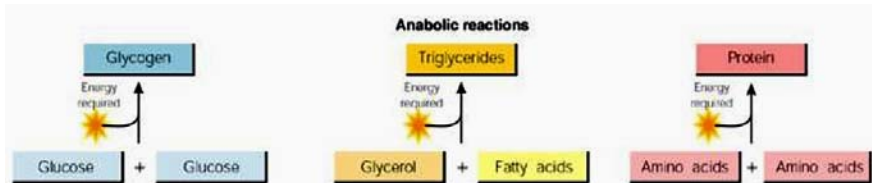


Metabolism - 1

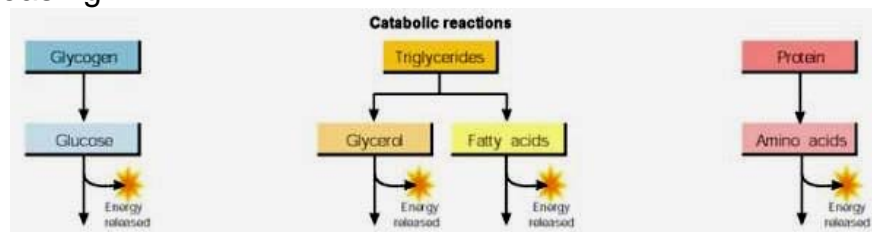
Our discussions of proteins, carbohydrates and lipids included the role of these nutrients as fuel or energy-providing molecules. For humans, the major function of carbohydrates is to provide fuel, and it's one of the important functions of lipids, as well. In our first unit, we also discussed how the liver converts one nutrient to a nutrient more useful to the body, or if in excess, to adipose the body can store. (Table 7-1 in your text reviews the functions of the liver.)

We turn now to the subject of metabolism, and specifically how our cells chemically process fuel to obtain the energy to do the work needed for a cell to function.

Some chemical reactions in cells build molecules for cell structure and function. Such reactions are called anabolic reactions, because they are building up. Typically anabolic reactions are energy requiring. Protein synthesis is an example of an anabolic reaction. Building tissues and other growth activities are anabolic processes.

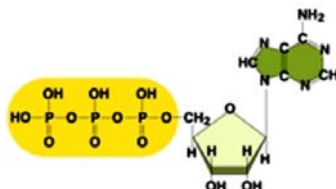


In contrast, chemical reactions that break down molecules are catabolic reactions. Often catabolic reactions release energy, but not always. The process of cell respiration is our major catabolic reaction in cells, since that is how we release energy to do cell work. The processes of digestion are also catabolic, but not energy releasing.



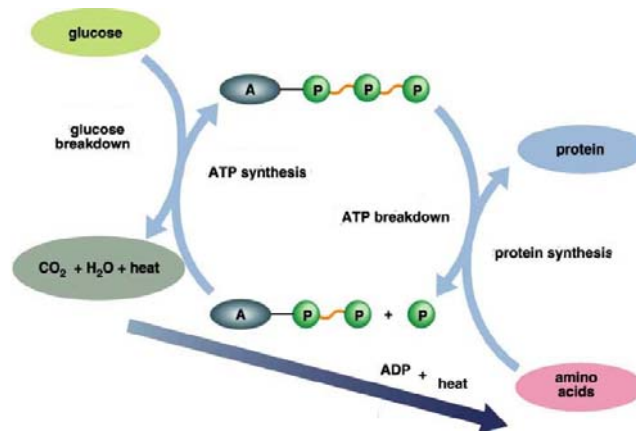
Much of metabolism, or cell work, involves controlled energy transfer, from an chemical reaction that releases energy to one that requires energy. When we do so we have **coupled reactions**. We also need a molecule that couples the reactions.

Our cells use a single molecule, the nucleotide, **ATP** (adenosine triphosphate) as our **energy coupler**. However, ATP is not stockpiled; it's such a good energy coupler precisely because it readily gives up its third phosphate to provide energy, so it's unstable.

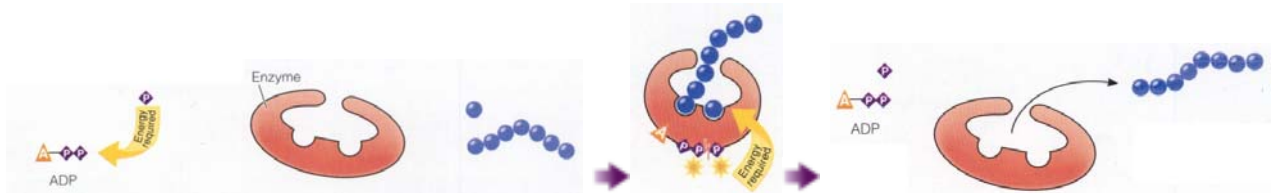


Metabolism - 2

To obtain ATP, we need to transfer the potential energy of our fuel molecules to form ATP from ADP and P_i . The energy-releasing processes known collectively as **cell respiration** release energy from fuel molecules to obtain the ATP needed to do cell work. Each cell must provide for its own ATP, so these activities occur in each of our cells twenty-four hours a day! We use about 88 pounds of ATP each day to keep our cells functioning. Fortunately, the molecule recycles; when the ATP is used in an energy-consuming reaction, ADP and P_i are released.



In addition, the reactions that occur in cell respiration, as well as all metabolism, are catalyzed by **enzymes**, each of which is specific for its particular reaction. Enzymes are proteins, and like all proteins, each enzyme has a specific shape that permits it to do its catalyst function. In addition, most of our enzymes require **coenzymes**, many of which have vitamin components, or mineral **cofactors** to function properly. For energy-consuming reactions, ATP must provide the energy needed.



Fuel Sources for Respiration

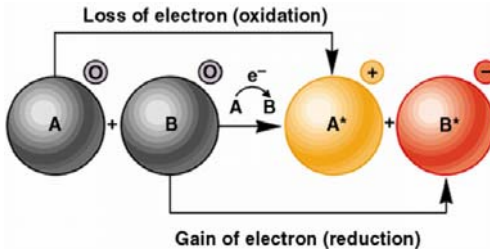
Most of our cells can use a variety of fuel molecules in cell respiration as long as oxygen is available. Several times we mentioned that moderate muscle activity routinely uses a mix of **fatty acids** and **glucose** to take optimal advantage of our fuel efficiency. The brain and nerve cells must have glucose fuel. They can not use alternative fuel molecules. If glucose is unavailable for these cells, the body must convert alternative fuel molecules into glucose. The non-carbohydrate fuels that can be converted to glucose are **glycerol** (from lipids) and some **amino acids*** (from dietary protein or from muscle tissue). **Alcohol** is also used as fuel. We shall look at how our different fuels fit into the cell respiration pathways in this section.

* alanine, cysteine, glycine, serine, tryptophan and threonine

Metabolism - 3

Most of cell respiration involves a series of oxidations and reductions of our fuel molecules, so that energy released can be used to synthesize ATP and be made available.

Recall that an oxidation is the loss of electrons, and a reduction is the gain of electrons. An oxidized molecule donates the electron to an electron acceptor that gets reduced.



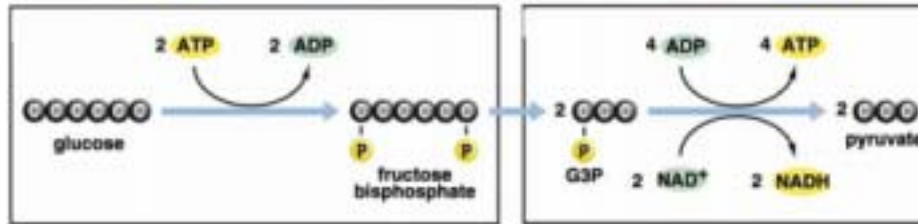
In cell respiration, fuel molecules are oxidized to release energy, and the electrons removed are passed to electron acceptors, controlling the release of energy to (ultimately) produce ATP. There are many intermediate oxidation-reductions and electron acceptors in our energy releasing pathways (**NAD to NADH** is the most important of these), but a final electron acceptor is critical at the end of the pathway that can form a stable end product. The final electron acceptor in cell respiration is usually **oxygen**. When oxygen gets reduced (accepts the electrons), we form water (because hydrogen ions accompany the electrons). In the absence of oxygen, we form **lactic acid** as the final reduced product of cell respiration.

We can now look at how cell respiration works, and the variety of fuel molecules that have a role in our cell respiration pathways.

Aerobic cell respiration involves three stages, and commences with the molecule, glucose.

- **Glycolysis**, an anaerobic stage that converts glucose to two molecules of the 3 carbon **pyruvate**
- **Krebs cycle** (or TCA cycle or Citric acid cycle) oxidizes pyruvate by transferring electrons and hydrogen to electron carrier molecules, such as NAD (many of which are coenzymes derived from B vitamins)
- **Electron transfer**, in which the energy of the electrons carried by the reduced electron transfer molecules is used to synthesize **ATP**. **Oxygen** is required to accept the electrons as they are passed through the electron transfer chain.

Glycolysis Details



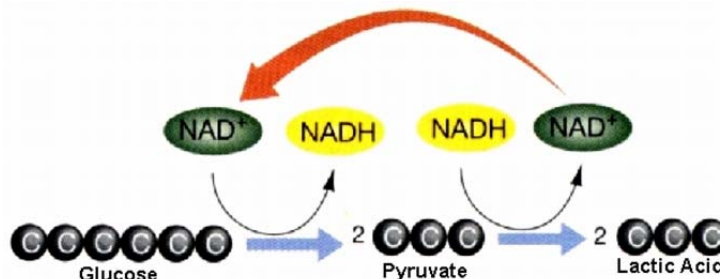
- **Glucose** is “activated” for the oxidations by two ATP-consuming reactions. Glucose must be "primed", or destabilized, in order to become reactive.
- Glucose is then broken into two molecules of the 3-carbon compound, **Pyruvate**.
- In addition:
 - Two molecules of NADH (an energy transfer molecule) are produced when hydrogen and its electrons are oxidized from the glucose molecule and transferred to NAD. The electrons NADH carries can be used later in the electron transport chain to produce ATP.
 - A net gain of two molecules of ATP are produced. (Four molecules of ATP are produced during glycolysis, but 2 molecules are consumed in activating the glucose.)
- Glycolysis always occurs in the cytoplasm of the cell.
- Glycolysis is an anaerobic process. No oxygen is used.

After the production of the metabolic intermediate, **pyruvate**, the pathways of cell respiration will differ depending on the availability of oxygen.

Pyruvate Pathway in the Absence of Oxygen – Lactic Acid Fermentation

Although discussed more in our chapter on fitness, when insufficient oxygen is available, cell will continue to process pyruvate through an anaerobic pathway that produces lactic acid. Muscle tissues are more likely to do this when we put demands on them that exceed our ability to provide oxygen to the muscle tissue.

Specifically cells use the NADH produced in glycolysis to reduce pyruvate to lactic acid. Formation of lactic acid from pyruvate does not yield any energy for the cell; all it does is free up NAD for accepting more electrons in glycolysis. Anaerobic respiration only produces the 2 ATP from glycolysis, which is why our survival without oxygen is limited to a few minutes.



Accumulated lactic acid can be recycled through the liver in a process called the **Cori cycle** and reforms glucose, but this is an energy consuming process.

Pyruvate Pathway in the Presence of Oxygen - Aerobic Respiration

When oxygen is available, the **Krebs**, or TCA, **cycle** and the **Electron Transport System**, a pathway that yield significant ATP for cells follows glycolysis. The enzymes needed to do the Krebs cycle and Electron Transport are located in the mitochondria of cells. Cells that are more metabolically active have more mitochondria.

The Krebs Cycle (or Citric Acid Cycle or the TCA Cycle)

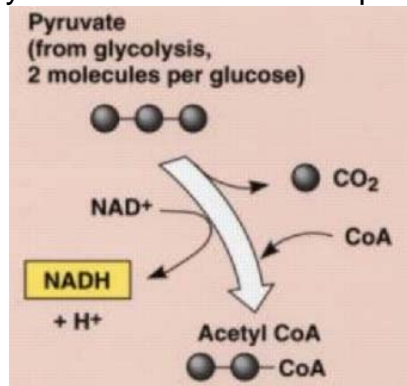
The second stage of aerobic respiration comprises the oxidation of pyruvate and the Krebs cycle.

- Pyruvate molecules are oxidized and lose a CO_2 forming **acetyl**. **NAD⁺** picks up the electrons and H^+ from the oxidation forming **NADH**.
- The two-carbon acetyl is carried to the **Krebs cycle** by coenzyme A (CoA). More oxidations occur in the Krebs cycle, releasing two more CO_2 for each pyruvate molecule and yielding many more NADHs as well as 1 FADH_2 and 1 ATP. Several B vitamins serve as coenzymes in fuel metabolism in the Krebs cycle.

The Details

Oxidation of Pyruvate to Acetyl

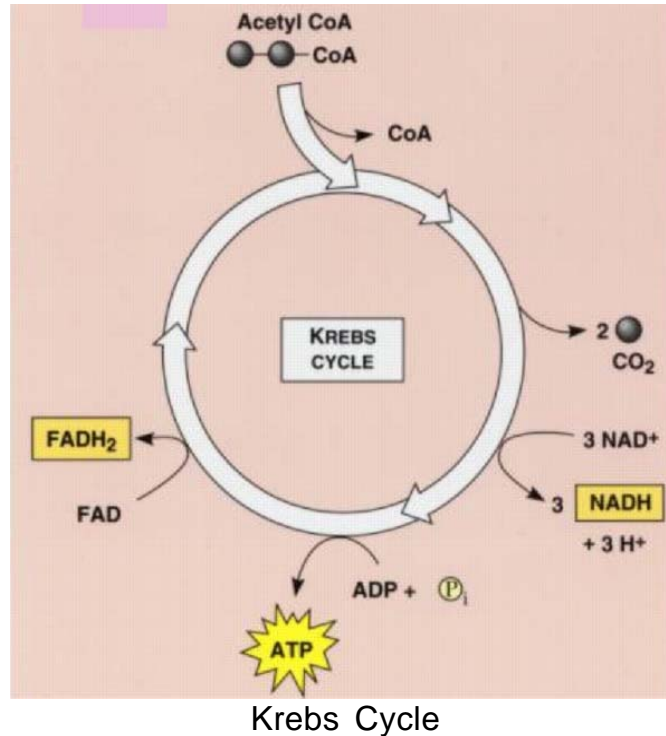
- The two Pyruvate molecules from the original glucose are transported into the **mitochondria**.
- Each pyruvate is oxidized releasing H^+ to reduce **NAD⁺** to **NADH**.
- CO_2 is removed producing **Acetyl** (A 2-carbon compound)
- Acetyl combines with Coenzyme A to form **Acetyl-CoA**, which can enter the Krebs cycle. Two acetyl-CoA molecules are produced from



The Krebs Cycle Proper

- Any cycle requires a substance to start the cycle (which will also be the end of the cycle). For the Krebs cycle the starter is **Oxaloacetic acid** (A 4-carbon acid), which is regenerated at the end of the cycle.
- **Acetyl-CoA** combines with **oxaloacetic acid** to begin the cycle forming the 6-carbon **citric acid** (citrate). Co-A is released to pick up more acetyl.
- Essentially, the acids of the Krebs cycle are substances, which in the right conditions can be **oxidized** (That is donate H^+ with its electrons). NADH is formed when the substances of the Krebs cycle get oxidized.

Metabolism - 6



The Krebs cycle, will turn two times for each glucose molecule that enters glycolysis, yielding a total of:

- 4 CO₂
- 2 ATP
- 2 FADH₂
- 6 NADH

In addition the preparation step of pyruvate oxidation adds an additional:

- 2 CO₂
- 2 NADH

The FADH₂ and NADHs will enter the electron transport system to produce ATP.

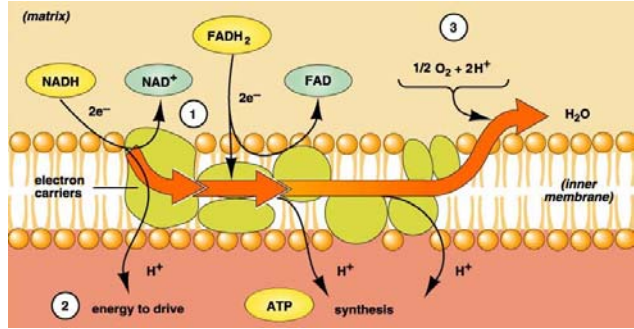
Electron Transport

The enzymes, proteins and electron carriers needed to do electron transport are found in the **inner membranes of the mitochondria**. ATP is produced by a mechanism called **chemiosmosis**. As the electrons are passed from one carrier to the next, the energy released is used to move their H⁺ ions through the membrane to build a H⁺ concentration. Chemiosmosis uses this H⁺ concentration gradient to run ATP synthesis pumps in the membrane to generate ATP.

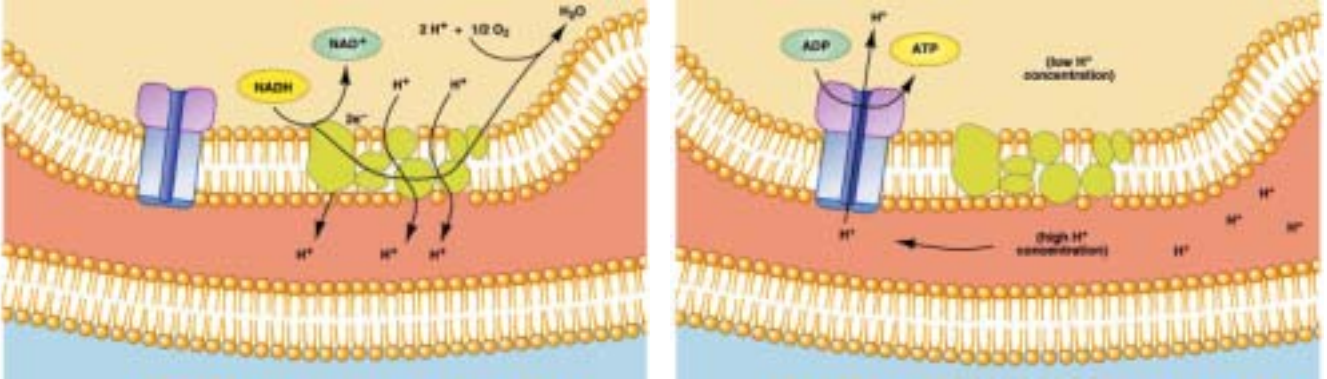
The Electron carriers, FADH₂ and NADH, produced in the Krebs cycle (and in glycolysis), provide the electrons and hydrogen needed in Electron Transport.

Oxygen is required at the final step take the electrons and hydrogen, producing water as a product. Without oxygen, we can not do electron transport or the Krebs cycle, since no NADHs can transfer their electrons, freeing NAD⁺ to pick up new electrons from Krebs.

Metabolism - 7

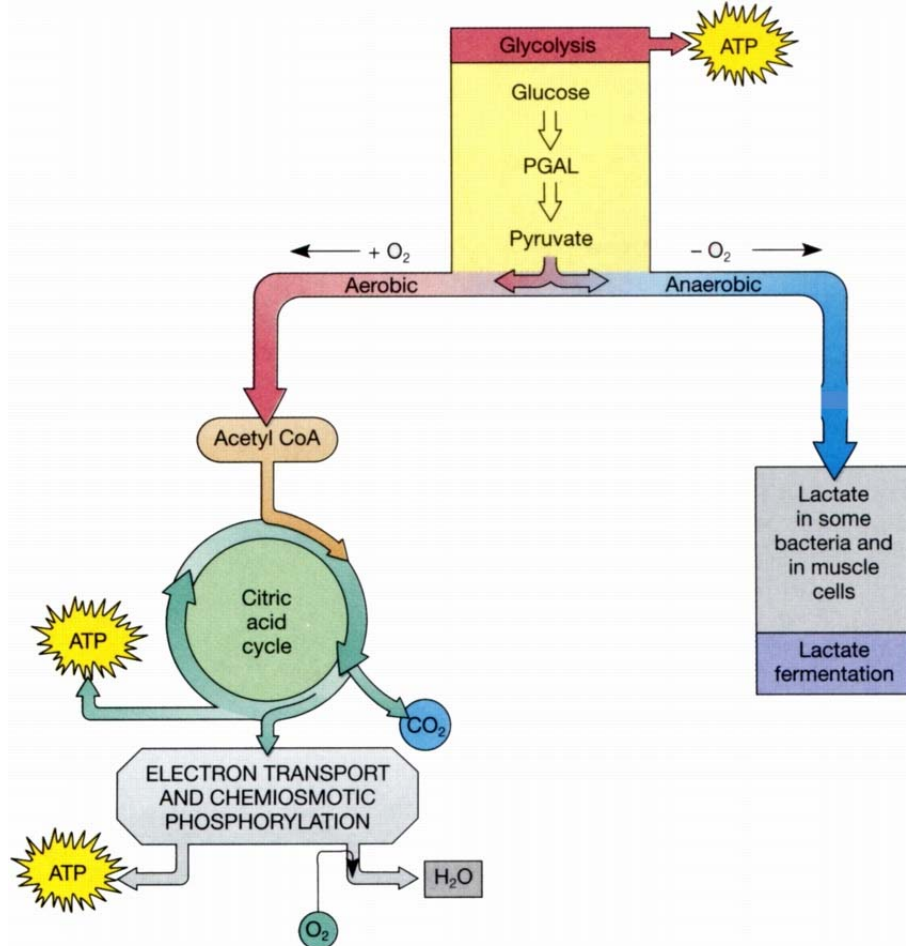


The Electron Transport Chain



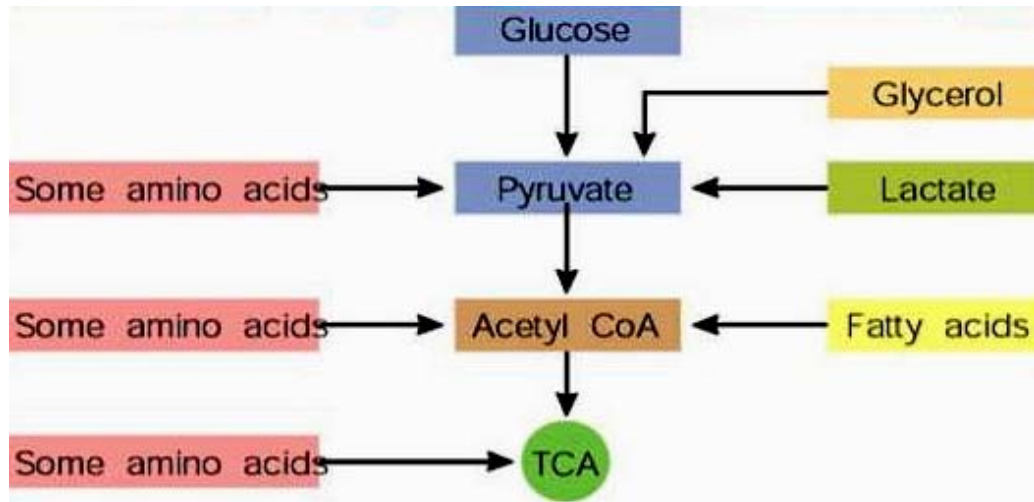
ATP Synthesis by Chemiosmosis

Summary of Cell Respiration



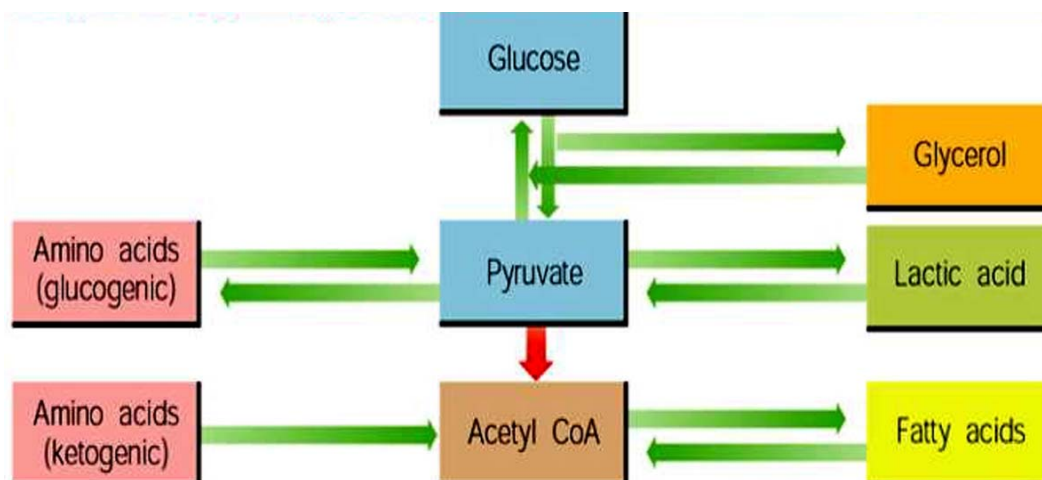
Using Alternative Fuel Molecules in Cell Respiration Pathways

All of our fuel molecules fit into the cell respiration pathways, not just glucose.



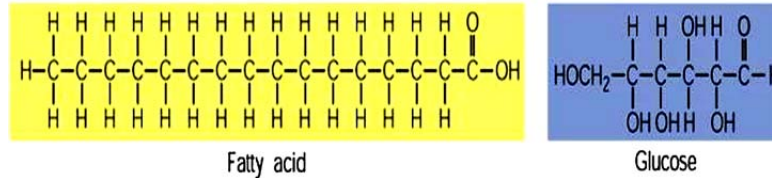
Two critical places for alternative fuel molecules to enter our respiration pathway are pyruvate and acetyl-CoA. For example, we know that when we have insufficient glucose for our brain and nerve cells, any molecule that can be converted to pyruvate can ultimately be used to form glucose, although it is an energy consuming step. In our respiration pathway, however, the step from pyruvate to acetyl is not reversible. Fuel molecules that are converted to acetyl, or to acids that are a part of the Krebs cycle are not only unavailable for conversion to glucose, but are useful only in aerobic respiration.

As an introduction to the metabolism of amino acids and fats, a look at the pyruvate to acetyl relationship relative to all of our fuel molecules is useful. It should be noted that acetyl is a major point for the conversion of all excess fuel molecules to fats as well. If we have sufficient energy, acetyl need not enter the Krebs cycle and is diverted to the formation of fatty acids for adipose storage. This acetyl can come from any fuel molecule: glucose, fatty acids or amino acids.

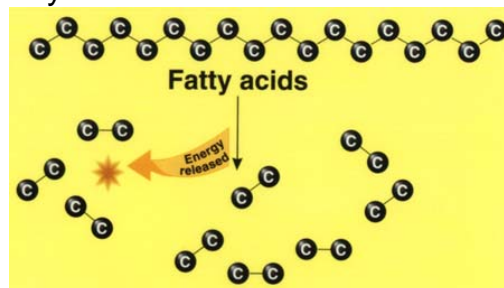


Lipids in Cell Respiration Pathways

- Fats are more energy rich than carbohydrates. A gram of fat *potentially* can produce two times as much ATP as a gram of carbohydrate, because there are more C-H bonds in fats than in carbohydrates



- Most moderate muscle activity, such as breathing and heartbeat, routinely uses a mixture of fats and carbohydrates for this reason and to ensure adequate glucose availability.
- For each fat molecule, one glycerol is produced. Glycerol is converted to glyceraldehyde-3-phosphate (G3P), an intermediate step in glycolysis, and then to pyruvate, and if, needed, to glucose. It takes two triglyceride molecules to form one glucose. Fats are not a way to obtain glucose for the brain and nervous system cells when carbohydrate is lacking in the diet.
- Depending on the fatty acids in the triglyceride, it is not unusual to produce 20 or more acetyl molecules for cell respiration. After activation by coenzyme-A, 2-carbon fragments are broken off from the fatty acid chains and converted to acetyl.

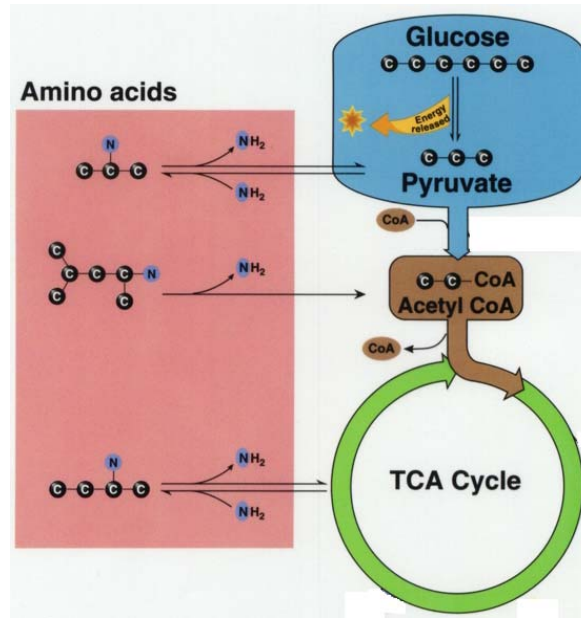


Proteins in Metabolic Pathways

- All amino acids must be deaminated prior to being used for fuel or when in excess converted to adipose for fuel storage. Deamination produces **ammonia** that must be converted to urea in the liver for excretion by the kidney. Recall that the osmotically active urea requires additional water for excretion.

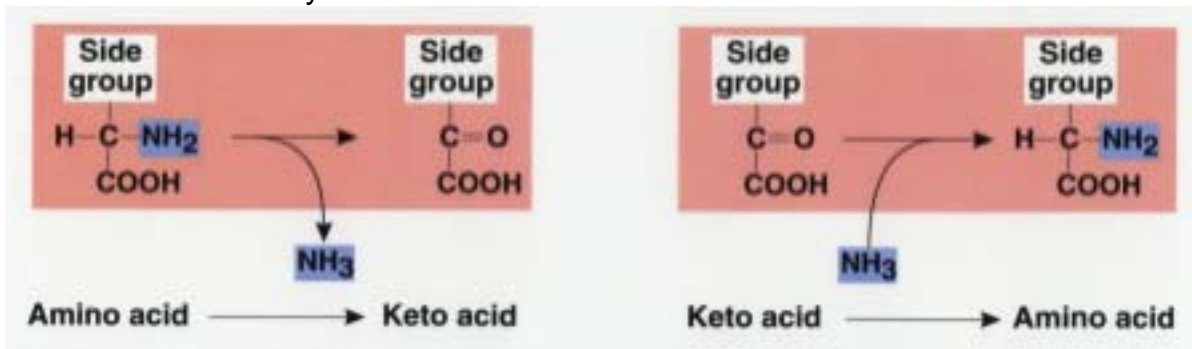
Amino Acids in Cell Respiration

- Amino acids that can be converted to pyruvate are called **glucogenic**, because they can be metabolized "back" to glucose to provide glucose to brain and nervous system cells and developing red blood cells.
- Amino acids that are converted to acetyl are called **ketogenic** and are available only to the Krebs cycle and aerobic respiration.
- Some amino acids are converted to acid intermediates of the Krebs cycle. The amount of ATP produced depends on the point of entry into the Krebs cycle.

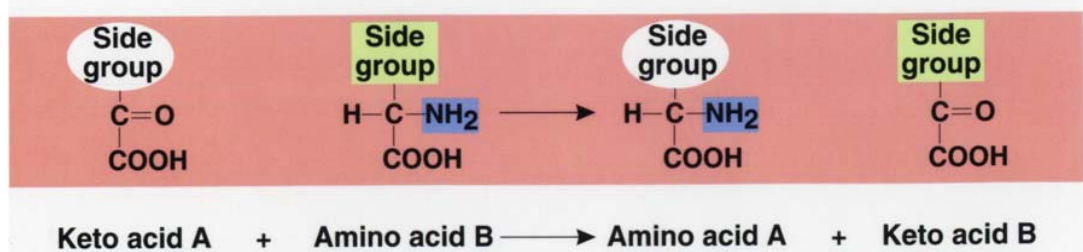


Amino Acid Inter-Conversions - Transaminations

- If there is excess nitrogen in the body, non-essential amino acids can be produced from keto acids. Keto acids can be formed from fatty acids. (They are called keto acids because they have a double-bonded oxygen atom (=O) in the middle of the carbon chain.) Some acids in the Krebs cycle can also be used to synthesize non-essential amino acids.



- Non-essential amino acid inter-conversion follows a similar process.

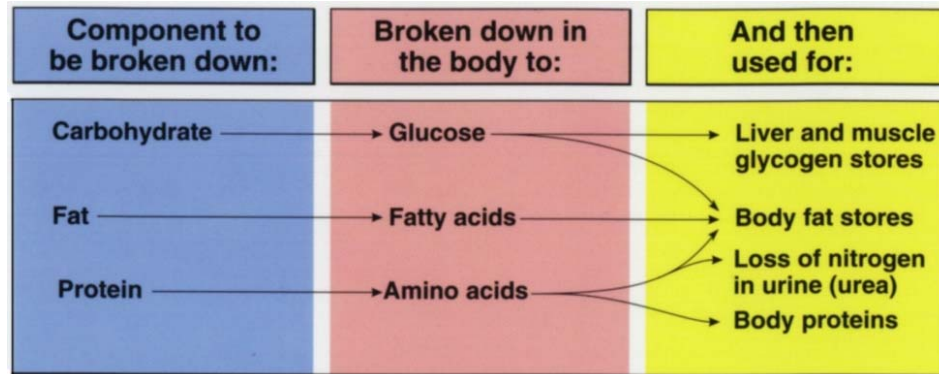


Amino Acid Conversion to Fat

- When there are too many proteins ingested for the body's needs, excess amino acids will be converted to adipose. Glucogenic and ketogenic amino acids are first deaminated and then converted to their "energy" intermediates and then to acetyl-CoA. The acetyl-CoA molecules are readily assembled into adipose for storage.
- When glucose is inadequate, but total calories are sufficient, protein in general is used to make glucose, but the amino acids in the proteins used that cannot be converted to pyruvate and are not needed for energy purposes will be converted to adipose. We can and do accumulate fat reserves from eating protein, in particular when we consume low levels of carbohydrate but more than enough total calories. Proteins in the diet are used first in metabolism, but glucose needs for brain and nervous system cells take priority over structural protein needs. Absence of carbohydrate can lead to loss of body protein no matter how plentiful fat reserves are.

Monitoring Energy Supplies: "Fasting" and "Feasting"

In an ideal situation, we consume calories and proportions of nutrients commensurate with our body's needs: Carbohydrates will be metabolized for fuel and short-term reserve, proteins will be metabolized for the body's protein needs and fats for fuel and lipid requirements, including essential fuel reserves. But we are seldom "ideal" Often we consume more calories than needed, a condition called "feasting" and sometimes consume too few calories for our needs, called "fasting" when it's voluntary and "starvation" when involuntary.



"Feasting" – More calories consumed than needed

When we have surplus nutrients, excesses are handled in different ways, but all excess calories consumed will ultimately be converted to adipose and stored.

- **Carbohydrates**

Excess carbohydrate is first converted to glycogen for short-term storage. Once glycogen stores are filled, and we continue to have excess glucose from foods consumed, the body automatically decreases the amounts of lipids and proteins being used for fuel and uses more glucose. If there is much excess glucose, some will be excreted by the kidney. Glucose, like urea, is osmotically active, and more water will also be excreted.

- **Proteins**

As discussed, protein intake beyond body protein needs leads to deamination and conversion to fuel intermediates. The body will decrease a bit the amounts of lipids being used for fuel when there are surplus amino acids, but when total calories of carbohydrate are sufficient for body needs, amino acids are oxidized to acetyl and then converted for fatty acids and stored as adipose reserves.

- **Fats**

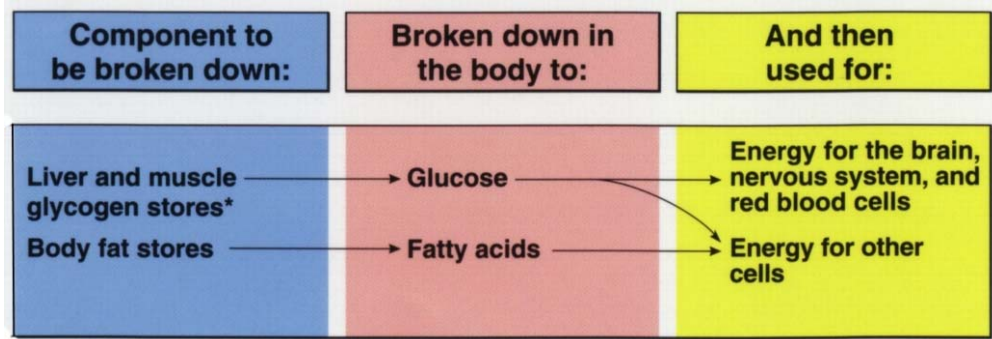
When we over-consume total calories, the fat component of our intake is readily converted to adipose rather than being used for fuel. However, all excess calorie intake will be converted to adipose, not just fat.

"Fasting"

When the diet does not supply sufficient molecules needed for fuel in circulation, the body responds by using its stores of fuel and body tissues.

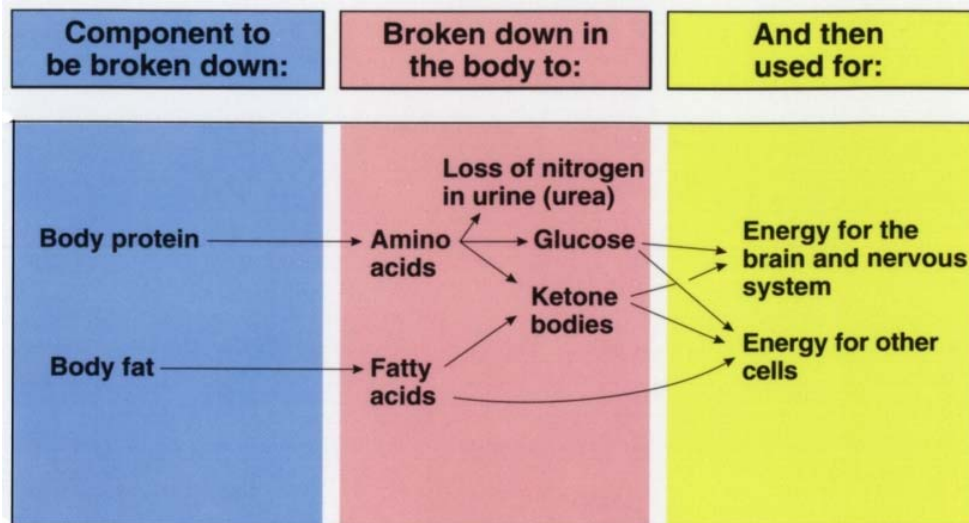
Immediate Response

- Reserve glycogen is converted to glucose to maintain the needed blood levels of glucose.
- Body fat reserves are drawn into circulation to supplement glucose levels for fuel purposes.



When Glycogen Reserve is Depleted

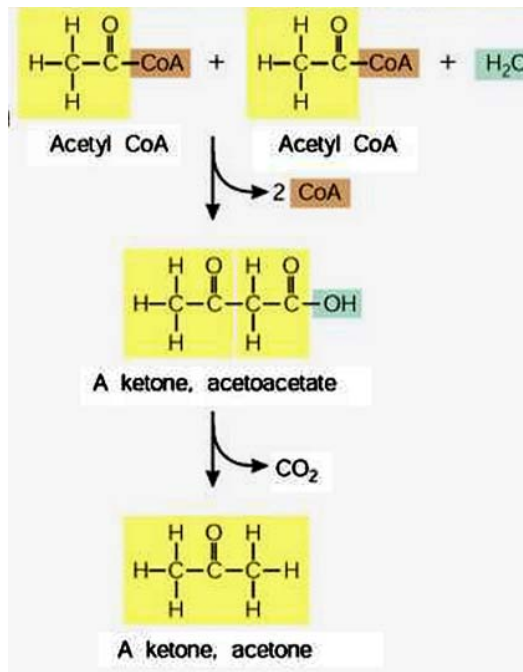
- When glucose levels are low, and glycogen is depleted, adipose breakdown is accelerated so that most cells will have acetyl for fuel.
- Brain, nervous system and red blood cells need glucose - about 20 – 25% of the total energy requirement. This cannot be met by acetyl from fat degradation.
- Protein (usually from muscle tissue) is used to supply brain with glucose (about 90% of its needs)
- Glycerol from fat breakdown supplies about 10% of the glucose needed for these tissues.



Longer-Term Response to Fasting - Ketosis

If fasting continues for more than a few days further adjustments are made to reduce the rate at which body protein tissues are degraded. Protein degradation is slowed (but not stopped) by a shift to **ketosis**

- Acetyl fragments from fatty acids are combined to form ketone bodies that can enter the brain and be used for fuel for some brain cells, but some glucose from protein is still needed.
- Keto acids (ketones with a carboxyl (COOH) acid group attached) and ketones lower blood pH and are also excreted by the kidney. This negative affect on blood pH and kidney function is toxic, and is a symptom of poor health.
 - Ketosis suppresses appetite
 - Ketosis lowers basal metabolism



- Protein degradation in muscles results in lowered muscle metabolism, too.

The long-term effects of starvation or fasting include

- Wasting of body tissues
- Slowed metabolism
- Lowered body temperature
- Suppressed immune function and increased susceptibility to infection and disease

Ketosis-Inducing Diets

Low carbohydrate diets mimic fasting, and trigger many of the same responses as fasting and starvation. Ketosis, although appetite suppressing, causes serious blood pH and kidney problems. Reduced calorie diets with a balance of carbohydrate, protein and fat, accompanied by exercise achieve a healthier weight loss, even if sometimes more slowly. Moreover, accumulated evidence shows that maintenance of long-term weight loss comes with a balanced diet, high in vegetables and fruits, along with exercise.

High protein diets are based on the idea that consuming enough dietary protein on a calorie restricted diet or fast will prevent the body from using its own stores of protein. By itself this does not work, and glucose is, in fact, a better fuel source for "sparing" the body's protein stores.

The promoters of specific high-protein diet may or may not claim to prevent ketosis, caused by the breakdown of fat, but to diminish those fat reserves without sufficient carbohydrate for brain tissues, automatically induces ketosis.

During this decade, the popularity of the high protein diet, primarily the Atkins diet has "boomed". There are a number of other popular high-protein, low carbohydrate diets, too. People lose weight and eat foods they have always enjoyed.

Psychologically, it helps to deprive yourself of calories if the foods you eat are ones you like and are exactly the foods health officials have been restricting for dieters for years. TV ads, including those for fast food chains are full of high protein and low carbohydrate recommendations. Whole new brands are marketed based on being "reduced carbs". All fail to consider long term health and diet planning.

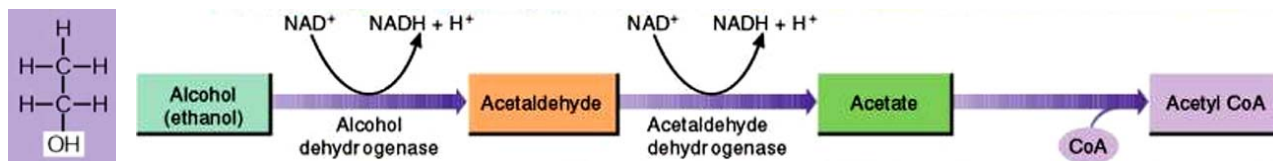
During periods of the 70's and late 80's, protein liquid diets were also popularized. Unfortunately, a number of deaths occurred in the 70's among those who used these diets. Under certain medical conditions, including morbid obesity, such diets are still used.

Protein-sparing is also of concern with illness. Patients are given glucose and amino acids to help the body recover from serious illness and trauma. It is also important during illness to prevent ketosis.

Highlight 8 of your textbook has more information about high-protein diet plans.

Alcohol and Metabolism

As mentioned, ethyl alcohol, a toxin often consumed by humans, can be oxidized as a fuel molecule. The 2-carbon ethyl alcohol can be converted to acetyl-CoA and used in aerobic respiration. Alcohol has about 7 calories/gram of energy.



The toxic effects of alcohol are unrelated to its energy value, although the processing of alcohol impacts liver, kidney and brain function, all of which contribute to maintaining optimum nutrient balance in our cells and tissues.

Alcohol in the Stomach

When we consume alcohol, about 20% crosses the stomach lining to immediately enter circulation, where it can target cells in all areas of the body. The rate at which alcohol crosses the stomach lining is related to foods consumed with the alcohol. The molecules have to reach the stomach lining, and when mixed with food, fewer do so. When consumed with carbonated beverages, more can because of the carbonated gas.

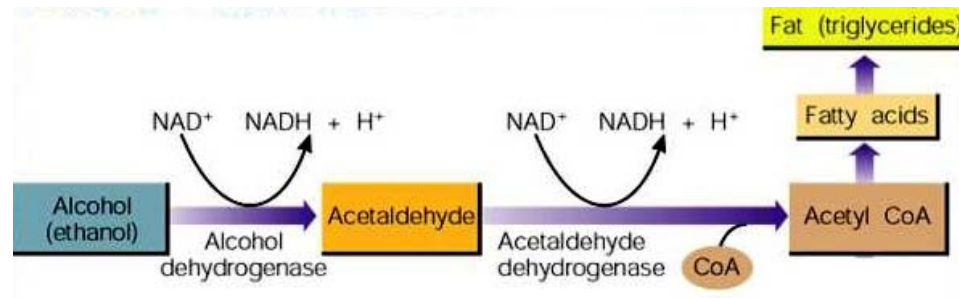
Alcohol that remains in the stomach is acted upon by **alcohol dehydrogenase**, which converts alcohol to acetaldehyde. High concentrations of acetaldehyde in body tissues are the cause of many of alcohol's negative effects.

Men produce more alcohol dehydrogenase than women. The amount of time alcohol stays in the stomach determines how much alcohol is degraded, and time is related to foods consumed with the alcohol.

Alcohol in the Liver

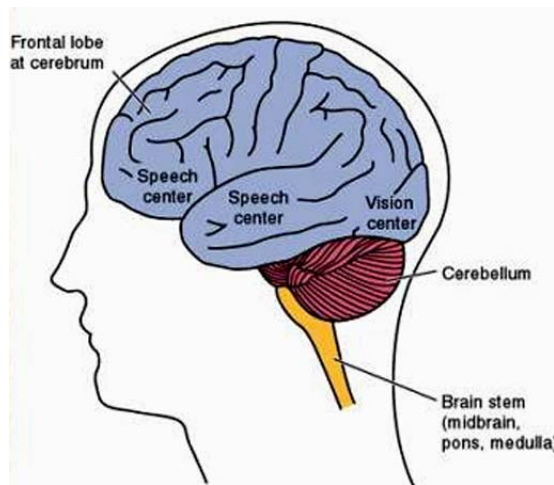
Alcohol that enters the small intestine is rapidly absorbed (it's a small molecule that readily passes through the membranes) and enters the liver which also produces alcohol dehydrogenase, sufficient to degrade about 1/2 ounce of alcohol in an hour. Alcohol in excess of that will pass through the liver and enter general circulation where it can enter all cells and tissues.

Alcohol, for reasons unknown, is given priority by the liver over nutrients, particularly fatty acids, which can accumulate in the liver tissue. Fatty deposits in the liver are a consequence of chronic over-consumption of alcohol. In addition, conversion of alcohol uses NAD, diverted from respiration metabolic pathways, so metabolism is less efficient. Without NAD for cell respiration, pyruvate and acetyl accumulate and are converted to fats, increasing the fatty build-up in liver tissue for chronic over-consumers of alcohol.



Alcohol in the Brain

Alcohol that enters general circulation from the stomach or the liver readily passes through the brain membranes and attacks brain cells as a sedative narcotic.



Alcohol specifically impairs:

- Perception – judgment and reasoning ability
- Speech and vision
- voluntary muscular control

And in high concentration:

- Respiration and breathing. People can die from toxic alcohol consumption.
- Regrettably, far more die from accidents, typically automobile accidents, caused by alcohol impairment of brain function.

In addition, alcohol suppresses ADH, thereby affecting kidney function so dehydration is a result of alcohol consumption

Chronic Alcohol Consumption and Malnutrition

Those who chronically over-consume alcohol are typically malnourished. Alcohol affects stomach secretions, affects the ability of the intestine to absorb, and inhibits a number of vitamin functions in many tissue areas, exacerbating the malnourishment.

Highlight 7 of your textbook has excellent information on the effects of alcohol.