Metabolism of Carbohydrates and Formation of Adenosine Triphosphate (from Guyton's bk)

Role of Adenosine Triphosphate (ATP) in Metabolism

A great proportion of the chemical reactions in the cells is concerned with making the energy in foods available to the various physiological systems of the cell, For instance, energy is required for (1) muscular activity, (2) secretion by the glands, (3) maintenance of membrane potentials in the nerve and muscle fibers, (4) synthesis of substances in the cells, and (5) absorption of foods from the gastrointestinal tract, The substance adenosine triphosphate (A TP) plays a key role in making the energy of the foods available for all these purposes,

ATP, a labile chemical compound present in all cells, has the chemical structure shown in Figure 45 -1. From this formula it can be seen that A TP is a combination of adenine, ribose, and three phosphate radicals, The last two phosphate radicals are connected with the remainder of the molecule by socalled *high energy bonds,* which are indicated by the symbol - , The amount of free energy in each of these **512 h**igh energy bonds per mole of A TP is approximately 7300 calories per mole under standard conditions but 12,000 calories under the conditions of temperature and concentrations of the reactants in the body. Therefore, removal of each phosphate radicalliberates 12,000 calories of energy, After loss of one phosphate radical from ATP, the compound becomes *adenosine diphosphate* (ADP), and after loss of the second phosphate radical the compound becomes *adenosine monophosphate* (AMP),

A TP is present everywhere in the cytoplasm and nucleoplasm of all cells, and essentially all of the physiological mechanisms that require energy for operation obtain it directly from the A TP (or some other similar high-energy compound-guanosine triphosphate, GTP, for example). In turn, the food in the cells is gradually oxidized, and the released energy is used to re-form the A TP, thus always maintaining a supply of this substance

In summary, ATP is an intermediary compound that has the peculiar ability of entering into many physiological mechanisms to provide energy for their operation, For this reason, A TP has frequently been called the energy *currency* of the body that can be gained and spent again and again The principal purpose of the present chapter is to explain how the energy from carbohydrates can be used to form ATP (or GTP) in the cells, At least 99 cent of all the carbohydrates utilized by the body is used
for this purpose,

TRANSPORT OF MONOSACCHARIDES THROUGH THE CELL MEMBRANE

From the previous chapter it will be recalled that the final products of carbohydrate digestion in the alimentary tract are almost entirely glucose, fructose, and galactose, with glucose representing by far the major amount ofthese, These three monosaccharides are absorbed into the portal blood and, after passing through the blood sinuses of the liver, are carried everywhere in the body by the circulatory system, But before they can be used by the cells, they must be transported through the cell membrane into the cellular cytoplasm,

Monosaccharides cannot diffuse through the usual pores of the cell membrane, for the maximum molecular weight of substances that can do this is about 100, whereas glucose, fructose, and galactose all have molecular weights of 180, Yet glucose and some of the other monosaccharides combine with a *protein carrier* in the membrane that then allows them to diffuse freely to the inside of the cell, After passing through the membrane they become dissociated from the carrier, The transport mechanism is one of *facilitated diffusion* and not of active transport, These concepts are discussed in more detail in Chapter 4,

Enhancement of Glucose Transport by Insulin

The rate of glucose transport through the cell membrane is greatly increased by insulin, When large amounts of insulin are secreted by the pancreas, the rate of glucose transport into most cells increases to as much as ten times the rate of transport when no insulin at all is secreted, The amounts of glucose that can diffuse to the insides of most cells of the body in the absence of insulin, with the unique exceptions of the liver and the brain, are far too little to supply anywhere near the amount of glucose normally required for energy metabolism, Therefore, in effect, the rate of carbohydrate utilization by the body is controlled mainly by the rate of insulin secretion in the pancreas, The functions of insulin and its control of carbohydrate metabolism will be discussed more fully in Chapter 52,

Phosphorylation of Glucose

Immediately upon entry into the cells, glucose combines with a phosphate radical in accordance with the following reaction:

$$\text{glucose} + \text{ATP} \xrightarrow{\text{glucokinase or hexokinase}} \text{glucose 6-phosphate}$$

This phosphorylation is promoted by the enzyme *glucokinase* in the liver or *hexokinase* in most other cells,

The phosphorylation of glucose is almost completely irreversible except in the liver cells, the renal tubular epithelium, and the intestinal epithelial cells in which glucose phosphatase is available for reversing the reaction, Therefore, in most tissues of the body, phosphory lation serves to *capture* the glucose in the cell- once *in* the cell, the glucose will not diffuse back out except from those special cells that have the necessary phosphatase,

Conversion of Fructose and Galactose into Glucose. In liver cells appropriate enzymes are available to promote interconversions between the monosaccharides, and the dynamics of the reactions are such that when the liver releases the monosaccharides back into the blood, the final product of these interconversions is almost entirely glucose, In the case of fructose, much of it is also converted into glucose as it is absorbed through the intestinal epithelial cells into the portal blood, Therefore, essentially all the monosaccharides that circulate in the blood are the final conversion product, glucose,

STORAGE OF GLYCOGEN IN LIVER AND MUSCLE

After absorption into the cells, glucose can be used immediately for release of energy to the cells, or it can be stored in the form of *glycogen,* which is a large polymer of glucose All cells of the body are capable of storing at least some glycogen, but certain cells can store large amounts, especially the liver cells, which can store up to 5 to 8 per cent of their weight as glycogen, and muscle cells, which can store up to 1 to 3 per cent of their weight as glycogen, The glycogen molecules can be polymerized to almost any molecular weight, the average molecular weight being five million or more; most of the glycogen precipitates in the form of solid granules,

Glycogenesis

Glycogenesis is the process of glycogen formation, the chemical reactions of which are illustrated in Figure 45 - 2, From this figure it can be seen that *glucose 6-phosphate* first becomes *glucose i-phosphate;* this is then converted to *uridine diphosphate glucose,* which is converted into glycogen, Several specific enzymes are required to cause these conversions, Any monosaccharide that can be converted into glucose obviously can enter into the reactions, and certain smaller compounds, including *lactic acid, glycerol, pyruvic acid,* and some *deaminated amino acids,* can also be converted into glucose or closely allied compounds and thence into glycogen,

Removal of Stored GlycogenGlycogenolysis

Glycogenolysis means the breakdown of glycogen to re-form glucose in the cells, Glycogenolysis does not occur by reversal of the same chemical reactions that serve to form glycogen; instead, each succeeding glucose molecule on each branch of the glycogen polymer is split away by the process of *phosphorylation* catalyzed by the enzyme *phosphorylase,*

Under resting conditions, the phosphorylase is in an inactive form, so that glycogen can be stored but not reconverted into glucose, When it is required to re-form glucose from glycogen, therefore, the phosphorylase must first be activated, This activation is accomplished in the following ways:

Activation of Phosphorylase by Epinephrine and Glucagon. Two hormones, epinephrine and glucagon, can specifically activate phosphorylase and thereby cause rapid glycogenolysis, The initial effect of each of these hormones is to increase the formation of *cyclic adenosine monophosphate (cAMP)* in the cells, This substance then initiates a cascade of chemical reactions that activate the phosphorylase, a process discussed in more detail in Chapter 52,

Epinephrine is released by the adrenal medullae when the sympathetic nervous system is stimulated, The epinephrine then activates phosphorylase, thus making glucose available for rapid metabolism, This function of epinephrine occurs markedly both in liver cells and in muscle, thereby contributing, along with other eftects of sympathetic stimulation, to preparation of the body for action, as discussed in Chapter 41,

Glucagon is a hormone secreted by the *alpha cells* of the pancreas when the blood glucose concentration falls low, It stimulates the formation of cAMP mainly in the liver and thereby activates phosphorylase, Its

effect is primarily to dump glucose out ofthe liver into the blood, thereby raising blood glucose concentration back toward the normal level. The function of glucagon in blood glucose regulation is discussed in Chapter 52,

Transport of Glucose Out of Liver Cells. The cells of the liver contain *phosphatase,* an enzyme that can split phosphate away from glucose 6-phosphate and therefore make the glucose available for retransport out ofthe cells into the interstitial fluids, Therefore, when glucose is formed in the liver as a result of glycogenolysis, most of it immediately passes into the blood, Thus, liver glycogenolysis causes an immediate rise in blood glucose concentration, Glycogenolysis in most other cells of the body, especially in the muscle cells, simply makes increased amounts of glucose 6phosphate available inside the cells and increases the local rate of glucose utilization, but it does not release the glucose into the extracellular fluids because the required phosphatase is not available to dephosphorylate the glucose 6-phosphate,

RELEASE OF ENERGY FROM THE GLUCOSE MOLECULE BY THE GLYCOLYTIC PATHWAY

Complete oxidation of 1 mole of glucose releases 686,000 calories of energy, but only 12,000 calories of energy are required to form 1 mole of adenosine tri
phosphate (ATP), Therefore it would be an extreme waste of energy if glucose decomposed at once into water and carbon dioxide while forming only a single ATP molecule, Fortunately, cells contain an extensive series of different protein enzymes that cause the glucose molecule to split a little at a time in many successive steps, with its energy released in small packets to form one molecule of ATP at a time, forming a total of 38 moles of A TP for each mole of glucose utilized by the cells, The purpose of the present section is to describe the basic principles by which the glucose molecule is progressively dissected and its energy released to form ATP,

Glycolysis and the Formation of Pyruvic Acid

By far the most important means by which energy is released from the glucose molecule is the process of *glycolysis,* followed by *oxidation of the end-products of glycolysis, Glycolysis* means splitting of the glucose molecule to form two molecules of pyruvic acid, This process occurs by ten successive steps of chemical reactions, illustrated in Figure 45 - 3, Each step is catalyzed by at least one specific protein enzyme, Note that glucose is first converted into fructose 1,6-phosphate and then split into two three-carbon atom molecules, each of which is then converted through five successive steps into pyruvic acid,

Formation of Adenosine Triphosphate (A TP)

During Glycolysis. Despite the many chemical reactions in the glycolytic series, only 2 moles of A TP are formed for each mole of glucose utilized, This amounts to 24,000 calories of energy stored in the form of ATP, but during glycolysis a total of 56,000 calories of energy is lost from the original glucose, giving an overall *efficiency* for A TP formation of 43 per cent, The remaining 57 per cent of the energy is lost in the form of heat,

Conversion of Pyruvic Acid to Acetyl Coenzyme A

The next stage in the degradation of glucose is conversion of its two derivative pyruvic acid molecules into two molecules of *acetyl coenzyme A* (acetyl Co-A) in accordance with the following reaction:

From this reaction it can be seen that two carbon dioxide molecules and four hydrogen atoms are released, while the remainders of the two pyruvic acid molecules combine with coenzyme A, a derivative of the vitamin pantothenic acid, to form two molecules of acetyl Co-A, In this conversion, no ATP is formed, but six molecules of A TP are produced when the four hydrogen atoms are later oxidized, as is discussed in a later section,

The Citric Acid Cycle

The next stage in the degradation of the glucose molecule is called the *citric acid cycle* (also called the *tricarboxylic acid cycle,* or *the Krebs cycle),* This is a sequence of chemical reactions, illustrated in Figure 45-4, in which the acetyl portion of acetyl Co-A is degraded to carbon dioxide and hydrogen atoms, These reactions all occur *in the matrix of the mitochondrion,* The released hydrogen atoms are subsequently oxidized, as discussed later, releasing tremendous
amounts of energy to form ATP,

The substances to the left in Figure 45 - 4 are added during the chemical reactions, and the products of the chemical reactions are shown to the right, Note at the top of the column that the cycle begins with *oxaloacetic acid,* and then at the bottom of the chain of reactions *oxaloacetic acid* is formed once again, Thus, the cycle can continue indefinitely,

In the initial stage of the citric acid cycle, *acetyl Co-A* combines with *oxaloacetic acid* to form *citric acid,* The coenzyme A portion of the acetyl Co-A is released and can be used again and again for the formation of still more quantities of acetyl Co-A from pyruvic acid, The acetyl portion, however, becomes an integral part of the citric acid molecule, During the successive stages of the citric acid cycle, several molecules of water are added, and *carbon dioxide* and *hydrogen atoms* are released at various stages in the cycle, as shown on the right in the figure,

The net results of the entire citric acid cycle are shown at the bottom of Figure 45 - 4, illustrating that for each molecule of glucose originally metabolized, two acetyl Co-A molecules enter into the citric acid cycle along with six molecules of water, These molecules are then degraded into four carbon dioxide molecules, 16 hydrogen atoms, and 2 molecules of coenzyme A,

Formation of A TP in the Citric Acid Cycle. No large amount of energy is released during the citric acid cycle itself, However, for each molecule of glucose metabolized, two molecules of A TP are formed,

Formation of ATP by Oxidative Phosphorylation of the Hydrogen Atoms

Despite all the complexities of glycolysis and the citric acid cycle, pitifully small amounts of A TP are formed during these processes - only 2 A TP molecules in the glycolysis scheme and another 2 in the citric acid cycle, Instead, almost 95 per cent of the final A TP is formed during subsequent oxidation of the hydrogen atoms that are released during these earlier stages of glucose degradation, Indeed, the principal

function of all these earlier stages is to make the hydrogen of the glucose molecule available in a form that can be utilized for oxidation,

Oxidation of hydrogen is accomplished by a series of enzymatically catalyzed reactions that (a) change the hydrogen atoms into hydrogen ions and electrons and (b) use the electrons eventually to change the dissolved oxygen of the fluids into hydroxyl ions, Then the hydrogen and hydroxyl ions combine to form water, During this sequence of oxidative reactions, tremendous quantities of energy are released to form A TP, Formation of A TP in this manner is called *oxidative phosphorylation,* It occurs entirely in the mitochondria by a highly specialized process called the chemiosmotic mechanism, illustrated in Figure 45-5,

The Chemiosmotic Mechanism for Forming ATP

Ionization of Hydrogen, the Electron Transport Chain, and Formation of Water. The first step in oxidative phosphorylation is to ionize the hydrogen atoms that are removed from the food substrates, These hydrogen atoms are removed in pairs during glycolysis and during the citric acid cycle; one immediately becomes a hydrogen ion, H+, and the other combines with NAD+ to form NADH, The upper portion of Figure 45 - 5 shows in color the subsequent disposition of the NADH and H+ in the mitochondrion, The initial effect is to release the other hydrogen atom bound with NAD to form another hydrogen ion, H+; this process also reconstitutes NAD+, which will be reused again and again,

During these changes, the electrons that are removed from the hydrogen atoms to cause their ionization immediately enter an *electron transport chain* that is an integral part of the inner membrane (the shelf membrane) of the mitochondrion, This transport chain consists of a series of electron acceptors that can be reversibly reduced or oxidized by accept ing or giving up electrons, The important members of this electron transport chain include *flavoprotein, several iron sulfide proteins, ubiquinone,* and *cytochromes*

B, Cv C, *A, and A3'* Each electron is shuttled from one of these acceptors to the next until it finally reaches cytochrome As, which is called *cytochrome oxidase* because it is capable, by giving up two electrons, of causing elemental oxygen to combine with hydrogen ions to form water, Thus, Figure 45 - 5 illustrates transport of electrons through the electron chain and their ultimate use by cytochrome oxidase to cause the formation of water molecules, During the transport of these electrons through the electron transport chain, energy is released that is later used to cause synthesis of A TP, as follows:

Pumping of Hydrogen Ions into the Outer Chamber of the Mitochondrion, Caused by the Electron Transport Chain. The energy released as the electrons pass through the electron transport chain is used to pump hydrogen ions from the inner matrix of the mitochondrion into the space between the inner and outer mitochondrial membranes, This creates a high concentration of hydrogen ions in this space, and it also creates a strong negative electrical potential in the inner matrix,

Formation of A TP. The final step in oxidative phosphorylation is to convert ADP into ATP, This conversion occurs in conjunction with a large protein molecule with a knoblike head that protrudes all the way through the inner mitochondrial membrane and into the inner matrix, This molecule is an ATPase, the physical

nature of which is illustrated in Figure 45-5, It is called *ATP synthetase,* The high concentration of hydrogen ions in the space between the two mitochondrial membranes and the large electrical potential difference across the inner membrane cause the hydrogen ions to flow into the mitochondrial matrix *through the substance of the A TPase molecule,* In doing so, energy derived from this hydrogen ion flow is utilized by the ATPase to convert ADP into ATP by combining an ADP with a phosphate radical, forming an additional high energy phosphate bond,

For each two hydrogen atoms ionized by the electron transport chain, up to three A TP molecules are synthesized,

Summary of ATP Formation During the Breakdown of Glucose

We can now determine the total number of A TP molecules formed by the energy from one molecule of glucose, The number is

1. Two during glycolysis
2, Two during the citric acid cycle and
3, During oxidative phosphorylation, 34, making a

total of 38 *A TP molecules* formed for each molecule of glucose degraded to carbon dioxide and water, Thus, 456,000 calories of energy are stored in the form of ATP, while 686,000 calories are released during the complete oxidation of each mole of glucose, This represents an overall *efficiency* of energy transfer of 66 per cent, The remaining 34 per cent of the energy
becomes heat and therefore cannot be used by the
cells to perform specific functions,

Control of Glycolysis and Glucose Oxidation by Intracellular Adenosine Diphosphate (ADP) Concentration

Continuous release of energy from glucose when the energy is not needed by the cells would be an extremely wasteful process, Fortunately, glycolysis and the subsequent oxidation of hydrogen atoms is continuously controlled in accordance with the needs of the cells for A TP, This control is accomplished mainly in the following manner:

Referring back to the various chemical reactions, we see that at different stages *ADP* is converted into *ATP, If ADP is not available, the reactions cannot occur, and the degradation of the glucose molecule is stopped,* Therefore, once all the ADP in the cells has been converted to ATP, the entire glycolytic and oxidative process stops, Then, when more A TP is used to
perform different physiological functions in the cell,
new ADP is formed, which automatically starts gly
colysis and oxidation once more, In this way, essen

tially a full store of ATP is automatically maintained all the time, except when the activity of the cell becomes so great that ATP is used more rapidly than it can be formed,

Release of Energy in the Absence of Oxygen - "Anaerobic" Glycolysis

Occasionally, oxygen becomes either unavailable or insufficient, so that cellular oxidation of glucose cannot take place, Yet, even under these conditions, a small amount of energy can still be released to the cells by glycolysis, for the chemical reactions in the glycolytic breakdown of glucose to pyruvic acid do not require oxygen, Unfortunately, this process is extremely wasteful of glucose because only 24,000 calories of energy are used to form A TP for each mole of glucose utilized, which represents only a little over 3 per cent of the total energy in the glucose molecule, Nevertheless, this release of glycolytic energy to the cells can be a lifesaving measure for a few minutes when oxygen becomes unavailable,

Formation of Lactic Acid During Anaerobic Glycosis. The *law of mass action* states that as the end-products of a chemical reaction build up in a
reacting medium, the rate of the reaction approaches zero, The two end-products of the glycolytic reactions (see Figure 45-3) are (1) pyruvic acid and (2) hydro
gen atoms in the forms NADH and H+, The buildup of excessive amounts of these would stop the glycolytic process and prevent further formation of A TP, Fortunately, when their quantities begin to be excessive, these end-products react with each other to form lactic acid, in accordance with the following equation,

Thus, under anaerobic conditions, by far the larger

portion of the pyruvic acid is converted into lactic acid, which diffuses readily out of the cells into the extracellular fluids and even into the intracellular fluids of other less active cells, Therefore, lactic acid represents a type of "sinkhole" into which the glyco

lytic end-products can disappear, allowing glycolysis

to proceed far longer than would be possible if the
pyruvic acid and hydrogen were not removed from the reacting medium, Indeed, glycolysis could proceed for only a few seconds without this conversion, Instead, it can proceed for several minutes, supplying the body with considerable quantities of A TP even in the absence of respiratory oxygen,

When a person begins to breathe oxygen again after a period of anaerobic metabolism, the extra NADH and H+ as well as the extra pyruvic acid that have built up in the body fluids are rapidly oxidized, mainly in the liver, thereby undergoing great reduction in their concentrations, As a result, the chemical reaction for formation of lactic acid immediately reverses itself, the lactic acid once again becoming pyruvic acid, which is eventually oxidized to supply additional cellular energy,

RELEASE OF ENERGY FROM GLUCOSE BY THE PENTOSE PHOSPHATE PATHWAY

Though essentially all the carbohydrates utilized
by the muscles are degraded to pyruvic acid by glycol

ysis and then converted to carbon dioxide and hydrogen atoms by the citric acid cycle, this glycolytic and citric acid schema is not the only means by which glucose can be degraded to provide energy, A second important schema for glucose breakdown is called the
pentose phosphate pathway, Though this process is not discussed here, it is responsible for as much as 30 per cent of the glucose breakdown in the liver and for even more than that in fat cells, It is especially important in providing energy and some of the substrates required for conversion of carbohydrates into fat, as will be discussed in the following chapter,

FORMATION OF CARBOHYDRATES FROM PROTEINS AND FATS-
"GLUCONEOGENESIS"

When the body's stores of carbohydrates decrease below normal, moderate quantities of glucose can be formed from *amino acids* and from the *glycerol* portion offat, This process is called *gluconeogenesis,* Approximately 60 per cent of the amino acids in the body proteins can easily be converted into carbohydrates, while the remaining 40 per cent have chemical configurations that make this difficult, Each amino acid is converted into glucose by a slightly different chemical process, For instance, alanine can be converted directly into pyruvic acid simply by deamination; the pyruvic acid then is converted into glucose by the liver,

Regulation of Gluconeogenesis. Diminished carbohydrates in the cells and decreased blood sugar are the basic stimuli that set off an increase in the rate of gluconeogenesis, The diminished carbohydrates can directly cause reversal of many of the glycolytic and phosphogluconate reactions, thus allowing conversion of deaminated amino acids and glycerol into carbohydrates, However, in addition, several of the
hormones secreted by the endocrine glands are especially important in this regulation, as follows:

Effect of Corticotropin and Glucocorticoids on Gluconeogenesis. When normal quantities of carbohydrates are not available to the cells, the anterior pituitary gland, for reasons not yet completely understood, begins to secrete increased quantities of
corticotropin, which stimulate the adrenal cortex to produce large quantities of *glucocorticoid hormones,* especially *cortisol.* In turn, cortisol mobilizes proteins from essentially all cells of the body, making them available in the form of amino acids in the body fluids, A high proportion of amino acids immediately becomes deaminated in the liver and therefore provides ideal substrates for conversion into glucose, Thus, one of the most important means by which gluconeogenesis is promoted is through the release of glucocorticoids from the adrenal cortex,

BLOOD GLUCOSE

The normal blood glucose concentration in a person who has not eaten a meal within the past 3 to 4 hours is approximately 90 mgper 100 ml of blood, and even after a meal containing large amounts of carbohydrates, this concentration rarely rises above 140 mg per 100 ml of blood unless the person has diabetes mellitus,

The regulation of blood glucose concentration is intimately related to insulin and glucagon; this subject will be discussed fully in relation to the functions of these two hormones in Chapter 52,