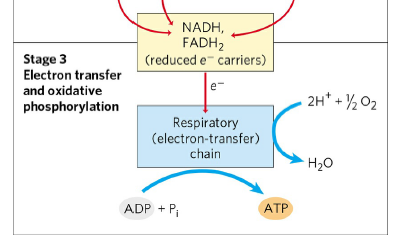
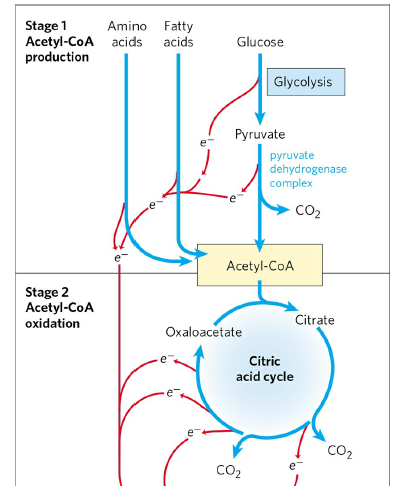
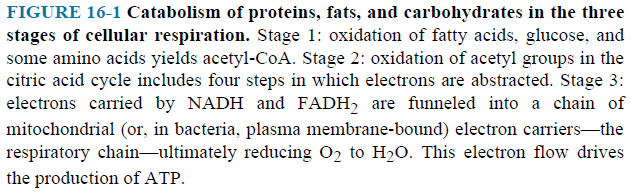
**Chapter 16 The Citric Acid Cycle**

* The pyruvate produced by glycolysis is oxidized to H2O and CO2.
* This aerobic phase of catabolism is called **respiration**.
* Catabolism of proteins, fats and carbohydrates occurs in the three stages of cellular respiration (**Fig. 16-1)**.

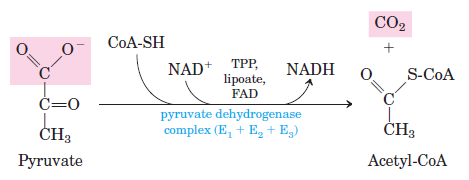


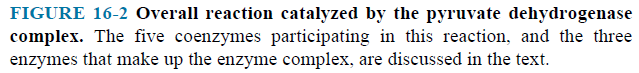


* Stage 1 : Oxidation of fatty acids, glucose and some amino acids yields acetly-CoA.
* Stage 2 : Oxidation of acetyl groups in the citric acid cycle yields CO2 and energy.
* The energy released is conserved in the reduced electron carriers NADH and FADH2.
* Stage 3 : The electrons are transferred to O2 (the final electron acceptor) via a chain of electron-carrying molecules known as the respiratory chain.
* In the course of electron transfer, the energy is conserved in the form of ATP by a process called oxidative phosphorylation.
* Citric acid cycle is also called the **tricarboxylic acid (TCA) cycle** or the **Krebs cycle**.

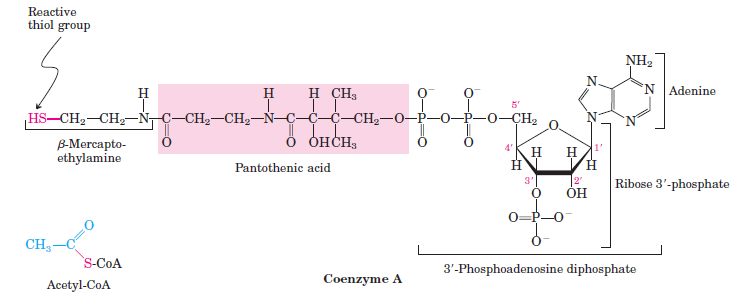
**16.1 Production of Acetyl-CoA (Activated Acetate)**

* Pyruvate is oxidized to acetly-CoA and CO2 by the **pyruvate dehydrogenase (PDH) complex** in the mitochondria of eukaryotic cells.
* The overall reaction is an oxidative decarboxylation (**Fig. 16-2)**.



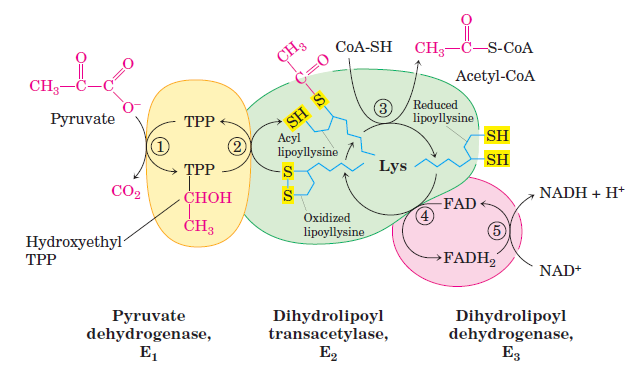


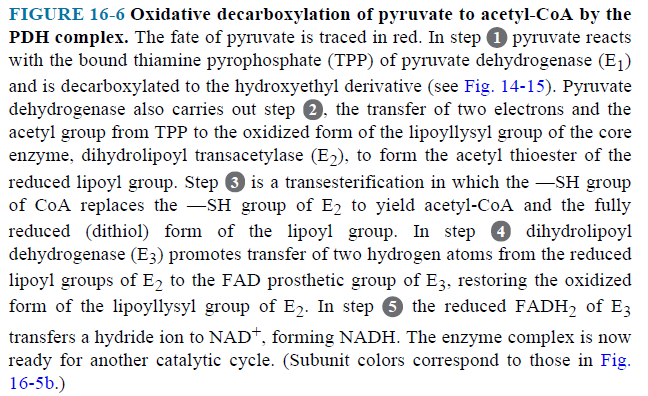
* Pyruvate dehydrogenase complex requires five coenzymes.
* FAD
* NAD+
* CoA : Coenzyme A (an acyl carrier) (**Fig. 16-3)**.
* TPP : Thiamine pyrophosphate
* Lipoate



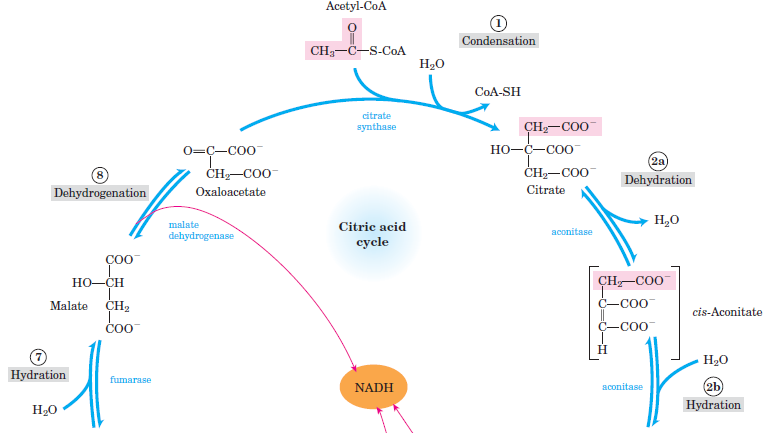
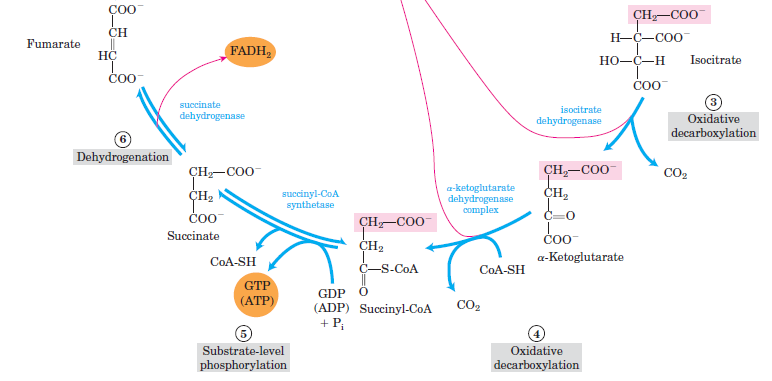


* Pyruvate dehydrogenase complex consists of three distinct enzymes.
* E1 : Pyruvate dehydrogenase
* E2 : Dihydrolipoyl transacetylase
* E3 : Dihydrolipoyl dehydrogenase
* PDH complex carries out the five consecutive reactions in the decarboxylation and dehydrogenation of pyruvate (**Fig. 16-6)**.
* E1 catalyzes first the decarboxylation of pyruvate, producing hydroxyethyl-TPP, and then the oxidation of the hydroxyethyl group to an acetyl group. The electrons from this oxidation reduce the disulfide of lipoate bound to E2, and the acetyl group is transferred into thioester linkage with one —SH group of reduced lipoate.

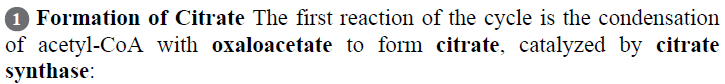


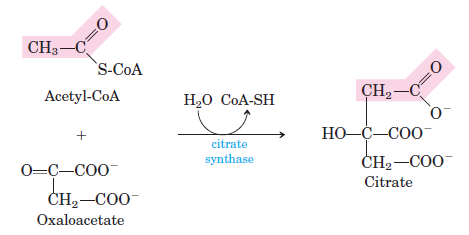


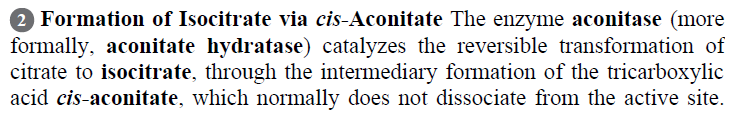
* E2 catalyzes the transfer of the acetyl group to coenzyme A, forming acetyl-CoA.
* E3 catalyzes the regeneration of the disulfide (oxidized) form of lipoate; electrons pass first to FAD, then to NAD+.
  1. **Reactions of the Citric Acid Cycle**
* Oxidation of acetyl- CoA is carried out by the citric acid cycle (eight steps) (**Fig. 16-7)**.
* In each turn of the cycle, one acetyl group (two carbons) enters as acetyl-CoA and two molecules of CO2 leave; one molecule of oxaloacetate is used to form citrate and one molecule of oxaloacetate is regenerated.
* The energy of this oxidation is conserved in the reduced coenzymes NADH and FADH2.
* Reactions occur in the mitochondria of eukaryotic cells.

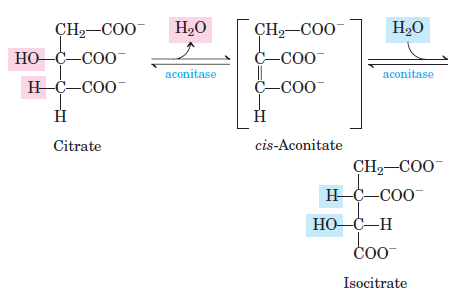
 

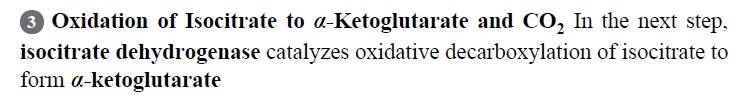
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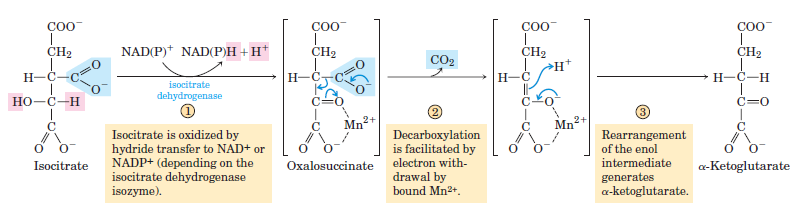
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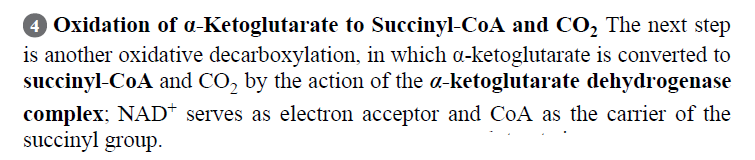


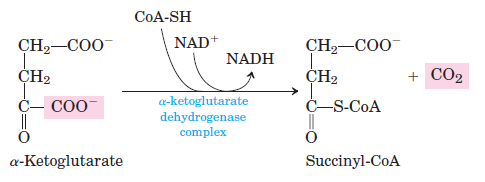
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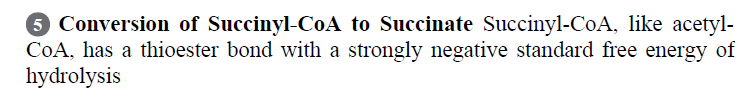
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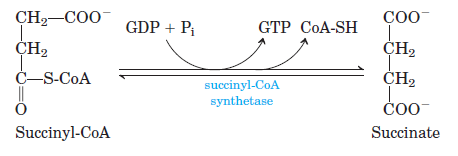


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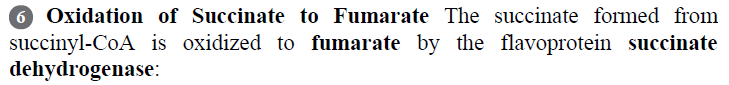
* -ketoglutarate dehydrogenase complex (E1+E2+E3) is similar to pyruvate dehydrogenase complex in both structure and function.

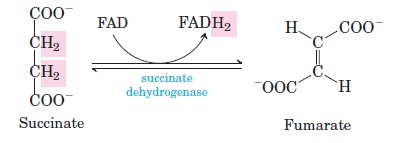
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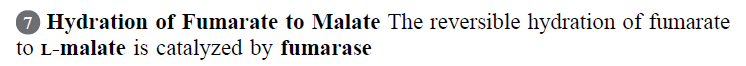


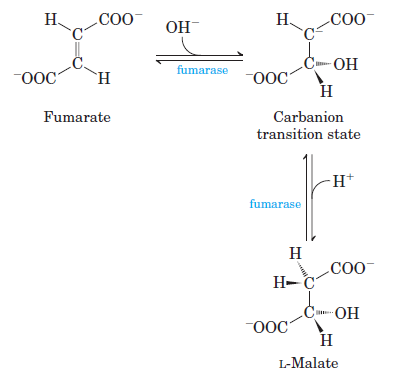
* A substrate-level phosphorylation occurs.
* The GTP formed by succinyl- CoA synthetase can donate its terminal phosphoryl group to ADP to form ATP, in a reversible reaction catalyzed by **nucleoside diphosphate kinase.**

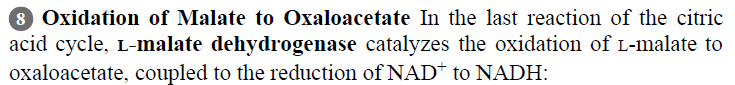
GTP + ADP GDP + ATP

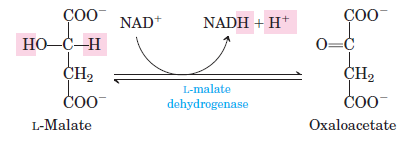
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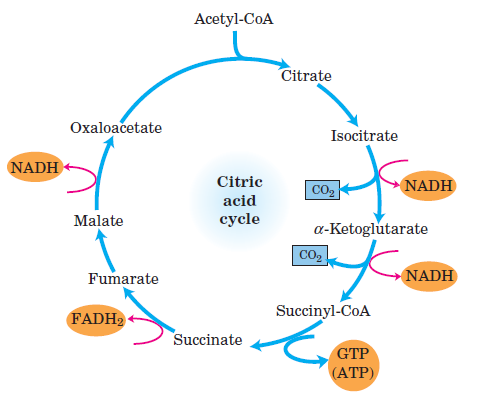


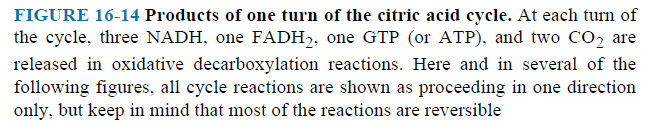
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**The Energy of Oxidations in the Cycle Is Efficiently Conserved**

* The energy released by these oxidations was conserved in the reduction of 3 NAD+ and 1 FAD and the production of 1 ATP or GTP.
* At the end of the cycle a molecule of oxaloacetate was regenerated.
* Products of one turn of the citric acid cycle (**Fig. 16-14)**.





* 3 NADH, 1 FADH2, 1 GTP (or ATP) and 2 CO2 are released in the oxidative decarboxylation reactions of 1 acetyl-CoA.
* Stoichiometry of NADH, FADH2 and ATP formation in the aerobic oxidation of 1 glucose

NADH FADH2 ATP (or GTP) CO2

Glycolysis 2 2

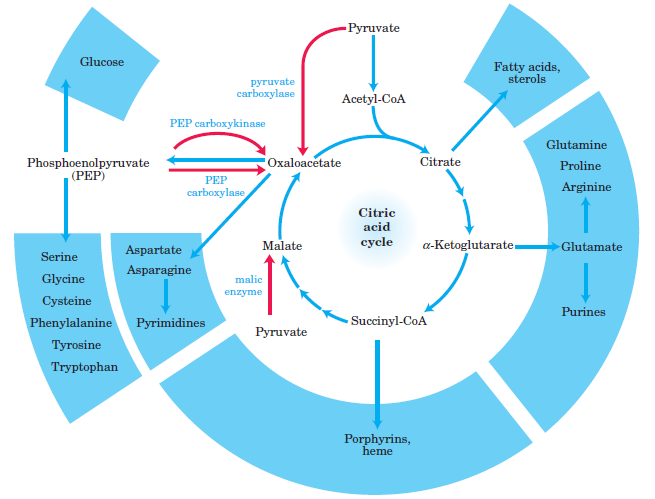
PDH Reaction 2 2

Citric Acid Cycle 6 2 2 4

* In oxidative phosphorylation,
* passage of two electrons from NADH to O2 yields about 2.5 ATP
* passage of two electrons from FADH2 to O2 yields about 1.5 ATP
* After oxidative phosphorylation, 32 ATP are obtained per glucose.

**Citric Acid Cycle Components Are Important Biosynthetic Intermediates**

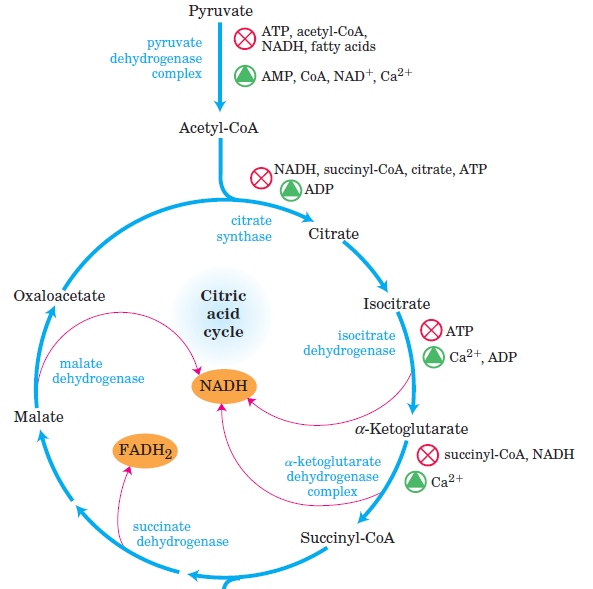
* Besides its role in the oxidative catabolism of carbohydrates, fatty acids, and amino acids, the cycle provides precursors for many biosynthetic pathways in anabolism (**Fig. 16-16).**



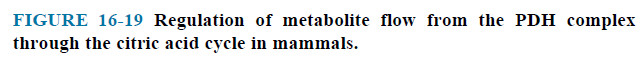


**16.3 Regulation of the Citric Acid Cycle**

* Pyruvate dehydrogenase complex of mammals
* is inhibited by ATP, acetyl-CoA, NADH and fatty acids
* is activated by AMP, CoA, NAD+ and Ca2+ **(Fig. 16-19)**.
* The citric acid cycle is regulated at its three exergonic steps catalyzed by citrate synthase, isocitrate dehydrogenase and -ketoglutarate dehydrogenase complex.
* Citrate synthase
* is inhibited by NADH, succinyl-CoA, citrate and ATP
* is activated by ADP **(Fig. 16-19)**.
* Isocitrate dehydrogenase
* is inhibited by ATP
* is activated by Ca2+and ADP **(Fig. 16-19)**.
* -ketoglutarate dehydrogenase complex
* is inhibited by succinyl-CoA and NADH
* is activated by Ca2+ **(Fig. 16-19)**.

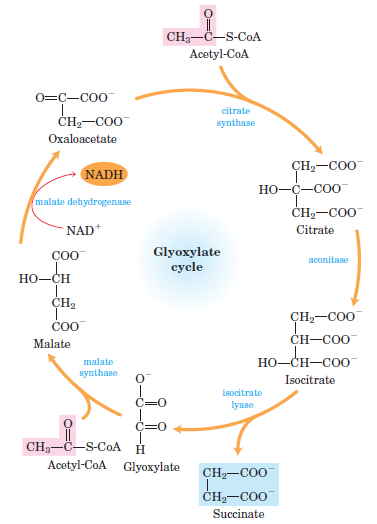


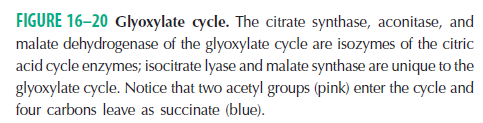


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**16.4 The Glyoxylate Cycle**

* Conversion of phosphoenolpyruvate to pyruvate and of pyruvate to acetyl-CoA are irreversible.
* Phosphoenolpyruvate can be synthesized from oxaloacetate in gluconeogenesis.
* A cell or organism is unable to convert fuels or metabolites that are degraded to acetate (fatty acids and certain amino acids) into carbohydrates.
* In many organisms other than vertebrates, the glyoxylate cycle serves as a mechanism for converting acetate to carbohydrate.
* In plants, the pathway takes place in glyoxysomes (specialized peroxisomes).
* The glyoxylate cycle produces four-carbon compounds from acetate (**Fig. 16-20)**.

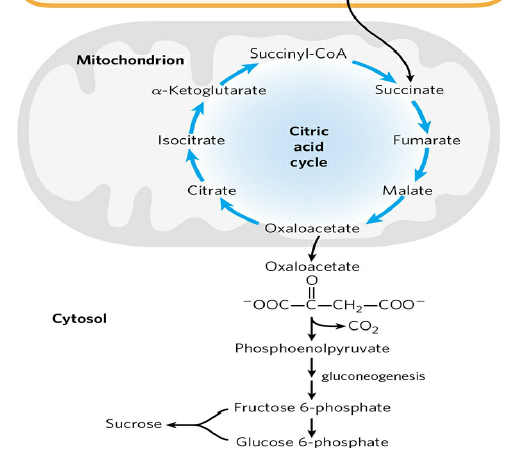
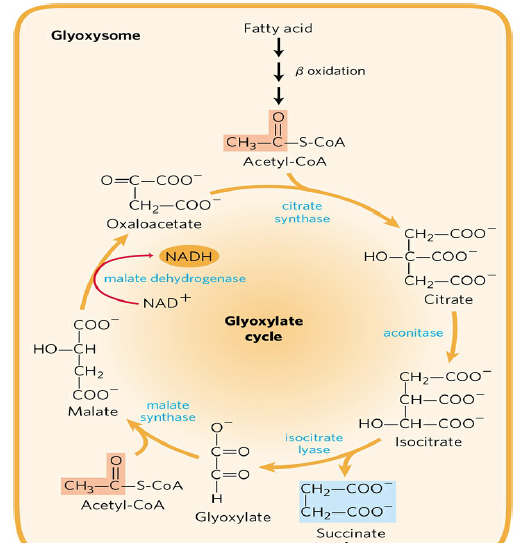




* Enzymes of the glyoxylate cycle catalyze the net conversion of acetate to succinate or other four-carbon intermediates of the citric acid cycle.
* Acetyl-CoA condenses with oxaloacetate to form citrate, and citrate is converted to isocitrate, exactly as in the citric acid cycle.
* The next step is not the breakdown of isocitrate by isocitrate dehydrogenase but the cleavage of isocitrate by **isocitrate lyase**, forming succinate and **glyoxylate**.
* The glyoxylate condenses with a second molecule of acetyl-CoA to yield malate by **malate synthase**.
* The malate is oxidized to oxaloacetate.
* Each turn of the glyoxylate cycle consumes two molecules of acetyl-CoA and produces one molecule succinate, available for biosynthetic purposes.

2 Acetyl-CoA + NAD+ succinate + 2 CoA + NADH + H+

* There is a relationship between the glyoxylate and citric acid cycle (**Fig. 16-24)**.
* Succinate may be converted through fumarate and malate into oxaloacetate.
* Oxaloacetate is converted to phosphoenolpyruvate and thus to glucose by gluconeogenesis.
* Vertebrates do not have the enzymes specific to the glyoxylate cycle.
* They cannot bring about the net synthesis of glucose from (acetyl-CoA) lipids.
* Germinating seeds can convert the carbon of stored lipids into glucose.



**FIGURE 16-24** Relationship between the glyoxylate and citric acid cycles.