

Chapter 4 - III

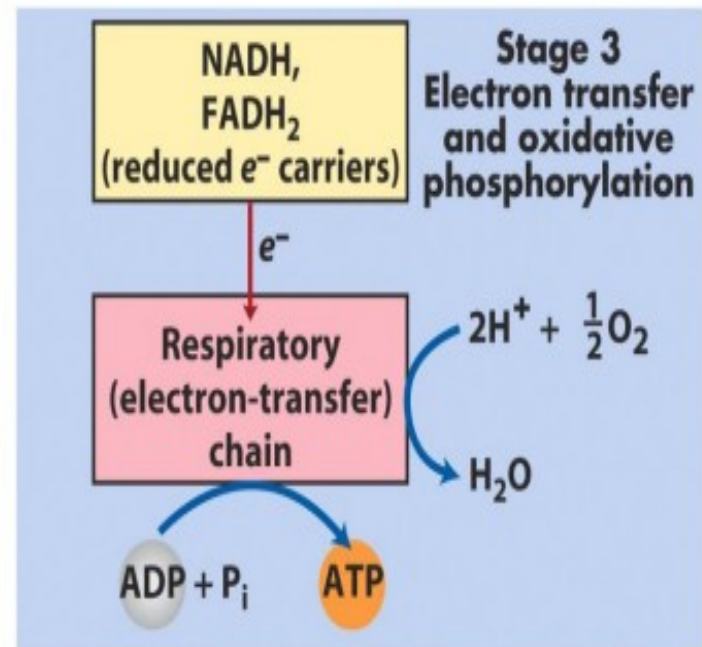
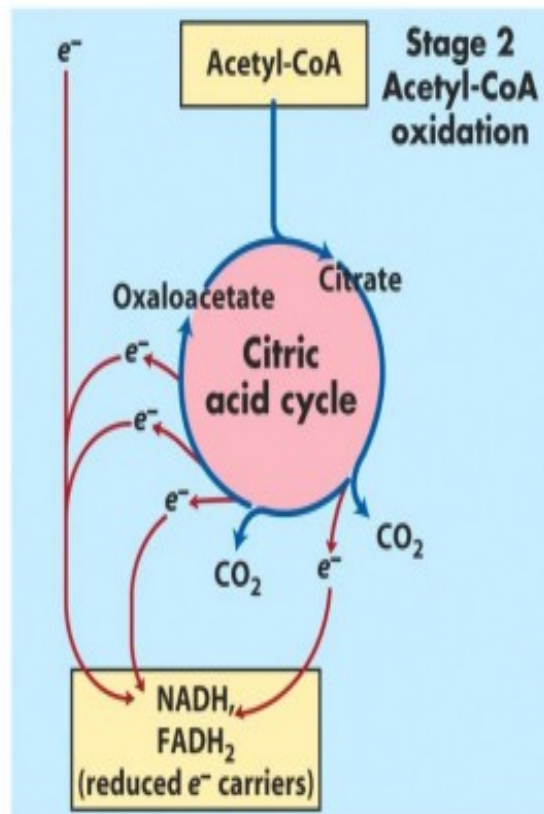
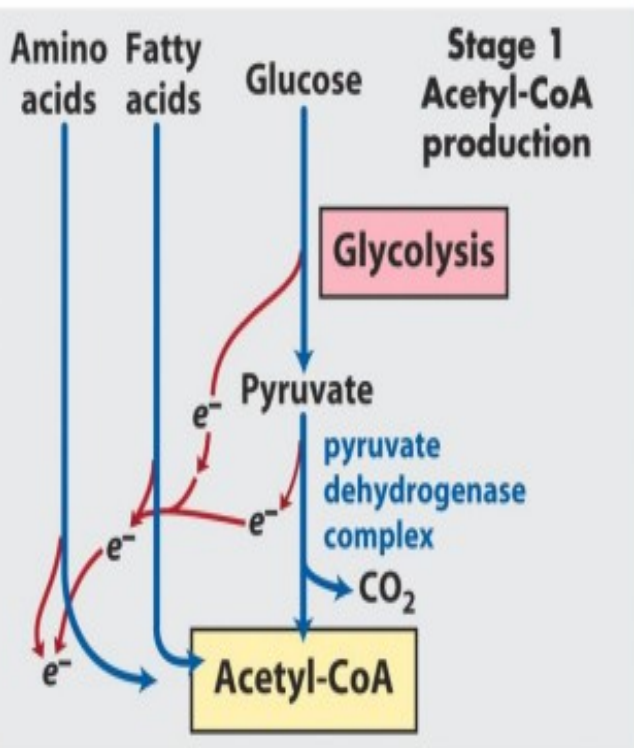
TCA Cycle

- **Discovered by Hans Krebs in 1937**
- **He received the Nobel Prize in physiology or medicine in 1953 for his discovery**



Three Phases

- [1] Acetyl-CoA production—Organic fuels (glucose, amino acids, fats) → Acetyl-CoA
- [2] Acetyl-CoA oxidation—Acetyl-CoA enters TCA and is enzymatically oxidized; energy is conserved in electron carriers: NADH, FADH₂
- [3] Electron transfer—energy rich e⁻ from NADH, FADH₂ reduce O₂ to H₂O



TCA cycle and ETC: Aerobic respiration

- One fate of pyruvate is that it enters to TCA cycle for complete oxidation. But there are intermediate processes that convert pyruvate to a acetyl coA. The enzyme complex converts pyruvate into Acetyl-CoA by the following chemical changes:
 - Decarboxylation of pyruvate (loss of CO₂)
 - Formation of acetyl group
 - Linkage of acetyl group to coenzyme A forming acetyl - CoA.

The Tricarboxylic Acid (TCA) Cycle (Phase III)

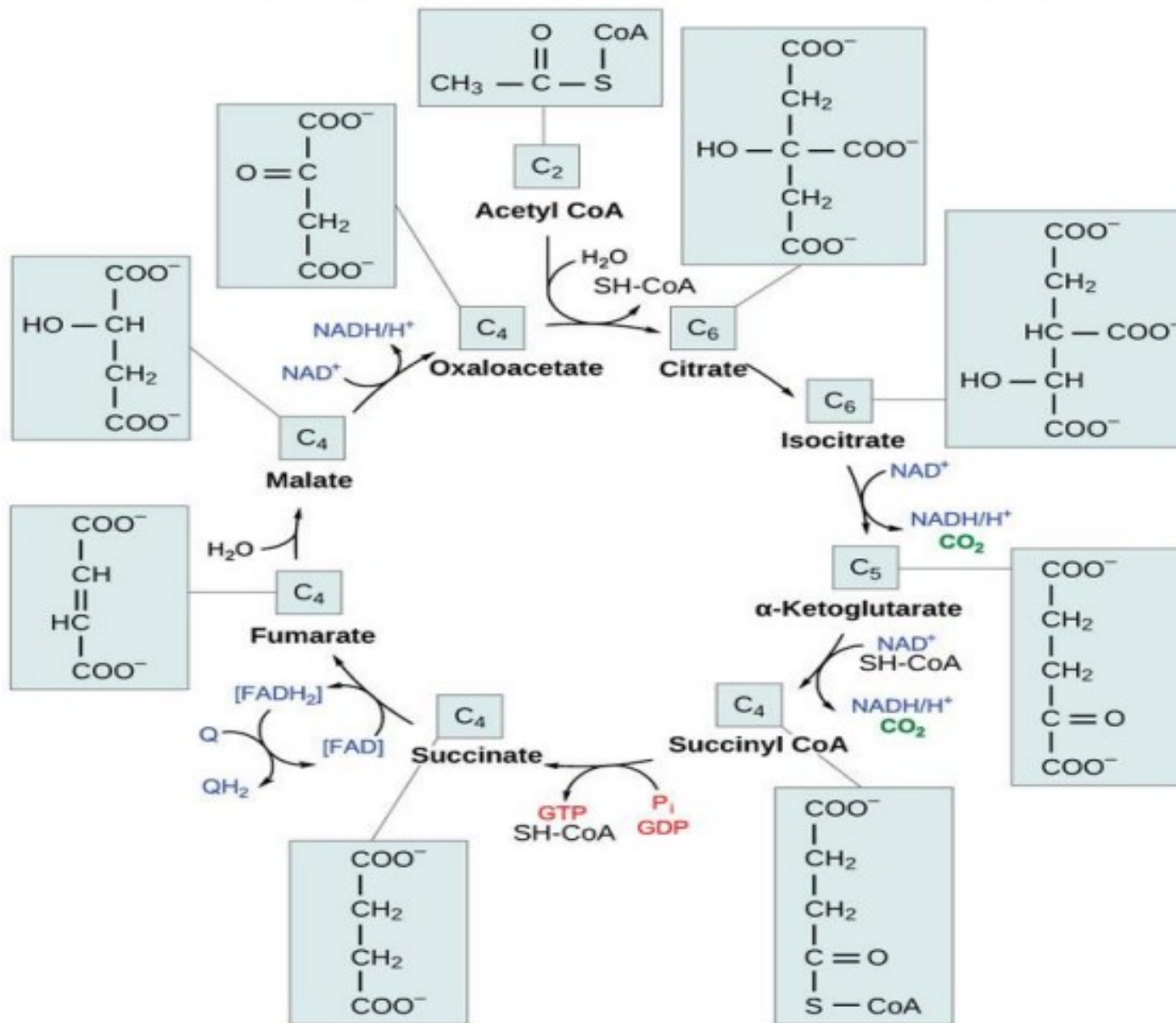
- The TCA cycle also called Krebs or Citric acid cycle, is considered as central pathway of aerobic metabolism, as it serves two purposes-bioenergetics and biosynthesis:

1. **Bioenergetic** - The cycle carries out complex degradation of acetyl group in acetyl - CoA to CO₂, resulting in release of energy (ATP or GTP) and reducing power (NADH and FADH₂).

- TCA oxidizes two-carbon units, producing two molecules of CO₂, one molecule of GTP, and high-energy electrons in the form of NADH and FADH₂.

Steps of the Krebs cycle

- Prior to the Krebs cycle, pyruvate first reacts with coenzyme A (CoA) to form a 2-carbon intermediate called acetyl CoA. At the same time, carbon dioxide is released and NAD is converted to NADH. Acetyl CoA then moves to the mitochondrial matrix. The reaction results in the production of two carbon dioxide molecules and two NADH.
 - The Krebs cycle begins with acetyl CoA combining with a 4-carbon compound to form a 6-carbon compound known as **citric acid**.
 - Citric acid is then broken down in the next series of steps, releasing two molecules of carbon dioxide and generating one ATP, three NADH, and one FADH. FAD is another electron carrier similar to NADH and NADPH.
 - Finally, acetyl CoA and citric acid are generated and the cycle continues.



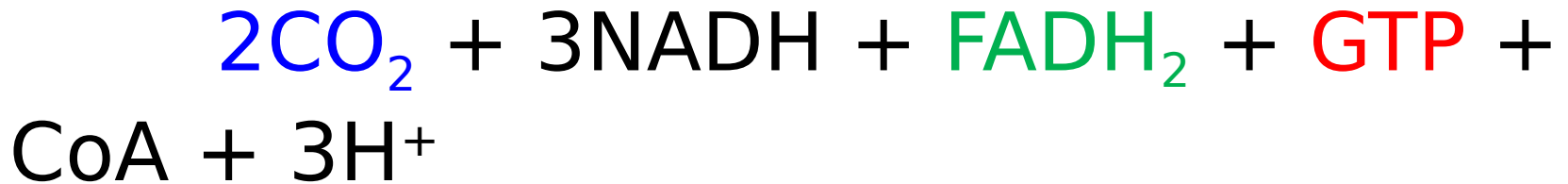
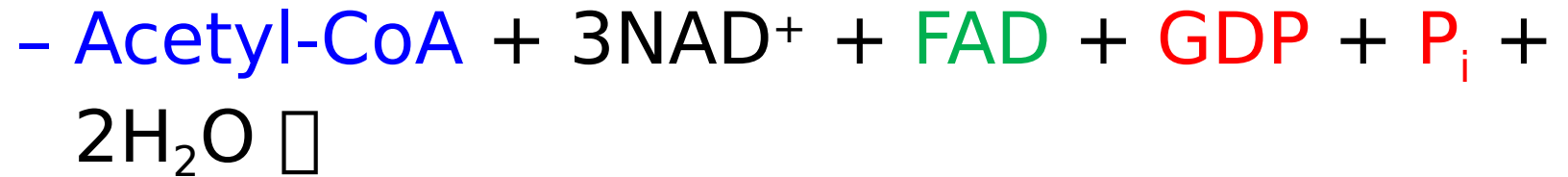
The TCA cycle

- Recall that two molecules of pyruvate are formed during glycolysis, resulting in two “turns” of the Krebs cycle for each glucose molecule. The net yield from the Krebs cycle is six carbon dioxide molecules, two ATP, eight NADH, and two FADH₂. NADH and FADH₂ move on to play a significant role in the next stage of aerobic respiration.

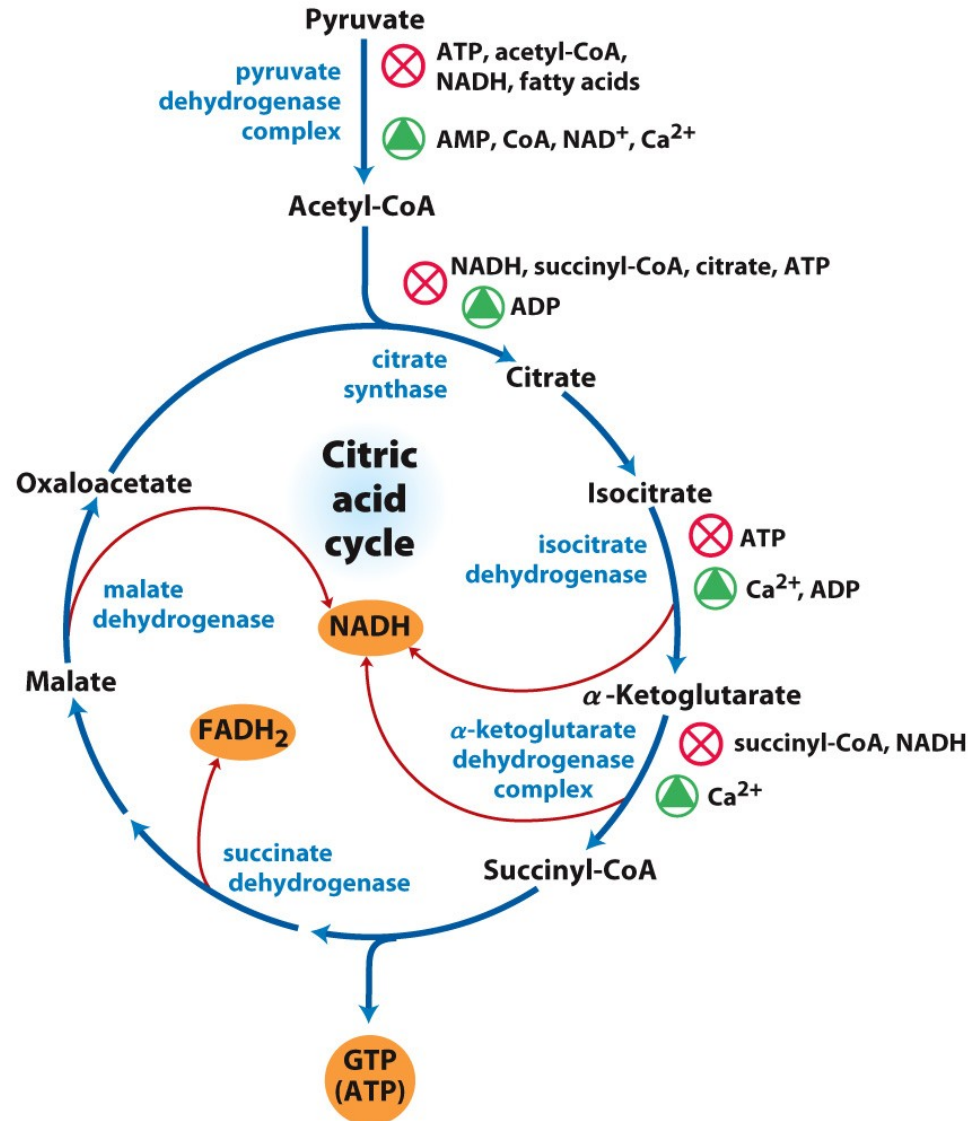
2. Biosynthesis - It supplies precursors for several biosynthetic pathways of amino acids, pyrimidines, purines etc.

- As already mentioned, the TCA cycle is also an important source of biosynthetic precursors e.g. α -ketoglutarate and oxaloacetate are used for synthesis of a number of amino acids like glutamic acid, aspartic acid etc.
- Succinyl - CoA is used to form porphyrin ring of cytochromes, chlorophyll etc.
- Oxaloacetate can also be converted to phosphoenolpyruvate, which is a precursor of glucose.
- Acetyl - CoA is the starting material for fatty acid biosynthesis.

- Net Result of the Citric Acid Cycle

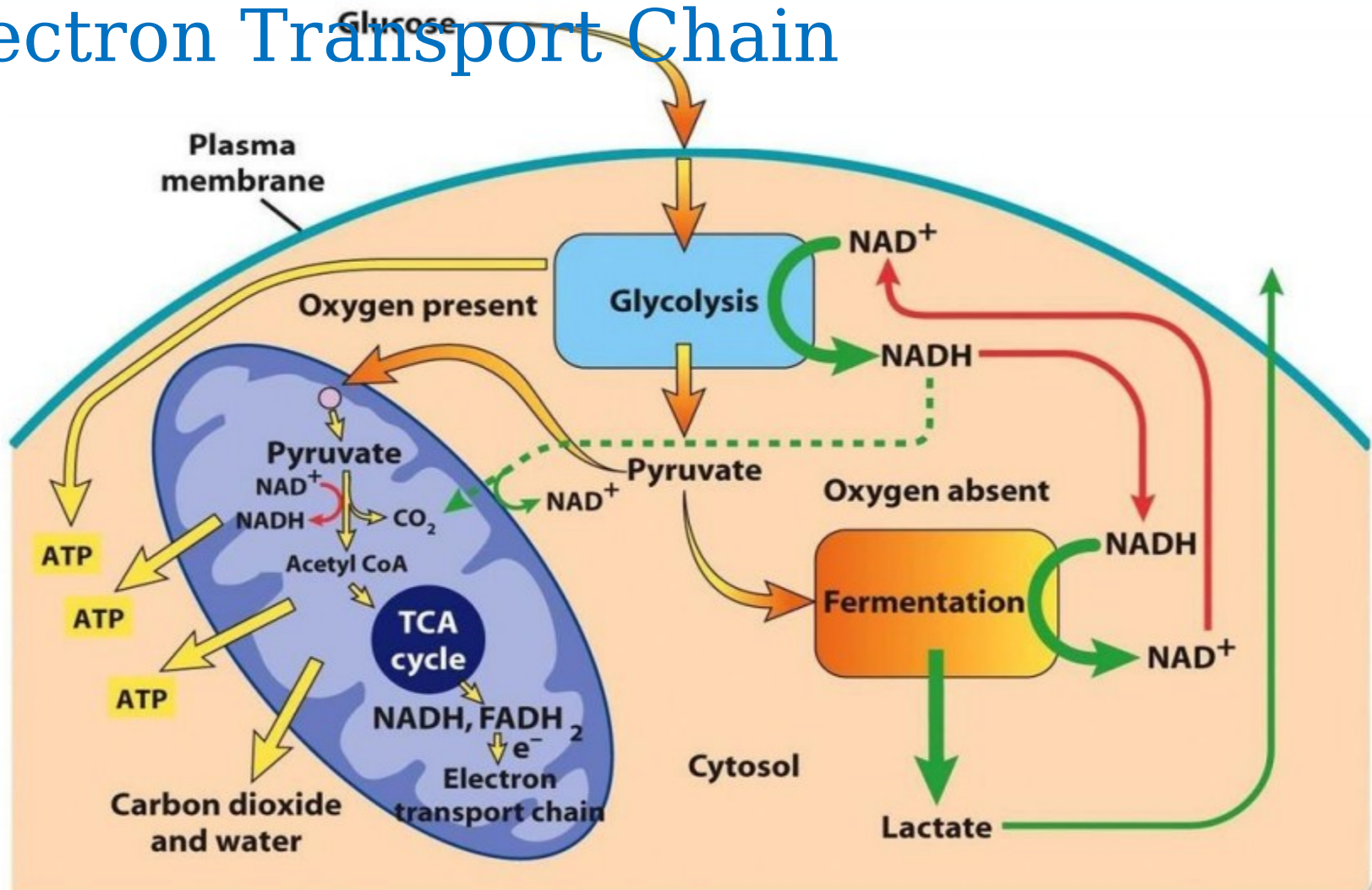


Regulation of Citric Acid Cycle



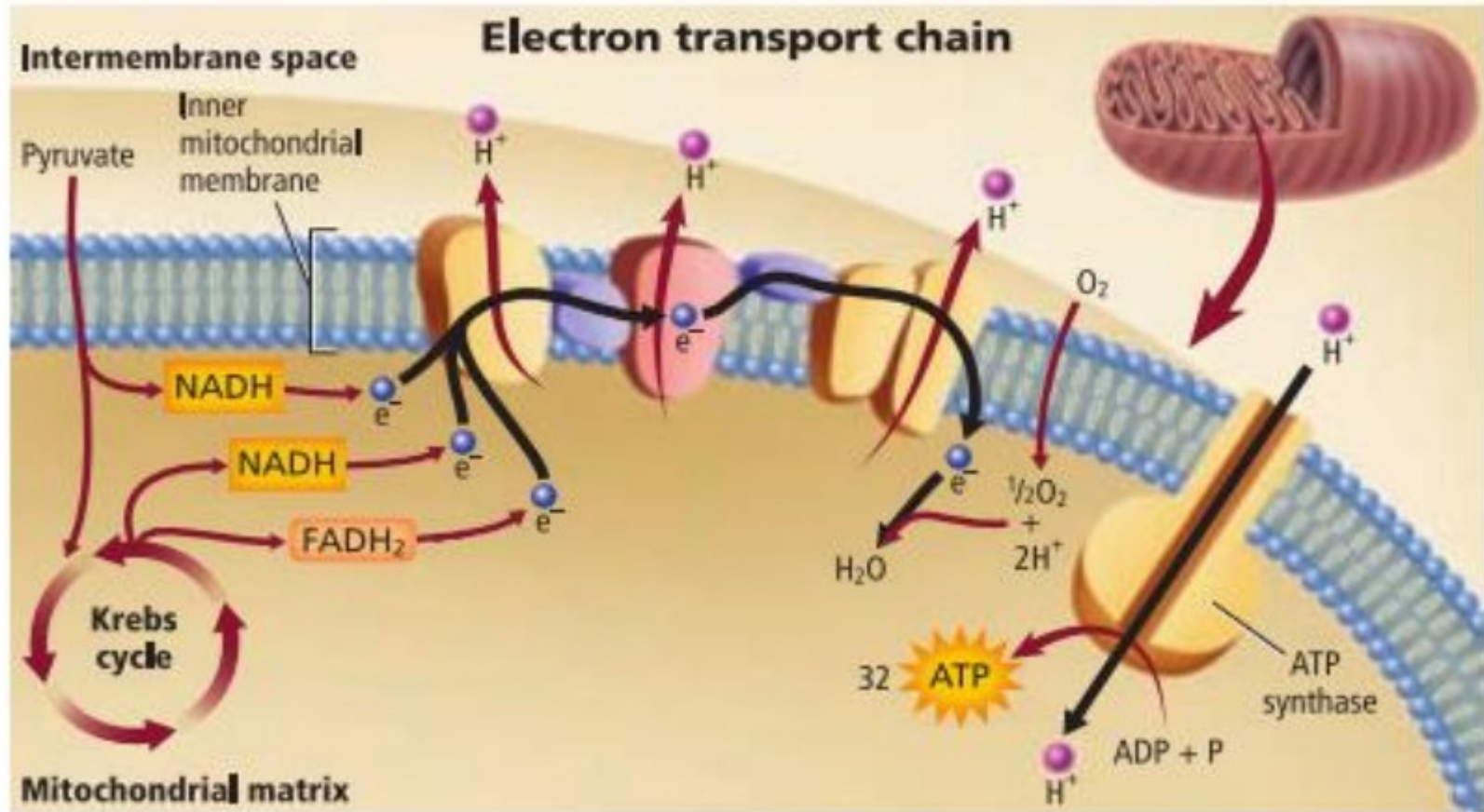
Where do all the NADH's and FADH₂'s Go?

Electron Transport Chain



Electron Transport Chain

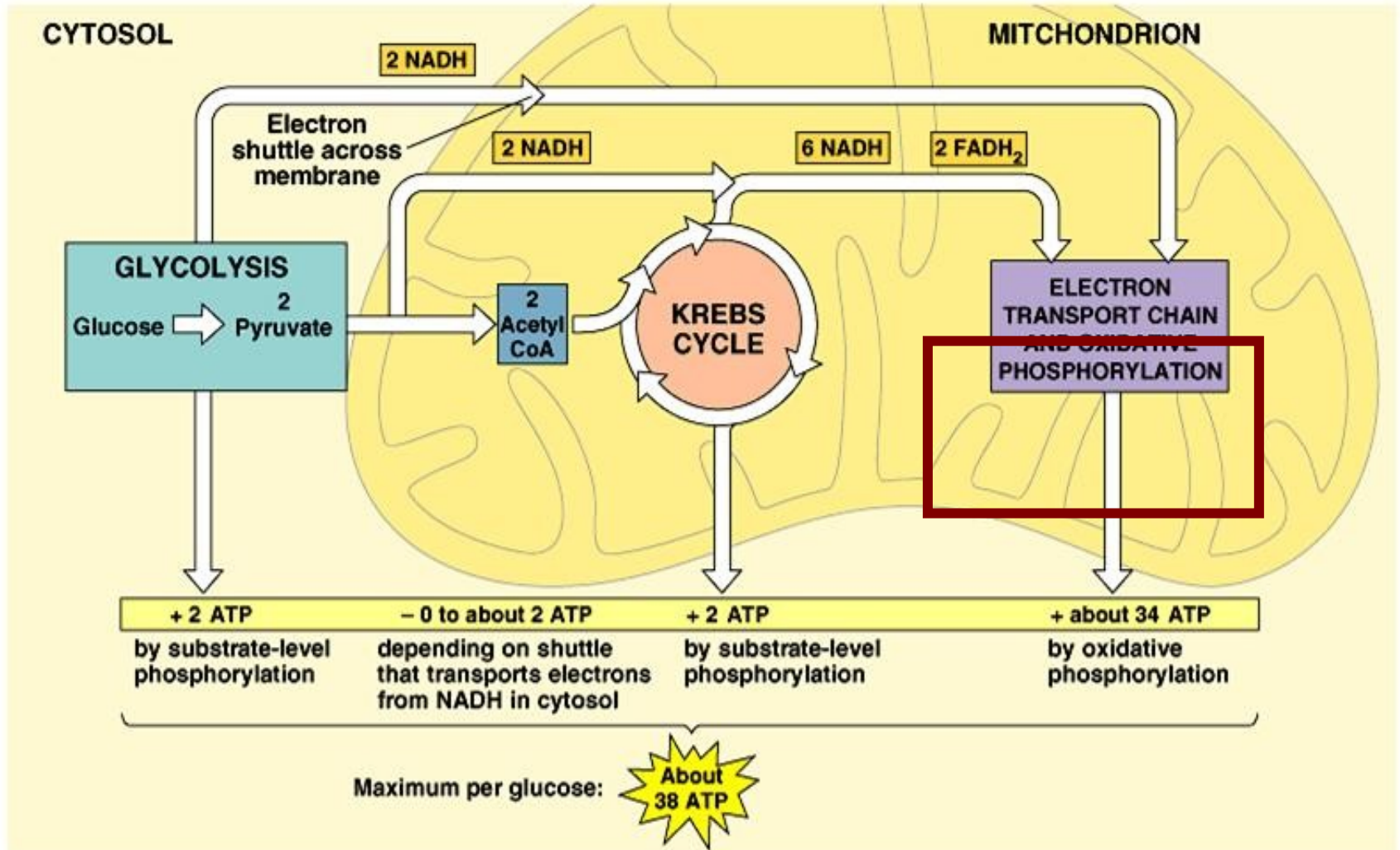
- In aerobic respiration, electron transport is the final step in the break-down of glucose. It also is the point at which most of the ATP is produced. High-energy electrons and hydrogen ions from NADH and FADH₂ produced in the Krebs cycle are used to convert ADP to ATP.

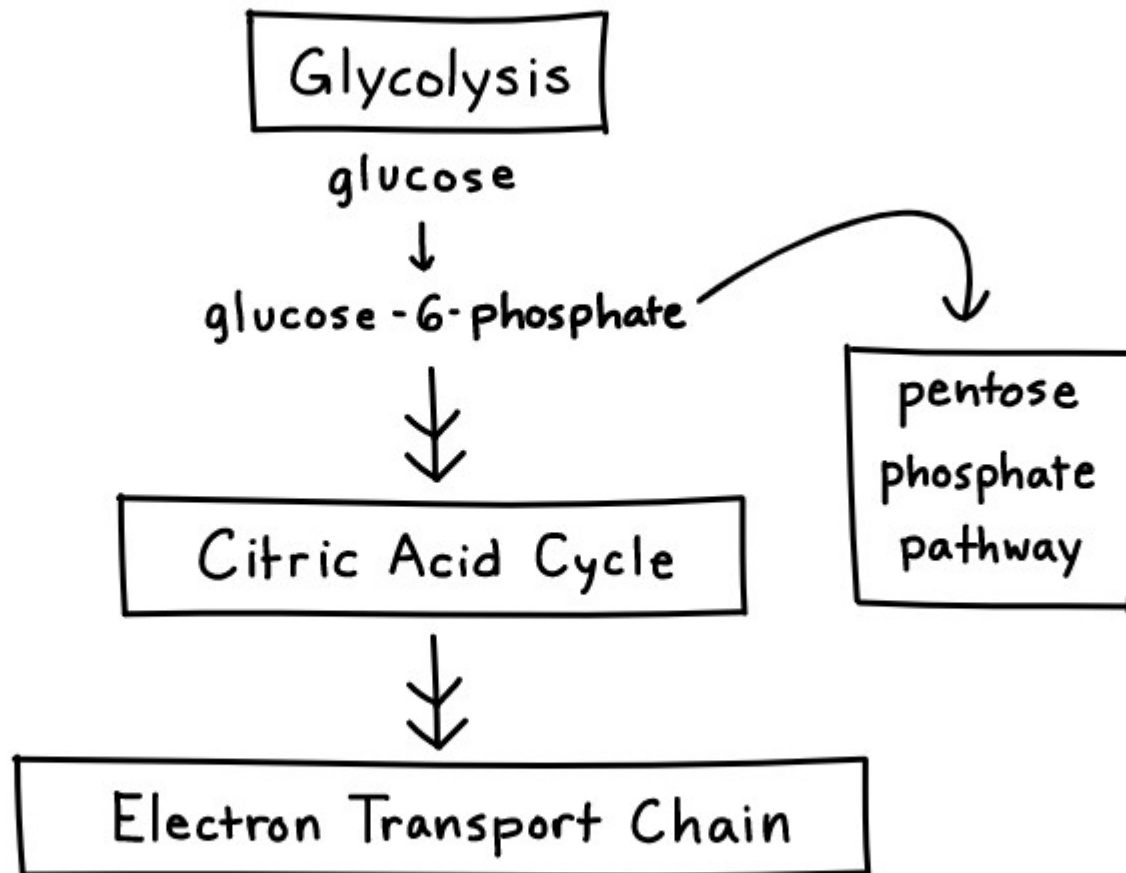


Electron Transport Chain

- As shown in Fig above, electrons move along the mitochondrial membrane from one protein to another. As NADH and FADH₂ release electrons, the energy carriers are converted to NAD⁺ and FAD, and H⁺ ions are released into the mitochondrial matrix. The H⁺ ions are pumped into the intermembrane space across the inner mitochondrial membrane. H⁺ ions then diffuse down their concentration gradient back across the membrane and into the matrix through ATP synthase molecules in chemiosmosis. Electron transport and chemiosmosis in cellular respiration are similar to these processes in photosynthesis. **Oxygen is the final electron acceptor in the electron transport system in cellular respiration.** Protons and electrons are transferred to oxygen to form water.

ETC:





Biosynthesis ...

- Biosynthesis is a multi-step, enzyme-catalyzed process where substrates are converted into more complex products in living organisms. In biosynthesis, simple compounds are modified, converted into other compounds, or joined together to form macromolecules. This process often consists of metabolic pathways. Some of these biosynthetic pathways are located within a single cellular organelle, while others involve enzymes that are located within multiple cellular organelles. Examples of these biosynthetic pathways include the production of lipid membrane components and nucleotides.

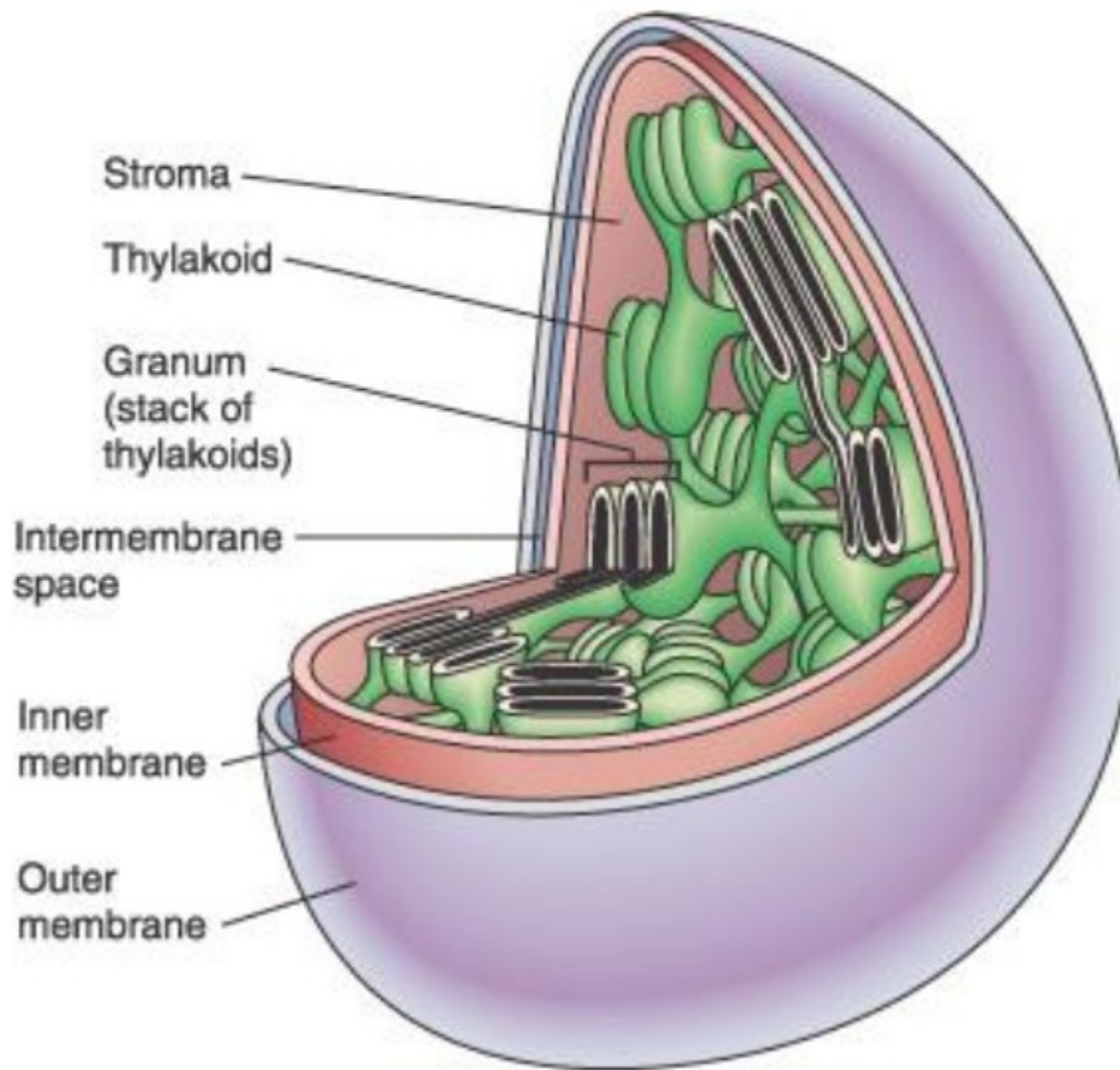
Biosynthesis is usually synonymous with anabolism.

- The prerequisite elements for biosynthesis include: precursor compounds, chemical energy (e.g. ATP), and catalytic enzymes which may require coenzymes (e.g. NADH, NADPH).
- These elements create monomers, the building blocks for macromolecules. Some important biological macromolecules include: proteins, which are composed of amino acid monomers joined via peptide bonds, and DNA molecules, which are composed of nucleotides joined via phosphodiester bonds.

Requirements of Biosynthesis

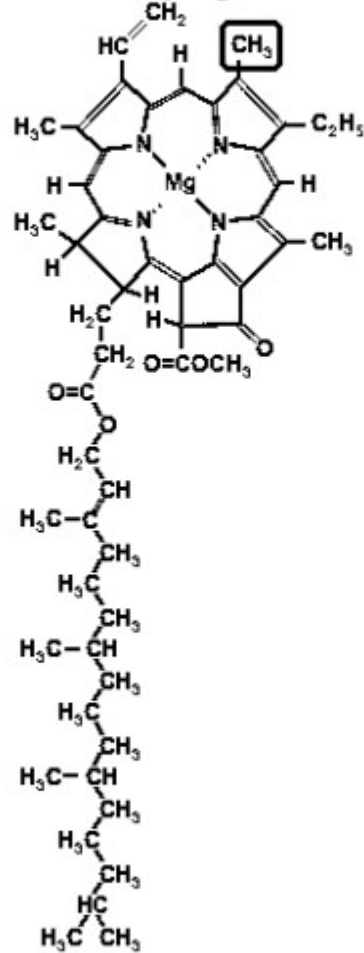
- Sometimes all that is required for biosynthesis is for two substances to physically join together to make a new physical substance, which is called a macromolecule. A very simplified equation for biosynthesis of one form of macromolecule: two substances join together to form a new, more complex substance.
- Photosynthesis ([reading assignment](#))

- Oxygenic photosynthesis is written as follows:
$$6\text{CO}_2 + 12\text{H}_2\text{O} + \text{Light Energy} \rightarrow \text{C}_6\text{H}_{12}\text{O}_6 + 6\text{O}_2 + 6\text{H}_2\text{O}$$
- Similarly, the various anoxygenic photosynthesis reactions can be represented as a single generalized formula:
$$\text{CO}_2 + 2\text{H}_2\text{A} + \text{Light Energy} \rightarrow [\text{CH}_2\text{O}] + 2\text{A} + \text{H}_2\text{O}$$
- The letter A in the equation is a variable and H_2A represents the potential electron donor. For example, A may represent sulfur in the electron donor hydrogen sulfide (H_2S).

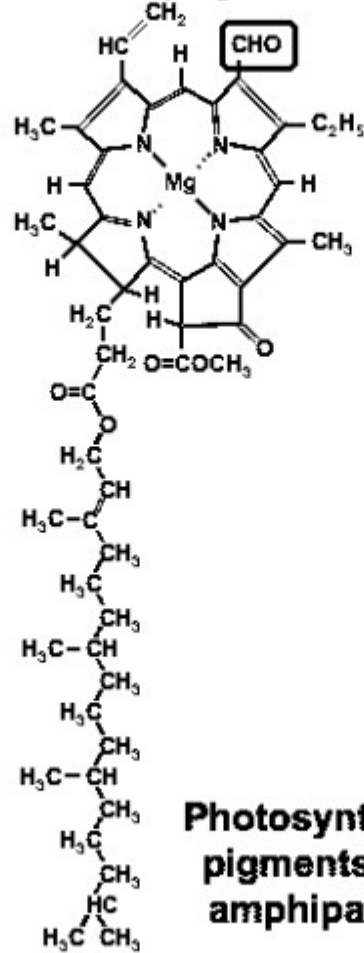


Structure of chloroplast

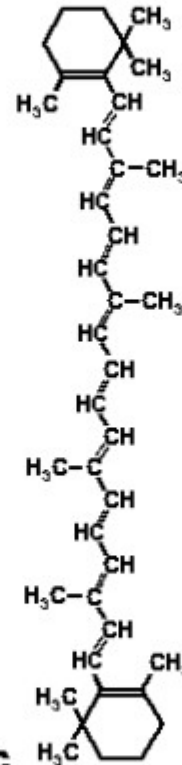
Chlorophyll a



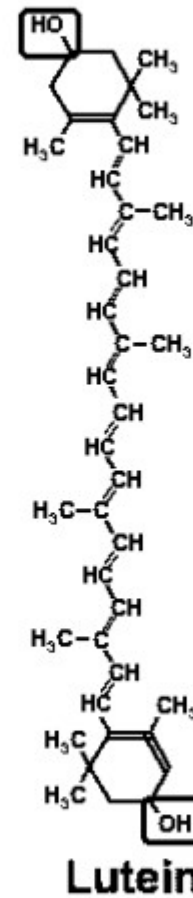
Chlorophyll b



β-Carotene



Zeaxanthin



Photosynthetic pigments are amphipathic

Basic structures of major photosynthetic pigments

Metabolic disorders, diagnosis and treatments

- Metabolism is the breaking down of food to its simpler components: proteins, carbohydrates (or sugars), and fats.
- Metabolic disorders occur when these normal processes become disrupted.
- Disorders in metabolism can be inherited, in which case they are also known as inborn errors of metabolism, or they may be acquired during your lifetime.

Inherited metabolic disorders

- Inherited metabolic disorders are one cause of metabolic disorders, and occur when a **defective gene** causes an **enzyme deficiency**. These diseases, of which there are many subtypes, are known as inborn errors of metabolism. Metabolic diseases can also occur when the **liver or pancreas do not function properly**.

- There are numerous examples of inherited metabolic disorders, which can be classified based on the **type of food-related building block that they affect**, including amino acids (the building block for proteins), carbohydrates, and fatty acids (the building block for fats). Inherited causes of metabolic disorders include:
 - Carbohydrate disorders; examples include Diabetes insipidus, hereditary fructose intolerance, galactosemia, pyruvate metabolism disorders, von Gierke's disease, McArdle disease, Pompe's disease, and Forbes' disease
 - Fatty acid oxidation defects; examples include Gaucher's disease, Niemann-Pick disease, Fabry's disease, and medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency



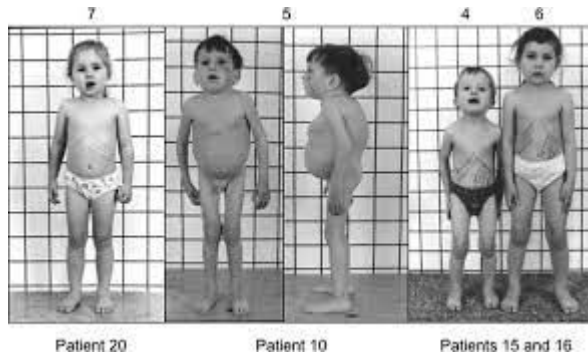
McArdle disease



von Gierke's disease



Forbes' disease



Gaucher's disease



Niemann-Pick disease



Fabry's disease



Tay-Sachs disease

- Amino acid disorders; examples include Tay-Sachs disease, phenylketonuria, tyrosinemia, maple syrup urine disease, and homocystinuria
- Acid-base imbalance, Disorders of calcium metabolism, DNA repair-deficiency disorders, Iron metabolism disorders, Mitochondrial diseases, Phosphorus metabolism disorders, Malabsorption syndromes, Water-electrolyte imbalance are some of the disorders associated with metabolism.

Other causes of metabolic disorders

- Metabolic disorders can be due to other factors, such as a combination of inherited and environmental factors. Some of the conditions that can cause metabolic disorders include:
 - Alcohol abuse, Diabetes (chronic disease that affects your body's ability to use sugar for energy)
 - Diuretic abuse, Gout (type of arthritis caused by a buildup of uric acid in the joints)
 - Ingestion of poison or toxins, including excessive aspirin, bicarbonate, alkali, ethylene glycol, or methanol
 - Kidney failure, Pneumonia, respiratory failure, or collapsed lung
 - Sepsis (life-threatening bacterial blood infection)

Risk factors of metabolic disorders

- A number of factors increase the risk of developing metabolic disorders. Not all people with risk factors will get metabolic disorders. Risk factors for metabolic disorders include:
 - Certain chronic medical conditions, such as lung or kidney disease (includes any type of kidney problem, such as kidney stones, kidney failure and kidney anomalies) and Diabetes (it is more likely to have metabolic syndrome if a person had diabetes during pregnancy (gestational diabetes) or if he/she have a family history of type 2 diabetes.
 - Family history of genetic metabolic disorder.
 - Race and ethnicity: people with African, Hispanic, First Nations, Asian, and Pacific Islander backgrounds are at higher risk than whites for type 2 diabetes.

- HIV/AIDS and other diseases; the risk of metabolic syndrome is higher if a person ever had nonalcoholic fatty liver disease, polycystic ovary syndrome or sleep apnea
- Age- the risk of metabolic syndrome increases with age.
- Obesity and lack of exercise: carrying too much weight, especially in your abdomen, increases your risk of metabolic syndrome
- Hormone imbalance: a hormone disorder such as polycystic ovary syndrome (PCOS), a condition in which the female body produces too much of certain hormones, is linked with metabolic syndrome.
- Insulin resistance: a situation in which a body cannot use insulin properly.

Diagnosis of metabolic disorders

- Metabolic syndrome is more effectively diagnosed by testing different blood markers (specific markers of insulin resistance), obesity (especially abdominal obesity), high blood pressure, and lipid abnormalities. Specifically, metabolic syndrome is diagnosed if any three of the following five markers are present:
 - Elevated waist circumference: 40 inches or more for men; 35 inches or more for women
 - Elevated triglycerides: 150 mg/dL or higher
 - Reduced high-density lipoprotein (HDL) levels (AKA "good" cholesterol): less than 40 mg/dL in men; less than 50 mg/dL in women
 - Elevated blood pressure: 130/85 mm Hg or higher or are already taking blood pressure medications
 - Elevated fasting glucose: 100 mg/dL or higher or are already taking glucose-lowering medications

Treatments of metabolic disorders

- The treatment approach for metabolic disorders depends on the specific disorder. Inborn errors of metabolism (inherited metabolic disorders) are often treated with nutritional counseling and support, periodic assessment, physical therapy, and other supportive care options. Multiple treatment options are available for inherited metabolic disorders and examples include: bone marrow transplantation, enzyme replacement therapy in selected patients, gene therapy in selected patients, medications to reduce symptoms, such as pain or low blood sugar, mineral supplementation, nutritional counseling, surgery to relieve pain or symptoms, vitamin supplementation and etc.
- Acquired metabolic disorder treatment will include normalizing the metabolic balance by both reversing the cause and administering medications.

Potential complications of metabolic disorders

- Complications of untreated metabolic disorders can be serious, even life threatening in some cases. The risk of serious complications can be minimized following the treatment plan designed by health care professional. Complications of metabolic disorders include: organ failure/dysfunction, seizures and tremors, and unconsciousness and coma.

Thank You!