

**BCM 225 LECTURE ON**

**INBORN ERRORS OF METABOLISM**

**BY**

**OJEMEKELE O.**

# OUTLINE (week 11 and 12)

- Inborn errors of carbohydrate metabolism
- Inborn errors of amino acid metabolism
- Inborn errors of fatty acid metabolism
- Organic acidemias
- Lysosomal storage diseases
- Mitochondrial disorders
- Urea cycle disorders
- Blood chemistry; blood as a tissue

# INBORN ERRORS OF METABOLISM

- Virtually every step of metabolic pathway is catalyzed by an enzyme. Defect in enzymes of metabolic pathways that result from abnormalities in their genes are known as inborn errors of metabolism.
- The cause of enzyme defect are genetic mutations that affect the structure and regulation of the enzyme, or create problems with binding of cofactors.
- The consequences of an enzyme defect are perturbations of cellular chemistry because of a reduction in the amount of an essential product, the build up of a toxic intermediate or the production of a toxic side product.

# **INBORN ERRORS OF CARBOHYDRATE METABOLISM**

- These are inborn errors that affect the catabolism and anabolism of carbohydrates.
- Carbohydrates account for a major portion of the human diet and are metabolized into three principal monosaccharides: galactose, fructose and glucose.

# **GALACTOSEMIA**

- Galactose is an aldohexose and is a constituent of lactose of milk. Inability to metabolize galactose results in galactosemia.
- Classic galactosemia is caused by defect in the enzyme galactose-1-phosphate uridyl transferase ; GAL-1-PUT (which catalyzes the rate limiting step of galatose metabolism pathway).

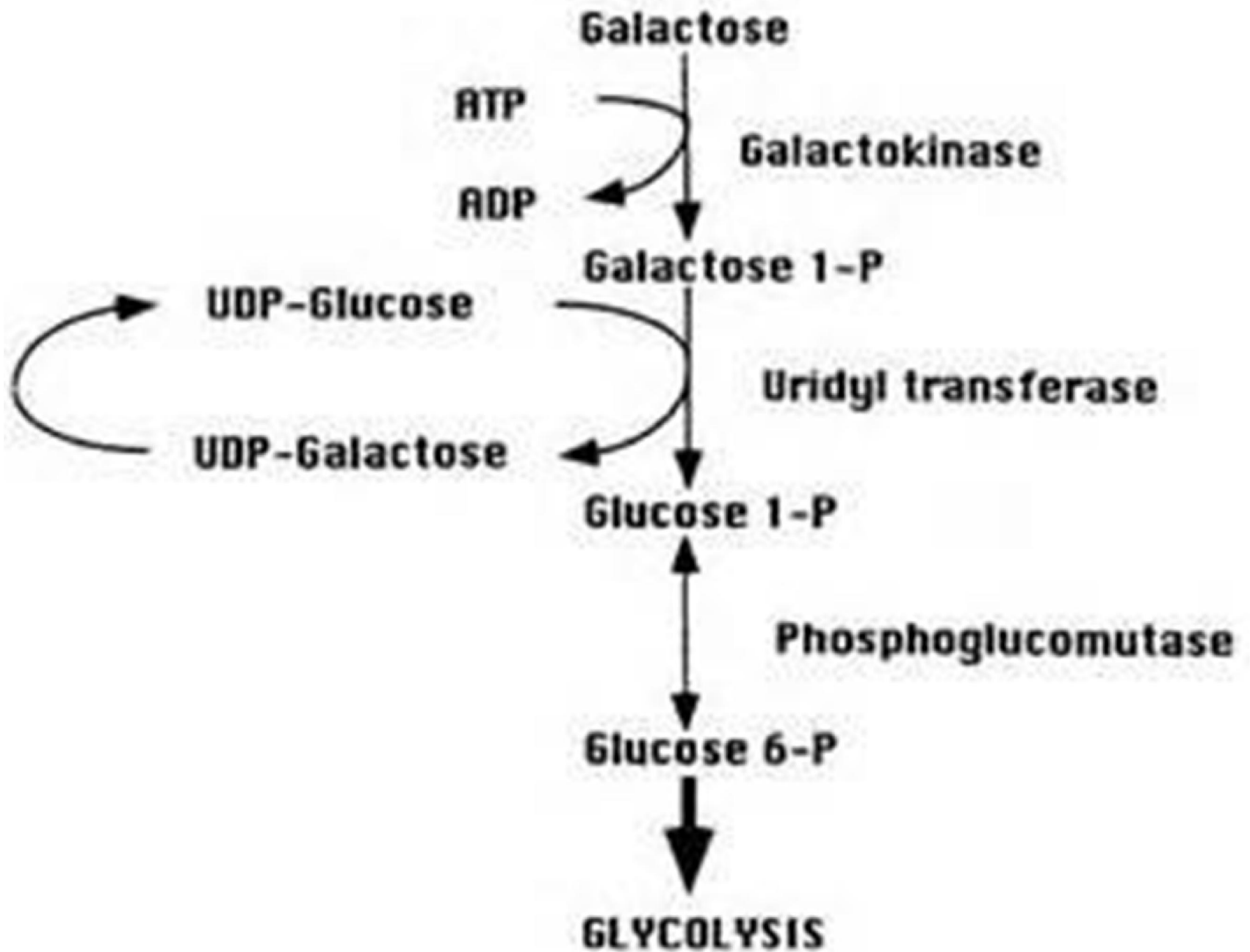
## **BIOCHEMICAL IMPLICATIONS AND CLINICAL FEATURES**

- Galactose-1-phosphate will accumulate in liver due to the block in the enzyme (GAL-1-PUT). This will inhibit galactokinase as well as glycogen phosphorylase, resulting in hypoglycemia.
- Bilirubin conjugation is reduced; so unconjugated bilirubin level is increased in blood.
- There is enlargement of liver, jaundice and severe mental retardation.

- Free galactose accumulates, leading to galactosemia. It is partly excreted in urine (galactosuria).
- Galactose is reduced to galactitol. The accumulation of galactitol in the lens results in cataract due to its osmotic effect.
- This is called congenital cataract and is a very important feature of galactosemia

Summary : (hypoglycemia, jaundice and severe mental retardation and cataract)

- A variant of galactosemia occurs due to the deficiency of **galactokinase**. But here the symptoms are milder.
- This is because galactose-1-phosphate is not formed and hence toxic effects of this compound (such as liver insufficiency, hypoglycemia) are not manifested.
- Cataract is the only manifestations of galactose kinase deficiency.



**FIG 1: GALACTOSE METABOLISM**



# DIAGNOSIS AND MANAGEMENT

- Collection of fetal cells by **amniocentesis** may be useful in prenatal diagnosis.
  - Screening is also performed by measuring GAL-1-PUT activity
  - Management is by elimination of galactose from the diet.
- (Elimination of implicating substance; measuring enzyme activity, amniocentesis)

# HEREDITARY FRUCTOSE INTOLERANCE (HFI)

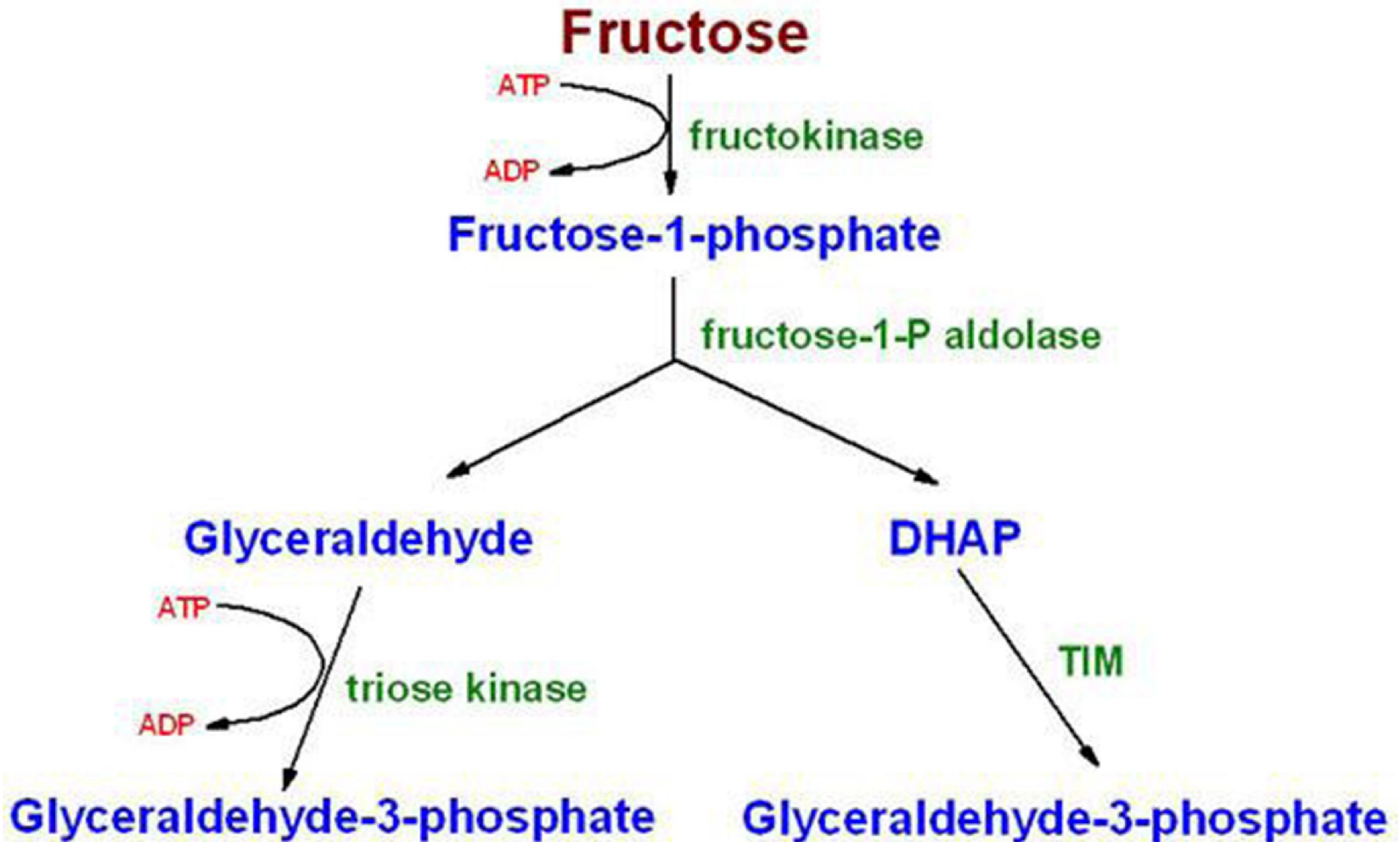
- HFI is caused by a defect in Aldolase B, hence fructose-1-phosphate cannot be metabolized and will accumulate.

## BIOCHEMICAL IMPLICATIONS AND SYMPTOMS

- Patients are asymptomatic unless they ingest fructose or sucrose.
- Accumulation of fructose-1-phosphate will inhibit glycogen phosphorylase. This leads to **hypoglycemia**.
- Vomiting and loss of appetite are seen.
- The infants often fail to thrive.
- Hepatomegaly and jaundice occur. If liver damage progresses, death will occur.

**DIAGNOSIS:** Genetic testing and Aldolase B assay.

**MANAGEMENT:** Withdrawal of fructose and sucrose from the diet will immediately relieve the symptoms.



**Fig.2 FRUCTOSE METABOLISM**

# INBORN ERRORS ASSOCIATED WITH GLUCOSE METABOLISM

- 1. Diabetes mellitus type 1 is a disorder caused by reduced or absent levels of insulin, a hormone that regulates the levels of glucose in blood.
- It causes hyperglycemia. Due to high osmotic effect of high glucose levels, polyuria (excessive urine output) results, this cause polydipsia (excessive thirst).
- Diagnosis is by measuring blood glucose concentrations
- Management can be achieved by insulin replacement therapy

2. **Glucose 6-Phosphate dehydrogenase deficiency** : is an X-linked recessive hereditary disease characterised by abnormally low levels of glucose-6-phosphate dehydrogenase (abbreviated **G6PD**).

- G6PD is a metabolic enzyme involved in the pentose phosphate pathway, especially important in red blood cell metabolism.
- Individuals with the disease may exhibit non immune hemolytic anemia in response to a number of causes, most commonly infection or exposure to certain medications or chemicals.
- Hemolytic anaemia can lead to paleness, hemolytic jaundice, fatigue, shortness of breath and a rapid heart rate.

## **GLYCOGEN STORAGE DISEASES (GSD)**

- Enzyme deficiencies that leads to impaired synthesis or degradation of glycogen are also considered disorders of carbohydrates metabolism.
- The two organs most commonly affected are the liver and the skeletal muscle
- Glycogen storage diseases that affect the liver typically cause hepatomegaly and hypoglycemia, relating to impaired mobilization of glucose for release to the blood during fasting
- Those that affect skeletal muscle cause exercise intolerance, progressive weakness and cramping resulting from low glucose levels, hence there is inability to increase glucose entry into glycolysis during exercise

**TABLE 1: GLYCOGEN STORAGE DISEASES**

Type	Name	Deficient enzyme	Clinical features
Type Ia	von Gierke's disease	Glucose-6-phosphatase	Fasting hypoglycemia; hepatomegaly
Type III	Limit dextrinosis Cori's disease	Debranching enzyme	Highly branched dextrin accumulates; Fasting hypoglycemia; hepatomegaly
Type IV	Amylopectinosis Anderson's disease	Branching enzyme	Glycogen with few branches; hepatosplenomegaly; mild hypoglycemia
Type V	McArdle's disease	Muscle phosphorylase	Excercise intolerance; accumulation of glycogen in muscles
Type VI	Hers' disease	Liver phosphorylase	Mild hypoglycemia; hepatomegaly; better prognosis than other types

# DIAGNOSIS AND MANAGEMENT

- Diagnosis is achieved by evaluating blood glucose levels, measurement of enzyme activity and genetic testing
- Management; corn starch and sucrose supplementation to increase blood glucose levels have been suggested
- Gene therapy and enzyme replacement therapy are currently being investigated as possible therapies for GSDs



# INBORN ERRORS OF AMINO ACID METABOLISM

## PHENYLKETONURIA (PKU)

- This disease is caused by deficiency of **phenyl alanine hydroxylase (PAH)**. The enzyme that converts phenyl alanine to tyrosine. Genetic mutation may be such that either the enzyme is not synthesized, or a non-functional enzyme is synthesized.

## BIOCHEMICAL ABNORMALITIES

- Phenylalanine can not be converted to tyrosine. So phenylalanine accumulates. Phenylalanine level in blood is elevated.
- So, alternate minor pathways are opened (Fig 4) Phenyl ketone (phenyl pyruvate), phenyl lactate and phenyl acetate are produced from phenylalanine which are excreted in urine.

## Clinical Manifestations

- The classical PKU child is mentally retarded. The mental retardation is caused by the accumulation of phenylalanine (and its toxic metabolites phenylpyruvate, phenyllactate and phenylacetate).
- Agitation, hyperactivity, tremors and convulsions are often manifested. This may be because high phenylalanine and low tyrosine levels reduces neurotransmitter synthesis.
- The child often has hypopigmentation (low melanin levels), explained by the decreased level of tyrosine.

## DIAGNOSIS

- **Blood phenylalanine:** Normal level is 1 mg/dl. In PKU, the level is >20 mg/dl.
- **Ferric chloride test:** Urine of the patient contains phenyl ketone. This could be detected by adding a drop of ferric chloride to the urine. Phenylketone reacts with ferric chloride to produce a transient blue-green color.

## MANAGEMENT

- PKU can be managed by providing a diet containing low in phenyl alanine . Food based on tapioca (cassava) have low phenyl alanine content.
- This special diet is to be continued during the first decade of life; after which the child can have a normal diet. Life-long compliance of special diet is recommended.

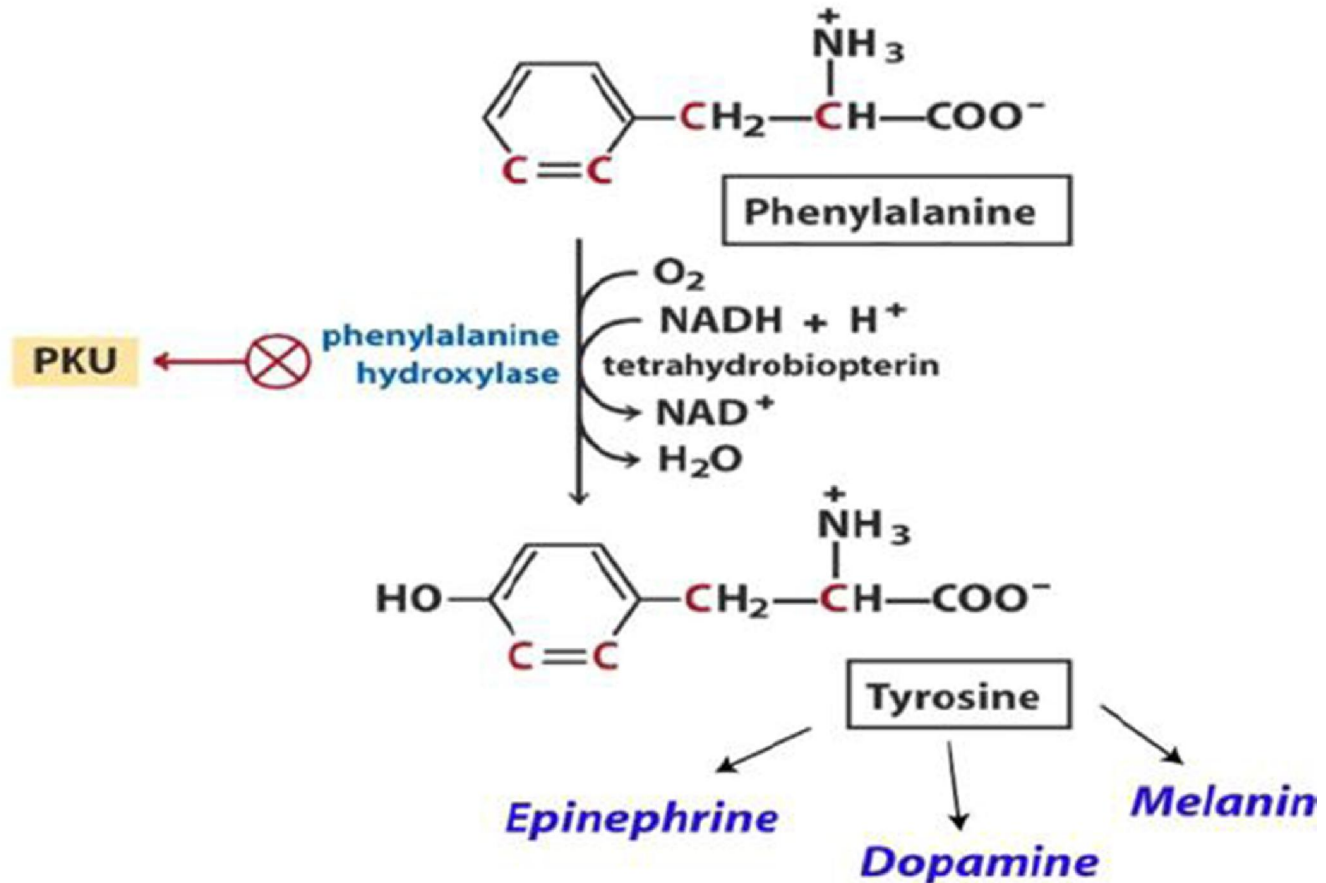
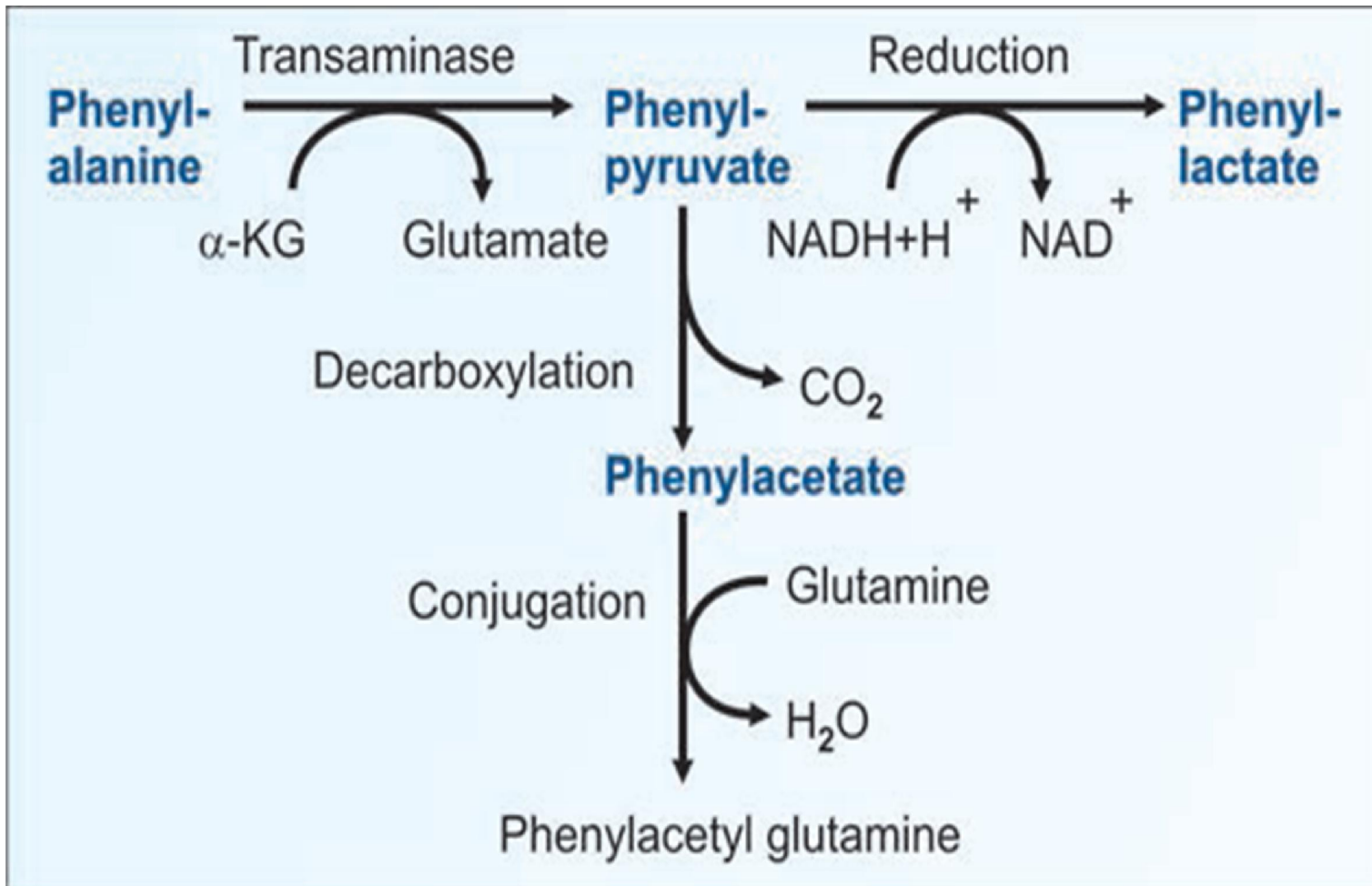


Fig 3: Tyrosine (a nonessential amino acid) is used not only for protein synthesis, but as shown in the figure above, tyrosine is also the precursor for neurotransmitters; dopamine, epinephrine, norepinephrine, thyroid hormones (T3&T4), as well as, skin pigments (melanin).

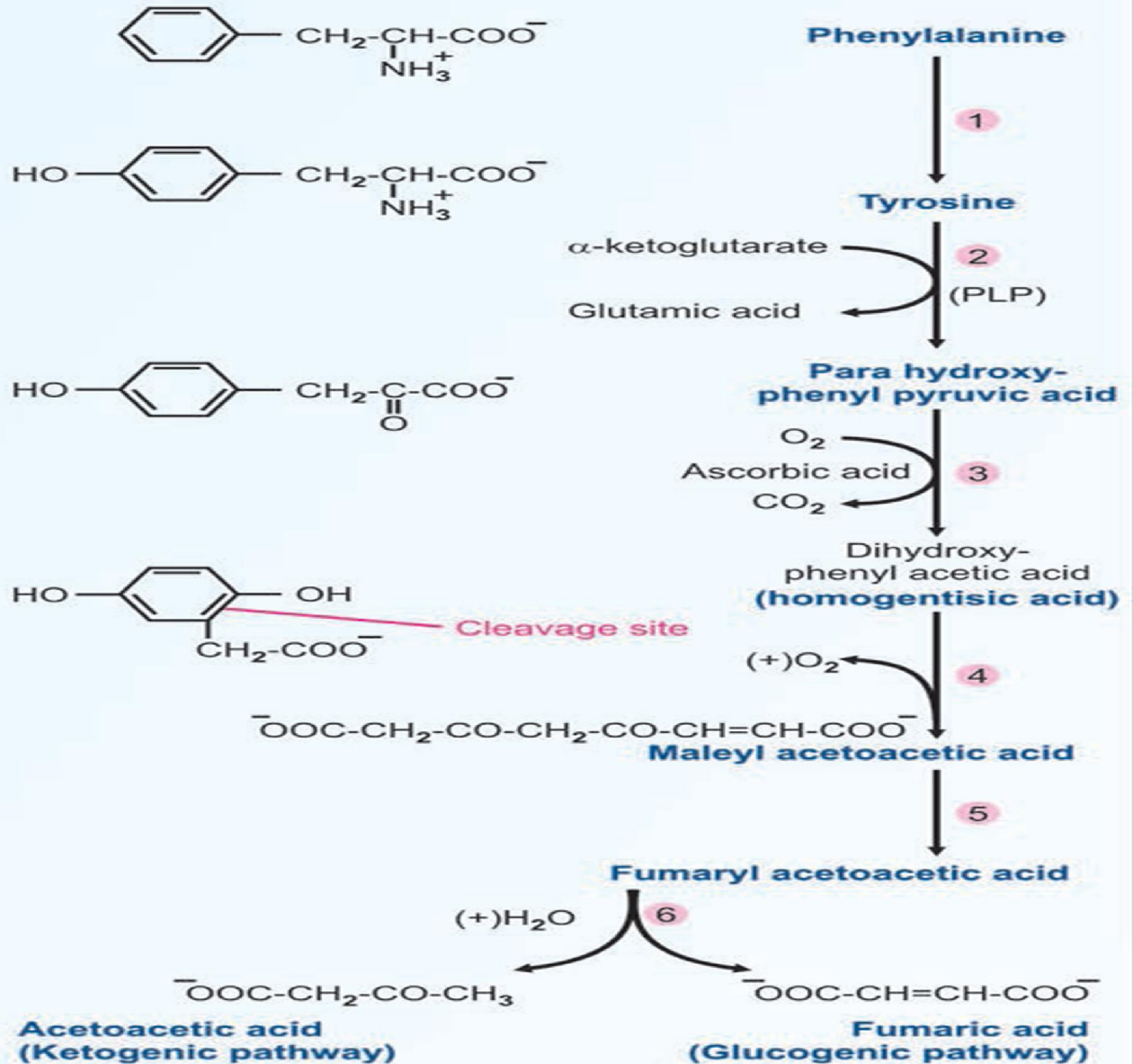


**Fig 4: Alternate pathways for phenylalanine in phenyl ketonuria**

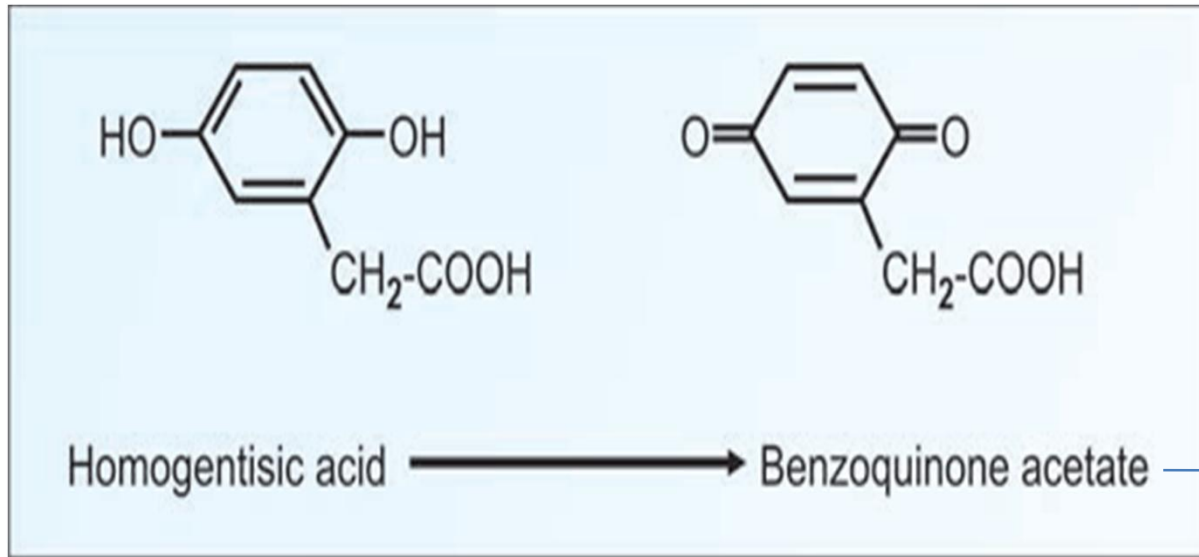
# ALKAPTONURIA

- This is due to the deficiency of the enzyme homogentisic acid oxidase (an enzyme of tyrosine metabolic pathway) resulting in Homogentisic acid (HGA) accumulation and excretion in urine.
- Alkaptonuria is an autosomal recessive condition with an incidence of 1 in 250,000 births.
- It is compatible with fairly normal life. The only abnormality is the blackening of urine on standing. The homogentisic acid is oxidized by polyphenol oxidase to benzoquinone acetate (Fig. 6). It is then polymerized to black coloured alkaptone bodies.
- By the 3rd or 4th decade of life, patient may develop ochronosis (deposition of alkaptone bodies in intervertebral discs, cartilages of nose, pinna of ear). Black pigments are deposited over the connective tissues including joint cavities to produce arthritis.
- **DIAGNOSIS:** 1. Urine becomes black on standing . Blackening is accelerated on exposure to sunlight and oxygen. The urine when kept in a test tube will start to blacken from the top layer.  
2. **Ferric chloride test** will be positive for urine
- **MANAGEMENT:** Minimal protein intake with phenylalanine less than 500 mg/day is recommended.

- 1 = Phenylalanine hydroxylase
- 2 = Tyrosine transaminase
- 3 = Parahydroxy phenylpyruvate hydroxylase
- 4 = Homogentisic acid oxidase
- 5 = Maleyl acetoacetate isomerase
- 6 = Fumaryl acetoacetate hydrolase



**FIG 5:  
PHENYLALANINE  
AND TYROSINE  
METABOLISM**



**Black coloured  
alkaptone bodies**

**FIG 6: ALTERNATIVE OXIDATION OF  
HOMOGENTISIC ACID IN ALKAPTONURIA**



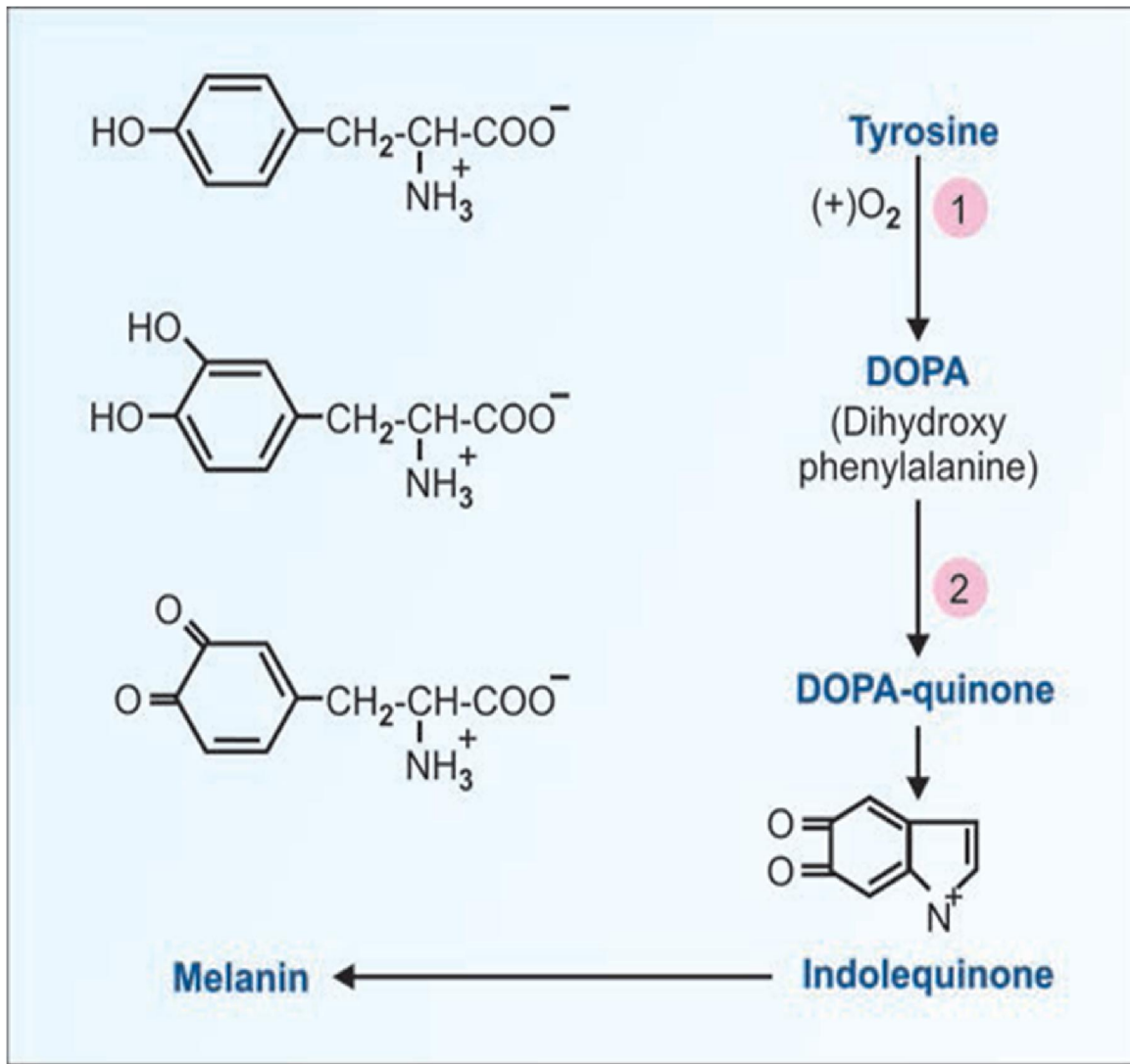
**Urine becomes  
black on exposure  
to air**



# ALBINISM

- Albinism is an autosomal recessive mutation in the gene for tyrosinase (the rate limiting enzyme of the melanin synthetic pathway), resulting in absent of melanin (the pigment that gives dark colour to the skin, hair and eyes).
- A deficiency in tyrosinase will result in loss of hair and skin pigments which explains the albino phenotype.

- There is photophobia, nystagmus and decreased visual acuity.
- The skin has low pigmentation, and so skin is sensitive to UV rays. Hair is also white.
- Management includes use of tinted glasses to reduce photophobia, use of sun protection cream on the skin.



**FIG 7: Melanin biosynthesis (reactions 1 and 2 are catalyzed by tyrosinase)**

# HOMOCYSTINURIA

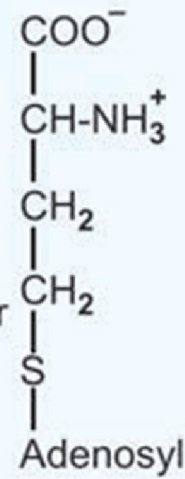
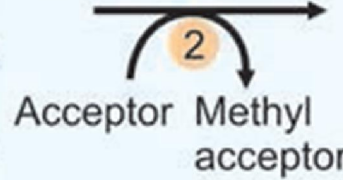
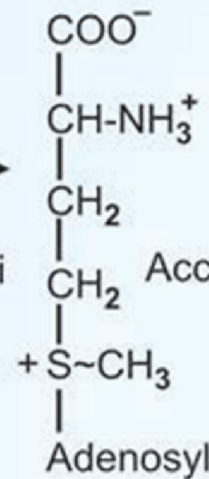
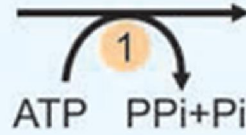
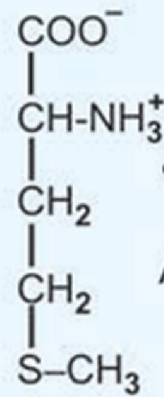
- Defect in cystathionine synthase (an enzyme involved in conversion of methionine into cysteine) leads to homocystinuria.
- It causes high concentration of homocysteine and methionine in the blood. There is increased excretion of methionine and homocystine in urine and blood cysteine is markedly reduced.
- Homocysteine is highly reactive molecule hence the disease is often associated with mental retardation, multi systemic disorder of connective tissue, muscle, CNS, and cardiovascular system.

- General symptoms are mental retardation, Skeletal deformities. In eyes, ectopia lentis (subluxation of lens), myopia and glaucoma may be observed. Homocysteine causes activation of Hageman's factor. This may lead to increased platelet adhesiveness and life-threatening intra-vascular thrombosis.
- **Diagnosis** : Cyanide-nitroprusside test will be positive in urine. Urinary excretion of homocystine is more than 300 mg/24 h.
- **Management** : is a diet low in methionine and rich in cysteine. Sometimes the affinity of apo-enzyme to the co-enzyme is reduced. In such cases, pyridoxal phosphate, the co-enzyme given in large quantities (500 mg) will be useful.

**Methionine**

**S-adenosyl  
methionine  
(SAM)**

**S-adenosyl  
homocysteine  
(SAH)**



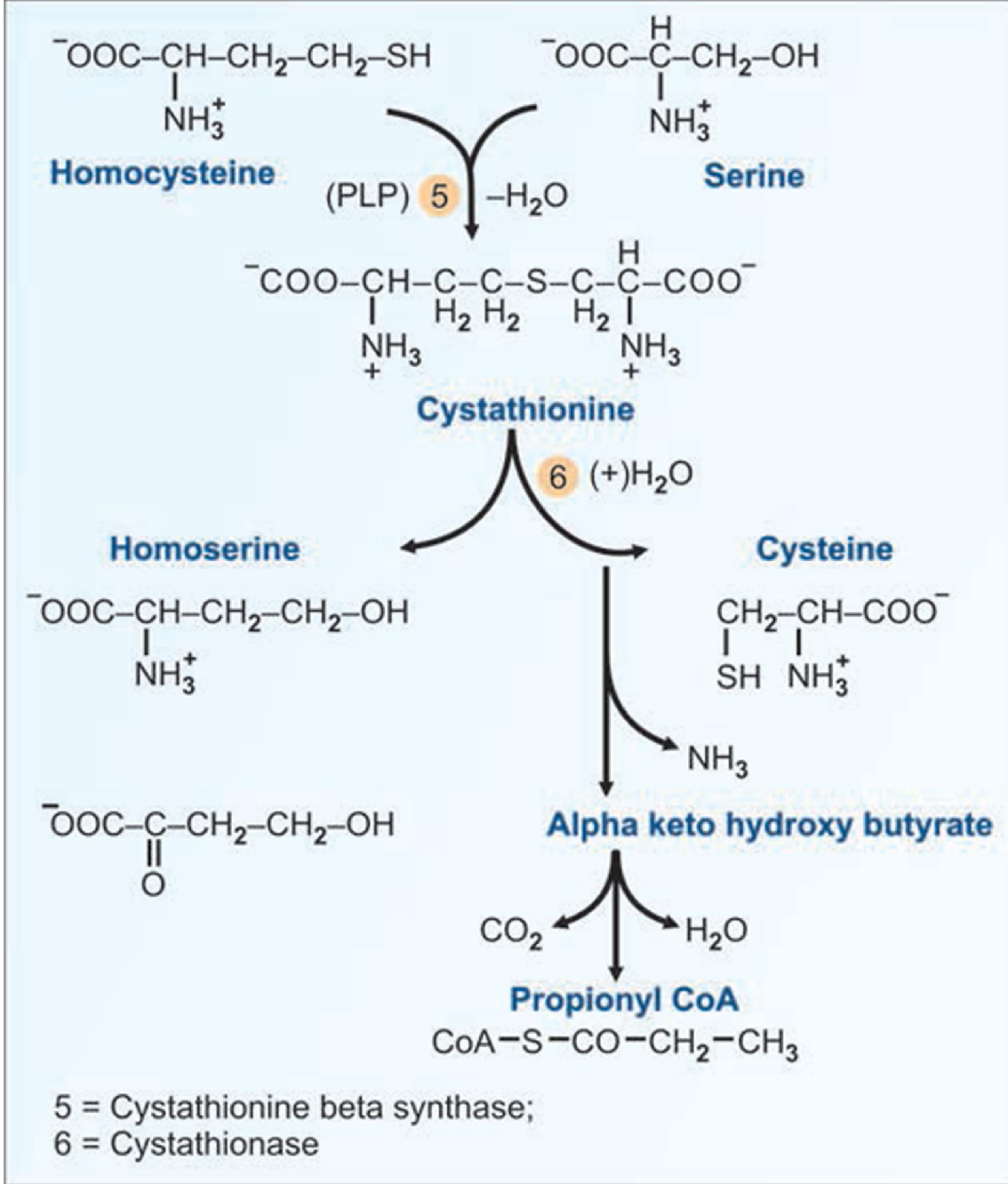
**Methionine**

+ CH<sub>3</sub> (1-C unit)  
**Vitamin B<sub>12</sub>**

**Homocysteine**

Cysteine synthesis

1 = methionine adenosyl transferase (MAT); 2 = methyltransferase;  
3 = adenosine homocysteinase; 4 = homocysteine  
methyltransferase, with vitamin B<sub>12</sub> as coenzyme



**Fig: Methionine metabolism**

# MAPLE SYRUP URINE DISEASE

- It is also called branched chain ketonuria. The name originates from the characteristic smell of urine (similar to burnt sugar or maple sugar) due to excretion of branched chain keto acids.

**BIOCHEMICAL DEFECT:** Deficiency of branched chain alpha ketoacid (BKA ) dehydrogenase complex

**SYMPTOMS AND LABORATORY FINDINGS:** Symptoms start in the first week of life. It is characterized by convulsions, severe mental retardation, vomiting, acidosis, coma and death within the first year of life if not properly managed.

Urine contains branched chain keto acids derived from valine, leucine and isoleucine.

**DIAGNOSIS:** Diagnosis is based on enzyme analysis in cells.

**MANAGEMENT:** Giving a diet low in branched chain amino acids (valine, leucine and isoleucine).



# FATTY ACID OXIDATION DISORDERS (FAOD)

- Fatty acid oxidation disorders are genetic conditions caused by mutations in genes that code for enzymes responsible for oxidation of fatty acids.
- When there is an alteration in these genes, enzyme levels go down and fatty acids build up in the blood.
- In the case of fatty acid oxidation disorders, the inability to break down fats for energy and the build up of fatty acids cause serious health problems.

**DIAGNOSIS:** Babies can be tested (newborn screening) for fatty acid oxidation disorders before they leave the hospital. The baby's heel is pricked and a few drops of blood are taken. The blood is sent to the state laboratory to find out if it has more than a normal amount of fatty acids.

- There are various types of fatty acid oxidation disorders. The following is a list of fatty acid oxidation disorders that can be screened for:
- Carnitine/Acylcarnitine Translocase deficiency (TRANS)
- Carnithine transporter deficiency (CTD)
- Long/Very Long Chain Acyl CoA Dehydrogenase deficiency (LCAD/VLACD)
- Medium Chain Acyl CoA Dehydrogenase deficiency (MCAD)
- Short Chain Acyl CoA Dehydrogenase deficiency (SCAD)
- Short-chain 3-Hydroxyacyl-CoA Dehydrogenase (SCHAD)
- Deficiency.
- Long-chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD)

## **Carnitine Transporter Deficiency (CTD).**

- Although most of the fatty acid oxidation disorders affect the heart, skeletal muscle and liver, **cardiac failure** is seen as the major presentation in CTD .
- Over half of the known cases of CTD first present with progressive heart failure and generalized muscle weakness.
- During the first years of life, extended fasting stress may provoke an attack of hypoketotic hypoglycemic and coma. This may lead to sudden unexpected infant death.
- Management: The outcome is usually very good with carnitine therapy. Without carnitine therapy, the cardiac failure can progress rapidly to death.

# Medium-chain Acyl-CoA Dehydrogenase (MCAD) Deficiency.

- This is the **most common** fatty acid oxidation disorder. It is also one of the **least severe**, with no evidence of chronic muscle or cardiac involvement.
- Affected individuals appear to be entirely normal until an episode of illness is provoked by an excessive period of fasting.
- Hypoglycemia develops because of excessive glucose utilization due to the inability to switch to fat as a source of energy. Severe symptoms of lethargy and nausea develop in association with the marked increase in plasma fatty acids.

# **Carnitine/Acylcarnitine Translocase (TRANS) Deficiency**

Symptoms include :

- fasting hypoketotic hypoglycemia
- Coma
- cardiopulmonary arrest
- ventricular arrhythmias.

- **Very-long-chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency.**

Many of the patients with VLCAD deficiency have severe clinical manifestations, including :

- chronic cardiomyopathy
- weakness
- fasting coma.

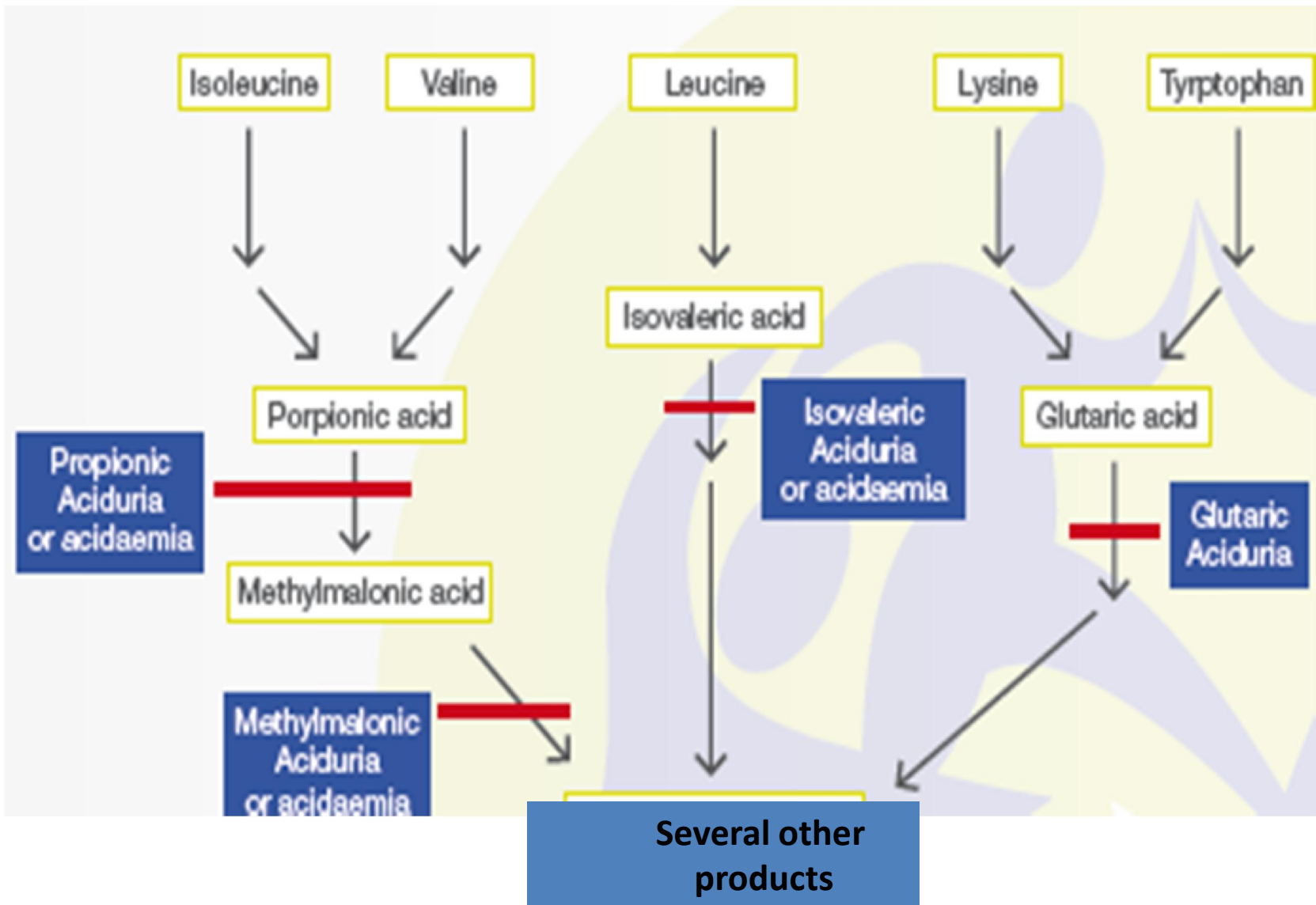
# ORGANIC ACIDURIAS

- They are disorders associated with metabolism of fatty acids, branched chain amino acids , aromatic amino acids and citric acid cycle.
- They are all characterised by the accumulation of organic acids in body tissues and their excretion in urine.
- The patients present with acidosis, vomiting, convulsions and coma. The children often die in infancy; in case they survive, there is severe mental and growth retardation.
- **Diagnosis** is confirmed by showing the presence of organic acids in urine by chromatography.
- **Management** : Dietary restriction, co- enzyme therapy and substrate removal are the general lines of management.

# SOME IMPORTANT ORGANIC ACIDURIAS

Disorders	Deficient enzyme	Clinical features
Methyl malonic aciduria	Methyl malonyl CoA mutase or B <sub>12</sub> co-enzyme	Ketoacidosis, hypotonia, hypoglycemia, hyperammonemia, hyperuricemia
Propionic acidemia	Propionyl CoA carboxylase	Ketoacidosis, hypotonia, vomiting, lethargy
MCADH deficiency	Medium chain acyl CoA dehydrogenase	Acidosis, hyperammonemia; hypoglycemia, fatty liver.
LCADH deficiency	Long chain acyl CoA dehydrogenase	Nonketotic hypoglycemia, low carnitine, increased acyl carnitine
Glutaric aciduria	Glutaryl CoA dehydrogenase	ketoacidosis, convulsions, progressive neurological defects, cerebral palsy.
Marple syrup Urine disease	Branched chain ketoacid dehydrogenase	convulsions, mental retardation, acidosis, vomiting , coma





**Fig: position of some defective enzymes in organic acidurias**

# MITOCHONDRIAL DISEASES

- Mitochondrial diseases are group of disorders caused by mutations in mitochondrial DNA (mtDNA) or in nuclear genes that code for mitochondrial proteins.

## SYMPTOMS

- Poor growth, muscle weakness, heart problems, liver disease, kidney disease, respiratory disorders, neurological problems.
- Mitochondria diseases are worse when the defective mitochondria are present in the cells of muscles, cerebrum or nerves, because these cells use more energy than most other cells in the body. Recall that mitochondria are double membrane cellular organelles, responsible for producing cellular energy (ATP) by oxidative phosphorylation.

# EXAMPLES OF MITOCHONDRIAL DISEASES

- Mitochondrial myopathy (disease of muscles)
- Leber's hereditary optic neuropathy (LHON) usually characterized by deterioration in vision
- Leigh syndrome: clinical features include encephalopathy (disorder that affects the brain), **seizures**, dementia.
- Mitochondrial encephalomyopathy with **lactic acidosis** and **stroke**-like episodes (MELAS)

# DIAGNOSIS

- Genetic testing: Although high levels of mutations can be detected in blood, it is always advisable to use muscle for detecting mtDNA mutations, because it contains much mitochondria.

# MANAGEMENT

Coenzyme Q and creatine supplementation. Coenzyme Q plays important role in oxidative phosphorylation. Creatine enhances ATP production in muscle cells.

# UREA CYCLE DISORDERS

- The urea cycle disorders (UCD) result from mutations in genes that code for enzymes of urea cycle.
- This leads to defects in the metabolism of the extra nitrogen produced by the breakdown of protein and other nitrogen-containing molecules.
- Severe deficiency or total absence of activity of any of the first four enzymes (CPSI, OTC, ASS, ASL) in the urea cycle or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life.

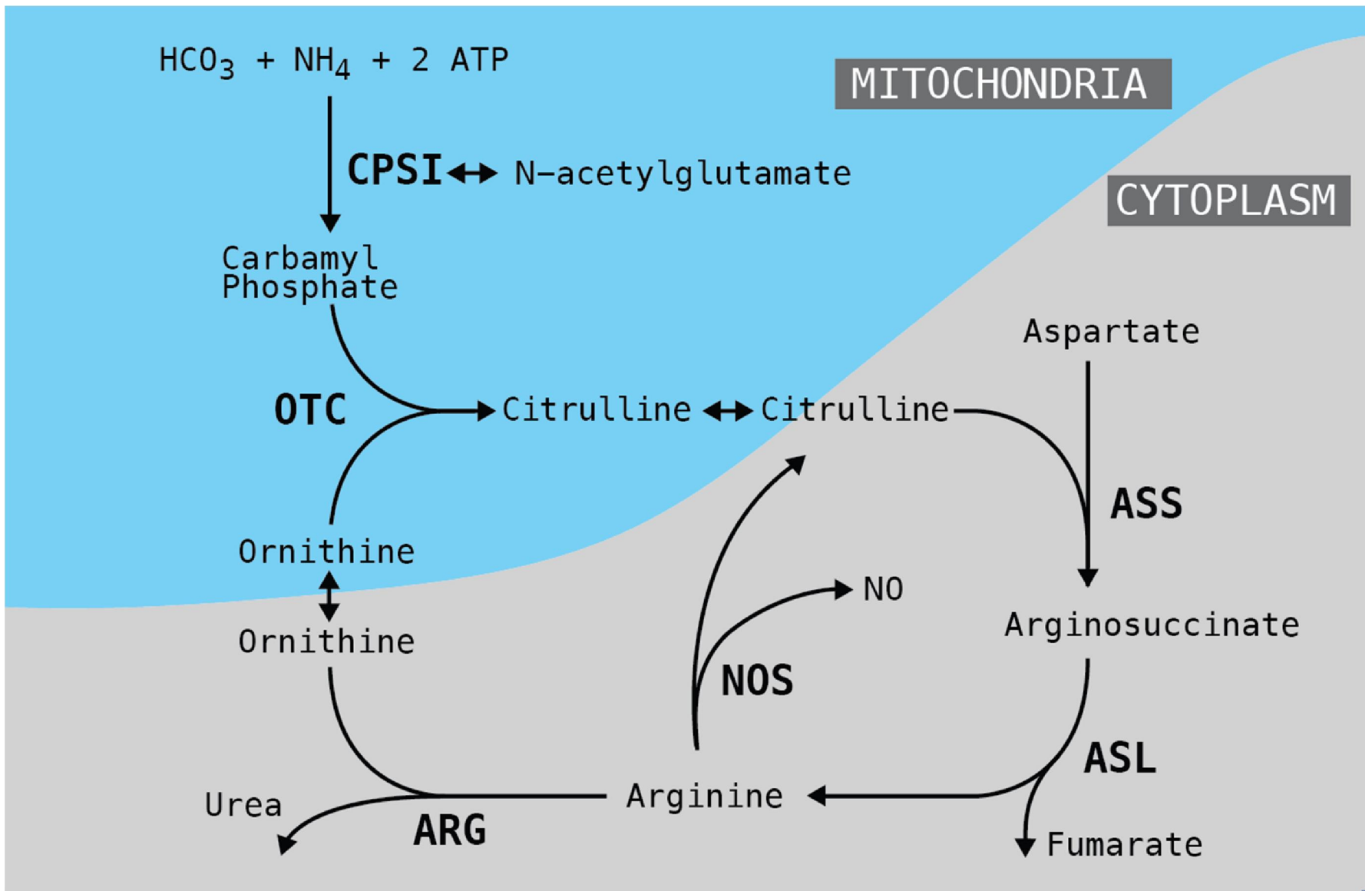


Fig: urea cycle

# Symptoms of Newborns with Urea Cycle Defects

- Normal appearance at birth
- Irritability progressing to lethargy and later coma
- Loss of thermoregulation (hypothermia)
- Neurologic posturing (from cerebral edema)
- Seizures
- Hyperventilation and then hypoventilation

- Examples are:
- CPS1 (Carbamoylphosphate Synthetase I) Deficiency
- ASS (Argininosuccinate Synthetase) Deficiency,
- ASL (Argininosuccinate Lyase) Deficiency,
- ARG (Arginase) Deficiency
- NAGS (N-Acetylglutamate Synthetase) Deficiency
- OTC (Ornithine Transcarbamylase) Deficiency



## **DIAGNOSIS**

- The most important step in diagnosing urea cycle disorders is clinical suspicion of hyperammonemia. A blood ammonia level is the first laboratory test in evaluating a patient with UCD
- Enzymatic and genetic diagnosis

## **MANAGEMENT**

- Fluids, dextrose to mitigate dehydration
- Remove protein from intake
- Dialysis is very effective for the removal of ammonia from blood.

# LYSOSOMAL STORAGE DISEASES (LSD)

- Lysosomes are involved in the degradation and recycling of extracellular material (via endocytosis) and intracellular material (via autophagy).
- Lysosomal storage diseases (LSDs) describe a group of rare inherited metabolic disorders that result from the defect in lysosomal hydrolases or transporters, resulting in the progressive accumulation of undigested material in lysosomes.
- The accumulation of these substances affects the function of lysosomes and other organelles, resulting in secondary alterations such as impairment of autophagy, mitochondrial dysfunction, inflammation and apoptosis.
- LSDs frequently involve the central nervous system (CNS), where neuronal dysfunction or loss results in progressive neurodegeneration and premature death.

# Gaucher's disease

- Gaucher's disease is a sphingolipidosis resulting from glucocerebrosidase deficiency, causing deposition of glucocerebroside and related compounds.
- **Type I (non-neuronopathic) is the adult form of the disease.** Onset ranges from age 2 yr to late adulthood.
- Type I Gaucher's disease cause anemia, fatigue, lung impairment and kidney impairment.

- **Type II (acute neuronopathic) is very rare and residual** enzyme activity in this type is lowest. Onset occurs during infancy. Type II Gaucher's disease causes severe neurological disorder, liver enlargement and spleen enlargement.
- **Type III (subacute neuronopathic) falls between types I and II** in incidence, enzyme activity and clinical severity. Type III Gaucher's disease cause progressive brain damage and seizures.

**Diagnosis** : is by enzyme analysis of WBCs.

**Treatment:**

- Enzyme replacement with placental or recombinant glucocerebrosidase is effective in types I and III; there is no treatment for type II disease.
- An oral treatment drug for Gaucher's disease (Zavesca/Miglustat) was licensed by the European authorities in April 2003 for those patients deemed unsuitable for enzyme replacement[

## Tay-sachs disease

- Gangliosides are complex sphingolipids present in the brain. There are 2 major forms, GM1 and GM2 . Taysachs disease is caused by the deficiency of hexosaminidase A (an enzyme that breaks down GM2) results in accumulation of GM2 in the brain.
- Children develop progressive cognitive and motor deterioration resulting in seizures, mental retardation and paralysis.
- **Diagnosis** is clinical and can be confirmed by enzyme assay.
- **Treatment** : Hexosaminidase A from human urine infused intravenously in patients with Tay-Sachs disease results in 43% reduction in the elevated quantity of globoside in the circulation.

## Niemann-pick disease

- Niemann-Pick disease is a rare inherited autosomal recessive disease caused by a defect in acid sphingomyelinase, this results in accumulation of sphingomyelin in lysosomes.
- Type A Niemann-Pick disease is a severe neurodegenerative disorder of infancy that leads to death by age 3 years. Patients have enlarged liver and spleen.
- Type B disease has a later age at onset, little or no neurologic involvement, and survival of most patients into adulthood. Patients also have enlarged liver and spleen.
- .
- **Diagnosis:** Prenatal diagnosis of Niemann-Pick disease types A and B is routinely accomplished by sphingomyelinase assay.
- **Treatment:** At present no specific treatment is available for patients with any Niemann-Pick disease subtypes and treatment is symptomatic. Bone marrow transplantation in a patient with Niemann-Pick disease type B was successful in reducing spleen and liver volumes

## **Sandhoff's disease**

- Sandhoff's disease is caused by the combined deficiency of hexosaminidase A and B.
- Clinical manifestations include progressive cerebral degeneration beginning at 6 months accompanied by seizures, blindness, cherry-red macular spot and hyperacusis (a hearing disorder in which patients cannot tolerate normal environmental sound).
- Diagnosis involves a test to measure enzyme activity of the two hexosaminidase . If the enzyme activity results indicate that there is no hexosaminidase activity, it means that the patient has Sandhoff disease. However, if there is still B subunit activity, then this indicates that the patient might have Tay-Sachs disease.

# BLOOD AS A TISSUE

- Blood is a liquid connective tissue
- The total blood volume makes up about 6-8 percent of the body's weight
- A 70kg person has approximately 5 to 6 litres of blood.
- Normal pH of blood is 7.35(venous blood)-7.45 (arterial blood)



# BLOOD COMPOSITION

- Blood consists of:
  - Liquid plasma (volume 55-60%)
  - Formed elements or cells (volume 40-45)
    - The formed elements include red blood cells, white blood cells and platelets

# ERYTHROCYTES

- Red blood cells or erythrocytes are the most abundant type of blood cell
- They are involved in the transport of oxygen and carbon dioxide.
- They lack nucleus and mitochondria in order to accommodate maximum space for hemoglobin

# LEUKOCYTES

- Leukocytes or white blood cells have nuclei
- The major function of leukocytes is protective function, they provide immunity and thus defends the body
- Lymphocytes, neutrophils, monocytes, eosinophils and basophils are types of lymphocytes

# PLATELETS

- These are tiny cell fragments
- They play critical roles in blood clotting
- They are produced in the bone marrow by large cells called megakaryocytes

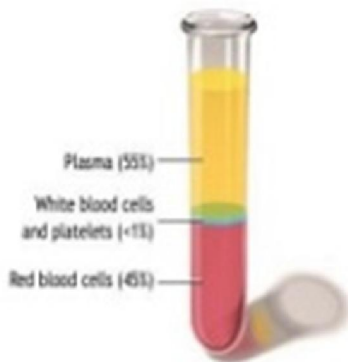
# SERUM AND PLASMA

- Serum is the liquid portion of blood obtained after centrifugation of coagulated blood. Serum therefore lacks clotting factors.
- Plasma on the other hand is the liquid portion of blood obtained by centrifuging blood sample that has been treated with anticoagulant (such as EDTA, heparin). Plasma therefore has clotting factors.

## 2. Plasma vs. serum

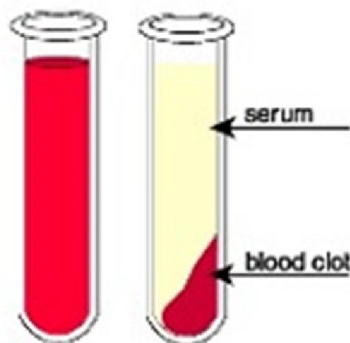
• **Plasma** is the liquid, cell-free part of blood, that has been **treated with anti-coagulants**.

Anticoagulated



**Serum** is the liquid part of blood **AFTER coagulation**, therefore devoid of clotting factors as fibrinogen.

Clotted



• serum = plasma - fibrinogen

# FUNCTIONS OF BLOOD

- TRANSPORTATION of dissolved gases (Carbon dioxide and oxygen), nutrients, hormones and metabolic wastes.

- PROTECTION

Platelets in the blood minimize blood loss when a blood vessel is damaged

White blood cells protect the body against infectious diseases

- REGULATION

Blood regulates pH and electrolyte composition of the body

blood regulates body temperature