

## 31 Gluconeogenesis and Maintenance of Blood Glucose Levels

*During fasting, many of the reactions of glycolysis are reversed as the liver produces glucose to maintain blood glucose levels. This process of **glucose production** is called **gluconeogenesis**.*

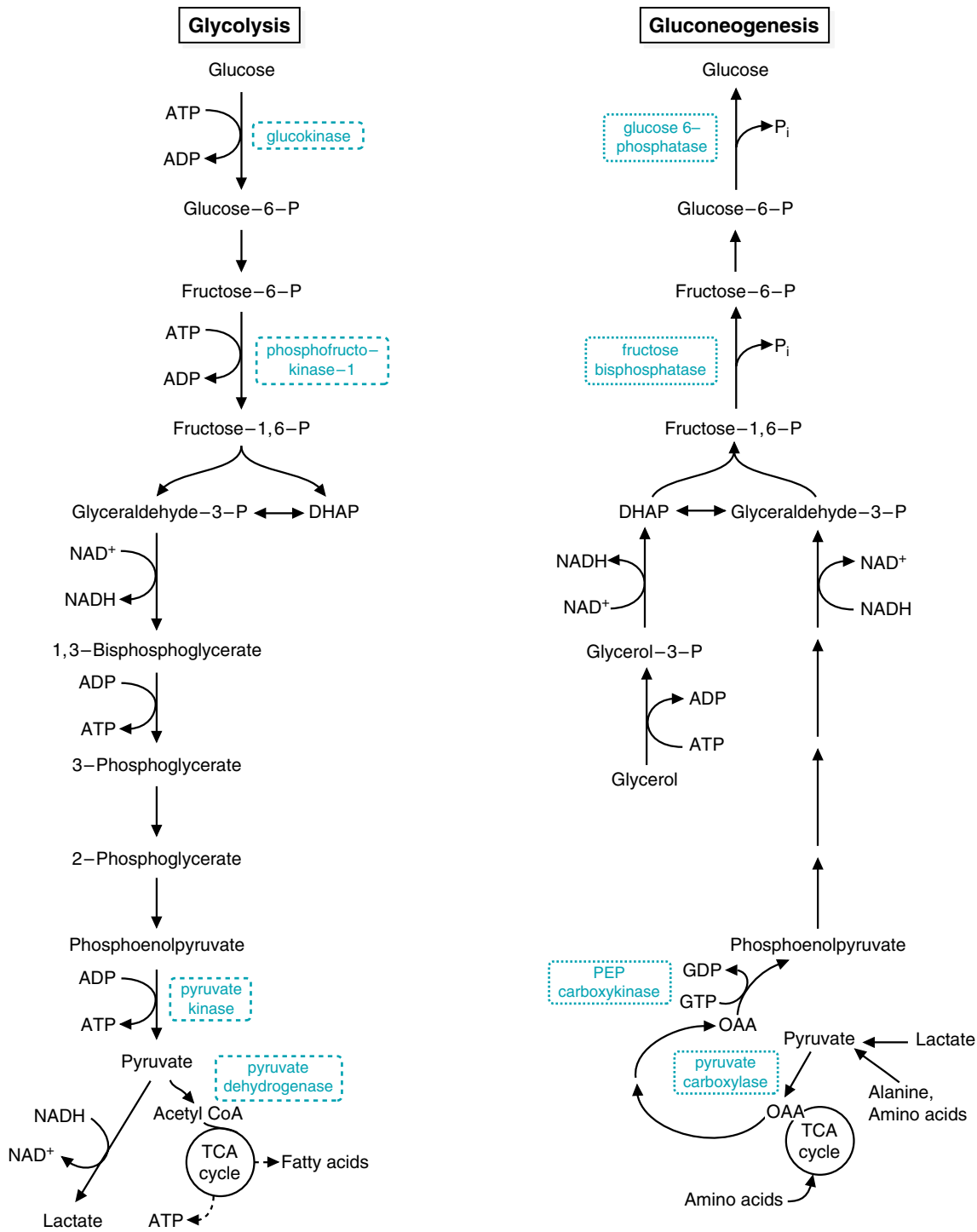
*Gluconeogenesis, which occurs primarily in the liver, is the pathway for the synthesis of glucose from compounds other than carbohydrates. In humans, the major precursors of glucose are **lactate**, **glycerol**, and **amino acids**, particularly **alanine**. Except for three key sequences, the reactions of gluconeogenesis are reversals of the steps of glycolysis (Fig. 31.1). The sequences of gluconeogenesis that do not use enzymes of glycolysis involve the irreversible, regulated steps of glycolysis. These three steps are the conversion of (a) pyruvate to phosphoenolpyruvate, (b) fructose 1,6-bisphosphate to fructose 6-phosphate, and (c) glucose 6-phosphate to glucose.*

*Some tissues of the body, such as the brain and red blood cells, cannot synthesize glucose on their own, yet depend on glucose for energy. On a long-term basis, most tissues also require glucose for other functions such as the synthesis of the ribose moiety of nucleotides or the carbohydrate portion of glycoproteins and glycolipids. Therefore, to survive, humans must have mechanisms for maintaining blood glucose levels.*

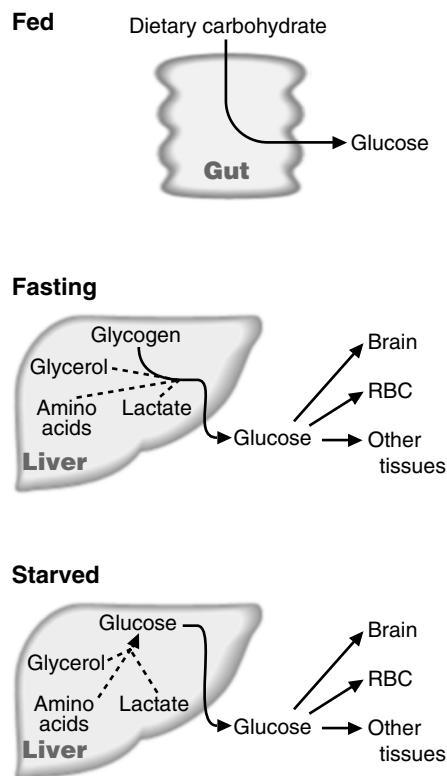
*After a meal containing carbohydrates, blood glucose levels rise (Fig. 31.2). Some of the glucose from the diet is stored in the liver as **glycogen**. After 2 or 3 hours of fasting, this glycogen begins to be degraded by the process of **glycogenolysis**, and glucose is released into the blood. As glycogen stores decrease, **adipose triacylglycerols** are also degraded, providing **fatty acids** as an alternative fuel and glycerol for the synthesis of glucose by gluconeogenesis. Amino acids are also released from the muscle to serve as gluconeogenic precursors.*

*During an overnight fast, blood glucose levels are maintained by both glycogenolysis and gluconeogenesis. However, after approximately 30 hours of fasting, liver glycogen stores are mostly depleted. Subsequently, gluconeogenesis is the only source of blood glucose.*

*Changes in the metabolism of glucose that occur during the switch from the fed to the fasting state are regulated by the hormones **insulin** and **glucagon**. Insulin is elevated in the fed state, and glucagon is elevated during fasting. Insulin stimulates the **transport** of glucose into certain cells such as those in muscle and adipose tissue. Insulin also alters the activity of key enzymes that regulate metabolism, stimulating the storage of fuels. Glucagon counters the effects of insulin, stimulating the release of stored fuels and the conversion of lactate, amino acids, and glycerol to glucose.*



**Fig. 31.1.** Glycolysis and gluconeogenesis in the liver. The gluconeogenic pathway is almost the reverse of the glycolytic pathway, except for three reaction sequences. At these three steps, the reactions are catalyzed by different enzymes. The energy requirements of these reactions differ, and one pathway can be activated while the other is inhibited.



**Fig. 31.2.** Sources of blood glucose in the fed, fasting, and starved states. RBC = red blood cells.

**Q:** What clinical signs and symptoms help to distinguish a coma caused by an excess of blood glucose and ketone bodies due to a deficiency of insulin (diabetic ketoacidosis [DKA]) from a coma caused by a sudden lowering of blood glucose (hypoglycemic coma) induced by the inadvertent injection of excessive insulin—the current problem experienced by **Di Abietes**?

*Blood glucose levels are maintained not only during fasting, but also during exercise, when muscle cells take up glucose from the blood and oxidize it for energy. During exercise, the liver supplies glucose to the blood by the processes of glycogenolysis and gluconeogenesis.*



## THE WAITING ROOM



**Al Martini**, a known alcoholic, was brought to the emergency room by his landlady, who stated that he had been drinking heavily for the past week. During this time his appetite had gradually diminished, and he had not eaten any food for the past 3 days. He was confused, combative, tremulous, and sweating profusely. His speech was slurred. His heart rate was rapid (110 beats per minute). As his blood pressure was being determined, he had a grand mal seizure. His blood glucose, drawn just before the onset of the seizure, was 28 mg/dL or 1.6 mM (reference range for overnight fasting blood glucose = 80–100 mg/dL or 4.4–5.6 mM). His blood ethanol level drawn at the same time was 295 mg/dL (intoxication level, i.e., “confused” stage = 150–300 mg/dL).



**Emma Wheezer** presented to the emergency room 3 days after discharge from the hospital following a 10-day admission for severe refractory bronchial asthma. She required high-dose intravenous dexamethasone (an anti-inflammatory synthetic glucocorticoid) for the first 8 days of her stay. After 2 additional days receiving oral dexamethasone, she was discharged on substantial pharmacologic doses of this steroid and instructed to return to her physician’s office in 5 days. She presented now with marked polyuria (increased urination), polydipsia (increased thirst), and muscle weakness. Her blood glucose was 275 mg/dL or 15 mM (reference range = 80–100 mg/dL or 4.4–5.6 mM).



**Di Abietes** could not remember whether she had taken her 6:00 PM insulin dose, when, in fact, she had done so. Unfortunately, she decided to give herself the evening dose (for the second time). When she did not respond to her alarm clock at 6:00 AM the following morning, her roommate tried unsuccessfully to awaken her. The roommate called an ambulance, and Di was rushed to the hospital emergency room in a coma. Her pulse and blood pressure at admission were normal. Her skin was flushed and slightly moist. Her respirations were slightly slow.



**Ann O’Rexia** continues to resist efforts on the part of her psychiatrist and family physician to convince her to increase her caloric intake. Her body weight varies between 97 and 99 lb, far below the desirable weight for a woman who is 5 feet 7 inches tall. In spite of her severe diet, her fasting blood glucose levels range from 55 to 70 mg/dL. She denies having any hypoglycemic symptoms.



**Otto Shape** has complied with his calorie-restricted diet and aerobic exercise program. He has lost another 7 lb and is closing in on his goal of weighing 154 lb. He notes increasing energy during the day, and remains alert during lectures and assimilates the lecture material noticeably better than he did before starting his weight loss and exercise program. He jogs for 45 minutes each morning before breakfast.



Diabetes mellitus (DM) should be suspected if a venous plasma glucose level drawn irrespective of when food was last eaten (a “random” sample of blood glucose) is “unequivocally elevated” (i.e.,  $\geq 200$  mg/dL), particularly in a patient who manifests the classic signs and symptoms of chronic hyperglycemia (polydipsia, polyuria, blurred vision, headaches, rapid weight loss, sometimes accompanied by nausea and vomiting). To confirm the diagnosis, the patient should fast overnight (10–16 hours), and the blood glucose measurement should be repeated. Values of less than 110 mg/dL are considered normal. Values greater than 140 mg/dL are indicative of DM. Glycosylated hemoglobin should be measured to determine the extent of hyperglycemia over the past 4 to 8 weeks. Values of fasting blood glucose between 111 and 140 mg/dL are designated impaired fasting glucose tolerance (IGT), and further testing should be performed to determine whether these individuals will eventually develop overt diabetes mellitus.

Although the oral glucose tolerance test (OGTT) is contraindicated for patients who clearly have diabetes mellitus, it is used for patients with fasting blood glucose in the IGT range (between 115 and 140 mg/dL). In the OGTT, a nonpregnant patient who has fasted overnight drinks 75 g glucose in an aqueous solution. Blood samples are drawn before the oral glucose load and at 30, 60, 90, and 120 minutes thereafter. If any one of the 30-, 60-, and 90-minute samples and the 120-minute sample are greater than 200 mg/dL, overt DM is indicated.

The diagnosis of IGT and the more severe form of glucose intolerance (DM) is based on blood glucose levels because no more specific characteristic for the disorder exists. The distinction between IGT and DM is clouded by the fact that a patient’s blood glucose level may vary significantly with serial testing over time under the same conditions of diet and activity.

The renal tubular transport maximum in the average healthy subject is such that glucose will not appear in the urine until the blood glucose level exceeds 180 mg/dL. As a result, reagent tapes (Tes-Tape or Dextrostix) designed to detect the presence of glucose in the urine are not sensitive enough to establish a diagnosis of early DM.

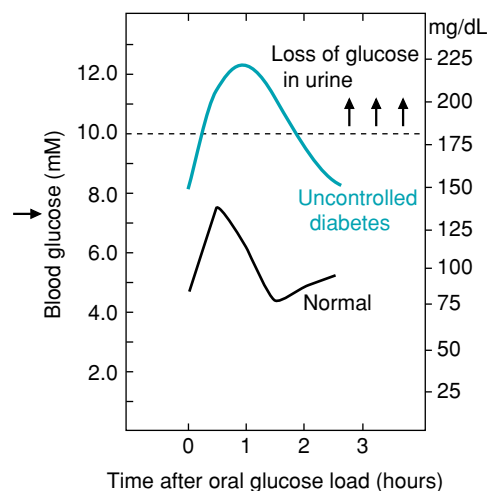
## I. GLUCOSE METABOLISM IN THE LIVER

Glucose serves as a fuel for most tissues of the body. It is the major fuel for certain tissues such as the brain and red blood cells. After a meal, food is the source of blood glucose. The liver oxidizes glucose and stores the excess as glycogen. The liver also uses the pathway of glycolysis to convert glucose to pyruvate, which provides carbon for the synthesis of fatty acids. Glycerol 3-phosphate, produced from glycolytic intermediates, combines with fatty acids to form triacylglycerols, which are secreted into the blood in very-low-density lipoproteins (VLDL; further explained in Chapter 32). During fasting, the liver releases glucose into the blood, so that glucose-dependent tissues do not suffer from a lack of energy. Two mechanisms are involved in this process: glycogenolysis and gluconeogenesis. Hormones, particularly insulin and glucagon, dictate whether glucose flows through glycolysis or whether the reactions are reversed and glucose is produced via gluconeogenesis.

## II. GLUCONEOGENESIS

Gluconeogenesis, the process by which glucose is synthesized from noncarbohydrate precursors, occurs mainly in the liver under fasting conditions. Under the more extreme conditions of starvation, the kidney cortex also may produce glucose. For the most part, the glucose produced by the kidney cortex is used by the kidney medulla, but some may enter the bloodstream.

Starting with pyruvate, most of the steps of gluconeogenesis are simply reversals of those of glycolysis (Fig. 31.3). In fact, these pathways differ at only three points. Enzymes involved in catalyzing these steps are regulated so that either glycolysis or gluconeogenesis predominates, depending on physiologic conditions.

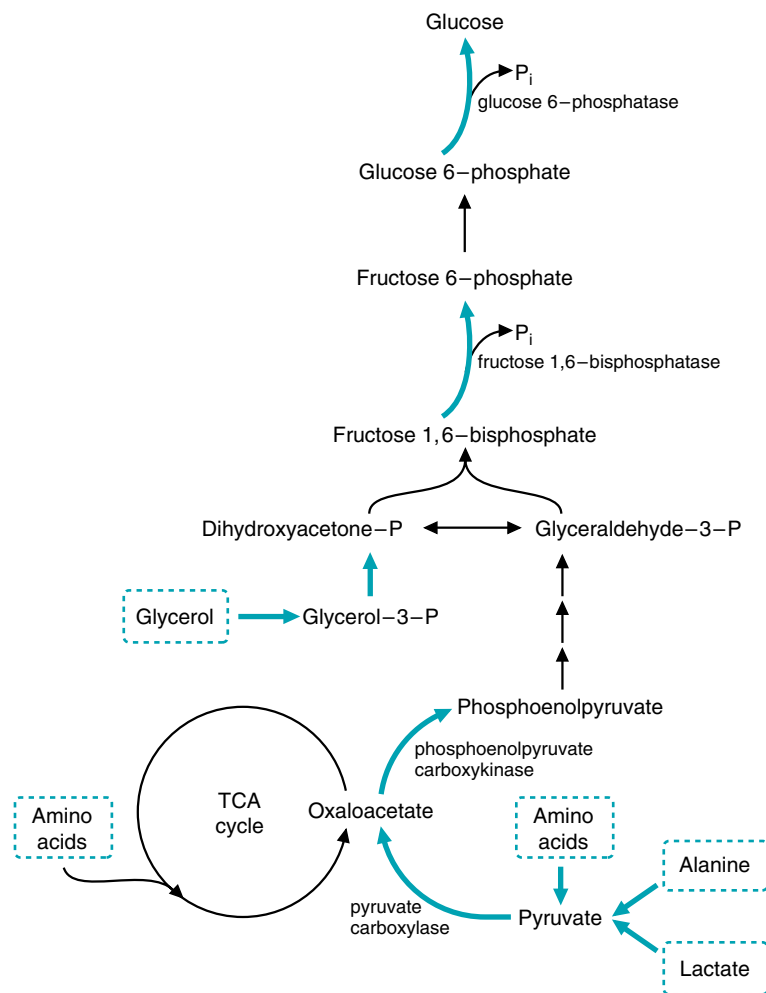


**A:** Comatose patients in diabetic ketoacidosis have the smell of acetone (a derivative of the ketone body acetoacetate) on their breath. In addition, DKA patients have deep, relatively rapid respirations typical of acidotic patients (Kussmaul respirations). These respirations result from an acidosis-induced stimulation of the respiratory center in the brain. More  $\text{CO}_2$  is exhaled in an attempt to reduce the amount of acid in the body:  $\text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2$  (exhaled).

The severe hyperglycemia of DKA also causes an osmotic diuresis (i.e., glucose entering the urine carries water with it), which, in turn, causes a contraction of blood volume. Volume depletion may be aggravated by vomiting, which is common in patients with DKA. DKA may cause dehydration (dry skin), a low blood pressure, and a rapid heartbeat. These respiratory and hemodynamic alterations are not seen in patients with hypoglycemic coma. The flushed, wet skin of hypoglycemic coma is in contrast to the dry skin observed in DKA.



Glucocorticoids are naturally occurring steroid hormones. In humans, the major glucocorticoid is cortisol. Glucocorticoids are produced in the adrenal cortex in response to various types of stress (see Chapter 43). One of their actions is to stimulate the degradation of muscle protein. Thus, increased amounts of amino acids become available as substrates for gluconeogenesis. **Emma Wheezer** noted muscle weakness, a result of the muscle-degrading action of the synthetic glucocorticoid dexamethasone, which she was taking for its anti-inflammatory effects.



**Fig. 31.3.** Key reactions of gluconeogenesis. The precursors are amino acids (particularly alanine), lactate, and glycerol. Heavy arrows indicate steps that differ from those of glycolysis.



Because ethanol metabolism only gives rise to acetyl-CoA, the carbons of ethanol cannot be used for gluconeogenesis.

Most of the steps of gluconeogenesis use the same enzymes that catalyze the process of glycolysis. The flow of carbon, of course, is in the reverse direction. Three reaction sequences of gluconeogenesis differ from the corresponding steps of glycolysis. They involve the conversion of pyruvate to phosphoenolpyruvate (PEP) and the reactions that remove phosphate from fructose 1,6-bisphosphate to form fructose 6-phosphate and from glucose 6-phosphate to form glucose (see Fig. 31.3). The conversion of pyruvate to PEP is catalyzed during gluconeogenesis by a series of enzymes instead of the single enzyme used for glycolysis. The reactions that remove phosphate from fructose 1,6-bisphosphate and from glucose 6-phosphate each use single enzymes that differ from the corresponding enzymes of glycolysis. Although phosphate is added during glycolysis by kinases, which use adenosine triphosphate (ATP), it is removed during gluconeogenesis by phosphatases that release  $P_i$  via hydrolysis reactions.

### A. Precursors for Gluconeogenesis

The three major carbon sources for gluconeogenesis in humans are lactate, glycerol, and amino acids, particularly alanine. Lactate is produced by anaerobic glycolysis in tissues such as exercising muscle or red blood cells, as well as by adipocytes during the fed state. Glycerol is released from adipose stores of

triacylglycerol, and amino acids come mainly from amino acid pools in muscle, where they may be obtained by degradation of muscle protein. Alanine, the major gluconeogenic amino acid, is produced in the muscle from other amino acids and from glucose (see Chapter 38).

## B. Formation of Gluconeogenic Intermediates from Carbon Sources

The carbon sources for gluconeogenesis form pyruvate, intermediates of the tricarboxylic acid (TCA) cycle, or intermediates common both to glycolysis and gluconeogenesis.

### 1. LACTATE, AMINO ACIDS, AND GLYCEROL

Pyruvate is produced in the liver from the gluconeogenic precursors lactate and alanine. Lactate dehydrogenase oxidizes lactate to pyruvate, generating NADH (Fig. 31.4A), and alanine aminotransferase converts alanine to pyruvate (see Fig. 31.4B).


Although alanine is the major gluconeogenic amino acid, other amino acids, such as serine, serve as carbon sources for the synthesis of glucose because they also form pyruvate, the substrate for the initial step in the process. Some amino acids form intermediates of the TCA cycle (see Chapter 20), which can enter the gluconeogenic pathway.

The carbons of glycerol are gluconeogenic because they form dihydroxyacetone phosphate (DHAP), a glycolytic intermediate (see Fig. 31.4C)

### 2. PROPIONATE

Fatty acids with an odd number of carbon atoms, which are obtained mainly from vegetables in the diet, produce propionyl CoA from the three carbons at the  $\omega$ -end of the chain (see Chapter 23). These carbons are relatively minor precursors of glucose in humans. Propionyl CoA is converted to methylmalonyl CoA, which is rearranged to form succinyl CoA, a 4-carbon intermediate of the TCA cycle that can be used for gluconeogenesis. The remaining carbons of an odd-chain fatty acid form acetyl CoA, from which no net synthesis of glucose occurs.

$\beta$ -Oxidation of fatty acids produces acetyl CoA. Because the pyruvate dehydrogenase reaction is thermodynamically and kinetically irreversible, acetyl CoA does not form pyruvate for gluconeogenesis. Therefore, if acetyl CoA is to produce glucose, it must enter the TCA cycle and be converted to malate. For every two carbons of acetyl CoA that are converted to malate, two carbons are released as  $\text{CO}_2$ : one in the reaction catalyzed by isocitrate dehydrogenase and the other in the reaction catalyzed by  $\alpha$ -ketoglutarate dehydrogenase. Therefore, there is no *net* synthesis of glucose from acetyl CoA.

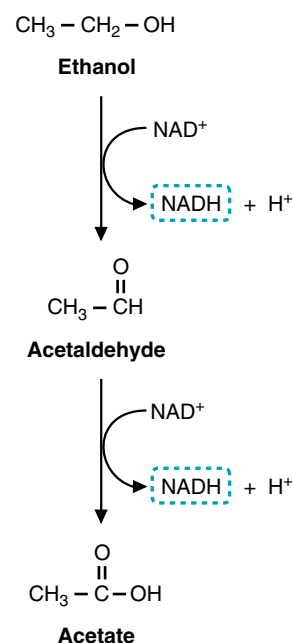
 In some species, propionate is a major source of carbon for gluconeogenesis. Ruminants can produce massive amounts of glucose from propionate. In cows, the cellulose in grass is converted to propionate by bacteria in the rumen. This substrate is then used to generate more than 5 lb glucose each day by the process of gluconeogenesis.



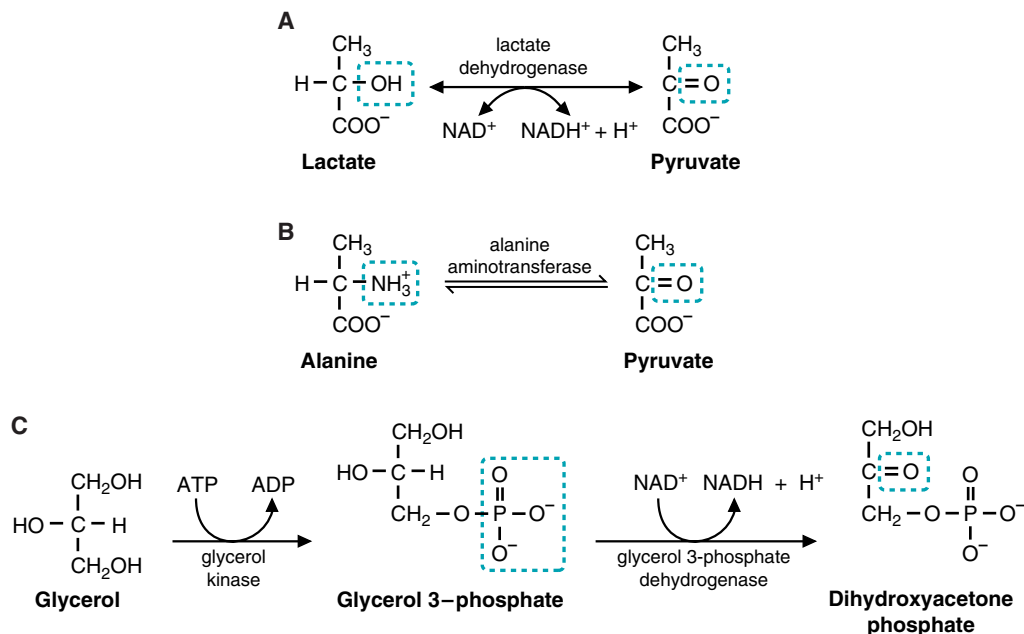
In a fatty acid with 19 carbons, how many carbons (and which ones) form glucose?



Excessive ethanol metabolism will block the production of gluconeogenic precursors. Cells have limited amounts of NAD, which exist either as  $\text{NAD}^+$  or as NADH. As the levels of NADH rise, those of  $\text{NAD}^+$  fall, and the ratio of the concentrations of NADH and  $\text{NAD}^+$  ( $[\text{NADH}]/[\text{NAD}^+]$ ) increases. In the presence of ethanol, which is very rapidly oxidized in the liver, the  $[\text{NADH}]/[\text{NAD}^+]$  ratio is much higher than it is in the normal fasting liver. High levels of NADH drive the lactate dehydrogenase reaction toward lactate. Therefore, lactate cannot enter the gluconeogenic pathway, and pyruvate that is generated from alanine is converted to lactate. Because glycerol is oxidized by  $\text{NAD}^+$  during its conversion to DHAP, the conversion of glycerol to glucose is also inhibited when NADH levels are elevated. Consequently, the major precursors lactate, alanine, and glycerol are not used for gluconeogenesis under conditions in which alcohol metabolism is high.







**Fig. 31.4.** Metabolism of gluconeogenic precursors. A. Conversion of lactate to pyruvate. B. Conversion of alanine to pyruvate. In this reaction, alanine aminotransferase transfers the amino group of alanine to  $\alpha$ -ketoglutarate to form glutamate. The coenzyme for this reaction, pyridoxal phosphate, accepts and donates the amino group. C. Conversion of glycerol to dihydroxyacetone phosphate.



Amino acids that form intermediates of the TCA cycle are converted to malate, which enters the cytosol and is converted to oxaloacetate, which proceeds through gluconeogenesis to form glucose. When excessive amounts of ethanol are ingested, elevated NADH levels inhibit the conversion of malate to oxaloacetate in the cytosol. Therefore, carbons from amino acids that form intermediates of the TCA cycle cannot be converted to glucose as readily.

## C. Pathway of Gluconeogenesis

Gluconeogenesis occurs by a pathway that reverses many, but not all, of the steps of glycolysis.

### 1. CONVERSION OF PYRUVATE TO PHOSPHOENOLPYRUVATE

In glycolysis, PEP is converted to pyruvate by pyruvate kinase. In gluconeogenesis, a series of steps are required to accomplish the reversal of this reaction (Fig. 31.5). Pyruvate is carboxylated by pyruvate carboxylase to form oxaloacetate. This enzyme, which requires biotin, is the catalyst of an anaplerotic (refilling) reaction of the TCA cycle (see Chapter 20). In gluconeogenesis, this reaction replenishes the oxaloacetate that is used for the synthesis of glucose (Fig. 31.6).

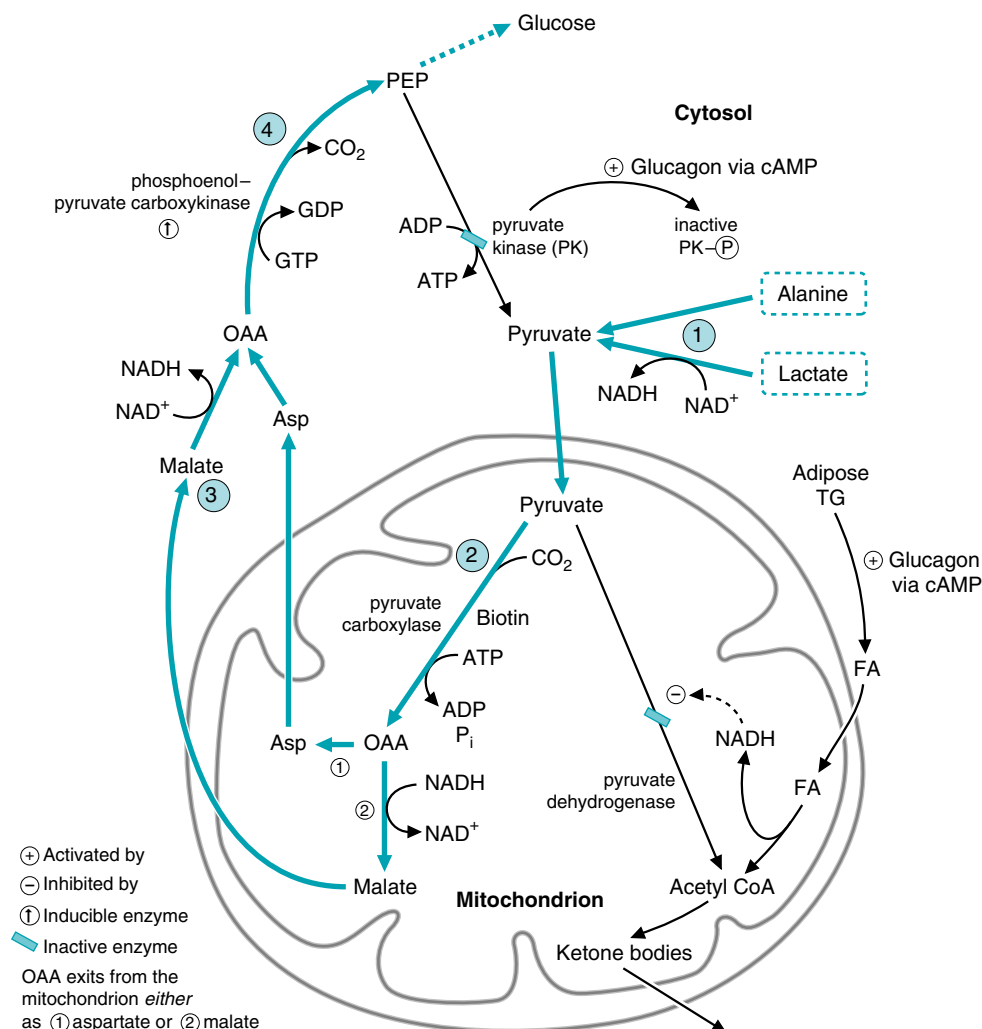
The  $\text{CO}_2$  that was added to pyruvate to form oxaloacetate is released in the reaction catalyzed by phosphoenolpyruvate carboxykinase (PEPCK), which generates PEP (Fig. 31.7A). For this reaction, GTP provides a source of energy as well as the phosphate group of PEP. Pyruvate carboxylase is found in mitochondria. In various species, PEPCK is located either in the cytosol or in mitochondria, or it is distributed between these two compartments. In humans, the enzyme is distributed about equally in each compartment.

Oxaloacetate, generated from pyruvate by pyruvate carboxylase or from amino acids that form intermediates of the TCA cycle, does not readily cross the mitochondrial membrane. It is either decarboxylated to form PEP by the mitochondrial PEPCK or it is converted to malate or aspartate (see Figs. 31.7B and 31.7C). The conversion of oxaloacetate to malate requires NADH. PEP, malate, and aspartate can be transported into the cytosol.

After malate or aspartate traverse the mitochondrial membrane (acting as carriers of oxaloacetate) and enter the cytosol, they are reconverted to oxaloacetate by reversal of the reactions given above (see Figs. 31.7B and C). The conversion of malate to oxaloacetate generates NADH. Whether oxaloacetate is transported



Only the three carbons at the  $\omega$ -end of an odd chain fatty acid that form propionyl CoA are converted to glucose. The remaining 16 carbons of a fatty acid with 19 carbons form acetyl CoA, which does not form any net glucose.



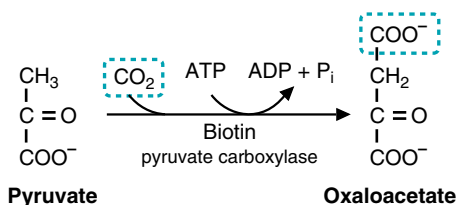
**Fig. 31.5.** Conversion of pyruvate to phosphoenolpyruvate (PEP). Follow the shaded circled numbers on the diagram, starting with the precursors alanine and lactate. The first step is the conversion of alanine and lactate to pyruvate. Pyruvate then enters the mitochondria and is converted to OAA (circle 2) by pyruvate carboxylase. Pyruvate dehydrogenase has been inactivated by both the NADH and acetyl-CoA generated from fatty acid oxidation, which allows oxaloacetate production for gluconeogenesis. The oxaloacetate formed in the mitochondria is converted to either malate or aspartate to enter the cytoplasm via the malate/aspartate shuttle. Once in the cytoplasm the malate or aspartate is converted back into oxaloacetate (circle 3), and phosphoenolpyruvate carboxykinase will convert it to PEP (circle 4). The white circled numbers are alternate routes for exit of carbon from the mitochondrion using the malate/aspartate shuttle. OAA = oxaloacetate; FA = fatty acid; TG = triacylglycerol.

across the mitochondrial membrane as malate or aspartate depends on the need for reducing equivalents in the cytosol. NADH is required to reduce 1,3-bisphosphoglycerate to glyceraldehyde 3-phosphate during gluconeogenesis.

Oxaloacetate, produced from malate or aspartate in the cytosol, is converted to PEP by the cytosolic PEPCK (see Fig. 31.7A).

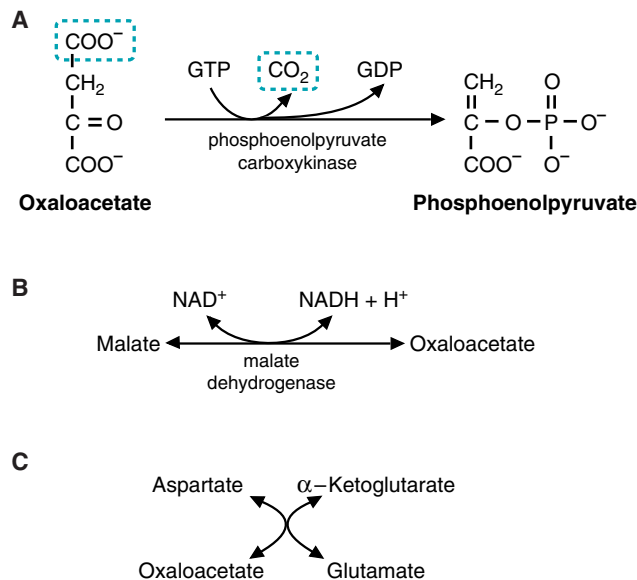
## 2. CONVERSION OF PHOSPHOENOLPYRUVATE TO FRUCTOSE 1,6-BISPHOSPHATE

The remaining steps of gluconeogenesis occur in the cytosol (Fig. 31.8). Starting with PEP as a substrate, the steps of glycolysis are reversed to form glyceraldehyde 3-phosphate. For every two molecules of glyceraldehyde 3-phosphate that are formed, one is converted to dihydroxyacetone phosphate (DHAP). These two triose



**Fig. 31.6.** Conversion of pyruvate to oxaloacetate.





**Fig. 31.7.** The generation of PEP from gluconeogenic precursors. A. Conversion of oxaloacetate to phosphoenolpyruvate, using PEP carboxykinase. B. Interconversion of oxaloacetate and malate. C. Transamination of aspartate to form oxaloacetate. Note that the cytosolic reaction is the reverse of the mitochondrial reaction as shown in Figure 31.5.

phosphates, DHAP and glyceraldehyde 3-phosphate, condense to form fructose 1,6-bisphosphate by a reversal of the aldolase reaction.

Because glycerol forms DHAP, it enters the gluconeogenic pathway at this level.

### 3. CONVERSION OF FRUCTOSE 1,6-BISPHOSPHATE TO FRUCTOSE 6-PHOSPHATE

The enzyme fructose 1,6-bisphosphatase releases inorganic phosphate from fructose 1,6-bisphosphate to form fructose 6-phosphate. This is not a reversal of the PFK-1 reaction; ATP is not produced when the phosphate is removed from the 1 position of fructose 1,6-bisphosphate, because that is a low-energy phosphate bond. Rather, inorganic phosphate is released in this hydrolysis reaction. In the next reaction of gluconeogenesis, fructose 6-phosphate is converted to glucose 6-phosphate by the same isomerase used in glycolysis (phosphoglucosomerase).

### 4. CONVERSION OF GLUCOSE 6-PHOSPHATE TO GLUCOSE

Glucose 6-phosphatase hydrolyzes  $P_i$  from glucose 6-phosphate, and free glucose is released into the blood. As with fructose 1,6-bisphosphatase, this is not a reversal of the glucokinase reaction, because the phosphate bond in glucose 6-phosphate is a low-energy bond, and ATP is not generated at this step.

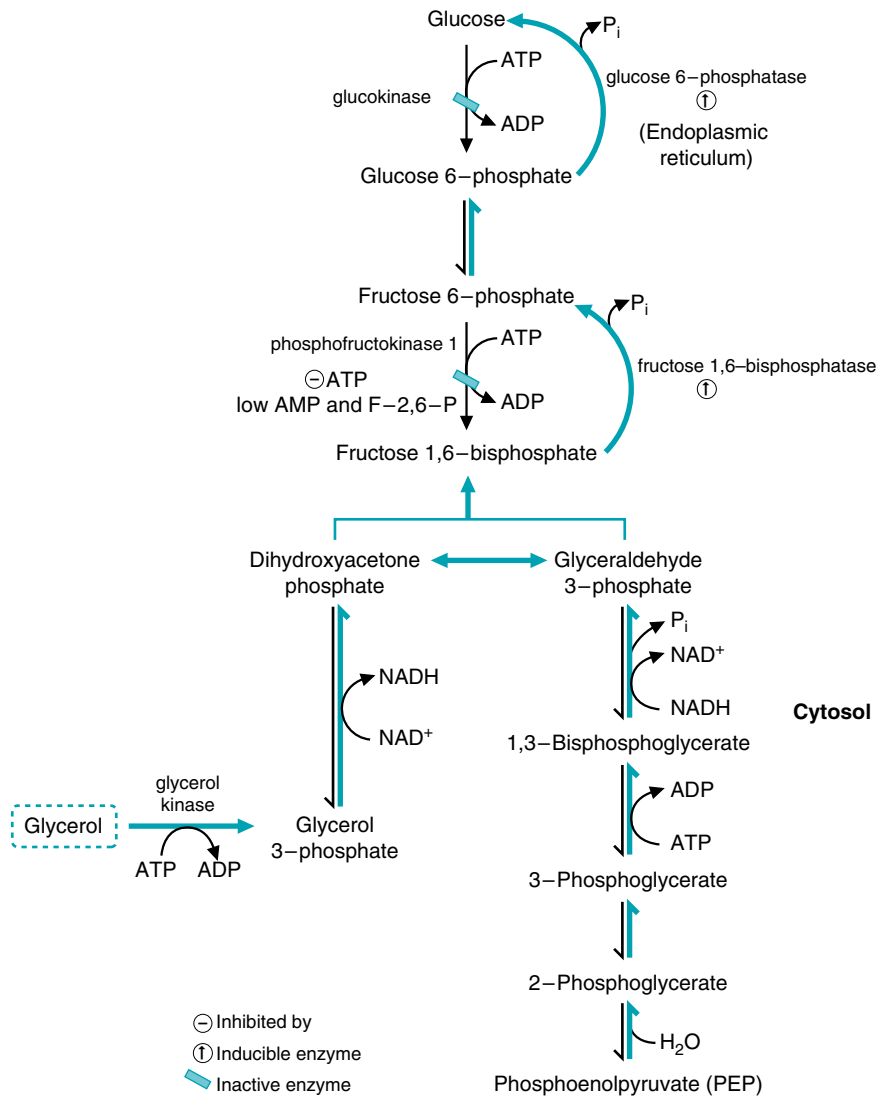
Glucose 6-phosphatase is located in the membrane of the endoplasmic reticulum. It is used not only in gluconeogenesis, but also to produce blood glucose from the breakdown of liver glycogen.

## D. Regulation of Gluconeogenesis

Although gluconeogenesis occurs during fasting, it is also stimulated during prolonged exercise, by a high-protein diet, and under conditions of stress. The factors that promote the overall flow of carbon from pyruvate to glucose include the availability of substrate and changes in the activity or amount of certain key enzymes of glycolysis and gluconeogenesis.



**Al Martini** had not eaten for 3 days, so he had no dietary source of glucose, and his liver glycogen stores were essentially depleted. He was solely dependent on gluconeogenesis to maintain his blood glucose levels. One of the consequences of ethanol ingestion and the subsequent rise in NADH levels is that the major carbon sources for gluconeogenesis cannot readily be converted to glucose. After his alcoholic binges, Mr. Martini became hypoglycemic. His blood glucose was 28 mg/dL.



**Fig. 31.8.** Conversion of phosphoenolpyruvate and glycerol to glucose.

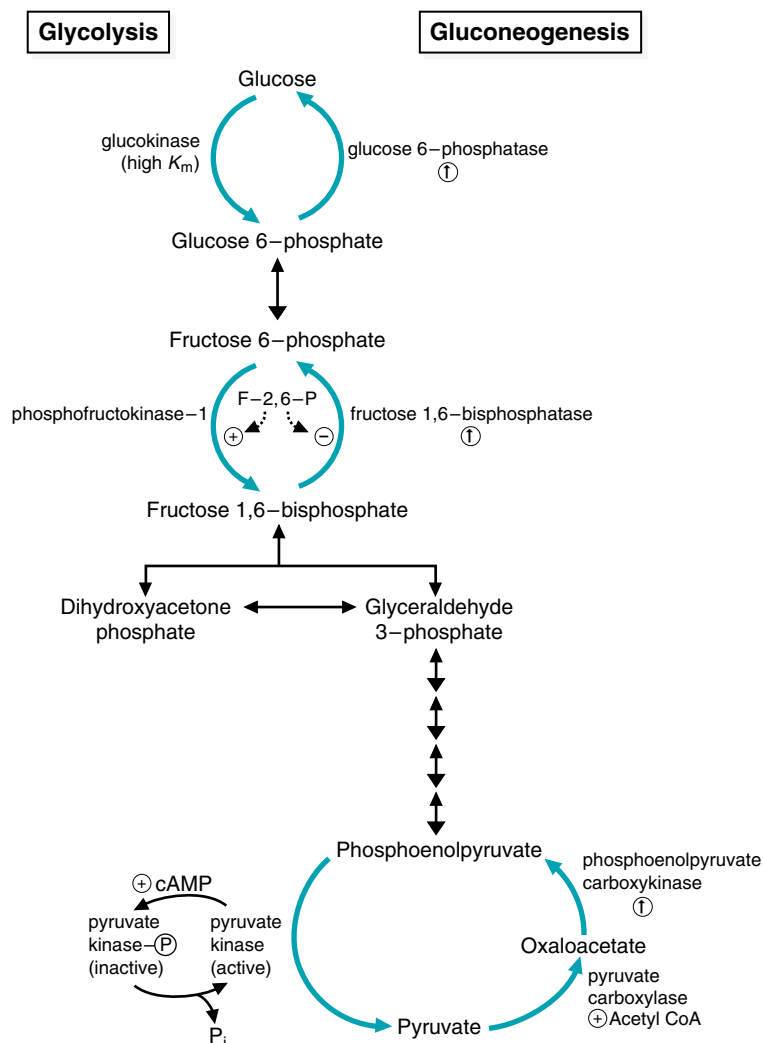
## 1. AVAILABILITY OF SUBSTRATE

Gluconeogenesis is stimulated by the flow of its major substrates from peripheral tissues to the liver. Glycerol is released from adipose tissue whenever the levels of insulin are low and the levels of glucagon or the “stress” hormones, epinephrine and cortisol (a glucocorticoid), are elevated in the blood (see Chapter 26). Lactate is produced by muscle during exercise and by red blood cells. Amino acids are released from muscle whenever insulin is low or when cortisol is elevated. Amino acids are also available for gluconeogenesis when the dietary intake of protein is high and intake of carbohydrate is low.

## 2. ACTIVITY OR AMOUNT OF KEY ENZYMES

Three sequences in the pathway of gluconeogenesis are regulated:

1. pyruvate  $\rightarrow$  phosphoenolpyruvate
2. fructose 1,6-bisphosphate  $\rightarrow$  fructose 6-phosphate
3. glucose 6-phosphate  $\rightarrow$  glucose.



**Fig. 31.9.** Enzymes involved in regulating the substrate cycles of glycolysis and gluconeogenesis. Heavy arrows indicate the three substrate cycles. F-2,6-P, fructose 2,6-bisphosphate; +, activated by; -, inhibited by; circled  $\uparrow$ , inducible enzyme.



PEPCK is an example of an inducible enzyme. The gene for the cytosolic form of the enzyme contains regulatory sequences in its 5'-flanking region. cAMP, which is produced as a result of the binding of hormones such as glucagon or epinephrine to receptors on the cell surface, causes one of these sequences to be activated. Glucocorticoids affect a different regulatory sequence. cAMP or glucocorticoids independently cause increased transcription of the PEPCK gene. The mRNA produced during transcription travels to the cytosol combines with ribosomes and is translated, producing increased amounts of the enzyme PEPCK.

These steps correspond to those in glycolysis that are catalyzed by regulatory enzymes. The enzymes involved in these steps of gluconeogenesis differ from those that catalyze the reverse reactions in glycolysis. The net flow of carbon, whether from glucose to pyruvate (glycolysis) or from pyruvate to glucose (gluconeogenesis), depends on the relative activity or amount of these glycolytic or gluconeogenic enzymes (Fig. 31.9 and Table 31.1).

### 3. CONVERSION OF PYRUVATE TO PHOSPHOENOLPYRUVATE

Pyruvate, a key substrate for gluconeogenesis, is derived from lactate and amino acids, particularly alanine. Pyruvate is not converted to acetyl CoA under conditions favoring gluconeogenesis because pyruvate dehydrogenase is relatively inactive. Instead, pyruvate is converted to oxaloacetate by pyruvate carboxylase. Subsequently, oxaloacetate is converted to PEP by PEPCK. Because of the activity state of the enzymes discussed in subsequent sections, PEP reverses the steps of glycolysis, ultimately forming glucose.

**Pyruvate dehydrogenase is inactive.** Under conditions of fasting, insulin levels are low, and glucagon levels are elevated. Consequently, fatty acids and glycerol are

**Table 31.1. Regulation of Enzymes of Glycolysis and Gluconeogenesis in Liver**

A. Glycolytic Enzymes	Mechanism
Pyruvate kinase	Activated by F-1, 6-P Inhibited by ATP, alanine Inhibited by phosphorylation (glucagon and epinephrine lead to an increase in cAMP levels, which activates protein kinase A)
Phosphofructokinase-1	Activated by F-2,6-P, AMP Inhibited by ATP, citrate
Glucokinase	High $K_m$ for glucose Induced by insulin
B. Gluconeogenic Enzymes	Mechanism
Pyruvate carboxylase	Activated by acetyl CoA
Phosphoenolpyruvate carboxykinase	Induced by glucagon, epinephrine, glucocorticoids Repressed by insulin
Fructose 1,6-bisphosphatase	Inhibited by F-2,6-P, AMP Induced during fasting
Glucose 6-phosphatase	Induced during fasting

released from the triacylglycerol stores of adipose tissue. Fatty acids travel to the liver, where they undergo  $\beta$ -oxidation, producing acetyl CoA, NADH, and ATP. As a consequence, the concentration of ADP decreases. These changes result in the phosphorylation of pyruvate dehydrogenase to the inactive form. Therefore, pyruvate is not converted to acetyl CoA.

**Pyruvate carboxylase is active.** Acetyl CoA, which is produced by oxidation of fatty acids, activates pyruvate carboxylase. Therefore, pyruvate, derived from lactate or alanine, is converted to oxaloacetate.

**Phosphoenolpyruvate carboxykinase is induced.** Oxaloacetate produces PEP in a reaction catalyzed by PEPCK. Cytosolic PEPCK is an inducible enzyme, which means that the quantity of the enzyme in the cell increases because of increased transcription of its gene and increased translation of its mRNA. The major inducer is cyclic adenosine monophosphate (cAMP), which is increased by hormones that activate adenylate cyclase. Adenylate cyclase produces cAMP from ATP. Glucagon is the hormone that causes cAMP to rise during fasting, whereas epinephrine acts during exercise or stress. cAMP activates protein kinase A, which phosphorylates a set of specific transcription factors (CREB) that stimulate transcription of the PEPCK gene (see Chapter 16 and Fig. 16.18). Increased synthesis of mRNA for PEPCK results in increased synthesis of the enzyme. Cortisol, the major human glucocorticoid, also induces PEPCK.

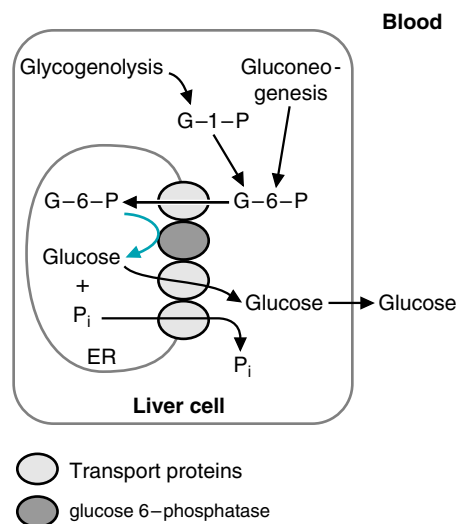
**Pyruvate kinase is inactive.** When glucagon is elevated, pyruvate kinase is phosphorylated and inactivated by a mechanism involving cAMP and protein kinase A. Therefore, PEP is not reconverted to pyruvate. Rather, it continues along the pathway of gluconeogenesis. If PEP were reconverted to pyruvate, these substrates would simply cycle, causing a net loss of energy with no net generation of useful products. The inactivation of pyruvate kinase prevents such futile cycling and promotes the net synthesis of glucose.

#### 4. CONVERSION OF FRUCTOSE 1,6-BISPHOSPHATE TO FRUCTOSE 6-PHOSPHATE

The carbons of PEP reverse the steps of glycolysis, forming fructose 1,6-bisphosphate. Fructose 1,6-bisphosphatase acts on this bisphosphate to release inorganic phosphate and produce fructose 6-phosphate. A futile substrate cycle is prevented at



The mechanism of action of steroid hormones on glucose homeostasis differs from that of glucagon or epinephrine (see Chapters 16 and 26). Glucocorticoids are steroid hormones that stimulate gluconeogenesis, in part because they induce the synthesis of PEPCK. **Emma Wheezer** had elevated levels of blood glucose because she was being treated with large pharmacologic doses of dexamethasone, a potent synthetic glucocorticoid.



**Fig. 31.10.** Location and function of glucose 6-phosphatase. Glucose 6-phosphate travels on a transporter (shaded oval) into the endoplasmic reticulum (ER), where it is hydrolyzed by glucose 6-phosphatase (black oval) to glucose and P<sub>i</sub>. These products travel back to the cytosol on transporters (shaded ovals).



Glucose 6-phosphatase is used in both glycogenolysis and gluconeogenesis.

this step because, under conditions that favor gluconeogenesis, the concentrations of the compounds that activate the glycolytic enzyme PFK-1 are low. These same compounds, fructose 2,6-bisphosphate (whose levels are regulated by insulin and glucagon) and AMP, are allosteric inhibitors of fructose 1,6-bisphosphatase. When the concentrations of these allosteric effectors are low, PFK-1 is less active, fructose 1,6-bisphosphatase is more active, and the net flow of carbon is toward fructose 6-phosphate and, thus, toward glucose. The synthesis of fructose 1,6-bisphosphatase is also induced during fasting.

## 5. CONVERSION OF GLUCOSE 6-PHOSPHATE TO GLUCOSE

Glucose 6-phosphatase catalyzes the conversion of glucose 6-phosphate to glucose, which is released from the liver cell (Fig. 31.10). The glycolytic enzyme glucokinase, which catalyzes the reverse reaction, is relatively inactive during gluconeogenesis. Glucokinase, which has a high  $S_{0.5}$  ( $K_m$ ) for glucose (see Fig. 9.3), is not very active during fasting because the blood glucose level is lower (approximately 5 mM) than the  $S_{0.5}$  of the enzyme.

Glucokinase is also an inducible enzyme. The concentration of the enzyme increases in the fed state, when blood glucose and insulin levels are elevated, and decreases in the fasting state, when glucose and insulin are low.

## E. Energy Is Required for the Synthesis of Glucose

During the gluconeogenic reactions, 6 moles of high-energy phosphate bonds are cleaved. Two moles of pyruvate are required for the synthesis of 1 mole of glucose. As 2 moles of pyruvate are carboxylated by pyruvate carboxylase, 2 moles of ATP are hydrolyzed. PEPCK requires 2 moles of GTP (the equivalent of 2 moles of ATP) to convert 2 moles of oxaloacetate to 2 moles of PEP. An additional 2 moles of ATP are used when 2 moles of 3-phosphoglycerate are phosphorylated, forming 2 moles of 1,3-bisphosphoglycerate. Energy in the form of reducing equivalents (NADH) is also required for the conversion of 1,3-bisphosphoglycerate to glyceraldehyde 3-phosphate. Under fasting conditions, the energy required for gluconeogenesis is obtained from  $\beta$ -oxidation of fatty acids.

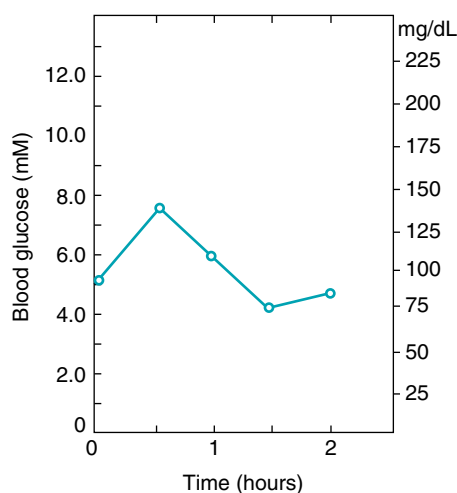
## III. CHANGES IN BLOOD GLUCOSE LEVELS AFTER A MEAL

The metabolic transitions that occur as a person eats a meal and progresses through the various stages of fasting have been described in detail in the previous chapters. This chapter summarizes the concepts presented in these previous chapters. Because a thorough understanding of these concepts is so critical to medicine, a summary is not only warranted but essential.

After a high-carbohydrate meal, blood glucose rises from a fasting level of approximately 80 to 100 mg/dL (~5 mM) to a level of approximately 120 to 140 mg/dL (8 mM) within a period of 30 minutes to 1 hour (Fig. 31.11). The concentration of glucose in the blood then begins to decrease, returning to the fasting range by approximately 2 hours after the meal (see also Chapter 26).

Blood glucose levels increase as dietary glucose is digested and absorbed. The values go no higher than approximately 140 mg/dL in a normal, healthy person because tissues take up glucose from the blood, storing it for subsequent use and oxidizing it for energy. After the meal is digested and absorbed, blood glucose levels decline because cells continue to metabolize glucose.

If blood glucose levels continued to rise after a meal, the high concentration of glucose would cause the release of water from tissues as a result of the osmotic effect of glucose. Tissues would become dehydrated, and their function would be affected. A hyperosmolar coma could result from dehydration of the brain.



**Fig. 31.11.** Blood glucose concentrations at various times after a meal.

Conversely, if blood glucose levels continued to drop after a meal, tissues that depend on glucose would suffer from a lack of energy. If blood glucose levels dropped abruptly, the brain would not be able to produce an adequate amount of ATP. Light-headedness and dizziness would result, followed by drowsiness and, eventually, coma. Red blood cells would not be able to produce enough ATP to maintain the integrity of their membranes. Hemolysis of these cells would decrease the transport of oxygen to the tissues of the body. Eventually, all tissues that rely on oxygen for energy production would fail to perform their normal functions. If the problem were severe enough, death could result.

Devastating consequences of glucose excess or insufficiency are normally avoided because the body is able to regulate its blood glucose levels. As the concentration of blood glucose approaches the normal fasting range of 80 to 100 mg/dL roughly 2 hours after a meal, the process of glycogenolysis is activated in the liver. Liver glycogen is the primary source of blood glucose during the first few hours of fasting. Subsequently, gluconeogenesis begins to play a role as an additional source of blood glucose. The carbon for gluconeogenesis, a process that occurs in the liver, is supplied by other tissues. Exercising muscle and red blood cells provide lactate through glycolysis; muscle also provides amino acids by degradation of protein; and glycerol is released from adipose tissue as triacylglycerol stores are mobilized.

Even during a prolonged fast, blood glucose levels do not decrease dramatically. After 5 to 6 weeks of starvation, blood glucose levels decrease to only approximately 65 mg/dL (Table 31.2).

### A. Blood Glucose Levels in the Fed State

The major factors involved in regulating blood glucose levels are the blood glucose concentration itself and hormones, particularly insulin and glucagon.

As blood glucose levels rise after a meal, the increased glucose concentration stimulates the  $\beta$  cells of the pancreas to release insulin (Fig. 31.12). Certain amino acids, particularly arginine and leucine, also stimulate insulin release from the pancreas.

Blood levels of glucagon, which is secreted by the  $\alpha$  cells of the pancreas, may increase or decrease, depending on the content of the meal. Glucagon levels decrease in response to a high-carbohydrate meal, but they increase in response to a high-protein meal. After a typical mixed meal containing carbohydrate, protein, and fat, glucagon levels remain relatively constant, whereas insulin levels increase (Fig. 31.13).



When **Di Abietes** inadvertently injected an excessive amount of insulin, she caused an acute reduction in her blood glucose levels 4 to 5 hours later while she was asleep. Had she been awake, she would have first experienced symptoms caused by a hypoglycemia-induced hyperactivity of her sympathetic nervous system (e.g., sweating, tremulousness, palpitations). Eventually, as her hypoglycemia became more profound, she would have experienced symptoms of “neuroglycopenia” (inadequate glucose supply to the brain), such as confusion, speech disturbances, emotional instability, possible seizure activity, and, finally, coma. While sleeping, she had reached this neuroglycopenic stage of hypoglycemia and could not be aroused at 6:00 AM.

**Ann O’ Rexia**, whose intake of glucose and of glucose precursors has been severely restricted, has not developed any of these manifestations. Her lack of hypoglycemic symptoms can be explained by the very gradual reduction of her blood glucose levels as a consequence of near starvation and her ability to maintain blood glucose levels within an acceptable fasting range through hepatic gluconeogenesis. In addition, lipolysis of adipose triacylglycerols produces fatty acids, which are used as fuel and converted to ketone bodies by the liver. The oxidation of fatty acids and ketone bodies by the brain and muscle reduces the need for blood glucose.

In **Di Abiete’s** case, the excessive dose of insulin inhibited lipolysis and ketone body synthesis, so these alternative fuels were not available to spare blood glucose. The rapidity with which hypoglycemia was induced could not be compensated for quickly enough by hepatic gluconeogenesis, which was inhibited by the insulin, and hypoglycemia ensued.

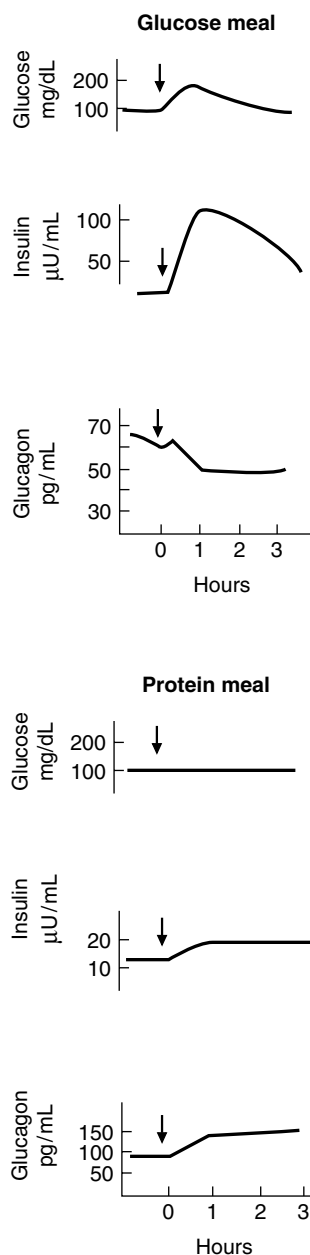
A stat finger stick revealed that Di’s capillary blood glucose level was less than 20 mg/dL. An intravenous infusion of a 50% solution of glucose was started, and her blood glucose level was determined frequently. When Di regained consciousness, the intravenous solution was eventually changed to 10% glucose. After 6 hours, her blood glucose levels stayed in the upper normal range, and she was able to tolerate oral feedings. She was transferred to the metabolic unit for overnight monitoring. By the next morning, her previous diabetes treatment regimen was reestablished. The reasons that she had developed hypoglycemic coma were explained to Di, and she was discharged to the care of her family doctor.

**Table 31.2. Blood Glucose Levels at Various Stages of Fasting**

Glucose (mg/dL)	
Glucose, 700 g/day IV	100
Fasting, 12 hr	80
Starvation, 3 days	70
Starvation, 5–6 weeks	65

Source of data: Ruderman NB, Aoki TT, Cahill GF Jr. Gluconeogenesis and its disorders in man. In: Hanson RW, Mehlerman MA, eds. Gluconeogenesis: Its Regulation in Mammalian Species. New York, John Wiley. 1976:517.





**Fig. 31.12.** Blood glucose, insulin, and glucagon levels after a high-carbohydrate and a high-protein meal.

## 1. FATE OF DIETARY GLUCOSE IN THE LIVER

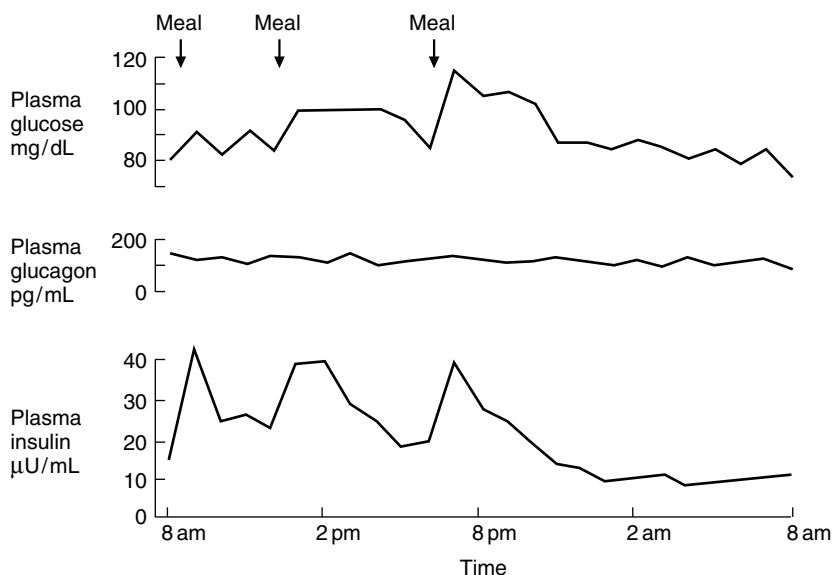
After a meal, the liver oxidizes glucose to meet its immediate energy needs. Any excess glucose is converted to stored fuels. Glycogen is synthesized and stored in the liver, and glucose is converted to fatty acids and to the glycerol moiety that reacts with the fatty acids to produce triacylglycerols. These triacylglycerols are packaged in very-low-density lipoproteins (VLDL) and transported to adipose tissue, where the fatty acids are stored in adipose triacylglycerols.

Regulatory mechanisms control the conversion of glucose to stored fuels. As the concentration of glucose increases in the hepatic portal vein, the concentration of glucose in the liver may increase from the fasting level of 80 to 100 mg/dL (~5 mM) to a concentration of 180 to 360 mg/dL (10–20 mM). Consequently, the velocity of the glucokinase reaction increases because this enzyme has a high  $S_{0.5}$  ( $K_m$ ) for glucose (Fig. 31.14). Glucokinase is also induced by a high-carbohydrate diet; the quantity of the enzyme increases in response to elevated insulin levels.

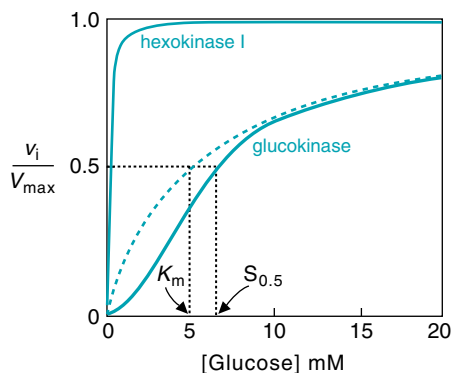
Insulin promotes the storage of glucose as glycogen by countering the effects of glucagon-stimulated phosphorylation. The response to insulin activates the phosphatases that dephosphorylate glycogen synthase (which leads to glycogen synthase activation) and glycogen phosphorylase (which leads to inhibition of the enzyme) (Fig. 31.15A). Insulin also promotes the synthesis of the triacylglycerols that are released from the liver into the blood as VLDL. The regulatory mechanisms for this process are described in Chapter 33.

## 2. FATE OF DIETARY GLUCOSE IN PERIPHERAL TISSUES

Almost every cell in the body oxidizes glucose for energy. Certain critical tissues, particularly the brain, other nervous tissue, and red blood cells, especially depend on glucose for their energy supply. The brain requires approximately 150 g glucose per day. In addition, approximately 40 g/day glucose is required by other glucose-dependent tissues. Furthermore, all tissues require glucose for the pentose phosphate pathway, and many tissues use glucose for synthesis of glycoproteins and other carbohydrate-containing compounds.



**Fig. 31.13.** Blood glucose, insulin, and glucagon levels over a 24-hour period in a normal person eating mixed meals. Reprinted with permission from Tasaka Y, Sekine M, Wakatsuki M, et al. *Horm Metab Res* 1975;7:206. Copyright © Thieme Medical Publishers, Inc.



**Fig. 31.14.** Velocity of the glucokinase reaction.

Insulin stimulates the transport of glucose into adipose and muscle cells by promoting the recruitment of glucose transporters to the cell membrane (see Fig. 31.15C). Other tissues, such as the liver, brain, and red blood cells, have a different type of glucose transporter that is not as significantly affected by insulin.

In muscle, glycogen is synthesized after a meal by a mechanism similar to that in the liver (see Fig. 31.15B). Metabolic differences exist between these tissues (see Chapter 28), but, in essence, insulin stimulates glycogen synthesis in resting muscle as it does in the liver. A key difference between muscle and liver is that insulin greatly stimulates the transport of glucose into muscle cells but only slightly stimulates its transport into liver cells.

### 3. RETURN OF BLOOD GLUCOSE TO FASTING LEVELS

After a meal has been digested and absorbed, blood glucose levels reach a peak and then begin to decline. The uptake of dietary glucose by cells, particularly those in the liver, muscle, and adipose tissue, lowers blood glucose levels. By 2 hours after a meal, blood glucose levels return to the normal fasting level of less than 140 mg/dL.

## B. Blood Glucose Levels in the Fasting State

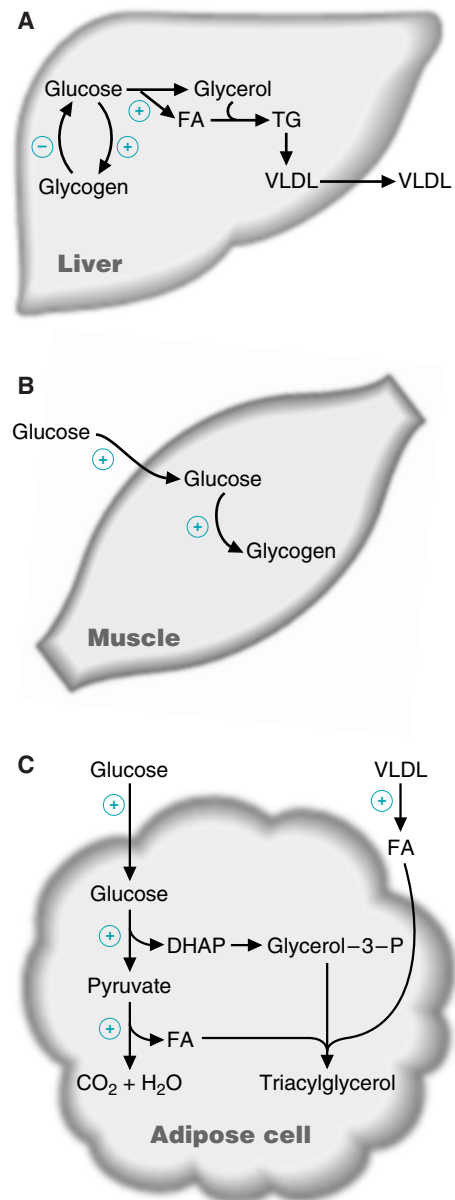
### 1. CHANGES IN INSULIN AND GLUCAGON LEVELS

During fasting, as blood glucose levels decrease, insulin levels decrease, and glucagon levels rise. These hormonal changes cause the liver to degrade glycogen by the process of glycogenolysis and to produce glucose by the process of gluconeogenesis so that blood glucose levels are maintained.

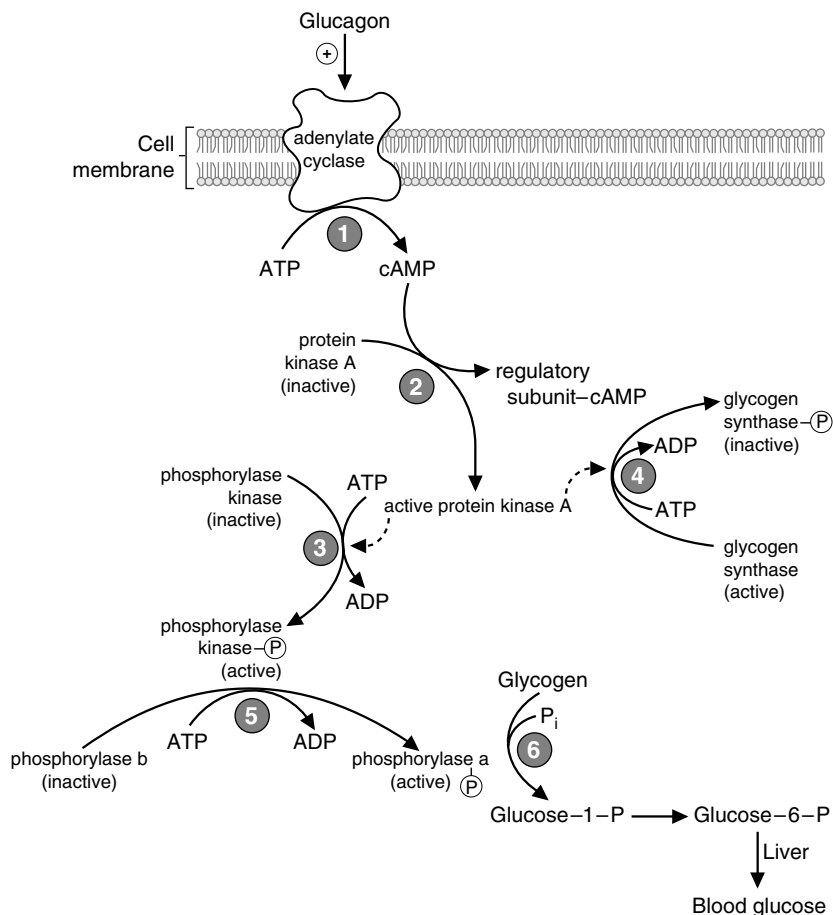
### 2. STIMULATION OF GLYCOGENOLYSIS

Within a few hours after a high-carbohydrate meal, glucagon levels begin to rise. Glucagon binds to cell surface receptors and activates adenylate cyclase, causing cAMP levels in liver cells to rise (Fig. 31.16). cAMP activates protein kinase A, which phosphorylates and inactivates glycogen synthase. Therefore, glycogen synthesis decreases.

At the same time, protein kinase A stimulates glycogen degradation by a two-step mechanism. Protein kinase A phosphorylates and activates phosphorylase kinase. This enzyme, in turn, phosphorylates and activates glycogen phosphorylase.



**Fig. 31.15.** Glucose metabolism in various tissues. A. Effect of insulin on glycogen synthesis and degradation and on VLDL synthesis in the liver. B. Glucose metabolism in resting muscle in the fed state. The transport of glucose into cells and the synthesis of glycogen are stimulated by insulin. C. Glucose metabolism in adipose tissue in the fed state. FA = fatty acids; DHAP = dihydroxyacetone phosphate. FA = fatty acids; TG = triacylglycerols; + = stimulated by insulin; - = inhibited by insulin.



**Fig. 31.16.** Regulation of glycogenolysis in the liver by glucagon. 1. Glucagon binding to its receptor leads to the activation of adenylate cyclase, which leads to an increase in cAMP levels. 2. cAMP binds to the regulatory subunits of protein kinase A, thereby activating the catalytic subunit. 3. Active protein kinase A phosphorylates and activates phosphorylase kinase, while simultaneously inactivating glycogen synthase (4). 5. Active phosphorylase kinase converts glycogen phosphorylase b to glycogen phosphorylase a. 6. Phosphorylase a degrades glycogen, producing glucose 1-phosphate, which is converted to glucose 6-phosphate, then glucose, for export into the blood.



The pathophysiology leading to an elevation of blood glucose after a meal differs between patients with type 1 diabetes mellitus and those with type 2 diabetes mellitus. **Di Abietes**, who has type 1 disease, cannot secrete insulin adequately in response to a meal because of a defect in the  $\beta$  cells of her pancreas.

**Ann Sulin**, however, has type 2 disease. In this form of the disorder, the cause of glucose intolerance is more complex, involving at least a delay in the release of relatively appropriate amounts of insulin after a meal combined with a degree of resistance to the actions of insulin in skeletal muscle and adipocytes. Excessive hepatic gluconeogenesis occurs even though blood glucose levels are elevated.

Glycogen phosphorylase catalyzes the phosphorolysis of glycogen, producing glucose 1-phosphate, which is converted to glucose 6-phosphate. Dephosphorylation of glucose 6-phosphate by glucose 6-phosphatase produces free glucose, which then enters the blood.

### 3. STIMULATION OF GLUCONEOGENESIS

By 4 hours after a meal, the liver is supplying glucose to the blood not only by the process of glycogenolysis but also by the process of gluconeogenesis. Hormonal changes cause peripheral tissues to release precursors that provide carbon for gluconeogenesis, specifically lactate, amino acids, and glycerol.

Regulatory mechanisms promote the conversion of gluconeogenic precursors to glucose (Fig. 31.17). These mechanisms prevent the occurrence of potential futile cycles, which would continuously convert substrates to products while consuming energy but producing no useful result.

These regulatory mechanisms inactivate the glycolytic enzymes pyruvate kinase, phosphofructokinase-1 (PFK-1), and glucokinase during fasting and promote the flow of carbon to glucose via gluconeogenesis. These mechanisms operate at the three steps where glycolysis and gluconeogenesis differ:

1. Pyruvate (derived from lactate and alanine) is converted by the gluconeogenic pathway to phosphoenolpyruvate (PEP). PEP is not reconverted to pyruvate (a potential futile cycle) because glucagon-stimulated phosphorylation inactivates pyruvate kinase. Therefore, PEP reverses the steps of glycolysis and forms fructose 1,6-bisphosphate.
2. Fructose 1,6-bisphosphate is converted to fructose 6-phosphate by a bisphosphatase. Because the glycolytic enzyme PFK-1 is relatively inactive mainly as a result of low fructose 2,6-bisphosphate levels, fructose 6-phosphate is not converted back to fructose 1,6-bisphosphate, and a second potential futile cycle is avoided. The low fructose 2,6-bisphosphate levels are attributable in part to the phosphorylation of phosphofructokinase-2 by protein kinase A, which has been activated in response to glucagon. Fructose 6-phosphate is converted to glucose 6-phosphate.
3. Glucose 6-phosphate is dephosphorylated by glucose 6-phosphatase, forming free glucose. Because glucokinase has a high  $S_{0.5}$  ( $K_m$ ) for glucose, and glucose concentrations are relatively low in liver cells during fasting, glucose is released into the blood. Therefore, the third potential futile cycle does not occur.

Enzymes that participate in gluconeogenesis, but not in glycolysis, are active under fasting conditions. Pyruvate carboxylase is activated by acetyl CoA, derived from oxidation of fatty acids. Phosphoenolpyruvate carboxykinase, fructose 1,6-bisphosphatase, and glucose 6-phosphatase are induced; that is, the quantity of the enzymes increases. Fructose 1,6-bisphosphatase is also active because levels of fructose 2,6-bisphosphate, an inhibitor of the enzyme, are low.

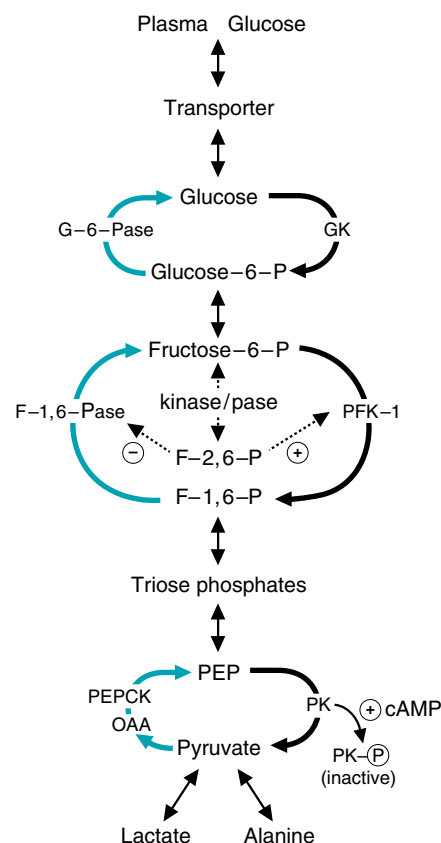
#### 4. STIMULATION OF LIPOLYSIS

The hormonal changes that occur during fasting stimulate the breakdown of adipose triacylglycerols (see Chapters 3, 33, and 43). Consequently, fatty acids and glycerol are released into the blood (Fig. 31.18). Glycerol serves as a source of carbon for gluconeogenesis. Fatty acids become the major fuel of the body and are oxidized to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  by various tissues, which enables these tissues to decrease their utilization of glucose. Fatty acids are also oxidized to acetyl CoA in the liver to provide energy for gluconeogenesis. In a prolonged fast, acetyl CoA is converted to ketone bodies, which enter the blood and serve as an additional fuel source for the muscle and the brain.

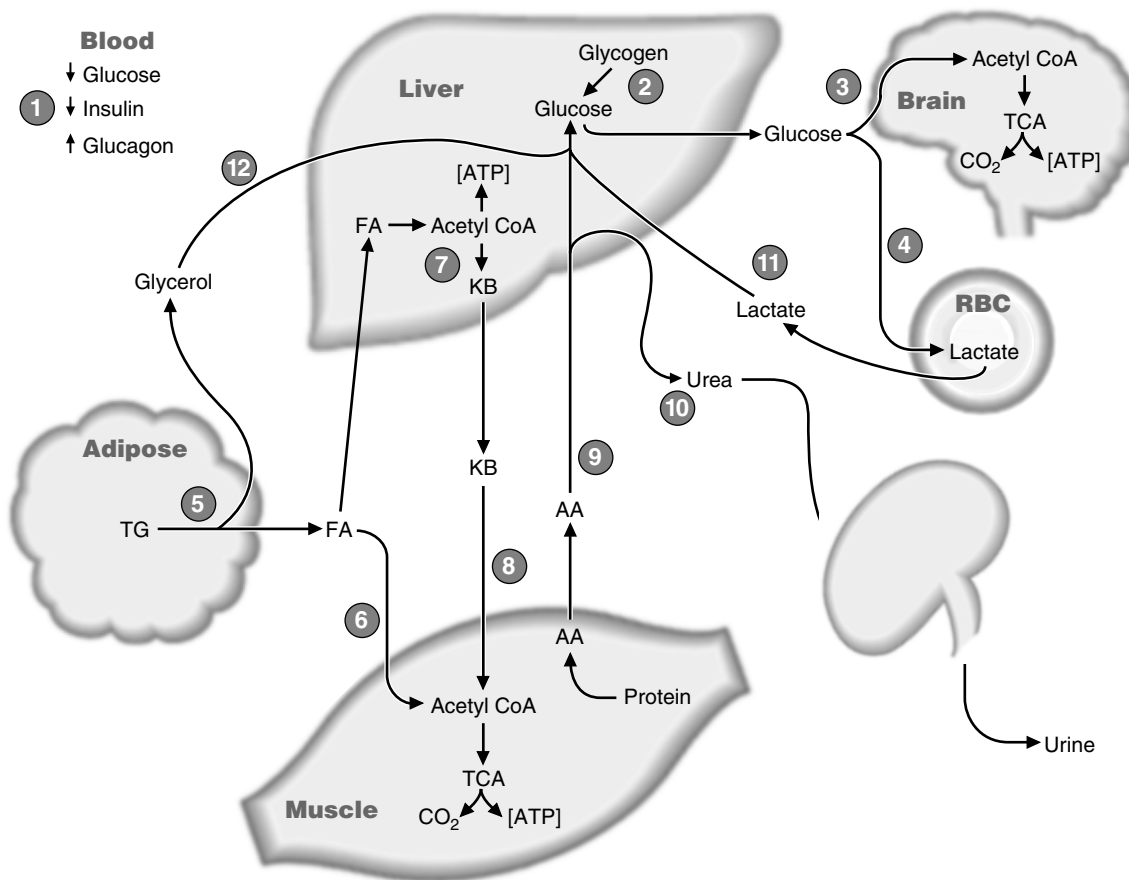
### C. Blood Glucose Levels during Prolonged Fasting (Starvation)

During prolonged fasting, a number of changes in fuel utilization occur. These changes cause tissues to use less glucose than they use during a brief fast and to use predominantly fuels derived from adipose triacylglycerols (i.e., fatty acids and their derivatives, the ketone bodies). Therefore, blood glucose levels do not decrease drastically. In fact, even after 5 to 6 weeks of starvation, blood glucose levels are still in the range of 65 mg/dL (Fig. 31.19, see Table 31.2).

The major change that occurs in starvation is a dramatic elevation of blood ketone body levels after 3 to 5 days of fasting (see Fig. 31.19). At these levels, the brain and other nervous tissues begin to use ketone bodies and, consequently, they oxidize less glucose, requiring roughly one third as much glucose (approximately 40 g/day) as under normal dietary conditions. As a result of reduced glucose utilization, the rate of gluconeogenesis in the liver decreases, as does the production of urea (see Fig. 31.19). Because in this stage of starvation amino acids, obtained



**Fig. 31.17.** Regulation of gluconeogenesis in the liver. GK = glucokinase; G-6-Pase = glucose 6-phosphatase; PK = pyruvate kinase; OAA = oxaloacetate; PEPCK = phosphoenolpyruvate carboxykinase; F-1,6-Pase = fructose 1,6-bisphosphatase; F-2,6-P = fructose 2,6-bisphosphate; PFK-1 = phosphofructokinase-1.



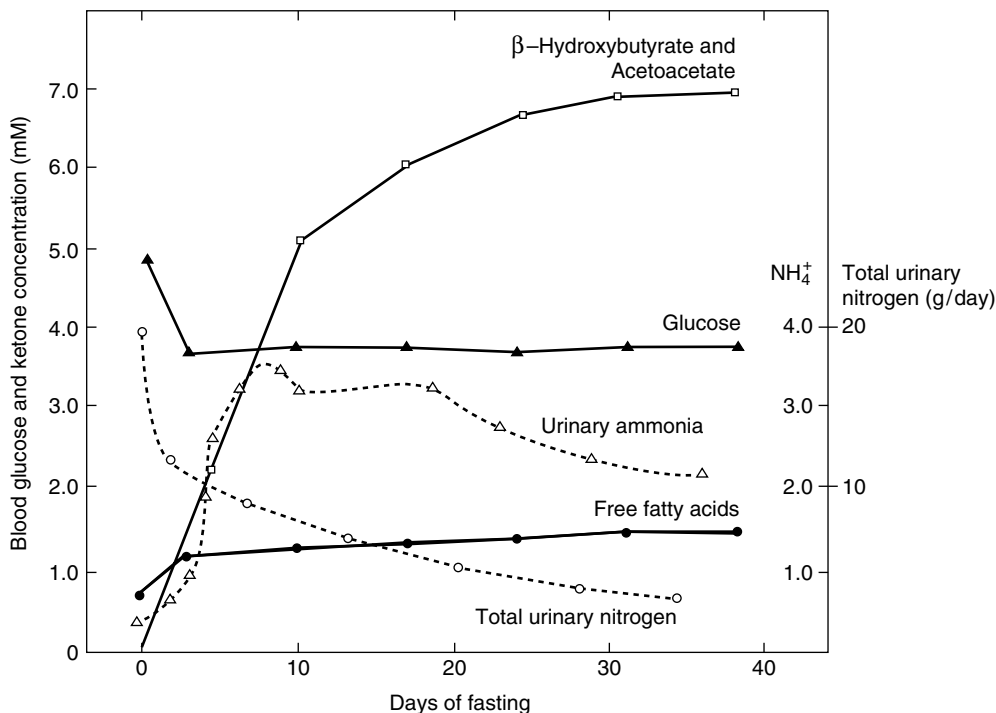
**Fig. 31.18.** Tissue interrelationships during fasting. 1. Blood glucose levels drop, decreasing insulin and raising blood glucagon levels. 2. Glycogenolysis is induced in the liver to raise blood glucose levels. 3. The brain uses the glucose released by the liver, as do the red blood cells (4). 5. Adipose tissues are induced to release free fatty acids and glycerol from stored triglycerides. 6. The muscle and liver use fatty acids for energy. 7. The liver converts fatty acid derived acetyl-CoA to ketone bodies for export, which the muscles (8) and brain can use for energy. 9. Protein turnover is induced in muscle, and amino acids leave the muscle and travel to the liver for use as gluconeogenic precursors. 10. The high rate of amino acid metabolism in the liver generates urea, which travels to the kidney for excretion. 11. Red blood cells produce lactate, which returns to the liver as a substrate for gluconeogenesis. 12. The glycerol released from adipose tissue is used by the liver set gluconeogenesis. KB = ketone bodies; FA = fatty acids; AA = amino acids; TG = triacylglycerols.

from the degradation of existing proteins, are the major gluconeogenic precursor, reducing glucose requirements in tissues reduces the rate of protein degradation, and, hence, the rate of urea formation. Protein from muscle and other tissues is therefore spared, because there is less need for amino acids for gluconeogenesis.

Body protein, particularly muscle protein, is not primarily a storage form of fuel in the same sense as glycogen or triacylglycerol; proteins have many functions beside fuel storage. For example, proteins function as enzymes, as structural proteins, and in muscle contraction. If tissue protein is degraded to too great an extent, body function can be severely compromised. If starvation continues and no other problems, such as infections, occur, a starving individual usually dies because of severe protein loss that causes malfunction of major organs, such as the heart. Therefore, the increase in ketone body levels that results in the sparing of body protein allows individuals to survive for extended periods without ingesting food.

#### D. Summary of Sources of Blood Glucose

Immediately after a meal, dietary carbohydrates serve as the major source of blood glucose (Fig. 31.20). As blood glucose levels return to the fasting range



**Fig. 31.19.** Changes in blood fuels during fasting. The units for fatty acids, glucose, and ketone bodies are millimolar (on left) and for urinary nitrogen and ammonia are grams/day (on right). Modified from Linder MC. *Nutritional Biochemistry and Metabolism*, 2nd Ed. Stamford, CT: Appleton & Lange, 1991:103. © 1991 Appleton & Lange.

within 2 hours after a meal, glycogenolysis is stimulated and begins to supply glucose to the blood. Subsequently, glucose is also produced by gluconeogenesis.

During a 12-hour fast, glycogenolysis is the major source of blood glucose. Thus, it is the major pathway by which glucose is produced in the basal state (after a 12-hour fast). However, by approximately 16 hours of fasting, glycogenolysis and gluconeogenesis contribute equally to the maintenance of blood glucose.

By 30 hours after a meal, liver glycogen stores are substantially depleted. Subsequently, gluconeogenesis is the primary source of blood glucose.

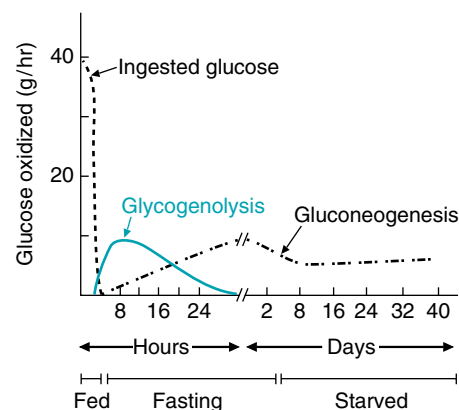
The mechanisms that cause fats to be used as the major fuel and that allow blood glucose levels to be maintained during periods of food deprivation result in the conservation of body protein and, consequently, permit survival during prolonged fasting for periods often exceeding 1 or more months.

### E. Blood Glucose Levels during Exercise

During exercise, mechanisms very similar to those that are used during fasting operate to maintain blood glucose levels. The liver maintains blood glucose levels through both glucagon- and epinephrine-induced glycogenolysis and gluconeogenesis. The use of fuels by muscle during exercise, including the uptake and use of blood glucose, is discussed in Chapter 47.



**Otto Shape** is able to jog for 45 minutes before eating breakfast without developing symptoms of hypoglycemia in spite of enhanced glucose utilization by skeletal muscle during exercise. He maintains his blood glucose level in an adequate range through hepatic glycogenolysis and gluconeogenesis.



**Fig. 31.20.** Sources of blood glucose in fed, fasting, and starved states. Note that the scale changes from hours to days. From Ruderman NB, et al. In: Hanson RW, Mehler MA, eds. *Gluconeogenesis: Its Regulation in Mammalian Species*. 1976:518. © 1976 John Wiley & Sons.



Remember that muscle glycogen is not used to maintain blood glucose levels; muscle cells lack glucose 6-phosphatase, so glucose cannot be produced from glucose 6-phosphate for export.





Epidemiologic studies have correlated the results of the OGTT with the current and subsequent development of the microvascular complications of DM in the eye (diabetic retinopathy) and in the kidney (diabetic nephropathy). Their development is usually limited to those patients whose fasting blood glucose level exceeds 140 mg/dL (7.8 mM) or whose 2-hour postprandial blood glucose level exceeds 200 mg/dL (11.1 mM).

As a consequence, the success of therapy with diet alone or with diet plus oral hypoglycemic agents is often determined by measuring blood glucose levels during fasting, before breakfast, and 2 hours after a meal. For patients taking an intermediate-acting insulin, blood glucose also may be measured at other times, such as when insulin action is expected to peak after its injection (e.g., around 5:00 PM, when intermediate-acting insulin has been given at 7:00 AM the same day).

## CLINICAL COMMENTS



The chronic excessive ingestion of ethanol concurrent with a recent reduction in nutrient intake caused **Al Martini's** blood glucose level to decrease to 28 mg/dL. This degree of hypoglycemia caused the release of a number of “counterregulatory” hormones into the blood, including glucagon, growth hormone, cortisol, and epinephrine (adrenaline).

Some of the patient's signs and symptoms are primarily the result of an increase in adrenergic nervous system activity after a rapid decrease in blood glucose. The subsequent increase in epinephrine levels in the blood leads to tremulousness, excessive sweating, and rapid heart rate. Other manifestations arise when the brain has insufficient glucose, hence the term “neuroglycopenic symptoms.” Mr. Martini was confused, combative, had slurred speech, and eventually had a grand mal seizure. If not treated quickly by intravenous glucose administration, Mr. Martini may have lapsed into a coma. Permanent neurologic deficits and even death may result if severe hypoglycemia is not corrected in 6 to 10 hours.



The elevation in blood glucose that occurred in **Emma Wheezer's** case was primarily a consequence of the large pharmacologic doses of a glucocorticoid that she received in an effort to reduce the intrabronchial inflammatory reaction characteristic of asthmatic bronchospasm. Although the development of hyperglycemia in this case could be classified as a “secondary” form of diabetes mellitus, most patients treated with glucocorticoids do not develop glucose intolerance. Ms. Wheezer, therefore, may have a predisposition to the eventual development of “primary” diabetes mellitus.

In hyperglycemia, increased amounts of glucose enter the urine, causing large amounts of water to be excreted. This “osmotic diuresis” is responsible for the increased volume of urine (polyuria) noted by the patient. Because of increased urinary water loss, the effective circulating blood volume is reduced. Therefore, less blood reaches volume-sensitive receptors in the central nervous system, which then trigger the sensation of thirst, causing increased drinking activity (polydipsia).

A diabetic diet and the tapering of her steroid dose over a period of several weeks gradually returned Ms. Wheezer's blood glucose level into the normal range.



Chronically elevated levels of glucose in the blood may contribute to the development of the microvascular complications of diabetes mellitus, such as diabetic retinal damage, kidney damage, and nerve damage, as well as macrovascular complications such as cerebrovascular, peripheral vascular, and coronary vascular insufficiency. The precise mechanism by which long-term hyperglycemia induces these vascular changes is not fully established.

One postulated mechanism proposes that nonenzymatic glycation (glycosylation) of proteins in vascular tissue alters the structure and functions of these proteins. A protein exposed to chronically increased levels of glucose will covalently bind glucose, a process called glycation or glycosylation. This process is not regulated by enzymes (see Chapter 9). These nonenzymatically glycosylated proteins slowly form cross-linked protein adducts (often called advanced glycosylation products) within the microvasculature and macrovasculature.

By cross-linking vascular matrix proteins and plasma proteins, chronic hyperglycemia may cause narrowing of the luminal diameter of the microvessels in the retina (causing diabetic retinopathy), the renal glomeruli (causing diabetic nephropathy), and the microvessels supplying peripheral and autonomic nerve fibers (causing diabetic neuropathy). The same process has been postulated to accelerate atherosclerotic change in the macrovasculature, particularly in the brain

(causing strokes), the coronary arteries (causing heart attacks), and the peripheral arteries (causing peripheral arterial insufficiency and gangrene). The abnormal lipid metabolism associated with poorly controlled diabetes mellitus also may contribute to the accelerated atherosclerosis associated with this metabolic disorder (see Chapters 33 and 34).

Until recently, it was argued that meticulous control of blood glucose levels in a diabetic patient would not necessarily prevent or even slow these complications of chronic hyperglycemia. The publication of the Diabetes Control and Complications Trial, however, suggests that maintaining long-term euglycemia (normal blood glucose levels) in diabetic patients slows the progress of unregulated glycation of proteins as well as corrects their dyslipidemia. In this way, careful control may favorably affect the course of the microvascular and macrovascular complications of diabetes mellitus in patients such as **Di Abietes** and **Ann Sulin**.

### BIOCHEMICAL COMMENTS



Plants are the ultimate source of the earth's supply of glucose. Plants produce glucose from atmospheric  $\text{CO}_2$  by the process of photosynthesis (Fig. 31.21A). In contrast to plants, humans cannot synthesize glucose by the fixation of  $\text{CO}_2$ . Although we have a process called gluconeogenesis, the term may really be a misnomer. Glucose is not generated anew by gluconeogenesis; compounds produced from glucose are simply recycled to glucose. We obtain glucose from the plants, including bacteria, that we eat and, to some extent, from animals in our food supply. We use this glucose both as a fuel and as a source of carbon for the synthesis of fatty acids, amino acids, and other sugars (see Fig. 31.21B). We store glucose as glycogen, which, along with gluconeogenesis, provides glucose when needed for energy (see Fig. 31.21C).

Lactate, one of the carbon sources for gluconeogenesis, is actually produced from glucose by tissues that obtain energy by oxidizing glucose to pyruvate through glycolysis. The pyruvate is then reduced to lactate, released into the bloodstream, and reconverted to glucose by the process of gluconeogenesis in the liver. This process is known as the Cori cycle (Fig. 31.21D).

Carbons of alanine, another carbon source for gluconeogenesis, may be produced from glucose. In muscle, glucose is converted via glycolysis to pyruvate and transaminated to alanine. Alanine from muscle is recycled to glucose in the liver. This process is known as the glucose–alanine cycle (Fig. 31.21E). Glucose also may be used to produce nonessential amino acids other than alanine, which are subsequently reconverted to glucose in the liver by gluconeogenesis. Even the essential amino acids that we obtain from dietary proteins are synthesized in plants and bacteria using glucose as the major source of carbon. Therefore, all amino acids that are converted to glucose in humans, including the essential amino acids, were originally synthesized from glucose.

The production of glucose from glycerol, the third major source of carbon for gluconeogenesis, is also a recycling process. Glycerol is derived from glucose via the dihydroxyacetone phosphate intermediate of glycolysis. Fatty acids are then esterified to the glycerol and stored as triacylglycerol. When these fatty acids are released from the triacylglycerol, the glycerol moiety can travel to the liver and be reconverted to glucose (see Fig. 31.21F).

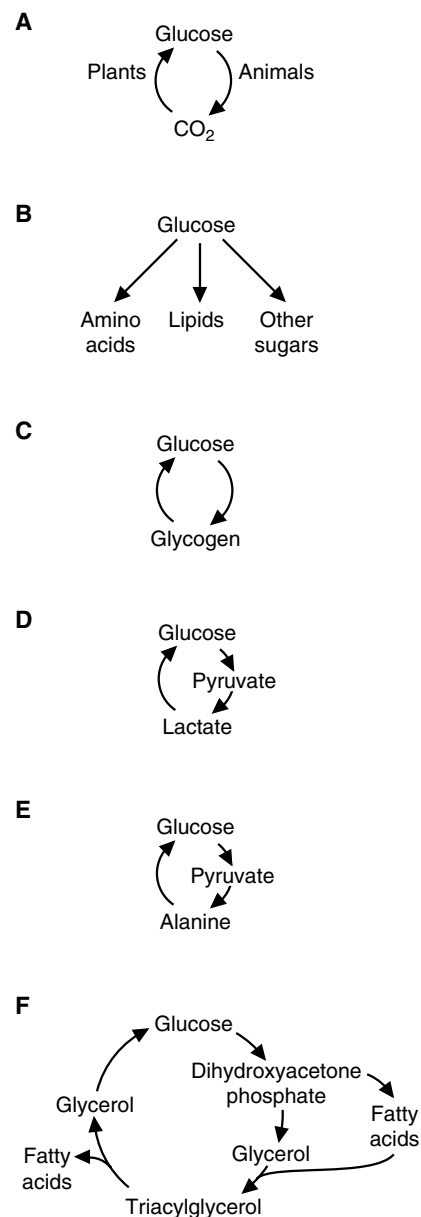


Fig. 31.21. Recycling of glucose.

### Suggested References

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**REVIEW QUESTIONS—CHAPTER 31**

1. A common intermediate in the conversion of glycerol and lactate to glucose is which of the following?
  - (A) Pyruvate
  - (B) Oxaloacetate
  - (C) Malate
  - (D) Glucose 6-phosphate
  - (E) Phosphoenolpyruvate
2. A patient presented with a bacterial infection that produced an endotoxin that inhibits phosphoenolpyruvate carboxykinase. In this patient, then, under these conditions, glucose production from which of the following precursors would be inhibited?
  - (A) Alanine
  - (B) Glycerol
  - (C) Even-chain-number fatty acids
  - (D) Phosphoenolpyruvate
  - (E) Galactose
3. Which of the following statements best describes glucagon?
  - (A) It acts as an anabolic hormone.
  - (B) It acts on skeletal muscle, liver, and adipose tissue.
  - (C) It acts primarily on the liver and adipose tissue.
  - (D) Its concentration in the blood increases after a high-carbohydrate meal.
  - (E) Its concentration increases in the blood when insulin levels increase.
4. Which of the following is most likely to occur in a normal individual after ingesting a high-carbohydrate meal?
  - (A) Only insulin levels decrease.
  - (B) Only insulin levels increase.
  - (C) Only glucagon levels increase.
  - (D) Both insulin and glucagon levels decrease.
  - (E) Both insulin and glucagon levels increase.
5. A patient arrives at the hospital in an ambulance. She is currently in a coma. Before lapsing into the coma, her symptoms included vomiting, dehydration, low blood pressure, and a rapid heartbeat. She also had relatively rapid respirations, resulting in more carbon dioxide exhaled. These symptoms are consistent with which of the following conditions?
  - (A) The patient lacks a pancreas.
  - (B) Ketoalkolosis
  - (C) Hypoglycemic coma
  - (D) Diabetic ketoacidosis
  - (E) Insulin shock in a diabetic patient