Metabolism Module

Clinical Biochemistry for 2nd Year Medical Students:

Lecture 4: Metabolic Defects in Amino Acids Metabolism.

Or (Inborn errors of metabolism)

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OBJECTIVES

- **Understand metabolic defects in amino acids metabolism.**
- **Describe Phenylketonuria, Maple Syrup Urine Disease, Albinism , Alkaptonuria and Hartnup Disease**

Amino acidopathies: Metabolic defects in amino acid metabolism:

- Inborn errors of metabolism are commonly caused by mutant genes that generally result in abnormal proteins, most often enzymes.
- The inherited defects may be expressed as a total loss of enzyme activity or, more frequently, as a partial deficiency in catalytic activity.

Without treatment, the inherited defects of amino acid metabolism almost result in mental retardation or other developmental abnormalities as a result of harmful accumulation of metabolites.

Phenylketonuria, maple syrup urine disease, albinism, and alkaptonuria are discussed.

*Phenylketonuria is the most important of these inherited defects because it is relatively common, can readily be detected by screening tests, and responds to dietary treatment.

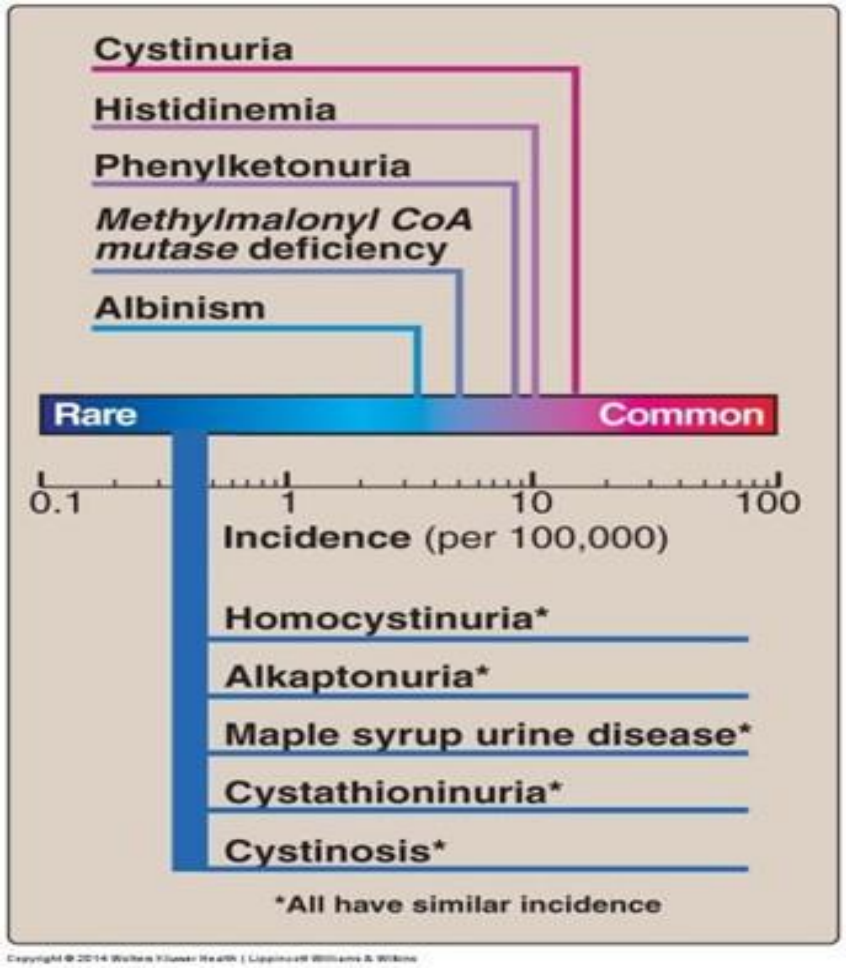

Figure: incidence of some amino acidopathies.

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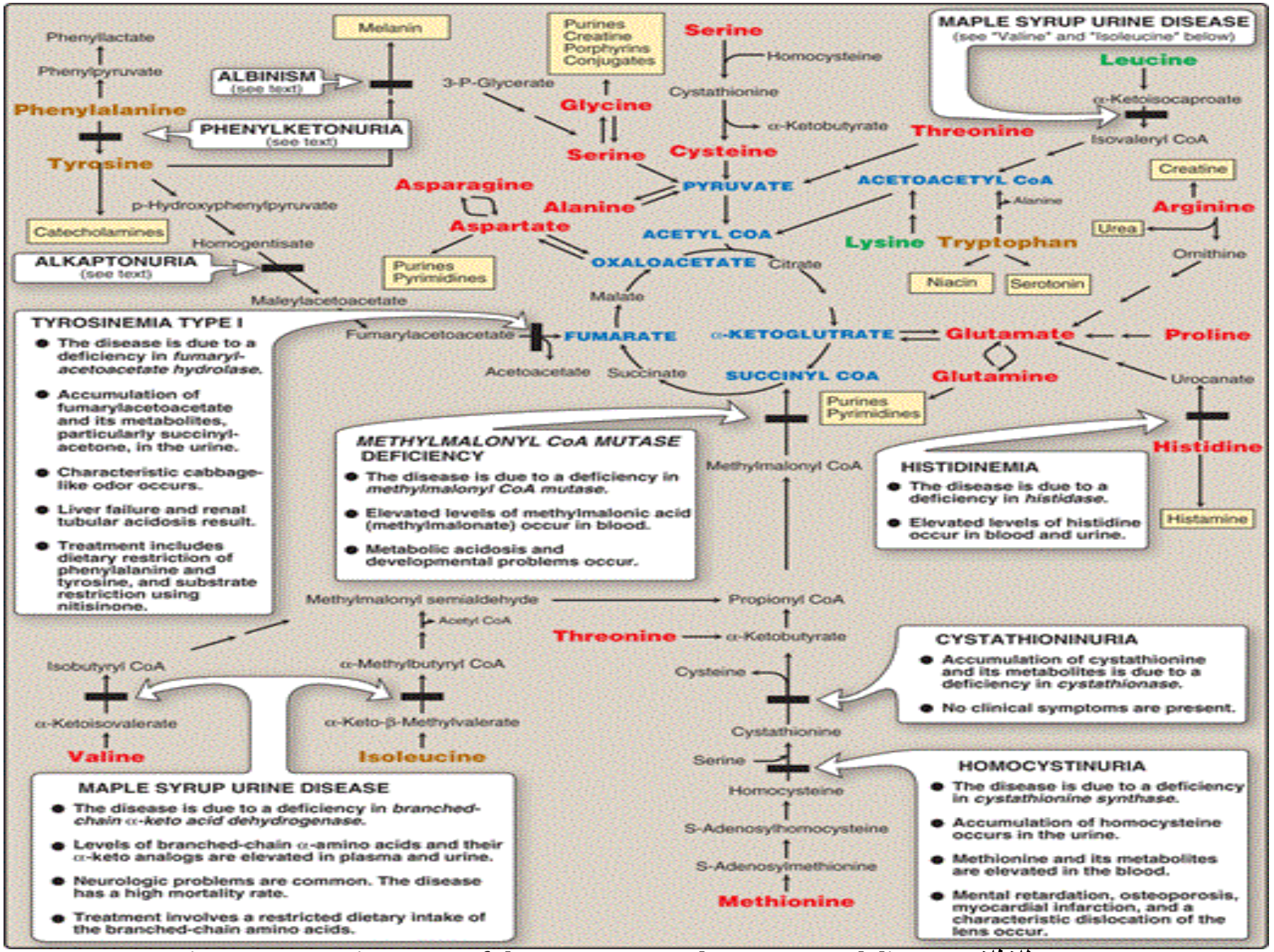


Figure: summarizes some of the more commonly encountered diseases للاطلاع

Phenylalanine and phenylketonuria

Phenylketonuria PKU:

- **Phenylalanine is an essential AA from which Tyrosine is formed by the action of the enzyme Phenylalanine hydroxylase.**
- **Tyrosine is then used in the synthesis of many essential metabolic products such as: thyroid hormones, melanin (the main pigment for the skin, eyes and hair), and adrenaline and dopamine (dihydroxyphenylalanine) which are the main neurotransmitters in the central nervous system.**
- **Inherited enzymatic abnormalities in the pathway of phenylalanine will lead to special clinical abnormalities.**

Phenylketonuria PKU:

- **PKU is the most common clinically encountered inborn error of amino acid metabolism (incidence 1:15,000). Classical PKU is an autosomal recessive disorder.**
- **This condition is caused by an abnormality of the phenylalanine hydroxylase enzyme System, which catalysis the conversion of phenylalanine to tyrosine.**
- **If this pathway is blocked or decreased then phenylalanine is converted into phenylketons and pyruvic acid which then execrated in the urine together with phenylalanine.**
- **On the other hand, there will be a shortage or absence of tyrosine in the body which will led to different pathologies.**

Characteristics of PKU:

- **Elevated phenylalanine:**

Phenylalanine is present in elevated concentrations in tissues, plasma, and urine. Phenyllactate, phenylacetate, and phenylpyruvate, which are not normally produced in significant amounts in the presence of functional phenylalanine hydroxylase, are also elevated in PKU. These metabolites give urine a characteristic musty odor.

- **CNS symptoms:**

Mental retardation (IQ below 50), failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow are characteristic findings in PKU. The patient with untreated PKU typically shows symptoms of mental retardation by the age of one year.

- **Hypopigmentation:**

➢ **Patients with phenylketonuria often show a deficiency of pigmentation (fair hair, light skin color, and blue eyes).**

➢ **The hydroxylation of tyrosine by tyrosinase, which is the first step in the formation of the pigment melanin, is competitively inhibited by the high levels of phenylalanine present in PKU.**

➢ **Early diagnosis of phenylketonuria is important because the disease is treatable by dietary means. Because of the lack of neonatal symptoms, laboratory testing for elevated blood levels of phenylalanine is mandatory for detection.**

- **The infant with PKU frequently has normal blood levels of phenylalanine at birth because the mother clears increased blood phenylalanine in her affected fetus through the placenta.**
- **Thus, tests performed at birth may show false negative results. Normally, feeding breast milk or formula for 48 hours is sufficient to raise the baby's blood phenylalanine to levels that can be used for diagnosis.**
- **<u>The aim of management:</u>**

is to lower blood phenylalanine levels by giving a low phenylalanine diet. Tyrosine must be included in the diet as it is the precursor of many important metabolites.

A. Phenylketonuria

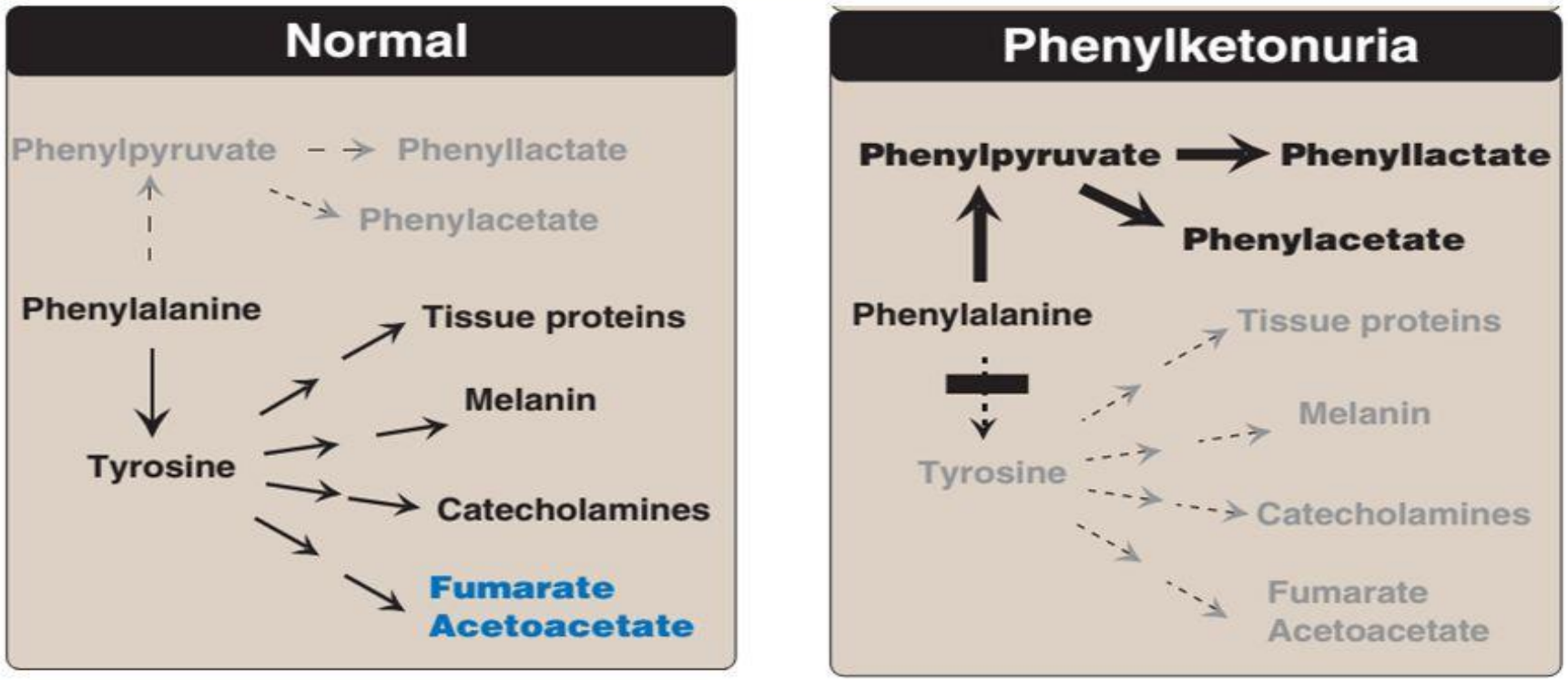


Figure 20.17 Pathways of phenylalanine metabolism in normal individuals and in patients with phenylketonuria

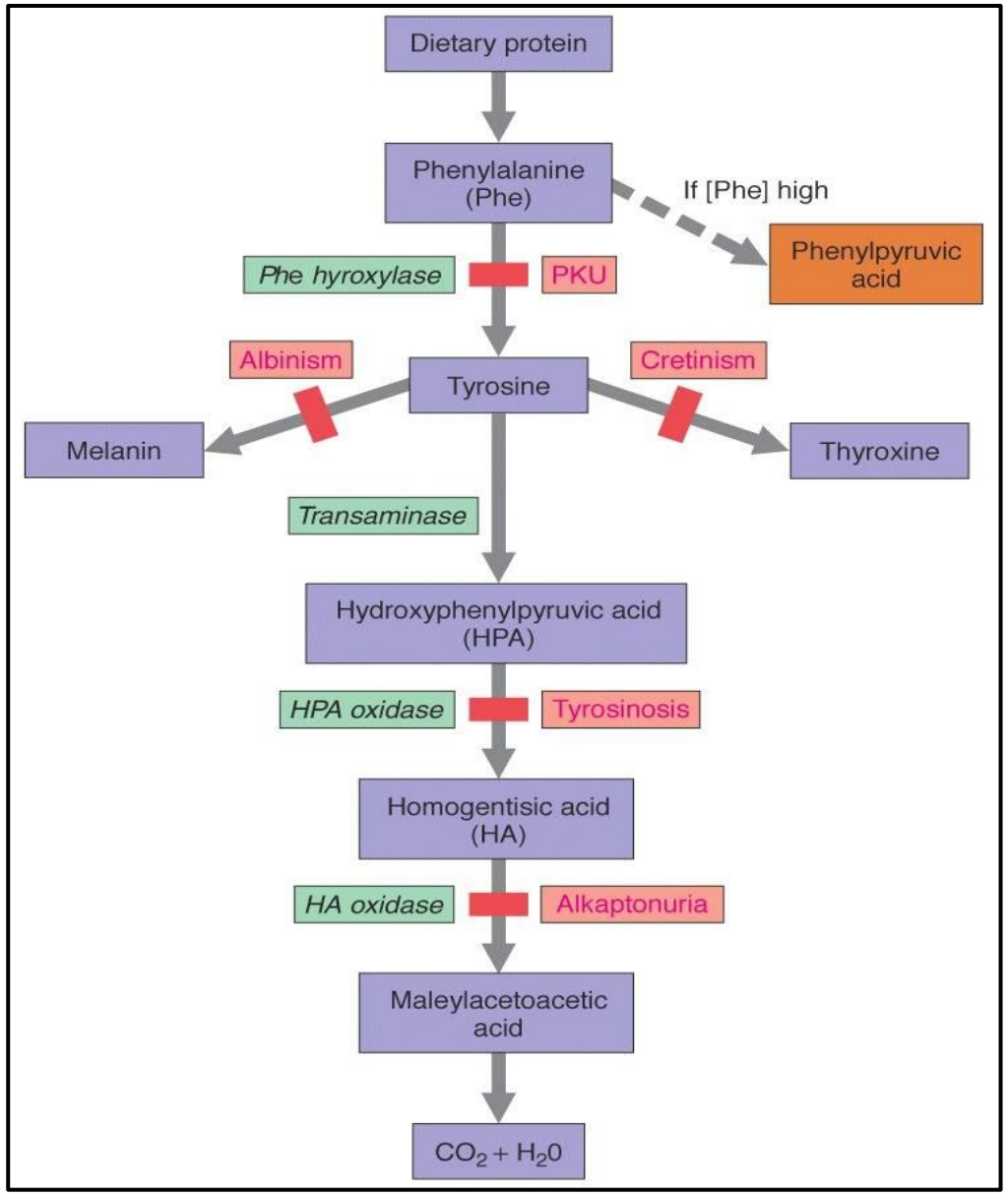


Figure: Metabolic pathway of phenylalanine المخطط للاطلاع

Maple Syrup Urine Disease:

Maple syrup urine disease (MSUD) is a rare recessive disorder (1:185,000) in which there is a partial or complete deficiency in ***branched-chain α-keto acid dehydrogenase,*** an enzyme that **decarboxylates the branched chain essential amino acids leucine, isoleucine, and valine**.

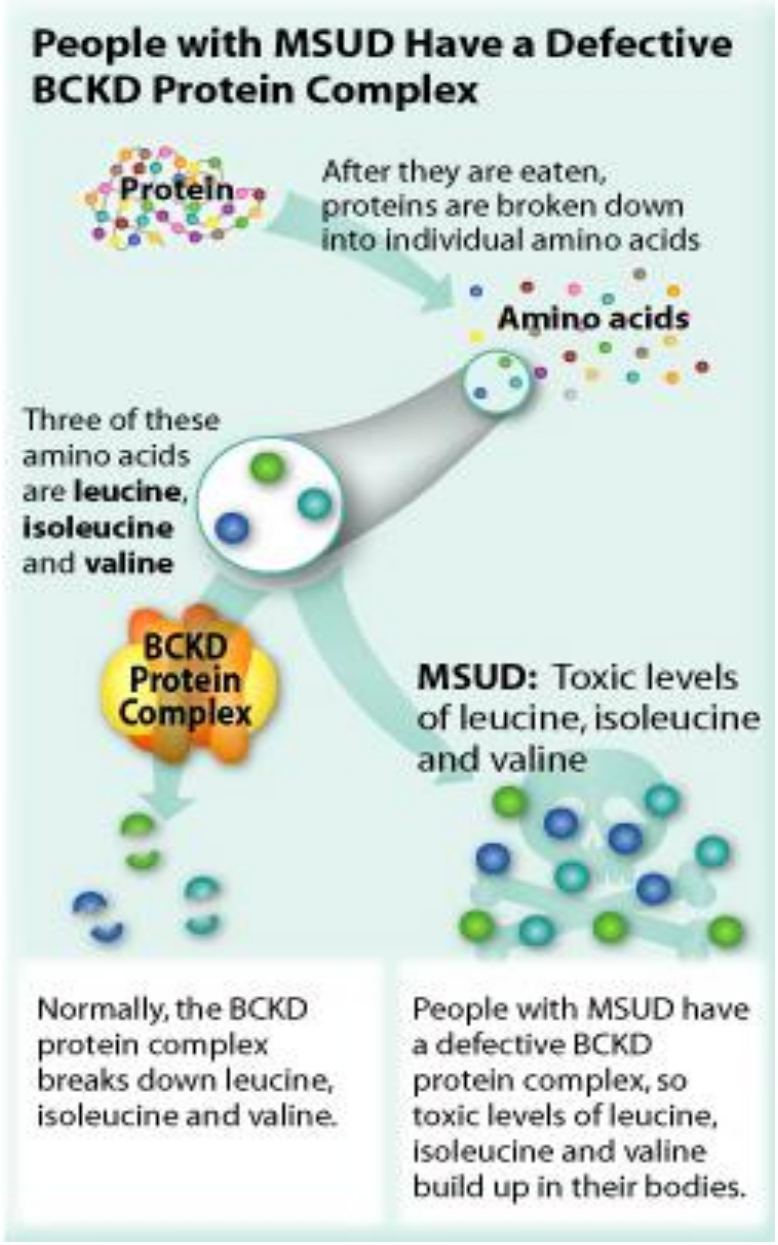
These amino acids and their corresponding α-keto acids accumulate in the blood, causing a toxic effect that interferes with brain functions.

The disease is characterized by feeding problems, vomiting, dehydration, severe metabolic acidosis, and a **characteristic maple syrup odor to the urine.**

Untreated, the disease leads to mental retardation, physical disabilities, and death.

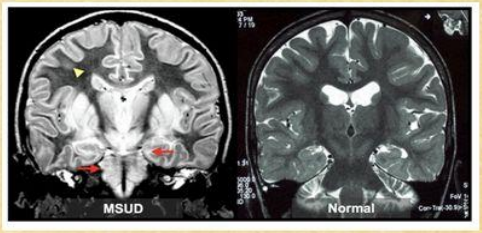
Treatment:

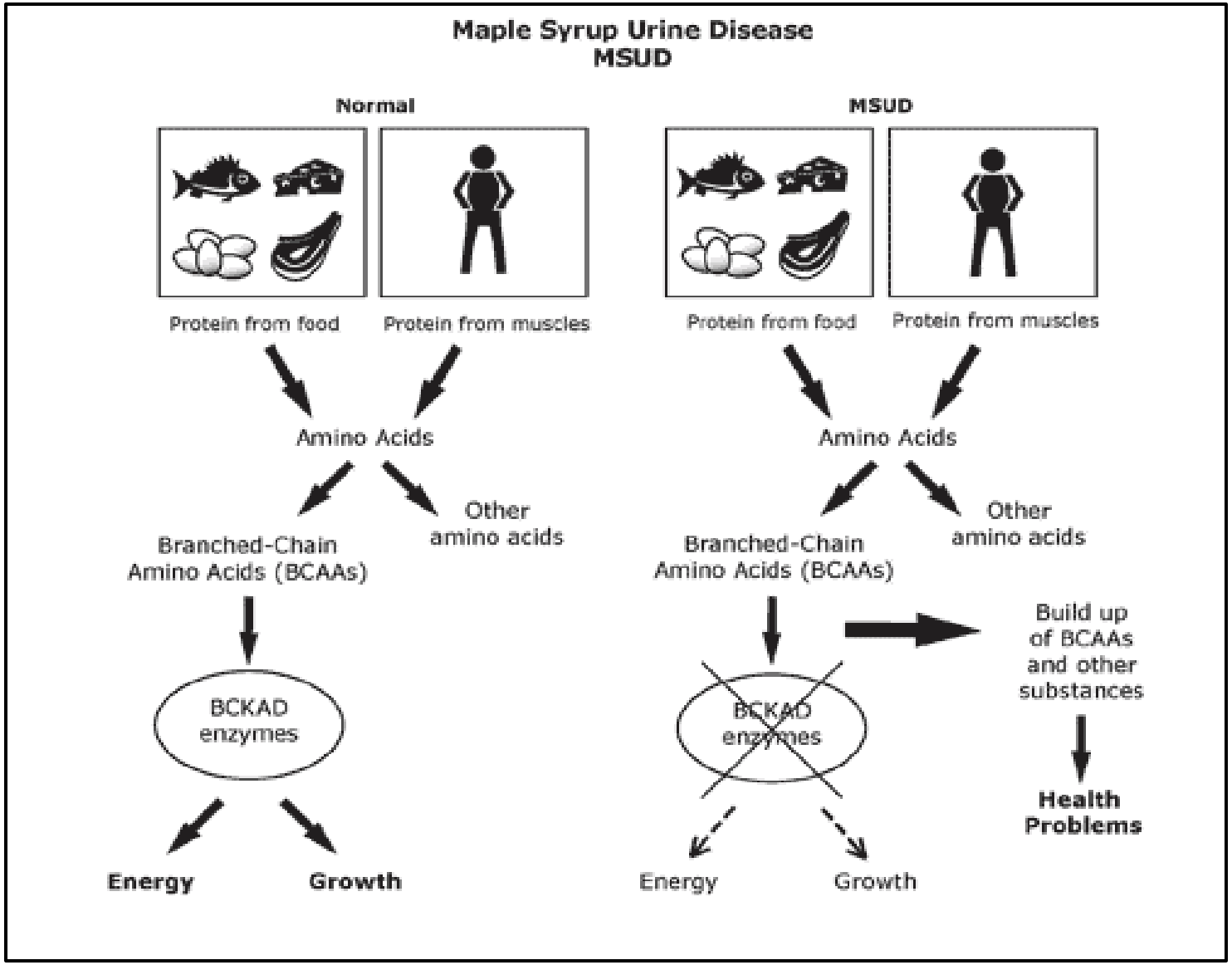
The disease is treated with a synthetic formula that contains limited amounts of leucine, isoleucine, and valine to provide the branched-chain amino acids necessary for normal growth and development without producing toxic levels. Infants suspected of having any form of MSUD should be tested within 24 hours of birth. Early diagnosis and treatment are essential if the child with MSUD is to develop normally.



Symptoms of Maple Syrup Urine Disorder:

- Vomiting
- lack of energy (lethargy)
- developmental delay
- Avoiding food
- Urine that smells like maple syrup
- If untreated, Maple Syrup Urine Disease can lead to seizures, coma, and death.




Maple Syrup Urine Disease
MSUD
Normal
MSUD
Protein from food
Protein from muscles
Protein from food
Protein from muscles
Amino Acids
Amino Acids
Other
amino acids
Other
amino acids
Branched-Chain
Amino Acids (BCAAs)
Branched-Chain
Amino Acids (BCAAs)
BCKAD
enzymes
BCKAD
enzymes
Build up
of BCAAs
and other
substances
Health
Problems
Energy
Growth
Energy
Growth

Albinism:

Albinism refers to a group of conditions in which a defect in **tyrosine metabolism** results in a deficiency in the production of **melanin**.

- These defects result in the partial or full absence of pigment from the skin, hair, and eyes.
- Albinism appears in different forms, and it may be inherited by one of several modes: autosomal recessive, autosomal dominant, or X-linked.
- Complete albinism **(also called tyrosinase-negative oculocutaneous albinism)** results from a deficiency of **tyrosinase** activity, causing a total absence of pigment from the hair, eyes, and skin, is the most severe form of the condition.
- Affected people may appear to have white hair, skin, and iris color, and they may have vision defects. They also have **photophobia** (sunlight is painful to their eyes), they sunburn easily, and do not tan.

Black and white twins

Born a minute apart, the two little sisters who strangers can't believe came from the same mum

From the Mail, February 21 2006

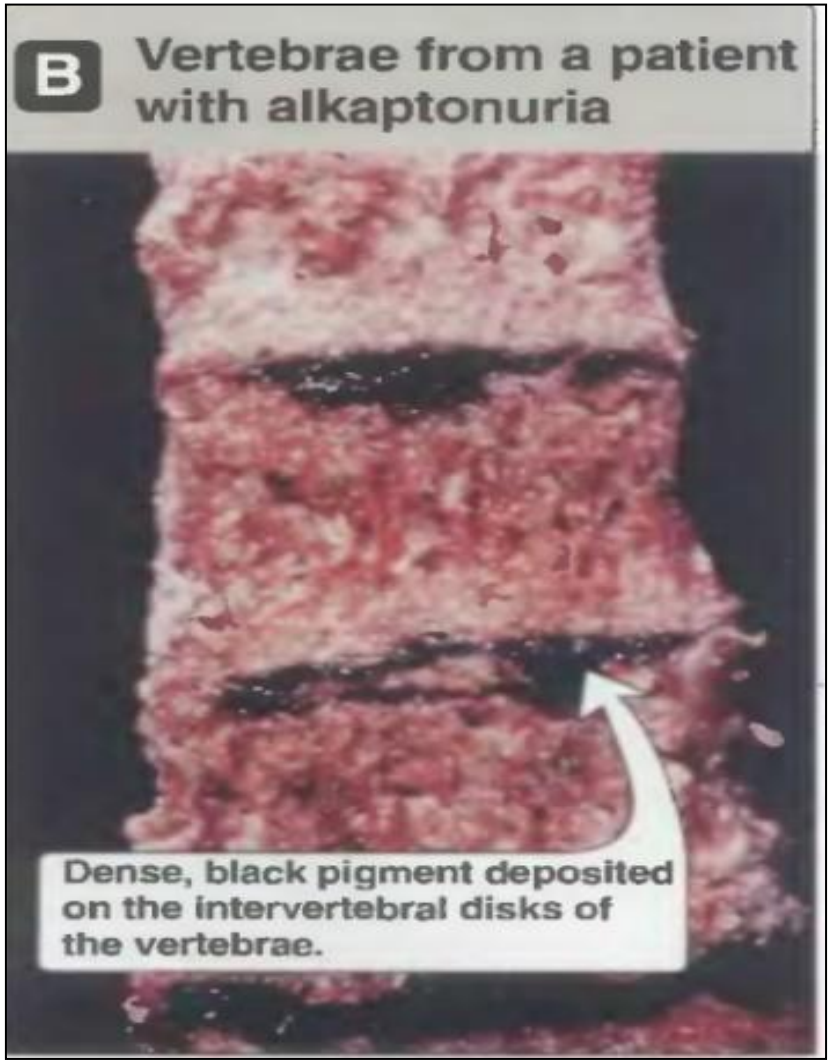
Alkaptonuria: Black urine disease

Is a rare metabolic disease involving a deficiency in **homogentisic acid oxidase**, resulting in the **accumulation of homogentisic acid**. [Note: This reaction occurs in the degradative pathway of tyrosine.]

The illness has three characteristic symptoms: **homogentisic aciduria** (the patient's urine contains elevated levels of **homogentisic acid, which is oxidized to a dark pigment** on standing.

Large joint arthritis, and black pigmentation of collagenous tissue. Patients with alkaptonuria are usually asymptomatic until about age forty. **Dark staining of the diapers** sometimes can indicate the disease in infants, but usually no symptoms are present until later in life.

Diets low in proteins especially in phenylalanine and tyrosine help reduce the levels of homogentisic acid, and decrease the amount of pigment deposited in body tissues. Although alkaptonuria is not life-threatening, the associated arthritis may be severely crippling.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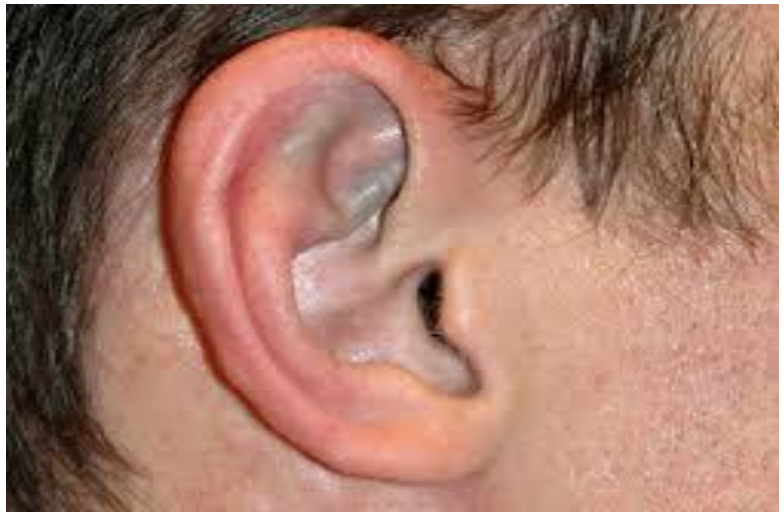
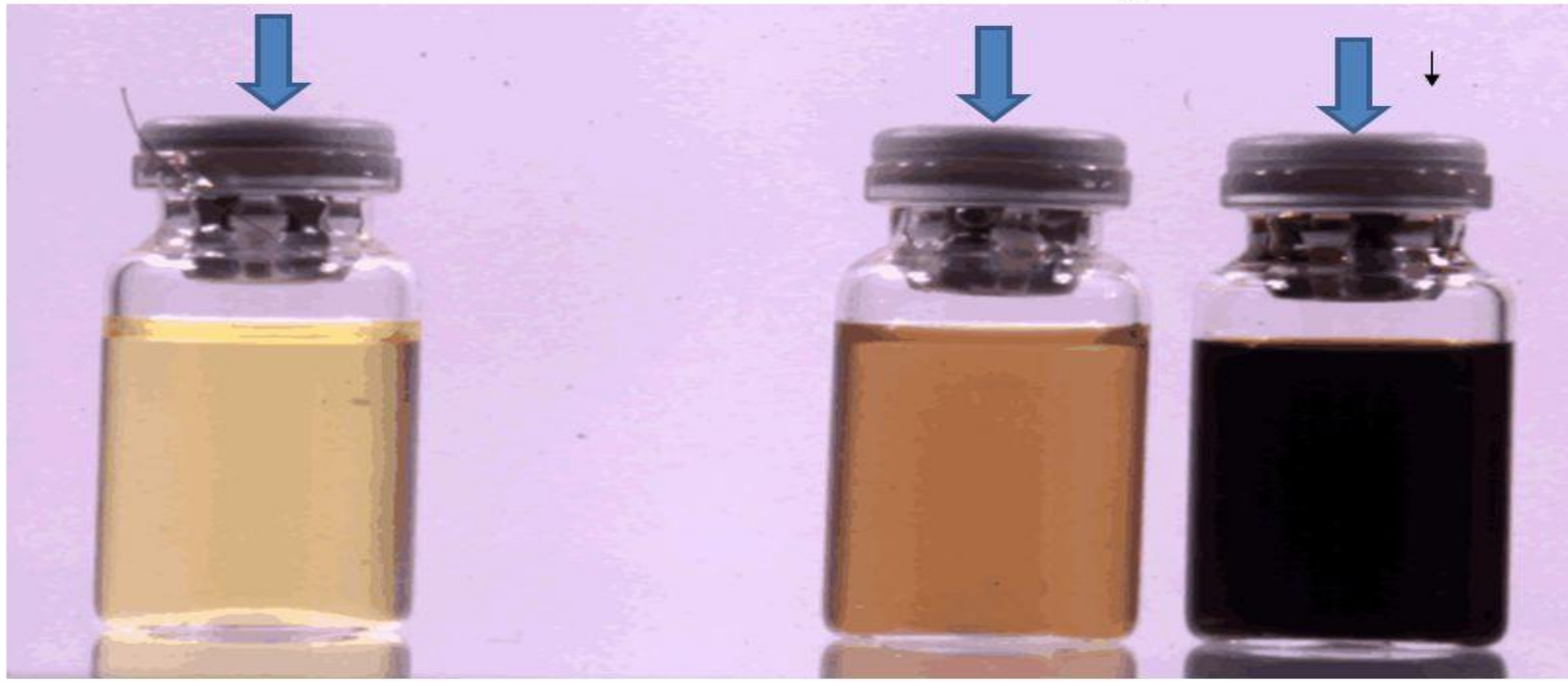
Vertebrae from a patient with alkaptonuria
Dense, black pigment deposited on the intervertebral disks of the vertebrae.



Symptoms of alkaptonuria

Normal urine

Urine from patients with alkaptonuria



Patients may display painless bluish darkening of the outer ears, nose and whites of the eyes. Longer term arthritis often occurs.

Hartnup disorder:

- Is a autosomal recessive metabolic disease in which there is a renal and intestinal transport defect involving absorption the amino acid tryptophan and increased urinary loss of the tryptophan.
- This amino acid is normally converted to nicotinamide (amide of niacin vit. B3). If the patient is also have a low nicotinamide intake, then the clinical picture of Hartnup disease will appear which are resembling those of pellagra due to niacin (nicotinamide) deficiency.
- Tryptophan is essential for the synthesis of nicotinamide, which is also supplemented through nutrition as a vitamin B3.
- Signs and symptoms may involve red scaly rash on the exposed skin.

Abnormalities and inflammation of tong and mouth. Weakness and anemia. Involvement of the CNS with loss of memory and confusion. GIT disturbance and diarrhea.

Case Studies:

Case PKU: A 10 – year –old mentally retarded child

A 10-year-old child, who was incontinent, unable to feed himself, and spoke incoherently was referred for investigations. He presented a picture of severe mental retardation with an I.Q. of 65. Detailed biochemical investigations with the plasma and the urine samples, and with the cell free extract* prepared from the hepatocytes (obtained by liver biopsy), led to the conclusion that the child had an impaired ability to convert phenylalanine to tyrosine. This is due to a defect in the enzyme, phenylalanine hydroxylase.

MSUD:

Case 1 :

was a 10-day-old male infant who had cyanotic episodes and recurrent generalized convulsions; the odor of burned sugar from the body and urine was also noted. Plasma and urine amino acid analysis disclosed a marked increase in the concentration of branched chain amino acids (BCAA). As a result of a BCAA-free diet and mega-doses of thiamine (vit B1), the condition stabilized. However, the patient was lost to follow-up and expired at two months of age due to inadequate management.

Case 2:

was a 20-day-old female infant with poor feeding, vomiting for one week, generalized convulsions and a peculiar burned sugar smell from the body and urine. Based on our experience with the first case, MSUD was suspected, and the infant was treated accordingly. However, subsequent follow-up revealed delayed developmental milestones.

Alkaptonuria

Male patient, 52 years old, sought medical help complaining about progressive appearance of hyperchromic papules on the lateral edge of the second finger of both hands for 2 years.

He also complained about darkening of urine, and underwear. biopsy of second hand finger and test for homogentisic acid in the urine results were positive.

The findings are compatible with the diagnosis of alkaptonuria. Given these findings, treatment was initiated, followed-up by other specialties and he was advised to avoid certain foods.

Summary:

- **Phenylketonuria (PKU)** is caused by a ***deficiency of phenylalanine hydroxylase enzyme that converts phenylalanine to tyrosine***. Untreated patients with PKU suffer from mental retardation, failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow. Treatment involves controlling dietary phenylalanine. Note that tyrosine becomes an essential dietary component for people with PKU.
- **Maple syrup urine disease (MSUD)** is a recessive disorder in which there is a partial or complete deficiency in ***branched-chain α-ketoacid dehydrogenase enzyme*** that decarboxylates leucine, isoleucine, and valine. Symptoms include feeding problems, vomiting, dehydration, severe metabolic acidosis, and a characteristic smell of the urine. Treatment of MSUD involves a synthetic formula that contains limited amounts of leucine, isoleucine, and valine.
- **Alkaptonuria a deficiency in homogentisic acid oxidase, resulting in the** accumulation of **homogentisic acid**. This reaction occurs in the degradative pathway of tyrosine.
- **Albinism due to deficiency of *tyrosinase enzyme***

Assessments and Evaluation:

Q:Write short notes on the following topics?

1. **Phenylketonuria**
2. **Albinism**
3. **Maple syrup urine disease**
4. **Alkaptonuria**
5. **Hartnup Disease**

Q: Explain briefly the biochemical defects in Phenylketonuria?