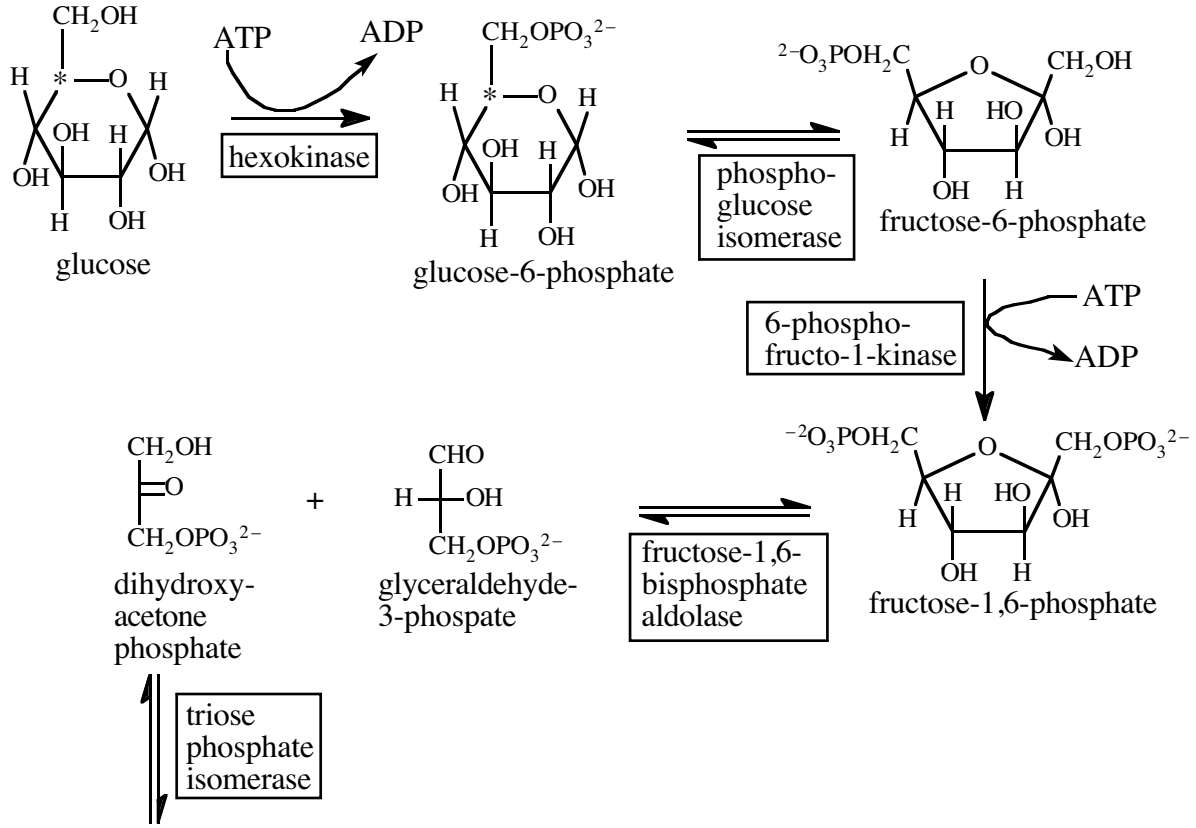
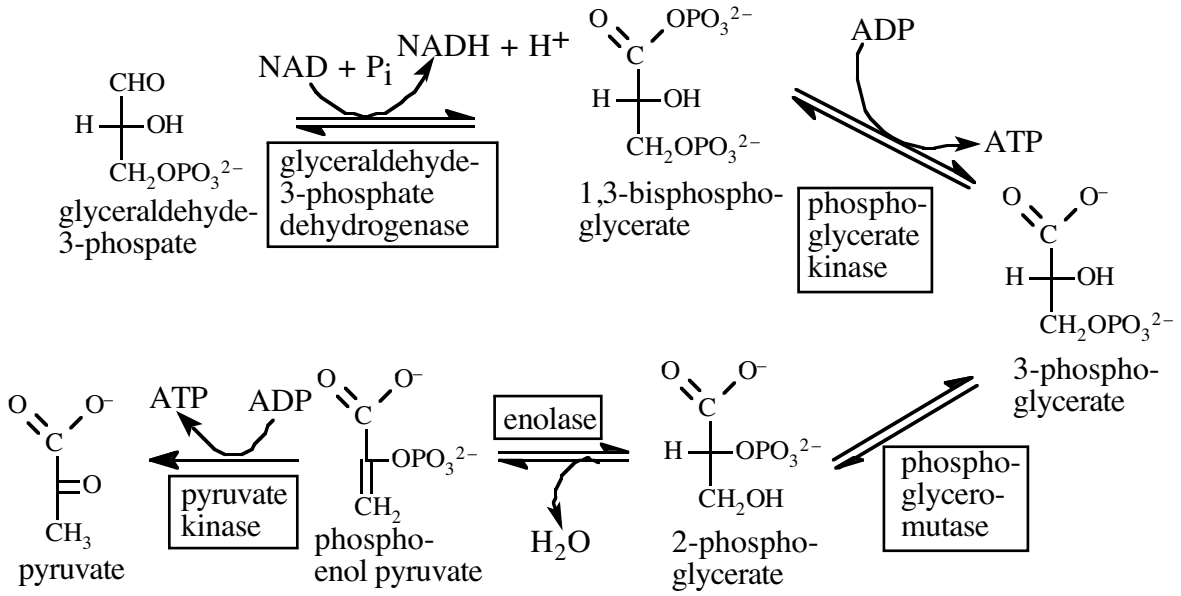
Carbohydrate Metabolism

Glycolysis - Glucose Catabolism: The most important hexose nutritionally is glucose. It is the most commonly found monosaccharide (with the possible exception of deoxyribose), and it has been studied more than any other sugar. Many sugars (especially complex carbohydrates) are converted into glucose in the body before anything else happens.

The steps of glucose catabolism are numerous and involve a myriad of enzymes. Though we will not describe the absolute mechanisms of the enzyme reactions, we will list the steps along with the associated mechanisms. In writing the reactions, it is customary to include side reactions (namely ATP to ADP) as curved arrows. These are real reactions, but the main reaction is what we are interested in.

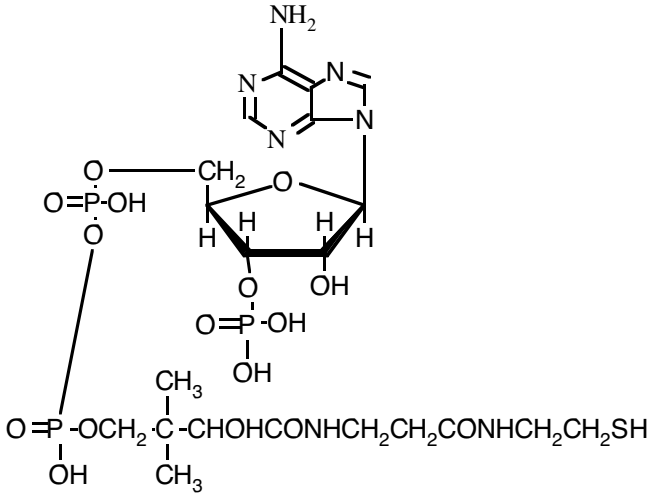




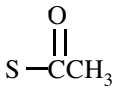
Of course, 2 pyruvates are produced for each glucose. It is also of interest to note that 2 ATP are used, and a total of 4 are formed. This is not great source of ATP, nor is it a big sink. Also, NADH must be oxidized back to NAD for it to be used again. This is a common consequence in metabolism, and we will look at this issue later.

More Energy - The Krebs Cycle: Since glycolysis produces only 2 ATP, why is it that we always hear that carbohydrates give you energy? The answer is that pyruvate is the starting point of the main energy producing metabolic pathway in the body. And, since sugars give two pyruvates relatively easily (I know, it didn't look so easy, but relative to other metabolic processes, it is!), two cycles can occur. We will now look at the Krebs cycle in more detail.

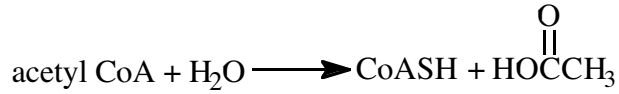
Before we actually get to it, however, we must introduce the cofactor **coenzyme A**, or **CoA**, and the related compound, **acetyl CoA**. Both are sulfur containing compounds derived from ATP and pantothenic acid (a B-vitamin). The structure of this compound is:



In acetyl CoA, the SH at the end is replaced by

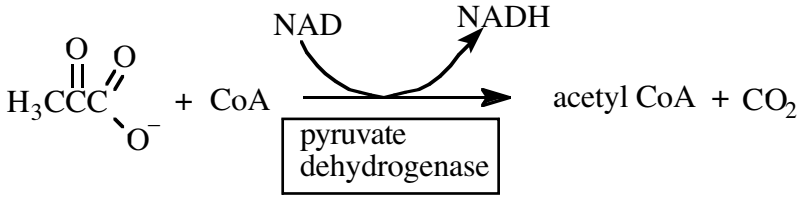


These compounds will play a major role in the TCA cycle. Acetyl CoA is a "source" of energy for several reactions, much like ATP was in glycolysis. The reaction that gives off the energy is the hydrolysis of the **thio-ester**:



We are now ready to begin the discussion of the citric acid cycle.

Pre-First Step: The pyruvate that was made by glycolysis is now ready to be used for some real energy production. The first thing that happens is that is converted to acetyl CoA by the reaction:

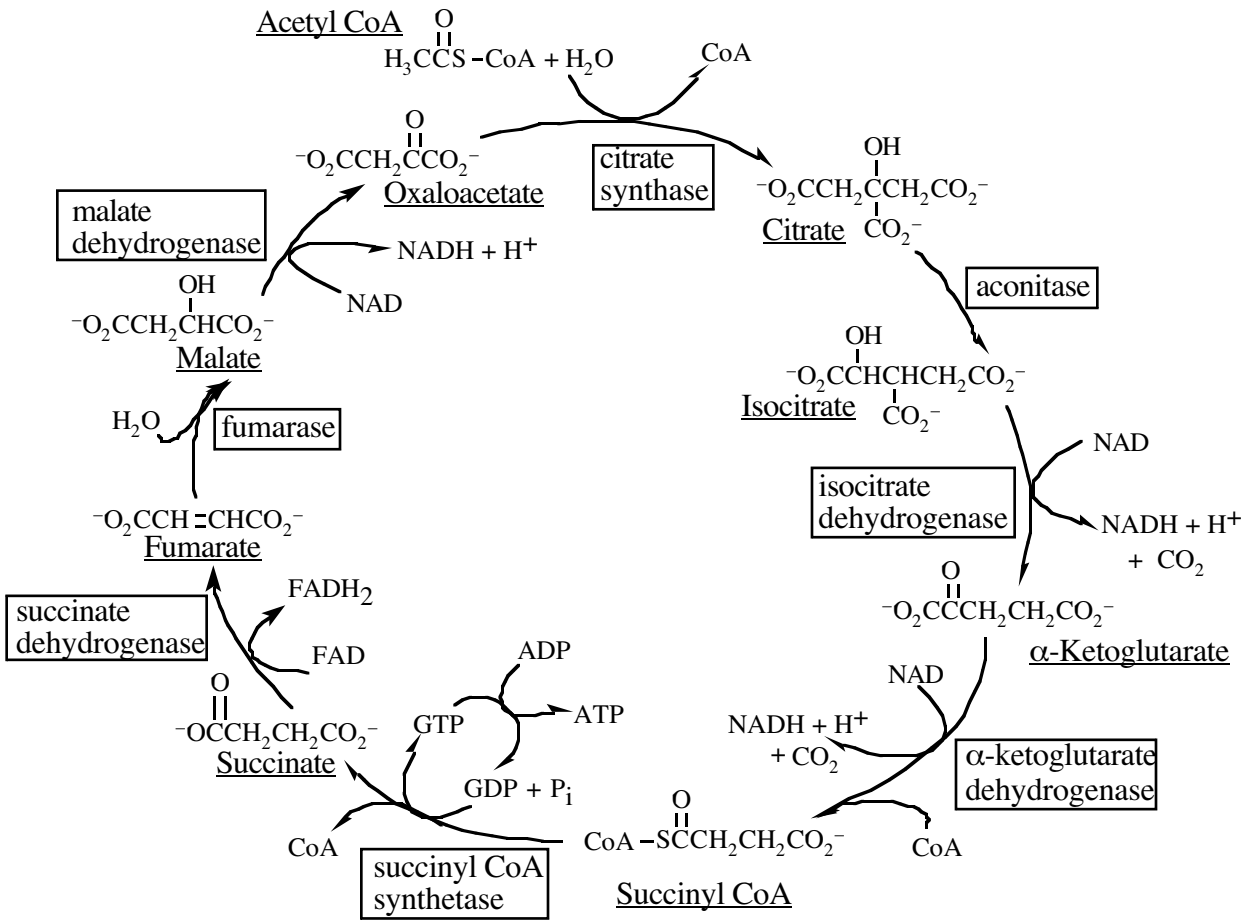


The enzyme pyruvate dehydrogenase is actually a complex of several enzymes, each with a specific task. There is one that **decarboxyaltes** (removes CO_2) the pyruvate; then there is one that attaches the acetyl group to the CoA. Each of these sub-enzymes has there own cofactors, which we will not go into here.

The TCA cycle also produces CO_2 as a waste product, which must be removed from the body. That's why we exhale!

The Krebs Cycle: The molecules involved in the cycle are relatively small di- and tri-carboxylic acids (TCA). The first step involves forming citric acid, hence the name "citric acid cycle", which itself is a TCA. Hans Krebs elucidated the cycle in about 1937, which is why we call it the "Krebs cycle". Whatever it is called, it is an important biochemical process that we will try to look at in some detail.

The acetyl CoA produced in the glycolysis pathway is the starting point of the cycle. Each turn of the cycle involves 8 steps, and produces 1 ATP molecule directly. However, as we will see shortly, the oxidation of NADH and $FADH_2$ (a co-enzyme derived from the B-vitamin **riboflavin**) to NAD and FAD, respectively, also involves the production of ATP (this process is called **oxidative phophorilation**).

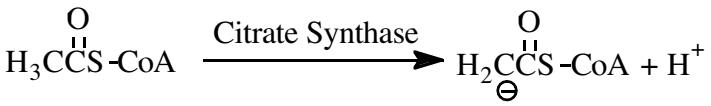


In the Krebs cycle, the ATP is not formed by the direct phosphorylation of ADP. Rather, a related compound, **GTP** (**guanosine** triphosphate) is made from GDP and P_i, which in turn gives up its P_i to ADP to form ATP. This is because of the specialized nature of the enzymes involved. However, ultimately, ATP is the storehouse of energy.

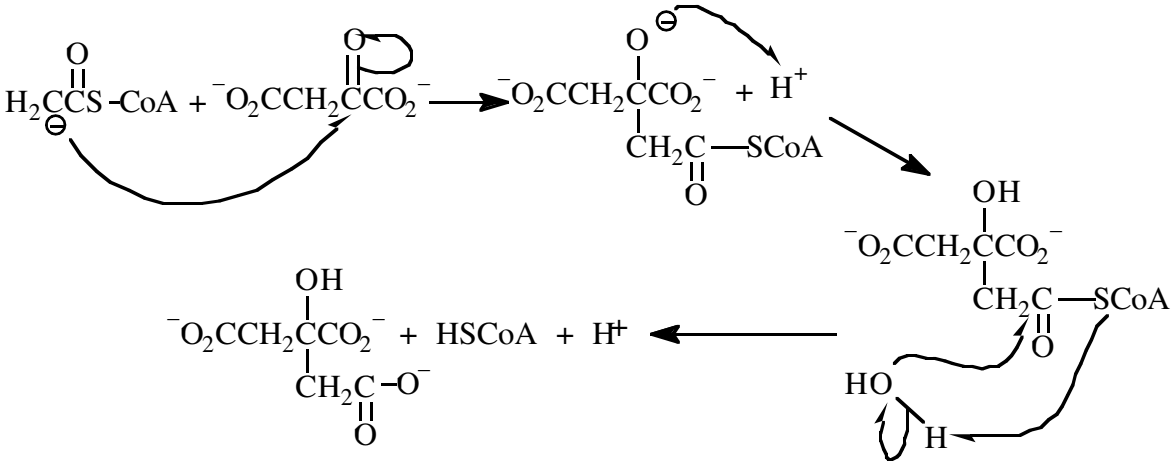
The TCA cycle is of fundamental importance, since it not only produces ATP by breaking down acetyl CoA, but it can also FORM acetyl CoA, which is a staring material in **fatty acid synthesis**, which we will discuss later. Because it is both anabolic and catabolic, it is sometimes referred to as an **amphibolic** pathway.

Closer Look at Some Steps: It is often very interesting to look at the chemistry (i.e., mechanism) of some of the steps in the reactions. In doing so, we can see how the enzymes' active sites are tailored to the specific reactions. As always, these mechanisms are postulated, but not proven. So, if one day these steps are shown to occur via a completely different path, don't get mad at me!

The very first step, forming citrate from oxaloacetate and acetyl CoA, is thought to occur as follows:

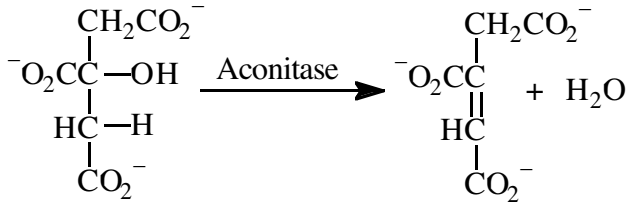


The deprotonation of the methyl group is accomplished by a strongly basic group in the active site of the enzyme. The anionic form of acetyl CoA is now ready to react with oxaloacetate:

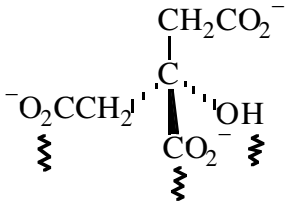


The first step is reminiscent of an **aldol condensation**, and the last step is a thio-ester hydrolysis.

Even though citrate is achiral, the next molecule, isocitrate, is chiral. The conversion of citrate to isocitrate requires that the citrate be positioned correctly so that the correct enantiomer of isocitrate is formed. In this instance, citrate is called **prochiral** since its orientation ultimately determines the chirality of the product. The reaction proceeds as follows:

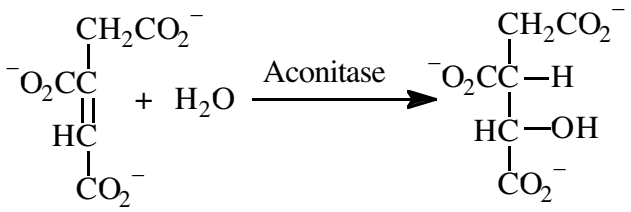


The second organic acid is called ***cis*-aconitate**. The orientation of the citrate must allow for the *cis* isomer to form instead of the *trans*. This can be accomplished if the citrate molecule is oriented as follows (relative to a binding site in the active site that corresponds to this shape):



The squiggly lines represent the binding site in the enzyme.

The next step in the process is the **anti-Markovnikov** hydration of the double bond to form isocitrate:



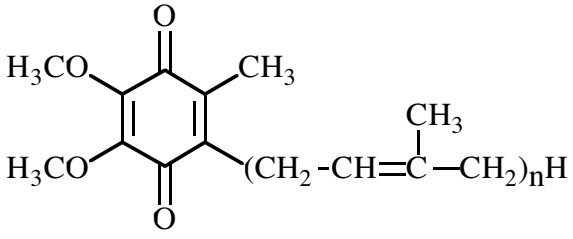
The *cis*-aconitate is still bound to the active site of the aconitase enzyme, so the hydration is also catalyzed by the enzyme.

Oxidative Phosphorylation - Part 1: The glycolysis pathway and the Krebs cycle require NAD and/or FAD to be reduced to NADH and/or $FADH_2$. However, once these molecules are reduced, they must be re-oxidized in order for them to be re-used. And, since oxidation is often a very exothermic process (think of the combustion of alkanes), it would seem that there ought to be a way of harnessing the energy released in the process. This is where the oxygen we inhale comes into play. The reduced NADH and $FADH_2$ are allowed to react with the oxygen (i.e. become oxidized), producing water and ATP. This process is called **oxidative phosphorylation**, since ADP is phosphorylated to form ATP while an oxidation is occurring. (The process takes place inside the **mitochondria** in the cell, which is why the mitochondria is sometimes referred to as the "power plant" of the cell).

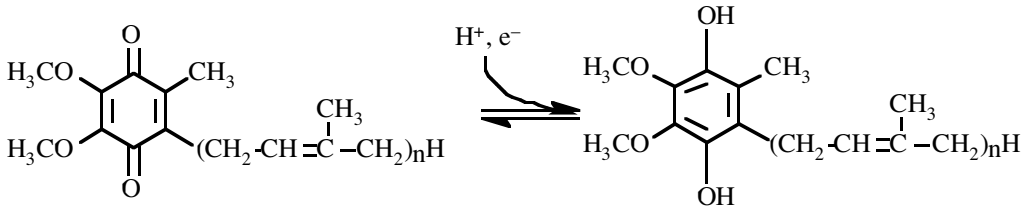
Ultimately, oxidation is the process of transferring an electron from one atom to another. The physical movement of the electrons in oxidative phosphorylation is governed by a group of enzymes and co-enzymes, known collectively as the **electron transport chain**. The enzymes fall into a general class known as **cytochromes**, where "cyto" refers to being inside the cells (not the mitochondria), and "chrome" implies something about the property of these enzymes to change color when they are oxidized or reduced.

Cytochromes all share a very crucial characteristic: they all contain iron ions as cofactors. The ions change from Fe^{3+} to Fe^{2+}, and vice versa, depending on whether oxidation or reduction is occurring.

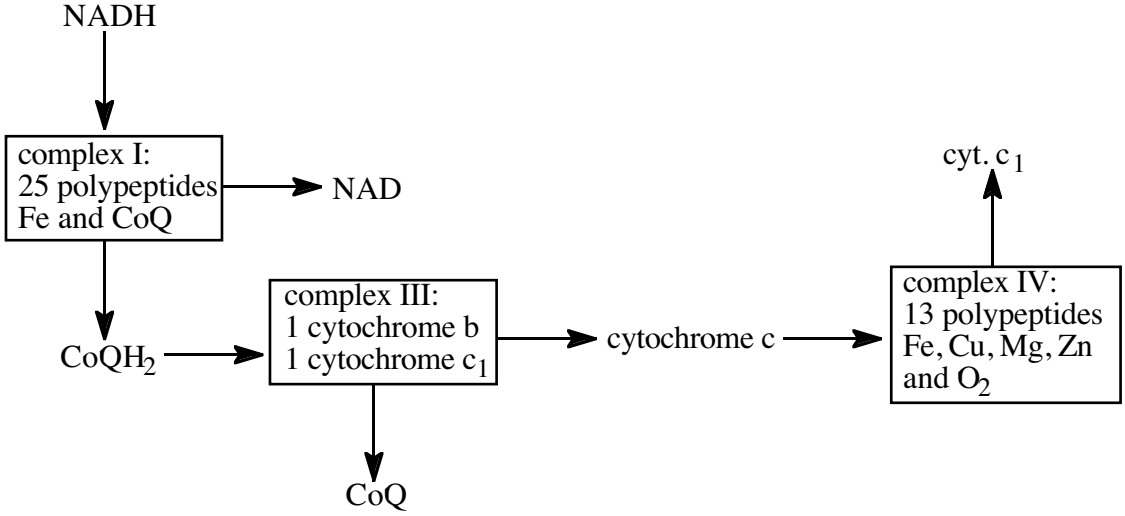
Another important component of the electron transport is a group of molecules called **ubiquinones** (or **coenzyme Q**, or CoQ for short):



The subscipt "n" denotes a repeating unit of variable length. Depending on the value of n, the CoQ takes on different names (e.g. CoQ_{10}), but the activity is always the same. The CoQ accepts 2 electrons (and 2 H^+s as well) to give ubiquinol (or $CoQH_2$):



The various molecules involved are grouped into different "respiratory complexes", each of which performs one step of the electron transport into the mitochondrion. Without going into detail, the following flow chart describes the processes (where we are starting with the reduced NADH as our example):



The respiratory complexes are **trans-membrane** proteins of the mitochondrial membrane. The reduced oxygen binds to 2 H^+s to produce water, and it is this reaction that is coupled to the phosphorylation.

Oxidative Phosphorylation - Part 2: In order for the energy generated by the electron transport to be harvested, the first thing needed is ADP and P_i. Two enzyme complexes, known as **carriers**, attract ADP and P_i into the mitochondrion. Interestingly, certain toxins (namely bongkrekic acid - a fungal toxin) inhibit the action of the carriers.

The synthesis of the ATP is then performed by a collection of proteins called **ATP syn-thase**, which is comprised of 9 subunits. Three of the subunits form a stalk imbedded in the mitochondrial membrane. The other 6, which consist of 3 proteins of one type and 3 of another, are located around the central stalk in an alternating pattern. It is believed that the two different proteins form an active site. It is also believed that each pair of proteins can form an ATP but that they do so in an allosteric way: as one site is forming ATP, another site is pulling in ADP and P_i, and the third site is spitting out a newly made ATP. In other words, each site is at a different stage of the synthesis process.

Net ATP Production: The amount of ATP produced per molecule of NADH oxidized turns out to be 2.5 (and for $FADH_2$ it is only 1.5). Therefore, since the catabolism of glucose produces 2 NADH (one for each pyruvate), there are 5 ATP + 2 ATP produced due to glycolysis.

The formation of acetyl CoA produces one NADH, and there are two produced per glucose, giving 5 more ATP. The TCA cycle produces 1 ATP, 1 $FADH_2$, and 3 NADH per turn, for a total of 10 ATP. Since glucose requires two turns of the cycle, a total of 20 ATP are obtained. Thus, a total of 32 ATP are produced when glucose is completely metabolized.