I. **Glucose Metabolism**

A. Glucose in the bloodstream comes from the digestion and/or from glycogen stored in the liver and muscle.

B. When glucose in the bloodstream enters the cytosol (internal fluid) of our cells, it is immediately converted to glucose – 6 – phosphate.

   1. This is an exergonic process and not reversible.

   \[
   \text{Glucose} + \text{ATP} \rightarrow \text{Glucose – 6 – phosphate} + \text{ADP} \quad \Delta G = -4.0 \text{ kcal/mol}
   \]

   2. Once phosphorylated, glucose cannot exit the cell.

C. There are three options for the fate of the glucose – 6 – phosphate depending on the metabolic needs of the body.

   1. Energy needed - The glucose-6-phosphate is converted to 2 pyruvate molecules via **glycolysis**

   2. Excess glucose – The excess glucose -6-phosphate is converted to glycogen via **glycogenesis** or to fatty acids by way of acetyl SCoA and lipid metabolic pathways.

   3. Need for reduced coenzymes and 5 carbon sugars – Glucose -6-phosphate enters the **pentose phosphate pathway** which produces the reduced coenzyme NADPH and five-carbon sugar phosphates (ribose). This happens when a cell’s need for NADPH exceeds its need for ATP.
**Glycolysis** – conversion of glucose to pyruvate  

**Gluconeogenesis** – synthesis of glucose from amino acids, pyruvate, and other non-carbohydrates.  

**Glycogenesis** – synthesis of glycogen from glucose  

**Glycogenolysis** – Breakdown of glycogen to glucose  

**Pentose phosphate pathway** – Conversion of glucose to five-carbon sugar phosphates.
II. Glycolysis

A. Glycolysis is a series of 10 enzyme catalyzed reactions that produces 2 pyruvate, 2 NADH, and two ATP for each glucose molecule.

B. Glycolysis occurs in the cytosol of all cells.

C. Look through the sequence of reactions in glycolysis and ponder these questions!

1. Glucose – 6 – phosphate is an allosteric regulator for step 1 of glycolysis. Is this most likely an inhibition or an activation?

2. Why are steps 1 – 5 referred to as the energy investment phase?

3. ATP and ADP are allosteric and feedback regulators of glycolysis. Which of these compounds most likely acts to inhibit glycolysis? Activate glycolysis?

4. ATP is made in steps 7 and 10. The ΔG for this reaction is +7.3 kcal/mol. Why are these steps highly exergonic?

5. Which is oxidized to a greater extent: pyruvate or glucose?

6. Which steps in glycolysis are oxidations? What is the oxidizing agent?

7. Is molecular oxygen involved in any of the steps of glycolysis? Where does molecular oxygen enter the picture?

*The free energy of hydrolysis of 1,2-bisphosphoglycerate and phosphoenolpyruvate is –11.8 and -14.8 kcal respectively.*
D. The Chemistry of Glycolysis

Step 1. Glucose undergoes reaction with ATP to yield glucose 6-phosphate plus ADP in a reaction catalyzed by hexokinase.

Step 2. Isomerization of glucose 6-phosphate yields fructose 6-phosphate. The reaction is catalyzed by the mutase enzyme, glucose 6-phosphate isomerase.

Step 3. Fructose 6-phosphate reacts with a second molecule of ATP to yield fructose 1,6-bisphosphate plus ADP. Phosphofructokinase, the enzyme for step 3, provides a major control point in glycolysis.

Step 4. The six-carbon chain of fructose 1,6-bisphosphate is cleaved into two three-carbon pieces by the enzyme aldolase. (Continued on next page.)
Step 5. The two products of step 4 are both three-carbon sugars, but only glyceraldehyde 3-phosphate can continue in the glycolysis pathway. Dihydroxyacetone phosphate must first be isomerized by the enzyme transketolase isomerase.

Step 6. Two reactions occur as glyceraldehyde 3-phosphate is first oxidized to a carboxylic acid and then phosphorylated by the enzyme glyceraldehyde 3-phosphate dehydrogenase. The coenzyme nicotinamide adenine dinucleotide (NAD\(^+\)) and inorganic phosphate ion (HOPO\(_2\)\(^2-\)) are required.

Step 7. A phosphate group from 1,3-bisphosphoglycerate is transferred to ADP, resulting in synthesis of ATP, and catalyzed by phosphoglycerate kinase.

Step 8. A phosphate group is next transferred from carbon 3 to carbon 2 of phosphoglycerate in a step catalyzed by the enzyme phosphoglycerate mutase.

Step 9. Loss of water from 2-phosphoglycerate produces phosphoenolpyruvate (PEP). The dehydration is catalyzed by the enzyme enolase.

Step 10. Transfer of the phosphate group from phosphoenolpyruvate to ADP yields pyruvate and generates ATP, catalyzed by pyruvate kinase.
E. Other monosaccharides enter glycolysis after being converted to reaction intermediates.

1. Fructose is phosphorylated in muscle to form fructose – 6 – phosphate. In the liver it is converted to glyceraldehyde – 3 – phosphate.
2. Galactose is converted to glucose – 6 – phosphate
3. Mannose is converted to fructose – 6- phosphate.

F. The overall glycolysis equation...

III. Fate of Pyruvate – Where does pyruvate go?
A. Oxygen rich (aerobic) conditions

1. In the mitochondrial matrix, pyruvate is oxidized forming carbon dioxide and an acetyl group (acetyl –SCoA).
2. Pyruvate must diffuse into the mitochondria from the cytosol. It is then transported by a carrier protein across the inner mitochondrial membrane into the matrix.

3. Where does the NAD+ come from?
B. Oxygen poor (anaerobic) conditions

1. Pyruvate is reduced to lactate.

\[
\text{CH}_3\text{C} = \text{C} = \text{C} - \text{O}^- \quad \xrightarrow{\text{Anaerobic conditions}} \quad \text{CH}_3\text{CH} = \text{C} - \text{O}^-
\]

2. A lack of oxygen will slow down electron transport, causing a build-up of NADH and decreasing the amount of NAD+ available for glycolysis. If there is no NAD+, glycolysis cannot continue. The reduction of pyruvate to lactate will generate the NAD+ needed for glycolysis (step 6).

3. Tissues with low oxygen content (such as skeletal muscle) rely on anaerobic production of ATP by glycolysis.

4. Some bacteria can convert pyruvate to lactate under anaerobic conditions. The preparation of kimchee, sauerkraut, and yogurt involve these types of bacteria.

C. Depleted glucose levels (starvation) – pyruvate is converted back to glucose via gluconeogenesis.

D. Yeast converts pyruvate to ethanol and CO₂ under anaerobic conditions.

\[
\text{Pyruvate} \quad \xrightarrow{\text{NADH \text{NAD}^+}} \quad \text{Acetaldehyde} \quad \xrightarrow{\text{NADH \text{NAD}^+}} \quad \text{Ethanol}
\]

NAD+ is regenerated for continued use in glycolysis.
IV. Overall Result of the Oxidation of One Glucose Molecule

A. The total energy yield from one glucose molecule is the sum of four processes

- glycolysis
- pyruvate → acetyl –S – CoA
- citric acid cycle
- electron transport

*Net result of catabolism of one glucose molecule*

**Glycolysis** (Section 23.3)

Glucose + 2 NAD⁺ +2 HOPO₃²⁻ + 2 ADP →→ 2 Pyruvate + 2 NADH + 2 ATP + 2 H₂O + 2 H⁺

**Pyruvate oxidation** (Section 23.5)

2 Pyruvate + 2 NAD⁺ + 2 HSCoA →→ 2 Acetyl-S-CoA + 2 CO₂ + 2 NADH + 2 H⁺

**Citric acid cycle** (Section 21.8)

2 Acetyl-S-CoA + 6 NAD⁺ + 2 FAD + 2 ADP + 2 HOPO₃²⁻ + 4 H₂O →→

2 HSCoA + 6 NADH + 6 H⁺ + 2 FADH₂ + 2 ATP + 4 CO₂

Glucose + 10 NAD⁺ + 2 FAD + 2 H₂O + 4 ADP + 4 HOPO₃²⁻ →→

10 NADH + 10 H⁺ + 2 FADH₂ + 4 ATP + 6 CO₂
B. The reduced coenzymes that enter electron transport yields ATP – a maximum of 3 ATP per NADH and 2 ATP per FADH₂.

C. The total energy that is released from the oxidation of one mole of glucose is 687 kcal/mol. If 32 moles of ATP are made per one mole of glucose, how much energy is produced in the cells from the hydrolysis of the 32 moles of ATP? The energy of hydrolysis of ATP is 7.3 kcal/mol. Can you account for the difference?