CASE DISCUSSIONS

STORAGE DISORDERS

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1.A 12 year old child was brought to the medical OPD with complaints of constant dribbling of thick mucous from mouth and was not responding to surroundings. The mother of the child reported that the child stopped making developmental progress at age of 2 years and developed coarse facial features.

Skeletal deformities appeared over the next year, and the child regressed to a vegetative state by age of 10 years.

A complete urine analysis was done and that revealed the presence of heparan sulfate and dermatan sulfate.

What is the probable diagnosis of this patient? What is the biochemical basis for these symptoms?

Case discussion:

- The child is suffering from **Hurler's syndrome**
- A type of mucopolysaccharidosis. Inborn errors of glycosaminoglycans
- Degradation cause neurodegradation and physical stigmata
- Described as “gargoylism”
- Glycosaminoglycans are long. Negatively charged, unbranched, heteropolysaccharide chains, generally composed of a repeating disaccharide unit (Acidic sugar-amino sugar)

Mucopolysaccharidosis:

Glycosaminoglycans are degraded by lysosomal hydrolases. A deficiency of one of the hydrolase results in a mucopolysaccharidosis. These are hereditary disorders, in which the glycosaminoglycans accumulate in tissues, causing symptoms such as skeletal and extracellular matrix deformities, and mental retardation.

CASE DETAILS

- Hurler's syndrome:

It is a Mucopolysaccharidosis- I (MPS-I) MPS- I is divided into three subtypes based on severity of symptoms. All three types result from an absence of or insufficient levels of, the enzyme alpha – L-Iduronidase. MPS- I H or Hurler's syndrome is the most severe of the MPS-I subtypes. The other two types are MPS-I S or Scheie syndrome and MPS- I H-S or Hyrler-Scheie syndrome.

Basic defect:

- There is deficiency of **L-Iduronidase** enzyme.
- This enzyme removes Iduronic acid from the chain and then subsequently, the other residues are removed by the specific enzymes.
- In its deficiency degradation of dermatan sulfate and heparan sulfate is affected.
- These GAGs (Glycosaminoglycans) get accumulated in the tissues producing a variety of symptoms characteristic of this disease.
- These GAGs are also excreted excessively in urine.

- Inheritance:

This disease is autosomal recessive in nature

- Frequency:

Approximately 1 in 150,000 infants are affected.

- Clinical manifestations:

The condition is marked by progressive deterioration, hepatosplenomegaly, dwarfism and gargoyle-like faces. There is a progressive mental retardation, with death frequently occurring by the age of 10 years.

- Newborn infants with this defect appear normal at birth, developmental delay is evident by the end of the first year, and patients usually stop developing betweeen ages 2 and 4. this is followed by progressive mental decline and loss of physical skills.

- Language may be limited due to hearing loss and an enlarged tongue.
- Affected children may be large at birth and appear normal but may have inguinal or umbilical hernias.
- Growth in height may be initially faster than normal, then begins to slow before the end of the first year and often ends around age 3.
- Many children develop a short body trunk and a maximum stature of less than 4 feet.
- Distinct facial features (including flat face, depressed nasal bridge, and bulging forehead) become more evident in the second year (figure- 1) by age 2, the ribs have widened and are oar-shaped.

- Carpal tunnel syndrome (or similar compression of nerves elsewhere in the body) and restricted joint movement are common.
- The children slowly develop corneal clouding and a conductive hearing loss is also present.
- The liver, spleen and heart are often enlarged.
- Children may experience noisy breathing and recurring upper respiratory tract and ear infections.
- Feeding may be difficult for some children and many experience periodic bowel problems.
- Children with Hurler syndrome often die before age 10 from obstructive airway disease, respiratory infections, or cardiac complications.

Diagnosis often can be made through clinical examination and laboratory tests.

1. Urine test, which shows the excessive excretion of Heparan and dermatan sulfate. Cetyl trimethyl ammonium bromide test is undertaken to confirm the presence of gylcosaminoglycans in urine (The basis of most urinary GAG screening tests is the binding of an flocculating agent to the acidic GAG macromolecules to give a visible reaction)

2. Absence of lysosomal alpha-L-Iduronidase (in cultured fibroblasts).

3. Culture of cells from amniotic fluid obtained by amniocentesis for enzyme testing (prenatal testing).

4. X-ray of spine and chest. Prenatal diagnosis using amniocentesis and chorionic villus sampling can verify if a fetus either carries a copy of the defective gene or is affected with the disorder.

Genetic counseling can help parents who have a family history of the mucopolysaccharidosis determine if they are carrying the mutated gene that causes the disorders.

- Treatment:

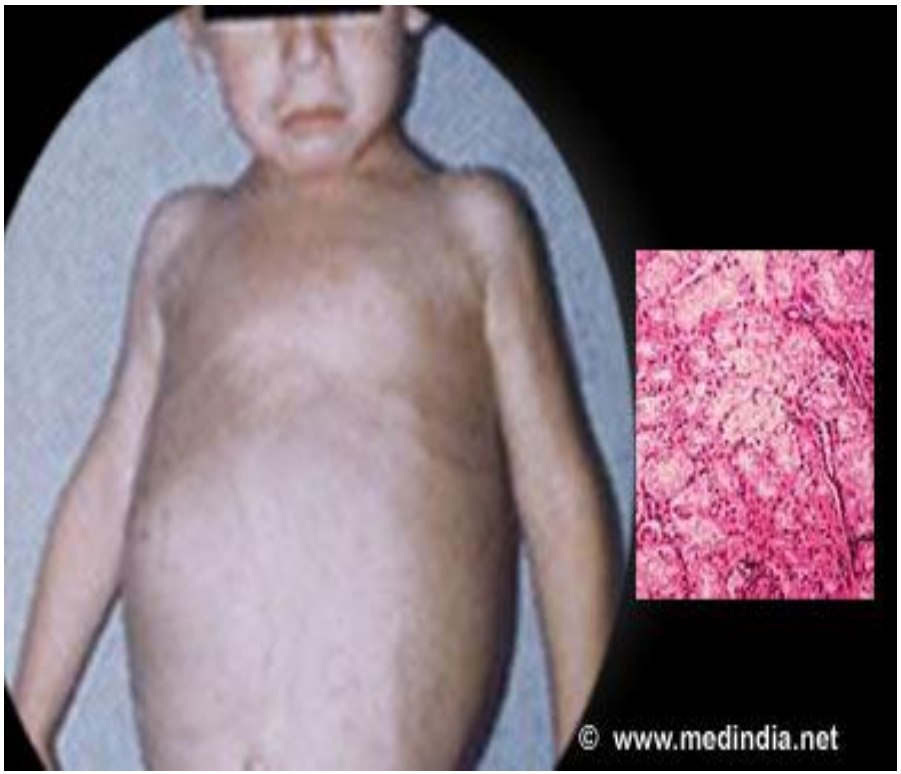
This disease can be treated by bone marrow transplantation (BMT) and Umbilical cord blood transplantation (UCBT) preferably before the age of 18 months. Abnormal physical characteristics, except for those affecting the skeleton and eyes, can be improved, and neurologic degeneration can often be halted.

Gene therapy trials are also going on as a permanent cure for this syndrome. Enzyme replacement therapies are currently in use they have proven useful in reducing non-neurological symptoms and pain.

- Scheie syndrome:

This mild form of MPS- I is characterized by joint stiffness, aortic valve disease, corneal clouding, and few other somatic features. Onset of significant symptoms is usually after the age of 5 years, with diagnosis made between 10 and 20 years. Patients with scheie syndrome have normal intelligence and stature but have significant joint and ocular involvement.

2. The patient was a 8 year-old girl who had a grossly enlarged abdomen. She had a history of frequent episodes of weakness, sweating and pallor that were eliminated by eating. Her development had been slow: she sat at the age of 1 year , walked unassisted at the age of 2 years, and was doing poorly in the school.



Physical examination revealed normal blood pressure, temperature and a normal pulse rate but a subnormal weight . The liver was enlarged, firm and was descended in to pelvis. The spleen was not palpable, not were the kidneys. The remainder of the physical examination was within the normal limits.

- Laboratory investigation report revealed, low blood glucose, low pH, high lactate, triglycerides, ketones and high free fatty acids. The liver biopsy revealed high glycogen content. Hepatic glycogen structure was normal.

What is the probable diagnosis?What is the possible treatment for this patient?

Case details:

The girl is suffering from **Von Gierke's Disease**. The clinical picture, biochemical findings, hypoglycemia and increased hepatic glycogen stores are all characteristic of von Gierke's disease.

- Von Gierke's disease:

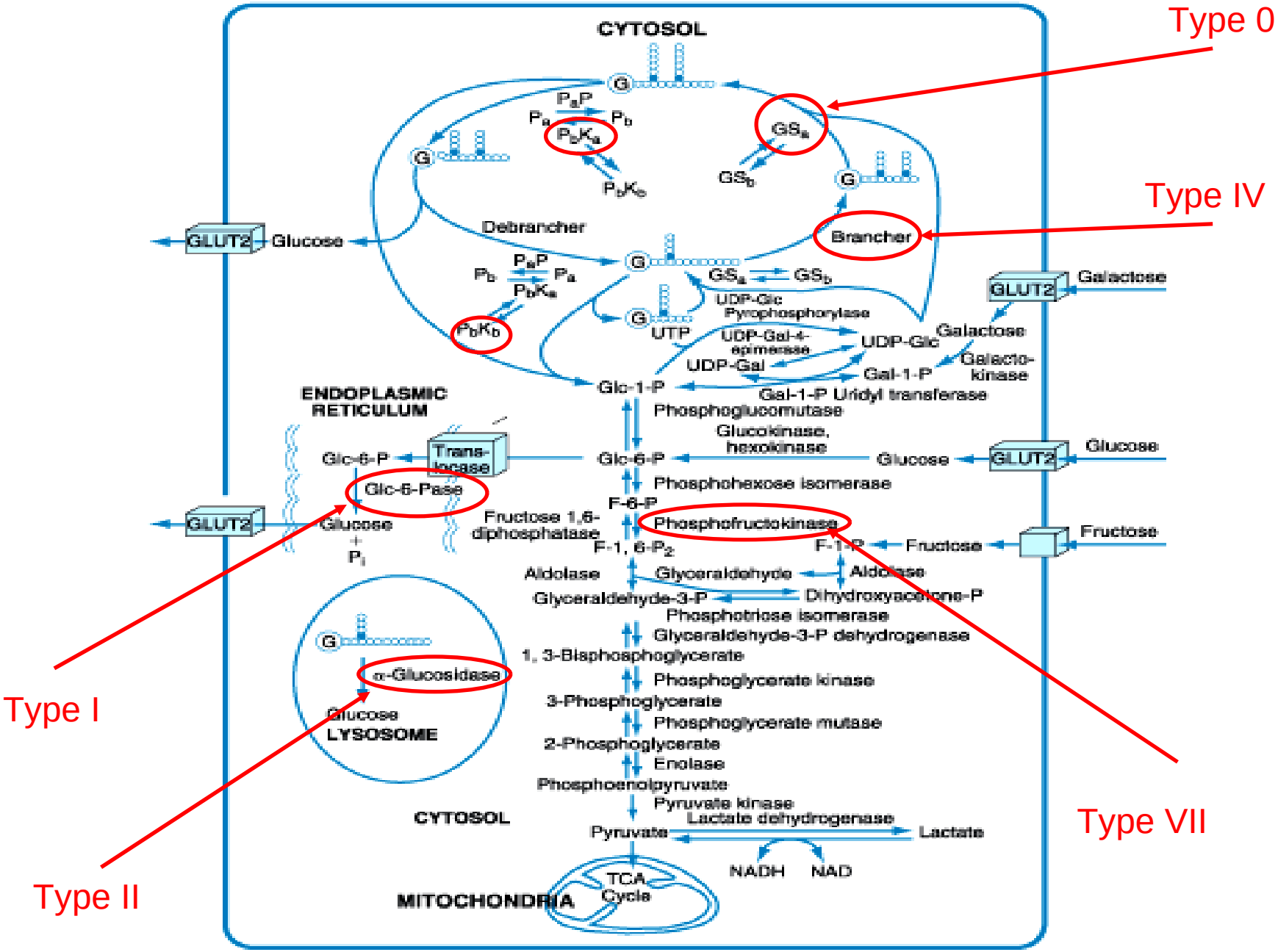
Glycogen storage disease (GSD) Type- I, is also known as von Gierke's disease or hepatorenal glycogenesis.

Type I Glycogen Storage Disease – GSD Type I

Synonyms: von Gierkes disease; Hepatorenal Glycogenosis; Type I Glycogenosis; Glucose-6-Phosphatase Deficiency Glycogen Storage Disease

Type I Glycogen Storage Disease accounts for about 25% of all cases of GSD diagnosed in the USA and in Europe and has an estimated incidence of about 1 in 100,000 live births.

GLYCOGEN STORAGE DISEASES



In Type I Glycogen Storage Disease (GSD I), the most frequent first symptoms include an enlarged liver and low blood sugar (hypoglycemia). After we eat, excess glucose is stored as glycogen mostly in the liver to be used later when we are fasting (not eating for 3-4 hours) to maintain normal glucose levels in our body. In GSD I, the metabolic problem is centered in the liver because the enzyme needed to release glucose from glycogen is missing.

Individuals with Type I Glycogen Storage Disease are unable to release glucose from glycogen mainly in the liver (see What is a Glycogen Storage Disease?). They cannot maintain their blood glucose (sugar) levels and within a few hours after eating they will develop hypoglycemia (low blood sugar).

The low levels of glucose in the blood of these individuals often result in chronic hunger, fatigue, and irritability. These symptoms are especially noticeable in infants.

Since people with Type I GSD are able to store glucose as glycogen but not able to release it normally, with time the stores of glycogen build up in the liver causing the liver to swell **(hepatomegaly**)

. Levels of hormones, lactic acid, triglycerides, lipids (fats), uric acid and other by-products of metabolism increase in the blood as the body tries to raise blood sugar.

Fats get stored in the liver along with the glycogen, which leads to the enlargement of the liver. The liver does its many other functions normally, and there is not usually any evidence of liver failure. The kidneys are also enlarged due to increased glycogen storage

The treatments of Type I Glycogen Storage Disease are aimed at correcting the metabolic changes in the body and promoting growth and development. Current treatments consist of providing small, frequent feedings during the day. Most agree that fructose and galactose should be restricted, but the degree of restriction is still debated.

COMPLICATIONS

Patients with Type I Glycogen Storage Disease may develop benign tumors in the liver called hepatic adenomas. Renal (kidney) disease is another complication in GSD I patients, and most patients with type I glycogen storage disease older than age 20 yr have proteinuria (proteins excreted in urine). Many also have hypertension (high blood pressure), and kidney stones, among other changes in kidney functions, require dialysis and eventually kidney transplantation.Other complications can include pulmonary hypertension, radiographic (X-ray) evidence of osteopenia (weak bones), and fractures.

- Laboratory investigations:

Glycogen storage disease (GSD) Type-I: serum glucose and blood pH levels are frequently decreased, while the serum lactate, uric acid, triglyceride, and cholesterol levels are elevated. Urea and creatinine levels might be elevated when renal function is impaired. The following laboratory values should be obtained:

- Serum glucose and electrolyte levels (Higher anion gap may suggest lactic acidosis).
- Serum lactate level
- Blood pH
- Serum uric acid level
- Serum triglyceride and cholesterol levels
- Gamma glutamyltransferase level

CBC and differential (e.g.anemia, leucopenia, neutropenia)

- Coagulation-bleeding and clotting time
- urinalysis for aminoaciduria, proteinuria, and microalbuminuria in older patients
- Urinary excretion levels of uric acid and calcium
- Serum alkaline phosphatase, calcium, phosphorus, urea and creatinine levels

- Imaging studies:

- In GSD type-I, liver and kidney ultrasonography should be performed for follow-up of organomegaly and detection of hepatic adenomas and nephrocalcinosis.

- Abdominal CT scanning or MRI is advised whenever the lesions are large, poorly defined or are growing rapidly.

- Other tests:

- Glucagon and epinephrine tests do not cause a rise in glucose levels, but plasma levels of lactic acid are raised.

- Ovally administered galactose and fructose (1.75g/kg) do not increase glucose levels, but plasma lactic acid levels do increase.

Glucose tolerance test (1.75g/kg PO) progressively lowers lactic acid levels over several hours after the administration of glucose.

- For diagnostic purposes, 13C nuclear magnetic resonance spectroscopy may be used for enzyme function assessment.
- Definitive diagnosis requires determination of G6Pase activity in fresh and frozen liver tissue specimens and or DNA based analysis. When assaying for translocases, an open surgical liver biopsy is needed for sampling an adequate tissue specimen.

- Treatment:

Most children with GSD type-I are admitted to the hospital to make a final diagnosis, to manage hepatomegaly or hypoglycemia.

- Because no specific treatment is available, symptomatic therapy is very important.

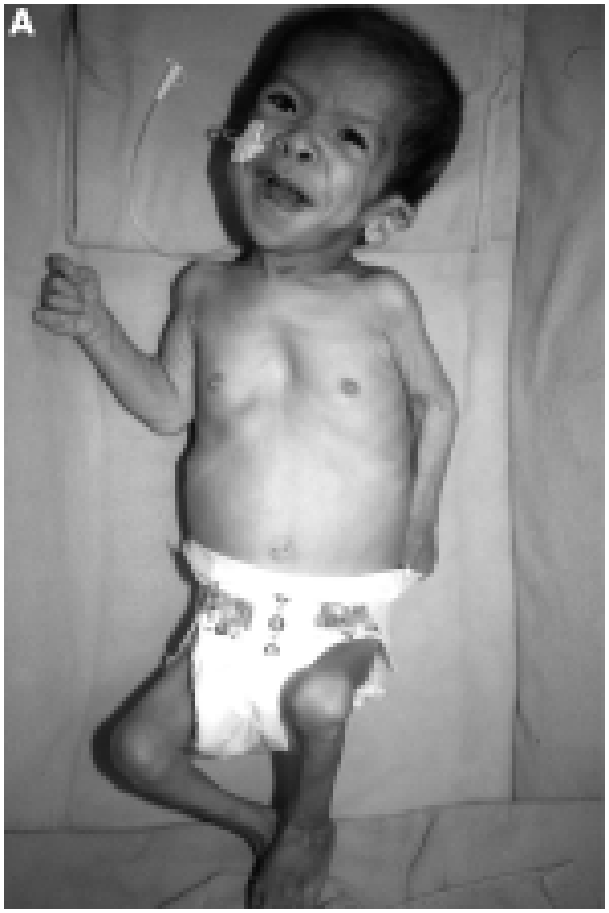
-Diet: The primary goal of treatment is to correct hypoglycemia and maintain a normoglycemic state. The normoglycemic state can be achieved with overnight nasogastric infusion of glucose, parenteral nutrition, or per oral administration of raw cornstarch. Glucose molecules are continuously released by hydrolysis of raw cornstarch in the digestive tract over 4 hours following its intake.

- Clinical pearls:

1. Glycogen storage disease (GSD) type-I is divided into GSD type -Ia caused by G6Pase deficiency and GSD type-Ib resulting from deficiency of a specific translocase T1.
2. The earliest signs of the disease may develop shortly after birth and are caused by hypoglycemia and lactic acidosis.
3. Serum glucose and blood pH levels are frequently decreased, while the serum lactate, uric acid, triglyceride, and cholesterol levels are elevated. Urea and creatinine levels might be elevated when renal function is impaired.
4. the primary goal of treatment is to correct hypoglycemia and maintain a normoglycemic state.
5. Long-term complications encompass growth retardtion, hepatic adenomas with a high rate of malignant change, xanthomas, gout, and glomerulosclerosis.

CASE DESCRIPTION

3. A female baby was delivered normally after an uncomplicated pregnancy. At the time of the infant's second immunization, she became fussy and was seen by a pediatrician, where examination revealed an enlarged liver and myopathy. The baby was referred to a gastroenterologist and later diagnosed to have metabolic disorder.



Type III Glycogen Storage Disease - GSD Type III

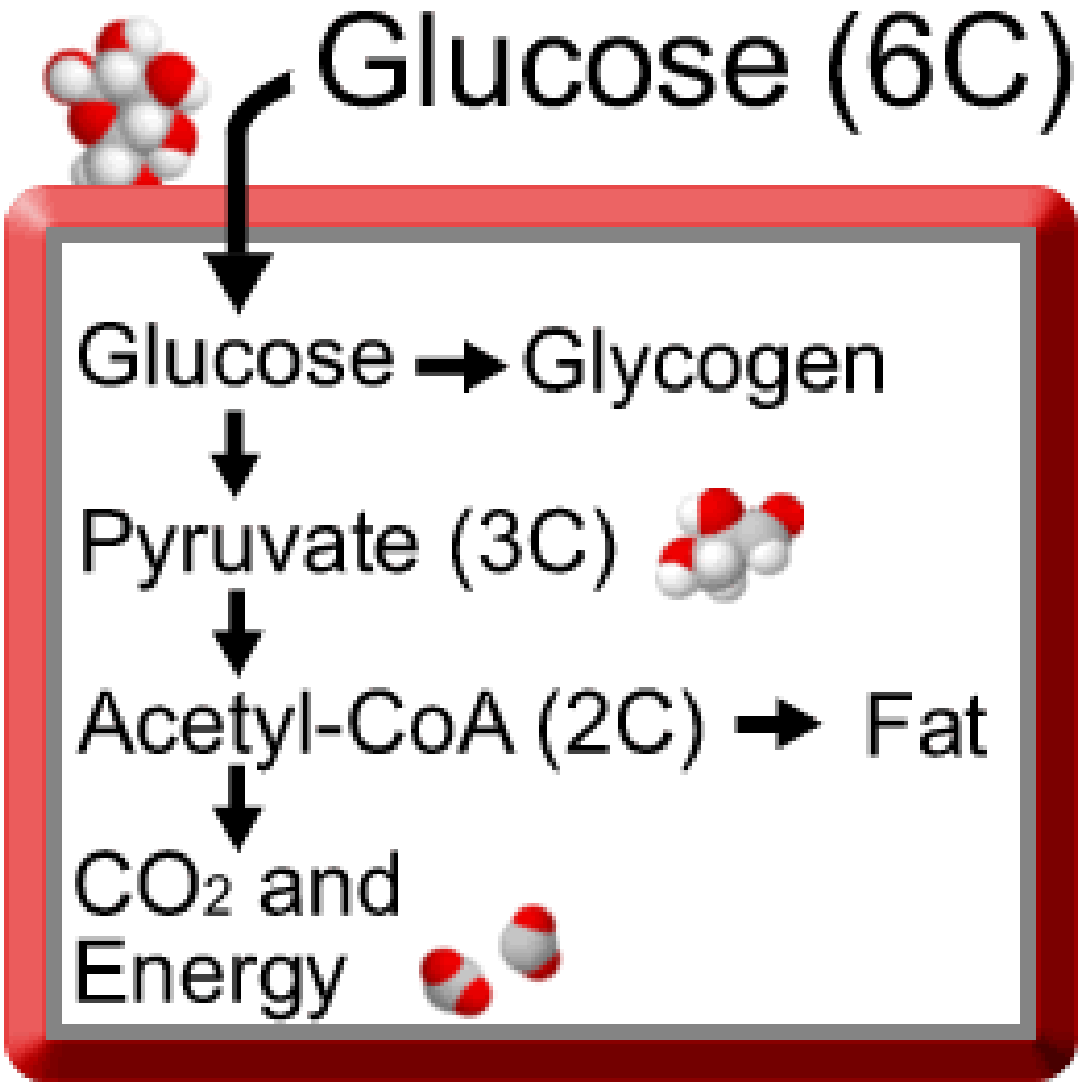
Synonyms: Debrancher Deficiency; Cori Disease; Forbes Disease; Limit Dextrinosis

GSD type III is caused by a deficiency of glycogen debrancher enzyme (GDE) activity. Glycogen debranching enzyme along with another enzyme, phosphorylase, helps break down the branches of glycogen to release free glucose. Deficiency of GDE results in glycogen with short outer chains in liver, muscle, and heart tissues. The abnormal glycogen is not soluble and causes damage to tissues where it collects (liver and/or muscle).

GLYCOGEN STORAGE DISEASE TYPE- IIIB

- Deficiency of debranching enzyme in the liver needed to completely break down glycogen to glucose
- Hepatomegaly and hepatic symptoms
  - Usually subside with age
- Hypoglycemia, hyperlipidemia, and elevated liver transaminases occur in children

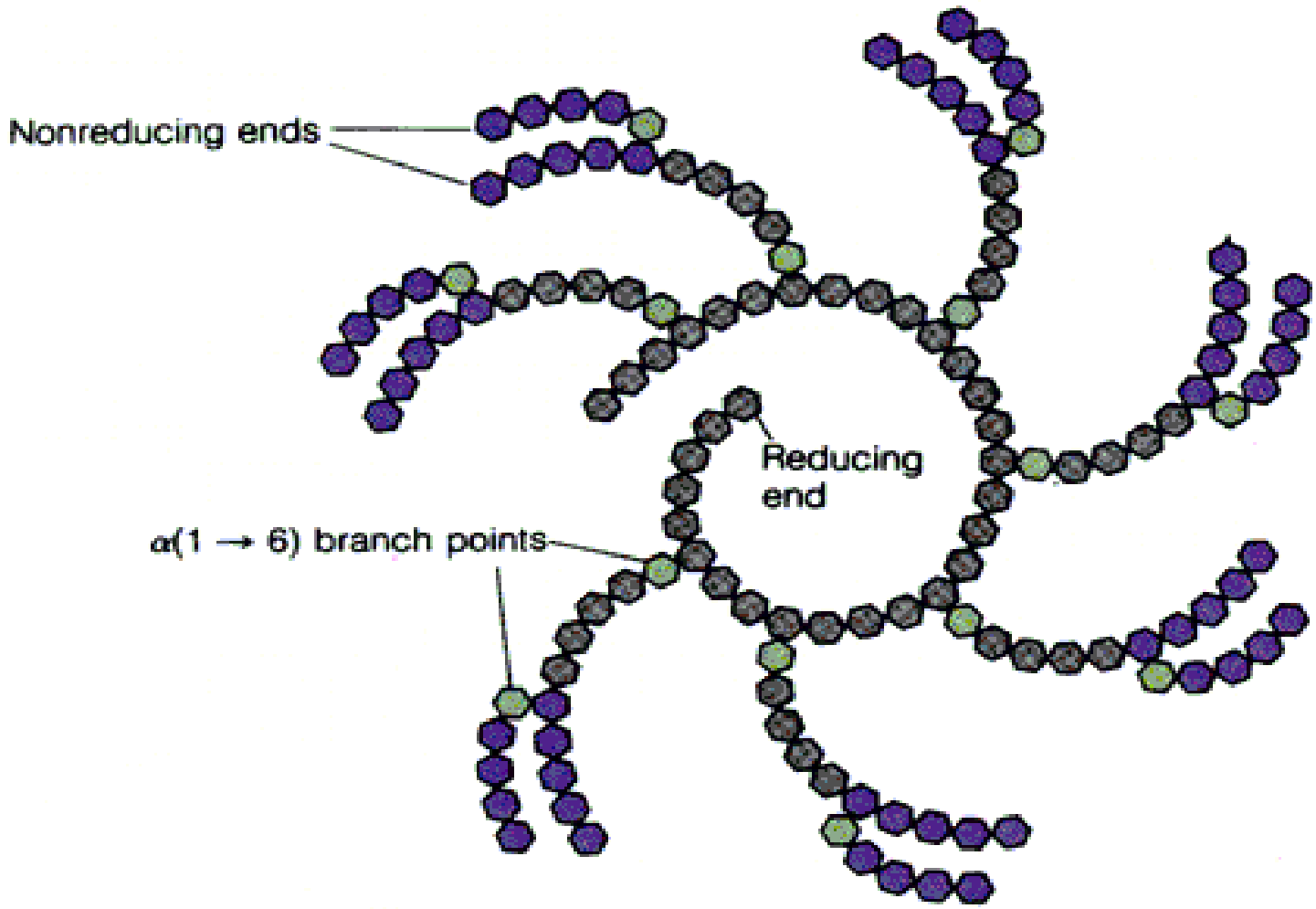
GLYCOGEN STORAGE DISEASE

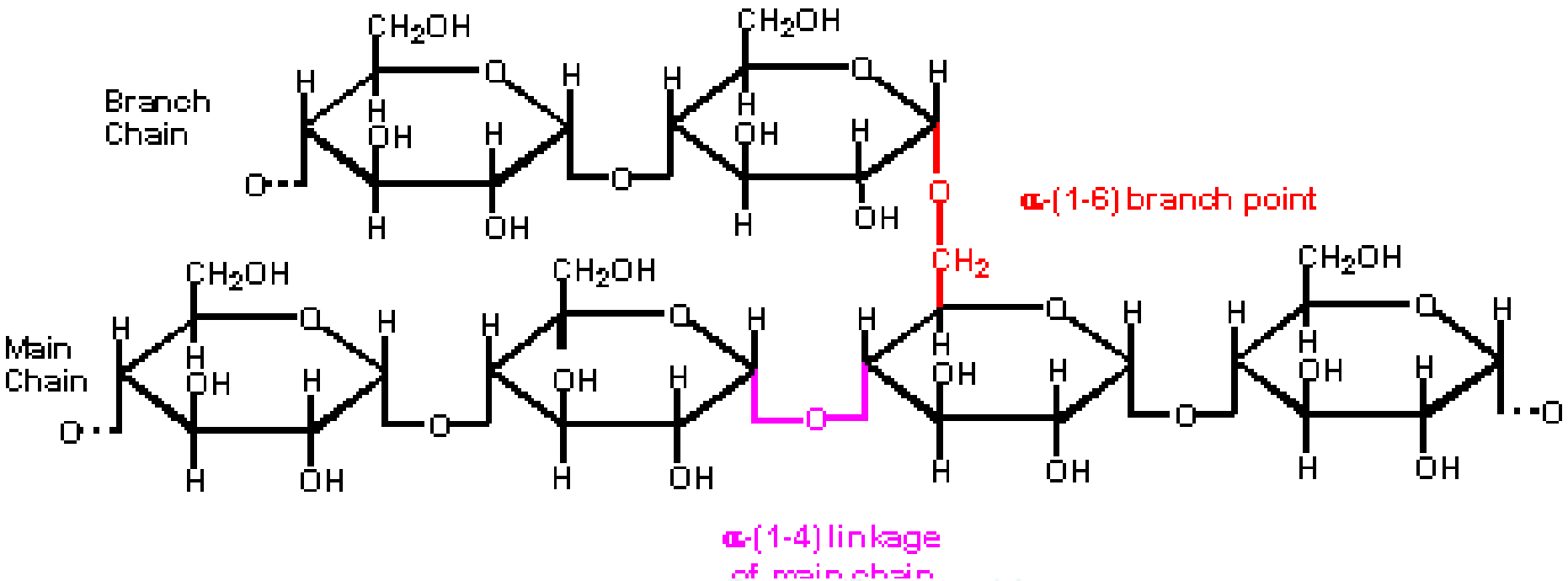


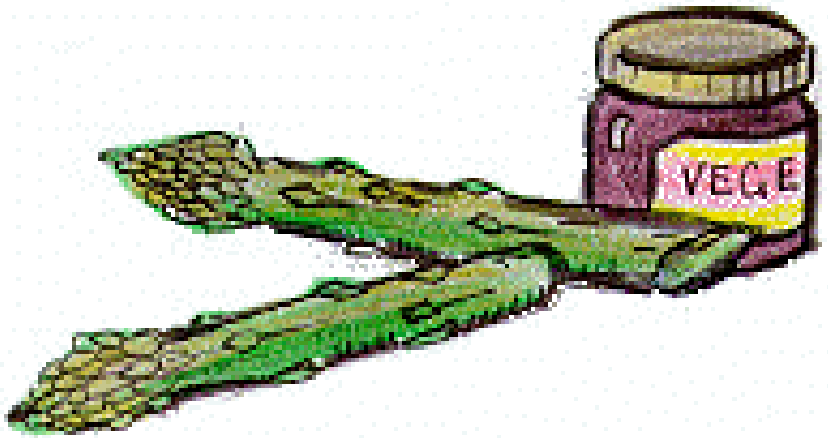
GLYCOGENOSES

Disorder	Affected Tissue	Enzyme	Inheritance	Gene	
Type 0	Liver	Glycogen synthase	AR	*GYS2*[125]	
Type IA	Liver, kidney, intestine	Glucose-6-phosphatase	AR	*G6PC*[96]	
Type IB	Liver	Glucose-6-phosphate transporter (T1)	AR	*G6PTI*[57][104]	
Type IC	Liver	Phosphate transporter	AR		
Type IIIA	Liver, muschle, heart	Glycogen debranching enzyme	AR	*AGL*	
Type IIIB	Liver	Glycogen debranching enzyme	AR	*AGL*	
Type IV	Liver	Glycogen phosphorylase	AR	*PYGL*[26]	
Type IX	Liver, erythrocytes, leukocytes	Liver isoform of -subunit of liver and muscle phosphorylase kinase	X-Linked	*PHKA2*	
	Liver, muscle, erythrocytes, leukocytes	B-subunit of liver and muscle PK	AR	*PHKB*	
	Liver	Testis/liver isoform of γ-subunit of PK	AR	*PHKG2*	

GLYCOGEN

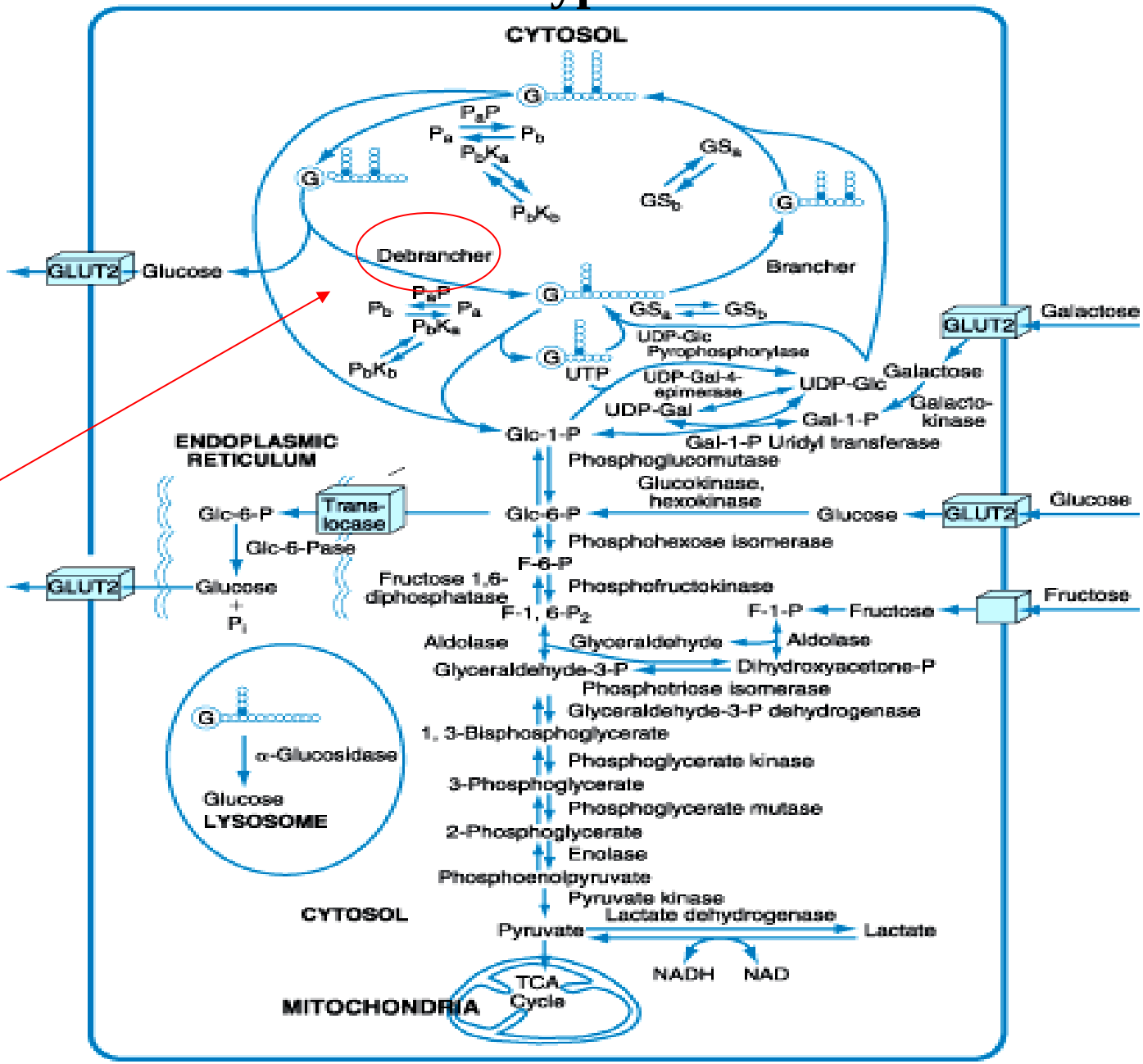



Branch Chain
Main Chain
α-(1-6) branch point
α-(1-4) linkage


VEGE

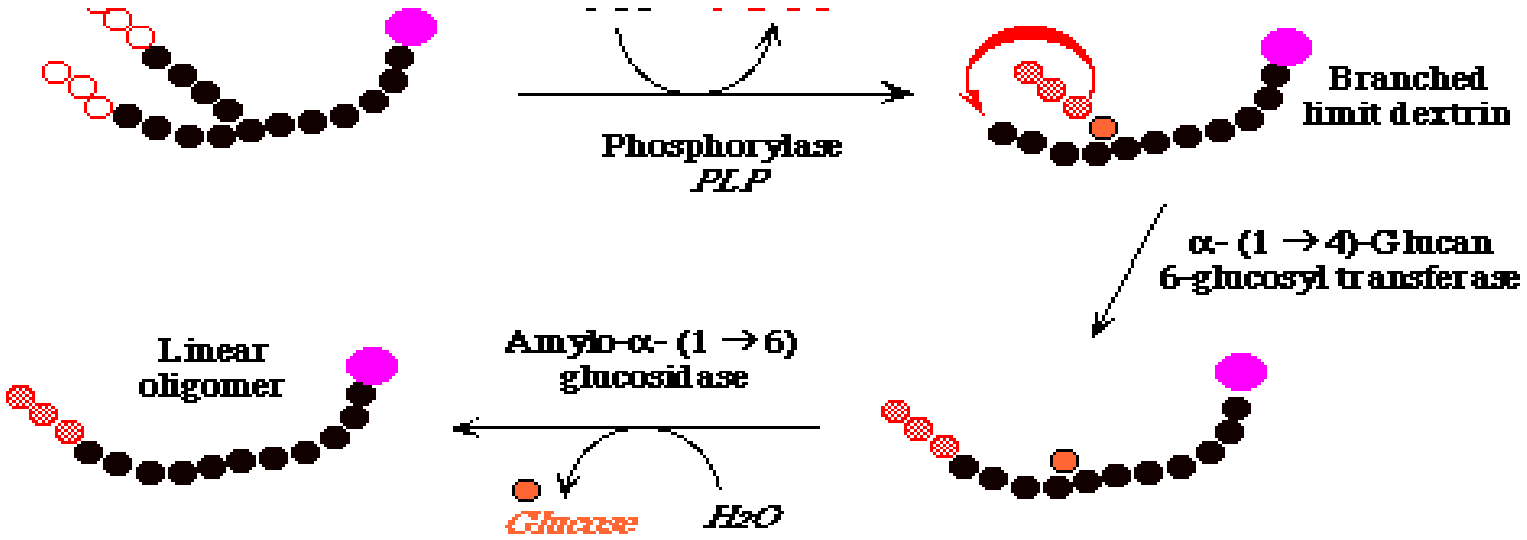
GSD Type III

Type III



DEBRANCHING ENZYME

- Amylo-1,6-glucosidase
  - Isoenzymes in liver, muscle and heart
  - Transferase function
  - Hydrolytic function



GENETIC HYPOTHESIS

- The two forms of GSD Type III are caused by different mutations in the same structural Glycogen Debranching Enzyme gene

CLINICAL FEATURES

Common presentation

- Hepatomegaly and fibrosis in childhood
- Fasting hypoglycemia (40-50 mg/dl)
- Hyperlipidemia
- Growth retardation
- Elevated serum transaminase levels

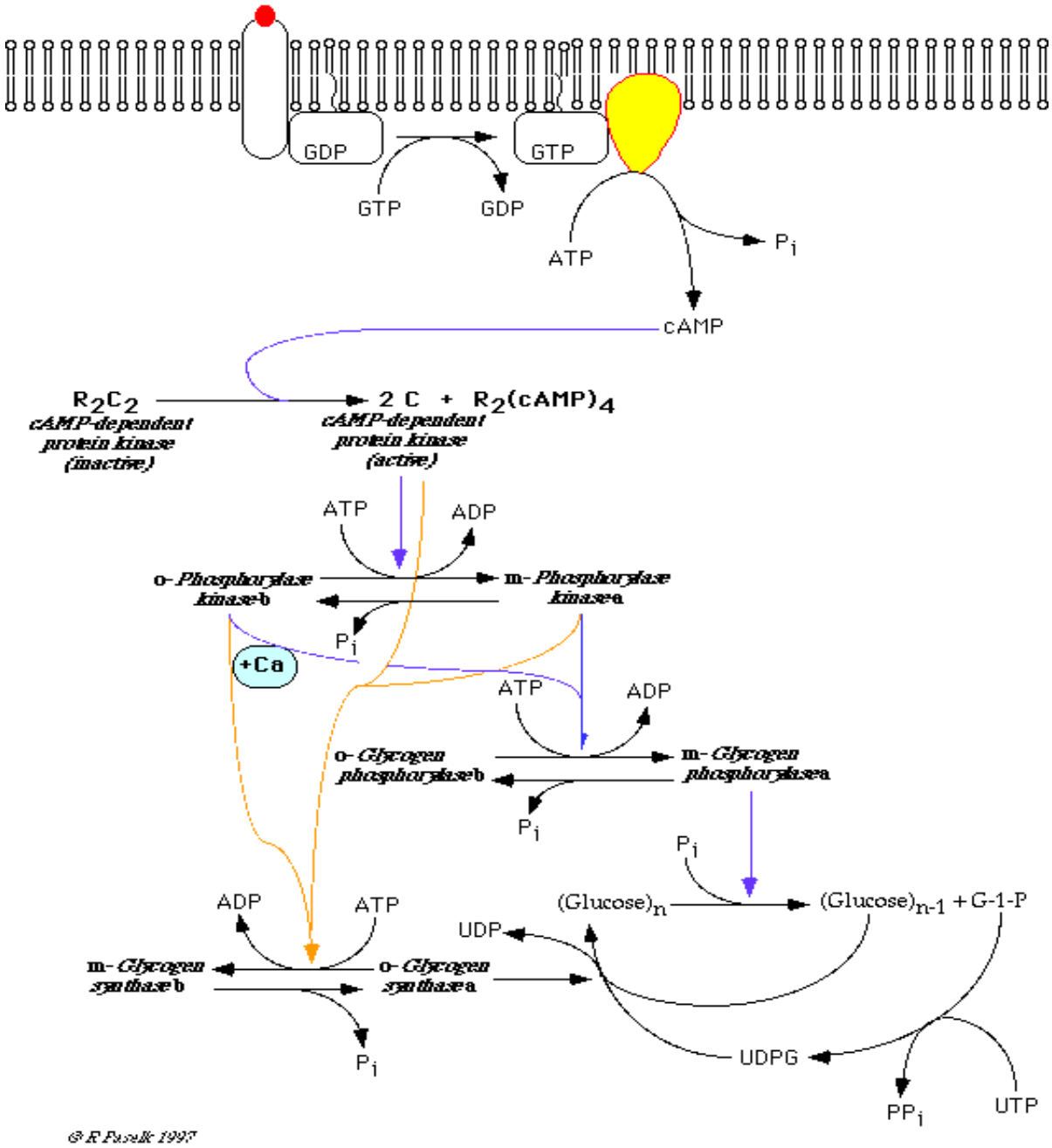
(aspartate aminotransferase and alanine aminotransferase > 500 units/ml)

One of the enzymes that helps break glycogen down into glucose in the muscles is called debranching enzyme. Individuals with GSD III either have a defective enzyme or lack a sufficient amount of this important enzyme. As a result, glycogen is not broken down completely and accumulates in the liver and/or muscle tissue. Accumulation of abnormal glycogen in the liver tissue causes it to become enlarged and not function properly.

During early years of infancy and childhood, the disease may present clinically just like GSD I: small stature, large liver, poor muscle tone (hypotonia) and hypoglycemia. Some liver symptoms (enlarged liver) often improve with age and may disappear after puberty. However, in some patients liver cirrhosis (damage to liver cells) can occur due to accumulation of abnormal glycogen. Children with GSD III are often first diagnosed because they have swollen (distended) abdomens (belly) due to a very large liver. Some children have problems with low blood sugars when fasting (not eating for 4 hours) but this is not as common or as severe as in GSD I.

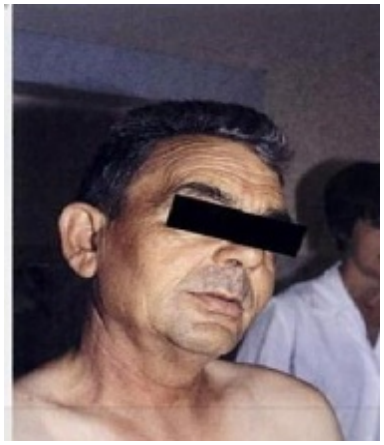
Growth may be delayed or slow during childhood but most individuals reach a normal adult height. Muscle weakness (GSD IIIa) is commonly present in childhood and can, at times, become severe in adult age (requiring use of a wheel chair for mobility by 50-60 years). Although the enzyme defect does not go away, the liver often returns to a smaller size at puberty

Glycogen Control



Elevated glycogen content is present in liver and muscle cells. A definite diagnosis and sub-typing (determining IIIa versus IIIb type) requires either liver biopsies or DNA based genetic testing. Biopsy of the liver shows inflammatory changes (swollen liver cells) with great elevations of abnormal-structured glycogen content and a deficiency of the debrancher enzyme (GDE). In GSD IIIa, biopsy of muscle and liver shows an accumulation of abnormal-structured glycogen and deficiency of debrancher enzyme. Hypoglycemia (low blood sugar) can be controlled by frequent meals high in carbohydrates.

4.A 47-year-old man presents with fatigue. He also complains of persistent aching joints. He has had the symptoms for several years. He has no other health complaints. He also reports a past history of excess alcohol use .He has seen two other doctors for his joint pain and fatigue. He has been advised to exercise regularly and take non-steroidal anti-inflammatory medications for his joint symptoms, but these measures have not provided symptomatic relief. He has not had any chest pain or shortness of breath. He denies symptoms of depression such as anhedonia, low self-esteem, or changes in appetite or sleep patterns.



Mild hepatomegaly, normal thyroid,cardic,lung and mental functions Stool cards are negative, TSH is 2.0, hematocrit is 45, and AST and ALT are mildly elevated.**What is probable diagnosis?**

IRON STORAGE DISEASE

There are many forms of iron storage disease, some hereditary and some acquired.

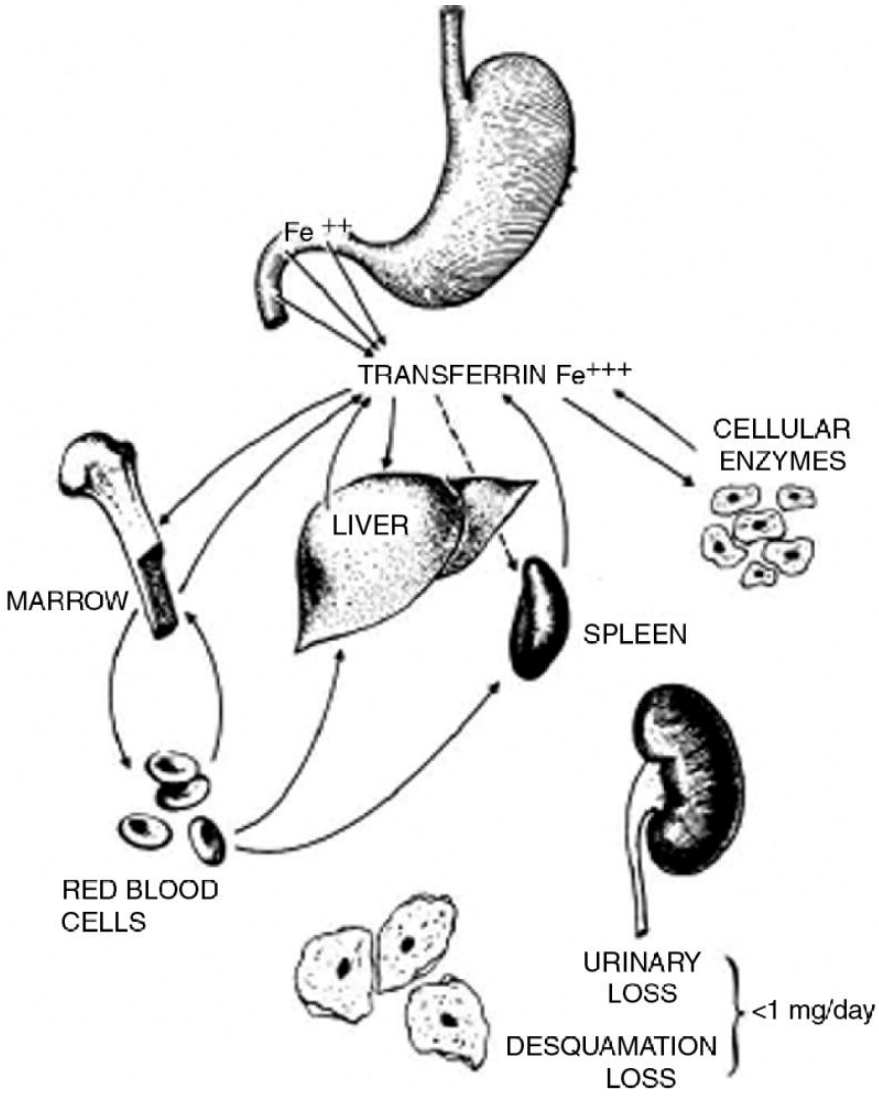
The most common of the hereditary forms is HFE-associated **hemochromatosis**, and it is this disorder that is the main focus of this presentation.

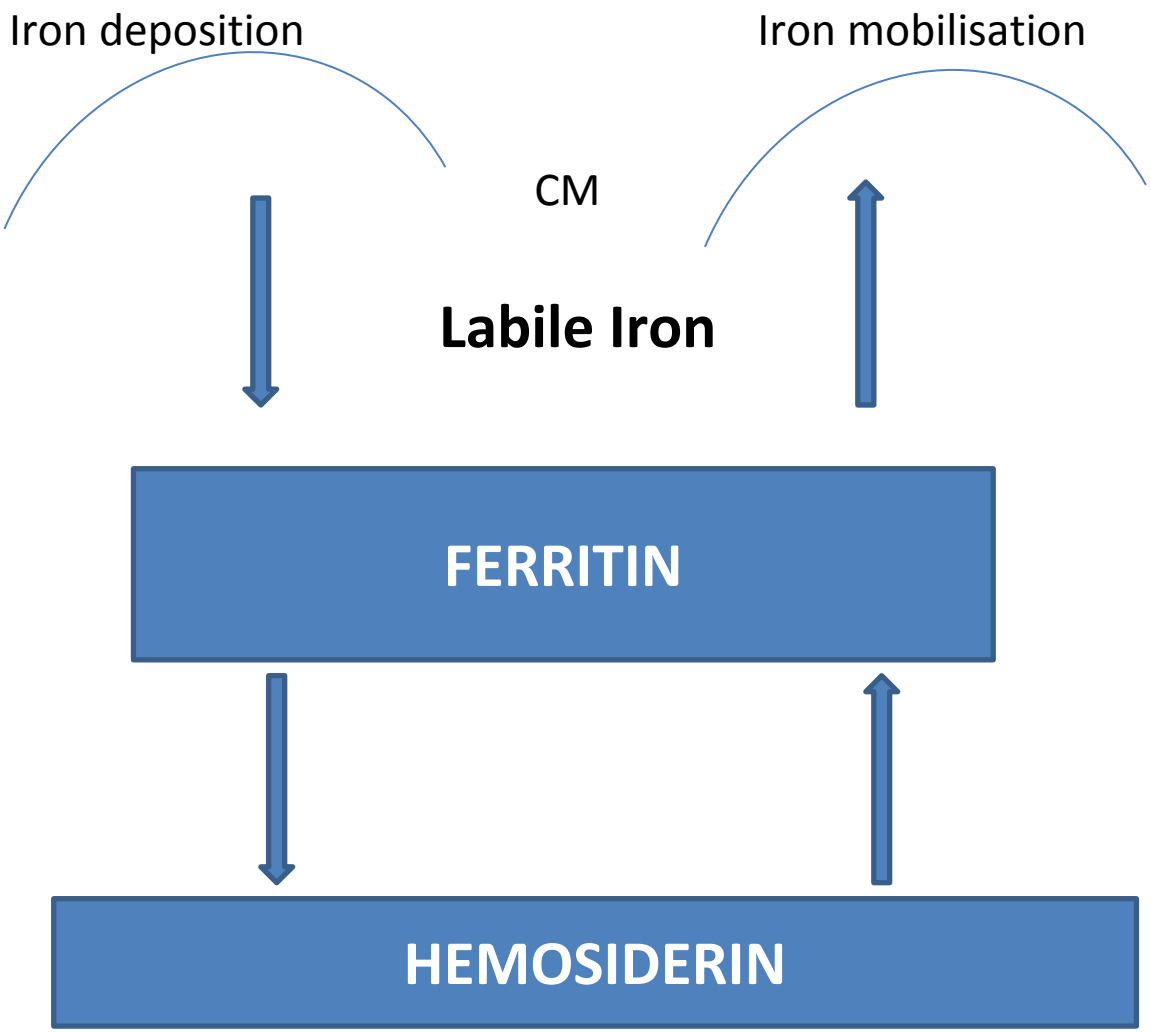
The body iron content is regulated by controlling absorption, and studies in the past decade have clarified, in part, how this regulation functions.

A 25 amino acid peptide **hepcidin** is upregulated by iron and by inflammation, and it inhibits iron absorption and traps iron in macrophages by binding to and causing degradation of the iron transport protein **ferroportin**. Most forms of hemochromatosis results from dysregulation of hepcidin or defects of hepcidin or ferroportin themselves.

Although small amounts of iron are lost from the body, chiefly through desquamation of cells, there is no regulated iron excretion. Rather, iron metabolism is a closed circuit in which the iron that the body has captured is reutilized (fig).

Hemochromatosis is characterized by excessive accumulation of iron in the body. Thus, it is a state in which the absorption of iron is dysregulated, and more iron is absorbed than is needed.





Iron pathways of ferritin and hemosiderin in iron deposition and mobilization

But how does the body “know” how much iron to absorb? Over the past 60 years attempts have been made to explain the regulation of iron absorption through the existence of a “mucosal block” , a flawed concept based on flawed data,as described in detail elsewhere . What the experimental data actually show is not the existence of a “ blocking ” of iron absorption after an initial dose of iron has been given, but rather “mucosal intelligence”.

Beutler E. History of iron in Medicine. Blood Cells Mol Dis. 2002;29:297–308.

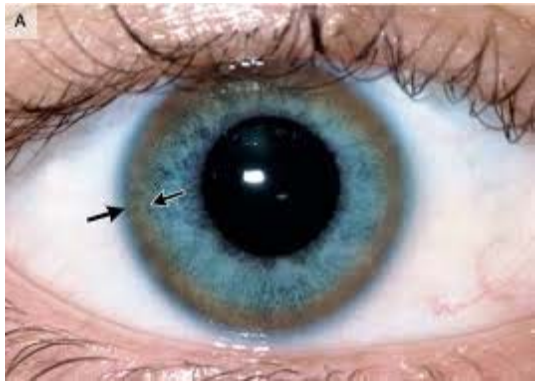
Iron-deficiency results in enhanced iron absorption and iron overload decreases iron absorption. Other factors that modulate iron absorption include anemia, which increases iron absorption probably largely through the enhanced erythropoiesis that is generally present, inflammation, which decreases iron absorption, and hypoxia which increases iron absorption.

Total iron binding capacity and transferrin receptor are helpful for the diagnosis of iron deficiency states. Body surface monitoring methods such as dual-energy X-ray CT, superconduction quantum interference device susceptometry (SQUID), and magnetic resonance imaging (MRI)28) were introduced.RIA was a break through.
Genetic studies- patients with the C282Y mutated hemochromatosis (*HFE1)*

Treatment of Iron Overload

The standard treatment for hereditary hemochromatosis is the removal of iron by phlebotomy. The evidence that the iron excess can be removed by this means is quite straightforward.

5.A 17-year-old girl with multiple complaints is brought to the OPD by her parents. Her parents have noticed that she has developed slowly progressive clumsiness over the past 6 months. Additionally, her speech and ability to walk have been deteriorating over several months. There is no history of fever, headache, focal weakness, visual changes, bladder dysfunction, convulsions or trauma. She has had no recent travel and there is no history of animal bites or known toxic exposures.A past history of jaundice that occurred 1 year ago Dark, brown-colored rings are noted around the periphery of the iris and are visible on naked eye examination.Increased TB,ALT,ALP.CBP,ESR normal



WILSONS DISEASE

The unusual dark, brownish rings around the periphery of the irises of this patient are known as Kayser-Fleischer (KF) rings.

This finding, in conjunction with the noted hepatic dysfunction and the hypodense regions in the basal ganglia (ie, caudate nucleus, putamen, and globus pallidus) on the MRI scan of the brain raised suspicion for a diagnosis of Wilson disease.

The serum copper concentration was elevated at 187 µg/dL (29.4 µmoI/L; normal range, 70-150 µg/dL) and the patient was noted to have a low ceruloplasmin level of 12 mg/dL (120 mg/L; normal range, 15-60 mg/dL). A 24-hour urine copper without penicillamine challenge was also markedly elevated at 1708 µg/24 hours (27.3 µmol/24 hours; normal range, 3-35 µg/24 hours).

What is Wilson disease?

Wilson disease is an inherited disorder in which excessive amounts of copper accumulate in the body, particularly in the liver, brain, and eyes. The signs and symptoms of Wilson disease usually first appear between the ages of 6 and 45, but they most often begin during the teenage years. The features of this condition include a combination of liver disease and neurological and psychiatric problems.

What other names do people use for Wilson disease?

- copper storage disease
- hepatolenticular degeneration syndrome
- WD
- Wilson's disease

Wilson disease is a rare disorder that affects approximately 1 in 30,000 individuals.

What genes are related to Wilson disease?

Wilson disease is caused by mutations in the *ATP7B* gene. This gene provides instructions for making a protein called copper-transporting ATPase 2, which plays a role in the transport of copper from the liver to other parts of the body. Copper is necessary for many cellular functions, but it is toxic when present in excessive amounts. The copper-transporting ATPase 2 protein is particularly important for the elimination of excess copper from the body.

A defect causing a decrease in biliary excretion and a decrease in formation and secretion of ceruloplasmin results in decreased copper elimination from the liver. This accumulation of copper progressively damages the organ until it becomes cirrhotic. Once cirrhosis occurs, copper will leak into the plasma and eventually damage other tissues and organs. Patients rarely present with the disease before 6 years of age, but almost 100% of patients will be diagnosed by the age of thirty.

Lab Findings

-Serum ceruloplasmin concentration- the majority of patients will have low serum ceruloplamsin levels. However, in a patient with Kayser- Fleishcer rings, a concentration less than 20 mg/dL confirms the diagnosis.

-Serum copper concentration-the majority of patients will have low serum copper concentrations despite a high total copper body stores.

-Urinary Copper Excretion-when 24 hour excretion of copper is equal or greater than 100mcg, a diagnosis of Wilson's disease can be confirmed.

-Penicillamine Challenge- To increase specificity, Wilson's Disease can be confirmed by administrating a one initial 500 mg dose and a second dose again at 12 hours during a 24 hour copper collection

Patients should avoid foods with a high copper content, such as liver, broccoli, legumes, chocolate, nuts, mushrooms, and shellfish. Drinking water from atypical sources (eg, well water) should be tested for copper concentration and replaced with purified water if greater than 0.2 parts per million of copper are found. Also, patients must avoid most alcohol consumption and potentially hepatotoxic drug therapy.

The patient in this case was started on penicillamine 500 mg 3 times daily (500 mg tid), along with dietary restriction of copper-containing foods

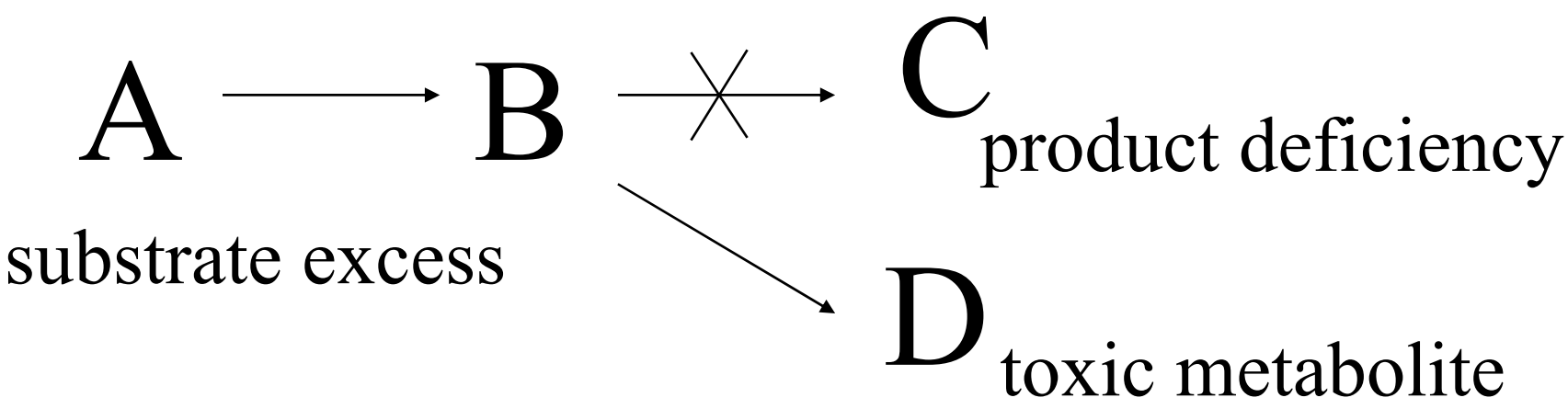
METABOLIC DISEASES

What is a metabolic disease?

- “Inborn errors of metabolism”
- Inborn error : an inherited (i.e. genetic) disorder
- Metabolism : chemical or physical changes undergone by substances in a biological system
- “any disease originating in our chemical individuality”

What is a metabolic disease?

- Garrod's hypothesis



What is a metabolic disease?

- Small molecule disease
  - Carbohydrate
  - Protein
  - Lipid
  - Nucleic Acids
- Organelle disease
  - Lysosomes
  - Mitochondria
  - Peroxisomes
  - Cytoplasm

How do metabolic diseases present ??

- Acute life threatening illness
  - encephalopathy - lethargy, irritability, coma
  - vomiting
  - respiratory distress
- Seizures, Hypertonia
- Hepatomegaly (enlarged liver)
- Hepatic dysfunction / jaundice
- Odour, Dysmorphism, FTT (failure to thrive), Hiccoughs

How do you recognize a metabolic disorder ??

- Index of suspicion
  - eg “with any full-term infant who has no antecedent maternal fever or PROM (premature rupture of the membranes) and who is sick enough to warrant a blood culture or LP, one should proceed with a few simple lab tests.

- Simple laboratory tests
  - Glucose, Electrolytes, Gas, Ketones, BUN (blood urea nitrogen), Creatinine
  - Lactate, Ammonia, Bilirubin, LFT
  - Amino acids, Organic acids, Reducing subst.

Index of suspicion
Family History

- Most IEM's are recessive - a negative family history is not reassuring!
- **CONSANGUINITY,** ethnicity, inbreeding
- neonatal deaths, fetal losses
- maternal family history
  - males - X-linked disorders
  - all - mitochondrial DNA is maternally inherited
- A positive family history may be helpful!

Index of suspicion
History

- **CAN YOU EXPLAIN THE SYMPTOMS?**
- Timing of onset of symptoms
  - after feeds were started?
- Response to therapies

Index of suspicion
Physical examination

- General – dysmorphisms (abnormality in shape or size), ODOUR
- H&N - cataracts, retinitis pigmentosa
- CNS - tone, seizures, tense fontanelle
- Resp - Kussmaul's, tachypnea
- CVS - myocardial dysfunction
- Abdo - HEPATOMEGALY
- Skin - jaundice

Index of suspicion
Laboratory

- ANION GAP METABOLIC ACIDOSIS
- Normal anion gap metabolic acidosis
- Respiratory alkalosis
- Low BUN relative to creatinine
- Hypoglycemia
  - especially with hepatomegaly
  - non-ketotic

A parting thought ...

- Metabolic diseases are individually rare, but as a group are not uncommon.
- There presentations in the neonate are often non-specific at the outset.
- Many are treatable.
- The most difficult step in diagnosis is considering the possibility!

TREATMENT

- Dietary Restriction
- Supplement deficient product
- Stimulate alternate pathway
- Supply vitamin co-factor
- **Organ transplantation(liver,bone marrow,umbilical cord…….)**
- Pharmacological chaperone therapy
- Enzyme replacement therapy
- Gene Therapy

TREATMENT

- Bone marrow transplant
- Enzyme Replacement therapy
- Umbilical cord transplant
- Pharmacological chaperone therapy
- Gene therapy