ppp

Clinical Hint: G6PD Deficiency

- A common disease
- characterized by hemolytic anemia
- 200 – 400 millions individuals worldwide
- Highest prevalence in Middle East, S.E. Asia, Mediterranean
- X-linked inheritance
- > 400 different mutations
- Deficiency provides resistance to falciparum malaria

Precipitating Factors in G6PD Deficiency

⇒ ↓NADPH = ↑ROS = cell death.

* anything that can increase ROS levels works as a (risk) factor in these patients ⇒ crisis.

examples:

- Oxidant drugs
  - Antibiotics e.g. Sulfomethxazole
  - Antimalaria Primaquine
  - Antipyretics Acetanalid
- Favism due to vicine and covicine in fava beans in some G6PD deficient patients
- Infection
- Neonatal Jaundice

⇒ has to with degradation process of heme groups ⇒ degradation produces bilirubin ⇒ v. destructive of CNS esp. in kids.

bilirubin: yellow

⇒ yellow skin in newborns

↳ not a disease, developmental process (waiting for enough enzyme formation to get rid of bilirubin)

↓ if newborn has jaundice & G-6-P DH deficiency ⇒ more susceptible to oxidative stress.

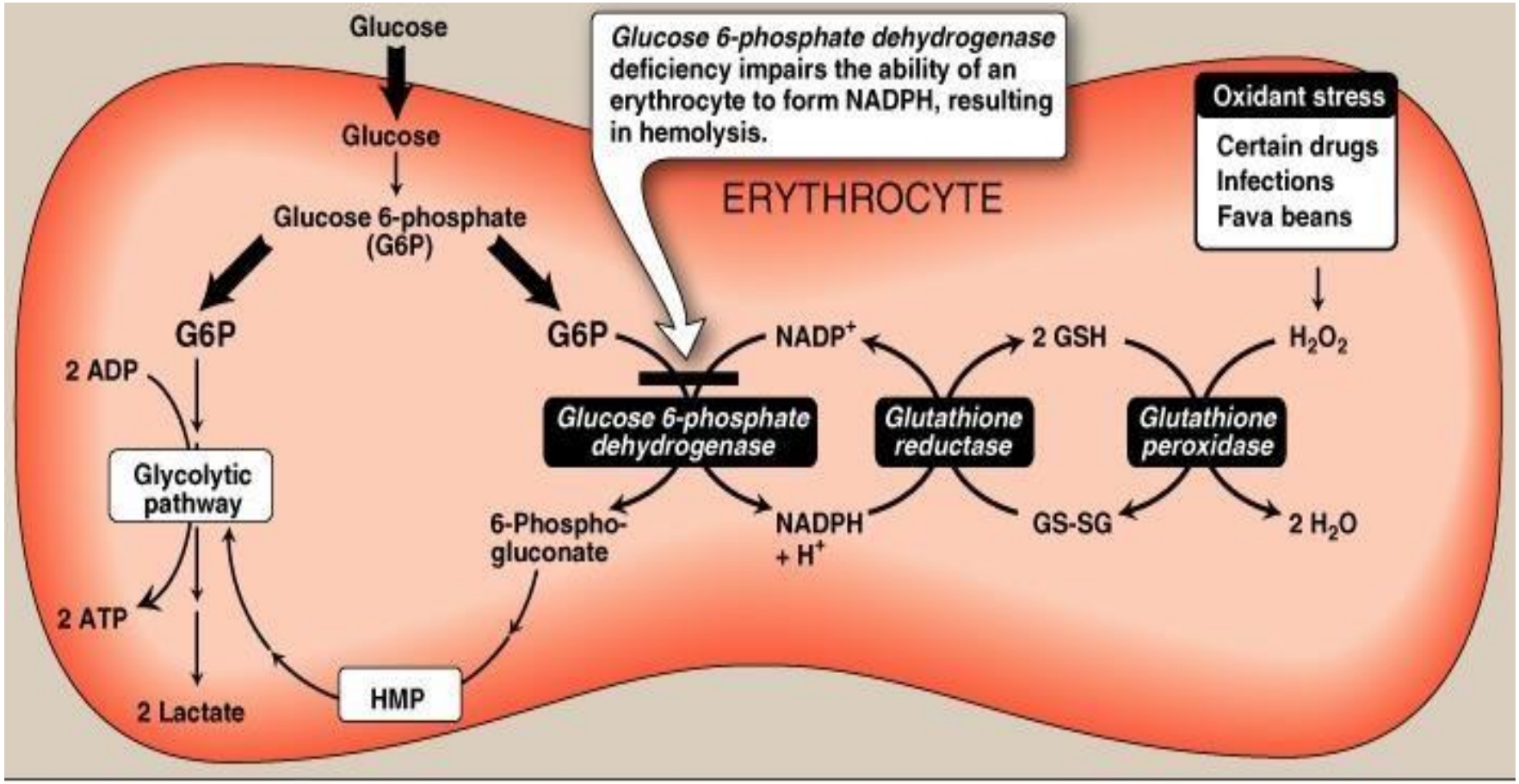
Role of G6PD in red blood cells

$H_2O_2 + GSH \longrightarrow G\text{-}S\text{-}S\text{-}G + 2H_2O$

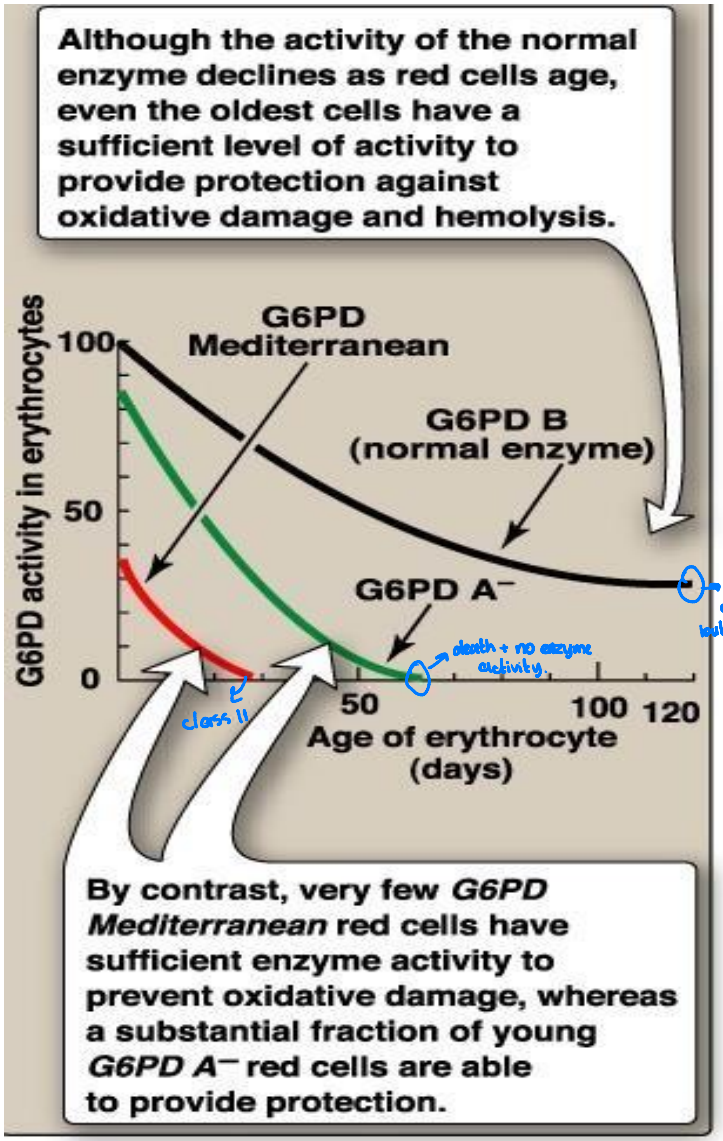
$G\text{-}S\text{-}S\text{-}G + NADPH \longrightarrow 2GSH + NADP+$

GSH helps maintain the SH groups in proteins in the reduced state

Oxidation ➔ denaturation of proteins and rigidity of the cells



Classification of G6PD Deficiency Variants



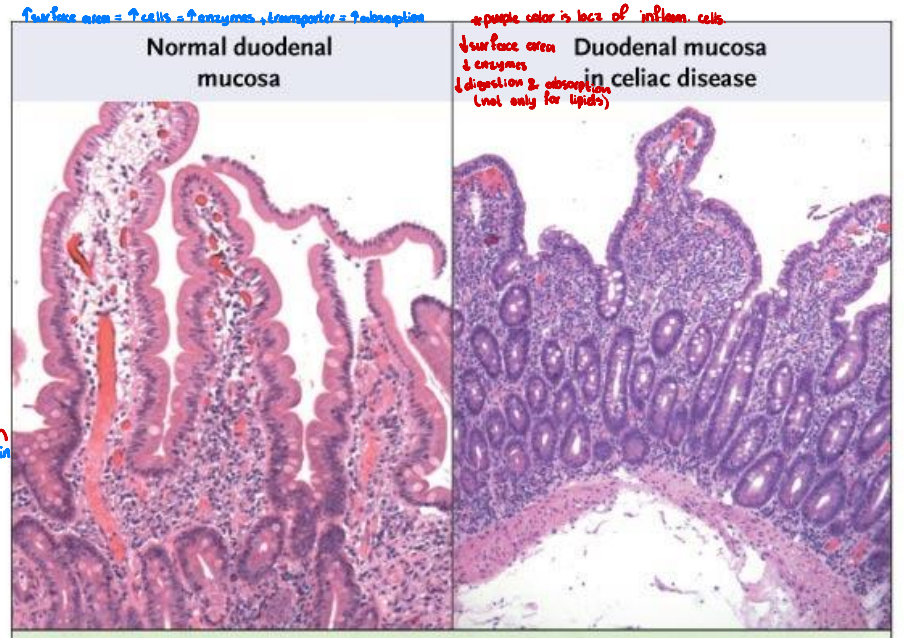
Class	Clinical symptoms	Residual enzyme activity
I	Very severe	<2%
II	Severe	<10%
III	Moderate	10–50%
IV	None	> 60%

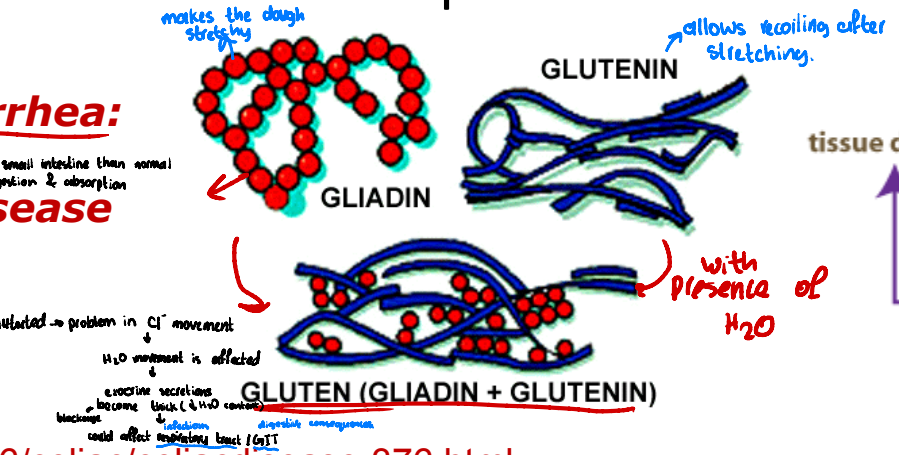
- Wild type B
- Mediterranean Variant B^- (Class II) : 563C→T
- African Variant A^- (Class III); two point mutation
- Majority missense mutation, point mutation
- Large deletions or frame shift; Not Observed

Lipid Digestion

Celiac disease (CD)

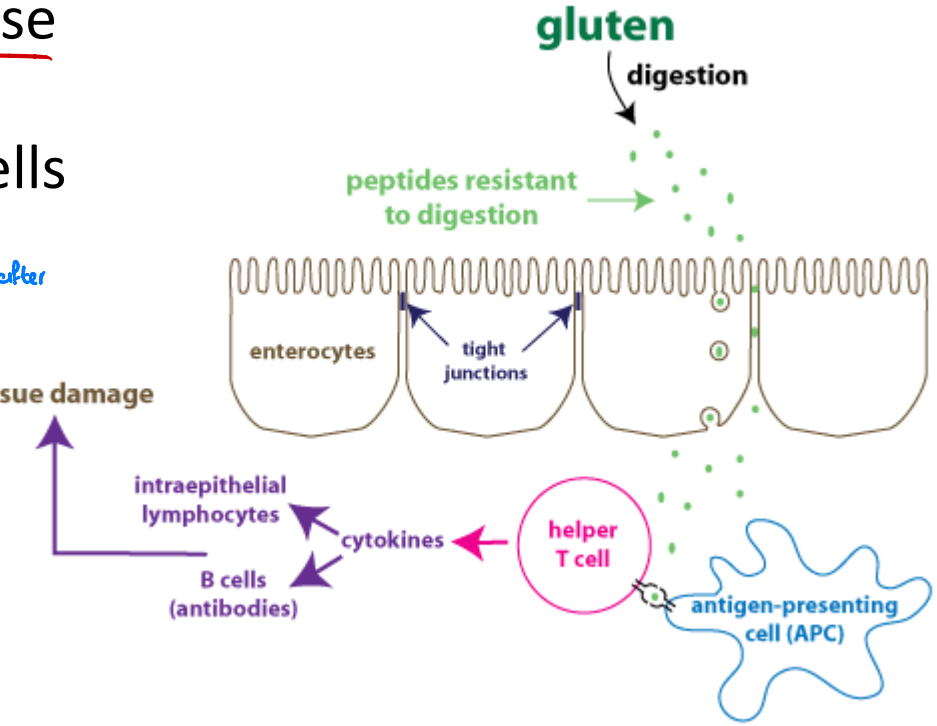
- Fat malabsorption leading to steatorrhea (excess lipids in feces)
- It is an autoimmune response to gliadin, a peptide found in gluten (wheat, rye, and barley).
- Gliadin contains many proline (14%) and glutamine (40%) residues, making it resistant to digestion.
- Lab tests: the presence of anti-tissue transglutaminase (anti-tTG) antibodies.
- Tissue biopsy: absence of villous surface epithelial cells resulting in decreased nutrient absorption.





Principal causes of steatorrhea:

1. ***Short bowel disease***
2. ***Liver or biliary tract disease***
3. ***Pancreatic exocrine insufficiency***
4. ***Cystic fibrosis***



http://courses.washington.edu/pbio376/celiac/celiacdisease-376.html

FA Degradation

Application: Carnitine deficiencies

- Primary carnitine deficiency
  - Defects in a membrane transporter (translocase): No uptake of carnitine by cardiac and skeletal muscles and the kidneys, causing carnitine to be excreted.
    - Treatment: carnitine supplementation.
- Secondary carnitine deficiency
  - Taking valproic acid (antiseizure) → decreased renal reabsorption ⇒ more excretion.
  - Defective fatty acid oxidation (enzymes) → acyl-carnitines accumulate (activated FAs accumulation) → urine (appears like carnitine deficiency.)
  - Liver diseases (b/c it's synth. in liver.) → decreased carnitine synthesis
  - ① CPT-I deficiency (transferases): affects liver; no use of LCFA, no energy for glucose synthesis during fasting → severe hypoglycemia, coma, and death
  - ② CPT-II deficiency (FA stays bound to carnitine): affects liver, cardiac muscle, and skeletal muscle
    - Treatment: avoidance of fasting (+ ketogenic diet) and adopting a diet high in carbohydrates and low in fat but supplemented with medium-chain TAG. ⇒ not highly obtained from diet.

⇒ small + v. frequent meals.

Application: MCAD deficiency

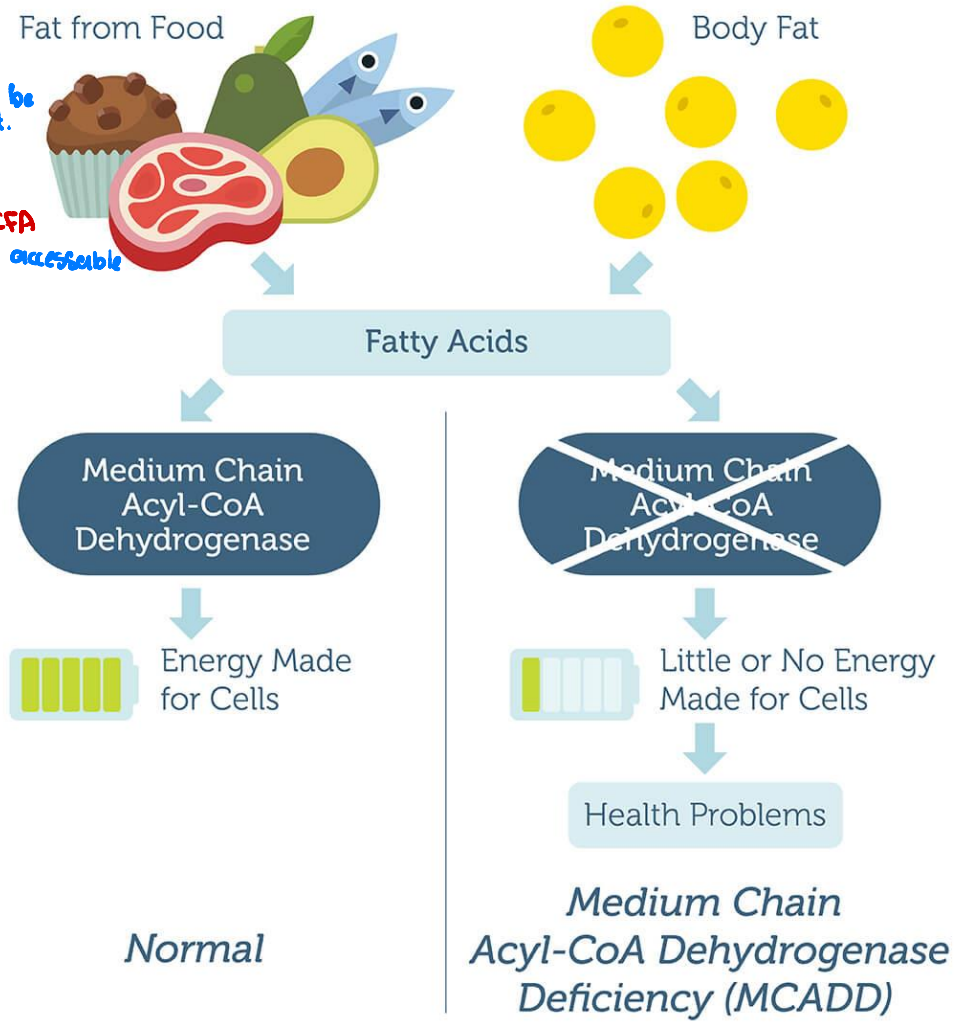
- There are 4 isozymes of fatty acyl CoA dehydrogenase for SCFA, MCFA, LCFA, and VLCFA.
- Medium-chain fatty acyl CoA dehydrogenase (MCAD) deficiency,
  - An autosomal-recessive disorder
  - Most common inborn error of β-oxidation (1:14,000 births worldwide)
  - Higher incidence among Caucasians of Northern European descent
  - Decreased ability to oxidize MCFAs (lack of energy)
  - Severe hypoglycemia and hypoketonemia
  - Treatment: avoidance of fasting

    Regular and frequent meals and snacks

    Diet high in carbohydrates and low in fat

→ most common to be deficient.

* mostly affected patients are newborns bcz their nutrition source (milk) is abundant in SCFA & MCFA which are v. imp for brain development. (easily accessable therefore faster source of energy)

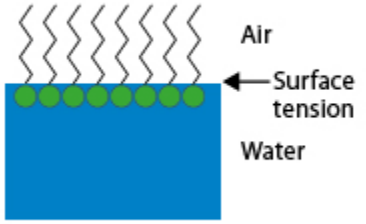


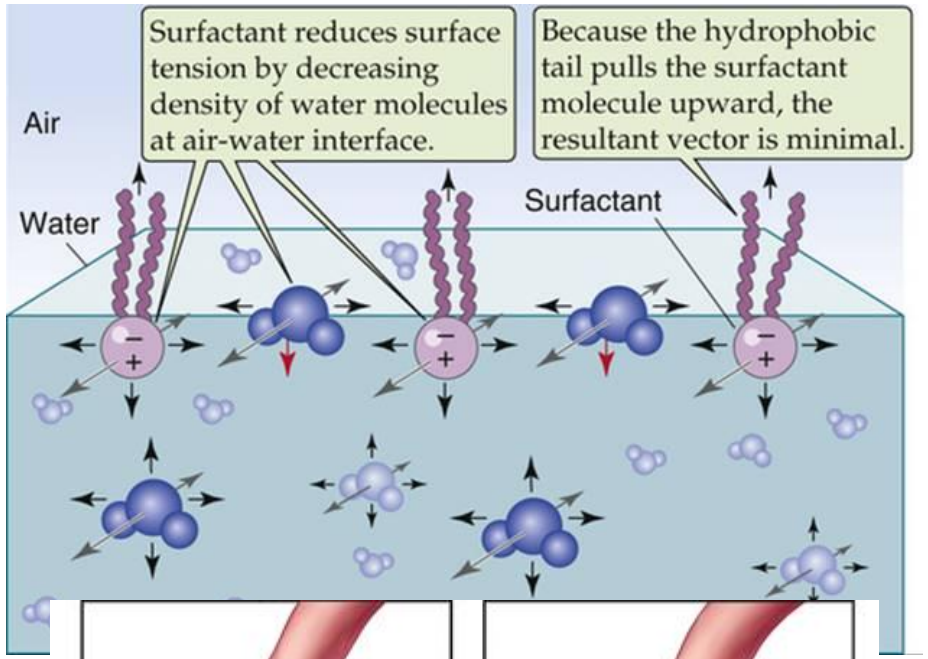
Glycerophospholipids

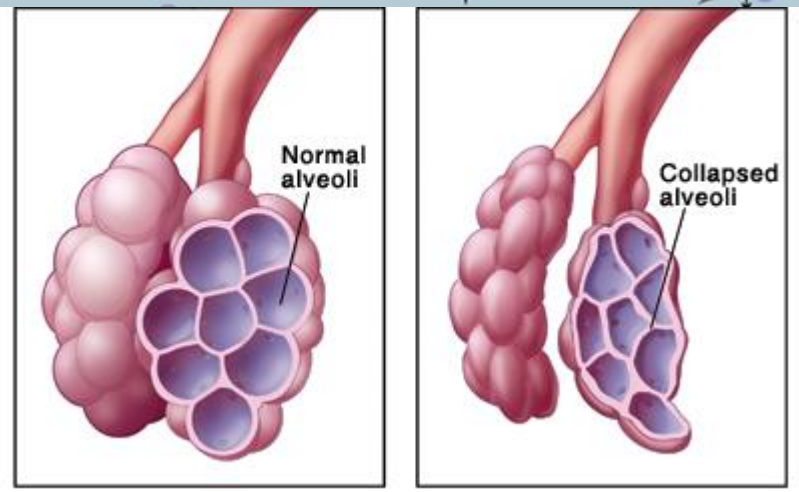
Application: Surfactants

- Surfactants are a complex mixture of lipids (90%) and proteins (10%) that make the extracellular fluid layer lining the alveoli and are secreted by type II pneumocytes in the lungs.
- Dipalmitoylphosphatidylcholine (DPPC) is the major lipid in surfactants.
- Surfactants serve to decrease the surface tension of the fluid layer allowing reinflation of alveoli and preventing alveolar collapse (atelectasis).
- Respiratory distress syndrome (RDS) in preterm infants is associated with insufficient surfactant production and/or secretion.
- Prenatal administration of glucocorticoids shortly before delivery to induce expression of specific genes.

in order to increase synth. of DPPC



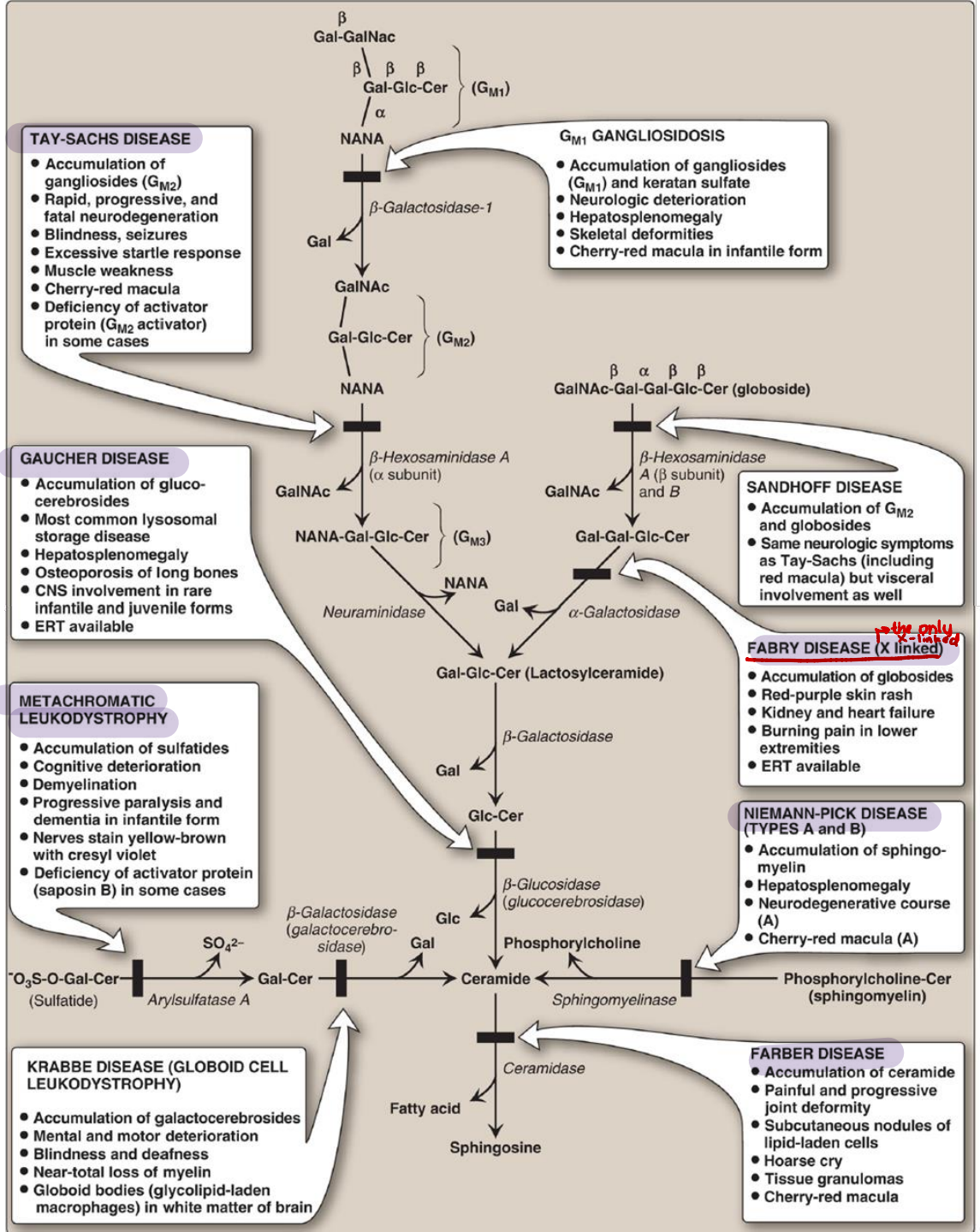




Sphingolipids

Diagnosis and treatment

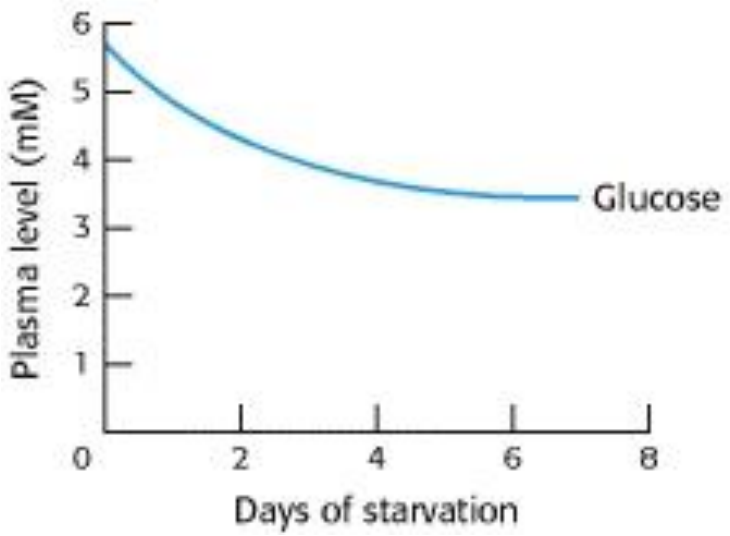
- Diagnosis:
  - Measure enzyme activity in cultured fibroblasts or peripheral leukocytes
  - Analyzing DNA
- Treatment:
  - Recombinant human enzyme replacement therapy
    - Gaucher disease and Fabry disease (expensive)
  - Bone marrow transplantation:
    - Gaucher disease
- Substrate reduction therapy
  - Gaucher disease: reducing the amount of glucocerebroside produced in the body pharmacologically

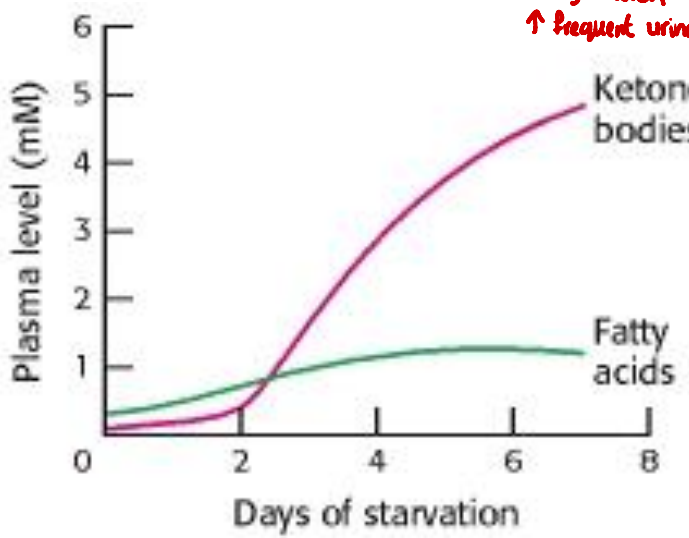


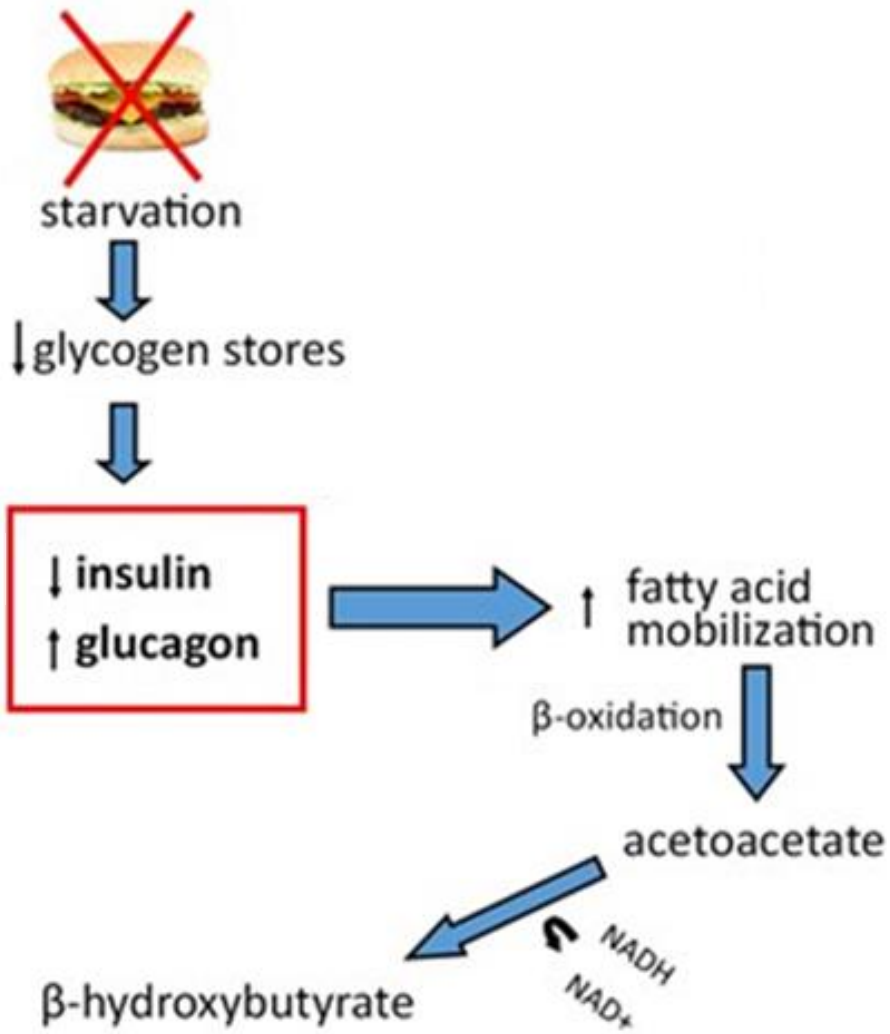
ketogenesis

Diabetic ketoacidosis

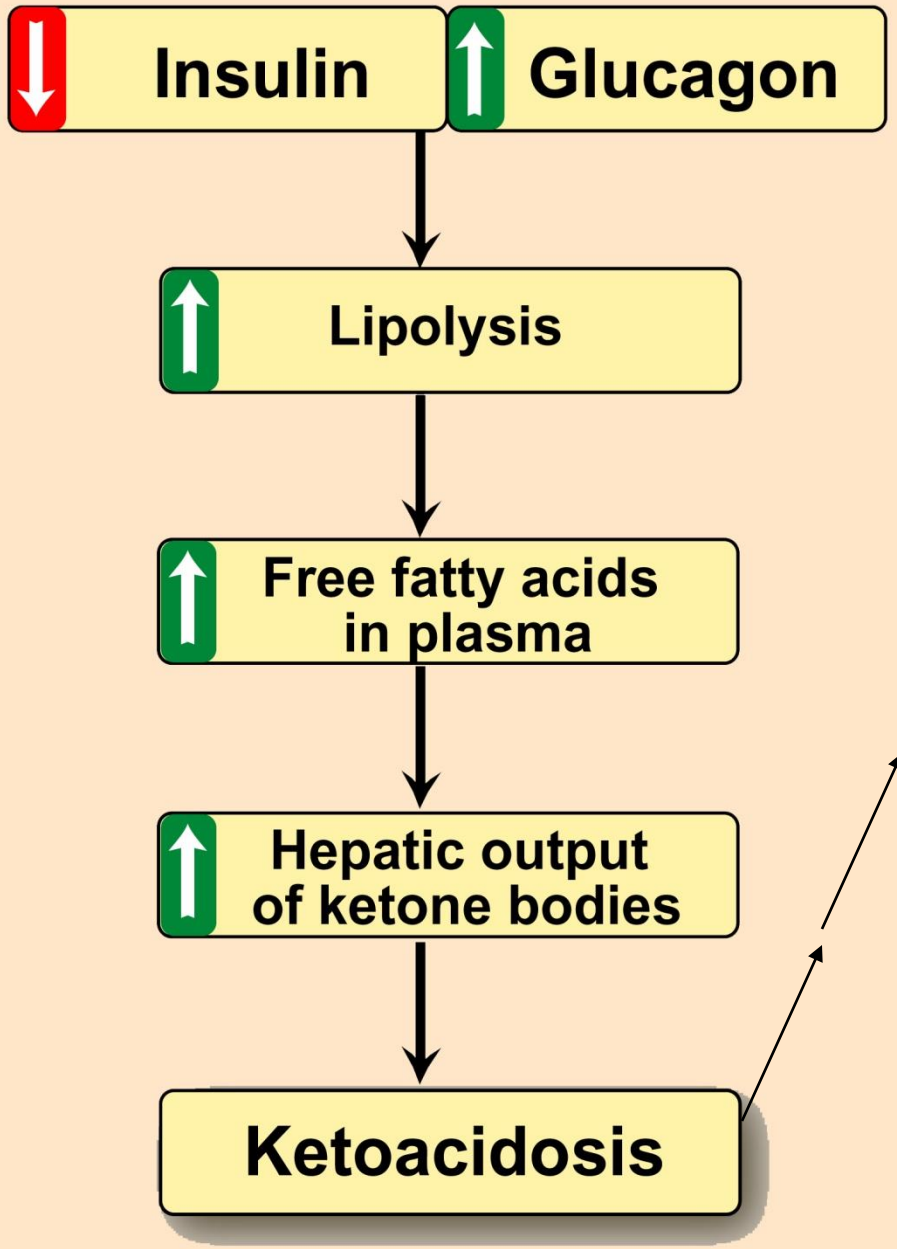
- Normally,
  - Levels of ketone bodies: <3 mg/dl
  - 3HB:AcAc is ~1:1
- Under uncontrolled diabetes,
  - Levels of ketone bodies: 90 mg/dl and urinary excretion of ketone bodies may be 5,000 mg/24 hours.
- The end-results:
  - Acidemia (ketoacidosis), dehydration and fruity odor of breath







Diabetic ketoacidosis



Increase Excretion in Urine as

Sodium Salt

↓

Loss of water

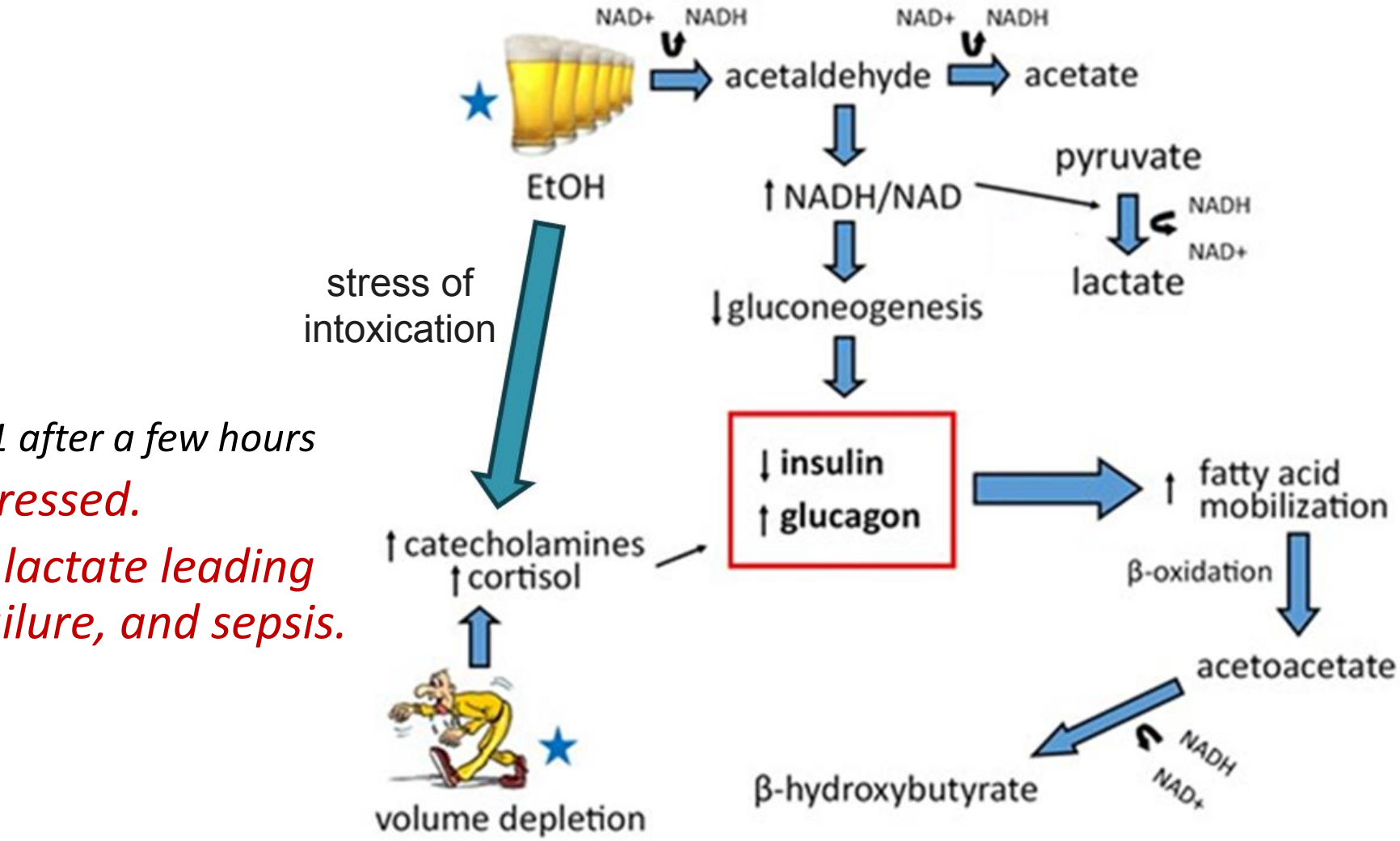
↓

Dehydration

Polyuria

Alcoholic ketoacidosis

- Alcohol also causes,
  - Acidemia (ketoacidosis)
- But,
  - 3HB:Ac is ~3:1
    - *The ratio gets back to 1:1 after a few hours*
  - *Gluconeogenesis is suppressed.*
  - *Pyruvate is converted to lactate leading to hypovolemia, heart failure, and sepsis.*



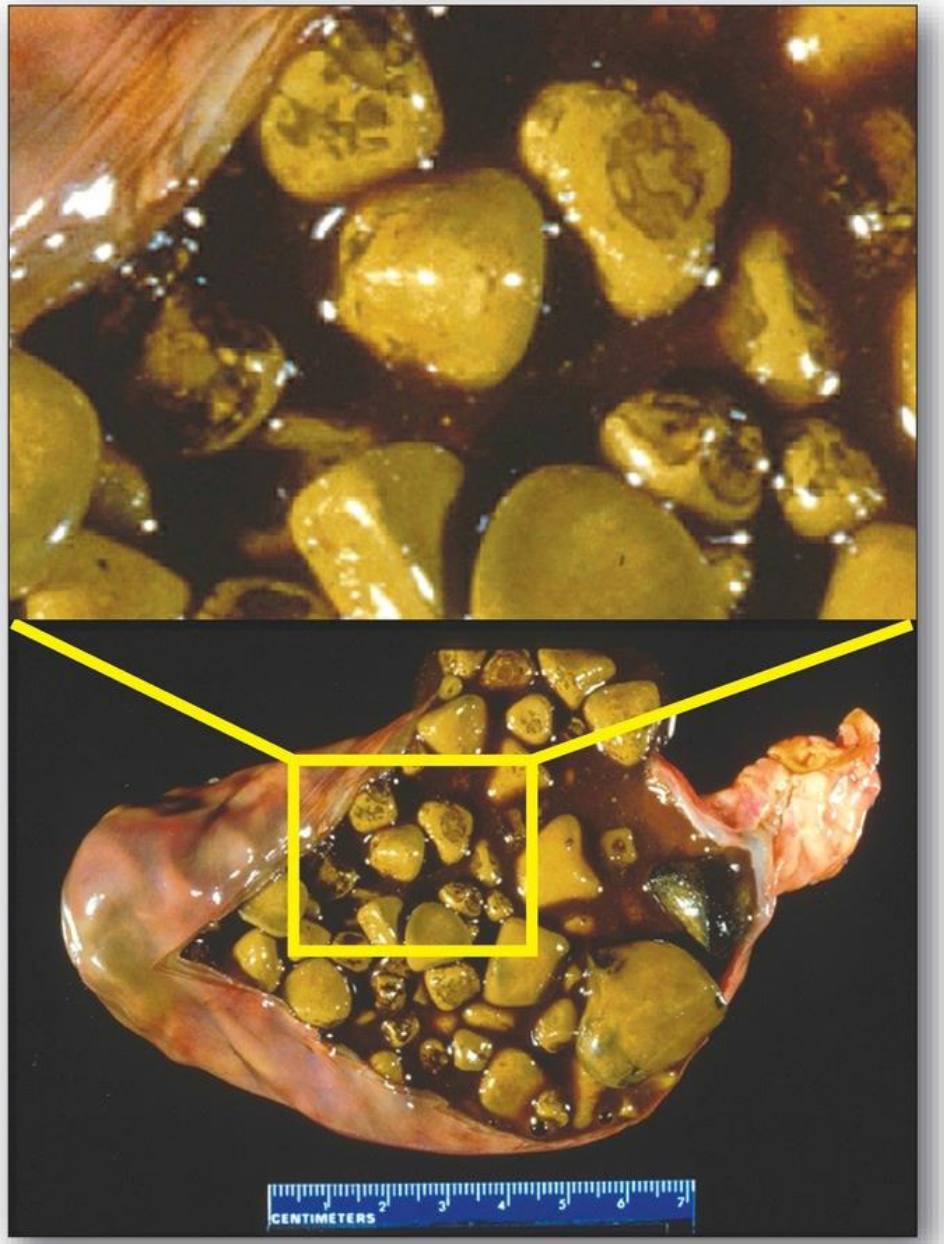
Cholestrol Metabolism

Application: Cholelithiasis

stone

* stones formation is usually associated with over-saturation

- ↑Cholesterol or ↓bile acids → insolubility → gallbladder stones (cholelithiasis)
- Treatment: cholecystectomy
  - Alternatively: oral administration of chenodeoxycholic acid results in a gradual (months to years) dissolution of the gallstones. ⇒ for less severe cases



Amino Acids

Clinical Hint: Abnormalities in protein digestion and Celiac disease

* problems with the pancreas.

* both result in deficiencies (i.e: vitamins)

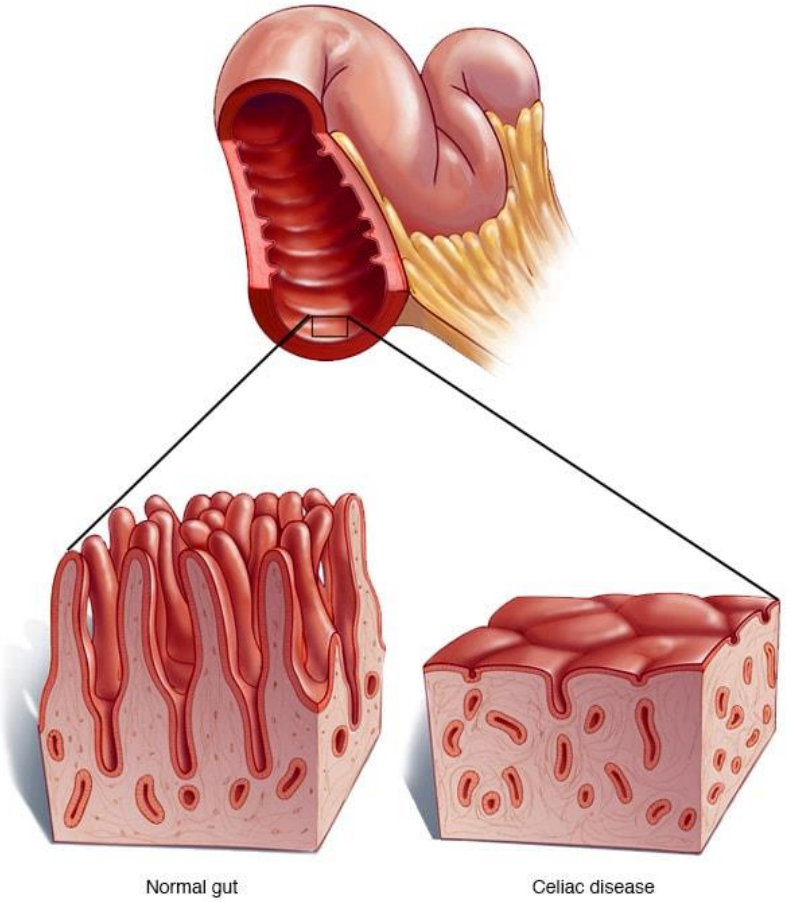
Pancreatic secretion deficiency due to chronic pancreatitis, cystic fibrosis, or surgical removal of the pancreas, results in incomplete fat and protein digestion. ⇒ accumulate

Symptoms: abnormal appearance of lipids (**steatorrhea**), and **undigested protein** in the feces.

↳ CANNOT be noted by patients themselves bcz H_2O-soluble.

Celiac disease (celiac sprue) is a disease of **malabsorption** resulting from immune-mediated damage to the small intestine in response to ingestion of **gluten** (or gliadin produced from gluten), a protein found in wheat, barley and rye.

↓ # of intestinal cells = ↓ [intestinal enzymes] + ↓ transporters for absorption



Clinical hint: Hyperammonemia

NH3 has a neurotoxic effect on the CNS (tremors, slurring of speech, somnolence, vomiting, cerebral edema, and blurring of vision). At high concentrations, ammonia can cause coma and death.

Types:

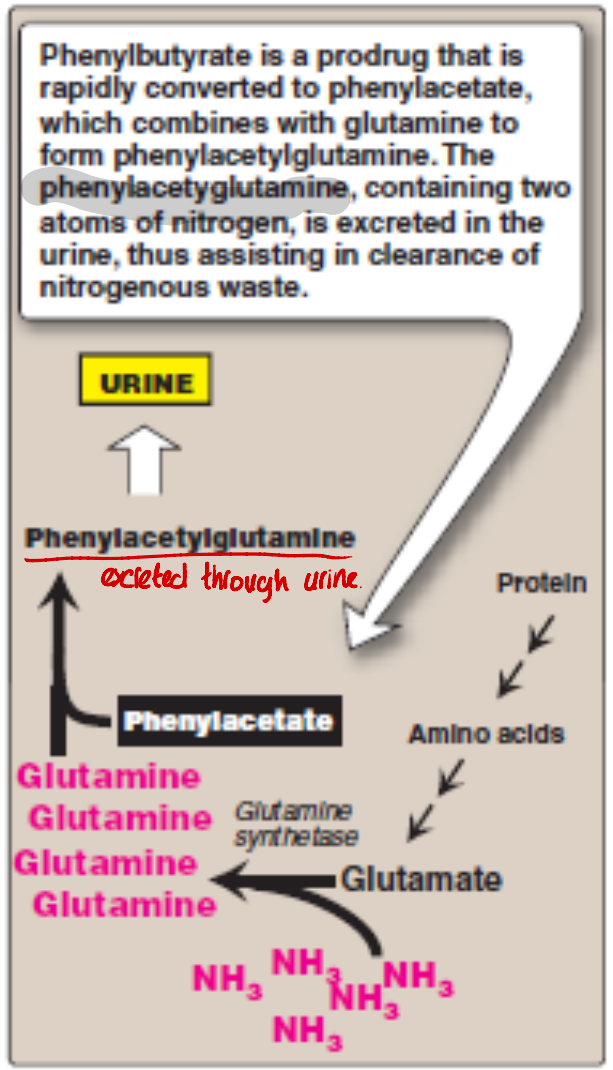
Acquired hyperammonemia: Liver disease due to viral hepatitis, or to hepatotoxins such as alcohol.

Congenital hyperammonemia: Genetic deficiencies of any of the five enzymes of the urea cycle leads to failure to synthesize urea

The overall prevalence estimated to be 1:25,000 live births.

Ornithine transcarbamoylase deficiency is the most common

Treatment: restriction of dietary protein, administration of compounds that bind covalently to AAs, producing nitrogen-containing molecules that are excreted in the urine



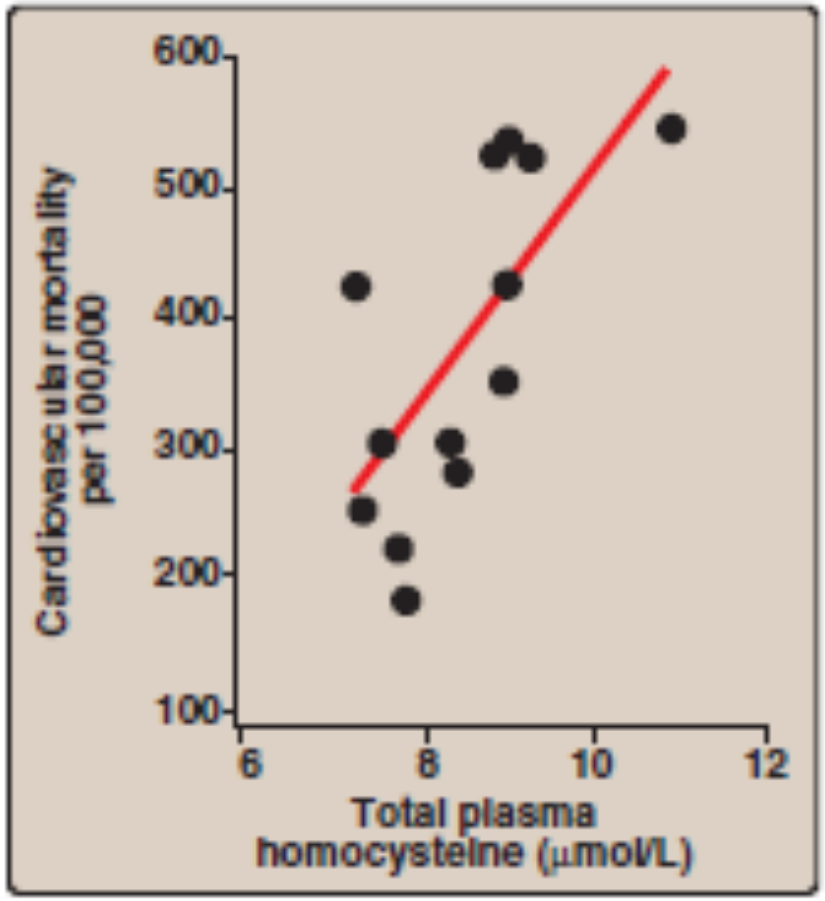
Clinical hint: Homocysteine and vascular disease

↑ homocysteine = ↑risk of CVD +other diseases.

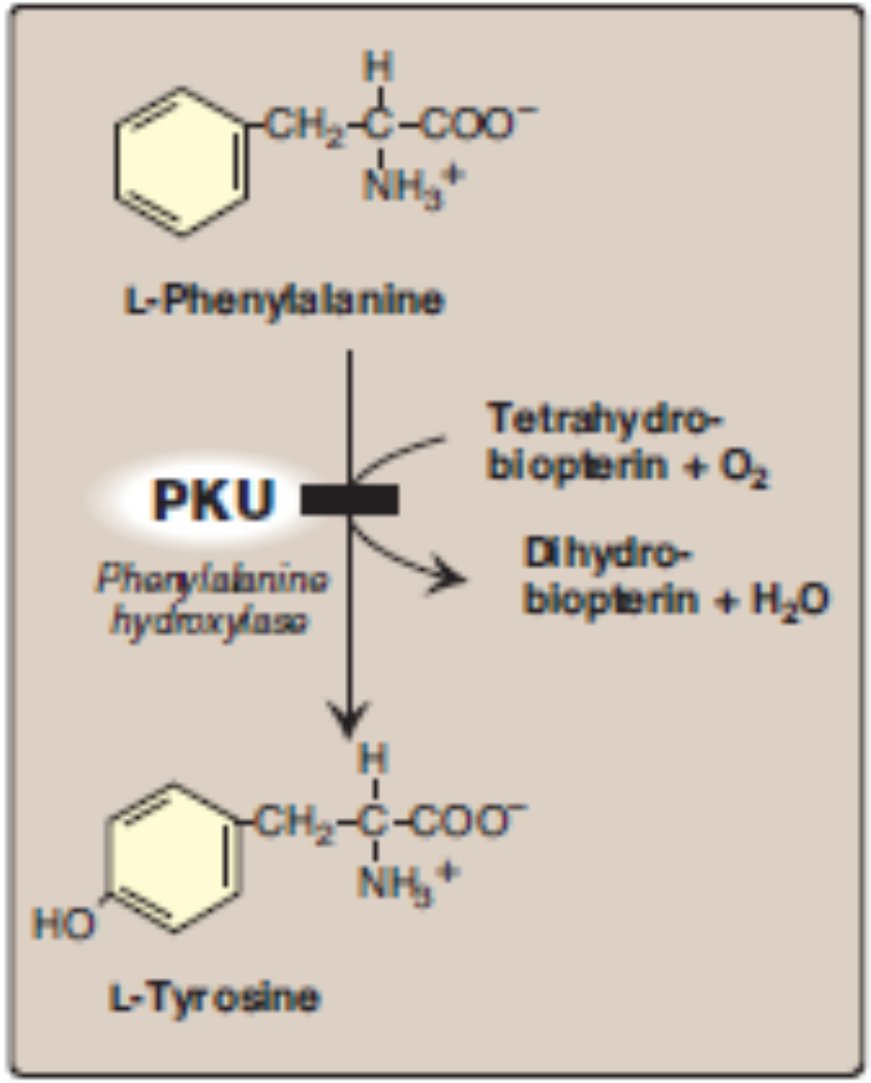
High homocysteine promote oxidative damage, inflammation, and endothelial dysfunction, and increases risk for occlusive vascular disease

Homocysteine levels are inversely related to levels of folate, B12, and B6. ⇒ taken as supplements

Elevated homocysteine or decreased folic acid levels during pregnancy increases the incidence of neural tube defects (improper closure, as in spina bifida) in the fetus.



Metabolic disorders: Phenylketonuria (PKU)



mutation of phenylalanine hydroxylase ⇒ accumulation of Phe → converted to other products including → phenyl acetate, phenyl pyruvate, phenyl lactate → they can cross the BBB causing mental retardation & they have a mousy odor

The most common inborn error of amino acid metabolism (prevalence 1:15,000).

Due to phenylalanine hydroxylase deficiency

Biochemical changes: accumulation of phenylalanine (and a deficiency of tyrosine)

Tyr cannot be synthesized from Phe and becomes an essential amino acid.

Caused by any of 100 or more different mutations in the gene that codes for phenylalanine hydroxylase (PAH).

Characteristics of classic PKU:

*these problems don't appear at birth bcz the fetus uses the mother's enzymes to catalize the rxn during pregnancy
BUT if they consume Phe after birth → accumulation → disease

- **Elevated phenylalanine** in tissues, plasma, and urine.

- **The characteristic musty "mousey" urine odor** due to phenyllactate, phenylacetate, and phenylpyruvate

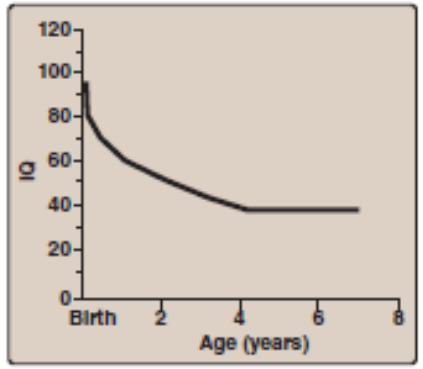
- **CNS symptoms:** Mental retardation (IQ < 50), failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow

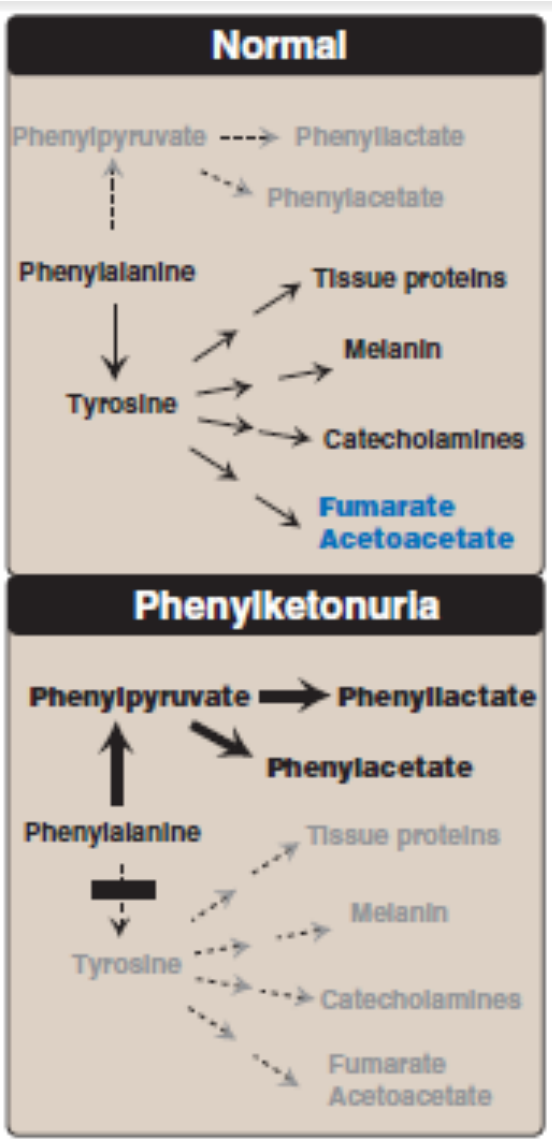
→ can appear in patients if they don't stick to the dietary restrictions (their IQ↓)

- **Hypopigmentation:** fair hair, light skin color, and blue eyes because the hydroxylation of Tyr by tyrosinase (the first step in melanin formation) is competitively inhibited by the high levels of Phe.

*since Tyr is used to make melanin pigment

Neonatal screening programs ⇒ biochemical test done early after birth (24-48 hrs)





Neonatal screening and diagnosis of PKU

PKU is treatable by dietary restriction.

Lack of neonatal symptoms

At birth, infants with PKU have normal blood levels of Phe because the mother clears the extra Phe through placenta

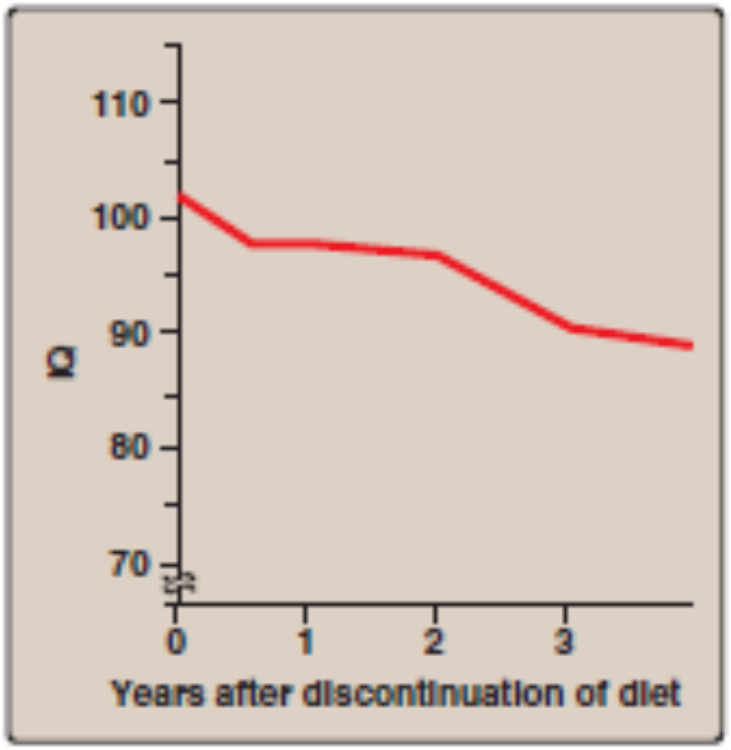
Exposure protein feeding for 24–48 hours elevates Phe, thus, screening should be done after this to avoid false negatives.

Treatment:
Dietary restriction: synthetic amino acid preparations low in Phe, supplemented with natural foods low in Phe content (fruits, vegetables, and certain cereals)

+ Tyr supplements bcz it is an essential aa

Earlier treatment (prevents neurologic damage days of life) prevents neurologic complications (mental retardation)

Aspartame should be avoided since it contains Phe.



Maternal PKU

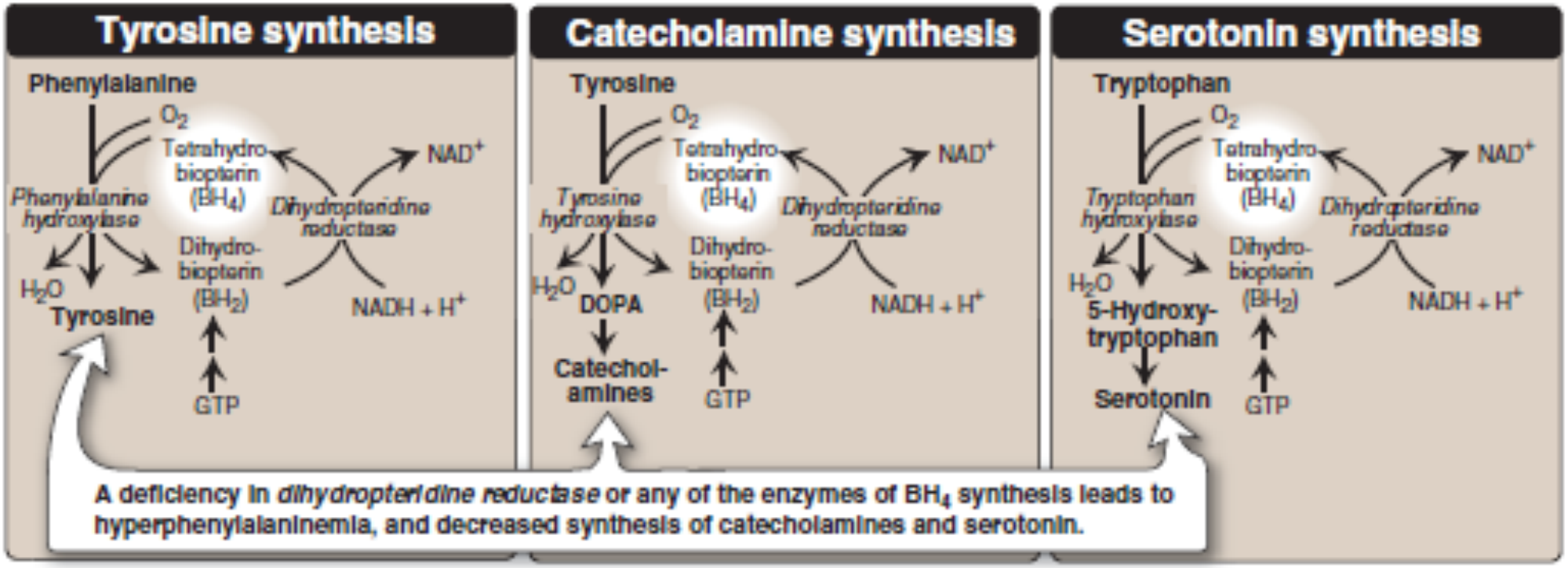
- High blood Phe levels in the mother cause microcephaly, mental retardation, and congenital heart abnormalities in the fetus

- Phenlyalanine is a teratogen (an agent or factor which causes malformation of an embryo). ⇒ cross the blood placental barrier

- Dietary control of blood phenylalanine must begin prior to conception, and must be maintained throughout the pregnancy.

https://www.npkua.org/Portals/0/PDFs/2018Conference/Breakouts/Maternal%20PKU%20NPKUA%202018%20hobbs%20RS%20FINAL.pdf?ver=2018-08-08-171024-600

Metabolic disorders: Hyperphenylalaninemia



Dihydropteridine reductase deficiency: ⇒ accumulation of Phe ⇒ hyperphenylalanemia

↳ worse than PKU bcz enzyme is needed for multiple rxns

↳ less conc. of catecholamines (NT_s)

Restricting dietary Phe does not reverse the CNS effects due to deficiencies in neurotransmitters.

Replacement therapy with BH4 or L-DOPA and 5-hydroxytryptophan (products of the affected tyrosine hydroxylase–and tryptophan hydroxylase–catalyzed reactions) improves the clinical outcome

Albinism

A group of conditions in which a defect in Tyr metabolism results in a deficiency in the production of melanin. (pigment)

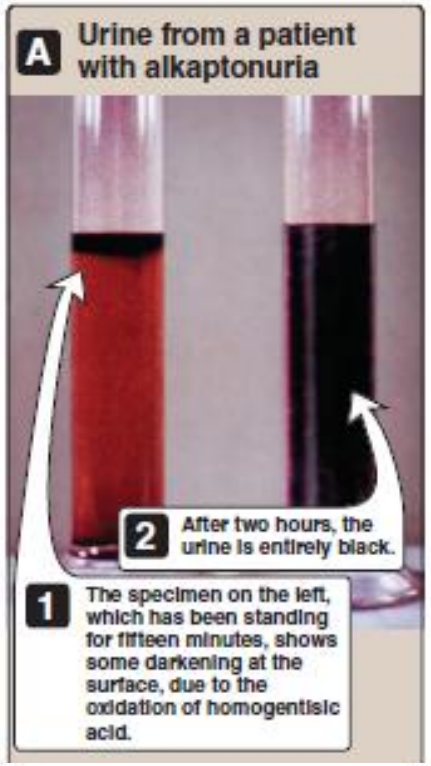
Partial or full absence of pigment from the skin, hair, and eyes.

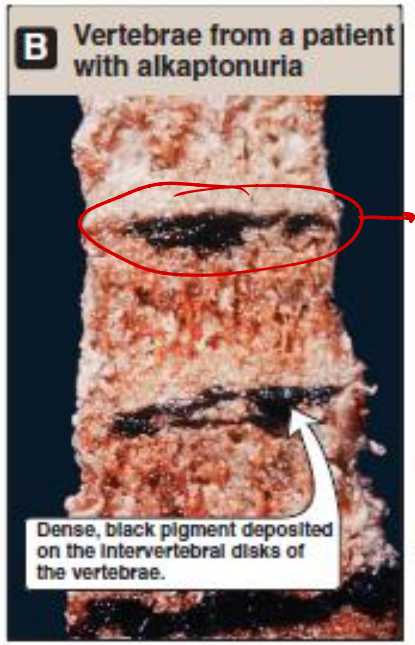
Inheritance modes: ⇒ diff. modes bcz there might be multiple genes affected in these patients
AR (primary mode), AD, or X-linked.
autosomal recessive
autosomal dominant.
↳ depending on the affected gene.

Complete albinism (tyrosinase-negative oculocutaneous albinism) results from a deficiency of copper-requiring tyrosinase

Complete albinism:
The most severe form.
Total absence of pigment from the hair, eyes, and skin, vision defects and photophobia (sunlight hurts their eyes).
Higher risk for skin cancer.

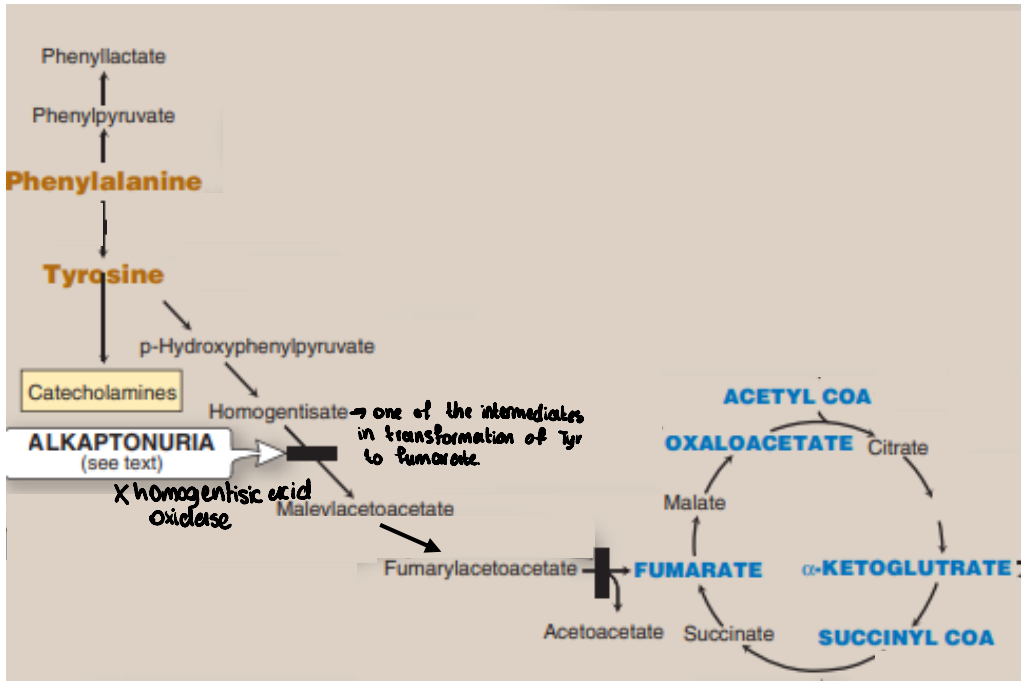
Alkaptonuria (Alcaptonuria) ⇒ affected Tyr degradation.





A rare metabolic condition, however, cases were found in Jordan

A deficiency in homogentisic acid oxidase, resulting in the accumulation of homogentisic acid (a reaction that occurs in the degradative pathway of Tyr)



Characteristic symptoms: Not life threatening

Patients are usually asymptomatic until age 40.

-Homogentisic aciduria ⇒ if urine is static for 1 time it appears black.

→ destructs & damages the cartilage structure which explains signs & symptoms.

-Large joint arthritis → show symptoms like intervertebral disc dislocation.

-Black ochronotic pigmentation of cartilage and collagenous tissue

-Dark staining of the diapers can indicate the disease in infants

Treatment: diets low in protein—especially in Phe and Tyr reduce homogentisic acid levels, and the pigment deposited in body tissues.

Homocystinuria

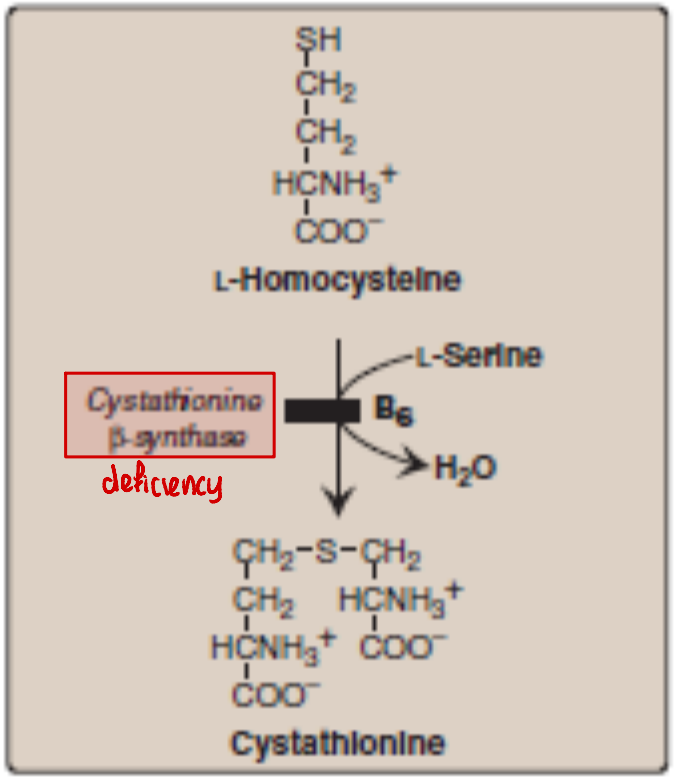
Defects in the metabolism of homocysteine.

Mode of inheritance: AR

a relatively rare metabolic disease.

High plasma and urinary levels of homocysteine and Met and low levels of Cys.

The most common cause is a defect in cystathionine β-synthase that converts homocysteine to cystathionine



Maple syrup urine disease (MSUD)

↳ affects metabolism of branched chain a.a. → they have their own pathway that starts with transamination, oxidative decarboxylation, oxidation (dehydrogenation)

Rare (1:185,000), autosomal recessive (AR) disorder, most cases are heterozygotes

Partial or complete deficiency in branched-chain α-keto acid dehydrogenase complex that decarboxylates Leu, Ile, and Val

Branched-chain amino acids are an important energy source in times of metabolic need

Accumulation in the blood causes a toxic effect that interferes with brain functions.

Signs and symptoms: feeding problems, vomiting, dehydration, severe metabolic acidosis, and a characteristic maple syrup odor to the urine.

If untreated, MSUD leads to mental retardation, physical disabilities, and even death.
Screening and diagnosis: prenatal diagnosis and neonatal screening are available.

Treatment: a synthetic formula that contains limited amounts of Leu, Ile, and Val to provide the branched-chain amino acids necessary for normal growth and development without producing toxic levels. ⇒ cannot be fully ditched.

Early diagnosis and lifelong dietary treatment is essential for child normal development.

Telegraph.co.uk