Metabolic disorders

- are diseases that disrupts metabolism.
- A metabolic disease is most frequently caused by an absence or deficiency in an enzyme (or protein).
- Inborn errors of metabolism are heritable disease due to defective gene or genes that are present at birth.
- When one of the enzymes is not working properly, the process of breaking down of specific foods can go more slowly or shut down completely.

Reye's Syndrome

- Extremely rare disorder that can cause brain and liver damage. The exact cause of Reye's syndrome is unknown
- Most commonly in kids between 4 and 14 years old recovering from a viral infection most commonly flu or chickenpox
- Studies have linked the use of aspirin or aspirin-containing medications during viral disease to development of Reye syndrome in children who have an underlying fatty acid oxidation disorder. Fatty acid oxidation disorders inherited disorders in which the body is unable to break down fatty acids because an enzyme is missing or not working properly.
- Early detection and treatment are critical — the chances for a successful recovery increase greatly when Reye syndrome is treated in its earliest stages.

- **Pathophysiology**
- Mitochondrial dysfunction that inhibits oxidative phosphorylation and fatty-acid beta-oxidation → Reye's syndrome

- All cells have swollen mitochondria that are in reduced number, along with glycogen depletion and minimal tissue inflammation.

- This lead to cerebral edema and increased intracranial pressure (ICP).

Symptoms

- persistent vomiting, lethargy or sleepiness in infants, diarrhea and rapid breathing. No Fever
- In the later stages, a child may exhibit irrational behavior, confusion, severe weakness, seizures, and loss of consciousness.
- There is usually no fever.

Treatment

- There is no cure for RS.
- Most children who have Reye's syndrome survive.
- Thus early diagnosis is important for protecting the brain against irreversible damage by reducing brain swelling, preventing complications in the lungs, and anticipating cardiac arrest. Without proper diagnosis and treatment, Reye's syndrome can be fatal within a few days.
- **What is the prognosis?**
- Recovery is directly related to the severity of the swelling of the brain.
- Some people recover completely, while others may sustain varying degrees of brain damage.
- When RS is diagnosed and treated in its early stages, chances of recovery are excellent. When diagnosis and treatment are delayed, the chances for successful recovery and survival are severely reduced.

[no aspirin for children below age of 18 for any disease]

Wilson disease

- It is a genetic disorder that prevents the body from getting rid of extra copper.
- People who get Wilson disease inherit two abnormal copies of the **ATP7B** gene, one from each parent. Wilson disease carriers, who have only one copy of the abnormal gene, do not have symptoms.
- Normally, copper from the diet is filtered out by the liver and released into bile.
- In WD when the copper storage capacity of the liver is exceeded, copper is released into the bloodstream and travels to other organs—including the brain, kidneys, and eyes. Over time, high copper levels can cause life-threatening organ damage.
- About 1 in 40,000 people get Wilson disease. It equally affects men and women. Symptoms usually appear between ages 5 to 35, but new cases have been reported in people aged 2 to 72 years.

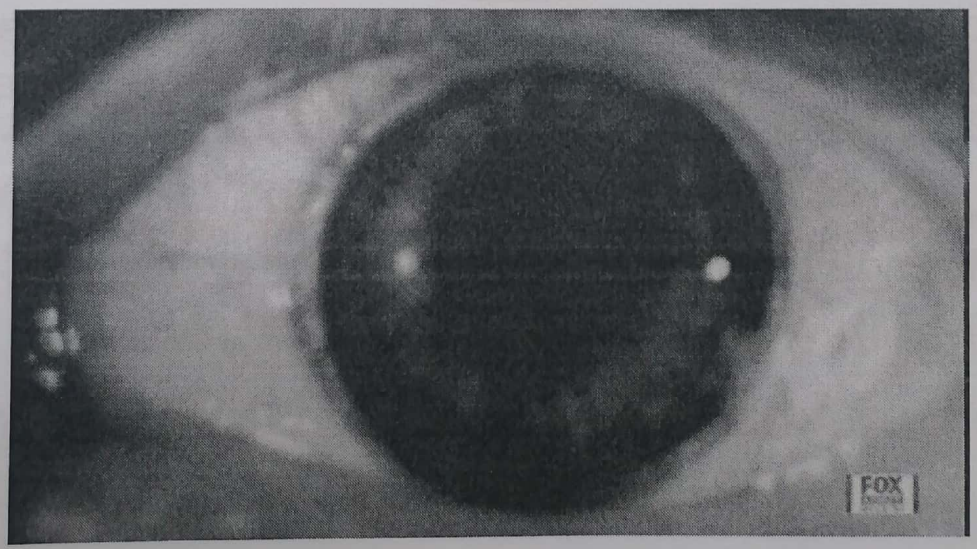
- **What are the symptoms of Wilson disease?**
- Wilson disease first attacks the liver, the central nervous system, or both.
- In Liver or spleen: swelling, yellowing of the skin and whites of the eyes. Rarely, acute liver failure
- In CNS: problems with speech, swallowing, or physical coordination.

- Other signs and symptoms: anemia, low platelet or white blood cell count, slower blood clotting, measured by a blood test.

- **Kayser-Fleischer rings** is the most unique sign of Wilson disease that result from a buildup of copper in the eyes. They appear in each eye as a rusty-brown ring around the edge of the iris and in the rim of the cornea

Kayser-Fleischer rings (KF rings) Wilson Disease

golden ring in eye around iris



Treatment

- Requires lifelong treatment to reduce copper in the body.

- **Initial therapy includes**

1- The removal of excess copper using drugs like (d-penicillamine and trientine)

2- A reduction of copper intake (liver, nuts, seeds sesame and cereals, chocolate)

3- The treatment of any liver or central nervous system damage.

(3)

Hemochromatosis

- Caused by too much absorption and storage of iron.
- Healthy people absorb about **10** percent of the iron in the food, People with hemochromatosis absorb up to **30** percent of iron. Over time, they absorb and retain between **5 to 20** times more iron than the body needs.
- Our body has no natural way to rid itself of the excess iron, it is stored in body tissues, specifically the liver, heart, and pancreas.

Causes

- Defect in a gene called **HFE**, which helps regulate the amount of iron absorbed from food.
- The most known mutation of HFE is C282Y.

- In people who inherit C282Y from both parents, the body absorbs too much iron and hemochromatosis can result.
- Those who inherit the defective gene from only one parent are carriers for the disease but usually do not develop it; however, they still may have higher than average iron absorption.

Diagnosis

1. **Serum transferrin saturation.** A plasma protein that transport iron in blood. Transferrin saturation values greater than 45 percent are considered too high.
2. **Ferritin.** intracellular protein that stores and releases iron in controlled way. This test measures the amount of iron stored in your body (most of ferritin is in liver).
3. Genetic testing to confirm the diagnosis blood test to detect the HFE mutation, which will confirm the diagnosis

Treatment

- Phlebotomy, which means removing blood the same way it is drawn from donors at blood banks.
- The goal of phlebotomy is to reduce your iron levels to normal. The amount of blood removed and how often it's removed depend on your age, your overall health and the severity of iron overload. It may take a year or longer to reduce the iron in your body to normal levels.
- **Initial treatment** Initially, you may have a pint (about 470 milliliters) of blood taken once or twice a week
- **Maintenance treatment schedule.** Once your iron levels have returned to normal, blood can be removed less often, typically every two to four months. The schedule depends on how rapidly iron accumulates in your body.
- Blood ferritin levels will be tested periodically to monitor iron levels.
- If treatment begins before organs are damaged associated conditions can be

(4) Glycogen Storage Disease

- Result from storage of abnormal quantities of glycogen or storage of glycogen with abnormal properties.
- Deficiencies of enzymes related to glycogen metabolism, affect the levels of glucose and glycogen because their deficiency can significantly alter the normal metabolism of glucose.

Type I Glycogen Storage Disease

- also known as von Gierke's disease, is the most common form of glycogen storage disease, accounting for 25% of all cases.
- **Cause** inherited deficiency of liver Glucose 6- phosphatase (release free glucose & phosphate thus providing glucose during starvation).
- The liver glycogen is normal in structure but present in abnormally large amounts.
- The absence of glucose 6-phosphatase in the liver causes hypoglycemia due to inability to release free glucose.
- The presence of excess glucose 6-phosphate triggers an increase in glycolysis in the liver, leading to a high level of lactate and pyruvate in the blood.
- Patients who have von Gierke disease also have an increased dependence on fat metabolism.

Four types of GSD I

The activity of G6P-ase activity is associated with three transport proteins (translocase 1 (T1), translocase 2 (T2), and translocase3 (T3) that facilitate movement of glucose-6-phosphate (G6P)

Types of GSD I:

1. **GSD type Ia** caused by Glucose 6- phosphatase defect
2. **GSD type Ib** resulting from deficiency of a specific translocase T1 which is a transporter of glucose-6-phosphate (G6P) into the endoplasmic reticulum compartment where it is hydrolyzed into glucose and inorganic phosphate
3. **GSD type Ic** is deficiency of translocase T2 that carries inorganic phosphates
4. **GSD type Id** is deficiency in a T3 that translocates free glucose molecules

genetic

Glycogen storage disease type II

- known as acid maltase deficiency or Pompe disease, is a lysosomal disease.
- Deficiency of a lysosomal enzyme, alpha-1,4-glucosidase causes GSD type II.
- Alpha-1,4-glucosidase function: degradation of glycogen in the lysosome.
- Deficiency of the enzyme leads to accumulation of glycogen in the cells mostly in lysosomes.
- The most abundant deposits are in the cardiac and skeletal muscles and liver, depending on the degree of residual enzyme activity.

= infantile form is characterized by heavy deposits of glycogen in the heart, liver, and tongue; as a result of the deposits, these tissues enlarge.

- The hypotonia (low muscle tone tension or resistance to stretch) **and** muscle weakness (myopathy) involve skeletal and respiratory muscles as well with progressive respiratory insufficiency.
- In the CNS, the disease primarily affects the nuclei of the brainstem and the cells of the ventral horn of the spinal cord. Mental functions are preserved.

= Juvenile and adult forms, is characterized by glycogen deposition in skeletal muscles. The involvement of the cardiac muscle varies in the juvenile form, whereas the muscle is unaffected in the adult form

- **Glycogen storage disease type III**
- also known as Forbes-Cori disease or limit dextrinosis.
- Both liver and skeletal muscles are involved in GSD type III.
- Deficiency of the cytosolic debrancher enzyme causes GSD type III.
- Abnormal glycogen with short external branches is stored in the liver, heart, and skeletal muscle cells.

- Two forms of the disease exist.

1- In GSD type IIIa, the liver, skeletal muscles, and cardiac muscle are involved.

2- In GSD type IIIb, only the liver is involved.

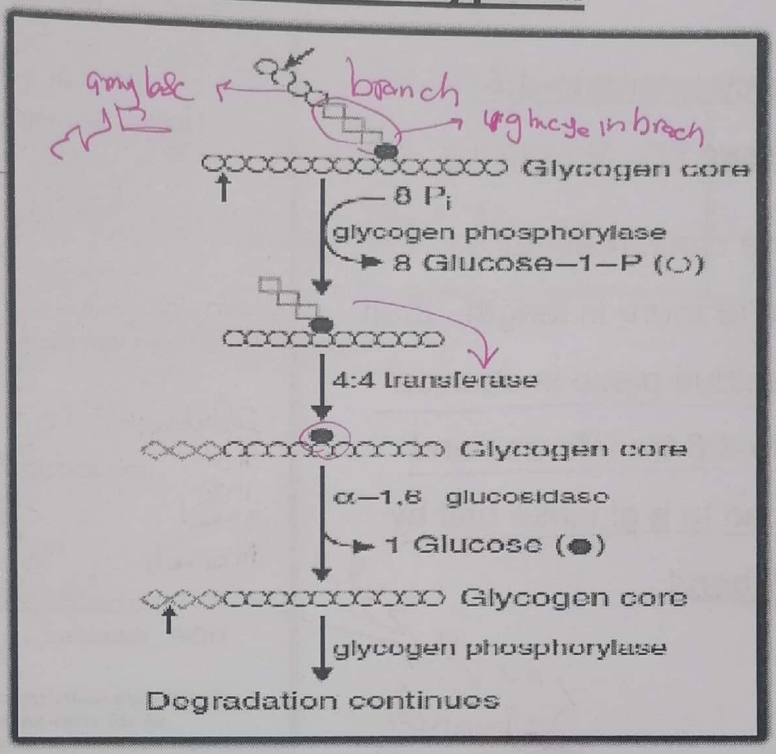
Glycogen storage disease type III

Deficiency of the cytosolic debrancher enzyme

The debrancher enzyme, catalyzes the removal of the last branched four residues. It has two catalytic activities it acts as a

1- As a transferase, it first removes the three glucose residues, and adds it to the end of a longer chain.

2- Alpha amylo-1,6-glucosidase activity resulting in the release of free glucose.



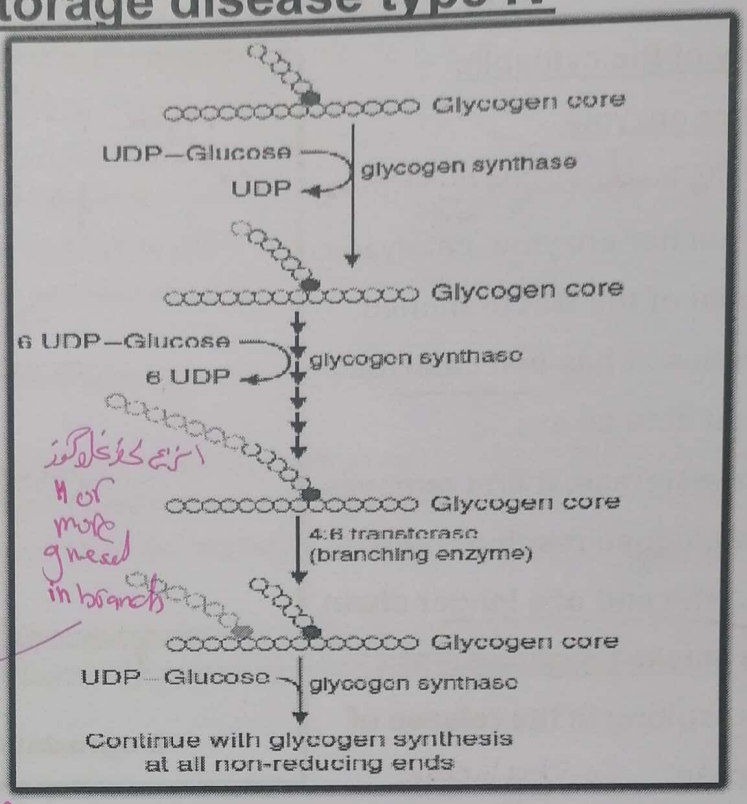
- **Glycogen storage disease type IV**
- also known as amylopectinosis or Andersen disease, is a rare disease that leads to early death
- **Causes** deficiency in amylo-4:6-transferase (branching enzyme).

- Accumulation of abnormally structured glycogen in the liver, heart, and neuromuscular system characterizes this disease.
- The abnormal glycogen has long external branches that resemble amylopectin.
- This form of glycogen is less soluble; liver cirrhosis probably arises as a reaction to this insoluble material.

Glycogen storage disease type IV

Deficiency in amylo-4:6-transferase

When the chain reaches 11 residues or more in length, then 6 to 8 residue piece is cleaved by amylo-4:6-transferase and reattached to a glucose unit by an α-1,6 bond.



branch
Cut 6-8 glucos
From this branch
and make new branch

So

branching enzy who can dis all glycogen??
the branch will be very long