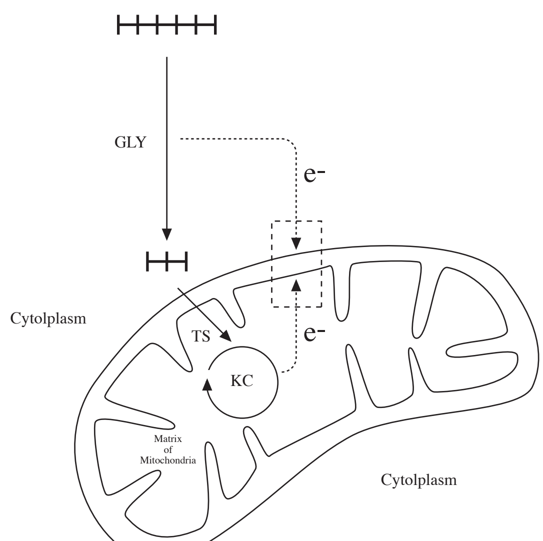
Glycolysis
and
Cellular Respiration

An Introduction to

Essential Cellular Metabolic Pathways



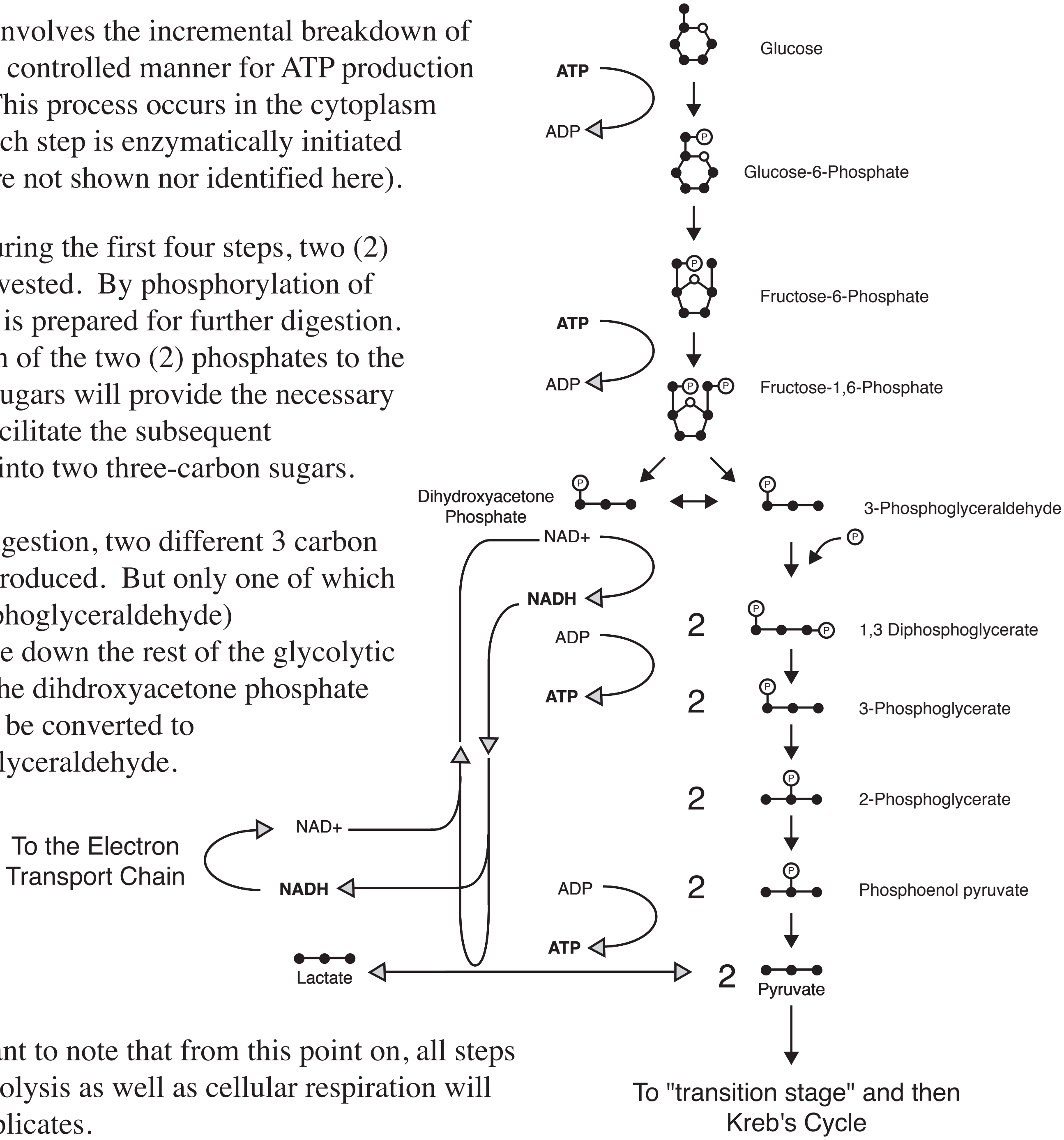
By Noel Ways

Basic Metabolic Pathways: Glycolosis, Part #1

Glycolosis involves the incremental breakdown of glucose in a controlled manner for ATP production purposes. This process occurs in the cytoplasm only, and each step is enzymatically initiated (enzymes are not shown nor identified here).

Note that during the first four steps, two (2) ATPs are invested. By phosphorylation of the sugar, it is prepared for further digestion. The addition of the two (2) phosphates to the six carbon sugars will provide the necessary energy to facilitate the subsequent breakdown into two three-carbon sugars.

After this digestion, two different 3 carbon sugars are produced. But only one of which (the 3 phosphoglyceraldehyde)
will continue down the rest of the glycolytic pathway. The dihdroxyacetone phosphate will have to be converted to 3-phosphoglyceraldehyde.



It is important to note that from this point on, all steps in both glycolysis as well as cellular respiration will occur in duplicates.

The next step involves 3-phosphoglyceraldehyde being oxidized (and NAD+ being reduced to NADH). These harvested high-energy electrons will be "shuttled" to the electron transport chain where ATP production is far more productive. Note also that a phosphate from the cytoplasm is added. Now, each 3 carbon sugar has two phosphates.

A "substrate level phosphorylation" occurs next, where ATP is produced. Since the process is occurring in duplicate, 2 ATPs are generated. The net ATP gain at this point is zero (0).

Basic Metabolic Pathways: Glycolosis, Part 2

What follows next are a few intermediate steps (series of manipulations), and then the final production of pyruvate. Note, again, that two (2) additional ATPs are generated by a "substrate level phosphorylation" during the production of pyruvate. The total ***net gain*** for ATP is therefore two (2).

2 ATP - initial investment
4 ATP - generated (S.L.P.)

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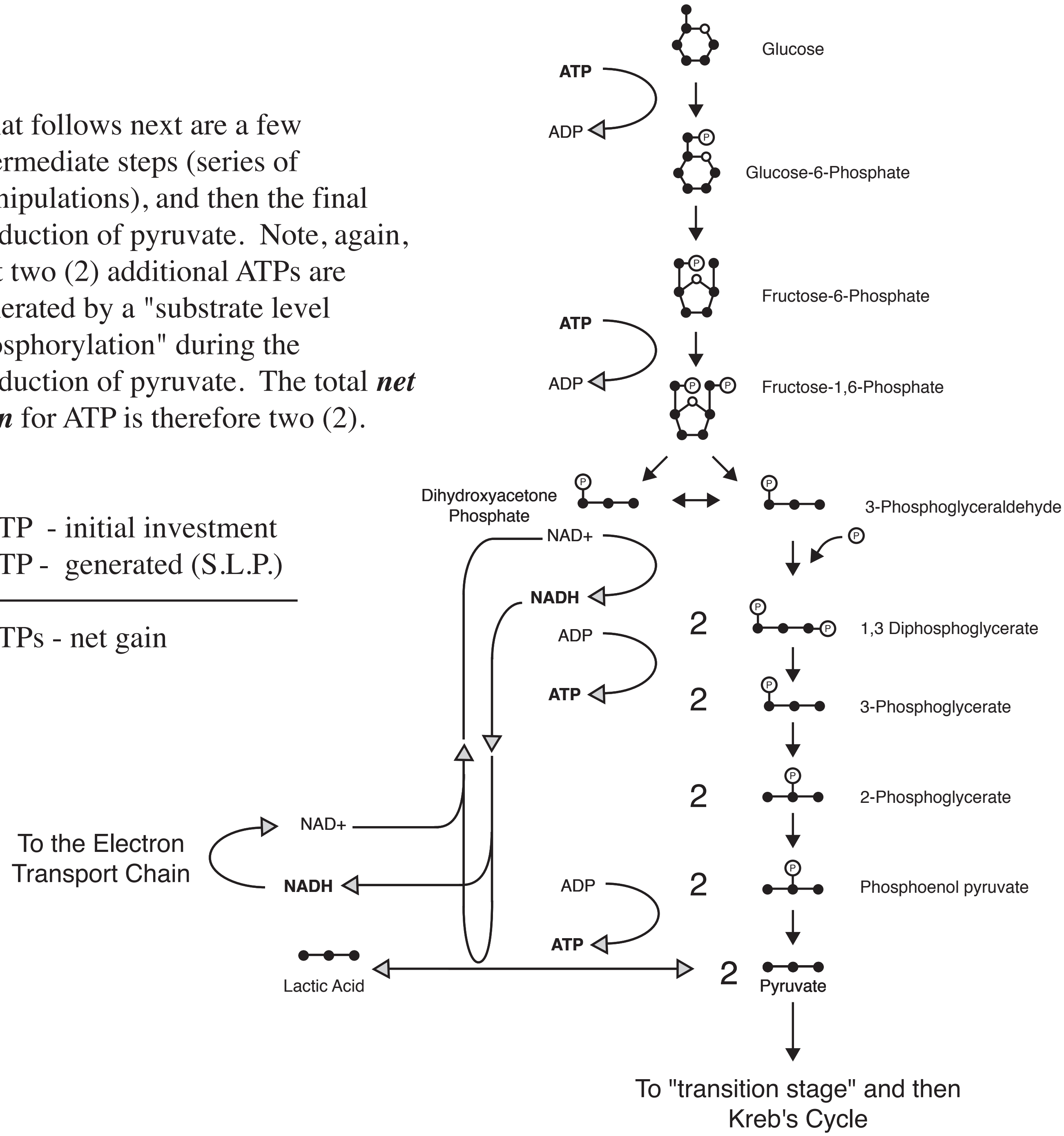
2 ATPs - net gain



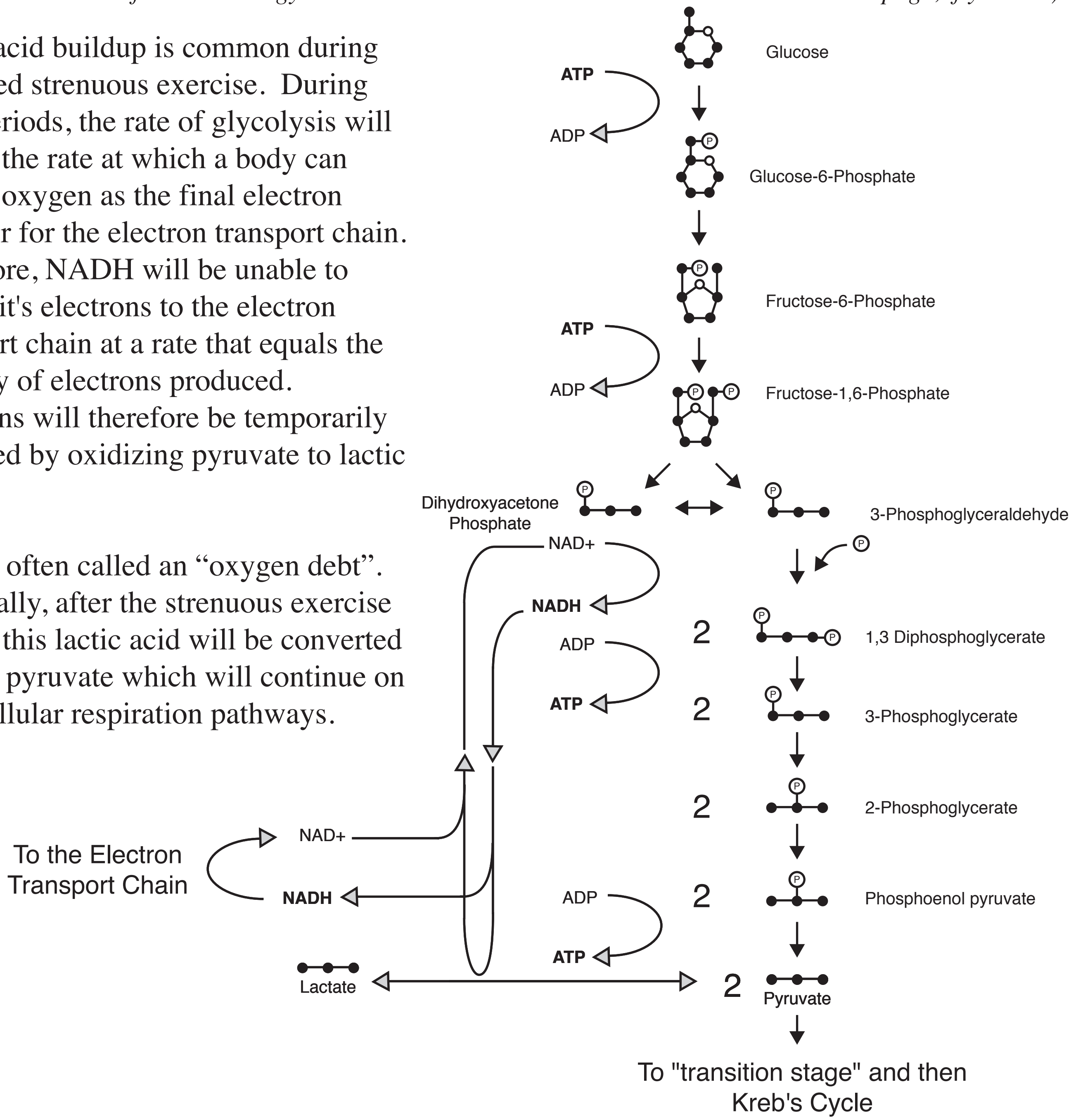
It is important to note that once NAD+ is reduced to NADH, it will not be able to pick up any more electrons until the current load is released. Therefore, NADH must be oxidized if it is to be used again. This can only occur if the electron transport chain accepts the electrons. If the electron transport chain cannot accept them, then pyruvate will be reduced to lactate (and NADH will be oxidized to NAD+). Now NAD+ will be available again to accept more electrons further up the glycolytic pathway. The pathway will continue to run, but there will be a lactic acid buildup.

Basic Metabolic Pathways: Glycolosis, Part 3

(This page will be useful when energy and muscle contaction is considered. Proceed to next page, if you like)

Lactic acid buildup is common during sustained strenuous exercise. During such periods, the rate of glycolysis will exceed the rate at which a body can deliver oxygen as the final electron accepter for the electron transport chain. Therefore, NADH will be unable to shuttle it's electrons to the electron transport chain at a rate that equals the quantity of electrons produced. Electrons will therefore be temporarily unloaded by oxidizing pyruvate to lactic acid.

This is often called an “oxygen debt”. Eventually, after the strenuous exercise ceases, this lactic acid will be converted back to pyruvate which will continue on with cellular respiration pathways.



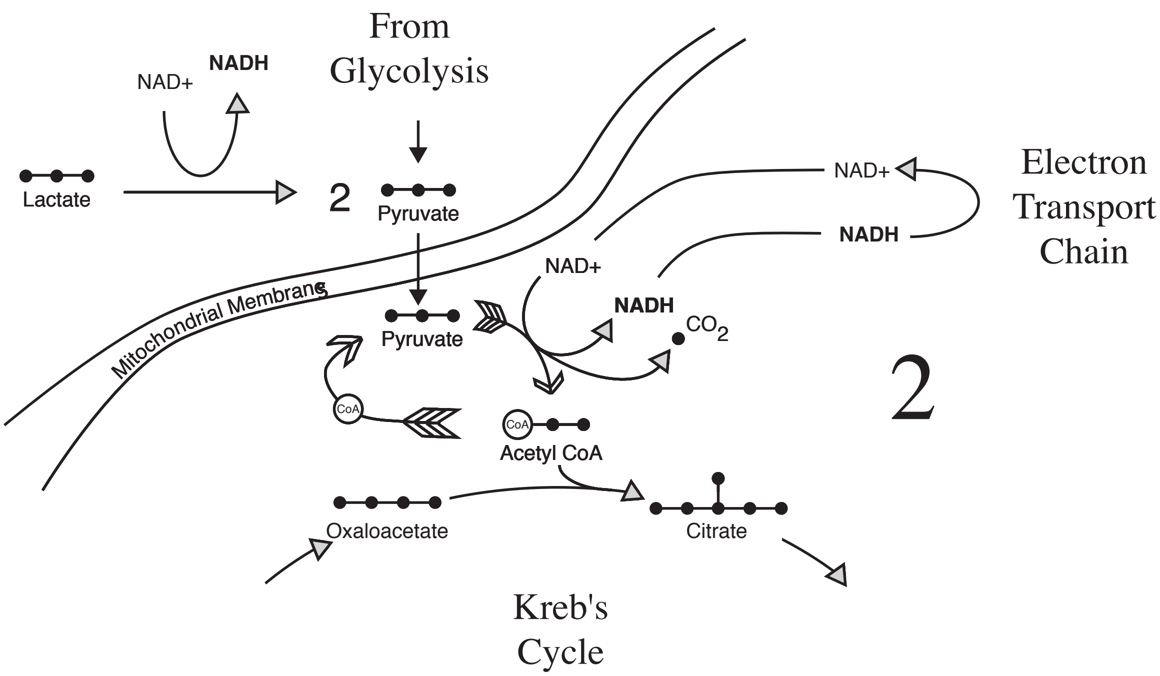
For those of you taking microbiology, you will recall that prokaryotic organisms lack mitochondria, and therefore do not do cellular respiration. Hence, glcolosis is the primary means by which ATP is produced, and pyruvate must continually be reduced.

Whereas in man, an oxygen debt will lead to lactic acid buildup; in bacteria, the final reduced product can be a number of species specific chemicals such as lactic acid, proprionic acid, ethanol, to name a few. These final end products can have important diagnositic functions for the microbiologist.

Basic Metabolic Pathways: Transition Stage

The transition stage is a short set of reactions that feeds pyruvate, the product of glycolysis into the Kreb's cycle. The importance of this "transition" lies in the fact that the Kreb's cycle is highly productive regarding the "harvesting" of high-energy electrons that can be "fed" into the electron transport chain.

The transition stage begins with pyruvate going through the mitochondrial membrane, and where it will be enzymatically broken down to a two-carbon acetyl group and carbon dioxide. This reaction requires Coenzyme A to bond to the acetyl group during which the CO_2 is liberated. Note also that during this process NAD+ is reduced as the pyruvate is oxidized. The NADH will take the high-energy electrons to the electron transport chain.



Once the Acetyl group has bonded to Coenzyme A (Co A), forming Acetyl CoA, the acetyl group then binds to the four (4) carbon oxaloacetate forming citrate. The CoA is liberated and is free to participate in bringing another acetyl group into Kreb's cycle.

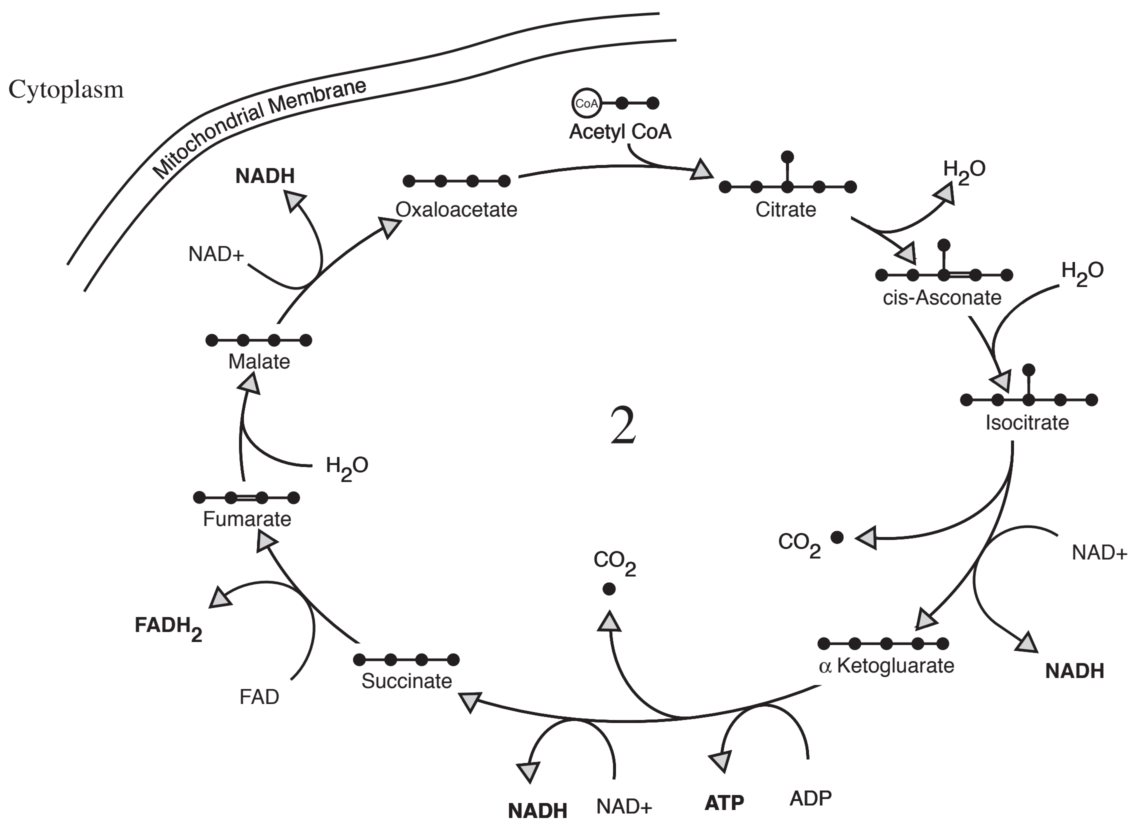
As you will see, the electrons associated with the NADH will produce 3 ATPs. Since this step is occurring twice for each glucose, the transition stage will yield 6 ATPs per glucose molecule.

If there has been a lactic acid buildup (oxygen debt), the lactic acid can also be oxidized to pyruvate, which will also enter the transition stage and then the Kreb's

Basic Metabolic Pathways: Kreb's Cycle, Part #1

Once the pyruvate has been oxidized to a two carbon acetyl-CoA, the acetyl group can now be added to a four carbon oxaloacetate resulting in the six-carbon citric acid.

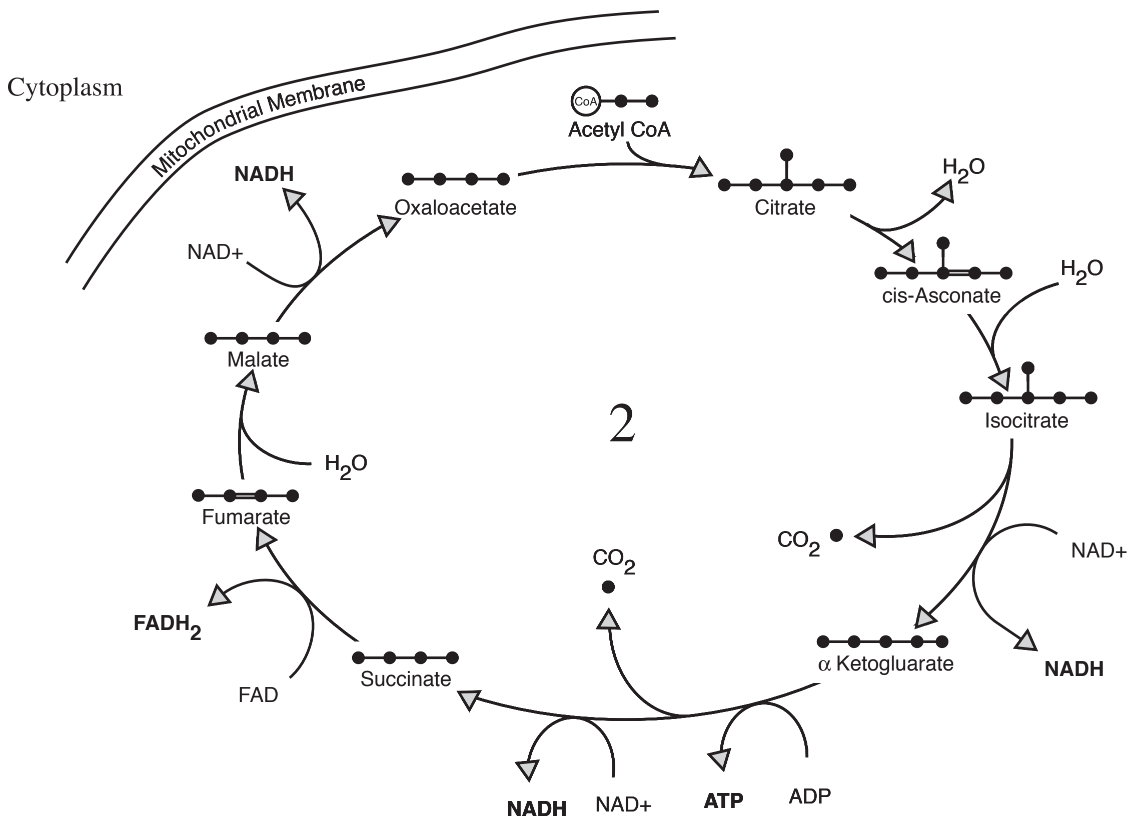
This six-carbon citric acid then undergoes several intermediate steps where it is rearranged until it is eventually oxidized and a carbon dioxide is liberated. In the process NAD+ is reduced to NADH, and this will ultimately result in the production of 3 ATPs. Since the process is happening in duplicate for each glucose, and total of 6 ATPs are produced per glucose molecule. Note this also resulted in a five-carbon compound.



This five-carbon compound is oxidized and loses another carbon dioxide to become a four-carbon compound. In the process, another NAD+ is reduced to NADH and this will again result in a total of 6 ATPS as the cycle is happening twice per one glucose. Note also that 2 ATPs are produced directly by a substrate-level phosphorylation.

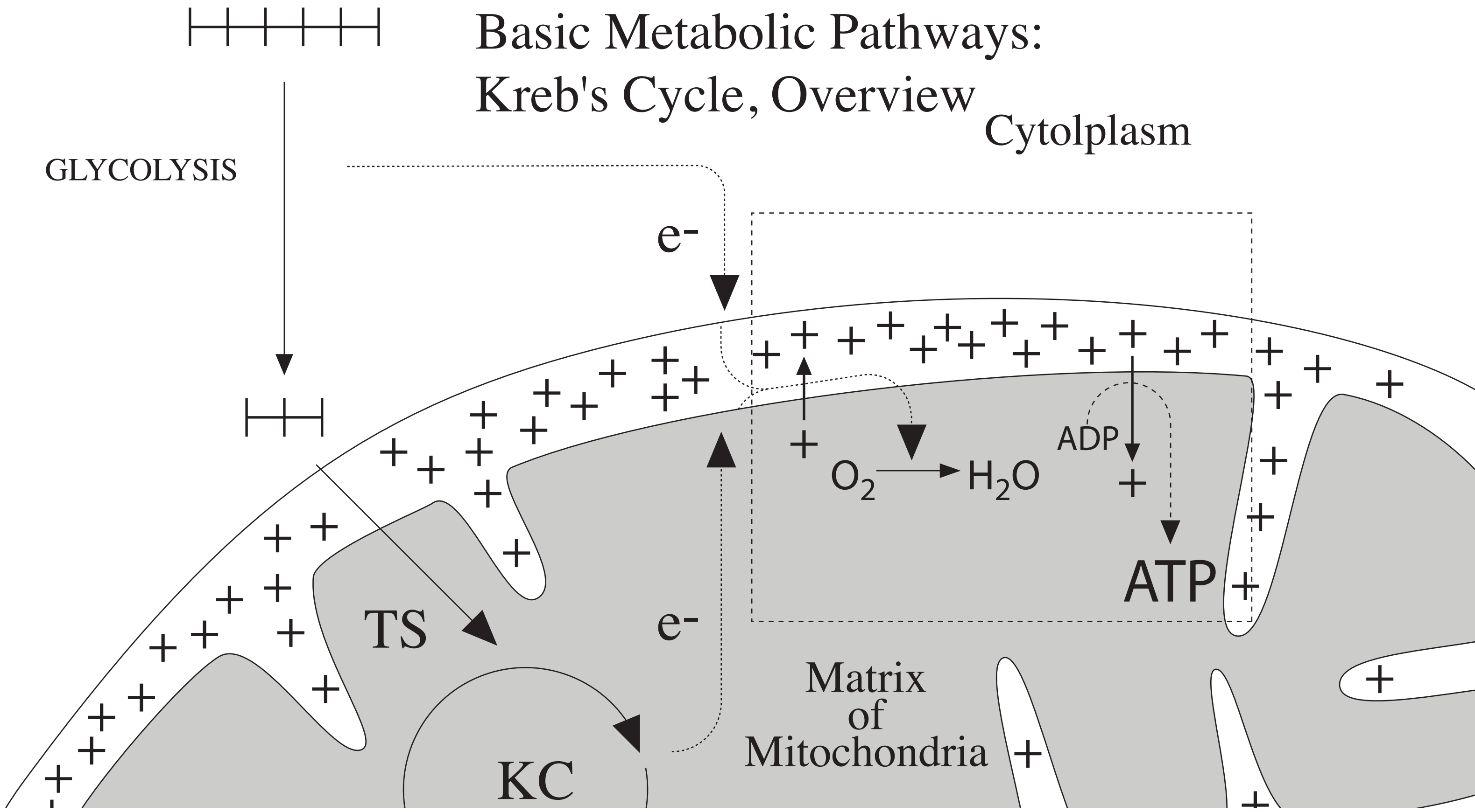
Basic Metabolic Pathways: Kreb's Cycle, Part #2

The next step results in a further oxidation, but with no loss of carbon, nevertheless, the molecule is rearranged. The electron acceptor however is FAD+ that will be reduced to $FADH_2$. As you will see shortly, $FADH_2$ can only yield 2 ATPs (total 4 ATPs per one glucose). This is because this carrier molecule will release its electrons at an intermediate point in the electron transport chain, bypassing an opportunity to generate an extra ATP.



The cycle continues, and note that there is one more oxidation with the reduction of NAD+ to NADH. Again, this NADH will yield 6 ATP total per one glucose. The resultant four-carbon compound is back at the starting point and now ready for another acetyl group to be added from the transition stage.

Basic Metabolic Pathways: Kreb's Cycle, Overview



The purpose of the electron transport chain is the efficient production of ATP from high-energy electrons. Because this system will involve several oxidation/reduction reactions in the process, ATP production here is called oxidation phosphorylation.

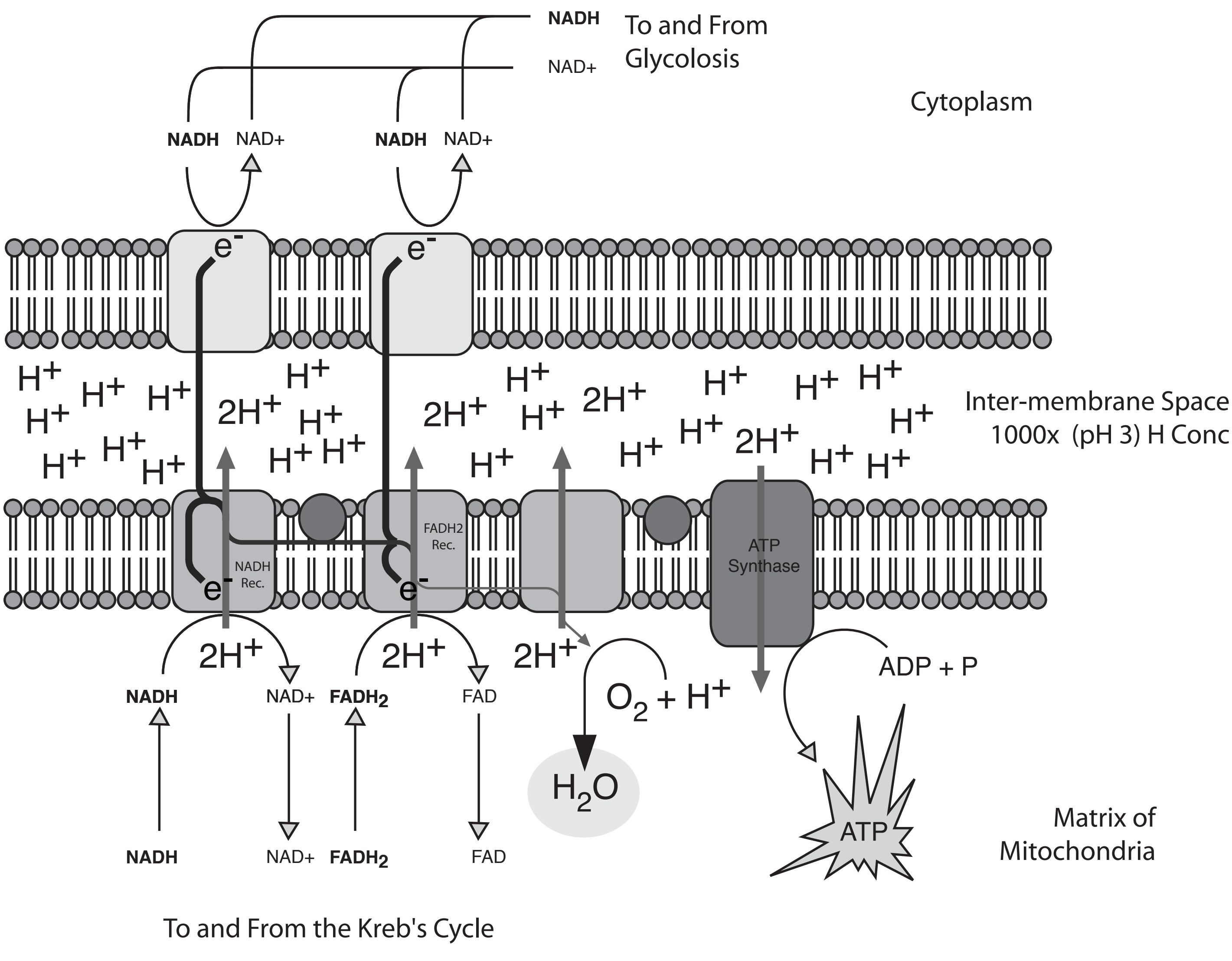
First we note that a mitochondrion consists of two membranes, one within the other. The inner membrane has many folds that increase the surface area for reaction purposes. It is these two membranes, and the space between them (inter-membrane space), that will produce ATP.

First note that electrons (associated now with NADH) have been produced both in the cytoplasm from glycolysis as well as the transition stage and kreb's cycle from within the mitochondria. As such, the electrons will be released onto the cooresponding adjacent membrane. Once the electrons are released, they are passed through a series of chemicals (cytochromes). As the electrons proceed through specific cytochromes, the electrons "fall" to lower energy states, and the energy released will be used to pump hydrogen into the inter-membrane space. This build up of hydrogen ions is significant and concentration is about 1000x greater than that of the mitcochondrial matrix (pH 3 difference). This build up creates an "electro-chemical gradient", where the hydrogen wants to go back into the matrix of the mitochondria. And as it does, this driving force is used to produce ATP.

By the time the electrons have finished their course through the electron transport chain, they will have become "low energy", and incapable pumping any more hydrogen. These low energy electrons are therefore "dumped" onto oxygen (oxygen is reduced to water - it is the final electron acceptor), and now more electrons can continue down the chain.

Basic Metabolic Pathways: Electron Transport Chain, Part #2

This chain consists of a series of cytochromes, molecules that have the ability to be reduced and subsequently be oxidized. In the process of electron passage, energy is lost and used to pump H+ into the inter-membrane space of the mitochondria. The sequential organization and characteristics of the cytochromes promotes the passage of the electrons, as energy is incrementally lost.



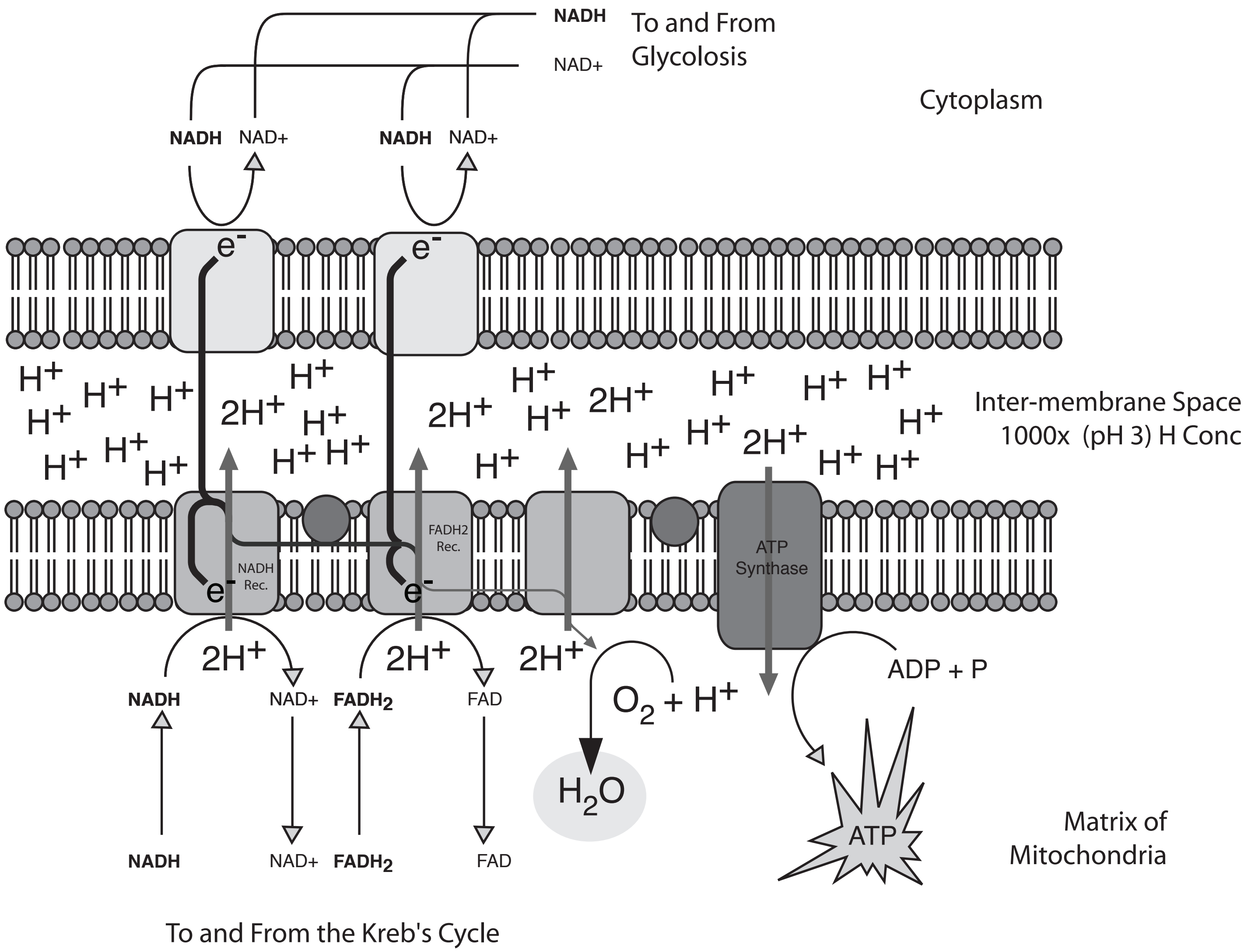
As the hydrogen pumps continue to pump protons into the inter-membrane space, the ion concentration becomes 1000x than that of the mitochondrial matrix. This lowered pH creates an electro/chemical gradient where the protons want to go down their concentration gradient; and the large numbers of positive charges (like charges repel) tend to push them out. Such a potential is harnessed by the enzyme, ATP synthase. As the hydrogen ions pass through this enzyme, ATP is synthesized from ADP and P.

Basic Metabolic Pathways: Electron Transport Chain, Part #2

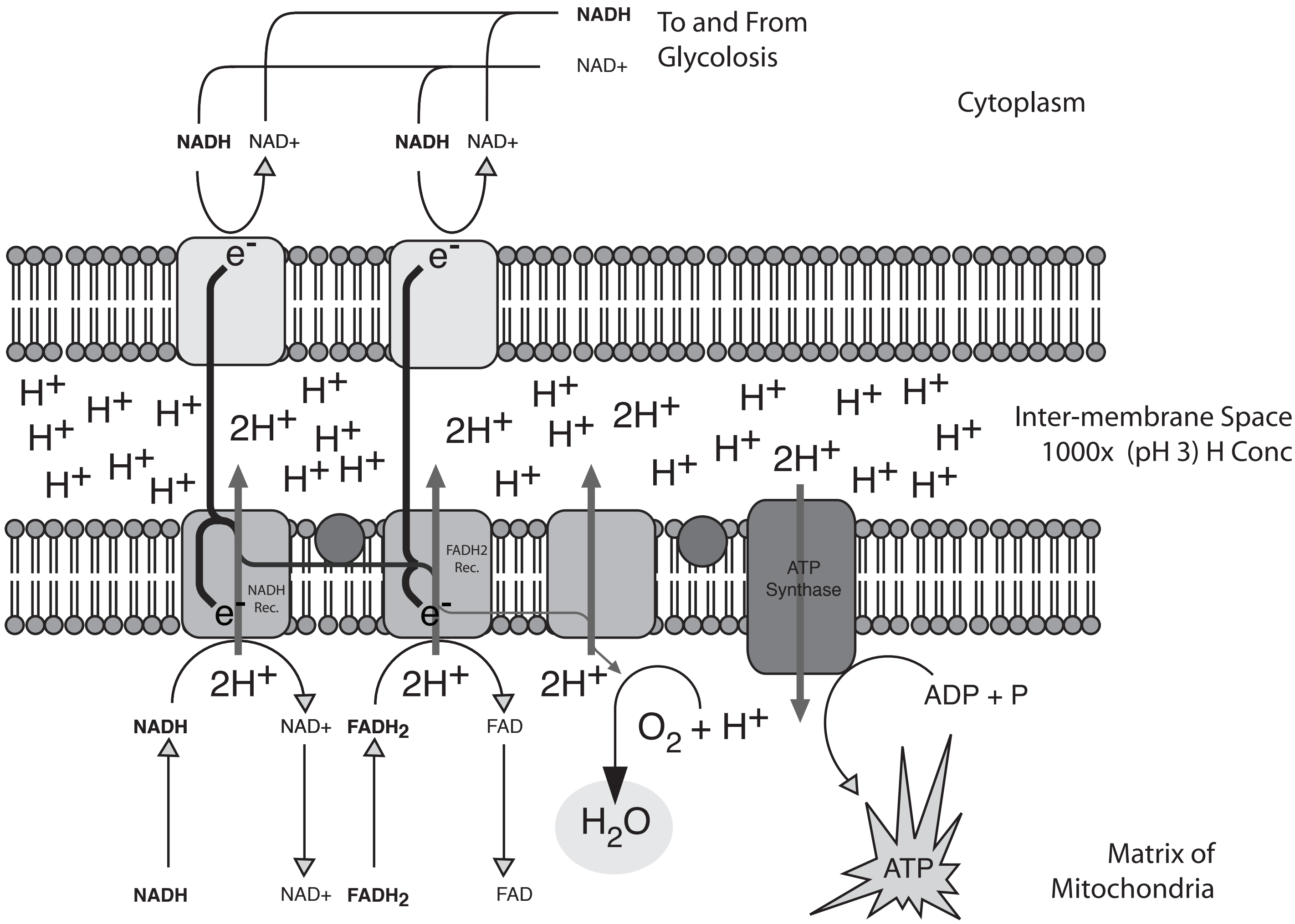
The supply of high-energy electrons needed for oxidative phosphorylation is provided by reduced the following Coenzymes: NADH from glycolysis, and NADH and FADH2 from the transition stage and the Kreb's Cycle.

Regarding glycolysis, two (2) NAH+ are reduced per one glucose. These high-energy electrons can then be used to reduce one of two cytochromes, each one of which is located at different positions along the electron transport chain. If the electrons oxidize an NAD carrier molecule, then sufficient protons will be pumped to generate three ATPs (total six per one glucose). If the electrons are used to oxidize the FAD carrier molecule, then sufficient protons will be pumped to generate only two ATPs (total four per one glucose).

Therefore, the amount of ATP generated via glycolysis can vary by two ATPs. As you will soon see, the net gain for all cellular respiration is 36-38 ATPs, and it is this point that accounts for the difference.



Basic Metabolic Pathways: Electron Transport Chain, Part #3



From within the matrix of the mitochondria, where the transition stage and the Kreb's cycle occur, reduced coenzymes (NADH and FADH2) are produced. However, unlike glycolysis, they each have a specific cytochrome upon which they deliver their electrons.

Regarding NADH, the NAD carrier molecules are at the beginning of the electron chain. As the electrons cascade from cytochrome to cytochrome, a total of six H+ will be pumped into the inter-membrane space, and these H+ will be able to produce 3 ATPs

The FADH2, however, will reduce it's corresponding cytochrome which is located at an intermediate point in the chain. As such, it will only be able to pump four H+ into the inter-membrane space, and therefore will only produce 2 ATPs.

Basic Metabolic Pathways: Conclusion

In conclusion, it is evident that one molecule of glucose yields a considerable quantity of ATP. Note the tally chart below:

Glycolysis

Initial investment: - 2 ATP
Direct gain by substrate level phosphorylation: 4 ATP

Net gain: 2 ATP

2 NADH: 4 ATP / 6 ATP

Transition Stage

2 NADH: 6 ATP

Krebs's Cycle

Net gain by substrate level phosphorylation: 2 ATP

6 NADH: 18 ATP

2 FADH2: 4 ATP

Total for Cellular Respiration

36 – 38 ATP

Basic Metabolic Pathways Chart