Principles of Bioenergetics

Living cells and organisms must perform work to stay alive, to grow, and to reproduce themselves. The ability to harness energy from various sources and to channel it into biological work is a fundamental property of all living organisms; it must have been acquired very early in the process of cellular evolution. Modern organisms carry out a remarkable variety of energy transductions, conversions of one form of energy to another. They use chemical energy in fuels to bring about the synthesis of complex molecules from simple precursors, producing macromolecules with highly ordered structure. They also convert the chemical energy of various fuels into concentration gradients and electrical gradients, motion, heat, and even, in a few organisms such as fireflies, light. Photosynthetic organisms transduce light energy into all of these other forms of energy. Animals somehow transform chemical fuels (foods) into heat and that this process of respiration is essential to life. Biochemical studies have revealed much of the chemistry of energy transductions in living organisms. Biological energy transductions obey the same physical laws that govern all other natural processes. It is therefore essential for a student of biochemistry to understand these laws and the ways in which they apply to the flow of energy in the biosphere.

Many quantitative observations made by physicists and chemists on the interconversion of different forms of energy led to the formulation, in the nineteenth century, of two fundamental laws of thermodynamics. The first law is the principle of the conservation of energy: *in any physical or chemical change, the total amount of energy in the universe remains constant, although the form of the energy may change.* The second law of thermodynamics, which can be stated in several forms, says that the universe always tends toward more and more disorder: in cell natural processes, the entropy of the universe increase.

Living organisms consist of collections of molecules much more highly organized than the surrounding materials from which they are constructed, and they maintain and produce order, seemingly oblivious to the second law of thermodynamics. Living organisms do not violate the second law; they operate strictly within it. To discuss the application of the second law to biological systems, we must first define those systems and the universe in which they occur. The reacting system is the collection of matter that is undergoing a particular chemical or physical process; it may be an organism, a cell, or two reacting compounds. The reacting system and its surroundings together constitute the universe. Some chemical or physical processes can be made to take place in isolated or closed systems, in which no material or energy is exchanged with the surroundings. Living cells and organisms are open systems, which exchange both material and energy with their surroundings; living systems are never at equilibrium with their surroundings.

Gibbs free energy

The Gibbs free energy of a system at any moment in time is defined as the enthalpy of the system minus the product of the temperature times the entropy of the system.

$G = H - TS$

The Gibbs free energy of the system is a state function because it is defined in terms of thermodynamic properties that are state functions. The change in the Gibbs free energy of the system that occurs during a reaction is therefore equal to the change in the enthalpy of the system minus the change in the product of the temperature times the entropy of the system.

$\Delta G = \Delta H - \Delta(TS)$

If the reaction is run at constant temperature, this equation can be written as follows.

$\Delta G = \Delta H - T\Delta S$

The change in the free energy of a system that occurs during a reaction can be measured under any set of conditions. If the data are collected under standard-state conditions, the result is the **standard-state free energy of reaction** (ΔG^o).

$\Delta G^o = \Delta H^o - T\Delta S^o$

The beauty of the equation defining the free energy of a system is its ability to determine the relative importance of the enthalpy and entropy terms as driving forces behind a particular reaction. The change in the free energy of the system that occurs during a reaction measures the balance between the two driving forces that determine whether a reaction is spontaneous. As we have seen, the enthalpy and entropy terms have different sign conventions.

Favorable	*Unfavorable*
$\Delta H^o < 0$	$\Delta H^o > 0$
$\Delta S^o > 0$	$\Delta S^o < 0$

The entropy term is therefore subtracted from the enthalpy term when calculating ΔG^o for a reaction.

Because of the way the free energy of the system is defined, ΔG^o is negative for any reaction for which ΔH^o is negative and ΔS^o is positive. ΔG^o is therefore negative for any reaction that is favored by both the enthalpy and entropy terms. We can therefore conclude that any reaction for which ΔG^o is negative should be favorable, or spontaneous.

Favorable, or spontaneous reactions: $\Delta G^o < 0$

Conversely, ΔG^o is positive for any reaction for which ΔH^o is positive and ΔS^o is negative. Any reaction for which ΔG^o is positive is therefore unfavorable.

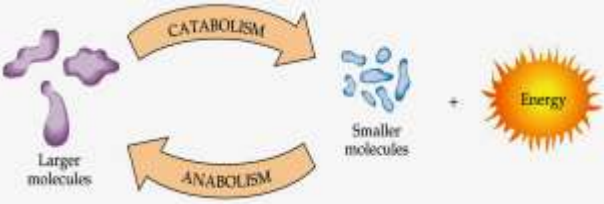
Unfavorable, or non-spontaneous reactions: $\Delta G^o > 0$

Reactions are classified as either **exothermic** ($\Delta H < 0$) or **endothermic** ($\Delta H > 0$) on the basis of whether they give off or absorb heat. Reactions can also be classified as **exergonic** ($\Delta G < 0$) or **endergonic** ($\Delta G > 0$) on the basis of whether the free energy of the system decreases or increases during the reaction.

When a reaction is favored by both enthalpy ($\Delta H^o < 0$) and entropy ($\Delta S^o > 0$), there is no need to calculate the value of ΔG^o to decide whether the reaction should proceed. The same can be said for reactions favored by neither enthalpy ($\Delta H^o > 0$) nor entropy ($\Delta S^o < 0$). Free energy calculations become important for reactions favored by only one of these factors.

Metabolism

Metabolism is the sum of all reactions that take place in an organism/living thing and can be divided into two parts: Catabolism where, compounds are broken down into smaller ones in processes that, usually, release energy and Anabolism which involves the biosynthesis of larger compounds from smaller ones in processes that, usually, require energy



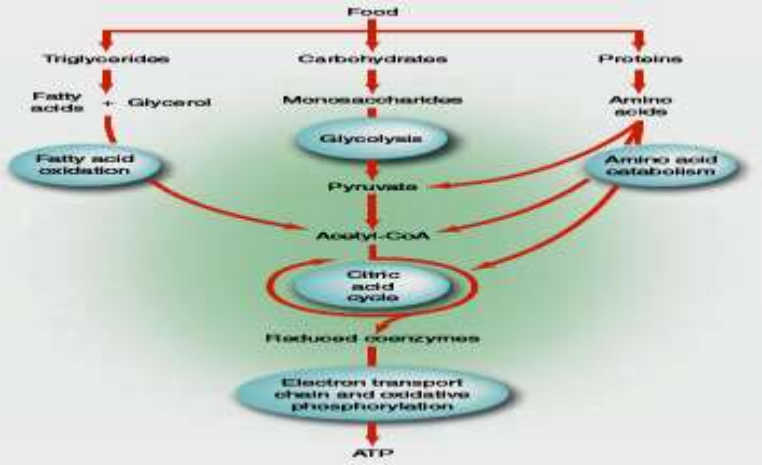
Differences between Catabolism and Anabolism

Table 7-2 Differences between Catabolism and Anabolism

Catabolism	Anabolism
All the catabolic reactions in a cell	All the anabolic reactions in a cell
Catabolic reactions release energy	Anabolic reactions require energy
Catabolic reactions involve the breaking of bonds; whenever chemical bonds are broken, energy is released	Anabolic reactions involve the creation of bonds; it takes energy to create chemical bonds
Larger molecules are broken down into smaller molecules (sometimes referred to as degradative reactions)	Smaller molecules are bonded together to create larger molecules (sometimes referred to as biosynthetic reactions)

Strategies of Metabolism: ATP and Energy Transfer

ADP and ATP are key players in metabolism. Adenosine triphosphate (ATP) is the storage form of energy in living organisms. Energy released during catabolism is used to drive the formation of ATP. Energy obtained by hydrolyzing ATP can, in turn, be used for anabolism or other energy requiring processes, such as muscle contraction. Catabolism begins with the digestion of food, during which triglycerides, carbohydrates, and proteins are split into their building blocks – fatty acids and glycerol, monosaccharides, and amino acids respectively. These are then further broken down to smaller molecules such as acetyl-CoA and intermediates of the citric acid cycle.

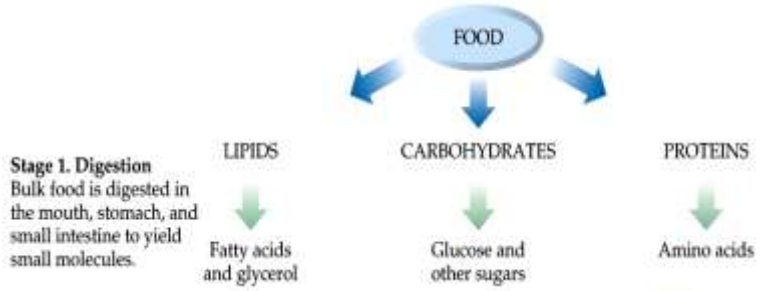


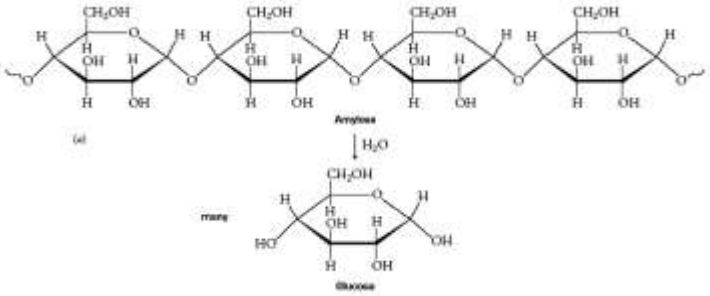
During anabolism, small molecules such as pyruvate, acetyl-CoA, and intermediates in the citric acid cycle are used to make fatty acids, monosaccharides, and amino acids for incorporation into lipids, polysaccharides, and proteins.

Catabolism

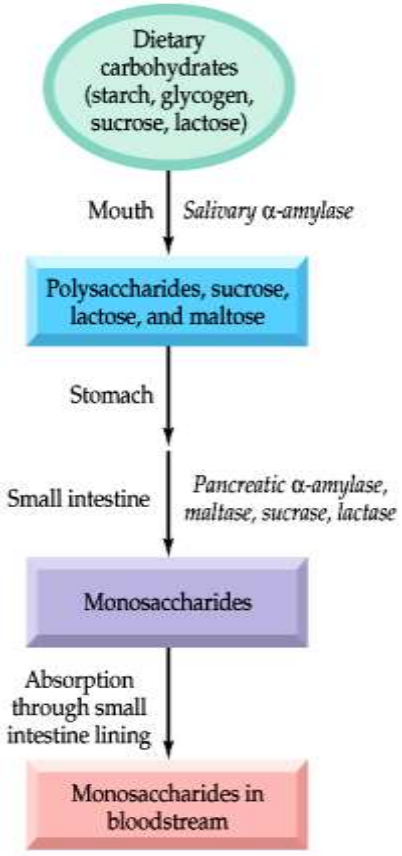
Stage 1: Digestion

During digestion the large molecules present in food are broken down into their respective building blocks.





(*a*) Hydrolysis of starch yields glucose molecules. The α-(1 → 4) glycosidic bonds in amylose and amylopectin are hydrolyzed by amylase and the α-(1 → 6) glycosidic bonds in amylopectin (not shown) are hydrolyzed by debranching enzyme.

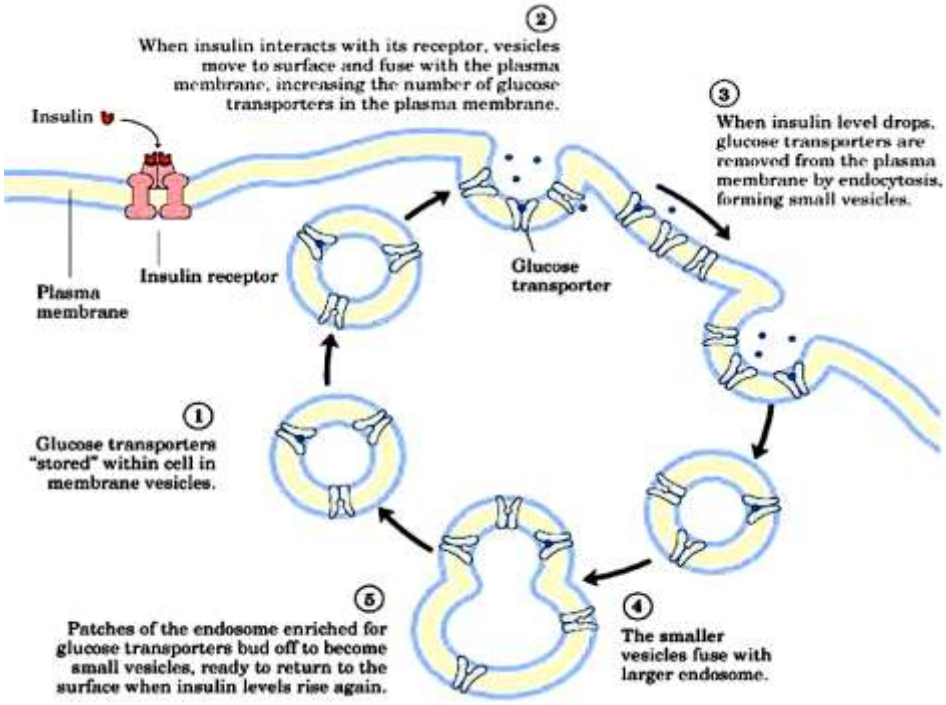


How does glucose enter the cell? The Fate of Glucose

Glucose is the body's preferred source for synthesizing ATP. 90 % of the polysaccharides and disaccharides in our diet are converted into glucose. The body has a feedback system that maintains the blood glucose level at about 90mg/100mL (= 5 mmol/L). Two hormones play a major role in blood glucose regulation:

1. Insulin is released when the blood glucose level rises.
2. Glucagon is released when blood glucose concentration drops.

Before glucose can be used by cells, it must pass through the cell membrane. The hormone insulin controls the diffusion of glucose into the cell.



STAGE 2: GLYCOLYSIS

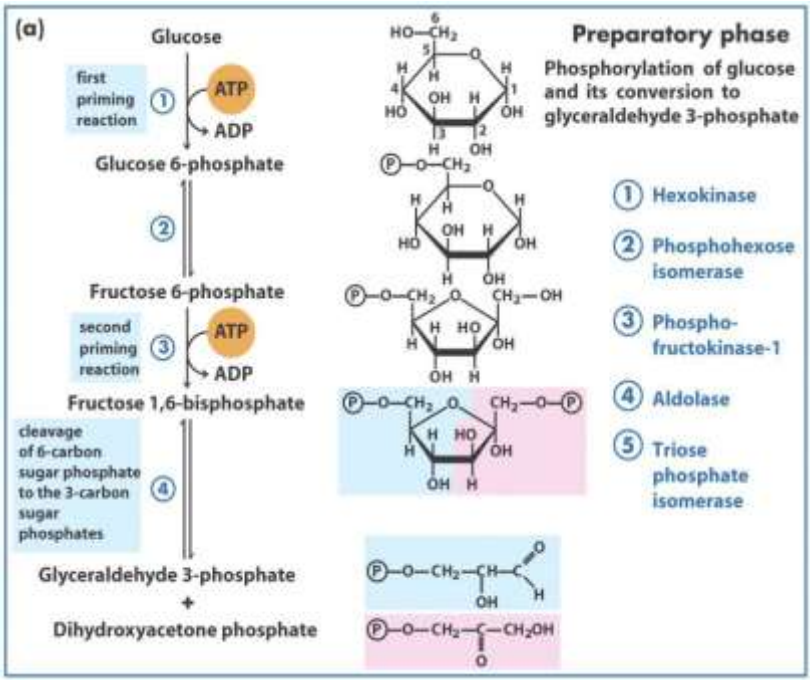
This is the aerobic process by which glucose is degraded to 2 molecules of pyruvic acid or anaerobic process by which glucose is converted to two molecules of along with the production of small amount of energy. Glycolysis occurs in the cytoplasm of virtually all tissues. Anaerobic glycolysis is important because it provides a mechanism for generating ATP without using oxygen.

The overall reactions of glycolysis can be divided into two:

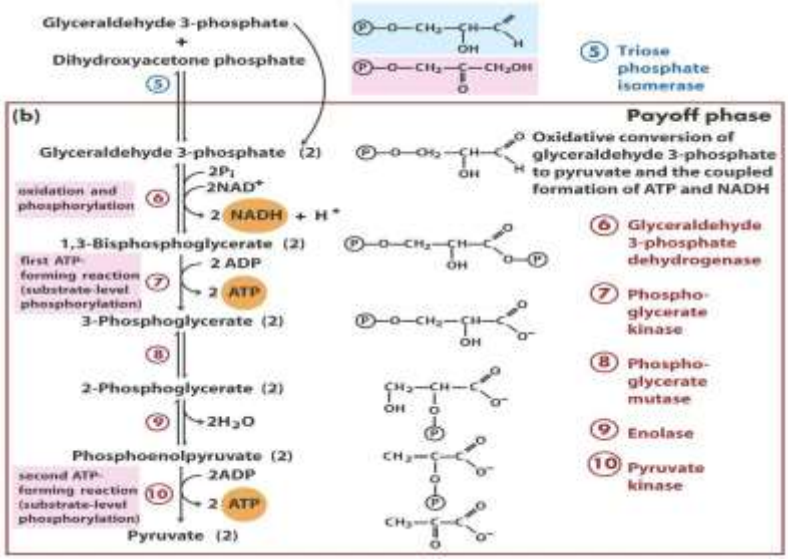
(1) Activation/Preparative phase: Glucose is converted to triose phosphates by phosphorylation
(2) Energy Producing/Pay off phase: Oxidation of triose phosphates to lactate or pyruvic acid depending on the oxygen supply conditions

The Glycolysis Reactions: 10-step reaction pathway

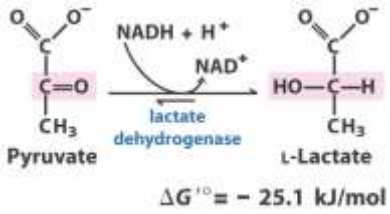
Activation/Preparative phase



Energy Producing/Pay off phase



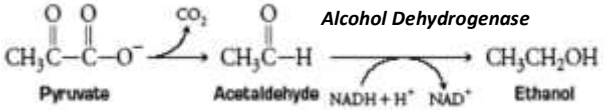
Pyruvate is the end product of glycolysis in aerobic condition, under anaerobic, pyruvate is reduced by Lactate dehydrogenase to lactate.



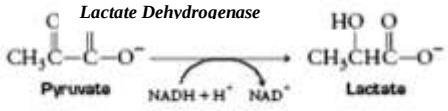
However under aerobic conditions, pyruvate is further oxidized in the mitochondria to generate more ATP.

The Fate of Pyruvate

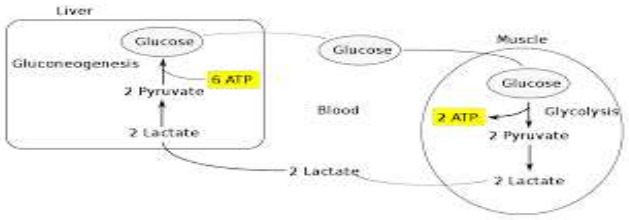
Conversion of glucose to pyruvate is a central metabolic pathway in most living organisms. Further reactions of pyruvate depend on metabolic conditions i.e. aerobic or anaerobic and type of organism. In yeast, pyruvate undergoes anaerobic decarboxylation. In this process pyruvate is split into acetaldehyde plus CO2, and acetaldehyde is reduced to ethanol.



These reactions serve to recycle NADH back into NAD+, allowing glycolysis to continue. In **humans**, pyruvate is reduced to lactate when conditions are anaerobic (O_2 deficient)

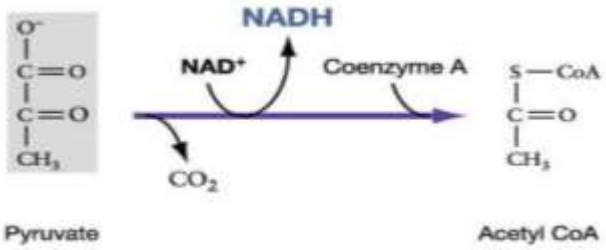


This reaction also converts NADH back into NAD+, allowing glycolysis to continue. Once produced, lactate is sent in blood to the liver, where it can be used to manufacture glucose through the Cori cycle and this glucose can be used by the muscle for purposes of contraction.



Cori cycle

Under aerobic conditions, pyruvate is further oxidized to acetyl-CoA by *Pyruvate decarboxylase* which enters the Citric Acid Cycle/Krebs cycle/Tri Carboxylic Acid cycle.



Regulation of glycolysis

Phosphofructokinase

- The most important control step of glycolysis is the irreversible reaction catalyzed by phosphofructokinase (PFK). The enzyme is regulated in several ways:
- *ATP/AMP*. PFK is allosterically inhibited by ATP but this inhibition is reversed by AMP. This allows glycolysis to be responsive to the energy needs of the cell, speeding up when ATP is in short supply (and AMP is plentiful) so that more ATP can be made, and slowing down when sufficient ATP is already available.
- *Citrate*. PFK is also inhibited by citrate, the first product of the citric acid cycle proper. A high level of citrate signals that there is a plentiful supply of citric acid cycle intermediates already and hence no additional breakdown of glucose via glycolysis is needed.
- *Fructose 2,6-bisphosphate*. Fructose 2,6-bisphosphate (F-2,6-BP) is synthesized from fructose 6-phosphate by an enzyme called **phosphofructokinase 2** (**PFK2**), a different enzyme from PFK. F-2,6-BP is hydrolyzed back to fructose 6-phosphate by **fructose bisphosphatase 2** (**FBPase2**).Amazingly, both PFK2 and FBPase2 are activities catalyzed by the same polypeptide; hence this is a **bi-functional enzyme**. Fructose 6-phosphate stimulates the synthesis of F-2,6-BP and inhibits its hydrolysis . F-2,6-BP in turn strongly activates PFK and hence stimulates glycolysis. The overall

effect is that when fructose 6-phosphate levels are high, PFK (and hence glycolysis) is stimulated. PFK2 and FBPase2 are also controlled by covalent modification. When blood glucose levels fall, the hormone glucagon is released into the bloodstream and triggers a cAMP cascade that leads to phosphorylation of the PFK2/FBPase2 polypeptide at a single serine residue. This activates FBPase2 and inhibits

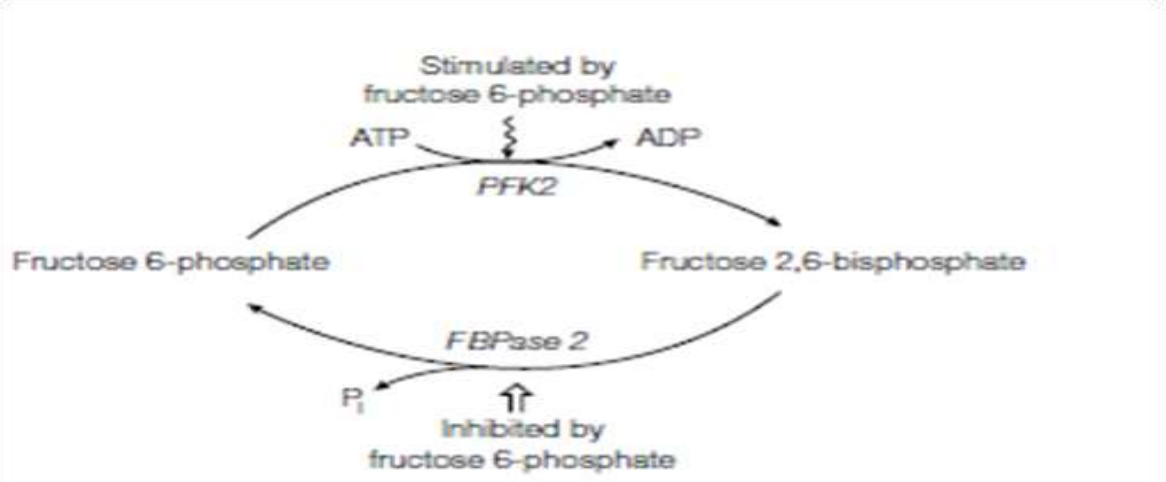


Fig. 4. Synthesis and degradation of fructose 2,6-bisphosphate.

PFK2, lowering the level of F-2,6-BP and hence decreasing the rate of glycolysis.

The reverse is true as glucose levels rise; the phosphate group is removed from the PFK2/FBPase2 polypeptide by a phosphatase, thus inhibiting FBPase2 and activating PFK2, raising the level of F-2,6-BP and hence increasing the rate of glycolysis. F-2,6-BP is also important in preventing glycolysis (glucose degradation) and gluconeogenesis (glucose synthesis) operating simultaneously. This is called **reciprocal regulation.**

- *H_ ions*. PFK is inhibited by H_ ions and hence the rate of glycolysis decreases when the pH falls significantly. This prevents the excessive formation of lactate (i.e. lactic acid) under anaerobic conditions (see above) and hence prevents the medical condition known as acidosis (a deleterious drop in blood pH).

Hexokinase

- Hexokinase, which catalyzes the first irreversible step of glycolysis, is inhibited by glucose 6-phosphate. Thus when PFK is inhibited, fructose 6-phosphate builds up and so does glucose 6-phosphate since these two metabolites are in equilibrium via phosphoglucoisomerase .
- The hexokinase inhibition then reinforces the inhibition at the PFK step. At first sight this seems unusual since it is usually the first irreversible step of a pathway

(the committed step) that is the main control step. On this basis, it may appear that hexokinase should be the main control enzyme, not PFK. However, glucose 6-phosphate, the product of the hexokinase reaction, can also feed into glycogen synthesis or the pentose phosphate pathway.

- Thus the first irreversible step that is unique to glycolysis is that catalyzed by PFK and hence this is the main control step.

Pyruvate kinase

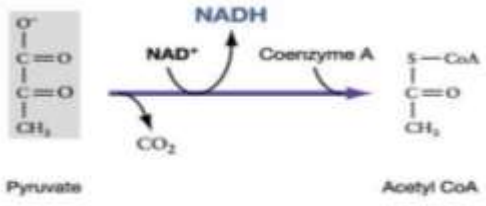
- Pyruvate kinase catalyzes the third irreversible step in glycolysis. It is activated by fructose 1,6-bisphosphate. ATP and the amino acid alanine allosterically inhibit the enzyme so that glycolysis slows when supplies of ATP and biosynthetic precursors (indicated by the levels of Ala) are already sufficiently high.
- In addition, in a control similar to that for PFK, when the blood glucose concentration is low, glucagon is released and stimulates phosphorylation of the enzyme via a cAMP cascade.
- This covalent modification inhibits the enzyme so that glycolysis slows down in times of low blood glucose levels.

STAGE 3: CITRIC ACID CYCLE

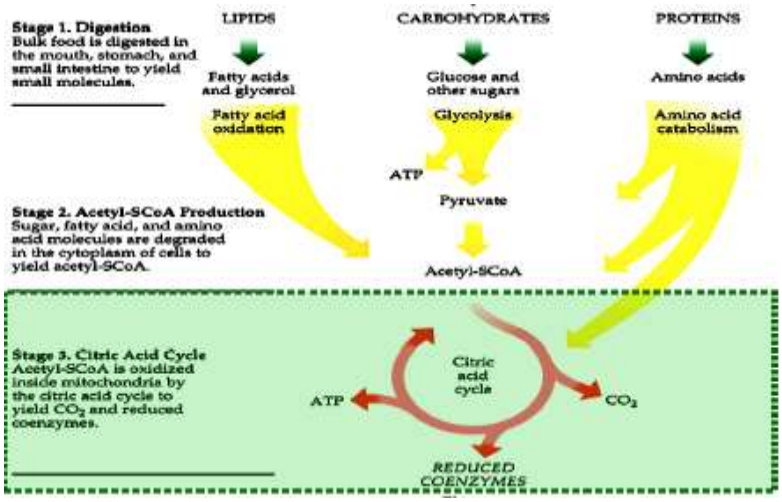
The goal of Krebs cycle is to further oxidize pyruvate in order to produce NADH and $FADH_2$ reducing equivalents for more ATP synthesis in the subsequent reactions. The Krebs/Citric acid cycle reactions occurs in the mitochondria matrix and involves two steps

1. The Conversion of Pyruvate to Acetyl CoA
2. The Krebs Cycle proper

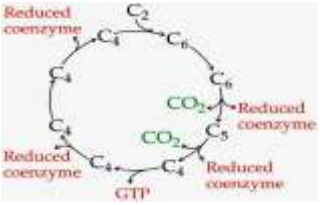
First the 2 pyruvate molecules generated in glycolysis are converted to 2 acetyl CoA molecules which then enter the Krebs cycle.

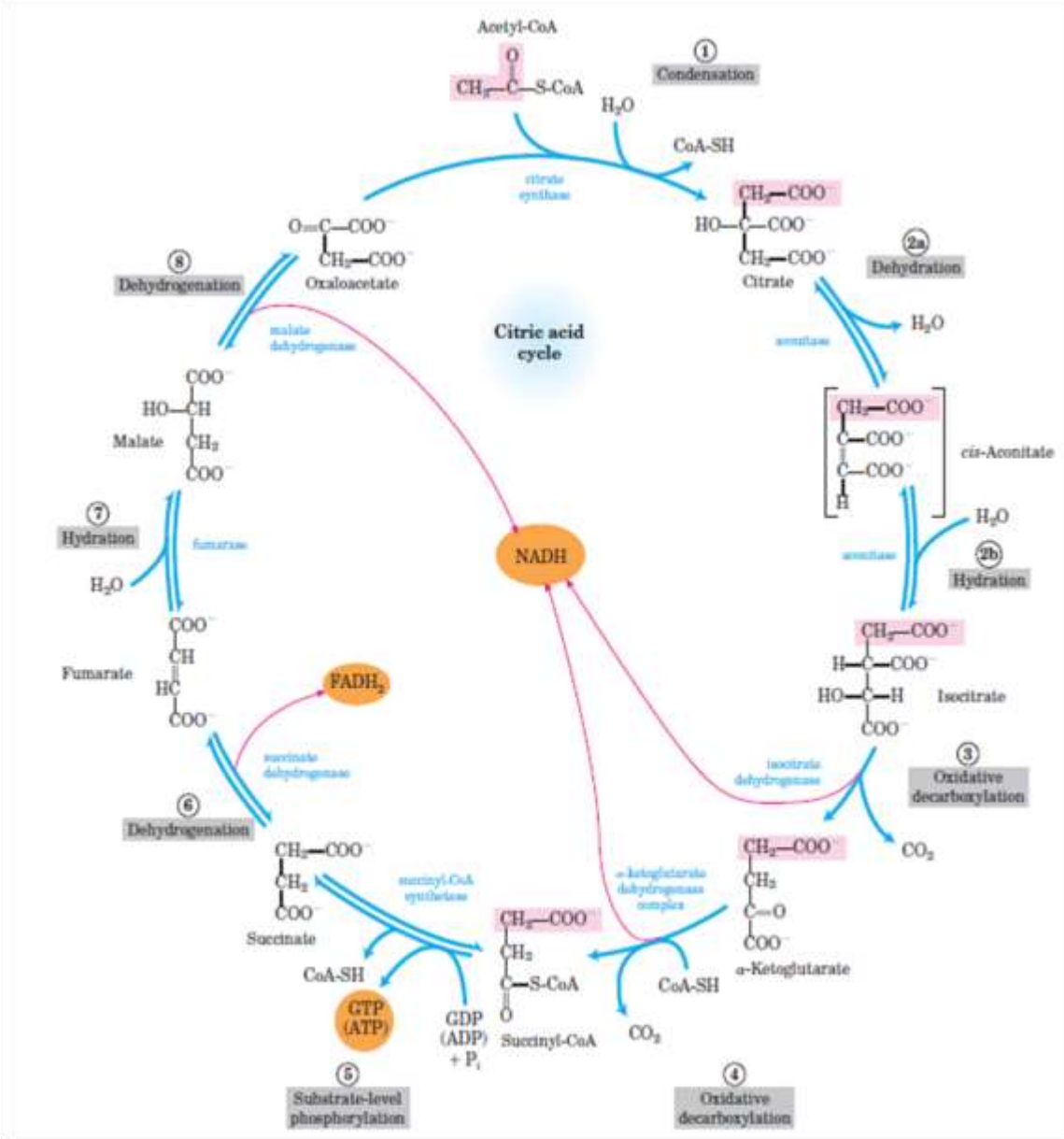


In this reaction 2 NADH's are generated (1 per pyruvate) and 2 CO_2 are released (1 per pyruvate)



The Citric acid cycle is also known as Krebs cycle, or the Tricarboxylic Acid Cycle (TCA). This cyclic series of reactions break down acetyl CoA to produce energy carried by reduced coenzymes. The 8 steps of the cycle produce two molecules of carbon dioxide, four molecules of reduced coenzymes, and one energy rich phosphate (ATP). The final step regenerates the reactant for step 1 of the next turn of the cycle.





Net Result of Citric Acid Cycle:

$$\text{Acetyl-CoA} + 3\text{NAD}^+ + \text{FAD} + \text{GDP} + \text{P}i \rightarrow 2\text{CO}_2 + \text{CoA} + 3\text{NADH} + \text{FADH}_2 + \text{GTP}$$

$\Delta G = -11$ kcal/mol

Note that this for one "turn" of the citric acid cycle; each glucose molecule turns the cycle twice. In some cells, GTP is directly converted to ATP, which is shown below.

$$\text{Acetyl-SCoA} + 3\ \text{NAD+} + \text{FAD} + \text{ADP} + \text{HOPO}_3^{2-} + \text{H}_2\text{O} \rightarrow$$
$$\text{HSCoA} + 3\ \text{NADH} + 3\ \text{H}^+ + \text{FADH}_2 + \text{ATP} + 2\ \text{CO}_2$$

- 6 NADH's are generated (3 per Acetyl CoA that enters)
- 2 $FADH_2$ is generated (1 per Acetyl CoA that enters)
- 2 ATP are generated (1 per Acetyl CoA that enters)
- 4 CO_2's are released (2 per Acetyl CoA that enters)

Regulation of the Citric Acid Cycle

Regulation of the cycle is governed by substrate availability, inhibition by accumulating products, and allosteric feedback inhibition by subsequent intermediates in the cycle. Three enzymes in the cycle itself are regulated (*citrate synthase, isocitrate dehydrogenase and a-ketoglutarate dehydrogenase*) and so is the enzyme which converts pyruvate to acetyl CoA to enter the cycle, namely *pyruvate dehydrogenase*

- *Citrate synthase* is inhibited by citrate and also by ATP (the *K*m for acetyl CoA is raised as the level of ATP rises);
- *Isocitrate dehydrogenase* is inhibited by NADH and ATP but activated by ADP;
- α-*ketoglutarate dehydrogenase* is inhibited by NADH and succinyl CoA;
- *Pyruvate dehydrogenase* is inhibited by NADH and acetyl CoA (i.e. product inhibition).

However, in eukaryotes the enzyme is also controlled by phosphorylation/ dephosphorylation via **pyruvate dehydrogenase kinase** and a **phosphatase**.
The kinase catalyzes the phosphorylation of a specific Ser residue in pyruvate dehydrogenase, using ATP as the phosphate donor, and this inactivates the enzyme. Removal of the phosphate group by the phosphatase reactivates the enzyme.
At any one time, the activity of pyruvate dehydrogenase is determined by the relative balance between the kinase and phosphatase reactions.
Increasing the NADH/NAD_, acetyl CoA/CoA or ATP/ADP ratio stimulates phosphorylation and hence inactivates pyruvate dehydrogenase. As pyruvate builds up, it inhibits the kinase and hence allows the phosphatase to reactivate pyruvate dehydrogenase, thus stimulating pyruvate conversion to acetyl CoA.
Overall, the cycle speeds up when cellular energy levels are low (high ADP concentration, low ATP and NADH) and slows down as ATP (and then NADH2, succinyl CoA and citrate) accumulates.

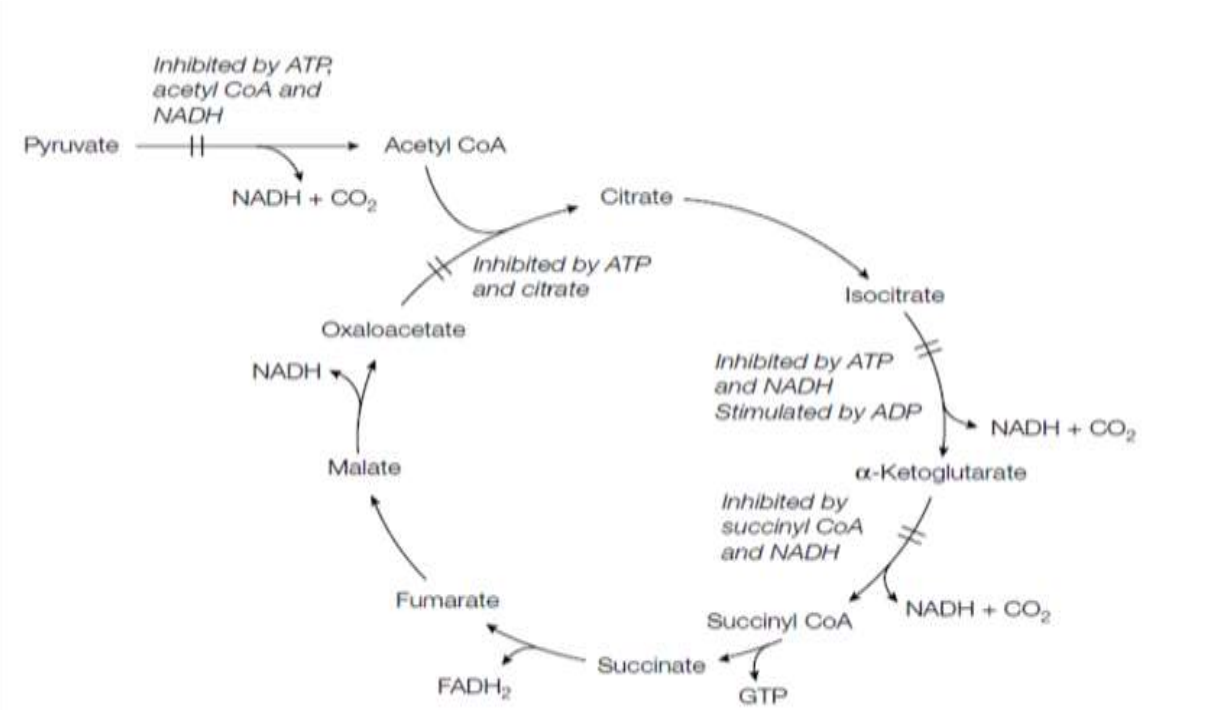


Fig. 2. Regulation points of the citric acid cycle.

ANAPLEROTIC REACTIONS

Anaplerosis or Anaplerotic reactions

- As intermediates of the citric acid cycle are removed to serve as biosynthetic precursors, they are replenished by anaplerotic reactions.
- The reactions concerned to replenish or to fill up the intermediates of citric acid cycle are called anaplerotic reactions or anaplerosis (Greek : fill up).
- Under normal circumstances, the reactions by which cycle intermediates are siphoned off into other pathways and those by which they are replenished are in dynamic balance, so that the concentrations of the citric acid cycle intermediates remain almost constant.

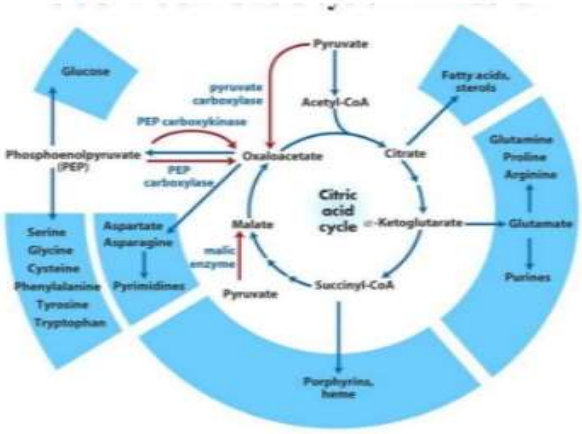
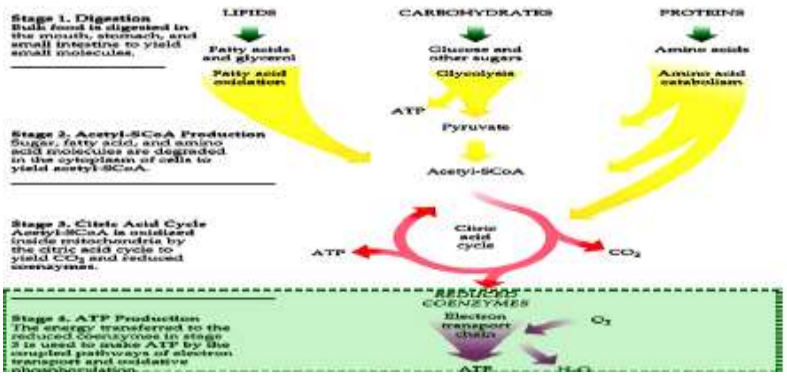


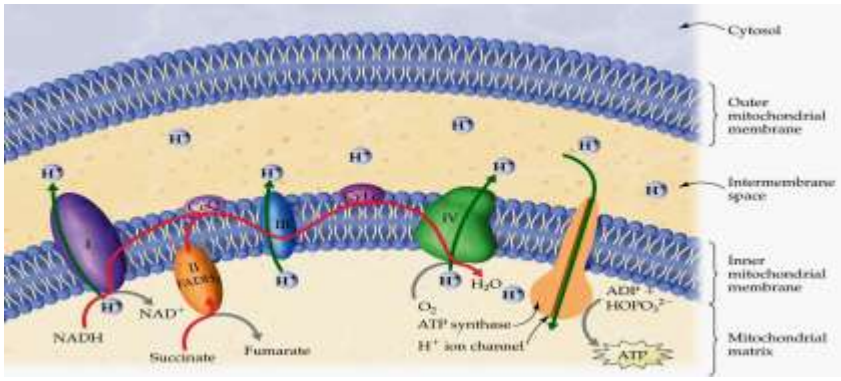
Fig. Role of citric acid cycle in anabolism.
Intermediates of the citric acid cycle are drawn off as precursors in many biosynthetic pathways. Shown in red are four anaplerotic reactions that replenish depleted cycle intermediates.

STAGE 4: ELECTRON TRANSPORT CHAIN AND OXIDATIVE mPHOSPHORYLATION

Overview of oxidative phosphorylation. The electron transport chain forms a proton gradient across the inner mitochondrial membrane, which drives the synthesis of ATP via chemiosmosis



The electron transport chain and oxidative phosphorylation use the reducing power present in NADH and FADH2 to make ATP. The electron transport chain is a group of proteins and other molecules embedded in the inner mitochondrial membrane.

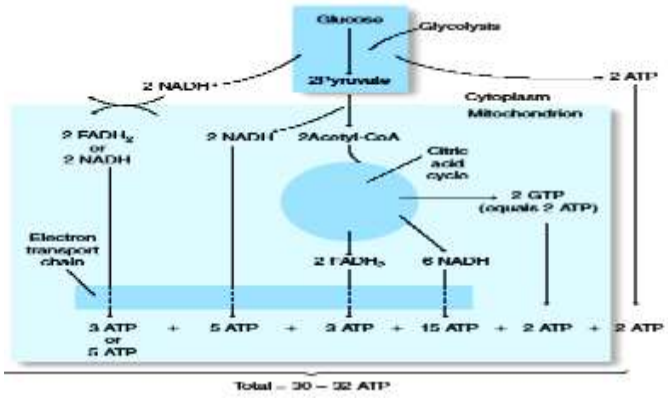


Electron transport involves four enzyme complexes held in fixed positions within the inner membrane of mitochondria and two e– carriers that move from one complex to another. Important electron acceptors are:

1. Various cyctochromes that contain heme groups in which the iron cycles between Fe2+ and Fe3+,
2. Proteins with iron-sulfur groups in which the iron also cycles between Fe2+ and Fe3+

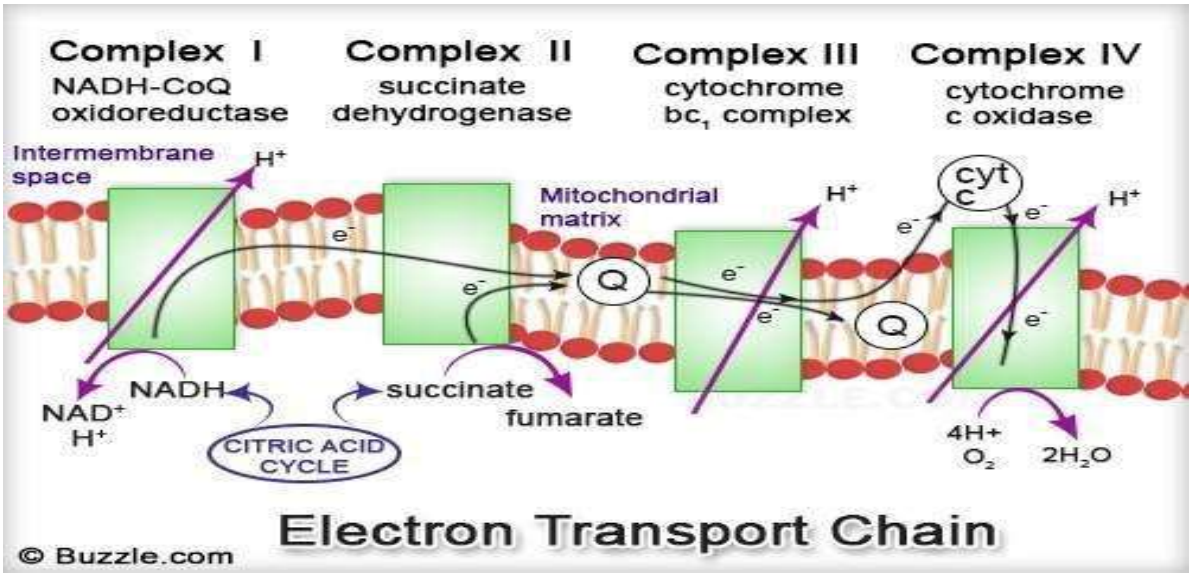
The goal of ETP is to break down NADH and $FADH_2$, pumping H^+ into the outer compartment of the mitochondria resulting to synthesis of more ATP. In this reaction, the ETC creates a gradient which is used to produce ATP. Electron Transport Phosphorylation typically produces 32 ATP's. ATP is generated as H+ moves down its concentration gradient through a special enzyme called ATP synthase. How much ATP is produced from the oxidation of each of the co-enzymes? On average…

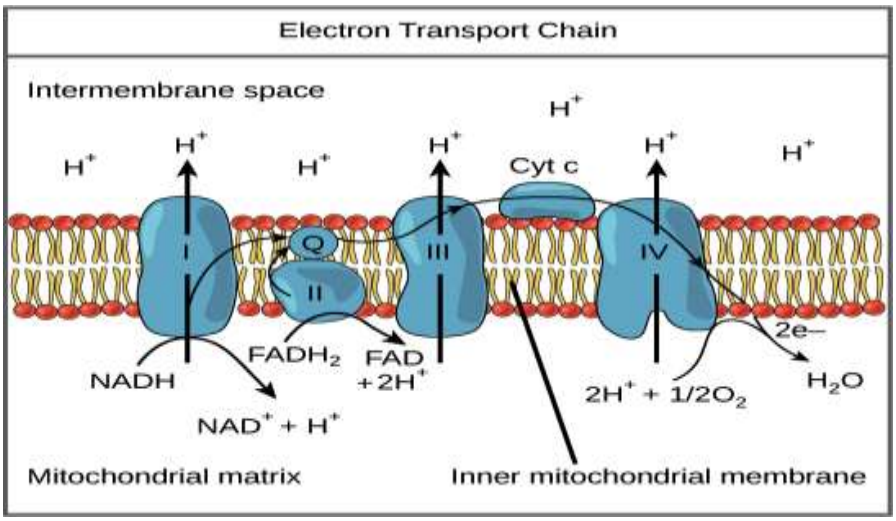
- Each NADH produces **2.5 ATPs**
- Each FADH2 produces **1.5 ATPs**



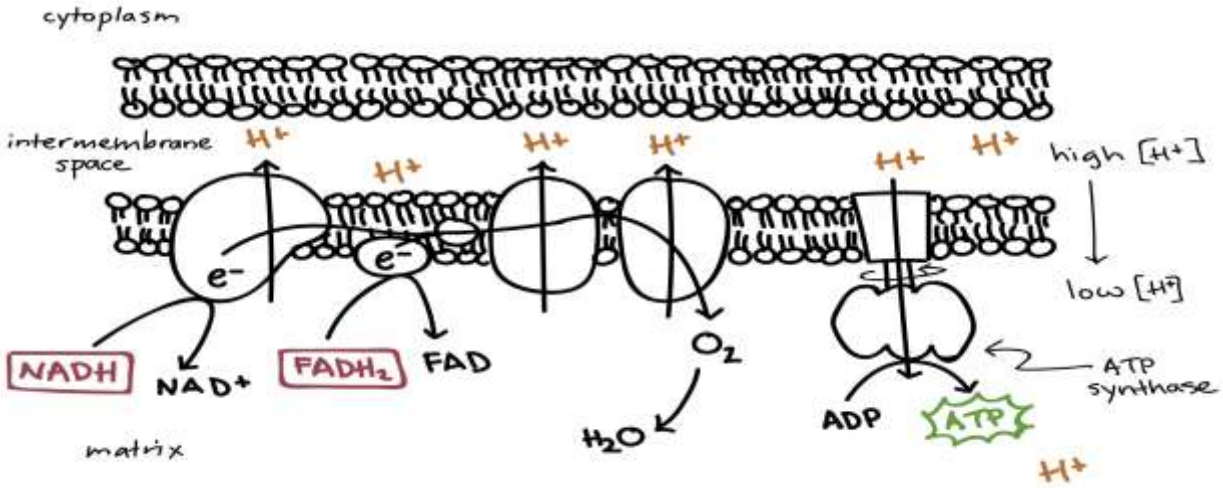
The **electron transport chain** is a series of proteins and organic molecules found in the inner membrane of the mitochondria. Electrons are passed from one member of the transport chain to another in a series of redox reactions. Energy released in these reactions is captured as a proton gradient, which is then used to make ATP in a process called **chemiosmosis**. Together, the electron transport chain and chemiosmosis make up **oxidative phosphorylation**. The key steps of this process, shown in simplified form in the diagram above, include:

- **Delivery of electrons by NADH and $FADH_2$.** Reduced electron carriers (NADH and $FADH_2$ from other steps of cellular respiration transfer their electrons to molecules near the beginning of the transport chain. In the process, they turn back into NAD^+ and FAD, which can be reused in other steps of cellular respiration.
- **Electron transfer and proton pumping.** As electrons are passed down the chain, they move from a higher to a lower energy level, releasing energy. Some of the energy is used to pump H^+, moving them out of the matrix and into the intermembrane space. This pumping establishes an electrochemical gradient.
- **Splitting of oxygen to form water.** At the end of the electron transport chain, electrons are transferred to molecular oxygen, which splits in half and takes up H^+ to form water.
- **Gradient-driven synthesis of ATP.** As H^+ ions flow down their gradient and back into the matrix, they pass through an enzyme called ATP synthase, which harnesses the flow of protons to synthesize ATP





Combination of electron transport chain and oxidative phosphorylation is seen below



Components of ETC

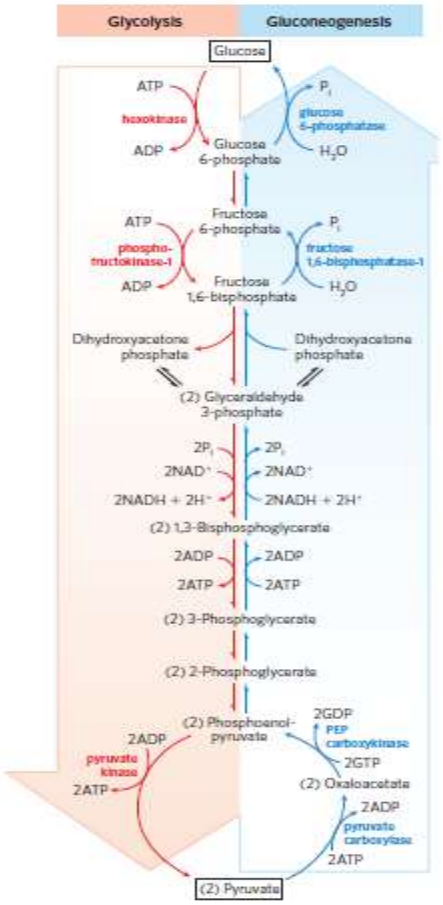
Complex	Name	No. of Proteins	Prosthetic Groups
Complex I	NADH Dehydrogenase	46	FMN, 9 Fe-S cntrs.
Complex II	Succinate-CoQ Reductase	5	FAD, cyt b_{560}, 3 Fe-S cntrs.
Complex III	CoQ-cyt c Reductase	11	cyt b_H, cyt b_L, cyt c_1, Fe-S_{Rieske}
Complex IV	Cytochrome Oxidase	13	cyt a, cyt a_3, Cu_A, Cu_B

GLUCONEOGENESIS

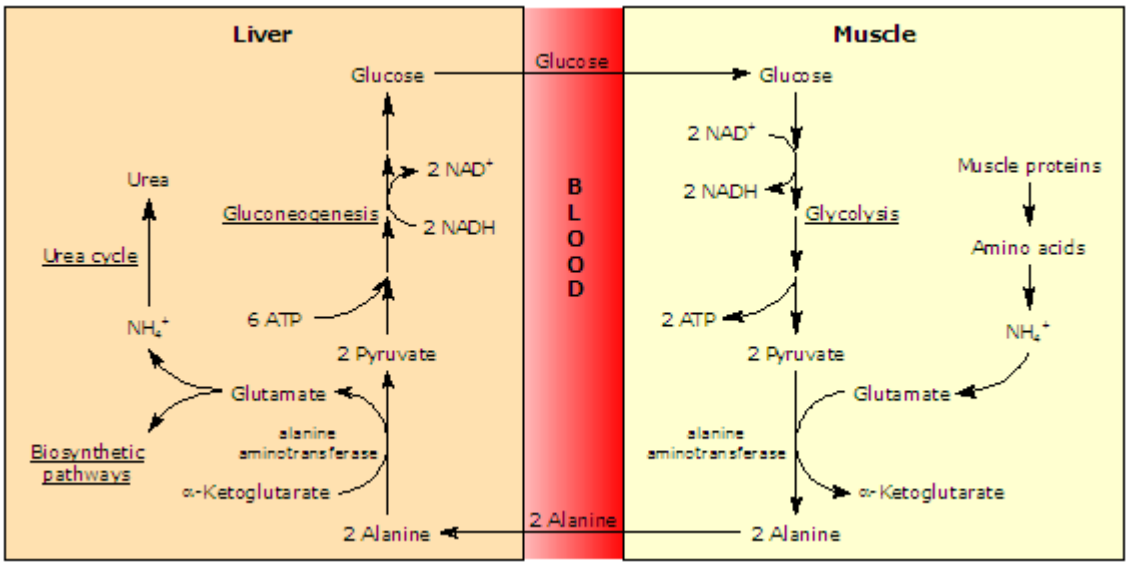
Gluconeogenesis is a metabolic pathway that results in the generation of glucose from non-carbohydrate carbon substrates such as lactate, glycerol, and glucogenic amino acids. This is the way in which the body meets its needs of glucose when carbohydrate is not available in sufficient amounts from the diet. The body then converts non glucose substances into glucose. Gluconeogenesis mainly occurs in the liver. The kidneys have limited capacity for gluconeogenesis. Gluconeogenesis rate is high under the following conditions

- Increased on high protein diets.
- During exercise when large amounts of lactic and pyruvic acids escape from the working muscles and there is no need to replenish the muscle glycogen supply therefore the liver acts to return to them sources of energy lost by the muscles.
- During starvation, from breakdown of amino acids of tissue protein
- In diabetic states when there is low blood glucose in the cell.

Overview: Gluconeogenesis is Anti-parallel to Glycolysis.

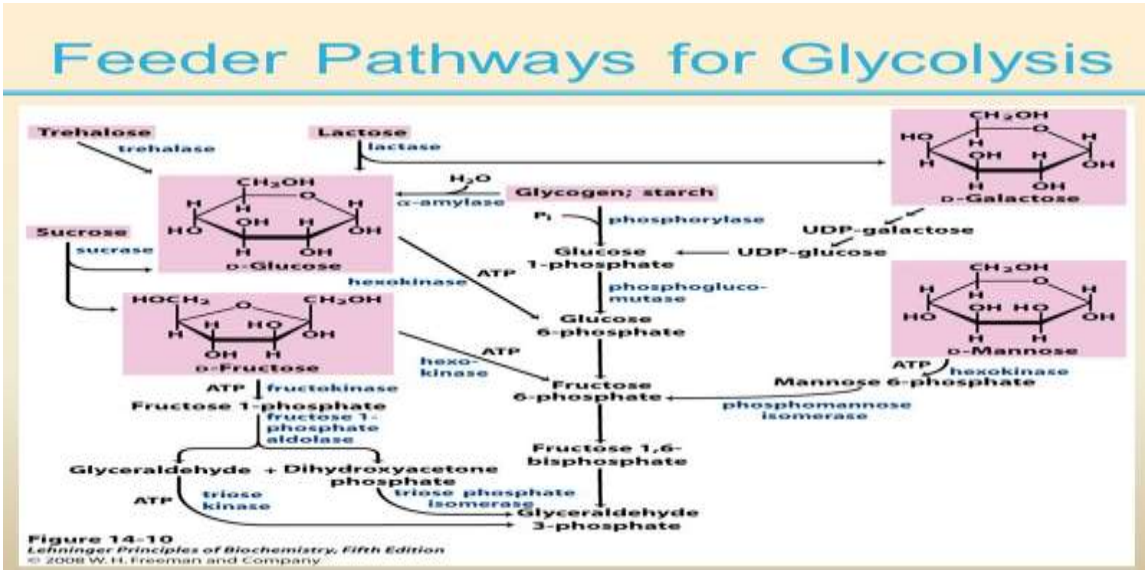


Involvement of alanine in gluconeogenesis is seen in the alanine cycle below and is similar to the cori cycle only that the substrate is alanine not lactate

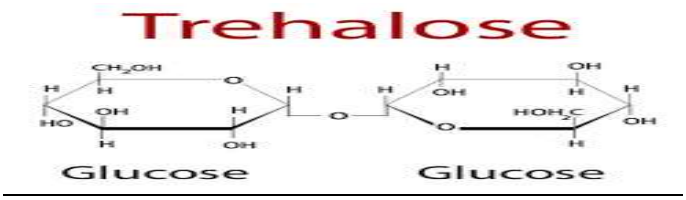


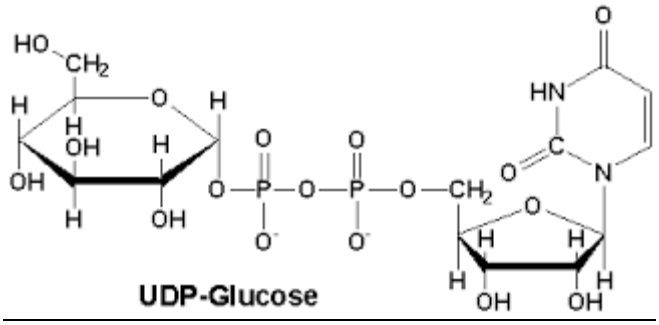
FEEDER PATHWAYS FOR GLYCOLYSIS

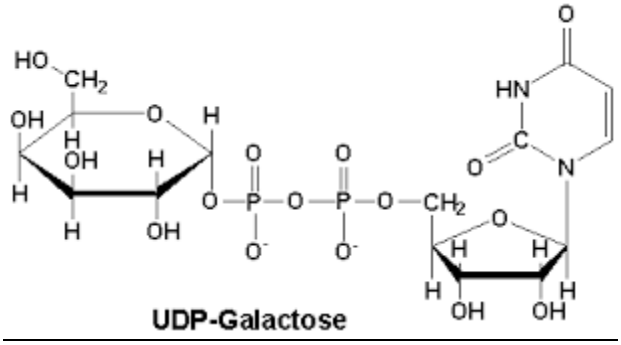
In addition to glucose, many other carbohydrates ultimately enter the glycolytic pathway to undergo energy-yielding degradation. The most significant are the storage polysaccharides glycogen and starch, the disaccharides maltose, lactose, trehalose, and sucrose, and the monosaccharides fructose, mannose, and galactose. We shall now consider the pathways by which these carbohydrates can enter glycolysis.



Structures







Hormonal Regulation of carbohydrates Metabolism

Blood glucose levels vary widely over the course of a day as periods of food consumption alternate with periods of fasting. **Insulin** and **glucagon** are the two hormones primarily responsible for maintaining homeostasis of blood glucose levels. Additional regulation is mediated by the thyroid hormones.

Regulation of Blood Glucose Levels: Insulin and Glucagon

Cells of the body require nutrients in order to function. These nutrients are obtained through feeding. In order to manage nutrient intake, storage of excess intake, and utilization of reserves when necessary, the body uses hormones to moderate these processes.

INSULIN

It is produced by the beta cells of the pancreas, which are stimulated to release insulin as blood glucose levels rise (for example, after a meal is consumed). Insulin lowers blood glucose levels by enhancing the rate of glucose uptake and utilization by target cells, which use glucose for ATP production. It also stimulates the liver to convert glucose to glycogen, which is then stored by cells for later use. As insulin binds to its target cell via **insulin receptors** and signal transduction, it triggers the cell to incorporate glucose transport proteins into its membrane. This allows glucose to enter the cell, where it can be used as an energy source. These actions mediated by insulin cause blood glucose concentrations to fall, called a **hypoglycemic**, or "low sugar" effect, which inhibits further insulin release from beta cells through a negative feedback. Impaired insulin function can lead to a condition called **diabetes mellitus**, which has many effects on the body. Diabetes mellitus can be caused by low levels of insulin production by the beta cells of the pancreas, or by reduced sensitivity of tissue cells to insulin. This prevents glucose from being absorbed by cells, causing high levels of blood glucose, or **hyperglycemia** (high sugar). High blood glucose levels make it difficult for the kidneys to recover all the glucose from urine, resulting in glucose being lost in urine. High glucose levels also result in less water being reabsorbed by the kidneys, causing high amounts of urine to be produced; this may result in dehydration. Over time, high blood glucose levels can cause nerve damage to the eyes and peripheral body tissues, as well as damage to the kidneys and cardiovascular system. Over secretion of insulin can cause *hypoglycemia,* low blood glucose levels. This causes insufficient glucose availability to cells, often leading to muscle weakness. It can sometimes cause unconsciousness or death if left untreated. Diabetes mellitus can cause a wide range of symptoms, including nausea, vomiting, blurred vision, lethargy, a frequency in urination, and high levels of glucose in the urine.

GLUCAGON

When blood glucose levels decline below normal levels, for example between meals or when glucose is utilized during exercise, the hormone **glucagon** is released from the pancreas. Glucagon *raises blood glucose levels*, eliciting what is called a **hyperglycemic effect**, by stimulating the breakdown of glycogen to glucose in skeletal muscle cells and liver cells in a process called **glycogenolysis**. Glucose can then be utilized as energy by muscle cells and released into circulation by the liver cells. Glucagon also stimulates absorption of amino acids from the blood by the liver, which then converts them to

glucose. This process of glucose synthesis is called **gluconeogenesis.** Rising blood glucose levels inhibit further glucagon release by the pancreas via a negative feedback mechanism.

In this way, insulin and glucagon work together to maintain homeostatic glucose levels.

Summary

Therefore as the levels of glucose in the blood rise, insulin stimulates the cells to take up more glucose and signals the liver to convert the excess glucose to glycogen, a form in which it can be stored for later use. When the levels of glucose in the blood fall, glucagon responds by stimulating the breakdown of glycogen into glucose and signals the production of additional glucose from amino acids.

HEXOSE MONOPHOSPHATE SHUNT (PENTOSE PHOSPHATE PATHWAY)

The **Hexose MonoPhosphate Shunt** is also known as "***Pentose phosphate Pathway***" (PPP). This is an *alternative Glucose oxidation pathway*. The *hexose monophosphate pathway* is used for production of *NADPH from NADP*$^+$. The NADPH is required for *biosynthetic reactions* such as fatty acid synthesis, cholesterol synthesis, drug reduction, and as a cofactor for some non-synthetic enzymatic reactions. In addition, this pathway is used for the production of ribose for nucleotide and nucleic acid synthesis. The hexose monophosphate shunt also allows the entry of some carbohydrates into the glycolytic pathway (especially ribose, but also some others), and therefore acts as a connection route between different pathways.

- Glycolysis – Glucose Catabolic Pathway
- Citric acid cycle : Central metabolic cycle and its Significance

Steroidogenic tissues, red blood cells, and the liver are the major sites of hexose monophosphate pathway. Muscle has small amounts of some of the **Hexose MonoPhosphate Shunt** enzymes, because it has little need for synthetic reactions, and therefore, little need for NADPH. The muscle, however, like all tissues, needs to be able to synthesize Ribose in order to make nucleotides and nucleic acids. The pentose phosphate pathway (also called "Phosphogluconate pathway" or "Hexose monophosphate Shunt") occurs in the cytoplasm. It is a source of NADPH and ribose-5-Phosphate for nucleic acid biosynthesis. It has an oxidative phase (NADPH generation) and a non-oxidative (non-oxidative sugar interconversion phase).

Phases of Hexose MonoPhosphate Shunt:

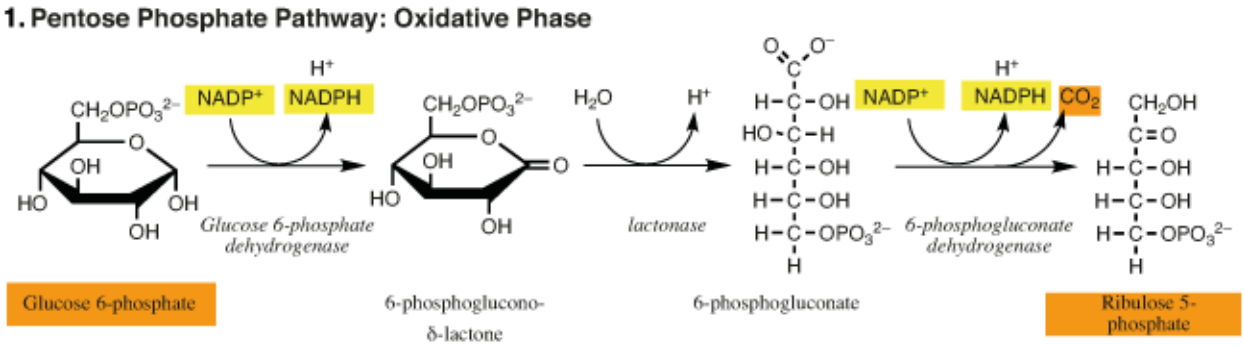
The pentose phosphate pathway occurs in the cytosol and can be divided into two phases:

- **Oxidative phase:** it generates NADPH.
- **Non-oxidative phase:** synthesize pentose-phosphate and other phosphate monosaccharides.

Oxidative phase:

The oxidative portion of HMP shunt consists of 3 reactions that lead to formation of Ribulose-5-Phosphate, Carbon dioxide and 2 molecules of NADPH, for each molecule of Glucose-6-Phosphate oxidized.

During oxidative phase, from glucose-6-phosphate obtained by phosphorylation of the free glucose, NADPH is released in addition to a pentose, ribulose 5-phosphate, hence the reason why this pathway is referred to as the "the Pentose Monophosphate Pathway".



Step 1: Dehydrogenation of Glucose – 6- Phosphate:

Glucose-6-Phosphate is converted into "*6-Phosphogluconate*" in the presence of the enzyme, *Glc-6-Phosphate dehydrogenase*. In this reaction NADP+ act as a coenzyme.

- The first reaction is the oxidation of glucose 6-phosphate, carried out by the enzyme glucose-6-phosphate dehydrogenase. In this first step the C1 group is dehydrogenated to give a carboxyl group, which, when next to the C5 forms a lactone, i.e. an ester intramolecularly.

- It is here that two free hydrogen ions (proton) and two electrons are transferred to $NADP^+$ which acts as electron acceptor being reduced to form the first molecule of NADPH; the remaining proton is released in the middle.

Step 2: Formation of Ribulose-5-Phosphate:

6-Phospho Gluconate is converted into *Ribulose-5-Phosphate* by eliminating CO_2 from Carbon one of Glucose, in the presence of the enzyme *6-Phosphogluconate dehydrogenase*.

- The Lactone is hydrolysed and by the action of the lactonase, a free acid 6-phosphogluconate is obtained.
- Then, the latter becomes ribulose-5-phosphate by the action of 6-phosphogluconate dehydrogenase.
- Here NADPH second molecule is obtained, in addition to the release of a molecule of CO_2 because of the oxidative decarboxylation.
- Finally, the enzyme pentose-5-phosphate isomerase, by an intermediary enediol, isomerizes the ribulose 5-phosphate and converts it to ribose-5-phosphate through the transformation of the group ketose into aldose.
- This latter reaction prepares a central component nucleotide synthesis for the biosynthesis of RNA, DNA and nucleotide cofactors. At the same time, it carries out the transition to non-oxidative metabolic phase of the pentose phosphate pathway.

It ends thus obtaining two NADPH molecules which, besides their use in reductive biosynthesis, is also responsible for maintaining a reducing environment within the cell. The **general reaction** of this first phase is:

Glucose-6-phosphate + 2 $NADP^+$ + H_2O

→ ribulose-5-phophate + 2 NADPH + 2 H^+ + CO_2

Non-oxidative phase:

The non-oxidative reaction of pentose phosphate pathway catalyzes the inter-conversion of 3, 4, 5 and 7- carbon sugars. The **non-oxidative phase** of the pentose phosphate pathway is initiated when the cell needs more NADPH than ribose-5-phosphate. In this second process are a complex sequence of reactions that finally form **glyceraldehyde-3-phosphate** and **fructose 6-phosphate** from C5 sugar, which can go directly to glycolysis.

Isomerization of Ribulose-5-Phosphate to Ribose-5-Phosphate:

Ribulose-5-Phosphate is isomerised into *Ribose-5-Phosphate* by the enzyme "*Ribulose-5-phosphate isomerase*". This enables us to eliminate excess ribose-5-phosphate by transforming it to intermediates of glycolysis.

Epimerization of ribulose-5-P into Xylulose-5-P:

Ribulose-5-Phosphate is converted into *Xylulose-5-Phosphate*; in the presence of the enzyme "*Ribulose-5-phosphate epimerase*" this reaction is an Epimerization. This phase includes a series of **reversible reactions**, the direction of which depends on the availability of substrate. Also the isomerization of ribulose-5-phosphate to ribose-5-phosphate is also reversible.

Transketolation:

Ribose-5-Phosphate then reacts with Xylulose-5-Phosphate to give *Sedoheptulose-7-Phosphate* and *Glyceraldehyde-3-Phosphate* through the action of enzyme *Transketolase*. Here TPP (Thiamine Pyrophosphate) acts as a Co-enzyme. In this reaction the first and second carbons of Xylulose-5-Phosphate are simply shifted onto the *Ribose-5-Phosphate* . Simply this is a 2 carbon shifting mechanism.

This will convert *Ribose-5-phosphate* into *sedoheptulose-7-phosphate* by transferring 2 carbon unit of the ketose (Xylulose-5-Phosphate) to an aldose, and will also produce *glyceraldehyde-3-phosphate*.

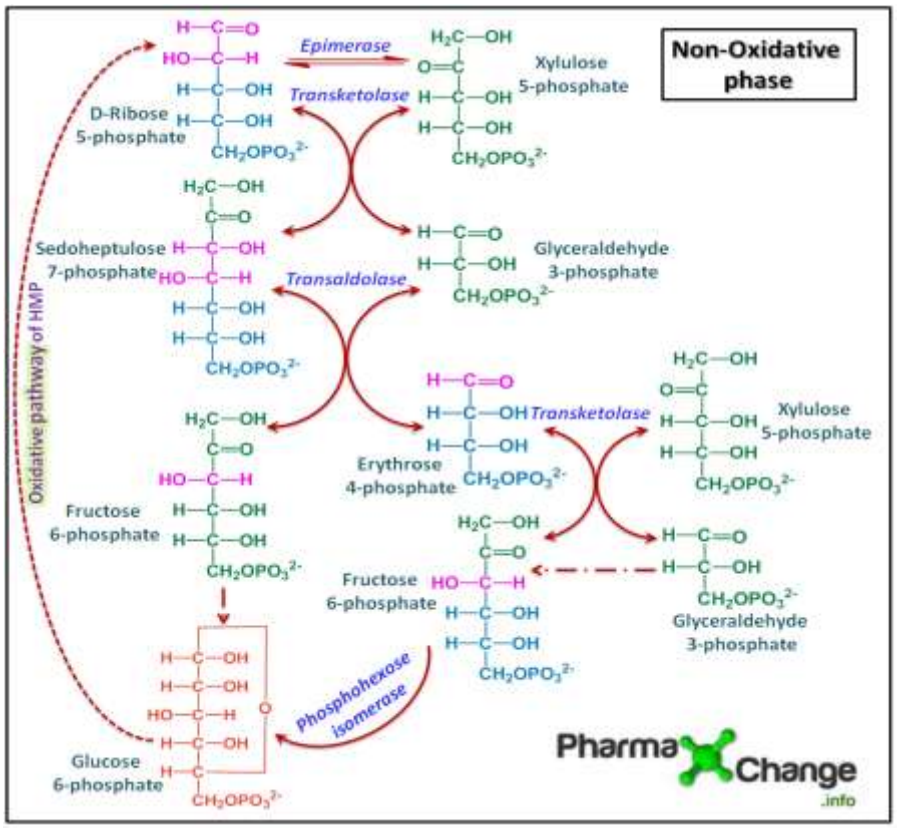
Transaldolation:

When *Sedoheptulose-7-Phosphate* reacts with *Glyceraldehyde-3-Phosphate*; it gives 4 carbon compound – *Erythrose-4-Phosphate* and 6 carbon compound *Fructose-6-Phosphate*. This reaction is catalyzed by the enzyme *Transaldolase*. In this reaction first 3 carbons of *Sedoheptulose-7-Phosphate* are shifted to the aldehyde group of the *Glycerldehyde-3-Phosphate* forming a fructose-6-phosphate molecule and an *Erythrose-4-phosphate*. The fructose-5-phosphate can then be isomerized to give glucose-6-phosphate that will be used to generate more NADPH in the HMP shunt through the action of phosphohexose isomerase enzyme.

Transketolation:

Erythrose-4-Phosphate reacts with *Xylulose-5-Phosphate* to give another molecule of Fructose-6-phosphate and *Glyceraldehyde-3-Phosphate* both are intermediates of glycolysis. This reaction is catalyzed by a "*Transketolase*" that is a TPP dependent

enzyme. This stage of the route will connect the metabolic processes that generate NADPH with those originating NADH/ATP. Furthermore, glyceraldehyde-3-phosphate and fructose 6-phosphate can be channeled into the glycolysis or in gluconeogenesis to form a new glucose synthesis depending on the bodies energy needs.



Overall Pathway:

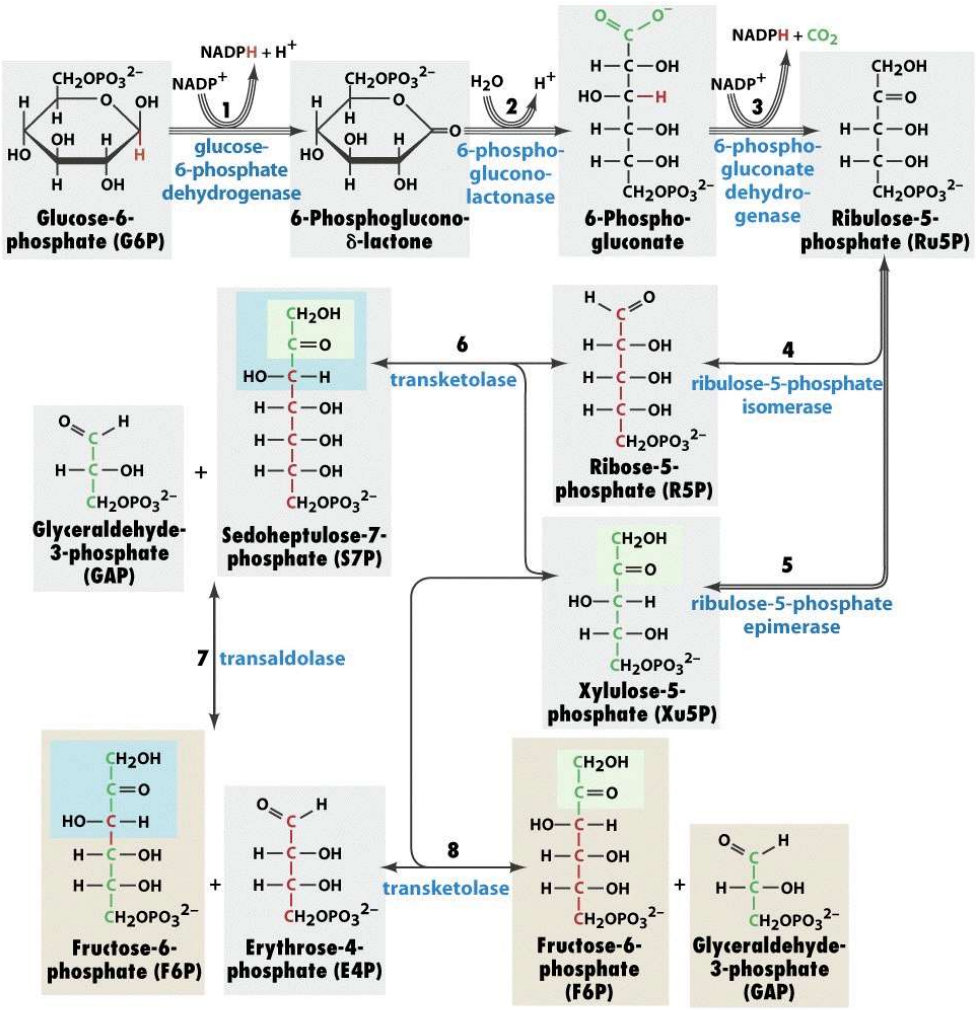


Figure 14-30 Fundamentals of Biochemistry, 2/e

Significance of HMP Shunt:

- Hexose MonoPhosphate Shunt producing Biochemical reductant NADPH + H^+. This reductant participating in reductive anabolic pathway. Especially in Fatty acid Biosynthesis
- NADPH involved in Glutathione Reductase catalysis as coenzyme. This enzyme neutralizes the superoxide and hydroxyl radicals from hydroxyl peroxide molecules and acts as an antioxidant preventing oxidative damage.
- The NADPH is one of the important coenzyme for liver microsomal, Cytochrome-P450 Mono-Oxygenase enzyme system. This is the major pathway for the hydroxylation of Aromatic and Aliphatic compounds such as Steroid alcohols and many drugs.

- In Phagocytosis mechanism NADPH + H^+ is very important in Respiratory Burst and hence required by the immune system to phagocytically destroy microorganisms through action of immune cells such as macrophages.
- Ribose-5-Phosphate is the precursor molecule for nucleotide synthesis. The concentration of Ribose-5-Phosphate is optimized by the enzyme Glucose-6-Phosphate dehydrogenase in HMP shunt.
- In the Hexose MonoPhosphate Shunt Pathway, few molecules of Glycolytic intermediates are produced these are directly involves in Glycolysis. The molecules are Glyceraldehyde-3-Phosphate and Fructose-6-Phosphate.

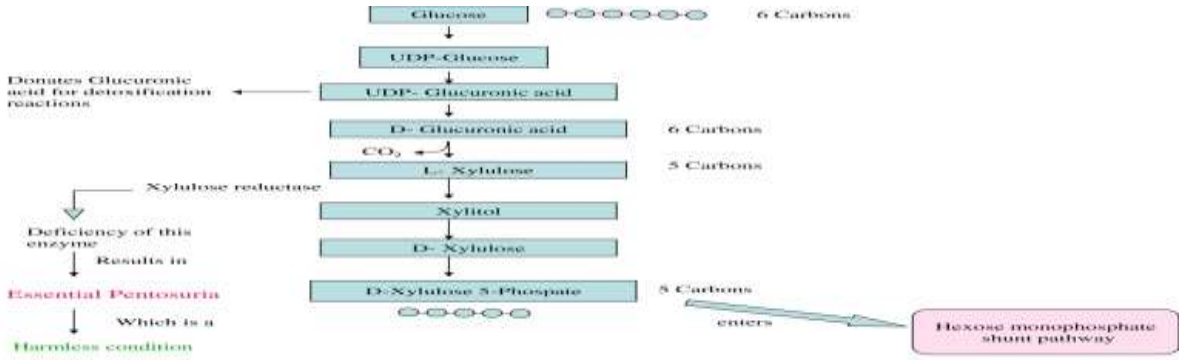
URONIC ACID PATHWAY

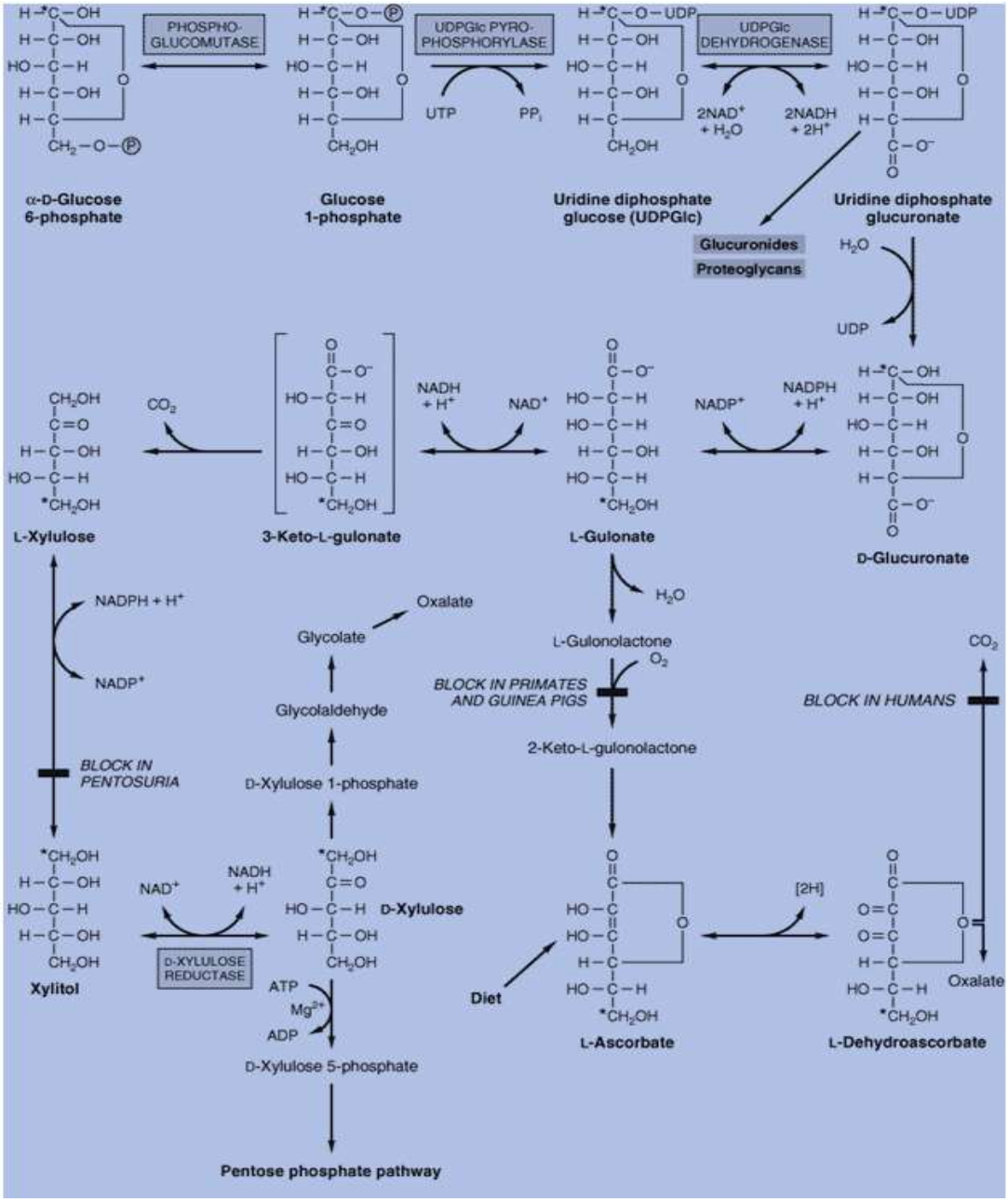
The Uronic acid pathway is an alternative pathway for the oxidation of glucose that does not provide a means of producing ATP but is utilized for the generation of the activate form of glucoronate (UDP-glucoronate). This is mainly used for the detoxification of forign chemicals and for the synthesis of mucopolysaccahrides. In some other animals other than man it is also a pathway that can lead to the production of vitamin C. The excess glucuronate produced from this pathway can also be converted to xylulose-5-phosphate that can be metabolized through the HMP shunt.

Steps of this pathway

1. Glucose is usually phosphorylated to glucose-6-phosphate through the action of hexokinase.
2. Glucose-6-phosphate is then isomerized to glucose-1-phosphate and this catalyzed by phosphoglucomutase
3. Glucose-1-phosphate then reacts with uridine triphosphate to give uridine diphosphate glucose (UDP-glucose) this reaction is catalyzed by UDP glucose pyrophosphorylase
4. The next thing is to form D-Glucuronic acid. UDP-glucose is oxidized at carbon 6 by NAD^+ dependent UDP- glucose dehydrogenase in a two step reaction to yield UDP-glucuronate
5. UDP-glucuronate is the hydrolyzed to form D-glucuronic acid.

The glucuronate (Glucuronic acid) can be incorporated into proteoglycans and glycosaminoglycans or also synthesis of vitamin C in some animals as well as L-Gulonic acid (gulonate) that in humans can be used to synthesis xylulose-5-phosphate


Glucose
6 Carbons
UDP-Glucose
Donates Glucuronic acid for detoxification reactions
UDP- Glucuronic acid
D- Glucuronic acid
6 Carbons
CO_2
L- Xylulose
5 Carbons
Xylulose reductase
Xylitol
Deficiency of this enzyme
Results in
D- Xylulose
Essential Pentosuria
Which is a
Harmless condition
D-Xylulose 5-Phospate
5 Carbons
enters
Hexose monophosphate shunt pathway

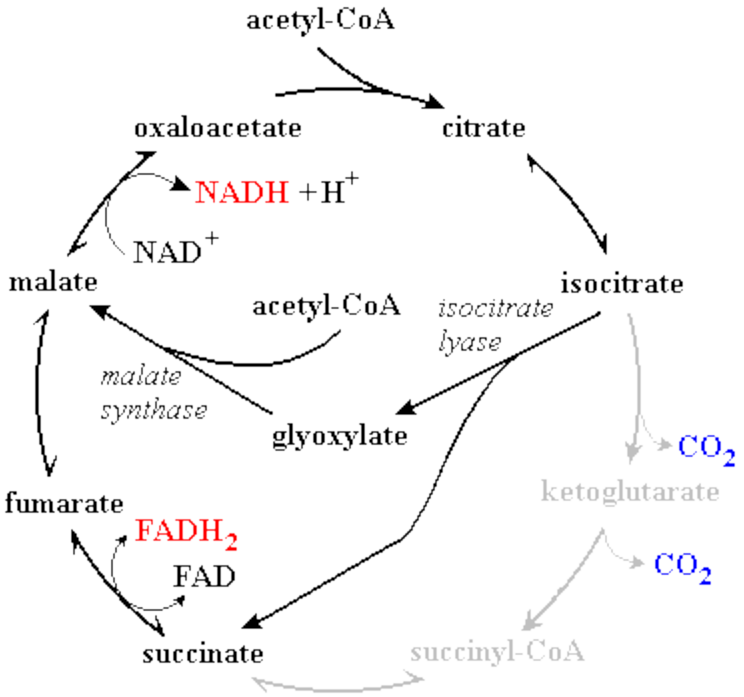

PHOSPHO-GLUCOMUTASE
UDPGlc PYRO-PHOSPHORYLASE
UTP
PP_i
UDPGlc DEHYDROGENASE
$2NAD^+ + H_2O$
$2NADH + 2H^+$
α-D-Glucose 6-phosphate
Glucose 1-phosphate
Uridine diphosphate glucose (UDPGlc)
Uridine diphosphate glucuronate
Glucuronides
Proteoglycans
H_2O
UDP
CO_2
NADH + H^+
NAD^+
$NADP^+$
NADPH + H^+
L-Xylulose
3-Keto-L-gulonate
L-Gulonate
D-Glucuronate
H_2O
L-Gulonolactone
O_2
BLOCK IN PRIMATES AND GUINEA PIGS
2-Keto-L-gulonolactone
BLOCK IN HUMANS
CO_2
Oxalate
Glycolate
Glycolaldehyde
D-Xylulose 1-phosphate
BLOCK IN PENTOSURIA
D-Xylulose
Xylitol
D-XYLULOSE REDUCTASE
ATP
Mg^{2+}
ADP
D-Xylulose 5-phosphate
Diet
[2H]
L-Ascorbate
L-Dehydroascorbate
Oxalate
Pentose phosphate pathway

Clinical significance of uronic pathway

1. The glucuronic acid produced from this pathway is important for detoxification of foreign compounds and drugs. The acid covalently attaches to this toxins during detoxification and since the acid is polar it makes the toxins soluble and readily excretable. These toxins can include bilirubin, certain hormones and drugs. The elimination of bilirubin helps to reduce jaundice
2. The acid is also utilized in the synthesis of mucopolysaccharides (glycosaminoglycans) eg; hyaluronic acid (found in most connective tissue to add fluidity and lubrication) and heparin (anti-coagulant).

GLYOXYLATE CYCLE

Glyoxylate cycle occurs in some microorganisms when acetate is sole source of carbon. This cycle has two unique enzyme- **isocitrate lyase** and **malate synthase** which bypass some of the reaction of TCA cycle.



Glyoxylate cycle is absent in higher organisms. At first acetylCoA is produced from acetate or by oxidation of higher fatty acids and not pyruvate. AcetylCoA then enter into TCA cycle and condensed with oxaloacetate to form citrate. Citrate then isomerized to isocitrate. Isocitrate lyase bypasses the TCA cycle by splitting isocitrate into **succinate** and **glycoxylate**. Succinate is then metabolized by TCA whereas Glycoxylate condenses with another molecule of acetylCoA to form malate in the

presence of malate synthase. Malate is converted into oxaloacetate by the enzyme malate dehydrogenase and the cycle continues when needed by the system.

Significance of Glyoxylate cycle

- It is a bypass reaction of TCA cycle
- It occurs in bacteria when they are cultured in acetate rich carbon source.
- When Higher fatty acids are oxidized into acetylCoA without forming pyruvate, then acetylCoA enters into glyoxylate cycle

GLYCOGEN DEGRADATION

Glycogen Phosphorylase **GP** catalyzes breakdown of glycogen into Glucose-1-Phosphate The reaction that produces G-1-P from glycogen is a phosphorylation but the phosphate does NOT come from ATP. Since ATP is NOT used to add phosphate on G-1-P, the reaction saves the cell of much needed energy since glycogen breakdown only occurs during times of low energy and reduced glucose supply. In addition, the phosphate on the G-1-P helps to maintain the molecule in the cell. Glycogen phosphorylase will only act on non-reducing ends of a glycogen chain that are at least 5-8 glucoses away from a branch point. A second enzyme, Glycogen Debranching Enzyme (**GDE**), is therefore needed to convert alpha (1-6) branches to alpha(1-4) branches. **GDE** acts on glycogen branches that have reached their limit of hydrolysis with **GP**. It acts to transfer a trisaccharide from a 1,6 branch onto an adjacent 1,4 branch, leaving a single glucose at the 1,6 branch. Note that the enzyme also catalyzes the hydrolysis of the remaining glucose at the 1,6 branch point. Thus, the breakdown products from glycogen are G-1-P and glucose (mostly G1P, however). Glucose can, of course, be converted to Glucose-6-Phosphate (G-6-P) as the first step in glycolysis by either hexokinase or glucokinase. G-1-P can also be converted to G-6-P by action of an enzyme called Phosphoglucomutase. Note that the mechanism of action of phosphoglucomutase involves formation of a transient intermediate of glucose-1,6-bisphosphate before the G-6-P is produced. This reaction is readily reversible, allowing G-6-P and G-1-P to be interconverted as the concentration of one or the other increases. This is important, because phosphoglucomutase is needed to form G-1-P for glycogen biosynthesis.

Regulation of Glycogen Phosphorylase

In order to avoid a futile cycle of glycogen synthesis and breakdown simultaneously, cells have evolved an elaborate set of controls that ensure only one pathway is primarily active at a time. Regulation occurs on the enzymes glycogen phosphorylase and glycogen synthase, and involves allosterism, covalent modification of enzymes and, ultimately, hormonal control.

Allosteric factors - ATP, G-6-P, AMP.

Glycogen phosphorylase is regulated by both allosteric factors and by covalent modification (phosphorylation). Its regulation is consistent with the energy needs of the cell. High energy substrates (ATP, G-6-P, glucose) inhibit GP, while low energy substrates (AMP, others) activate it. The enzyme uses a cofactor, pyridoxal phosphate (PLP). Regulation of glycogen phosphorylase varies a bit, depending on the tissue in which it is found. For example, the liver makes glucose for the body, but muscles do not and depend on the liver for much of their glucose. Regulation of glycogen breakdown in these tissues is adjusted accordingly, as will be seen. **C**alcium activates glycogen breakdown.

GLYCOGEN BIOSYNTHESIS

Glycogen is a polymer of glucose (up to 120,000 glucose residues) and is a primary carbohydrate storage form in animals. The polymer is composed of units of glucose linked alpha (1-4) with branches occurring alpha(1-6) approximately every 8-12 residues. The end of the molecule containing a free carbon number one on glucose is called a reducing end. The other ends are all called non-reducing ends. Glycogen provides an additional source of glucose besides that produced via gluconeogenesis. Because glycogen contains so many glucoses, it acts like a battery backup for the body,

providing a quick source of glucose when needed and providing a place to store excess glucose when glucose concentrations in the blood rise. The branching of glycogen is an important feature of the molecule metabolically as well. Since glycogen is broken down from the "ends" of the molecule, more branches translate to more ends, and more glucose that can be released at once. Liver and skeletal muscles are primary sites in the body where glycogen is found.

The anabolic pathway contrasting with glycogen breakdown is that of glycogen synthesis. Just as cells reciprocally regulate glycolysis and gluconeogenesis to prevent a futile cycle, so too do cells use reciprocal schemes to regulate glycogen breakdown and synthesis. Let us first consider the steps in glycogen synthesis.

1) Glycogen synthesis from glucose involves phosphorylation to form G-6-P, and isomerization to form G-1-P (using phosphoglucomutase common to glycogen breakdown). There is an energetic barrier to the direct incorporation of G-1-P into glycogen due to concentrations of factors that favor breakdown of glycogen under normal conditions over synthesis of glycogen. Cells provide a pathway around the glycogen synthesis barrier with the use of UTP. This is akin to the barrier of reversing Pyruvate to PEP in gluconeogenesis, which is overcome by going through oxaloacetate. The first reaction, catalyzed by **UDP-Glucose Pyrophosphorylase** (**UGPP**), converts G-1-P and UTP into uridine diphosphoglucose (UDPG).

G-1-P + UTP <=> UDPG + PPi

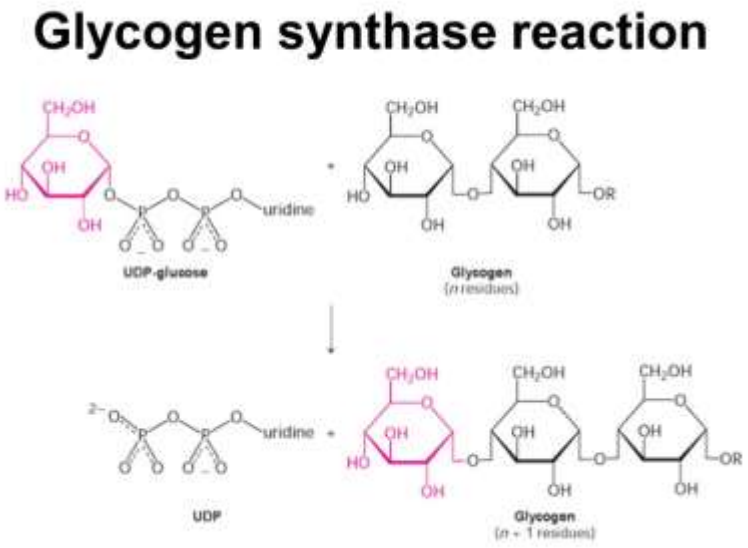
The high energy phosphate bonds of UTP make the formation of UDPG energetically favorable. In addition, note that the product on the right side include pyrophosphate. Pyrophosphate can readily be broken down to Pi + Pi by the enzyme pyrophosphatase (in a hydrolysis reaction). Breaking the PPi product down in this manner helps to pull the reaction even further to the right.

2) The second step of glycogen synthesis is catalyzed by the enzyme **Glycogen Synthase**. The reaction combines carbon #1 of the UDPG-derived glucose onto the carbon #4 of the non-reducing end of a glycogen chain. To form the familiar alpha (1,4) glycogen links. Another product of the reaction is UDP. This reaction too, is energetically favorable. The UDPG "side step" in glycogen synthesis thus uses the energy of UTP and UDP to make energetically favorable a reaction (addition of glucose to glycogen) that otherwise would not be. Thus by inputting energy via a side-stepping reaction, the cell manages to overcome a significant energy barrier. It is also worth noting in passing that Glycogen Synthase will only add glucose units from UDPG onto a preexisting glycogen chain that has at least four glucose residues. Linkage of the first

few glucose units to form the minimal "primer" needed for **glycogen synthase** recognition is catalyzed by a protein called **Glycogenin**, which attaches to the first glucose and catalyzes linkage of the first eight glucoses by alpha (1,4) bonds.

3) The characteristic alpha (1,6) branches of glycogen are the products of an enzyme with the name **Amylo-(1,4 to 1,6)-transglycosylase** also referred to as the **Branching Enzyme**. **Branching Enzyme** breaks alpha(1,4) chains and carries the broken chain to the carbon #6 and forms an alpha(1,6) linkage. A few structural parameters of the chain must be considered.

Branching enzyme prefers chains about 7 glucose residues in length from a branch at least 11 glucose residues long, and the new branch must be at least 4 residues from the previous one. Interestingly, hydrolysis of alpha (1,4) bonds releases more energy than hydrolysis of alpha (1,6) bonds. Thus branching, which breaks alpha (1,4) bonds and forms alpha(1,6) bonds is energetically favored. Remember that the reverse reaction, debranching (catalyzed by **GDE**) involves transfer of a trisaccharide (cleaved at alpha (1,4)) to another alpha(1,4) bond. This reaction is energetically neutral. The last glucose, linked alpha (1,6) from the original branch is cleaved to release glucose, which is also energetically favored. If instead, the reaction involved transfer of the entire branch, which would require an alpha (1,6) cleavage and an alpha(1,4) linkage, the reaction would not be energetically favored. Thus, puzzling reactions inside cells, such as formation of UDPG in glycogen synthesis and cleavage one glucose residue from a glycogen alpha (1,6) branch point followed by hydrolysis of the remaining glucose at the alpha(1,6) joint, have simple explanations as mechanisms for working around energy barriers.



Regulation of Glycogen Synthesis

High energy substrates (ATP, G-6-P, glucose) activate Glycogen synthase enzyme, while low energy substrates (AMP, others) deactivate the enzyme. Calcium inhibits glycogen synthesis.

INBORN ERRORS OF METABOLISM AND OTHER COMPLICATIONS OF METABOLISM

Inborn errors of metabolism are rare genetic (inherited) disorders in which the body cannot properly turn food into energy. The disorders are usually caused by defects in specific proteins (enzymes) that help break down (metabolize) parts of food.

A food product that is not broken down into energy can build up in the body and cause a wide range of symptoms. Several inborn errors of metabolism cause developmental delays or other medical problems if they are not controlled. The major classes of inborn errors of metabolism (IEM) and their characteristic clinical and biochemical features are described below.

There are many different types of inborn errors of metabolism.

Hereditary fructose intolerance

Hereditary fructose intolerance is a disorder in which a person lacks the protein (enzyme-Aldolase B) needed to break down fructose. Fructose is a fruit sugar that

naturally occurs in the body. Man-made fructose is used as a sweetener in many foods, including baby food and drinks. Hereditary fructose intolerance is a condition that affects a person's ability to digest the sugar fructose. Fructose is a simple sugar found primarily in fruits. Affected individuals develop signs and symptoms of the disorder in infancy when fruits, juices, or other foods containing fructose are introduced into the diet. After ingesting fructose, individuals with hereditary fructose intolerance may experience nausea, bloating, abdominal pain, diarrhea, vomiting, and low blood sugar (hypoglycemia). Affected infants may fail to grow and gain weight at the expected rate (failure to thrive).

Repeated ingestion of fructose-containing foods can lead to liver and kidney damage. The liver damage can result in a yellowing of the skin and whites of the eyes (jaundice), an enlarged liver (hepatomegaly), and chronic liver disease (cirrhosis). Continued exposure to fructose may result in seizures, coma, and ultimately death from liver and kidney failure. Due to the severity of symptoms experienced when fructose is ingested, most people with hereditary fructose intolerance develop a dislike for fruits, juices, and other foods containing fructose.

Hereditary fructose intolerance **should not be confused** with a condition called fructose malabsorption. In people with fructose malabsorption, the cells of the intestine cannot absorb fructose normally, leading to bloating, diarrhea or constipation, flatulence, and stomach pain. Fructose malabsorption is thought to affect approximately 40 percent of individuals in the Western hemisphere; its cause is unknown.

Causes

Mutations in the *ALDOB* gene cause hereditary fructose intolerance. The *ALDOB* gene provides instructions for making the aldolase B (Fructose-1-phosphate) enzyme. This enzyme is found primarily in the liver and is involved in the breakdown (metabolism) of fructose so this sugar can be used as energy. Aldolase B is responsible for the second step in the metabolism of fructose, which breaks down the molecule fructose-1-phosphate into other molecules called glyceraldehyde and dihydroxyacetone phosphate.

ALDOB gene mutations reduce the function of the enzyme, impairing its ability to metabolize fructose. A lack of functional aldolase B results in an accumulation of fructose-1-phosphate in liver cells. This buildup is toxic, resulting in the death of liver cells over time. Additionally, the breakdown products of fructose-1-phosphate are needed in the body to produce energy and to maintain blood sugar levels. The

combination of decreased cellular energy, low blood sugar, and liver cell death leads to the features of hereditary fructose intolerance.

If a person without aldolase B eats fructose or sucrose (cane or beet sugar, table sugar), complicated chemical changes occur in the body. The body cannot change its stored form of sugar (glycogen) into glucose. As a result, blood sugar falls and dangerous substances build up in the liver.

Hereditary fructose intolerance is inherited, which means it can be passed down through families. If both parents carry a nonworking copy of the adolase B gene, each of their children has a 25% (1 in 4) chance of being affected.

Galactosemia

Galactosemia, which means "galactose in the blood", is a rare inherited condition. People with galactosemia have problems digesting a type of sugar called galactose from the food they eat. Because they cannot break galactose down properly, it builds up in their blood. Galactose is found in milk and all foods that contain milk. Galactosemia occurs when an enzyme, called 'galactose-1-phosphate uridyl transferase' (GALT), is either missing or not working properly. Without enough GALT enzyme activity, galactose cannot be changed to glucose so it builds up in the blood in large amounts.

There are different types of galactosemia: classic galactosemia (also known as type I, is the most common and most severe form of the condition), galactosemia type II (also called galactokinase deficiency), and type III (also called galactose epimerase deficiency). The different types of galactosemia are caused by mutations in the *GALT*, *GALE*, and *GALK1* genes. The condition is inherited in an autosomal recessive fashion

If infants with classic galactosemia are not treated promptly with a low-galactose diet, life-threatening complications appear within a few days after birth. Affected infants typically develop feeding difficulties, a lack of energy, failure to grow and gain weight as expected (failure to thrive), yellowing of the skin and whites of the eyes (jaundice), liver damage, and abnormal bleeding. Other serious complications can include overwhelming bacterial infections (sepsis) and shock. Affected children are also at increased risk of developmental delay, clouding of the lens of the eye (cataract), speech difficulties, and intellectual disability. Females with classic galactosemia may experience reproductive problems caused by premature ovarian failure.

Pyruvate kinase deficiency

Pyruvate kinase deficiency is an inherited lack of the enzyme pyruvate kinase, which is used by red blood cells. Without this enzyme, red blood cells break down too easily, resulting in a low level of these cells (hemolytic anemia).

Pyruvate kinase deficiency (PKD) is passed down as an autosomal recessive trait. This means that a child must receive a non-working gene from each parent to develop the disorder.

There are many different types of enzyme-related defects of the red blood cell that can cause hemolytic anemia. PKD is the second most common cause, after glucose-6-phosphate dehydrogenase (G-6-P DH) deficiency.

PKD is found in people of all ethnic backgrounds. But, certain populations, such as the Amish, are more likely to develop the condition.

Pyruvate dehydrogenase deficiency

Pyruvate dehydrogenase deficiency is characterized by the buildup of a chemical called lactic acid in the body and a variety of neurological problems. Signs and symptoms of this condition usually first appear shortly after birth, and they can vary widely among affected individuals. The most common feature is a potentially life-threatening buildup of lactic acid (lactic acidosis), which can cause nausea, vomiting, severe breathing problems, and an abnormal heartbeat. People with pyruvate dehydrogenase deficiency usually have neurological problems as well. Most have delayed development of mental abilities and motor skills such as sitting and walking. Other neurological problems can include intellectual disability, seizures, weak muscle tone (hypotonia), poor coordination, and difficulty walking. Some affected individuals have abnormal brain structures, such as underdevelopment of the tissue connecting the left and right halves of the brain (corpus callosum), wasting away (atrophy) of the exterior part of the brain known as the cerebral cortex, or patches of damaged tissue (lesions) on some parts of the brain. Because of the severe health effects, many individuals with pyruvate dehydrogenase deficiency do not survive past childhood, although some may live into adolescence or adulthood.

The genes involved in pyruvate dehydrogenase deficiency each provide instructions for making a protein that is a component of a group of proteins called the pyruvate dehydrogenase complex. This complex plays an important role in the pathways that convert the energy from food into a form that cells can use. The pyruvate dehydrogenase complex converts a molecule called pyruvate, which is formed from the

breakdown of carbohydrates, into another molecule called acetyl-CoA. This conversion is essential to begin the series of chemical reactions that produce energy for cells.

The pyruvate dehydrogenase complex links glycolysis to the TCA cycle (also known as the Krebs cycle or the citric acid cycle). It is a large multi-enzyme complex composed of three enzymes involving five cofactors. The oxidation of pyruvate occurs in the mitochondria of the cell though pyruvate is made through glycolysis that occurs at the cytosol. Pyruvate is transported there via pyruvate translocase. Pyruvate dehydrogenase is a multi-enzyme complex that uses three enzymes:

1. E_1: Pyruvate dehydrogenase which uses thiamine pyrophosphate (TPP) as its prosthetic group.
2. E_2: Dihydrolipoyl transacetylase which uses lipoamide and coenzyme A (also known as coASH) as its prosthetic groups.
3. E_3: Dihydrolipoyl dehydrogenase which uses flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide (NAD^+) as its cofactors.

Other associated proteins control the activity of the complex: pyruvate dehydrogenase phosphatase turns on (activates) the complex, while pyruvate dehydrogenase kinase turns off (inhibits) the complex.

The E1 enzyme, also called pyruvate dehydrogenase, is composed of four parts (subunits): two alpha subunits (called E1 alpha) and two beta subunits (called E1 beta). Mutations in the gene that provides instructions for making E1 alpha, the *PDHA1* gene, are the most common cause of pyruvate dehydrogenase deficiency, accounting for approximately 80 percent of cases. These mutations lead to a shortage of E1 alpha protein or result in an abnormal protein that cannot function properly. A decrease in functional E1 alpha leads to reduced activity of the pyruvate dehydrogenase complex.

Other components of the pyruvate dehydrogenase complex are also involved in pyruvate dehydrogenase deficiency. Mutations in the genes that provide instructions for E1 beta (the *PDHB* gene), the E2 enzyme (the *DLAT* gene), E3 binding protein (the *PDHX* gene), and pyruvate dehydrogenase phosphatase (the *PDP1* gene) have been identified in people with this condition. Although it is unclear how mutations in each of these genes affect the complex, reduced functioning of one component of the complex appears to impair the activity of the whole complex. As with *PDHA1* gene mutations, changes in these other genes lead to a reduction of pyruvate dehydrogenase complex activity.

With decreased function of this complex, pyruvate builds up and is converted in another chemical reaction to lactic acid. The excess lactic acid causes lactic acidosis in

affected individuals. In addition, the production of cellular energy is diminished. The brain, which requires especially large amounts of energy, is severely affected, resulting in the neurological problems associated with pyruvate dehydrogenase deficiency.

Pyruvate carboxylase deficiency

Pyruvate carboxylase deficiency is an inherited disorder that causes lactic acid and other potentially toxic compounds to accumulate in the blood. High levels of these substances can damage the body's organs and tissues, particularly in the nervous system. Researchers have identified at least three types of pyruvate carboxylase deficiency, which are distinguished by the severity of their signs and symptoms. Type A, which has been identified mostly in people from North America, has severe symptoms that begin in infancy. Characteristic features include developmental delay and a buildup of lactic acid in the blood (lactic acidosis). Increased acidity in the blood can lead to vomiting, abdominal pain, extreme tiredness (fatigue), muscle weakness, and difficulty breathing. In some cases, episodes of lactic acidosis are triggered by an illness or periods without food (fasting). Children with pyruvate carboxylase deficiency type A typically survive only into infancy or early childhood. Pyruvate carboxylase deficiency type B has life-threatening signs and symptoms that become apparent shortly after birth. This form of the condition has been reported mostly in Europe, particularly France. Affected infants have severe lactic acidosis, a buildup of ammonia in the blood (hyperammonemia), and liver failure. They experience neurological problems including weak muscle tone (hypotonia), abnormal movements, seizures, and coma. Infants with this form of the condition usually survive for less than 3 months after birth. A milder form of pyruvate carboxylase deficiency, sometimes called type C, has also been described. This type is characterized by slightly increased levels of lactic acid in the blood and minimal signs and symptoms affecting the nervous system.

Mutations in the *PC* gene cause pyruvate carboxylase deficiency. This gene provides instructions for making an enzyme called pyruvate carboxylase. This enzyme is active in mitochondria, which are the energy-producing centers within cells. It is involved in several important cellular functions, including the generation of glucose, a simple sugar that is the body's main energy source. Pyruvate carboxylase also plays a role in the formation of the protective sheath that surrounds certain nerve cells (myelin) and the production of brain chemicals called neurotransmitters that allow nerve cells to communicate with one another.

Mutations in the *PC* gene reduce the amount of pyruvate carboxylase in cells or disrupt the enzyme's activity. The missing or altered enzyme cannot carry out its essential role

in generating glucose, which impairs the body's ability to make energy in mitochondria. Additionally, a loss of pyruvate carboxylase allows compounds such as lactic acid and ammonia to build up and damage organs and tissues. Researchers suggest that the loss of pyruvate carboxylase function in the nervous system, particularly the role of the enzyme in myelin formation and neurotransmitter production, also contributes to the neurologic features of pyruvate carboxylase deficiency.

Glucose-6-phosphate dehydrogenase deficiency

Glucose-6-phosphate dehydrogenase deficiency is a genetic disorder that occurs almost exclusively in males. This condition mainly affects red blood cells, which carry oxygen from the lungs to tissues throughout the body. In affected individuals, a defect in an enzyme called glucose-6-phosphate dehydrogenase causes red blood cells to break down prematurely. This destruction of red blood cells is called hemolysis. The most common medical problem associated with glucose-6-phosphate dehydrogenase deficiency is hemolytic anemia, which occurs when red blood cells are destroyed faster than the body can replace them. This type of anemia leads to paleness, yellowing of the skin and whites of the eyes (jaundice), dark urine, fatigue, shortness of breath, and a rapid heart rate. In people with glucose-6-phosphate dehydrogenase deficiency, hemolytic anemia is most often triggered by bacterial or viral infections or by certain drugs (such as some antibiotics and medications used to treat malaria). Hemolytic anemia can also occur after eating fava beans or inhaling pollen from fava plants (a reaction called favism). Glucose-6-phosphate dehydrogenase deficiency is also a significant cause of mild to severe jaundice in newborns. Many people with this disorder, however, never experience any signs or symptoms and are unaware that they have the condition.

Glucose-6-phosphate dehydrogenase deficiency results from mutations in the *G-6-P D*H gene. This gene provides instructions for making an enzyme called glucose-6-phosphate dehydrogenase. This enzyme is involved in the normal processing of carbohydrates. It also protects red blood cells from the effects of potentially harmful molecules called reactive oxygen species (free radicals), which are byproducts of normal cellular functions. Chemical reactions involving glucose-6-phosphate dehydrogenase produce compounds that prevent reactive oxygen species (free radicals) from building up to toxic levels within red blood cells.

If mutations in the *G-6-P DH* gene reduce the amount of glucose-6-phosphate dehydrogenase or alter its structure, this enzyme can no longer play its protective role. As a result, reactive oxygen species can accumulate and damage red blood cells. Factors such as infections, certain drugs, or ingesting fava beans can increase the levels of

reactive oxygen species, causing red blood cells to be destroyed faster than the body can replace them. A reduction in the number of red blood cells causes the signs and symptoms of hemolytic anemia.

Researchers believe that people who have a *G6PD* mutation may be partially protected against malaria, an infectious disease carried by a certain type of mosquito. A reduction in the amount of functional glucose-6-phosphate dehydrogenase appears to make it more difficult for this parasite to invade red blood cells. Glucose-6-phosphate dehydrogenase deficiency occurs most frequently in areas of the world where malaria is common. It mostly affects African, African-American and Mediterranean males

Hemolytic anemia due to G-6-P DH deficiency

Hemolytic anemia is a condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over. Red blood cells are disc-shaped and look like doughnuts without holes in the center. These cells carry oxygen to your body. They also remove carbon dioxide (a waste product) from your body. Red blood cells are made in the bone marrow—a sponge-like tissue inside the bones. They live for about 120 days in the bloodstream and then die. White blood cells and platelets (PLATE-lets) also are made in the bone marrow. White blood cells help fight infections. Platelets stick together to seal small cuts or breaks on blood vessel walls and stop bleeding. When blood cells die, the body's bone marrow makes more blood cells to replace them. However, in hemolytic anemia, the bone marrow can't make red blood cells fast enough to meet the body's needs. Hemolytic anemia can lead to many health problems, such as fatigue (tiredness), pain, irregular heartbeats called arrhythmias (ah-RITH-me-ahs), an enlarged heart, and heart failure.

Fumarase deficiency

Fumarase deficiency is a condition that primarily affects the nervous system, especially the brain. Affected infants may have an abnormally small head size (microcephaly), abnormal brain structure, severe developmental delay, weak muscle tone (hypotonia), and failure to gain weight and grow at the expected rate (failure to thrive). They may also experience seizures. Some people with this disorder have unusual facial features, including a prominent forehead (frontal bossing), low-set ears, a small jaw (micrognathia), widely spaced eyes (ocular hypertelorism), and a depressed nasal bridge. An enlarged liver and spleen (hepatosplenomegaly) may also be associated with this disorder, as well as an excess of red blood cells (polycythemia) or deficiency of white blood cells (leukopenia) in infancy. Affected individuals usually survive only a few months, but a few have lived into early adulthood. Fumarase deficiency is caused by mutations in the *FH* gene. This gene provides instructions for making an enzyme

called fumarase (also known as fumarate hydratase). Fumarase participates in an important series of reactions known as the citric acid cycle or Krebs cycle, which allows cells to use oxygen and generate energy. Specifically, fumarase helps convert a molecule called fumarate to a molecule called malate. Mutations in the *FH* gene disrupt the enzyme's ability to help convert fumarate to malate, interfering with the function of this reaction in the citric acid cycle. Impairment of the process that generates energy for cells is particularly harmful to cells in the developing brain, and this impairment results in the signs and symptoms of fumarase deficiency.

Leber hereditary optic neuropathy (LHON)

Leber hereditary optic neuropathy (LHON) is an inherited form of vision loss. Although this condition usually begins in a person's teens or twenties, rare cases may appear in early childhood or later in adulthood. For unknown reasons, males are affected much more often than females.

Blurring and clouding of vision are usually the first symptoms of LHON. These vision problems may begin in one eye or simultaneously in both eyes; if vision loss starts in one eye, the other eye is usually affected within several weeks or months. Over time, vision in both eyes worsens with a severe loss of sharpness (visual acuity) and color vision. This condition mainly affects central vision, which is needed for detailed tasks such as reading, driving, and recognizing faces. Vision loss results from the death of cells in the nerve that relays visual information from the eyes to the brain (the optic nerve). Although central vision gradually improves in a small percentage of cases, in most cases the vision loss is profound and permanent.

Vision loss is typically the only symptom of LHON; however, some families with additional signs and symptoms have been reported. In these individuals, the condition is described as "LHON plus." In addition to vision loss, the features of LHON plus can include movement disorders, tremors, and abnormalities of the electrical signals that control the heartbeat (cardiac conduction defects). Some affected individuals develop features similar to multiple sclerosis, which is a chronic disorder characterized by muscle weakness, poor coordination, numbness, and a variety of other health problems.

Mutations in the *MT-ND1*, *MT-ND4*, *MT-ND4L*, or *MT-ND6* gene can cause LHON. These genes are found in the DNA of cellular structures called mitochondria, which convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA, known as mitochondrial DNA or mtDNA.

The genes associated with LHON each provide instructions for making a protein involved in normal mitochondrial function. These proteins are part of a large enzyme complex in mitochondria that helps convert oxygen, fats, and simple sugars to energy. Mutations in any of the genes disrupt this process. It remains unclear how these genetic changes cause the death of cells in the optic nerve and lead to the specific features of LHON.

A significant percentage of people with a mutation that causes LHON do not develop any features of the disorder. Specifically, more than 50 percent of males with a mutation and more than 85 percent of females with a mutation never experience vision loss or related health problems. Additional factors may determine whether a person develops the signs and symptoms of this disorder. Environmental factors such as smoking and alcohol use may be involved, although studies have produced conflicting results. Researchers are also investigating whether changes in additional genes contribute to the development of signs and symptoms.

Glycogen storage diseases

This is disorder caused by enzyme deficiencies affecting either glycogen synthesis, glycogen breakdown or glycolysis (glucose breakdown), typically within muscles and/or liver cells. GSD has two classes of cause: genetic and acquired

Table 21.1 Glycogen-storage diseases

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen	Branching enzyme (α-1,4 → α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.

Table 21.1
Biochemistry, Seventh Edition

Lactic acidosis

In basic terms, lactic acid is the normal endpoint of the anaerobic breakdown of glucose in the tissues. The lactate exits the cells and is transported to the liver, where it is oxidized back to pyruvate and ultimately converted to glucose via the Cori cycle. In the setting of decreased tissue oxygenation, lactic acid is produced as the anaerobic cycle is utilized for energy production. With a persistent oxygen debt and overwhelming of the body's buffering abilities (whether from chronic dysfunction or excessive production), lactic acidosis ensues. Lactic acidosis is a form of metabolic acidosis that begins in the kidneys. People with lactic acidosis have kidneys that are unable to remove excess acid from their body. If lactic acid builds up in the body more quickly than it can be removed, acidity levels in bodily fluids — such as blood — spike. This buildup of acid causes an imbalance in the body's pH level, which should always be slightly alkaline instead of acidic.

Lactic acid buildup occurs when there's not enough oxygen in the muscles to break down glucose and glycogen. This is called anaerobic metabolism. Other causes include carbon monoxide poisoning, cholera, malaria, and asphyxiation.

There are two types of lactic acid: L-lactate and D-lactate. Most forms of lactic acidosis are caused by too much L-lactate. Lactic acidosis has many causes and can often be treated. But if left untreated, it may be life-threatening. Several symptoms of lactic acidosis represent a medical emergency: fruity-smelling breath (a possible indication of a serious complication of diabetes, called ketoacidosis), confusion, jaundice (yellowing of the skin or the whites of the eyes) and trouble breathing or shallow, rapid breathing

Lactose intolerance

Lactose intolerance is a common digestive problem where the body is unable to digest lactose, a type of sugar mainly found in milk and dairy products. Symptoms of lactose intolerance usually develop within a few hours of consuming food or drink that contains lactose. They may include: flatulence (wind), diarrhoea, bloated stomach, stomach cramps and pains, stomach rumbling and feeling sick. The severity of symptoms and when they appear depends on the amount of lactose that has been consumed. Some people may still be able to drink a small glass of milk without triggering any symptoms, while others may not even be able to have milk in their tea or coffee. The body digests lactose using a substance called lactase. This breaks down lactose into two sugars called glucose and galactose, which can be easily absorbed into the bloodstream. People with lactose intolerance don't produce enough lactase, so lactose stays in the digestive system where it's fermented by bacteria. This leads to the

production of various gases, which cause the symptoms associated with lactose intolerance.

Depending on the underlying reason why the body isn't producing enough lactase, lactose intolerance may be temporary or permanent. Most cases that develop in adults are inherited and tend to be lifelong, but cases in young children are often caused by an infection in the digestive system and may only last for a few weeks.

Vitamin C deficiency (Scurvy)

Vitamin C is a water-soluble vitamin that plays a role in maintaining the health of the body's connective tissue as well as acting as an antioxidant. The body needs to ingest vitamin C foods, on a daily basis in order to maintain necessary supplies.

The body does not make vitamin C on its own, and it does not store it either, so it is important that one includes plenty of fruits and vegetables that contain vitamin C in daily diets. The benefits of vitamin C may include protection against immune system deficiencies, cardiovascular disease, prenatal health problems, eye disease, and even skin wrinkling.

Vitamin C Deficiency Symptoms; A deficiency in vitamin C shows itself in several common ways in the body. While the signs and symptoms of Vitamin C deficiency are not too bothersome, the results of long-term low levels of vitamin C are very detrimental and worth making a priority. A severe vitamin C deficiency will result in scurvy, a disease resulting from the breakdown of collagen. Scurvy will make you feel fatigued and lethargic. It affects bone and muscle strength and it stifles the immune system. Scurvy is rarely seen today, as only a very small amount of vitamin C is needed to prevent it. It is important to understand, however, that less noticeable signs of Vitamin C deficiency are still very serious such as: Easy bruising, Swollen gums, Bleeding gums, Slow wound healing, Gingivitis (inflammation of the gums), Dry and splitting hair, Dry red spots on the skin, Rough, dry, scaly skin, Nosebleeds, Weakened immune system, Digestive disorders like leaky gut and autoimmune disease, Possible weight gain because of slowed metabolism and Swollen and painful joints

Health problems related to a vitamin C deficiency can get much worse over time, and may lead to some serious health issues. Long Term Problems from Low Levels of Vitamin C include: High blood pressure, Gallbladder disease, Stroke, Certain cancers and Atherosclerosis

Vitamin C Side Effects; Vitamin C is not stored in the body (excess amounts are excreted), so overdose is not a concern. Your body will get rid of excess vitamin C in your urine. It is still important not to exceed the safe upper limit of 2,000 milligrams a day to avoid stomach upset and diarrhea. A recent study found a link between taking vitamin C supplements and kidney stones. The study found that men who take vitamin C supplements are twice as likely to develop kidney stones as men who don't take any dietary supplements. These results do not apply to men who get their vitamin C from eating fruits and vegetables, and women were not studied.

Vitamin C Interactions; Water-soluble vitamins must be continuously supplied in the diet to maintain healthy levels. Eat vitamin-C-rich fruits and vegetables raw, or cook them with minimal water so you don't lose some of the water-soluble vitamin in the cooking water. Aluminum interacts with vitamin C because vitamin C can increase how much aluminum the body absorbs, so take vitamin C two hours before or four hours after you have any antacids. Vitamin C might decrease how quickly the body gets rid of estrogens. Taking vitamin C along with estrogens might increase the effects and side effects of estrogens. Because vitamin C is an antioxidant, there are some concerns that it may decrease the effectiveness of some medications used for cancer. Taking large doses of vitamin C may also reduce how much of some medications used for HIV/AIDS stays in the body. This includes medications such as Agenerase, Viracept, Norvir, and Fortovase. Large amounts of vitamin C may decrease the effectiveness of warfarin (Coumadin) because it is used to slow blood clotting.

Beriberi or thiamine deficiency

Thiamine deficiency, or beriberi, refers to the lack of thiamine pyrophosphate, the active form of the vitamin known as thiamine (also spelled thiamin), or vitamin B-1 (see the image below). Thiamine pyrophosphate, the biologically active form of thiamine, acts as a coenzyme in carbohydrate metabolism through the decarboxylation of alpha ketoacids. It also takes part in the formation of glucose by acting as a coenzyme for the transketolase in the pentose monophosphate pathway.

Beriberi is a disease caused by a vitamin B-1 deficiency, also known as thiamine deficiency. There are two types of the disease: wet beriberi and dry beriberi. Wet beriberi affects the heart and circulatory system. In extreme cases, wet beriberi can cause heart failure. Dry beriberi damages the nerves and can lead to decreased muscle strength and eventually, muscle paralysis. Beriberi can be life-threatening if it isn't treated.

If you have access to foods rich in thiamine, your chances of developing beriberi are low. Today, beriberi mostly occurs in people with an alcohol use disorder, those with AIDS, those with extreme nausea during pregnancy and those undergoing kidney dialysis

The symptoms of beriberi vary depending on the type. Wet beriberi symptoms include: shortness of breath during physical activity, waking up short of breath, rapid heart rate and swollen lower legs. Dry beriberi symptoms include: decreased muscle function, particularly in the lower legs, tingling or loss of feeling in the feet and hands, pain, mental confusion, difficulty speaking, vomiting, involuntary eye movement and paralysis

In extreme cases, beriberi is associated with Wernicke-Korsakoff syndrome. Wernicke encephalopathy and Korsakoff syndrome are two forms of brain damage caused by thiamine deficiency.

INHIBITORS AND UNCOUPLERS OF ELECTRON TRANSPORT CHAIN AND OXIDATIVE PHOSPHORYLATION

Respiratory Inhibitors:

The ETC chain contains 4 complexes (I, II, III and IV) which participate in the transfer of electrons. In general, it may be stated that the structural integrity of these complexes

appears essential for its interaction with most inhibitors, since the soluble, phospholipid free enzymes do not exhibit the characteristic inhibitory pattern.

- Components in Electron Transport Chain system in Mitochondria
- Electron transport chain mechanism

The following compounds inhibit both electron transport and oxidative phosphorylation.

There are six distinct types of poison which may affect mitochondrial function:

1) **Respiratory chain inhibitors** (e.g. cyanide, antimycin, rotenone & TTFA) block respiration in the presence of either ADP or uncouplers.

2) **Phosphorylation inhibitors** (e.g. oligomycin) abolish the burst of oxygen consumption after adding ADP, but have no effect on uncoupler-stimulated respiration.

3) **Uncoupling agents** (e.g. dinitrophenol, CCCP, FCCP) abolish the obligatory linkage between the respiratory chain and the phosphorylation system which is observed with intact mitochondria.

4) **Transport inhibitors** (e.g. atractyloside, bongkrekic acid, NEM) either prevent the export of ATP, or the import of raw materials across the mitochondrial inner membrane.

5) **Ionophores** (e.g. valinomycin, nigericin) make the inner membrane permeable to compounds which are ordinarily unable to cross.

6) **Krebs cycle inhibitors** (e.g. arsenite, aminooxyacetate) which block one or more of the TCA cycle enzymes, or an ancillary reation.

Inhibitors of Electron Transport:

These are the inhibitors that arrest respiration by combining with members of the respiratory chain, rather than with the enzymes that may be involved in coupling respiration with ATP synthesis.

They appear to act at 3 loci that may be identical to the energy transfer sites I, II and III. The given below are the inhibitors of Electron transport chain.

1. Rotenone: It is the non-toxic inhibitors of Electron transport chain. This compound is extracted from roots of tropical plant Derris elliptica and Lonchoncarpus nicou. It binds at Complex I between Fe-S protein and Ubiquinone. This is non-toxic to mammals because poorly absorbed. Shows toxic effect in fishes.

2. Piericidin A: It is an Antibiotic. It is produced by species of streptomyces. The action is similar to Rotenone.

3. Barbiturates (Amytal, Seconal): It blocks NADH dehydrogenase and Coenzyme Q(Ubiquinone).

4. Antimycins: These are antibiotic, produced by Streptomyces. It inhibits around site II and block electron flow between cytochromes b and c1, which prevents ATP synthesis coupled to the generation of a proton gradient at site II. About 0.07 micromole of antimycin A per gram of mitochondrial protein is effective.

5. Dimercaprol: It is identical in action to the antimycins.

6. Cyanides: The cyanide ion (CN^-) combines tightly with cytochrome oxidase, leading to prevention of oxygen from binding to the final molecule in the electron transport chain. Individuals poisoned with cyanide die from oxygen deprivation even though their cells may have abundant oxygen.

7. Azide: Azide blocks the electron flow between the cytochrome oxidase complex and oxygen. Azide reacts with the ferric form (Fe_3^+) of this carrier.

8. Hydrogen Sulfide: H_2S is toxic, with bad odor. It inhibits Cytochrome Oxidase.

9. Carbon Monoxide: It blocks between cytochrome oxidase and replaces Oxygen. Without oxygen to accept electrons from the mitochondrial electron transport chains, aerobic respiration cannot occur. As a result brain cells must rely on glycolysis alone to produce ATP. Glycolysis is much less efficient than aerobic respiration and the cells cannot make enough ATP to meet their needs. Which means that without oxygen cells cannot produce ATP which will stop aerobic respiration in cellular respiration.

Inhibitors of Oxidative Phosphorylation:

The given below are the list of inhibitors in Oxidative Phosphorylation.

1. **Oligomycins:** Is a polypeptide antibiotic obtained from various species of "Streptomyces. It inhibits the transfer of high-energy phosphate to ADP and also inhibits electron transfer coupled to phosphorylation. The antibiotic is potent inhibitor to ATP synthase complex.

2. **Rutamycin:** This antibiotic inhibits both ETC and oxidative phosphorylation.
3. **Atractylate:** It blocks oxidative phosphorylation by competing with ATP & ADP for a site on the ADP-ATP antiport of the mitochondrial membranes.
4. **Bongkrekate:** It is a toxin formed by bacteria (Pseudomonas). It also blocks the ADP-ATP antiport.

Uncouplers of Oxidative Phosphorylation:
Uncouplers can be defined as *substances that uncouples phosphorylation of ADP from electron transfer.*
Uncoupling agents are compounds which dissociate the synthesis of ATP from the transport of electrons through the cytochrome system. This means that the electron transport continues to function, leading to oxygen consumption but phosphorylation of ADP is inhibited.

Below are few uncoupling agents,

1. **2,4-Dinitrophenol:** A classic uncoupler of oxidative phosphorylation. In the presence of these uncouplers, electron transport from NADH to O_2 proceeds normally, but ATP is not formed in the mitochondria. This is because the proton motive force across the inner mitochondrial membrane is dissipated.
2. **Calcium:** Transport of Ca^{+2} ion into mitochondria can cause uncoupling. Mitochondrial transport of Ca^{+2} is energetically coupled to oxidative phosphorylation. It is coupled with uptake of p^i When calcium is transported into mitochondria, electron transport can proceed but energy is required to pump the Ca^{+2} into the mitochondria. Hence, no energy is stored as ATP.
3. **CCCP (Chloro carbonyl cyanide phenyl hydrazone):** Most active uncoupler. These lipid soluble substances can carry protons across the inner mitochondrial membrane preventing oxidative phosphorylation
4. **Physiological un-couplers:** Excessive thyroxin hormone, Long chain FA in brown adipose tissue, Unconjugated hyperbilirubinaemia
5. **Valinomycin:** This is similar to Ionophore of oxidative phosphorylation inhibition. Produced by a type of *streptomyces.* It is a repeating macrocyclic molecule made up of four kinds of residues (L-lactate, L-Valine, D-hydroxyisovalarate and D-Valine). Transports K^+ from the cytosol into matrix and H^+ from matrix to cytosol, thereby decreasing the proton gradient.
6. **Thermogenin:** The uncoupling protein (UCP) or thermogenin is a 33 kDa inner-membrane mitochondrial protein exclusive to brown adipocytes in mammals that functions as a proton transporter, allowing the dissipation as heat of the proton gradient

generated by the respiratory chain and thereby uncoupling oxidative phosphorylation. Thermogenesis (heat production) in brown adipose tissue, which is activated in response to cold exposure or chronic overeating, depends largely on UCP activity. Norepinephrine, released from sympathetic terminals and acting via beta-adrenoceptors and cAMP, is the main positive regulator of both UCP synthesis and activity. Brown fat thermogenesis plays a critical role in thermoregulation and in overall energy balance, at least in rodents. Manipulation of thermogenesis, whether through UCP or through analogous uncoupling proteins, could be an effective strategy against obesity.

Nutritional balance and dietary intake

A balanced diet is one that gives your body the nutrients it needs to function correctly. Being in a nutritional balance means that you consume just the right amount of calories, macronutrients and micronutrients from your diet. In an optimal nutritional state, all of your nutritional needs are met without exceeding your caloric needs. Maintaining a stable healthy weight, having low blood cholesterol and healthy blood-pressure levels are just a few signs of being nutritionally balanced.

Over And Under-Nutrition

Nutrition and physical activity are the two most important influences on health. It is the balance of nutrients contained in the calories one consumes weighed against the calories they burn that specifically impacts ones health. Nutritional imbalances like overnutrition and undernutrition may lead to severe health difficulties.

Overnutrition is frequent or habitual overconsumption of nutrients by eating too much food to the point that it becomes dangerous to your health. Nutrients are all compounds necessary for bodily function, including minerals, vitamins, fats, carbohydrates and proteins. Although most nutrients can be harmful in excess, the danger of overnutrition relates mostly to carbohydrates and fats. Overeating differs conceptually from overnutrition, although they are essentially the same thing in action; whereas overeating is a compulsion considered a psychological disorder, overnutrition is volitionally choosing to eat more food than you need, even if you don't realize it.

Undernutrition is the opposite of overnutrition, meaning that it is a nutrient deficiency from not eating enough food. Undernutrition usually affects the balance of all the nutrients in your body. Nonetheless, problems relating to a deficiency in carbohydrates and fats will manifest first and most acutely. Initially, the body starts using its glycogen -- or sugar -- reserves, stored water and body protein. Then, your body consumes stored fatty acids and lean muscle. These two effects of undernutrition result in a dramatic

decrease in body weight. Short-term undernutrition is possible if you inexplicably lose at least 10 percent of your body weight over three to six months.

Protein Calorie Malnutrition

Protein-calorie malnutrition is also called protein-energy undernutrition, or PEU. The two disorders most commonly associated with PCM in children are marasmus, sometimes called the "dry" form of the disorder, and kwashiorkor, known as the "wet" form. Lack of calorie and protein intake is the primary cause of PCM, but many secondary causes can also cause the disorder. Cancer, alcoholism, cardiac diseases, AIDS infection and kidney disease can all cause cachexia, loss of appetite and muscle wasting. Disorders that cause the body to use up a higher number of calories than usual, such as severe burns or other trauma, can also cause PCM. Gastrointestinal diseases that affect absorption may lead to PCM as well. Symptoms of PCM include muscle wasting, lack of subcutaneous fat, slow heart beat, difficulty maintaining body temperature, poor wound healing and low energy levels. Hair becomes dry, brittle and sparse, while skin turns dry, cool to the touch and rough. Diarrhea commonly occurs. In patients with kwashiorkor, fluid accumulates in the abdomen and other tissues. Blood pressure and respiratory rate may also slow, and the person becomes susceptible to infection as the immune system fails. If the disease progresses, organs such as the heart, liver and kidneys fail. Death will occur if the disease continues to progress without intervention. Increasing calorie intake will normally increase protein intake to normal levels. Liquid diets may be better tolerated at first than solid foods. Giving yogurt may lessen diarrhea caused by lactose intolerance. Use of a feeding tube or total parenteral nutrition given via intravenous infusion may be necessary in severe cases. Children may need intravenous hydration for 24 hours before starting feedings to prevent worsening diarrhea. Care must be taken not to overhydrate, which can place an extra burden on the heart. Electrolyte abnormalities can also occur, leading to heartbeat irregularities and muscle weakness. Between 5 and 40 percent of children with PCM will die, according to the Merck Manuals Online Medical Library. Children with kwashiorkor recover faster than children with marasmus, the same source reports. Permanent mental retardation or cognitive problems may remain. Elderly patients may have difficulty recovering from surgery or infections.

PHOTOSYNTHESIS

Photosynthesis, the process by which green plants and certain other organisms transform light energy into chemical energy. During photosynthesis in green plants,

light energy is captured and used to convert water, carbon dioxide, and minerals into oxygen and energy-rich organic compounds

Photosynthesis is divided into two parts:

1. Light-dependent reactions (light reactions)

2. Light-independent reactions (dark reactions).

Light reactions need light to produce organic energy molecules (ATP and NADPH). They are initiated by colored pigments, mainly green colored chlorophylls. Therefore light is need to produce organic energy molecules such as ATP and NADPH

Dark reactions make use of these organic energy molecules (ATP and NADPH). This reaction cycle is also called Calvin Benison Cycle, and it occurs in the stroma. ATP provides the energy while NADPH provides the electrons required to fix the CO2 (carbon dioxide) into carbohydrates. Uses the energy molecules ATP and NADPH to produce energy molecules and doesn't depend on light.

This means Dark reactions will fail to continue if the plants are deprived of light for too long since they use the output of the initial light-dependent reactions.