0.035%) would seemingly be too low to be considered realistically as a raw material for the process. An important advantage is that carbon dioxide, as an atmospheric component, makes exchange and cycling more feasible and allows plants to establish a foothold over a greater portion of the earth's surface. Carbon dioxide, despite all its apparent disadvantages, is the substrate from which all sugars are made.

Although photosynthesis has been taking place for billions of years it was only ≈50 y ago that the path of carbon in the process was actually revealed. To set the stage for carbon fixation, carbon dioxide from the atmosphere enters into the leaf through small pores on the surface (2). These pores called stomata are capable of opening and closing to regulate gas flow. The benefit of a stoma to the plant is not to restrict the flow of carbon dioxide but to suppress the loss of water. The interior surfaces of the leaf are moist and carbon dioxide dissolves in the aqueous solution and moves into the cells. However, because of the moisture on the internal surfaces, evaporation accompanies the uptake of carbon dioxide and dehydration results. The stoma responds by closing. Hence, as a consequence of the conservation of water by the plant, photosynthesis in the leaf may be effectively halted at least until a more favorable water status develops. Nevertheless, all of the carbon in sugars would be expected to enter the leaf by diffusion through the stomata as carbon dioxide. Once within the cells, carbon dioxide migrates through the aqueous solution into the chloroplast.

Fixation of carbon

The mechanism for carbon fixation is central to the formation of sugars (3). In the chloroplast, carbon dioxide is captured as it interfaces with a magnesium atom that is coordinately stabilized at the active site of the carboxylation enzyme (4, 5). At the same site, the enzyme constrains ribulose bisphosphate by ionic bonds through one of the phosphates. The enzyme responsible for binding carbon dioxide and mediating fixation (ribulose bisphosphate carboxylase) deserves special consideration because it is a unique component of photosynthesis. It is an abundant protein that makes up more than 50% of the soluble leaf protein. As a consequence of its abundance, it is the major nutritional protein found in leaves. Because it catalyzes the incorporation of nearly all carbon introduced into organic molecules it is clearly the definitive starting point for the formation of sugars. At this stage in the formation of

carbon-carbon bonds no energy is required nor is there a net change in the oxidation-reduction state of the products. Immediately after the attachment of carbon dioxide the adjacent bond within ribulose bisphosphate breaks and two molecules of 3-phosphoglyceric acid are released (5) (**Figure 1**). Plants that yield 3-phosphoglyceric acid as the initial fixation step are referred to as C_3 plants.

The next step in the reaction sequence requires ATP to energize 3-phosphoglyceric acid with the transfer of an additional phosphate to the 1-position of the three-carbon triose. After the addition of phosphate, the subsequent reaction transfers an electron from NADPH. This is the first reaction to actually change the oxidation state of the carbon complex (**Figure 2**) and represents an important transition. Up until this stage in fixation the overall oxidation state of the products is the same as the overall oxidation state of the precursors. Upon reduction, one of the phosphates is liberated and the product (a triose) has in essence the attributes of a sugar. The functional groups in glyceraldehyde-3-phosphate are now equivalent to those that are used to define a carbohydrate.

Glyceraldehyde-3-phosphate may be reversibly converted to dihydroxyacetone phosphate (**Figure 3**). Dihydroxyacetone phosphate and glyceraldehyde-3-phosphate represent an important metabolic intersection within the chloroplast from which carbon traffic may be diverted to several destinations. Through a series of intermediates these three-carbon units may be used to regenerate ribulose bisphosphate to reestablish the acceptor for the introduction of a single new carbon as a part of the carbon reduction cycle. As the net inflow of carbon progressively adds to the pool of intermediates, some are used for the synthesis of phosphorylated fructose (Figure 3). In this reaction there is a consolidation of two three-carbon units, a step that represents the formation of an additional carbon-carbon bond. At this point it is important to recognize that sugars and indeed all biological compounds result from an incremental increase of carbon through the formation of just two different carbon-carbon linkages (Figures 1 and 2). As a result we can consider that all biological structures have these two reactions as part of their heritage. To maintain the overall efficiency of the photosynthetic process and to not overload the chloroplast, some intermediates are diverted from the pool at this stage. Within the chloroplast the enzymic isomerization of fructose phosphate yields glucose-6-phosphate, which is converted to glu-
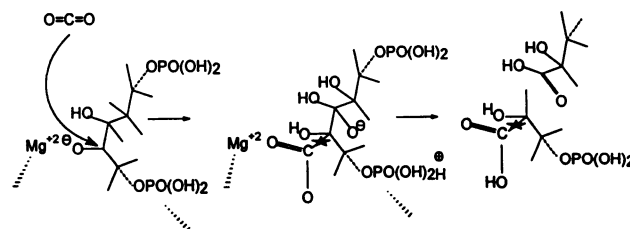

FIGURE 1. Representation of the reaction sequence at the active site of ribulose-1,5-bisphosphate carboxylase. Magnesium forms a coordinate bond with the enzyme and combines with carbon dioxide. One of the phosphates of ribulose-1,5-bisphosphate orients the structure relative to the binding site of the enzyme. Immediately after carbon dioxide associates with ribulose-1,5-bisphosphate, the complex dissociates from the enzyme as two 3-phosphoglyceric acid molecules. The star represents the position in the structure of the new carbon-carbon bond established in this reaction.
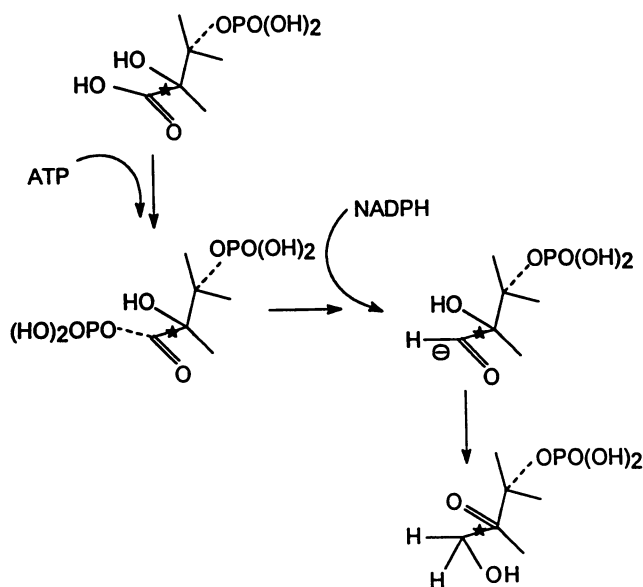
FIGURE 2. After 3-phosphoglyceric acid dissociates from ribulose-1,5-bisphosphate carboxylase, it reacts in the presence of ATP and then is reduced by accepting an electron from NADPH. This reaction represents the first point at which the oxidation state of carbon is changed in photosynthesis and the product has properties consistent with a carbohydrate. The star traces the new carbon bond in the reaction sequence.

cose-1-phosphate. In the presence of the appropriate enzyme, glucose-1-phosphate reacts with the nucleotide ATP to form ADP-glucose to serve as the glucosyl donor for the formation of chloroplast starch (**Figure 4**). Starch formation within the chloroplast represents a transient storage for sugar pending later mobilization and export. Chloroplast starch undergoes considerable turnover during a 24-h cycle and although the amount of the total sugar in the chloroplast that is converted to starch is relatively high, most of it is quickly remobilized so that the net amount of chloroplast starch fluctuates widely compared with starch accumulation in storage tissues.
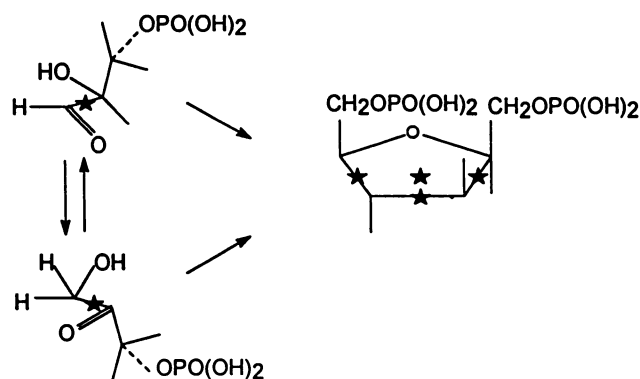
FIGURE 3. Concentrations of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate are maintained in a reversible reaction. The two combine in the presence of an enzyme to form fructose-1,6-bisphosphate. This is the second carbon-carbon bond formed in the synthesis of a hexose. The double star represents the position of the new carbon-carbon bond and the single star traces the expected position of the original bond formed during carboxylation.
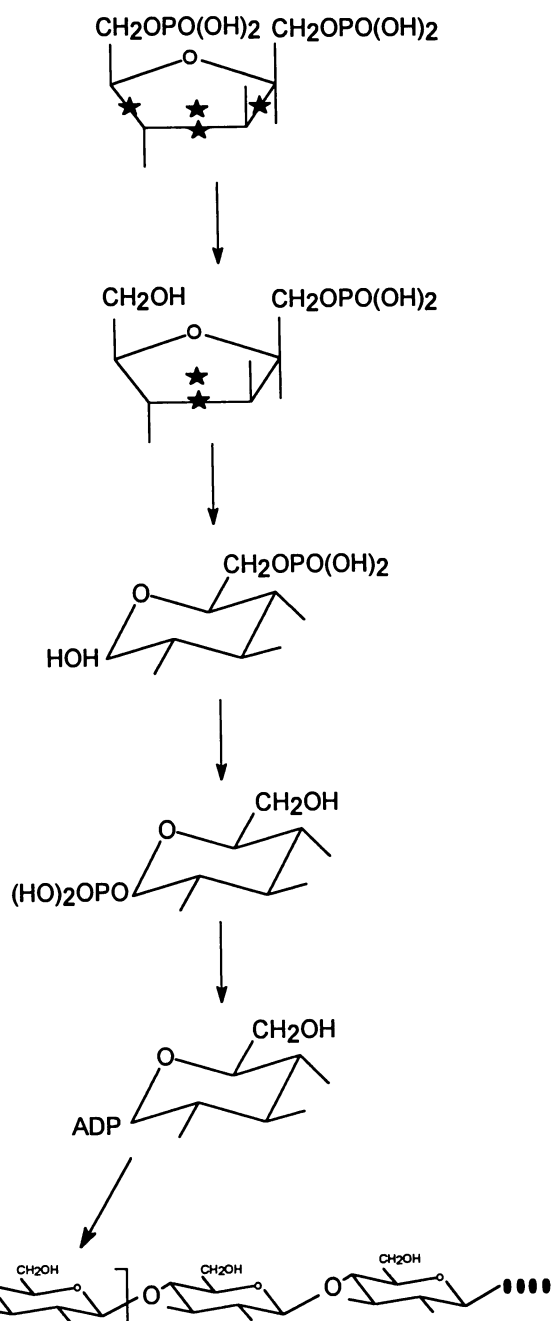
FIGURE 4. Fructose-1,6-bisphosphate is converted to fructose-6-phosphate, from which glucose-6-phosphate is formed. This is the first appearance of glucose in the sequence. Glucose-6-phosphate is converted to glucose-1-phosphate and is activated in the chloroplast by ATP. ADP-glucose is the glycosyl donor for starch synthesis in the chloroplast. Not shown is the synthesis of starch in storage tissues, where UDP-glucose is the glycosyl donor. The double star represents the position of the carbon-carbon bond formed in the linkage of two triose units and the single star continues to show the expected position of the original bond formed during carboxylation.

As carbon is accumulated in the chloroplast some of it also undergoes a net export to the cytoplasm as the trioses dihydroxyacetone phosphate and glyceraldehyde-3-phosphate (2). Outside the chloroplast membrane, in the cytosol, these trioses are converted to the hexoses fructose phosphate, glucose phos-

phate, and in the presence of uridine triphosphate (UTP), uridine diphosphate (UDP)-glucose (6). Fructose-6-phosphate and UDP-glucose react to yield sucrose-6-phosphate which is then dephosphorylated (**Figure 5**). Sucrose is the product of this reaction. In both the synthesis of starch and sucrose from hexoses no new carbon-carbon bonds are formed. The interconnection of sugars in disaccharides and polysaccharides is through glycosidic bonds. Glycosidic linkages are oxygen bridges between sugars; during normal metabolism these linkages are frequently formed and broken. An extensive array of combinations of sugars through glycosidic linkages is possible including polysaccharides and other complex sugars.

The photosynthetic system described above represents the general path of carbon observed in sugar synthesis for all green plants. However, some plants have adopted an additional initial carbon-capture mechanism (2). In these plants, which include sugar cane, the initial acceptor for carbon dioxide is the triose unit phosphoenolpyruvate. The enzyme phosphoenolpyruvic carboxylase mediates the formation of a bond between carbon dioxide and phosphoenolpyruvic acid, resulting in the four-carbon acid oxaloacetic acid (**Figure 6**). Carbon fixation via this route is referred to as C_4 photosynthesis because the initial product has four carbons, one carbon added to a three-carbon acceptor unit. Once carbon is incorporated, oxaloacetic acid is usually reduced to malic acid or converted to asparagine via transamination. These four-carbon acids are formed in leaf mesophyll cells but in most instances they are then translocated to adjacent bundle sheath cells wherein the fixed carbon dioxide is released. Normally the three-carbon unit is then returned to the mesophyll cells where it is staged for accepting additional carbon dioxide. The result of this organic acid shuttle is the delivery and release of carbon dioxide in the bundle sheath cell. During this sequence, because carboxylation is followed by decarboxylation, no net incorporation of carbon has occurred. In the bundle sheath cells, however, the released carbon dioxide is recaptured by ribulose bisphosphate carboxylase and

Photosynthetic carbon reduction cycle
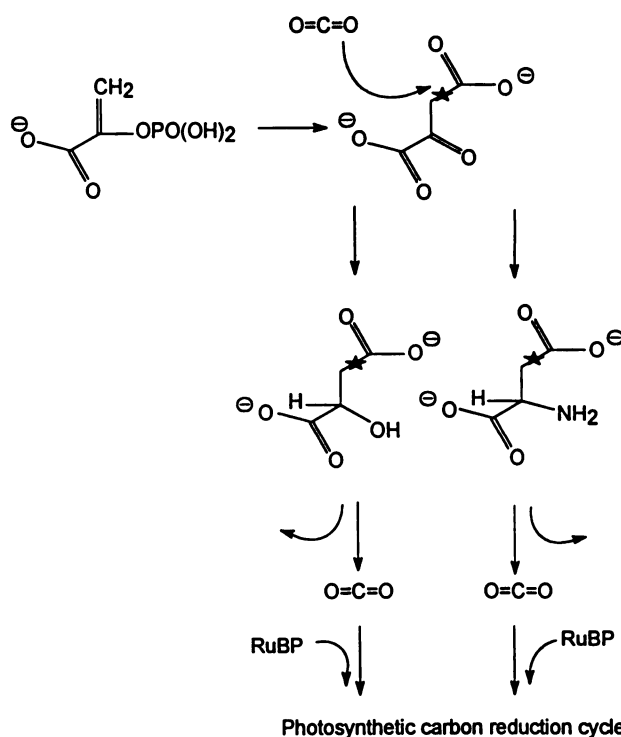
FIGURE 6. In C_4 photosynthesis, carbon dioxide is combined with phosphoenolpyruvate to form oxaloacetic acid. Oxaloacetic acid is reduced to malate or transaminated to aspartic acid. The four carbon acids are shuttled from the mesophyll cells to the bundle sheath cells where they are decarboxylated and the carbon dioxide is reincorporated in the presence of ribulose-1,5-bisphosphate (RUBP) carboxylase. The star represents the bond formed during carboxylation resulting in the formation of the four-carbon acid.
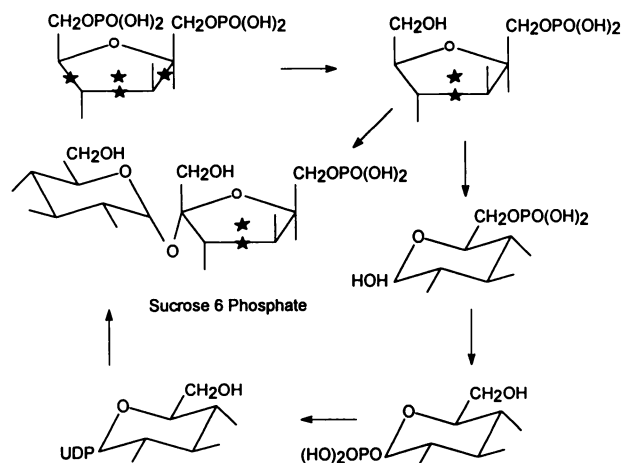
FIGURE 5. In the cytoplasm, fructose-1,6-bisphosphate is converted through a series of steps similar to those involved in starch synthesis in the chloroplast. However, the glucosyl donor is UDP-glucose. The product of UDP-glucose and fructose-6-phosphate is sucrose-6-phosphate. The first appearance of sucrose occurs when sucrose-6-phosphate is dephosphorylated. The double star follows the new carbon-carbon bond formed during the formation of the hexose and the single star continues to represent the original carboxylation step.

processed by the reactions shown in Figures 1–5. The initial capture of carbon by phosphoenolpyruvate carboxylation represents a unique means of directing carbon into organic molecules. Although the C_4 process is seemingly more complex, the overall process is very efficient in the acquisition of carbon dioxide.

As carbon is acquired, sucrose accumulates in the cytosol and starch in the chloroplast. Both processes are a rather direct result of the photosynthetic process. Sucrose is unique because both glucose and fructose are linked through anomeric carbon groups (7). A few other sugars are also combined by a linkage that disarms the functional reducing groups but sucrose and its derivatives are the most abundant examples. Sucrose is the primary exported form of sugar delivered from the photosynthetic cells and loaded into the transport stream for other parts of the plant. Plant roots represent one of the important destinations because they cannot conduct photosynthesis; however, seeds and developing fruits also are sites toward which sucrose may be directed. The demand for sucrose is based on the need for energy and mass resources at some target tissue regardless of whether the use is for some immediate application or for storage. In route to any of these destinations, sucrose is distributed to adjacent cells along the pathway. Upon arrival sucrose may be held as in the stems of cane or the roots of beets or it may be converted to monomers and subsequently to starch or other complex polysaccharides. Starch synthesis in storage

organs is somewhat different than in chloroplasts in that glucose-1-phosphate and UTP form UDP-glucose as the glucosyl donor. Seeds, grains, and other bulk tissues are harvested for the concentrated carbohydrate they contain. It is somewhat unusual for tissues to accumulate high concentrations of sucrose rather than starch. Hence, although sucrose is the common medium of sugar exchange, the accumulation of this sugar in tissues is restricted to relatively few plants.

Whereas plants form a variety of products from photosynthesis they also consume a portion of these products in respiration and growth. In addition, sugars and products of sugar formed in plants are consumed by other organisms that have an absolute dependency on the products of photosynthesis. Because of this system of allocation of energy and mass, all life is destined to eat and to be eaten. If all organisms were capable of photosynthesis there would be no need for plants to initiate the flow of energy and mass. Because plants do initiate the process as primary producers of food, one expects that at each stage in the transfer from one organism to another, some energy and some mass will be retained and some released to the surroundings. The release of carbon dioxide into the atmosphere constitutes a normal cycle. Beginning with plants, the photosynthetic products are consumed by the first level of plant-eating animals. The next level is a predatory sequence for the consumption of the plant consumers, and so on. At each step the process transfers a portion of mass and energy to the next higher level. Because feeding is opportunistic, there is no clear linear progression in consumption of prey by predators; therefore the allocation of photosynthetic products is best described as a food web. At each level a variable amount (usually between 7% and 45% of the total) of the mass and energy is maintained by the consumer population. In the growth and maintenance of metabolic functions there is the obligatory dissipation of organic materials, a cost of living, that makes less available to the next level. Hence, efficiency at each step determines how many steps are possible and how large the population might be; the extent of this sequence is based on the original input, ie, the net production of sugar via photosynthesis.

As a result of the food web, the super predators at the very top of the food chain are not usually eaten by other organisms, not because these animals are large or dangerous, but because by the time photosynthetic energy and mass have been concentrated into them so much has been lost to the environment that they would be an inadequate food source to sustain any further trophic levels. Humans have acquired a distinctive niche in this system. Although we are a part of the food chain we are rarely preyed upon because we have acquired insights to dangers that might put us at risk and the organization of societies precludes this possibility. Humans are omnivorous, making it possible to secure food at several trophic levels. A major factor in providing nutrition of people is ecosystem management, the most important component of which is agriculture. Nevertheless, there are limits within which humans will be able to sustain the flow of energy and mass by management even on a global scale. Fundamental to sustaining production is the conversion of solar energy through photosynthesis. The carbon embodied in humans is eventually recycled. It might be that ashes to ashes, dust to dust is more appropriately ashes to ashes, carbon dioxide to carbon dioxide.

Unique components of sugar metabolism in animals

The consumption of sugars by humans occurs in many forms. Probably most of the intake continues to be as polysaccharides but simple sugars are also a regular part of the contemporary diet. The intermittent intake of sugar (usually because of spacing of meals) would impart striking oscillations in blood sugar concentrations if it were not for sugar interconversions governed by hormonal regulation. The synthesis and degradation of the sugar polymer glycogen in the liver provides a major part of that balance. Here sugars are maintained by synthesis and degradation of polymers; sugars are not actually being made but are being delivered at appropriate concentrations through the forming and breaking of glycosidic bonds. In many respects the structure of glycogen in animals resembles that of starch in plants. Both are α-1,4 glucosyl polymers but glycogen usually has shorter chain lengths and is more highly branched. Even the synthesis of glycogen has features in common with synthetic mechanisms described for starch. Glucose is converted to glucose-1-phosphate and combined with UTP to form UDP-glucose. Glycogen synthetase next transfers the glucose from UDP-glucose to the nonreducing end of the growing glycogen molecule. The degradation of glycogen to release glucose is catalyzed by phosphorylase together with a complex glycosyl transferase required to trim extended branches that would otherwise make glycogen inaccessible to phosphorylase. The formation and mobilization of glycogen serves as a major means of maintaining blood sugar concentrations and of providing an immediate source of energy during strenuous activity. The emphasis here is on the fact that sugar metabolism in this case is restricted to the formation and dissociation of glycosidic bonds.

The focus of this discussion has been to provide a perspective for the origin of sugars used as energy and for carbon structures in the nutrition of animals. These organisms clearly require a net input of sugars or sugar derivatives for metabolism, maintenance, and growth. In addition, humans and other animals have a direct need for specific sugars. Glucose is one example. Glucose, derived from sucrose or starch, is maintained within certain limits in the blood and serves as an essential substrate for certain blood cells and for metabolism of brain and nerve cells. Normally during sugar deprivation glycogen reserves are sufficient to meet the glucose requirements for ≥ 1 d. Once the glycogen reserves are exhausted, the liver is capable of implementing an emergency system to make sugar. This process called gluconeogenesis converts noncarbohydrate reserves into glucose. Sugar synthesis occurs in the liver during starvation and utilizes glycerol and lactate and certain amino acids derived from the breakdown of proteins. Whereas the specific enzymes for gluconeogenesis in humans have functions similar to enzymes for carbon dioxide fixation in plants, the enzymes themselves are different and the conversion process is directed toward the carboxylation of pyruvate and the formation of oxaloacetic acid (also a product found in C_4 carboxylation in plants). The reaction requires energy from ATP. The four-carbon acid is decarboxylated to yield phosphoenolpyruvate. Once phosphoenolpyruvate is formed it is converted to form glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, these two triose units are combined to yield 1,6-fructose diphosphate and subsequently the formation of glucose. In a sense the formation of sugar in

gluconeogenesis resembles, in part, the metabolic steps described previously for sugar formation in plants with one of the reactions generating an essential carbon-carbon bond. However, although the process includes carboxylation as an intermediate step, it does not introduce a net increase of carbon into the system. We nevertheless conclude that under unusual circumstances animals can, in fact, form sugar. It is clear that the strategy is to meet a critical demand and that the system cannot be sustained without reestablishing dietary intake of sugars.

The synthesis of sugars in photosynthesis occurs after just a few reaction steps. This apparent simplicity obscures the specificity with which these reactions are directed. In each case the addition of carbon might occur through multiple mechanisms, but catalysis in photosynthesis results in a precise attachment and a bond that is invariable. Although we have explored the sequence of fundamental steps from triose to hexose and then to sucrose and starch, we must come to grips with the fact that these sugars represent only a small part of the diversity that is expressed by sugars. Specific types of sugar monomers are based on the positions of hydroxyl groups and the nature of the reducing group. Almost all sugars are synthesized in the D-configuration but a few L- sugars also are. The real complexity is found in the complex arrangement of sugars in polysaccharides, in which, in addition to monomer diversity, there are configurations of anomeric bonds, sequences of monomers, and discrete branching patterns. Biological systems prescribe these arrangements as messages derived from the genetic core of the cell. But in the end we return to glucose. It is certainly the most abundant sugar and serves unique and essential roles in biological function. Nuances in its structure dictate function and it is becoming increasingly clear that glucose, although it may serve as a simple nutrient or sweetener, also conveys molecular information inherent in its structure that governs and regulates events in physiology that require further clarification.   ◪

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