UNIT 1: METABOLIC PROCESSES

A. Cellular Respiration: *An Overview*

- since the beginning of life organisms have evolved mechanisms to harness environmental energy and convert it into usable forms to power any and all endergonic processes of life
- for example, **photoautotrophs**, meaning "light-using self-feeders", transform light energy into chemical potential energy in glucose – this makes them the only self-sufficient organisms on earth
- everything else is a **heterotroph**, meaning "other-eaters" – they rely on **autotrophs** for energy
- most of life is heterotrophic (animals, fungi, most protists, and bacteria)
- almost all that heterotrophs eat was once alive
- there are a group of organisms, called **chemoautotrophs**, meaning "chemical self-feeders", that take in inorganic materials, such as iron and sulfur-containing matter, and convert them into usable energy – much like a car battery extracts energy from sulfuric acid
- these are usually found in extreme environments like volcanoes, sulfur springs, and salt flats
- with the exception of chemoautotrophs, all organisms use glucose as their "fuel" to make usable energy
- the process involves a series of enzyme-controlled redox rxs that rip apart a glucose molecule and rearrange its constituents into more stable configuration molecules
- since the products of this process are more chemically stable, i.e. they contain less chemical potential, the reaction is exergonic – free energy is released
- this free energy goes into making ATP molecules
- basically electrons are transferred from glucose to oxygen – therefore oxygen is reduced to water, and glucose is oxidized to carbon dioxide
- the over all summary of the reaction is: $C_6H_{12}O_6$ (aq) + $6O_2$ (g) $\rightarrow$ $6CO_2$ (g) + $6H_2O$ (l) + heat energy + 36 ATP molecules
- the average human consumes more than their weight in ATP molecules in one day!!
- the process that yields 36 ATP molecules from one glucose molecule is called **aerobic cellular respiration**
- "aerobic" means that oxygen is used in the process
- the actual process takes about 20 steps, where the product of one step becomes the reactant of another with the help of specific catalysts for each step

First Half of the Combustion Process

$$C_6H_{12}O_6\,(aq) + 6O_2\,(g) \rightarrow 6CO_2\,(g) + 6H_2O\,(l)$$

- the burning of any organic substance, which in this case is glucose, results in the pulling of hydrogen apart from a carbon atom by a strong oxidizing agent, which in this case is oxygen
  - this is because as each hydrogen is pulled away from a carbon and combines with oxygen, it carries electrons with it and transfers them to the oxygen
  - the transferred electrons that were beside the carbon atoms (and were almost equally shared by both the hydrogen and the carbon in the glucose molecule) are now with the oxygen atoms and are not equally shared, since oxygen has a stronger pull on them then hydrogen does

- this means that the electrons end up closer to the oxygen's nucleus, which in turn results in them possessing less potential energy – electrons that are closer to any nucleus possess less energy than if they were further away from a nucleus
- however, since the electrons went from being equally shared between the carbon and hydrogen in the organic molecule, to being unequally shared between the oxygen and hydrogen in the water molecule, they increased in randomness or entropy
- therefore, the oxidation process, which caused the transferred electrons to decrease in potential, yet increase in entropy, resulted in a decrease of free energy and an overall exergonic condition

Second Half of the Combustion Process

$C_6H_{12}O_6\,(aq) + 6O_2\,(g) \rightarrow 6CO_2\,(g) + 6H_2O\,(l)$

- six oxygen atoms from the oxygen gas molecule, plus the six oxygen atoms from the glucose molecule, combine with the carbon atom to make six CO_2 (g) molecules
- this process is also an oxidation process since once the C=O bonds form in the CO_2, the oxygen draws the electrons closer to it, making them possess less potential energy, while at the same time they go from being equally shared to being unequally shared, which now means they have more randomness or entropy

- due to both halves; the transfer of hydrogens, thus electrons, from the glucose to the oxygen, and the attachment of the oxygens to the carbon, valence electrons go from a high potential to a low potential, and from a low entropy to a high entropy
- the result is a decrease in free energy (i.e. a release of energy)
- Figure 2, p. 92 shows the free energy diagram of glucose being burned in a test tube – carbon dioxide and water are formed as well as a substantial amount of light and heat energy
- living cells, however, trap some of the free energy released in this process (about 34% of it) by moving the positions of electrons in certain molecules to higher free energy states, such as into an ATP molecule, which in turn becomes a readily available source of free energy to power endergonic processes throughout the cell
- it is important to note that the mere presence of oxygen alone does not automatically result in the oxidation of hydrocarbons – every time an oxygen atom collides with a hydrocarbon molecule (like glucose or any other organic molecule) it doesn't automatically have the power to strip away electrons from it
- otherwise combustion would always be spontaneous – since organic molecules are continuously in contact with air (21% oxygen)
- the activation energy necessary to push the reaction to completion is what controls the oxidation of organic molecules (i.e. respiration)
- for example, in order for paper to burn, a spark or flame is necessary
- in living systems, the "spark" is provided by catalytic enzymes
- specific enzymes catalyze every step in the aerobic respiration process – see Figure 2, p. 92
- it is interesting to note that oxygen is not always used in cellular respiration as the "electron grabber" – some microorganisms use NO_2, SO_4, CO_2, and even Fe^{3+} as final electron acceptors

- these organisms are called **obligate anaerobes**, which include *Clostridium tetani* (tetanus), *Clostridium botulinum* (a form of food poisoning), and *Clostridium perfringes* (gas gangrene) – seen in Figure 3a, p. 92
- obligate anaerobes only live in areas with no oxygen
- most organisms are **obligate aerobes**, such as most animals, plants, protists, fungi, and bacteria
- these organisms require oxygen to survive since they use this gas as their final electron acceptor in the respiration process
- organisms that can withstand both aerobic and anaerobic conditions are called **facultative anaerobes** – most of which are bacteria, including *Escherichia coli* (dysentery), *Vibrio cholerae* (cholera), and *Salmonella enteritidus* (common food poisoning) – these are seen in Figure 3b, p. 92

Homework: p. 93, 1-4.

B. Cellular Respiration: *A Detailed View*

- the overall equation is $C_6H_{12}O_6$ (aq) + 6 O_2 (g) $\rightarrow$ 6 CO_2 (g) + 6 H_2O (l)
- as a result of this process, 36 ATP molecules are made
- essentially, entire process meets three major goals:

1. breaks the bonds between the six carbon atoms of glucose, resulting in six carbon dioxide molecules
2. moves hydrogen atom electrons from glucose to oxygen, forming six water molecules
3. traps as much of the free energy released in the process as possible in the form of ATP

- the entire process takes place in four stages and in three different places within the cell:

NAME OF STAGE	***DESCRIPTION***	***LOCATION***
Glycolysis	• a 10-step process that begins with glucose and ends with pyruvate (pyruvic acid)	cytoplasm
Pyruvate Oxidation a.k.a Oxidative Decarboxylation	• a one-step process that begins with pyruvate and ends with acetyl CoA	mitochondrial matrix

Kreb's Cycle a.k.a Tricarboxylic Acid Cycle, a.k.a. TCA cycle, a.k.a. Citric Acid Cycle	• an eight-step cyclical process that begins with acetyl CoA combining with oxaloacetate to form citric acid • the citrate cycles through and ends up as oxaloacetate again, since it loses two carbons along the way	mitochondrial matrix
Electron Transport Chain and Chemiosmosis a.k.a. Electron Transport System a.k.a Oxidative Phosphorylation	• a multi-step redox process that transfers high energy electrons along a chain of proteins, while establishing a chemiosmotic gradient • the gradient is used to activate an enzyme (ATPase) which helps make ATP	inner mitochondrial membrane

- Figure 1, p. 94 shows the four stages of respiration, making reference to the location of each stage
- you should think of respiration as a play, where each stage is like an act, and the steps or reactions in each stage are like scenes of the play
- basically, the ultimate goal of respiration is to extract energy from nutrient molecules (preferably glucose) and store it in a form that the cell "recognizes" as free energy – the "baton" of energy is passed from glucose to ATP
- the goal of capturing as much of the available free energy as possible in the form of ATP is accomplished through two distinctly different energy-transfer mechanisms called:

1. **Substrate-Level Phosphorylation**

    - ATP is formed directly in an enzyme-catalyzed reaction
    - a phosphate-containing compound (phosphoenolpyruvate – PEP) transfers a phosphate group directly to ADP, forming ATP (see Figure 2, p. 95)
    - for every glucose molecule processed, six ATP are made this way – 4 in glycolysis, and 2 in Kreb's Cycle
    - Figure 3, p. 95 illustrates where this takes place

2. **Oxidative Phosphorylation**

    - ATP is formed indirectly
    - it involves a series of redox reactions – a passing down of electron "batons", where the oxidizing agent becomes the reducing agent for the next oxidizer in the chain
    - oxygen is the final electron acceptor

- this mechanism is more efficient at producing ATP per glucose molecule
- basically, coenzyme compounds, one of them called **nicotinamide adenine dinucleotide (NAD^+)**, and the other called **flavin adenine dinucleotide (FAD)**, remove two hydrogen atoms, therefore two protons and two electrons, from a portion of the original glucose molecule
- they work a little differently – for NAD^+, both electrons, and only one of the protons, attach to the NAD^+ to produce NADH + H^+ -- the other proton just dissolves in the surrounding solution as H^+ (aq)
- whereas in FAD, both protons and both electrons bind directly onto the FAD to produce $FADH_2$
- of course, both reductions (of NAD^+ or of FAD) do not take place unless a **dehydrogenase enzyme** is present to catalyze the reaction
- the oxidized form and the reduced form of NAD^+ are both seen in Figure 5, p. 96
- the reduction of NAD^+ takes place at three separate points during the entire respiratory process:
    1. once during one of the steps of the glycolysis stage
    2. once during the pyruvate oxidation stage
    3. three times during the Kreb's Cycle
- Figure 6, p. 96 shows the 5 different places where the NAD^+ is reduced to NADPH + H^+ (usually written as NADPH)
- the reduction of FAD takes place at only spot during the entire respiratory process – in the Kreb's Cycle (see Figure 7, p. 96)
- the reaction that produce both NADH and $FADH_2$ are considered to be "energy-harvesting" processes because these intermediate energy carriers will eventually transfer most of their free energy to ATP molecules during the electron transport and chemiosmosis stage of respiration

THE "ACTS"

ACT I. *Glycolysis*

- the word means "sugar splitting"
- basically, 1 six carbon glucose molecule is "put through the ringer" – it is added to, rearranged, modified, split apart, and broken up until it ends up being two 3-carbon molecules of pyruvate (see Figure 9, p. 97)
- glycolysis occurs in the cytoplasm (see Figure 8, p. 97)
- the ten "scenes", or reactions, of glycolysis are outlined in Figure 11, p. 97
- the major events of each scene are as follows:
    - ACT I, scene 1: - glucose enters the cell via protein channels and is immediately phosphorylated to make G6P
      - an ATP molecule is invested to "prime" the glucose and prevent it from escaping the cell
    - ACT I, scene 2: - the glucose 6-phosphate is rearranged into fructose 6-phosphate via enzyme involvement

- ACT I, scene 3: - another ATP is used up to phosphorylate, thus stabilize, the fructose 6-phosphate -- a very unstable structure that would spontaneously revert back to the more stable glucose 6-phosphate form, which ensures that the whole respiratory process moves forward – this scene is the "engine" of respiration

- ACT I, scene 4/5: - fructose 1,6-bisphosphate is split into dihydroxyacetone phosphate (DHAP) and glyceraldehydes 3-phosphate (G3P), and then an enzyme called isomerase converts the DHAP into another G3P molecule, resulting in 2 G3P molecules by the end of the scenes 4 and 5

- from here on in, each G3P molecule then undergoes the exact process from then on – like identical twin characters in a movie that experience the exact same events (see Figure 17, p. 103)

- ACT I, scene 6: - two NADH molecules are produced, one from each of the G3Ps, as each pick up a phosphate and lose 2 electrons and 2 protons to an NAD^+ molecule, resulting in the production of 1,3-biphosphoglycerate

- ACT I, scene 7: - two ATP molecules via substrate level phosphorylation are made as each molecule of 1,3 bisphosphoglycerate (BPG) loses a phosphate to ADP to become 3-phosphoglycerate

- ACT I, scene 8/9: - the purpose of these two scenes is to rearrange and dehydrate the 3-phosphoglycerate so that the second phosphate is accessible to another ADP molecule – first the two 3PGs are rearranged into two 2PG, via enzymatic involvement in scene 8, then each loses a water to become 2 PEP molecules, which now can be "pick-pocketed" by an ADP

- ACT I, scene 10: - 2 ADPs each pick up the readily accessible phosphate from the PEP molecules to yield two more ATP molecules via substrate level phosphorylation, resulting in two pyruvate molecules

- the overall equation of glycolysis is:

$$\text{glucose} + 2\,\text{ATP} + 2\,\text{ADP} + 2\,P_i + 2\,NAD^+ \rightarrow 2\,\text{pyruvate} + 4\text{ATP} + 2\,(NADH + H^+)$$

- notice that the net result of glycolysis is a gain of 2 ATP, an "investment" into 2 NADHs, and the breaking apart of glucose into two pyruvate molecules

- the vast majority of the energy of glucose is still trapped inside the two pyruvates and the 2 NADHs

- the production of ATP from glycolysis alone may be enough to sustain small, simple, less energy-demanding organisms, however, it is not enough to satisfy the energy needs of most multicellular organisms

- regardless of the energy demands of the organism, glycolysis will occur, as either the only mechanism to make ATP, or the first part of a more elaborate and more productive energy-yielding process, such as aerobic respiration

- the next "ACTS" in the play are ACT II pyruvate oxidation, ACT III the Kreb's Cycle, and ACT IV electron transport and chemiosmosis

- all three of the next ACTS occur inside the mitochondria of eukaryotic cells, and all three require the presence of oxygen to occur

- refer to p. 100, Figure 12, for a detailed view of the mitochondrion – the setting for the last three "ACTS" of aerobic cellular respiration

ACT II. *Pyruvate Oxidation*

- the two pyruvates are transported through the two mitochondrial membranes, via a transport protein channel, into the matrix (see Figure 13 and 14, p. 100)
- there are three "scenes" in this act, with the following changes taking place to each pyruvate molecule from glycolysis:

  - ACT II, scene 1: - a carboxyl group is removed as CO_2 by pyruvate decarboxylase
  - ACT II, scene 2: - a redox rx occurs whereby NAD^+ is reduced to NADH (by two electrons and two protons from organic molecules of food) and pyruvate is oxidized into acetate
  - ACT II, scene 3: - a sulfur-containing enzyme (coenzyme A) binds to the acetate group to form acetyl-CoA

- the overall equation is:

$$2 \text{ pyruvate} + 2 NAD^+ + 2 CoA \rightarrow 2 \text{ acetyl-CoA} + 2 NADH + 2H^+ + 2 CO_2$$

- the net result of this stage is that two CO_2 molecules are liberated, two NADHs are made, and an acetyl Co-A is made, which will enter the next stage of cellular respiration
- the 2 NADHs will proceed to the last stage (electron transport and chemiosmosis) to produce ATP via oxidative phosphorylation
- the CO_2 leaves the mitochondrion and exits the cell as cellular waste
- the two H^+ ions remain dissolved in the matrix
- the acetyl-CoA molecules goes into the third stage of respiration called Kreb's Cycle
- the acetyl-CoA molecule is extremely versatile – all nutrients, whether protein, lipid, or carbohydrate, are converted to acetyl-CoA and then channeled toward triglyceride production or ATP production, depending on the organism's immediate energy needs
- if ATP levels in the body are low, acetyl-CoA goes into the Kreb's Cycle, if ATP levels are high then anabolic proteins help link the acetyl-CoAs into lipid molecules
- this is why overindulgence causes obesity – animals accumulate fat when they consume more food than their bodies require to satisfy their energy needs

ACT III. *Kreb's Cycle*

- discovered by Hans Krebs, in 1937 (see Figure 16, p. 102)
- the entire process happens in the matrix, and each step in Kreb's is catalyzed by a specific enzyme
- it is a cyclic process because the reactant molecule of "scene 1", oxaloacetate, which brings the acetyl Co-A into the cycle, is reproduced in the last "scene", to help bring in the next acetyl-CoA that enters the cycle

- the following changes take place to each acetyl-CoA molecule that enters the Kreb's Cycle:

  - ACT III, scene 1: - acetyl-CoA enters by reacting with an existing molecule of oxaloacetate (OAA) to produce a molecule called citrate, which has three carboxyl groups – thus the a.k.a. name of citric acid cycle or tricarboxylic acid cycle

    - the CoA is released during this reaction and is reused for another acetyl

  - ACT III, scene 2: - citrate is rearranged to isocitrate

  - ACT III, scene 3: - the first CO_2 spins off as waste, and the first NADH is made as 2 H^+ ions reduce an NAD^+

    - the product that results is called a-ketogluterate

  - ACT III, scene4: - the second CO_2 spins off as waste as a-ketogluterate is converted to succinyl-CoA, and the second NADH is made as two more H^+ ions reduce NAD^+

  - ACT III, scene 5: - succinyl-CoA is converted into succinate, coenzyme A is released, and the first Kreb's ATP is made via substrate level phosphorylation

    – what happens is that the coenzyme A is displaced by a free phosphate, a GDP then picks it off of the succinyl to convert it to succinate, and then loses the phosphate to a stronger "phosphate pick-pocketter" ADP, resulting in the direct formation of ATP

  - ACT III, scene 6: - in the process of succinate being converted to fumerate, two hydrogen atoms reduce FAD to $FADH_2$

    - $FADH_2$ is produced instead of NADH because this conversion is not exergonic enough to reduce an NAD^+, but it is exergonic enough to reduce an FAD

  - ACT III, scene 7: - fumerate is converted to malate

  - ACT III, scene 8: - in the process of malate being converted to the reusable oxaloacetate, two hydrogen atoms reduce NAD^+ to NADH

- the overall equation of each Kreb's Cycle is:

$$\text{oxaloacetate} + \text{acetyl-CoA} + \text{ADP} + P_i + 3NAD^+ + \text{FAD} \rightarrow \text{CoA} + \text{ATP} + 3\,\text{NADH} + 3H^+ + FADH_2 + 2CO_2 + \text{oxaloacetate}$$

- by the end of Kreb's, the original glucose molecule is entirely consumed

- the six carbon atoms of glucose leave as low-energy CO_2 molecules, released by the cell as waste – two CO_2s are released from the two simultaneous pyruvate oxidation rxs, and four spin off from both of the Kreb's cycles

- the energy from the "torn-apart" glucose molecule went into:

  - 4 ATPs (two from glycolysis, two from Kreb's)
  - 12 reduced coenzymes – 2 NADHs from glycolysis, 2 NADHs from pyruvate oxidation, 6 NADHs from Kreb's, and 2 $FADH_2$s from Kreb's

- the following summarized the fate of glucose's carbon atoms:

CCCCCC	→	CCC + CCC	→	CC + CC + CO_2 + CO_2	→	CO_2 + CO_2 + CO_2 + CO_2		
	glycolysis		pyruvate oxidation		Kreb's Cycle			
glucose		2 pyruvate		2 acetyl-CoA + 2 CO_2		4 CO_2		

- the last stage, electron transport and chemiosmosis, will convert the energy contained in these intermediate energy carriers into ATP

ACT IV. *Electron Transport and Chemiosmosis*

- the final stage of cellular respiration has two distinct scenes – the first establishes a potential to do work, the second uses the potential to synthesize ATP

  - ACT IV, scene 1:

    - to begin this scene of stepwise redox reactions, the NADHs and $FADH_2$s that were made from Kreb's, pyruvate oxidation, and glycolysis, transfer the hydrogen atom electrons they carry to a series of compounds, mainly proteins, which are embedded within the inner mitochondrial membrane, called the **electron transport chain (ETC)** – see Figure 18, p. 103, and Figure 19, p. 104

    - the components of the chain are arranged in order of increasing electronegativity

    - the order from weakest to strongest is: (i) NADH dehydrogenase

      (ii) ubiquinone (Q)

      (iii) cytochrome b-c_1 complex

      (iv) cytochrome c

      (v) cytochrome oxidase

    - each component is alternately reduced by gaining two electrons from the component before in the chain, then oxidized by the component after it in the chain when it loses the electrons it gained – gaining, losing, gaining, losing, etc. electrons results in a redox chain of reactions

    - with each energy transfer, the electrons lose potential, which liberates energy

    - the electrons start off at NADH dehydrogenase, and end up at cytochrome oxidase

    - three of the five components are embedded proteins, and two (ubiquinone and cytochrome c) are mobile within the hydrophobic fluid part of the mitochondrial inner membrane – they act as "electron carrying shuttles" as they pass electrons from one embedded protein to the next

    - the free energy is used to pump H^+ ions from the matrix into the fluid-filled intermembrane space

    - as the electrons are being transferred from the NADH dehydrogenase to the cytochrome oxidase complex, three H^+ ions move up into the intermembrane space – one going up through each of the embedded proteins via symport

movement

- NADH transfers its high energy electrons to the first component in the chain (NADH dehydrogenase), resulting in the symport movement of three H^+ ions, while $FADH_2$ injects its high energy electrons to the second component in the chain (ubiquinone – Q), resulting in the symport movement of two H^+ ions into from the matrix to the intermembrane space

- for every H^+ ion pumped out of the matrix, one ATP is made – therefore, the energy form the electrons carried by each NADH will produce 3 ATP, and the energy from the electrons carried by each $FADH_2$ will produce 2 ATP

- Figure 20, p. 105 illustrates the effects of NADH and $FADH_2$ on the ETC

How do the two glycolysis NADHs get into the matrix so their high energy electrons can help produce ATP?

- the 2 NADHs that were produced in glycolysis (cystolic NADHs) must make their way into the matrix in order to transfer their high energy electrons to the first component in the ETC – the molecule is small enough to get through the outer mitochondrial membrane, but is too large to go through the inner membrane, thus cannot get into the matrix

- the inner membrane is impermeable to NADH, therefore the entire NADH molecule cannot enter the matrix, however, the high-energy electrons it is carrying can enter the matrix via two options, or "electron shuttle systems"

  1. the most common of the two is called the **glycerol-phosphate shuttle** – cystolic NADH electrons are transferred to FAD (in the matrix) to produce an $FADH_2$, which then transfers the electrons to Q, like the $FADH_2$ produced in Kreb's, resulting in the production of 2 ATP, instead of 3
  2. the least common, called the **aspartate shuttle** – cystolic NADH electrons are transferred to a matrix NAD^+, forming NADH, and then 3 ATP molecules

- the stored potential energy due to the established electrochemical gradient of H^+ ions between the intermembrane space and the mitochondrial matrix, will be utilized to power ATP synthesis in the second "scene" of the electron transport and chemiosmosis "ACT"

- ACT IV, scene 2:

  - as protons accumulate in the intermembrane space, there are two gradients that are established

  - the increased level of protons establishes a chemical gradient, and the increased intensity of positive charge establishes an electrical gradient

  - thus the gradient established is called an **electrochemical gradient**

  - the intermembrane space becomes a H^+ reservoir since the inner mitochondrial membrane is practically impermeable to hydrogen ions

  - basically, the increased electrochemical gradient across the inner membrane creates a "battery" effect where the potential for hydrogen ions to move back into the matrix is high – the free energy stored in the electrochemical gradient is referred to as a **proton-motive force (PMF)**

  - the mitochondria now have voltage and are like a battery that is fully charged!!

  - since the protons cannot diffuse through the lipid bilayer of the inner membrane, they are forced to move through a special protein channel linked to ATP synthase – the enzyme responsible for the phosphorylation of an ADP molecule

- the PMF drives the hydrogen ions to move back into the matrix, via ATPase, releasing its free energy to the enzyme, causing ADP to pick up a free phosphate in the matrix and become ATP

- this is the final "scene" of cellular respiration, and concludes the entire process

THE "FACTS"

- in a nutshell….the energy is taken from glucose with the help of: (i) ATP to energize it, (ii) enzymes to cleave it, (iii) more enzymes to alter it, (iv) intermediate carriers to steal hydrogens (protons and electrons) from it, and (v) a chain of progressively increasing oxidizers to pass the electrons down to the final electron hydrogen (proton and electron) acceptor, oxygen -- the overall purpose of these "domino" reactions is to take the potential energy, stored in the bonds of glucose, and free it up so it can charge up the "chemiosmotic battery" in the mitochondrion, which will in turn, power ATPase to phosphorylate ADP into ATP!

- without food (glucose/lipids/proteins), there is not source of electrons – this is why heterotrophs need to continuously eat!

- without oxygen, the electrons stop flowing in the ETC because there is no final electron acceptor to "siphon" off the electrons at the end of the chain – this would "jam" up the redox reactions between the components of the chain and not free up NADH dehydrogenase to accept more high energy electrons, preventing all matrix intermediate carriers (NADH, and $FADH_2$) from being oxidized -- the whole process would come to a halt!

- all four stages of respiration are linked to each other and are all dependent on each other – ATP synthesis by chemiosmosis is *coupled* with electron transport, and both of these are dependent on the availability of electrons from food and oxygen for its electron-grabbing ability

- Figure 22, p. 108, shows an overview of oxidative phosphorylation – a "downhill" flow of electrons, from high to low potential

- the inorganic formation of water is highly exergonic – a lot of heat energy is released in the process – it is actually explosive!

- the organic formation of water in the mitochondrial matrix, forms water via a different mechanism which releases the heat slowly, in a more controlled manner

- the heat generated is useful in thermal regulation of internal body temperature

- the actual amount of ATP produced is not the theoretical value

- the actual amount is not 36 ATPs, but 30 ATPs -- 2.5 ATPs for every NADH, and 1.5 ATPs for every $FADH_2$

- this is because the total electrochemical potential (voltage) gained across the inner membrane is not completely realized since:

    1. the inner mitochondrial membrane is not completely impermeable to H^+ ions, which results in some of them "cheating" and leaking back into the matrix side without having to go through ATPase – it's kind of like a "leak" in the battery
    2. some of the H^+ ions may actually pass out of the outer mitochondrial membrane and into the cytoplasm, where the cell uses them for other energy-requiring activities

- an organisms rate of ATP consumption is called the **metabolic rate**

- the minimum amount of energy consumed by a person at rest, in a lying down position, doing absolutely nothing, is called the **basal metabolic rate (BMR)**

- the BMR varies with age – it increases from zero to one years old, then drops continuously until the person dies, and sex – males have a higher BMR than females (see Figure 26, p. 111)

- a person's BMR is indirectly measured by the amount of heat that dissipates from the body surface – the greater the person's surface area, the higher the BMR

- Table 2, p. 112 lists the BMRs for some activities performed by both adult males and females

CONTROLLING ATP PRODUCTION

- Figure 28, p. 113 shows that cellular respiration has both activators and inhibitors that regulate ATP production
- all activation and inhibition mechanisms operate on the assumption that oxygen is present
- the two enzymes that are affected in the regulation of ATP production are phosphofructokinase and pyruvate decarboxylase

Coenzyme Phosphofructokinase Activators

1. *ADP* - increased levels of ADP means that no phosphorylation is taking place – this activates phosphofructokinase to help phosphorylate fructose 6-phosphate, thus making it more stable so it can continue through the process and not revert back to the more stable glucose 6-phosphate – the "engine" of respiration is given a boost!

2. *citrate* - low levels of citrate mean that very little Krebs cycles are happening – this means that low levels of NADH and $FADH_2$s exist, which in turn means less oxidative phosphorylation occurring

   - when levels are low, this also turns on the "engine"enzyme, phosphofructokinase

Coenzyme Phosphofructokinase Inhibitor

1. *ATP* - increased levels of ATP inhibit phosphofructokinase, shutting the respiratory "engine" off, resulting in fructose 6-phosphate reverting back to the more stable glucose 6-phosphate

Coenzyme Pyruvate Decarboxylase Inhibitor

1. *NADH* - increased levels of NADH, thus high levels of ETC activity, inhibits pyruvate decarboxylase from removing carbon dioxide from pyruvate, causing a halt in the production of acetyl-CoA

Homework: p. 115 (1-18)

C. The Alternative Pathways of Cellular Respiration

- the preferred macromolecule for an organism to use as a source of electrons is glucose, since glucose produces the maximum yield of ATP
- however, organisms may "choose" to use any of the other macromolecules as source of electrons to produce ATP
- Figure 1, p. 117, illustrates how the breakdown of each macromolecule results in a component that is injected into the respiratory pathway, and ultimately leads to the production of ATP

Protein Catabolism

- proteins first undergo **deamination** – the removal of the amino group as ammonia (NH_3), and the remaining portions of the protein are converted to pyruvate, acetyl-CoA, or other Kreb's cycle components
- for example, the amino acid leucine is converted into acetyl-CoA, alanine is converted into pyruvate, and praline is converted into a-ketoglutarate

Lipid Catabolism

- fats are broken down into glycerol and fatty acids
- the glycerol portion is converted to glucose via a process called **gluconeogenesis** or it is converted to DHAP, then G3P
- fatty acids get transported to the mitochondrial matrix where they undergo a process called **b-oxidation** – the sequential removal of two-carbon acetyl groups from the fatty acid chain by a number of enzymes, starting from the carboxyl end of the chain, followed by the addition of coenzyme A, resulting in acetyl-CoA
- every cleavage reaction of a fatty acid uses up 1 ATP and produces 1 NADH and 1 $FADH_2$

Question: What happens if a 12-carbon fatty acid is used as an electron source for ATP production?

Answer: A 12-carbon fatty acid is cleaved 5 times, resulting in the use of 5 ATPs and the production of 5 NADHs and 5 $FADH_2$s – this means that a net of 15 ATP are directly made by the incorporation of one 12-carbon fatty acid into the respiratory pathway. The resulting 6 acetyl-CoAs will enter the Kreb's cycle and ultimately yield 6 ATPs via substrate level phosphorylation, 18 NADHs and 6 $FADH_2$s. The 18 NADHs and 6 $FADH_2$s will help make to 54 ATP via oxidative phosphorylation. The total yield of ATP is 75 ATP (15 ATP + 54 ATP + 6 ATP) – 15 ATPs more than two molecules of glucose which contain the same number of carbon atoms, which demonstrate why fats actually store more energy.

Anaerobic Respiration

- when oxygen is absent, NADH builds up resulting in a decrease in available NAD^+
- since the cells are limited in the number of NAD^+ molecules, and none are being "freed up" by the ETC, scene 6 of glycolysis does not occur, glycolysis stops, and the entire 4 stage process of respiration comes to a halt!
- when NADH cannot "dump" its electrons onto the NADH dehydrogenase of the ETC, it goes to "plan B" – it transfers hydrogen atoms to certain organic molecules via a process called **fermentation**

- bacteria have evolved many different kinds of fermentation, however only two types of fermentation occur in eukaryotic cells:

1. *Alcoholic (ethanol) Fermentation* (see Figure 2, p. 119)

   - accumulating NADH passes its Hs onto acetaldehyde – formed when pyruvate decarboxylase removes CO_2 from pyruvate
   - this forms ethanol -- the alcohol found at parties!
   - as pyruvate is being consumed, it allows the glycolytic pathway to continue, producing P via substrate level phosphorylation
   - this is how yeast cells make their ATP
   - it is the activity of yeast cells that is responsible for making bread rise in the oven and making grapes turn into wine
   - a mixture of live yeast cells and starch is used to help make bread – the yeast ferment the glucose from the starch and release carbon dioxide, which cause the bread to rise, and ethanol, which evaporates away
   - yeast cells ferment the sugars found in carbohydrate-rich juices, like grape juice, resulting in CO_2 and ethanol
   - for grape juice fermentation, when the ethanol content reaches approx. 12%, the yeast cells die as a result of alcohol accumulation, and the product that results is wine
   - the reason why plants die if you overeater them is because the roots are flooded and have no oxygen, resulting in alcoholic fermentation, thus ethanol build up and the death of the root system

2. *Lactic Acid Fermentation* (see Figure 4, p. 120)

   - during strenuous exercise, the ATP demands are high
   - oxygen cannot be delivered to the cells fast enough to facilitate the oxidative phosphorylation process – ETC stops, NADH accumulates, NAD^+ runs out, and step 6 of glycolysis does not occur, which causes glycolysis to stop
   - as a result, an alternative, “plan B” strategy must be adopted to meet the body’s immediate energy needs
   - the accumulating NADH transfers its hydrogens to pyruvate, making lactate
   - the transfer of hydrogens to pyruvate does two things – it produces NAD^+, which feeds back into step 6 of glycolysis and turns the whole process back on again, and it consumes the pyruvate to continue ATP production via substrate level phosphorylation
   - the disadvantage is that lactate accumulates in the area of need, and causes stiffness, soreness, and fatigue
   - after the vigorous activity ceases, and O_2 reaches the mitochondria, the lactate is eventually transported to the liver and is oxidized back into pyruvate, which then goes through the Kreb’s cycle and oxidative phosphorylation
   - the extra oxygen required to oxidize the lactate into pyruvate, and then CO_2 and H_2O, is called **oxygen debt**
   - panting after strenuous exercise is how the body “pays back” the debt (see Figure 5, p. 121)

Exercise and VO_2 max

- a determination of the **VO_2 max** – the maximum amount of oxygen consumption – is a measure of a person’s capacity to generate the energy required for physical activity

- professional athletes have a higher VO_2 max than the average person, which means that they are more efficient at delivering oxygen to the cells of the body that need it the most, thus possessing a higher lactate threshold

Homework: p. 124 (1-13)

For animated illustrations of cellular respiration and its related pathways click on the following web site:
http://www.wiley.com/legacy/college/boyer/0470003790/animations/animations.htm