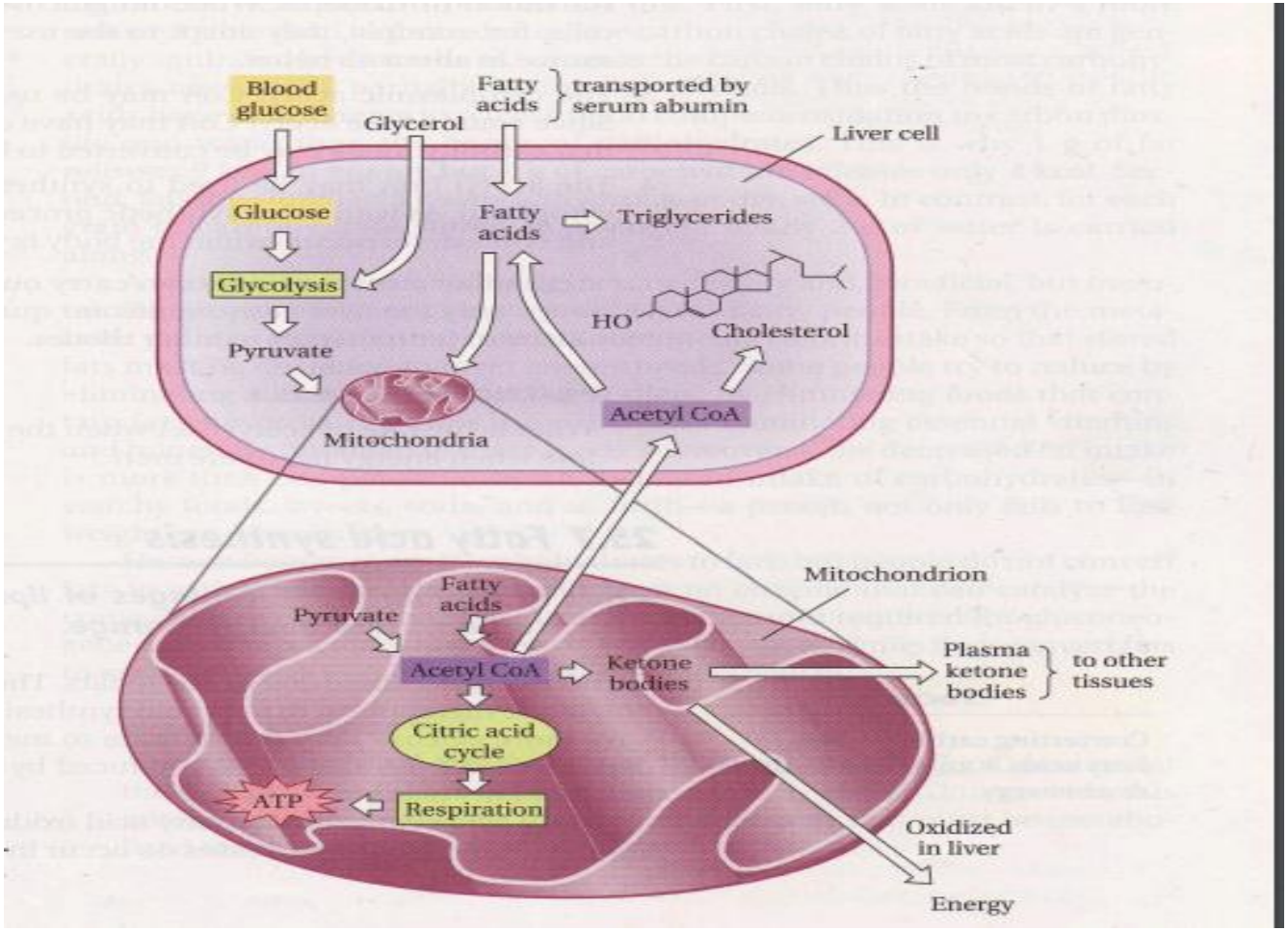
UTILIZATION AND DISSIMILATION OF ACETYL COA

LECTURE # 3

BCH 504

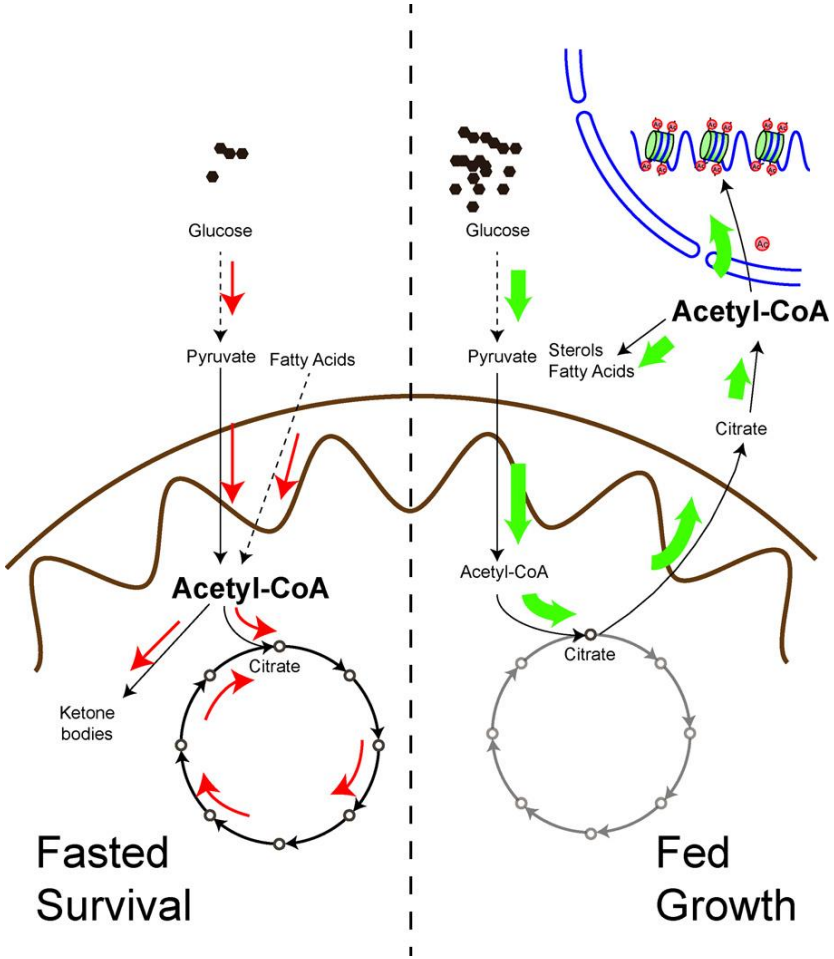
Figure below shows the major pathways of lipid metabolism in the liver and their relationship to carbohydrate metabolism



- The Figure shows fatty acids entering the liver from the blood may be resynthesized into triglycerides and stored in the adipose tissue there. Alternatively, fatty acids may be broken down to acetyl CoA. Glucose is also broken down to acetyl CoA. If you are beginning to suspect that **acetyl CoA must be a key compound** in the metabolic interplay between carbohydrate and fatty acid metabolism, you are certainly correct.
- Four possible fates await the acetyl CoA produced from fatty acids or glucose in the liver:
- 1. The acetyl CoA in the mitochondria may be oxidized to carbon dioxide and water in the citric acid cycle and respiratory chain. This pathway, which is used if the liver cells need to generate energy through respiration, makes it clear that the citric acid cycle is shared by both glucose metabolism and fatty acid metabolism.

- 2. The acetyl CoA in mitochondria may be used to synthesize the substances called **ketone bodies**. Some ketone bodies are oxidized for energy production by the liver. The remainder are transported to other tissues that can use them for energy production. Extensive production of ketone bodies from acetyl CoA occurs only when no glucose is available, as in starvation or diabetes. When no glucose is available to starving brain cells, for example, they adapt to the use of ketone bodies as an energy source in about 48 hours.
- The cytoplasmic acetyl CoA may be used to **resynthesize fatty acids**. Since some of the acetyl CoA may have come from glucose, this means that carbohydrates may be converted to fatty acids.
- The acetyl CoA may be used to synthesize cholesterol in the cellular cytoplasm. As with other synthetic processes, the synthesis of fatty acids and cholesterol occurs when the body is well supplied with energy.

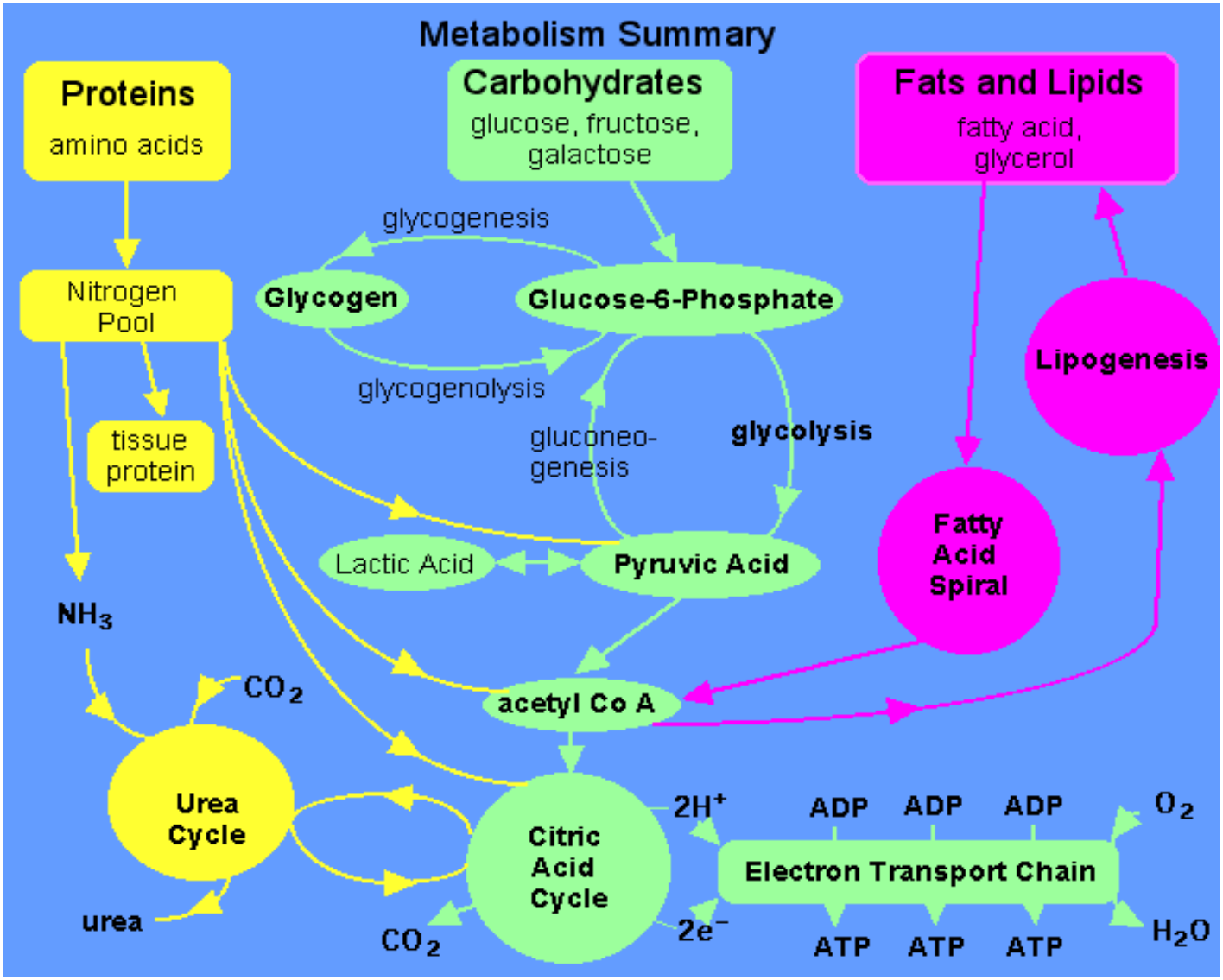
Schematic model proposing a general logic of acetyl-CoA utilization under fed versus fasted or growth versus survival states



- Figure in the previous slide shows that
- Under fed or growth states, acetyl-CoA is directed out of the mitochondria and to the cytosol and nucleus for use in lipid synthesis or histone acetylation. Nucleocytosolic amounts of acetyl-CoA increase relative to mitochondrial amounts.
- Under fasted or survival states, acetyl-CoA is channeled into the mitochondria for synthesis of ATP and ketone bodies. Mitochondrial amounts of acetyl-CoA increase relative to nucleocytosolic amounts. Fatty acid oxidation significantly increases mitochondrial acetyl-CoA.

Acetyl CoA - Cross Roads Compound

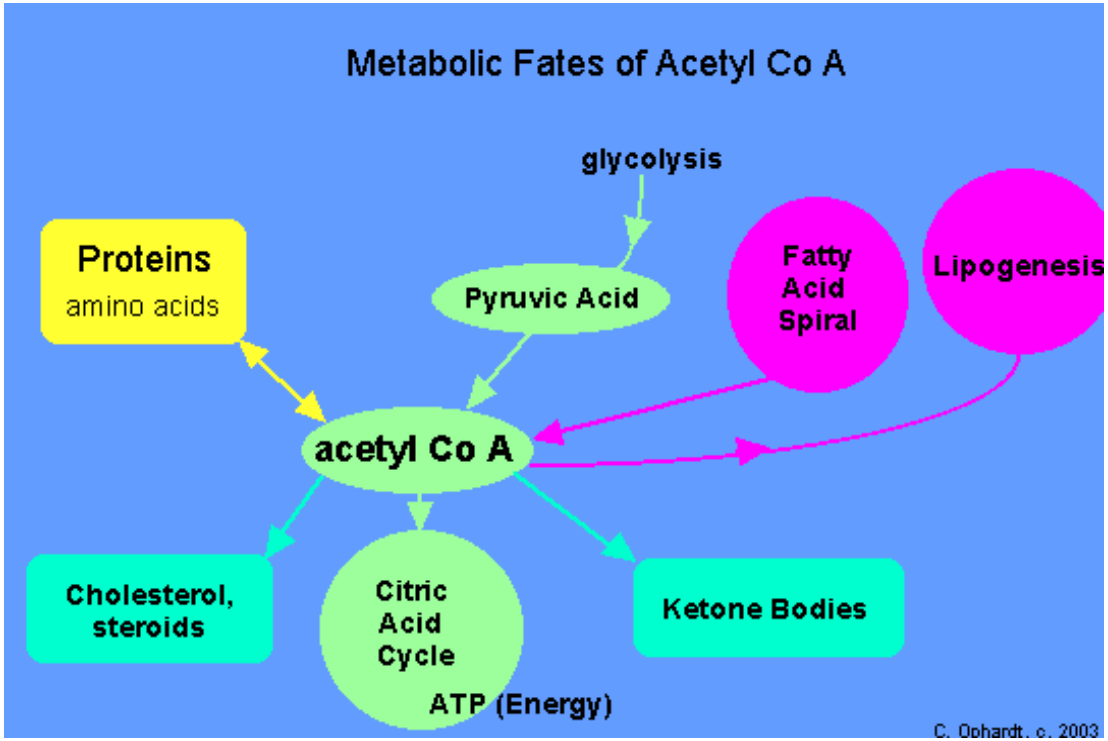
- Acetyl CoA acts both as a metabolic "receiving and shipping department" for all classes of biomolecules and as a major source of useful metabolic energy.
- Notice that acetyl CoA can react "reversibly" in the degradation or synthesis of lipids and amino acids. This is not the case with carbohydrate metabolism. In mammals, it is impossible to use acetyl CoA to make carbohydrates.


Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose, fructose, galactose
Fats and Lipids
fatty acid, glycerol
glycogenesis
Nitrogen Pool
Glycogen
Glucose-6-Phosphate
Lipogenesis
glycogenolysis
tissue protein
gluconeo-genesis
glycolysis
Fatty Acid Spiral
Lactic Acid
Pyruvic Acid
NH3
CO2
acetyl Co A
Urea Cycle
Citric Acid Cycle
2H+
ADP ADP ADP
O2
Electron Transport Chain
urea
CO2
2e−
ATP ATP ATP
H2O

Synthesis of Cholesterol and other Steroids

- Acetyl CoA forms the basis from which the fairly complicated steroids are synthesized. Some steroids of importance include cholesterol, bile salts, sex hormones, aldosterone, and cortisol.
- The sequence of reactions involved in the formation of lipids is known as Lipogenesis. Lipogenesis is not simply the reverse of the fatty acid spiral, but does start with acetyl CoA and does build up by the addition of two carbons units. The synthesis occurs in the cytoplasm in contrast to the degradation (oxidation) which occurs in the mitochondria. Many of the enzymes for the fatty acid synthesis are organized into a multienzyme complex called fatty acid synthetase.
- The major points in the overall lipogenesis reactions are:
  1) ATP is required
  2) The reactions are reductions (addition of H^+ and use of NADPH) which are the reverse of the oxidations in the fatty acid spiral.

Metabolic Fates of Acetyl CoA



- When the body is deprived of food whether by voluntary or involuntary fasting, starvation is the net result. During starvation, glycogen reserves are rapidly depleted and the body begins to metabolize reserves of fat and protein.
- The entry of acetyl CoA into the citric acid cycle depends on the availability of oxaloacetate for the formation of citric acid. In starvation or uncontrolled diabetes situations, oxaloacetate is used to synthesize glucose and is therefore not available to combine with acetyl CoA. Under these conditions, acetyl CoA is diverted from the citric acid cycle to the formation of acetoacetic and 3 - hydroxbutyrate (ketone bodies).

Thank you