DISORDERS OF AMINO Acids Metabolism

DISORDERS OF AMINO & IMINO ACIDs

1. AROMATIC AMINO ACIDS
2. SULPHUR CONTAINING AMINO ACIDS
3. BRANCHED -CHAIN AMINO ACIDS

AROMATIC AMINO ACIDS

1. PHENYLKETONURIA
2. ALKAPTONURIA
3. ALBINISM

SULFER AMINO ACIDS

1. CYSTINOSIS
2. HOMHCYSTINURIA

BRANCHED-CHAIN AMINO ACICDS

* MAPLE SYRUP URINE DISEASE

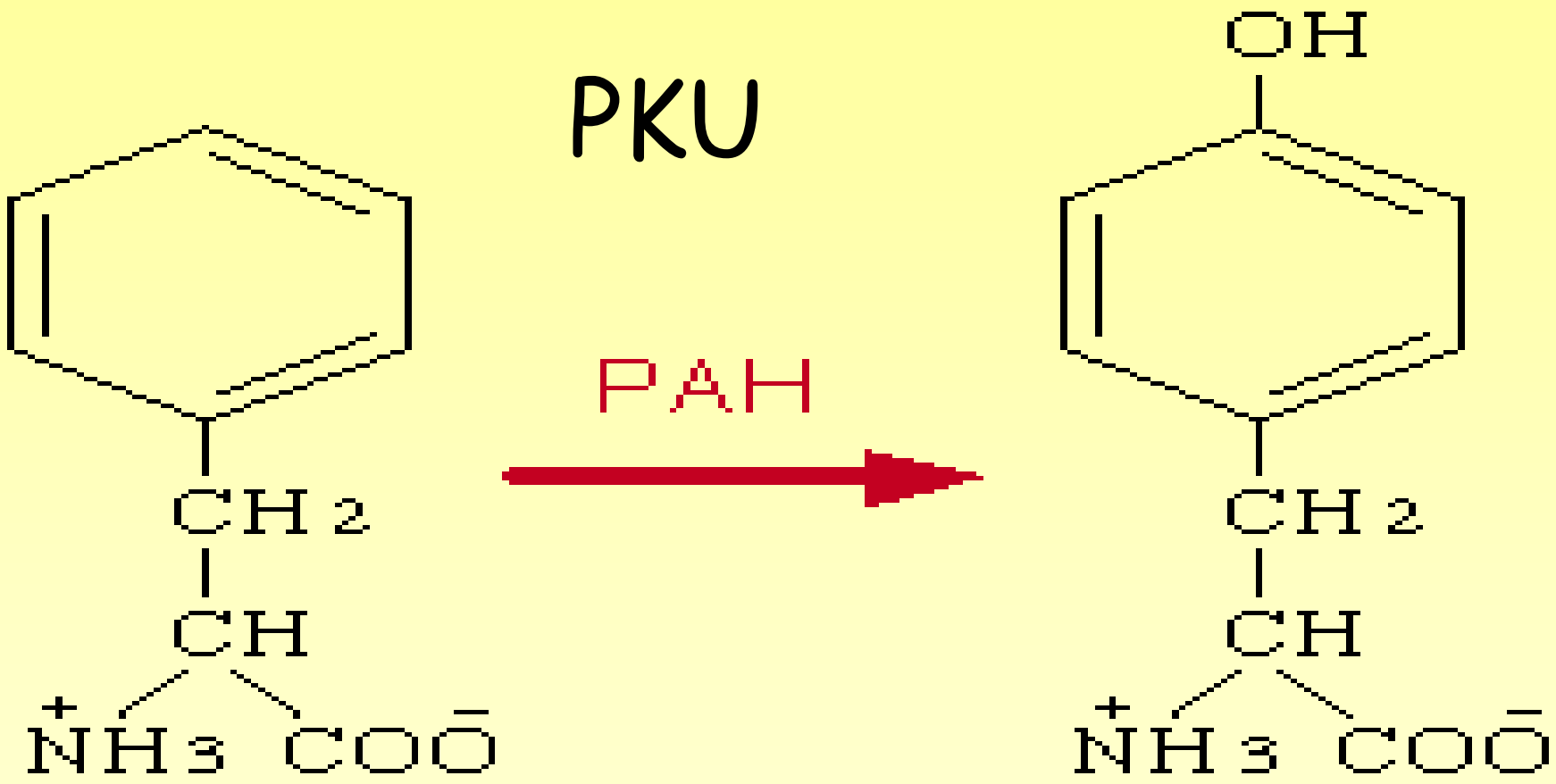
Phenylketonuria (PKU)

- **Definition**
- (PKU) is a rare hereditary condition in which the amino acid phenylalanine is not properly metabolized.

Causes And Risk

- **Cause**
- Phenylketonuria (PKU) is inherited as an autosomal recessive trait (both parents must pass on the defective gene for the child to be affected). The genetically determined abnormality in phenylketonuria is a missing enzyme called phenylalanine hydroxylase.

PKU

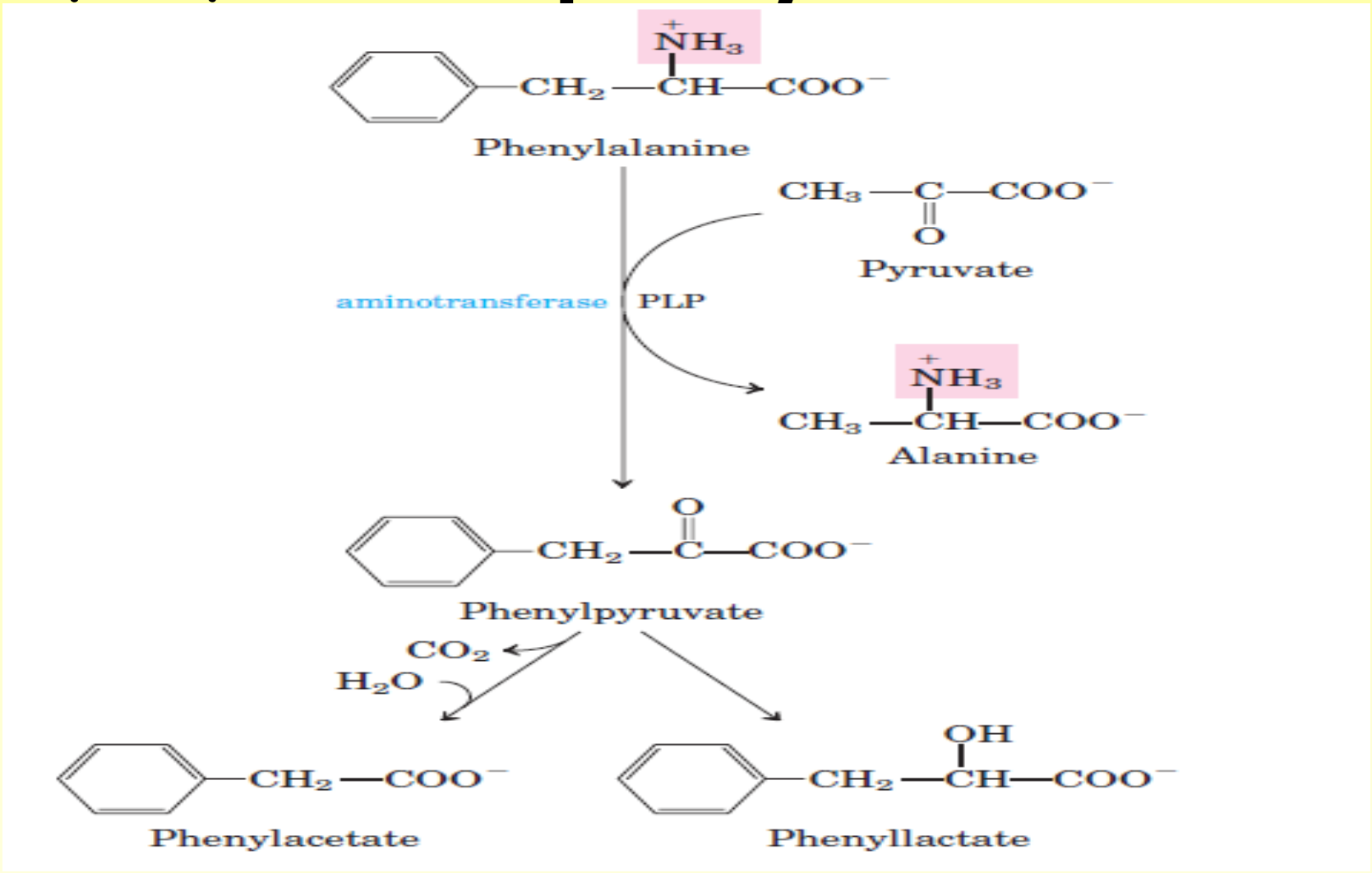


L-phenylalanine

L-tyrosine

The enzyme phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine.

Alternative pathways for catabolism of phenylalanine in **phenylketonuria.**



RISKS

- Damage to the brain causes marked mental retardation by the end of the first year of life if the offending proteins are not avoided. Older children may develop movement disorders (athetosis), rocking and hyper activity .

Prevention

- Genetic counseling is recommended for prospective parents with a family history of PKU. The carrier state for PKU can be detected by enzyme assays, and PKU can be diagnosed prenatally.
- It is imperative that women with PKU who becomes pregnant adhere closely to the special low-phenylalanine diet, since accumulation of phenylalanine will damage the unborn baby even if the baby has not inherited the abnormality.

Symptoms

- Skin rashes (ecsema)
- Microcephaly
- Tremors .
- Jerking movements of the arms or legs spasticity .
- Unusual hand posturing
- Seizures .
- Hyperactivity .
- Delayed mental and social skills
- Mental retardation .
- A distinctive "mousy" odor to the urine and sweat
- Light coloration (frequent finding of light complexion, blond hair, and blue eyes)

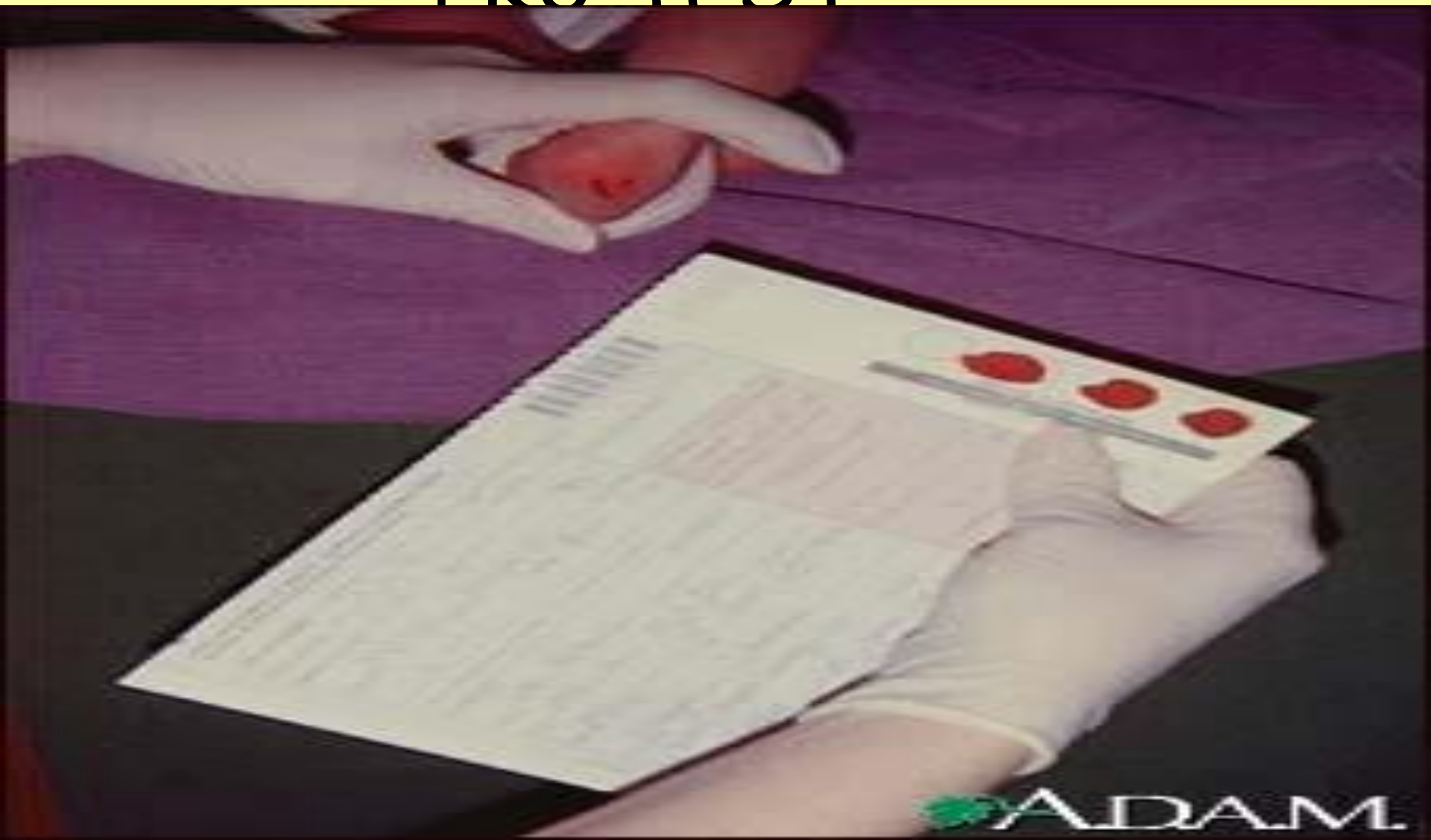
Phenylketonuria

Tests

- Tests include:
- Enzyme assay to detect the carrier state (parents)
- Chorionic villus sample to detect fetal PKU (prenatal diagnosis)
- PKU screening (a heelstick blood sample from the infant to screen for PKU, mandatory in most states)


A.D.A.M.

PKU TEST



Treatment

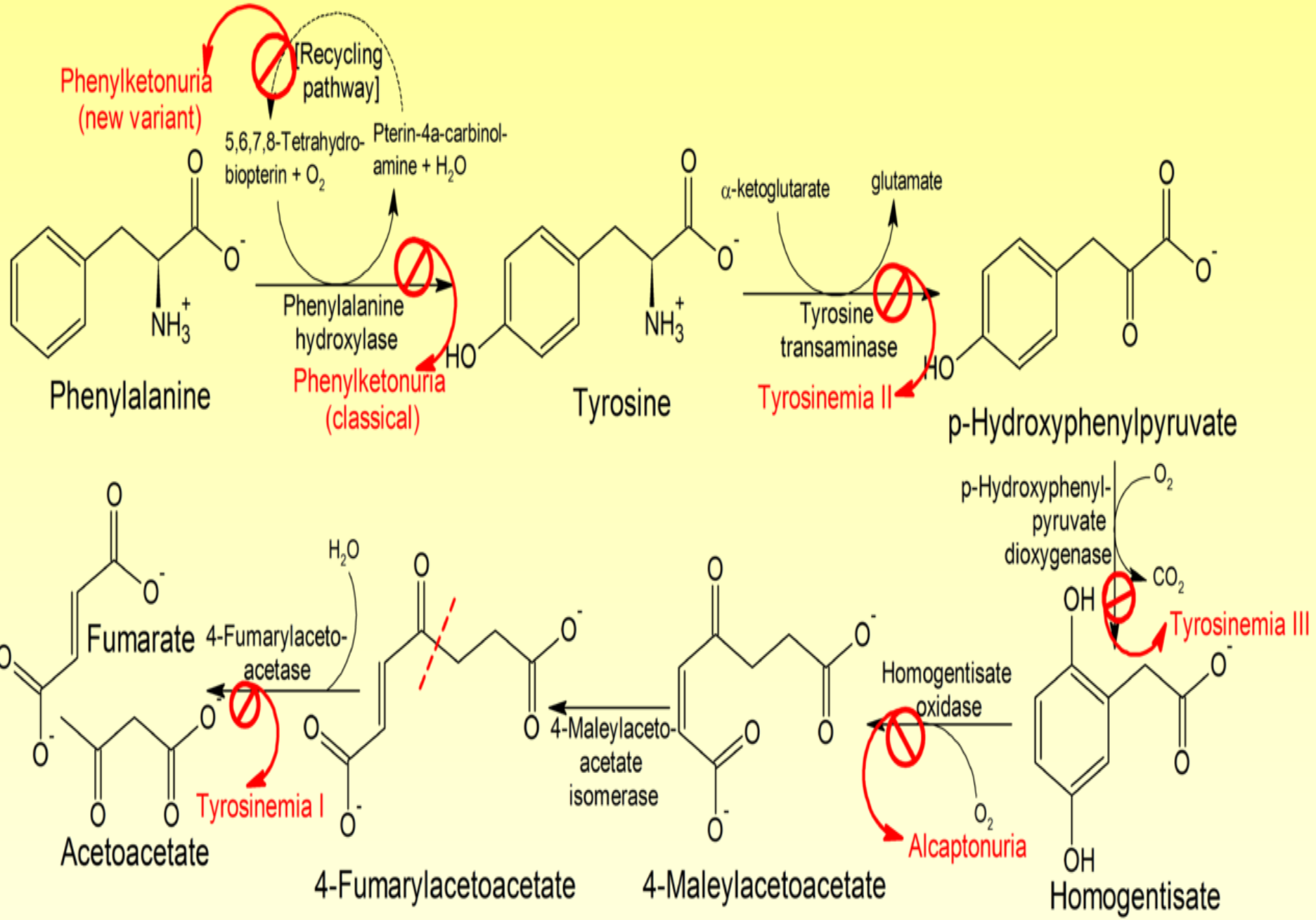
- Treatment includes a diet that is extremely low in phenylalanine;
- Phenylalanine occurs in significant amounts in milk, eggs and other common foods. Nutrasweet (aspartame) also contains phenylalanine
- Adult women who have PKU and who plan to become pregnant should also adhere to a strict low-phenylalanine diet both before becoming pregnant and throughout the pregnancy.

Complications

- Severe mental retardation occurs if the disorder is untreated.

Alkaptonuria (Disease)

- **Definition**
- Alkaptonuria is a rare inherited disorder of metabolism characterized by urine which turns black when exposed to air. Another characteristic is the development of arthritis in adulthood.


Phenylketonuria
(new variant)
[Recycling
pathway]
5,6,7,8-Tetrahydro-
biopterin + O_2
Pterin-4a-carbinol-
amine + H_2O
Phenylalanine
hydroxylase
Phenylketonuria
(classical)
Phenylalanine
Tyrosine
α-ketoglutarate
glutamate
Tyrosine
transaminase
Tyrosinemia II
p-Hydroxyphenylpyruvate
p-Hydroxyphenyl-
pyruvate
dioxygenase
O_2
CO_2
Tyrosinemia III
Homogentisate
Homogentisate
oxidase
O_2
Alcaptonuria
4-Maleylaceto-
acetate
isomerase
4-Maleylacetoacetate
H_2O
4-Fumarylaceto-
acetase
Tyrosinemia I
Fumarate
Acetoacetate
4-Fumarylacetoacetate

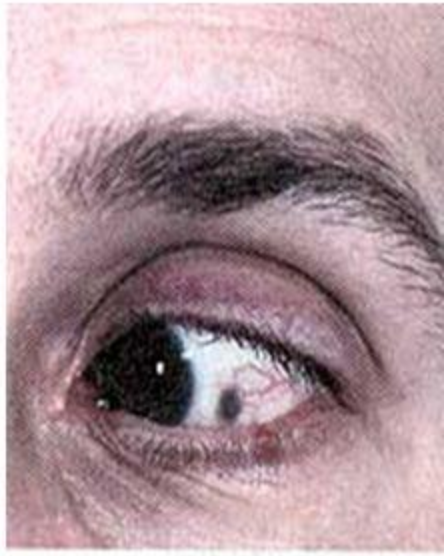
Alternative Names

- Alcaptonuria; Homogentisic acid oxidase deficiency; Ochronosis
- **Black urine disease, Black bone disease.**

INBORN ERRORS OF AMINO ACIDS METABOLISM

Alcaptonuria - inherited disorder of the tyrosine metabolism caused by the absence of ***homogentisate oxidase***.

- homogentisic acid is accumulated and excreted in the urine
- turns a black color upon exposure to air

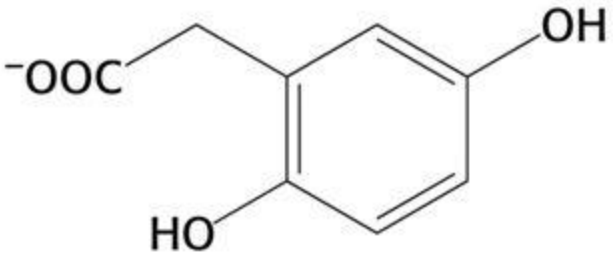


➢ **In children:**

- urine in diaper may darken

➢ **In adults:**

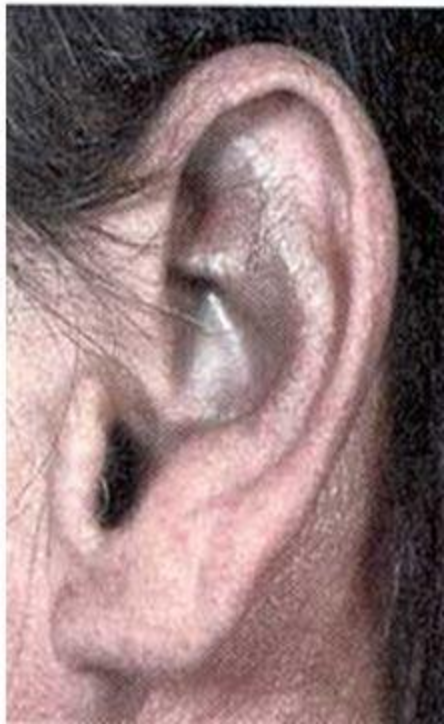
- darkening of the ear
- dark spots on the on the sclera and cornea
- arthritis



Homogentisate

Air

Highly colored polymer



Signs And Tests

- Urinalysis is positive for reducing substance. Further urine testing shows a positive ferric chloride test.

Treatment

- Some patients benefit from high-dose of vitamin C. This has been shown to decrease the build up of brown pigment in the cartilage, which may slow the rate of development of arthritis.
- Prognosis :The outcome is expected to be good

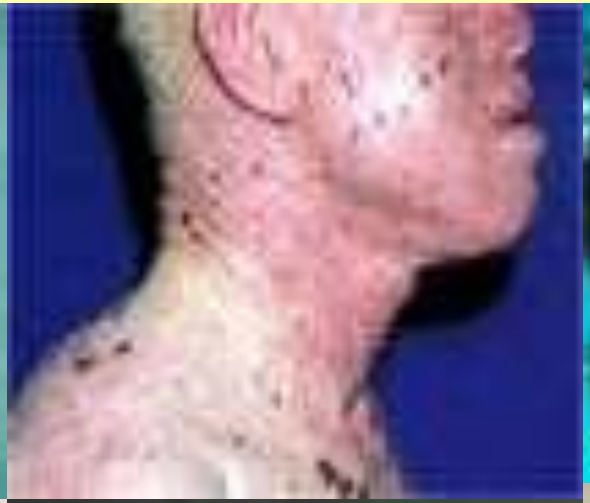
Complications

- Accumulation of homogentisic acid products in the cartilage causes arthritis in about 50% of older adults with alkaptonuria.
- Homogentisic acid products can accumulate on the heart valves, especially the mitral valve, sometimes leading to the need for valve replacement.
- Coronary artery disease may develop earlier in people with alkaptonuria.
- Kidney and prostate stones may be more common in people with alkaptonuria.

ALBINISM

- **Albinism:** refers to a group of related conditions. These conditions are the result of altered genes that cause a defect of melanin production. This defect results in the partial or full absence of pigment from the skin, hair, and eyes.

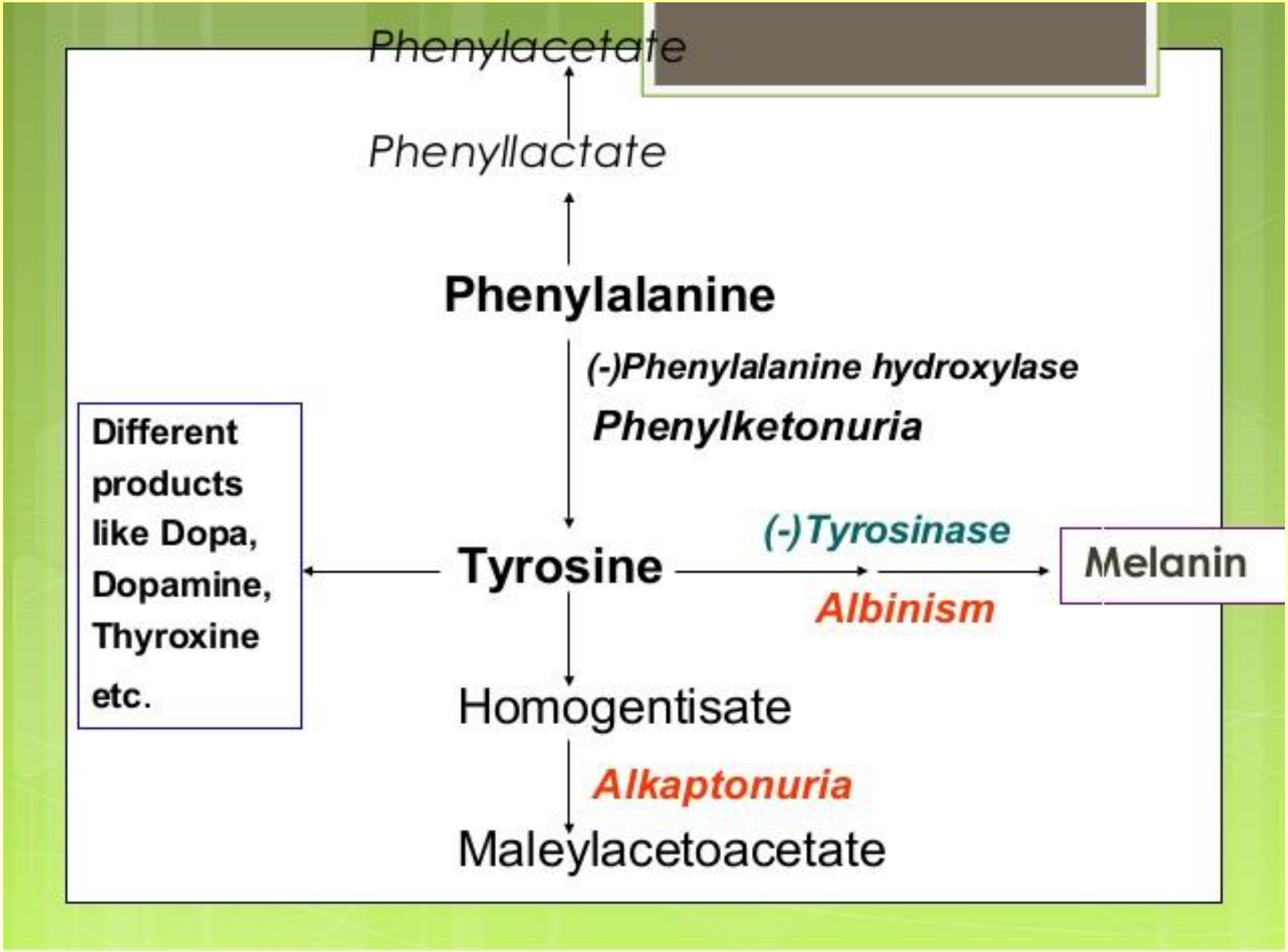
Albinism




Alternative Names

- Hypopigmentation; Oculocutaneous albinism; Ocular albinism


Phenylacetate
Phenyllactate
Phenylalanine
(-)Phenylalanine hydroxylase
Phenylketonuria
Different products like Dopa, Dopamine, Thyroxine etc.
Tyrosine
(-)Tyrosinase
Albinism
Melanin
Homogentisate
Alkaptonuria
Maleylacetoacetate

Causes And Risk

- Causes
- An amino acid called tyrosine is normally converted by the body to the pigment melanin. Albinism results when the body is unable to produce or distribute melanin because of one of several possible defects. In particular, defects in the metabolism of tyrosine leading to failure to convert it into melanin, can cause albinism.

Risk

- Affected people may appear to have hair, skin, and iris color that are white as well as vision defects. They also have photophobia (sunlight is painful to their eyes), they sunburn easily, and do not tan.

FORMS OF ALBINISM

- Albinism appears in different forms and may be inherited by one of several modes: autosomal recessive, autosomal dominant, or X-linked inheritance. Complete albinism involves a total absence of pigment from the hair, eyes, and skin (this is also called tyrosinase-negative oculocutaneous albinism). It is the most severe form of the condition.

Prevention

- As this is a large group of inherited conditions genetic counseling is important. Genetic counseling should be considered for individuals with a family history of albinism or hypopigmentation

Symptoms

- Absence of pigment from the hair, skin, or irisof eyes
- Patchy absence of pigment (skin ,color , patchy) including in the carrier-mothers of affected boys with X-linked recessive albinism
- Lighter than normal skin and hair or complete albinism

Albinism have some of the following possible symptoms:

- Rapid eye movements (nystragmus)
- Strabismus (eyes not tracking properly)
- Photophobia (avoidance of light because of discomfort)
- Decreased visual acuity .
- Functional blindness .

Signs And Tests

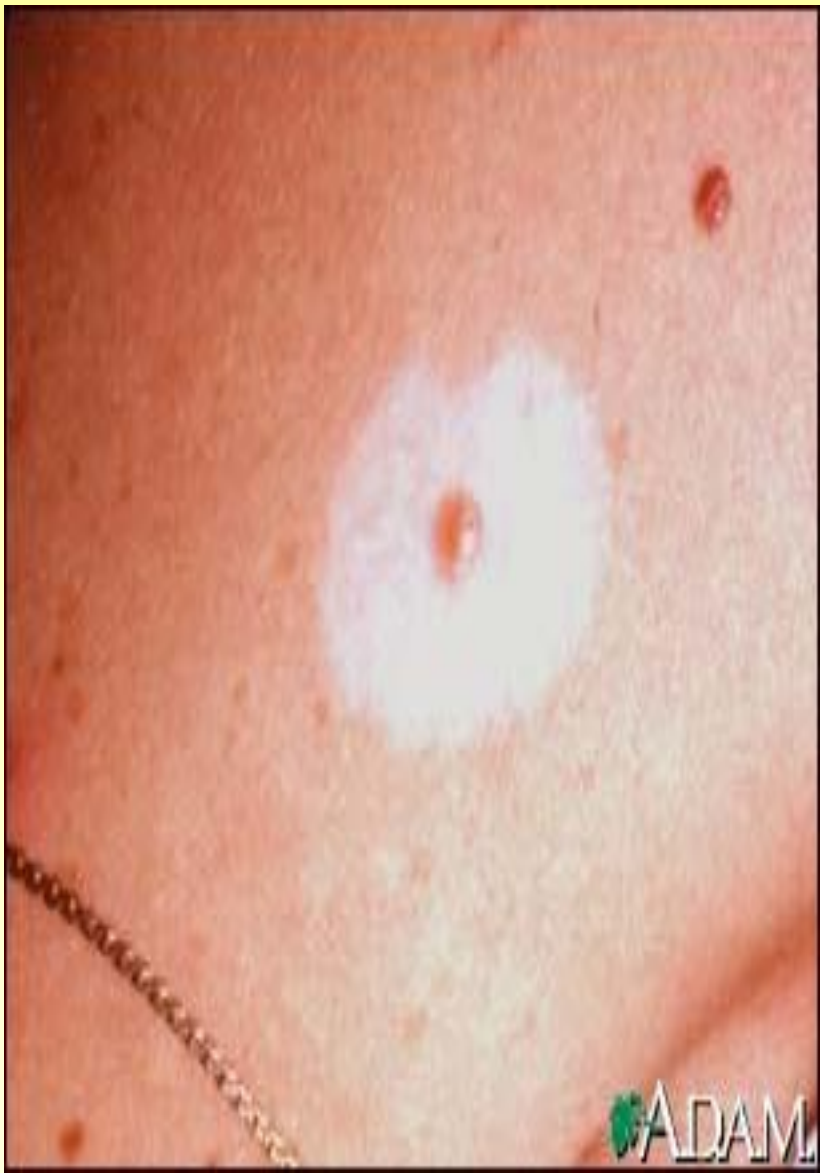
- The most accurate way to determine albinism and the specific type is genetic testing. This is helpful only in families with albinism and is not useful for the general population. A small blood sample is obtained from the affected individual and the parents and genetic analysis of the DNA code is performed to identify the affected genes.

Treatment

- The skin and eyes must be protected from the sun. Sunglasses (UV protected) may relieve photophobia. Sunburn risk can be reduced by avoiding the sun, by using sunscreens and covering completely with clothing when exposed to sun. Sunscreens should have a high SPF (sun protection factor).

Albinism

- A halo nevus occurs when the body develops antibodies to the pigment cells around a nevus. The pigment disappears and the area becomes white. Often in the process, the nevus itself disappears, leaving a circular white spot (macula).



END Part I

Sulphur amino acids

1. Cystonosis
2. Homocystinuria

cystenosis

Definition :

Cystinosis is a metabolic disease characterized by an abnormal accumulation of the amino acid cystine in various organs of the body such as the kidney, eye, muscle, pancreas, and brain. Different organs are affected at different ages.

IS IT INHERITED?

- The disease is inherited in an autosomal recessive fashion, meaning that each parent of a child with cystinosis carries one defective gene and one normal gene. The parents never have any signs of the disease.

CAUSES

- The cystine content of cystinotic cells averages 50-100 times the normal value. The cause is a defect in the transport of cystine out of a cell compartment called the lysososme, in which cystine accumulates. Because of cystine's low solubility, this amino acid forms crystals within the lysosomes of cells, and this is probably what destroys the cells.

Forms of cystinosis

- There are three clinical forms of cystinosis. Infantile (or nephropathic) cystinosis; late-onset cystinosis; and benign cystinosis.

SYMPTOMS

- thirst and urination, failure to thrive, rickets, and episodes of dehydration. And kidney damage. But benign cystinosis not produce kidney damage .

Cystinosis






cystinosis

Treatment

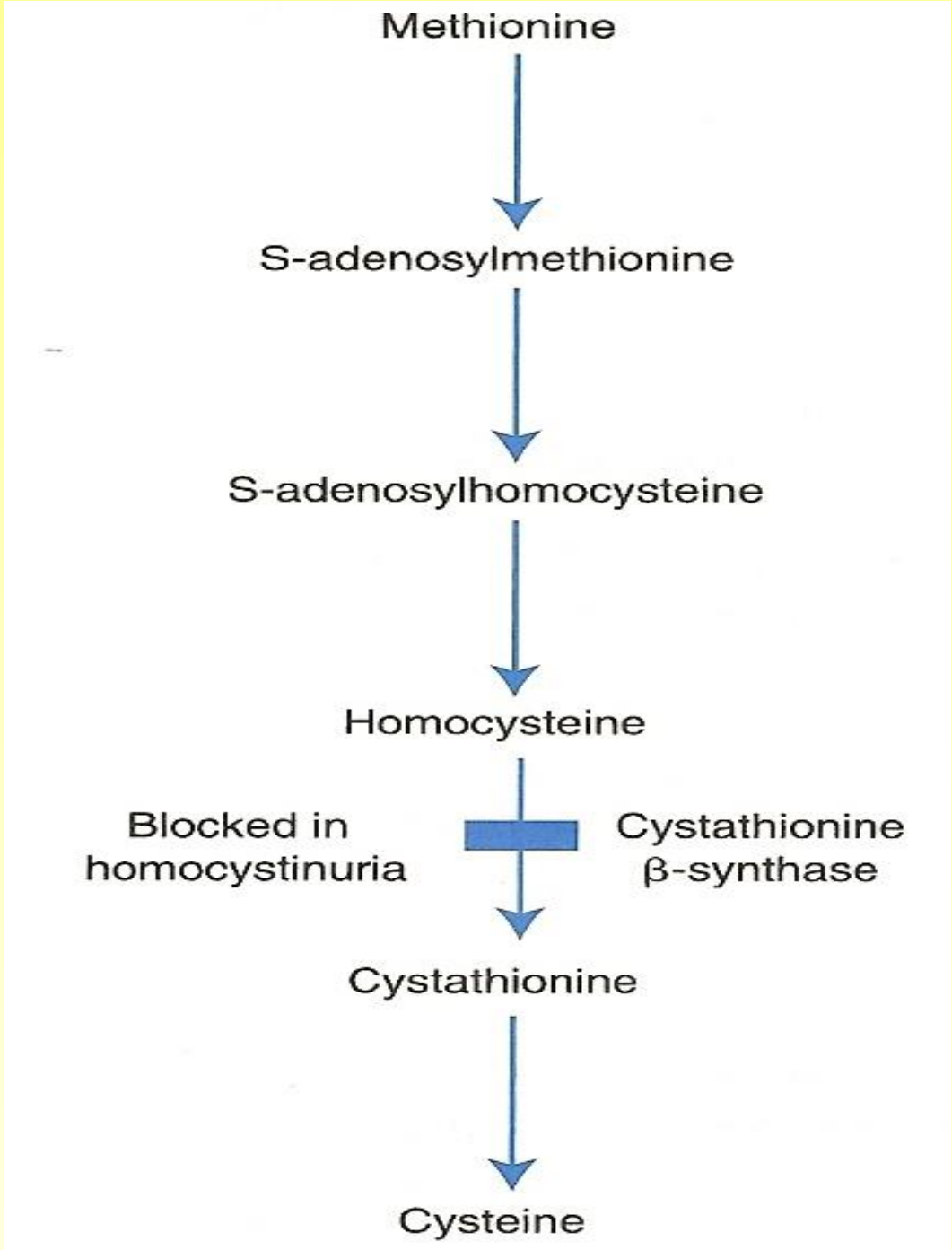
- The symptomatic treatment of the Fanconi syndrome is essential. The urinary losses of water, salts, bicarbonate, and minerals must be replaced. Most children receive a solution of sodium and potassium citrate, as well as phosphate. Some also receive extra vitamin D.

IS PRENATAL DETECTION POSSIBLE?

- Today, prenatal diagnosis is available for families known to be at risk for having a child with cystinosis. Chorionic villus sampling is performed at 8-9 weeks of gestation; amniocentesis can be performed at 14-16 weeks of gestation.

Homocystinuria

- **Definition:**
- Homocystinuria is an inherited disorder of the metabolism of the amino acid methionine.


Methionine
S-adenosylmethionine
S-adenosylhomocysteine
Homocysteine
Blocked in homocystinuria
Cystathionine β-synthase
Cystathionine
Cysteine

Alternative Names:

- Cystathionine beta synthase deficiency

Causes

- Homocystinuria is inherited as an autosomal recessive trait, which means that the child must inherit the defective gene from both parents to be seriously affected.

Risk

- Usual findings in homocystinuria are nearsightedness, dislocation of the lens of the eye, and a tendency to develop blood clots in the veins and arteries. Mental retardation and failure to thrive .

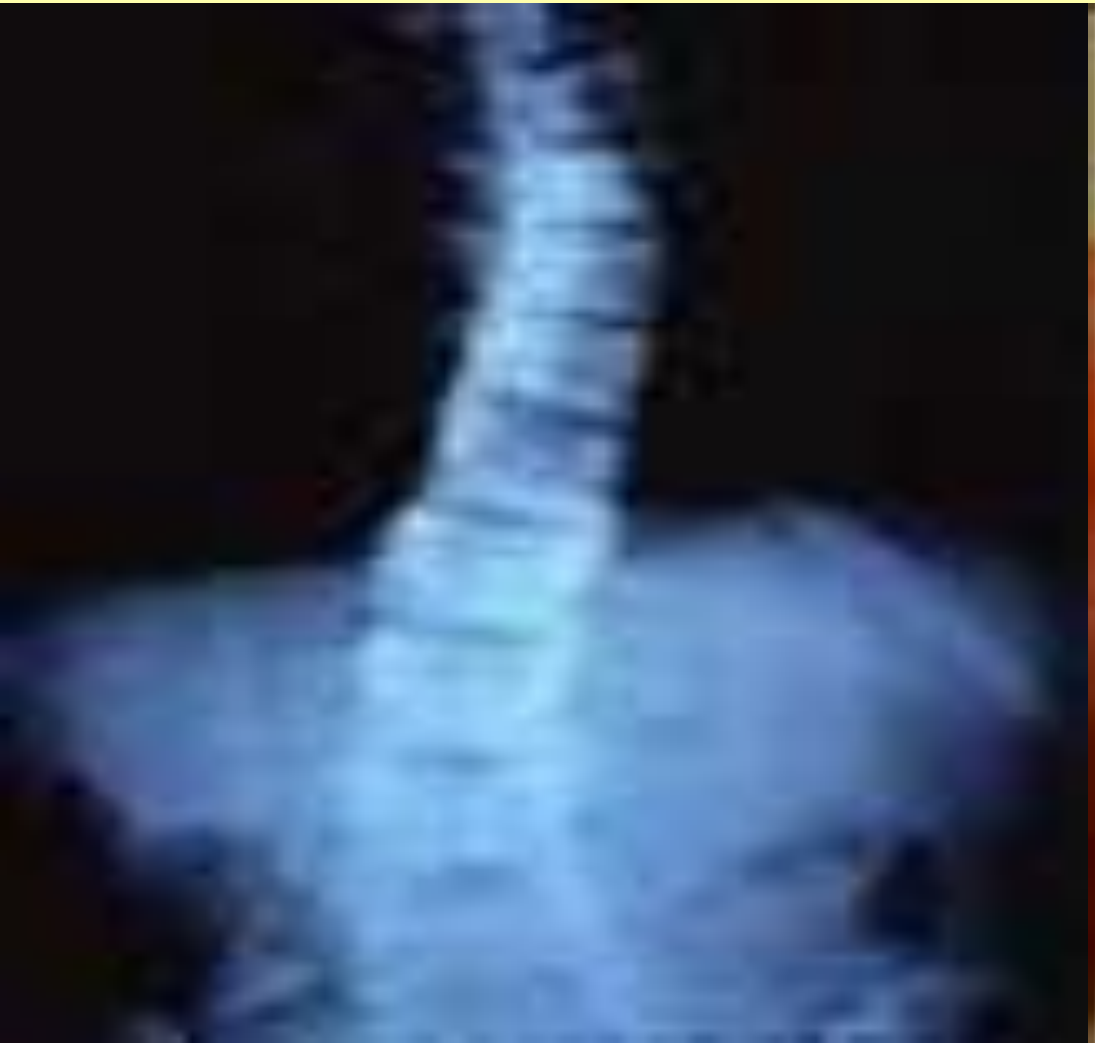
Prevention:

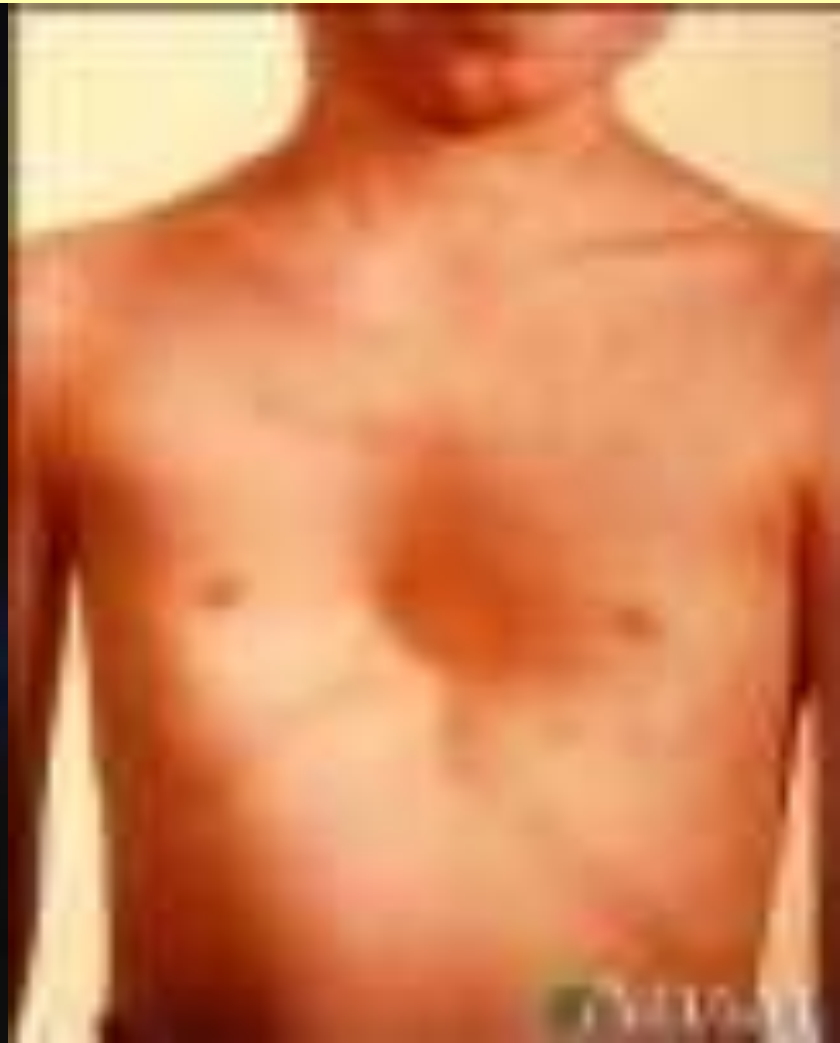
- Genetic counseling is recommended for prospective parents with a family history of homocystinuria. Intrauterine diagnosis of homocystinuria is available and is made by culturing amniotic cells or chorionic villi in order to test for the presence or absence of cystathionine synthase (the enzyme that is missing in homocystinuria).

Symptoms

- A family history of homocystinuria
- Nearsightedness
- Flush across the cheeks
- Tall, thin build
- Long limbs
- High-arched feet (pes cavus)
- Knock-knees (genu valaum)
- Pectus excavutum .
- Pectus carinatum .
- Mental retardation
- Psychiatric disease

Homocystinuria





Signs

- During a physical examination of the child, the health care provider may notice a tall, thin (Marfanoid) stature with pectus deformity of the chest or scoliosis. If there is poor or double vision, an ophthalmologist should perform a dilated eye exam where dislocation of the lens of the eye or nearsightedness may be observed.

Tests

- A skeletal x-ray shows osteoporosis.
- A standard ophthalmic exam confirms nearsightedness and a dislocated lens. Affected children may also have cataracts ,glaucoma, andretinal detachment.
- An amino acid screen of blood and urine shows elevated methionine and homocysteine levels.
- A liver biopsy and enzyme assay shows an absence of the enzyme cystathionine beta synthase.
- A skin biopsy with a fibroblast culture shows an absence of cystathionine beta synthase.

Treatment:

- There is no specific cure for homocystinuria. However, many people respond to high doses of vitamin B6 (also known as pyridoxine). Slightly less than 50% respond to this treatment; those that do respond need supplemental vitamin B6 for the rest of their lives. Those that do not respond require a low methionine diet, and most will need treatment with trimethylglycine (a medication).

Prognosis

- Although no specific cure exists for homocystinuria, approximately half of the affected people can be helped by vitamin B6 therapy.

Complications:

- Most serious complications result from blood clots , and these episodes can be life threatening. Dislocated lenses of the eyes can severely impair vision and lens replacement surgery should be considered. Mental retardation is a serious consequence of the disease which can be moderated if diagnosed early.

Maple syrup urine disease

- **Alternative names**
- MSUD

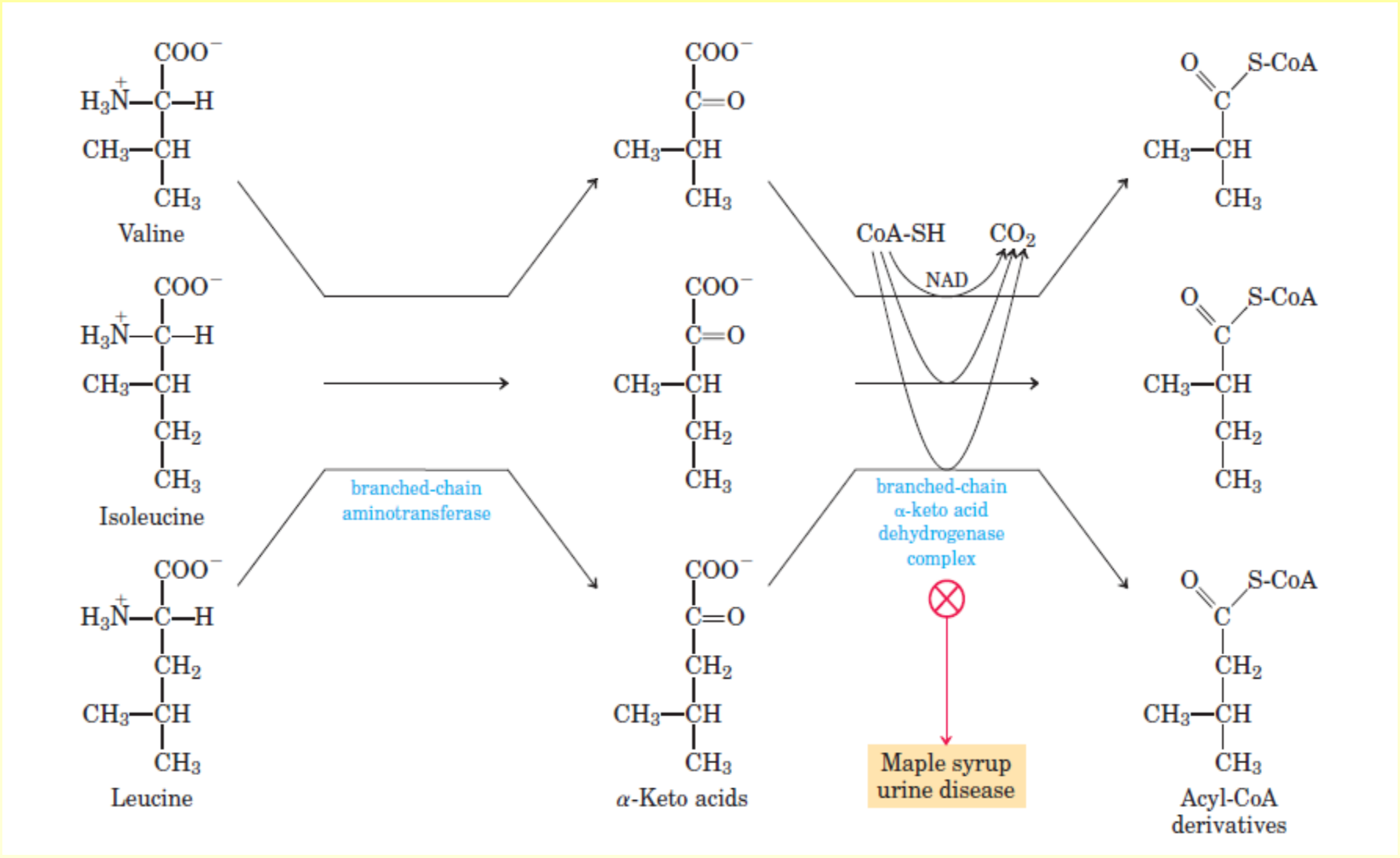
Definition

- Maple syrup urine disease is an inherited disease of amino acid metabolism that causes acidosis , central nervous system symptoms, and urine that may smell sweet like maple syrup.

Causes

- Maple syrup urine disease (MSUD) is caused by the inability to metabolize the branched-chain amino acids leucine, isoleucine, and valine. The disease is called MSUD because urine from affected people smells like maple syrup.

Catabolic pathways for the three branched-chain amino acids: valine, isoleucine, and leucine.



risk factors

- In the most severe form, MSUD causes severe acidosis during the first week of life. This is characterized by progressively poorer feeding, vomiting, seizures , lethargy, and finally coma.
- Untreated infants may die in the first few weeks of life in severe forms of the disease. MSUD also occurs in an intermittent form and a mild form. Even in the mildest form, infections can cause mental retardation and bouts of acidosis.

Symptoms

- Family history of MSUD or unexplained infant death
- Urine which smells like maple syrup
- Feeding difficulties
- Lethargy
- Vomiting
- Seizures
- Coma
- Avoiding food

Signs and tests

- Urine amino acids (elevated levels of the amino acids leucine, isoleucine, and valine)
- Plasma amino acids (elevated levels of leucine, isoleucine, and valine)
- Ketosis (elevated levels of ketone bodies in urine and plasma)
- Acidosis (excess acid in blood)

Screening Test

- Historically screening has been based on measurement of leucine in the dried blood spot using a bacterial inhibition assay similar to the original Guthrie assay for PKU. Screening is now possible using tandem mass spectrometry to measure the amino acids. Predictive values are not documented but should be high.

Treatment

- Treatment of the acute episode:
- Acute acidosis is treated to restore normal pH.
- Because this is a protein intolerance disease, protein is cut from the diet .
- High doses of intravenous fluid, sugar and fat are given to prevent dehydration and provide energy to stimulate protein synthesis, which lowers the levels of the amino acids which cannot be broken down.
- Peritoneal dialysis or hemodialysis are used to remove the high levels of amino acids.
- A special diet free of branched-chain amino acids is started immediately.

Prognosis

- If left untreated, life-threatening neurological damage may result. Even with dietary treatment, stressful situations and illness can still cause bouts of acidosis. Death may occur during these episodes. With strict dietary treatment, children have grown into healthy adulthood.

Complications

- Neurological damage such as low IQ, if poorly treated
- Possibly fatal acidosis episodes

Prevention

- Genetic counseling is suggested for prospective parents with a family history of maple syrup urine disease. A follow-up blood test for amino acid levels should be done right away to find out if your baby does have the disease.

Maple syrup urine disease

The

END