An Introduction to Metabolism

I. All of an organism's chemical reactions taken together is called metabolism.
   A. Metabolic pathways begin with a specific molecule, which is then altered in a series of steps to form a specific product. A specific enzyme catalyzes each step of the pathway.
   B. **Catabolic pathways** release energy by breaking down complex molecules to simpler compounds.
   C. **Anabolic pathways** consume energy to build complicated molecules from simpler compounds. They are also called biosynthetic pathways.
   D. The energy released by catabolic pathways can be stored and then used to drive anabolic pathways.

II. **Energy** is the capacity to do work. Energy exists in various forms, and cells transform energy from one type into another. These energy transformations are subject to two laws of **thermodynamics.** Thermodynamics is the study of energy transformations.
   A. The **first law of thermodynamics** states that energy can be transferred and transformed, but it cannot be created or destroyed. The first law is also known as the principle of conservation of energy.
      1. During every transfer or transformation of energy, some energy is converted to heat, which is the energy associated with the random movement of atoms and molecules.
      2. Heat can be used to do work only when there is a temperature difference that results in heat flowing from a warmer location to a cooler one. In living cells, temperature is uniform so heat can only be used to warm the organism.
      3. This loss of usable energy during energy transfers and transformations makes the universe more disordered.
      4. **Entropy** is a quantity used as a measure of disorder or randomness. The more random a collection of matter, the greater its entropy.
   B. The **second law of thermodynamics** states that every energy transfer or transformation increases the entropy of the universe.
      1. While order can increase locally, there is an unstoppable trend toward randomization of the universe.
      2. Much of the increased entropy of the universe takes the form of increasing heat, which is the energy of random molecular motion.
      3. In energy transformations within living cells, organized forms of energy are converted to heat.
      4. For a process to occur on its own, without any energy input from the outside, it must increase the entropy of the universe. Such a process is described as being *spontaneous*. Spontaneous processes do not necessarily occur quickly.
      5. Another way to state the second law of thermodynamics is for a process to occur spontaneously, it must increase the entropy of the universe.
   C. Living systems create ordered structures from less ordered starting materials. For example, amino acids are ordered into polypeptide chains, and the structure of a multicellular body is organized and complex.
      1. However, an organism also takes in organized forms of matter and energy from its surroundings and replaces them with less ordered forms. For example, an animal consumes organic molecules as food and catabolizes them to low-energy carbon dioxide and water.
      2. Organisms are islands of low entropy in an increasingly random universe.
   D. The free energy change of a reaction tells us whether it is spontaneous.

1. **Free energy** is the portion of a system's energy that is able to perform work when temperature and pressure is uniform throughout the system, as in a living cell.
2. The free energy (G) in a system is related to the total **enthalpy** (in biological systems, equivalent to energy) (H) and the entropy (S) by the relationship $G = H - T\Delta S$, where T is temperature in Kelvin units.
3. Not all the energy in a system is available for work because the entropy component must be subtracted from the enthalpy component. What remains is the free energy that is available for work.
4. For a process to be spontaneous, the system must either give up enthalpy (decrease in H), give up order (increase in S), or both. In other words, the change in free energy must be negative for a process to be spontaneous. The greater the decrease in free energy, the more work a spontaneous process can perform.
5. In a chemical reaction at equilibrium, the rates of forward and backward reactions are equal, and there is no change in the concentration of products or reactants. Thus, at equilibrium $\Delta G = 0$, and the system can do no work.
6. A process is spontaneous and can perform work only when it is moving toward equilibrium. Movements away from equilibrium are nonspontaneous and require the addition of energy from an outside energy source (the surroundings).
7. This means that a cell that has reached metabolic equilibrium has a $\Delta G = 0$ and is dead. Metabolic disequilibrium is one of the defining features of life. Cells maintain disequilibrium because they are open systems. The constant flow of materials into and out of the cell keeps metabolic pathways from ever reaching equilibrium.
   a. To avoid this, reversible reactions are constantly "pulled" in one direction, as the product of one reaction does not accumulate but becomes the reactant in the next step. Waste products are eliminated.
E. Chemical reactions can be classified as either exergonic or endergonic based on free energy.
   1. An **exergonic reaction** proceeds with a net release of free energy; ΔG is negative. The greater the decrease in free energy, the greater the amount of work that can be done.
   2. An **endergonic reaction** is one that absorbs free energy from its surroundings. Endergonic reactions store energy in molecules; ΔG is positive. Endergonic reactions are nonspontaneous, and the magnitude of ΔG is the quantity of energy required to drive the reaction.

III. ATP powers cellular work by coupling exergonic reactions to endergonic reactions.
   A. A cell does three main kinds of work:
      1. Mechanical work, such as the beating of cilia, contraction of muscle cells, and movement of chromosomes during cellular reproduction.
      2. Transport work, the pumping of substances across membranes against the direction of spontaneous movement.
      3. Chemical work, driving endergonic reactions such as the synthesis of polymers from monomers.
   B. Cells manage their energy resources to do this work by **energy coupling,** the use of an exergonic process to drive an endergonic one.
   C. In most cases, the immediate source of energy to power cellular work is ATP.
      1. Hydrolysis of the end phosphate group forms adenosine diphosphate.

2.   This reaction releases 7.3 kcal of energy per mole of ATP under standard conditions (1 M of each reactant and product, 25°C, pH 7).

3.   In the cell, ΔG for hydrolysis of ATP is about -13 kcal/mol.

4.   The phosphate bonds of ATP are weak, unstable covalent bonds and their hydrolysis yields energy because the products are more stable.

5.   The release of energy during the hydrolysis of ATP comes from the chemical change to a state of lower free energy, not from the phosphate bonds themselves.

D.   In the cell, the energy from the hydrolysis of ATP is directly coupled to endergonic processes by the transfer of the phosphate group to another molecule. The phosphorylated molecule undergoes a change that performs work.

E.   ATP is regenerated by the addition of a phosphate group to ADP using energy from catabolic reactions in the cell.

IV.   Enzymes are catalytic proteins that speed up metabolic reactions by lowering energy barriers.

A.   The energy needed to get a reaction started is the **free energy of activation** or **activation energy** (E_A). Activation energy is the amount of energy necessary to push the reactants over an energy barrier so that the reaction can proceed.

B.   The bonds of the reactants break only when the molecules have absorbed enough energy to become unstable and, therefore, more reactive. As the molecules settle into new, stable bonding arrangements, energy is released to the surroundings.

C.   Enzymes are substrate specific.

1.   The enzyme binds to a substrate, or substrates, forming an **enzyme-substrate complex.** While the enzyme and substrate are bound, the catalytic action of the enzyme converts the substrate to the product or products.

2.   The specificity of an enzyme results from the three-dimensional shape of the **active site**, a pocket or groove on the surface of the protein into which the substrate fits. The active is usually formed by only a few amino acids so even changing one of those can alter the enzyme's activity. The specificity of an enzyme is due to the fit between the active site and the substrate.

3.   As the substrate enters the active site, interactions between the substrate and the amino acids of the protein causes the enzyme to change shape slightly, leading to a tighter **induced fit** that brings chemical groups in position to catalyze the reaction.

D.   The active site is an enzyme's catalytic center.

1.   In most cases, substrates are held in the active site by weak interactions, such as hydrogen bonds and ionic bonds.

2.   R groups of a few amino acids on the active site catalyze the conversion of substrate to product. The product then leaves the active site.

3.   A single enzyme molecule can catalyze thousands of reactions a second.

4.   Most metabolic enzymes can catalyze a reaction in both the forward and reverse directions. The actual direction depends on the relative concentrations of products and reactants. Enzymes catalyze reactions in the direction of equilibrium.

E.   Enzymes do not change ΔG but speed reactions by lowering E_A in a variety of ways.

1.   In reactions involving more than one reactant, the active site brings substrates together in the correct orientation for the reaction to proceed.

2.   As the active site binds the substrate, it may put stress on bonds that must be broken, making it easier for the reactants to reach the transition state.

3.   R groups at the active site may create a microenvironment that is conducive to a specific reaction. For example, an active site may be a pocket of low pH, facilitating H^+ transfer to the substrate as a key step in catalyzing the reaction.

F.   The rate that a specific number of enzymes convert substrates to products depends in part on substrate concentrations. At low substrate concentrations, an increase in substrate concentration speeds binding to available active sites. However, there is a limit to how fast a reaction can occur. At high substrate concentrations, the active sites on all enzymes are engaged. We say the enzyme is saturated. The rate of the reaction is determined by the speed at which the active site can convert substrate to product. The only way to increase productivity at this point is to add more enzyme molecules.

G.   The activity of an enzyme is affected by general environmental conditions, such as temperature and pH. Each enzyme works best at certain optimal conditions, which favor the most active conformation for the enzyme molecule.

     1.   Temperature has a major effect on reaction rate. As temperature increases, collisions between substrates and active sites occur more frequently as molecules move more rapidly. As temperature increases further, the molecular motion caused by the heat begins to disrupt the weak bonds that stabilize the protein's active conformation, and the protein denatures. Each enzyme has an optimal temperature.

     2.   Each enzyme also has an optimal pH. Changing the pH can disrupt interactions betweeb amino acids so maintenance of the active conformation of the enzyme requires a particular pH.

H.   Many enzymes require nonprotein helpers, called **cofactors,** for catalytic activity. Cofactors bind permanently or reversibly to the enzyme. Some inorganic cofactors include zinc, iron, and copper. Organic cofactors are called **coenzymes.** Many vitamins are coenzymes.

I.   Binding by inhibitors prevents enzymes from catalyzing reactions. If inhibitors attach to the enzyme by covalent bonds, inhibition may be irreversible. If inhibitors bind by weak bonds, inhibition may be reversible.

     1.   Some reversible inhibitors resemble the substrate and compete for binding to the active site. These molecules are called **competitive inhibitors.** Competitive inhibition can be overcome by increasing the concentration of the substrate.

     2.   **Noncompetitive inhibitors** impede enzymatic reactions by binding to another part of the molecule. Binding by the inhibitor causes the enzyme to change shape, rendering the active site less effective at catalyzing the reaction.

V.   Metabolic control often depends on allosteric regulation.

A.   In many cases, the molecules that naturally regulate enzyme activity behave like reversible noncompetitive inhibitors.

B.   Regulatory molecules often bind weakly to an **allosteric site,** a specific receptor on the enzyme away from the active site. Binding by these molecules can either inhibit or stimulate enzyme activity.

C.   The binding of an **activator** stabilizes the conformation that has functional active sites, while the binding of an **inhibitor** stabilizes the inactive form of the enzyme.

D.   By binding to key enzymes, reactants and products of ATP hydrolysis may play a major role in balancing the flow of traffic between anabolic and catabolic pathways. For example, ATP binds to several catabolic enzymes allosterically, inhibiting their activity by lowering their affinity for substrate.

     1.   ADP functions as an activator of the same enzymes.

     2.   ATP and ADP also affect key enzymes in anabolic pathways.

     3.   In this way, allosteric enzymes control the rates of key reactions in metabolic pathways.

E.   In enzymes with multiple catalytic subunits, binding by a substrate to one active site stabilizes favorable conformational changes at all other subunits, a process called

cooperativity. This mechanism amplifies the response of enzymes to substrates, priming the enzyme to accept additional substrates.

    F.   A common method of metabolic control is **feedback inhibition** in which an early step in a metabolic pathway is switched off by the pathway's final product. The product acts as an inhibitor of an enzyme in the pathway. Feedback inhibition prevents a cell from wasting chemical resources by synthesizing more product than is needed. Instead, precursors can be used in other pathways.

VI.   The localization of enzymes within a cell helps order metabolic pathways.

    A.   A team of enzymes for several steps of a metabolic pathway may be assembled as a multienzyme complex. The product from the first reaction can then pass quickly to the next enzyme until the final product is released.

    B.   Some enzymes and enzyme complexes have fixed locations within the cells as structural components of particular membranes. Others are confined within membrane-enclosed eukaryotic organelles.