



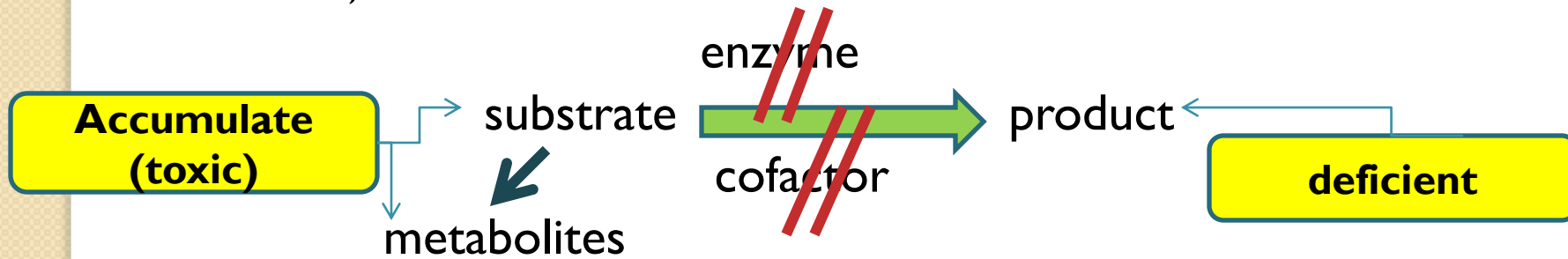
Inborn Error Of Metabolism :

Inborn Error Of Metabolism

- ❖ inborn error of metabolism are a large group of hereditary biochemical diseases in which specific gene mutation cause **abnormal** or **missing proteins** that lead to **alter function**
- ❖ The function of a protein, whether it is an **enzyme, receptor, transport vehicle, membrane, or structural element**, may be relatively or seriously compromised

Pathophysiology:


- Single gene defects result in abnormalities in the synthesis or catabolism of proteins, carbohydrates, or fats.
- Most are due to a defect in an enzyme or transport protein, which results in a block in a metabolic pathway.
- Effects are due to toxic accumulations of substrates before the block and by a deficiency of products beyond the block, or a combination of these metabolic deviations.



Common Characteristics of Genetic Disorders of Metabolism

Although the manifestations of genetic metabolic disorders are quite variable, the following features are shared among most of these conditions:

- 1- The affected infant is **normal at birth** and becomes symptomatic later on in life.
- 2- The nature of the mutation that causes the dysfunction of the gene usually **varies from family to family**.
- 3- Mutations causing severe malfunction of the gene or its product result in clinical manifestations shortly after birth. In general, **the earlier the appearance of clinical symptoms the more severe is the disease**.


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- 4- The majority of conditions are inherited as autosomal recessive traits. Therefore, a history of **consanguinity** in the parents or of **an unexplained death** in the neonatal period may raise the question of an inherited metabolic disease in the sick infant.

 - 5- Most of the genetic metabolic conditions can be controlled successfully by some form of therapy, and a few can be potentially cured by the use of bone marrow or liver transplants. These patients can have a normal life if diagnosed and treated early, before irreversible damage to organs, especially to the brain, occurs. **This underlines the importance of early diagnosis**, which can be achieved through screening of all newborn infants.

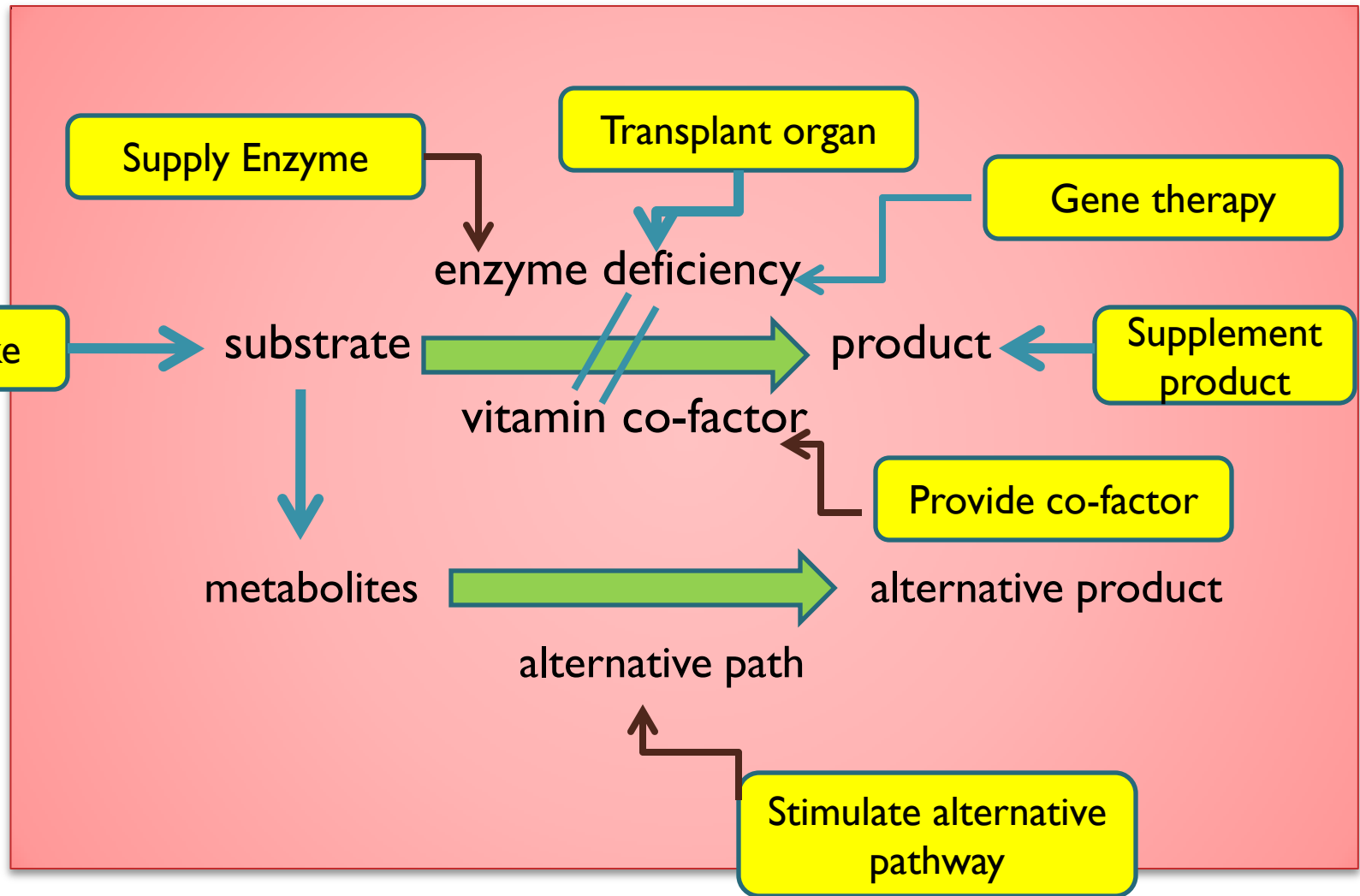
presentation

- ❑ An inborn error of metabolism may be suspected before birth from
 - a. a positive family history
 - b. previous unexplained deaths in the family.

- ❑ After birth, inborn errors of metabolism usually, but not invariably, present in one of five ways:
 1. As a result of newborn screening, e.g. phenylketonuria (PKU), or family screening, e.g. familial hypercholesterolaemia
 2. After a short period of apparent normality, with
 - a. a severe neonatal illness with poor feeding,
 - b. vomiting,
 - c. encephalopathy,
 - d. acidosis,
 - e. coma and death,e.g. organic acid or urea cycle disorders

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3. As an infant or older child with an illness similar to that described above but **with hypoglycaemia as a prominent feature** or as an ALTE (**acute life-threatening episode**) or **near-miss 'cot death'**,
 4. In older children it should be considered in any child with one or more of the following manifestations:
 - a. unexplained mental retardation, developmental delay, motor deficits or convulsions.
 - b. unusual odor particularly during an acute illness
 - c. intermittent episodes of unexplained vomiting, acidosis, mental retardation or coma.
 - d. hepatomegaly.
 - e. renal stones.
 5. In a subacute way, after a period of normal development, with regression, organomegaly and coarse facies, or As a dysmorphic syndrome.

Approach to Inborn Error of Metabolism



Approach to Inborn Error of Metabolism

The majority of patients with genetic disorders of metabolism respond to one or all of the following treatments:

- **Special diets** play an important role in the treatment of affected children.
- **Peritoneal dialysis** or **hemodialysis** for removal of accumulated noxious compounds. This is a very effective modality for treatment of the **acute phase of the condition**.
- Administration of the **deficient metabolite**.
- Administration of the **deficient enzyme**.

Approach to Inborn Error of Metabolism (cont.)

- Administration of **the cofactor** or **coenzyme** to maximize the residual enzyme activity.
- Activation of **alternate pathways** to reduce the noxious compounds accumulated because of the genetic mutation.
- **Bone marrow transplantation** (to cure the metabolic abnormalities)
- **Liver transplantation.** (to cure the metabolic abnormalities)
 - Replacement of the mutant gene** with a normal one (gene therapy) is still in the experimental phase.

Mass Screening of Newborn Infants

- Common characteristics of genetic metabolic conditions make a strong argument for screening all newborn infants for the presence of these conditions.
- During the past half-century, methods have been developed to screen all infants inexpensively with accurate and fast-yielding results.
- Tandem mass spectrometry (MS/MS) is the latest technical advance in the field.

The tests are done on a spot of blood from a heel-prick collected onto a filter paper and mailed to a central laboratory for assay



Defects in Metabolism of Amino Acids

Phenylketonuria

- ❖ This occurs in 1 in 10 000-15 000 live births in the UK.
- ❖ It is either due to a deficiency of the enzyme **phenylalanine hydroxylase** (classical PKU) or in the synthesis or **recycling of the bipterin cofactor** for this enzyme.

Defects in Metabolism of Amino Acids

Homocystinuria

- ❑ This is due to **cystathionine synthetase deficiency**.
- ❑ Presentation is with:
 - developmental delay
 - eventually subluxation of the ocular lens (ectopia lentis).
 - There is progressive learning difficulty, psychiatric disorders and convulsions.
 - Skeletal manifestations resemble Marfan syndrome.
 - The complexion is usually fair with brittle hair.
 - Thromboembolic episodes may occur at any age.

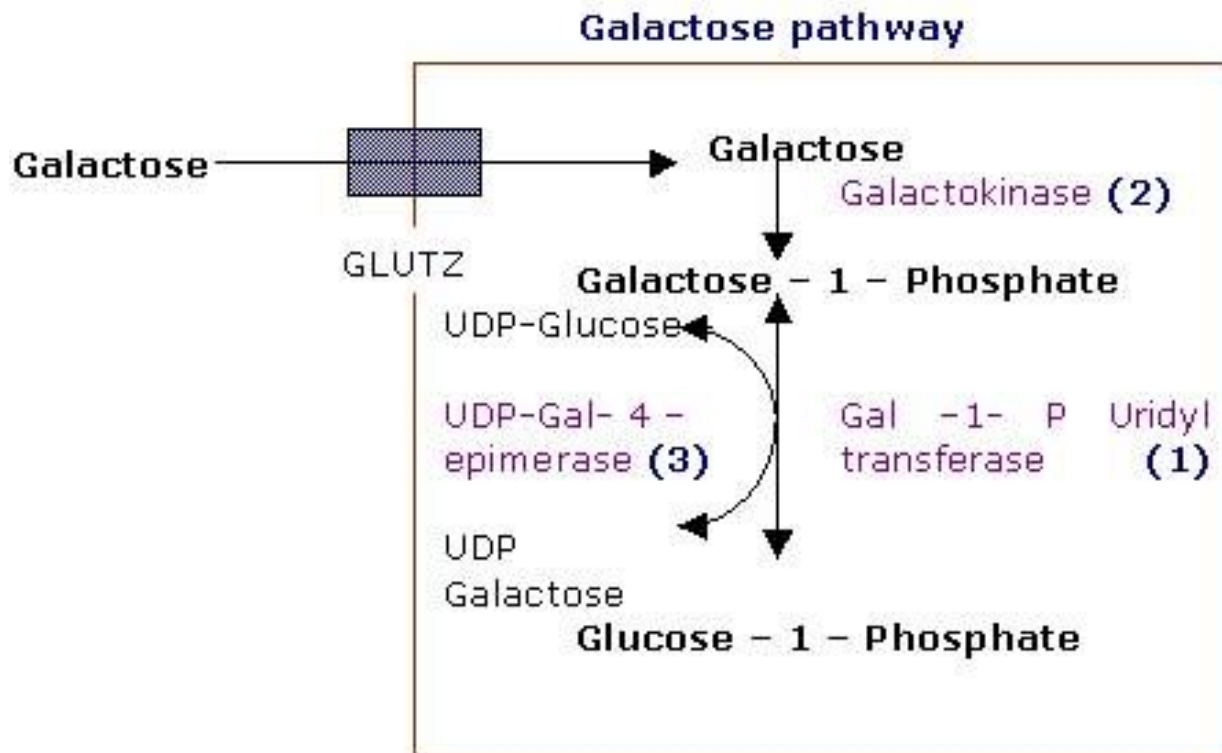
Defects in Metabolism of Amino Acids

Homocystinuria

- ❑ Almost half respond to **large doses of the coenzyme pyridoxine**.
- ❑ Those who do not respond are treated with a **low-methionine diet, supplemented with cysteine** and with the addition of the re-methylating agent **betaine**

Defects in Metabolism of Carbohydrates

Galactosaemia



Defects in Metabolism of Carbohydrates

Galactosaemia

- ❖ This rare, recessively inherited disorder results from deficiency of the enzyme **galactose-1-phosphate uridylyltransferase**, which is essential for galactose metabolism.
- ❖ When lactose-containing milk feeds such as breast or infant formula are introduced, affected infants:
 - feed poorly,
 - vomit
 - hypoglycemia
 - develop jaundice
 - increase risk of sepsis by E.coli
 - hepatomegaly and hepatic failure.
- ❖ Chronic liver disease, cataracts, developmental delay are inevitable if the condition is untreated.
- ❖ Even if treated early, there are usually moderate learning difficulties (adult IQ 60-80).

Defects in Metabolism of Carbohydrates

Galactosaemia

❑ Diagnosis:

- positive reducing substance in urine (galactose)
- elevated level of galactose in the blood (during neonatal screening)
- enzyme assay in blood sample

❑ Management is with a lactose- and galactose-free diet for life.

Defects in Metabolism of Carbohydrates

Glycogen storage disorders

- These mostly recessively inherited disorders have specific enzyme defects which prevent mobilization of glucose from glycogen, resulting in an abnormal storage of glycogen in liver and/or muscle.
- There are eleven main enzyme defects.

Defects in Metabolism of Carbohydrates

Glycogen storage disorders

Type I (von Gierke)

- ❖ In this type the enzyme deficient is **Glucose-6-phosphatase**
- ❖ the disease started at infancy and the liver is the main organ of storage,
- ❖ hepatomegaly and hypoglycaemia are prominent.
- ❖ There is also an enlarged kidneys and growth failure,
- ❖ Long-term complications include:
 - hyperlipidaemia,
 - hyperuricaemia,
 - the development of hepatic adenomas
 - the development cardiovascular disease



Defects in Metabolism of Carbohydrates

Glycogen storage disorders

Type II (Pompe disease)

- In this type the enzyme deficient is **Lysosomal α -glucosidase**
- the disease started at infancy there is generalised intralysosomal storage of glycogen (**liver and muscles**)
- The disorder may predominantly affect muscle leading to skeletal muscle weakness.
- The **heart is severely affected**, leading to death from cardiomyopathy.
- Treatment with enzyme replacement therapy (Myozyme) is now available

Lysosomal storage disorders

e.g. lipid storage disorders & mucopolysaccharidoses, in which **absence of an enzyme leads to accumulation of a harmful metabolite**

Lipid storage disorders

In lipid storage disorders, which are sphingolipidoses, there is an accumulation of sphingolipids, essential components of CNS membranes. They are diagnosed on testing white cell enzymes.

A - Tay-Sachs disease

- This disease results from the deficiency of **β -hexosaminidase activity** and the lysosomal accumulation of **GM₂ gangliosides**, particularly in the central nervous system.

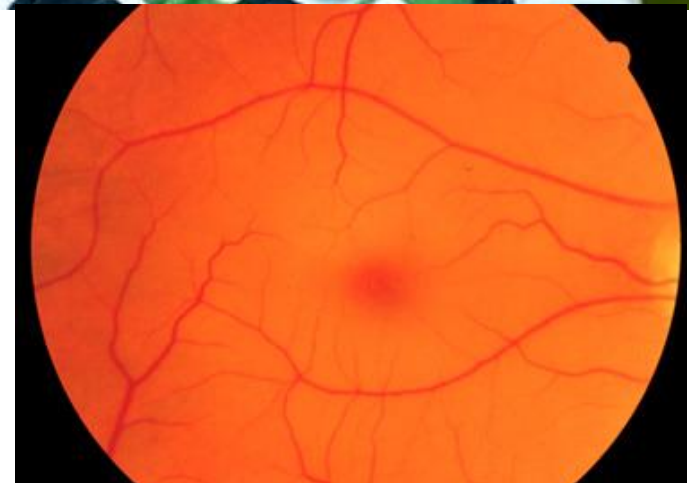
Lipid storage disorders

A - Tay-Sachs disease

- ❑ It is an Autosomal recessive disorder,
- ❑ Most common among Ashkenazi Jews,

Clinical features

- Developmental regression in late infancy,
- exaggerated startle response to noise,
- visual inattention
- social unresponsiveness
- Severe hypotonia,
- enlarging head,
- Cherry red spot at the macula,
Death by 2-5 years



Lipid storage disorders

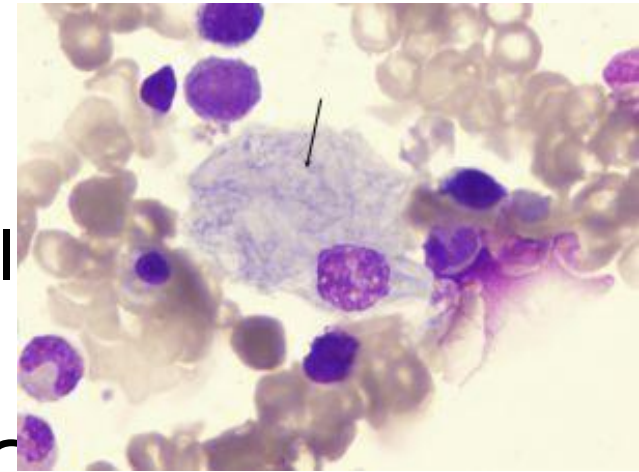
B- Gaucher disease

- ❖ It results from the deficient activity of the lysosomal hydrolase, **acid β -glucosidase**,
- ❖ The enzymatic defect results in the accumulation **glucosylceramide**, in cells of the reticuloendothelial system.
- ❖ Chronic childhood form Occurs in 1 in 500 Ashkenazi Jews
- ❖ presented by :
 - splenomegaly,
 - bone marrow suppression,
 - bone involvement,
 - normal IQ

Lipid storage disorders

B- Gaucher disease

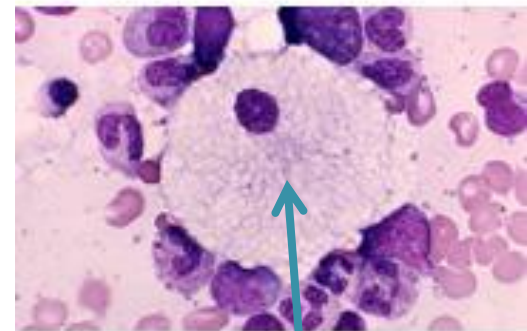
- Bone marrow aspiration shows presence of gaucher cell
- Definite diagnosis by assess the enzyme level in the WBC.
- Splenectomy may alleviate hypersplenism
- Enzyme replacement therapy is available, but is expensive
- Acute infantile form - splenomegaly, neurological degeneration with seizures



Lipid storage disorders

C- Niemann-Pick disease

- Result from the deficient activity of acid **sphingomyelinase**, a lysosomal enzyme
- The enzymatic defect results in the pathologic accumulation of **sphingomyelin, in the monocyte-macrophage** system
- usually presented at 3-4 months with:
 - feeding difficulties
 - failure to thrive,
 - hepatosplenomegaly,
 - developmental delay,
 - hypotonia
 - Cherry red spot in macula affects 50%
 - deterioration of hearing and vision
 - Death by 4 years



foam cells

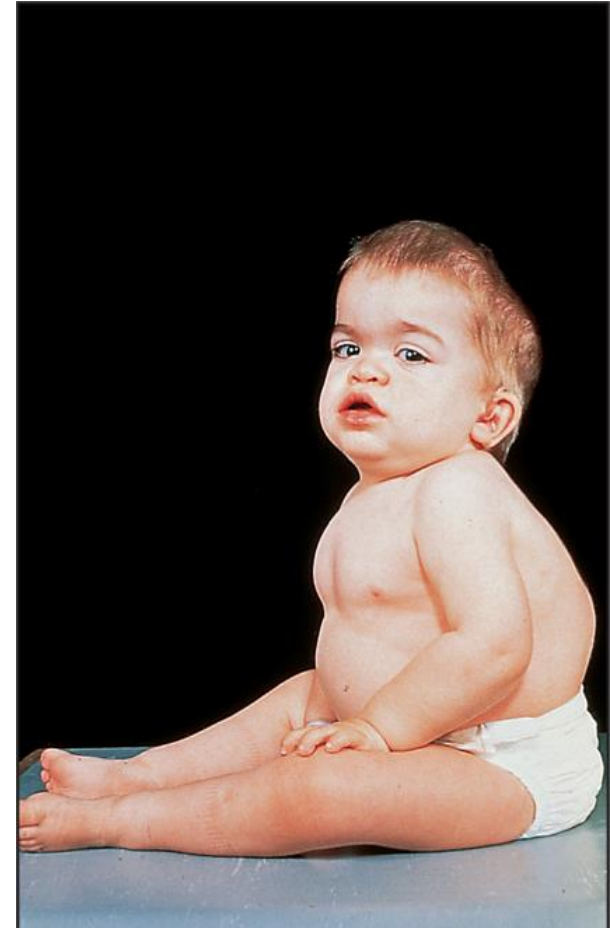
mucopolysaccharidoses

Hurler syndrome:(MPS I)

- ❖ AR disorder caused by deficiency of **α -iduronidase**.
- ❖ Signs and symptoms occur due to **accumulation of heparan and dermatan sulphate**.

Clinical features:

- usually normal at birth.
- Short stature
- Short neck , low hair line
- Mental retardation
- Hepatosplenomegaly
- Stiff joint.
- Inguinal and umbilical hernia



mucopolysaccharidoses

- Coarse facial features:
 - (depressed nasal bridge, large prominent tongue ,corneal opacity, copious nasal secretion).
- .recurrent chest and ear infection
- Developmental delay mainly by end of 1st Year.
- .Cardiomyopathy and aortic valve regurgitation



mucopolysaccharidoses

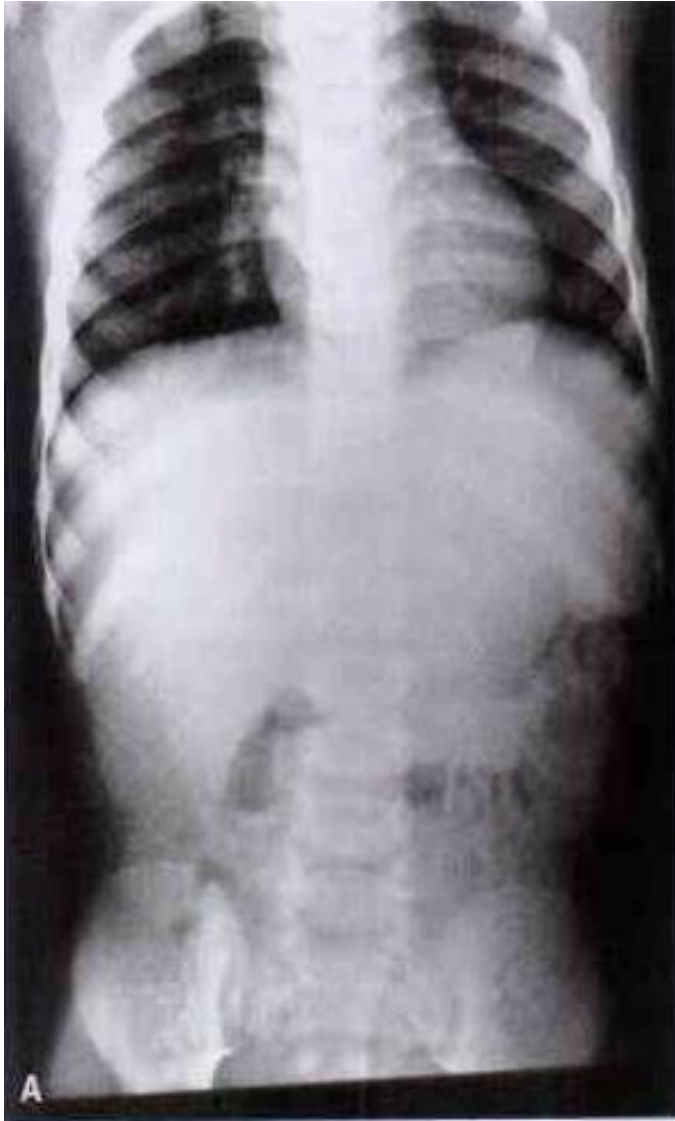
Hurler syndrome:(MPS I) (cont.)

Diagnosis:

- 1.clinical examination
- 2.heparan and dermatan sulphate in urine.
- 3.enzyme assay in the WBC or fibroblast.
- 4.radiological changes :
in ribs (oar-rod),
In vertebrae (hook or beaked vertebra mainly in lumbar region),
in fingers (bullet shape).,
Skull(j shape sella turcica,thick calvarium).



mucopolysaccharidoses



mucopolysaccharidoses

Hunter syndrome :

it is the only X linked MPS.

It is due to deficiency in **iduronate 2-sulphatase**.

It resemble Hurler syndrome clinically and radiologically but:

there is **no corneal clouding**

there is hearing defect

It is milder and with slower progression than Hurler syndrome and life expectancy is near 20 years or more.

Diagnosis is by radiological changes and enzyme assay in WBC.