Inborn Errors of Carbohydrates Metabolism

Part I

١. Definition

- Inborn errors of metabolism are often referred to as **congenital metabolic diseases** or **inherited metabolic diseases**

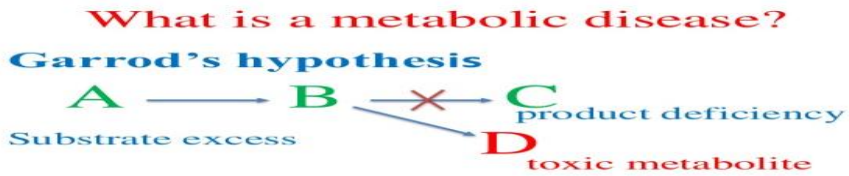
- Inborn errors of metabolism comprise a large class of genetic diseases involving disorders of metabolism

- The majority of these diseases are due to defects of single genes that code for enzymes that facilitate conversion of various substances (substrates) into others (products).

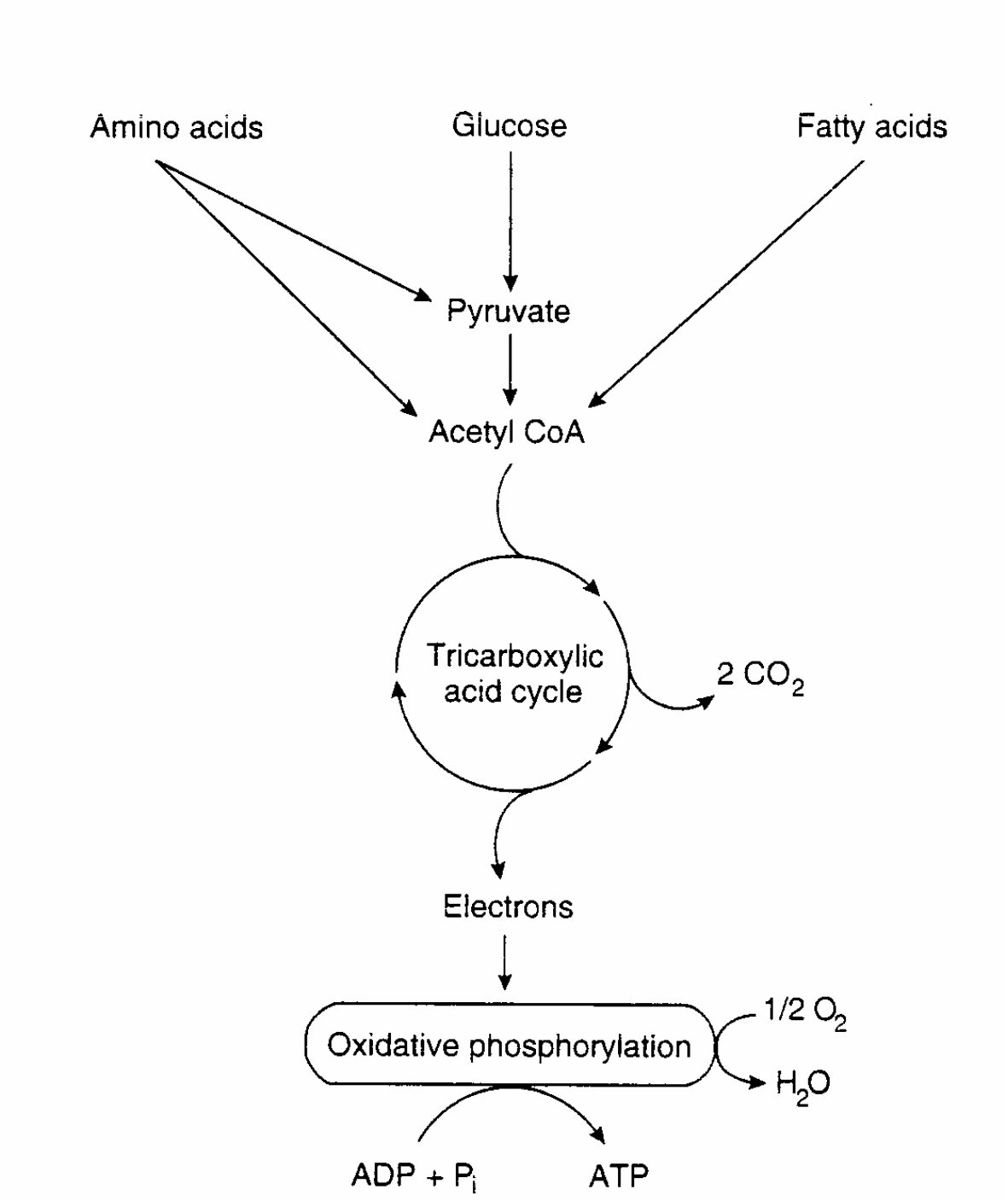
- In most of the disorders, problems arise due to accumulation of substances which are **toxic** or **interfere** with normal function,

- These substances may reduce the ability of body to synthesize essential compounds.

٢. Garrod's hypothesis



٣. Revision of Carbohydrate of Metabolism



۳,۱ Glycolysis

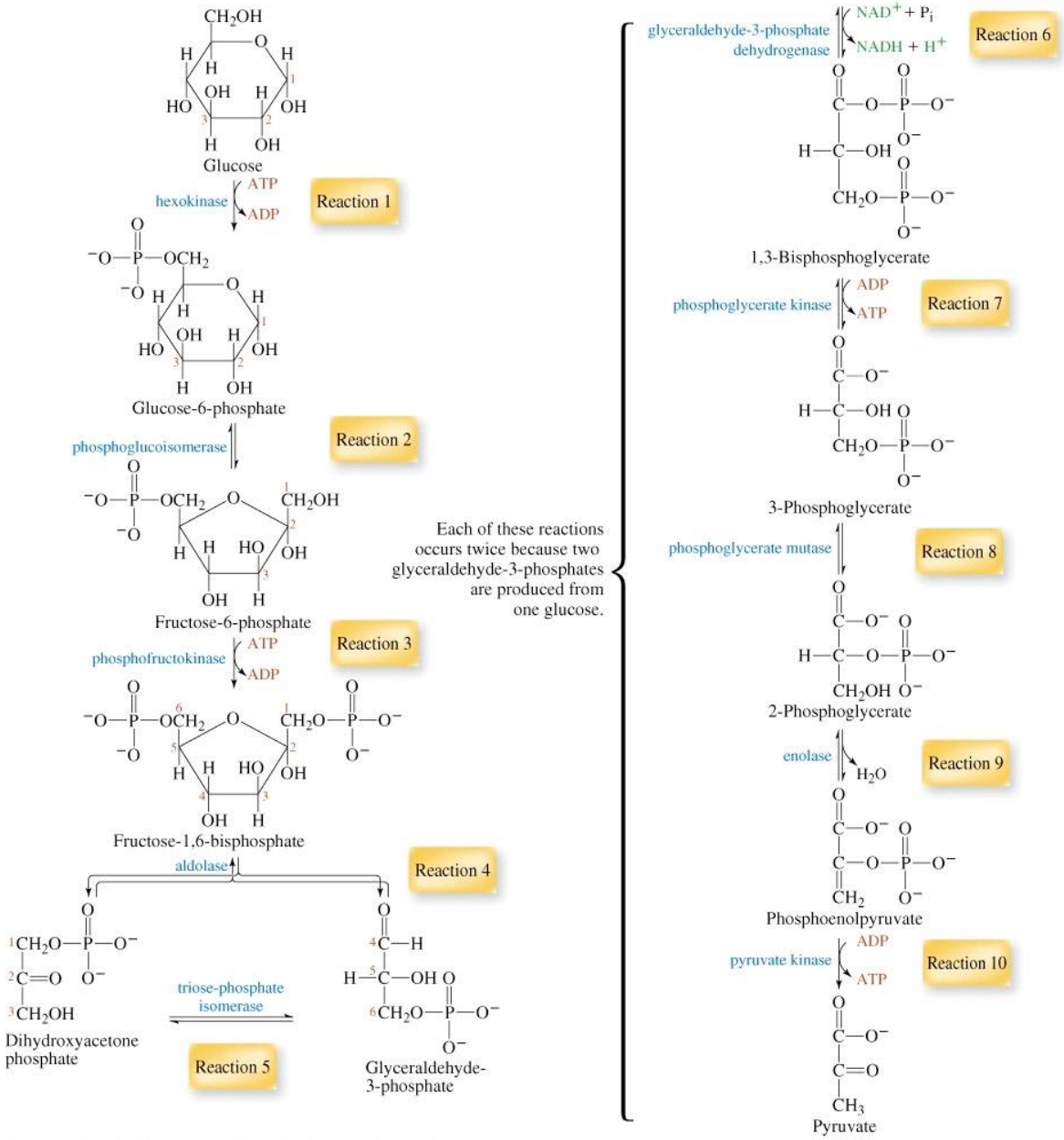
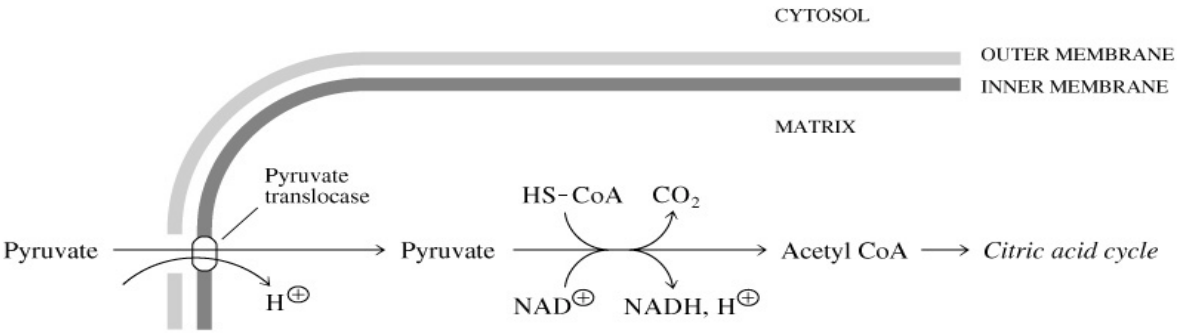
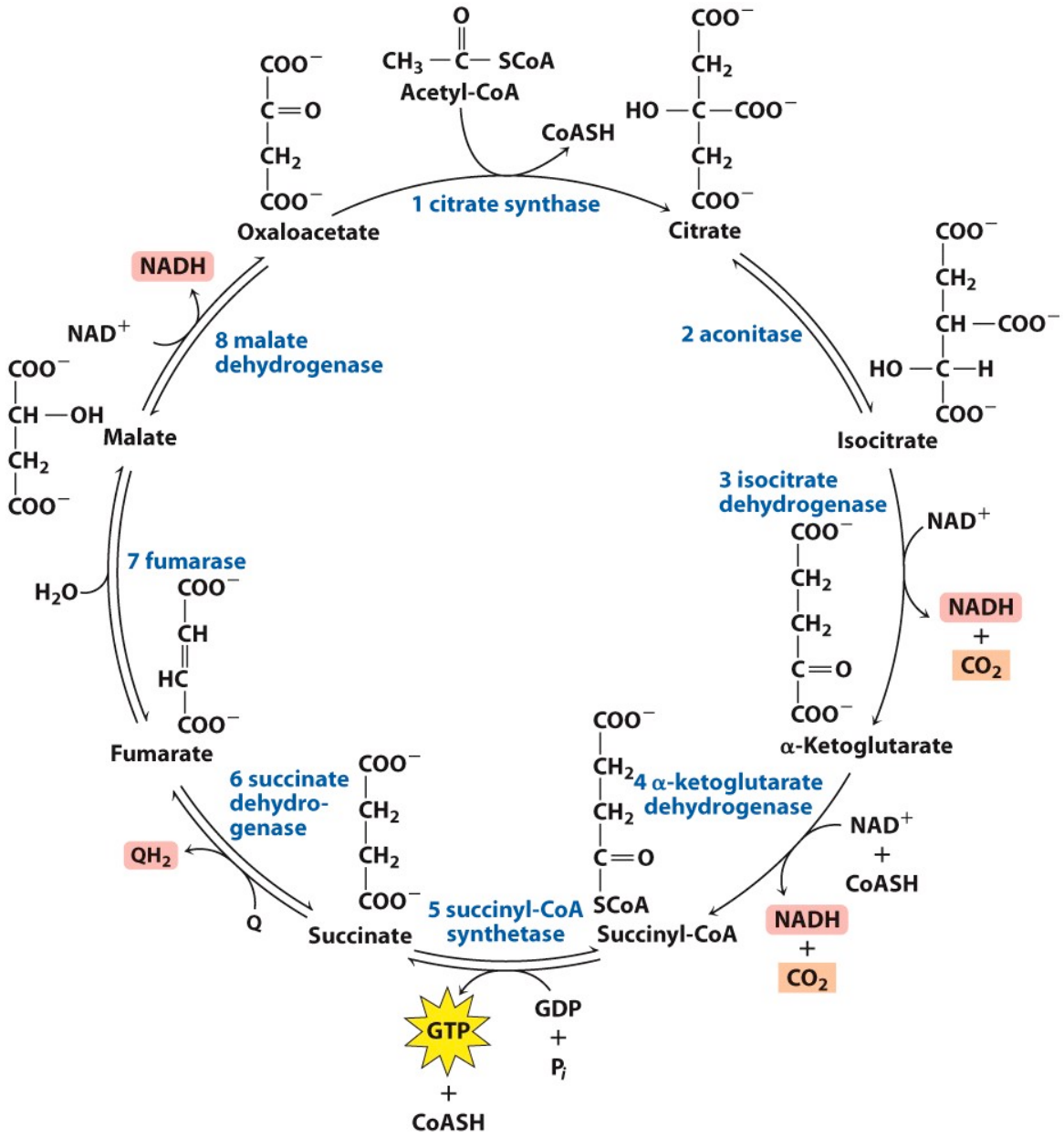


Figure 15-2 Concepts in Biochemistry, 3/e

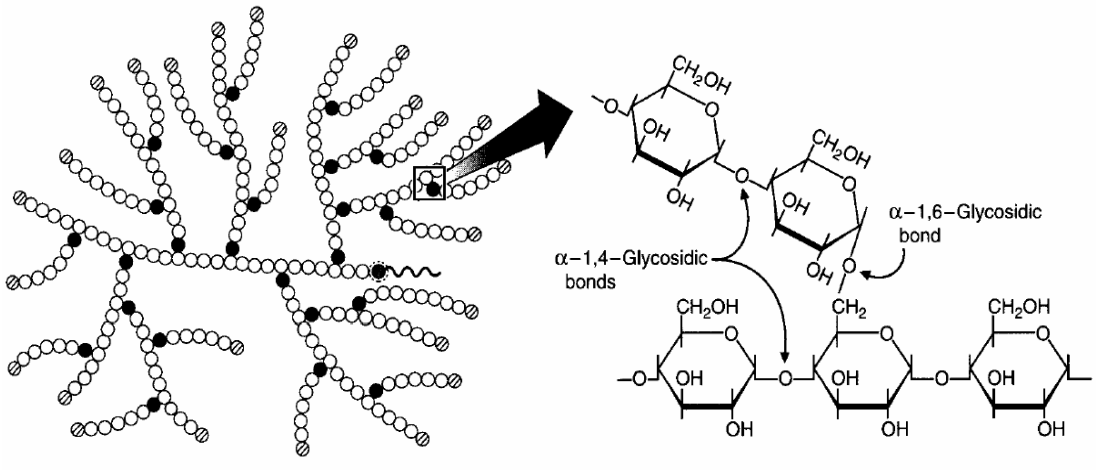
۳,۲ Pyruvate dehydrogenase



۳,۳ Krebs Cycle



٣,٤ Glycogen



٣,٥ Glycogenolysis

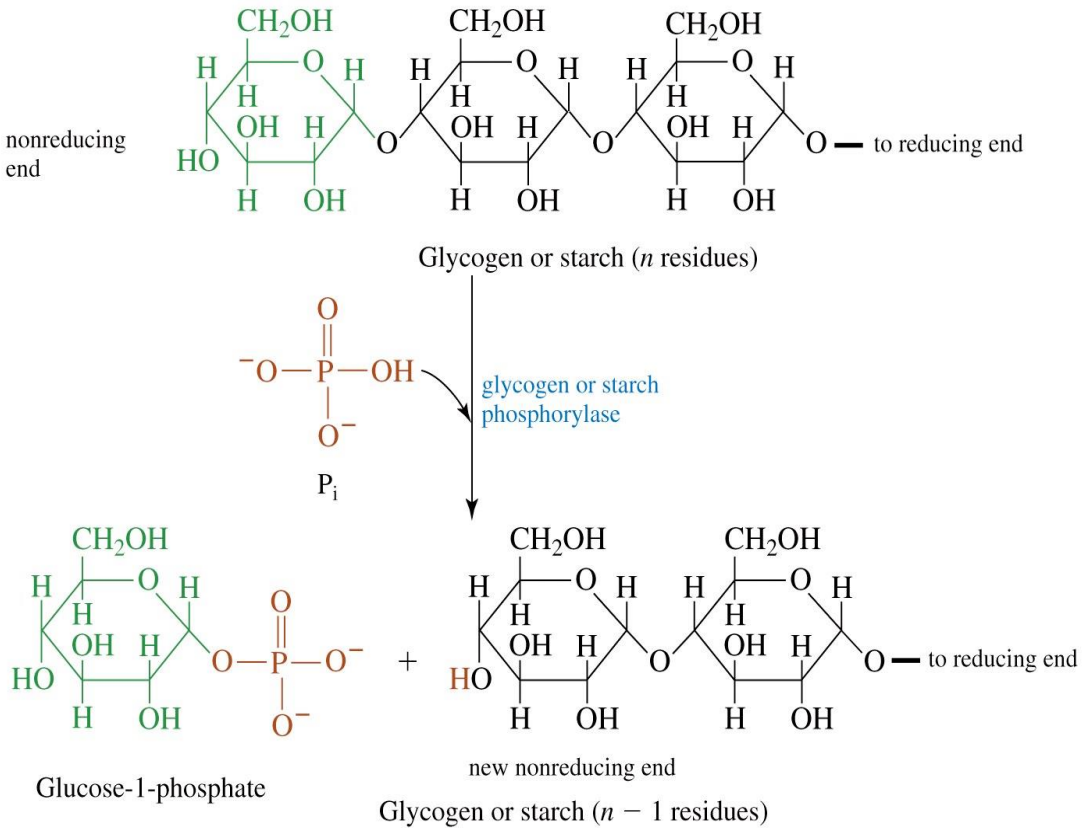
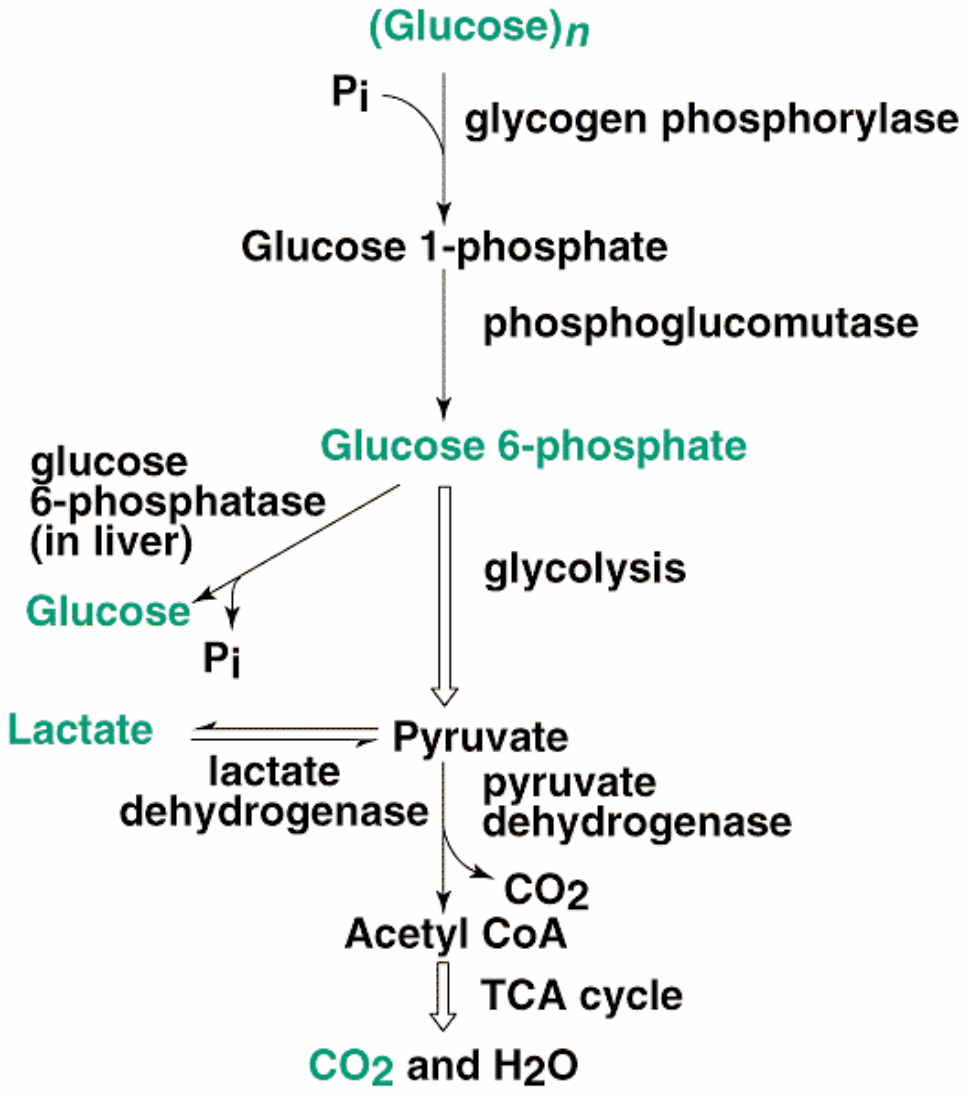
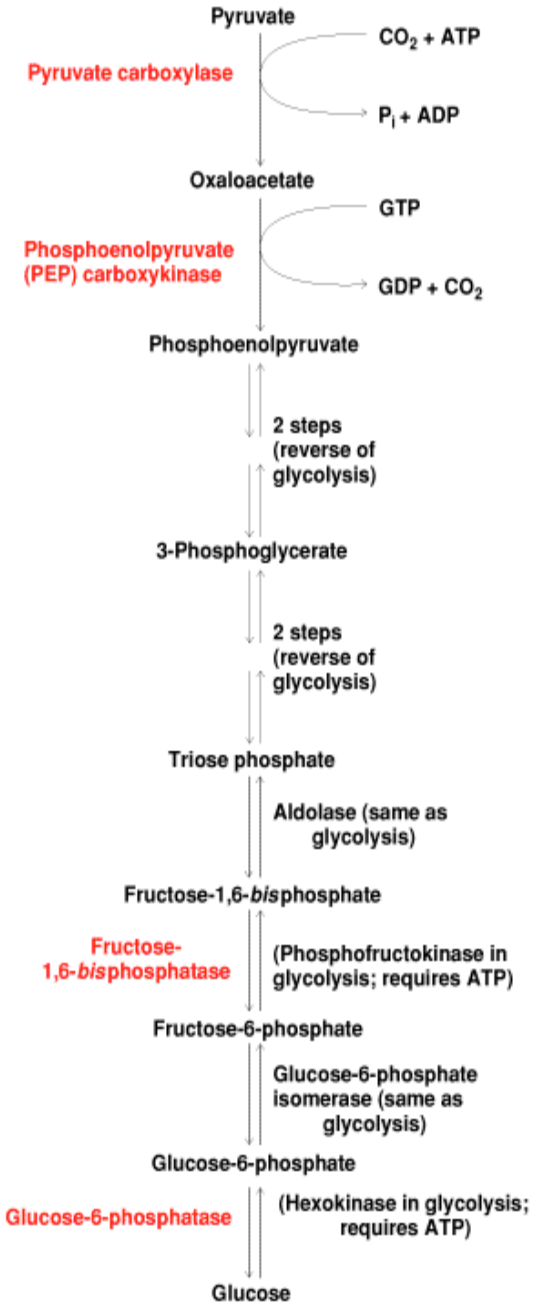


Figure 15-5 Concepts in Biochemistry, 3/e

٣,٦ Glycogenesis



٣,٧ Gluconeogenesis



٣,٨ Metabolism of other sugars

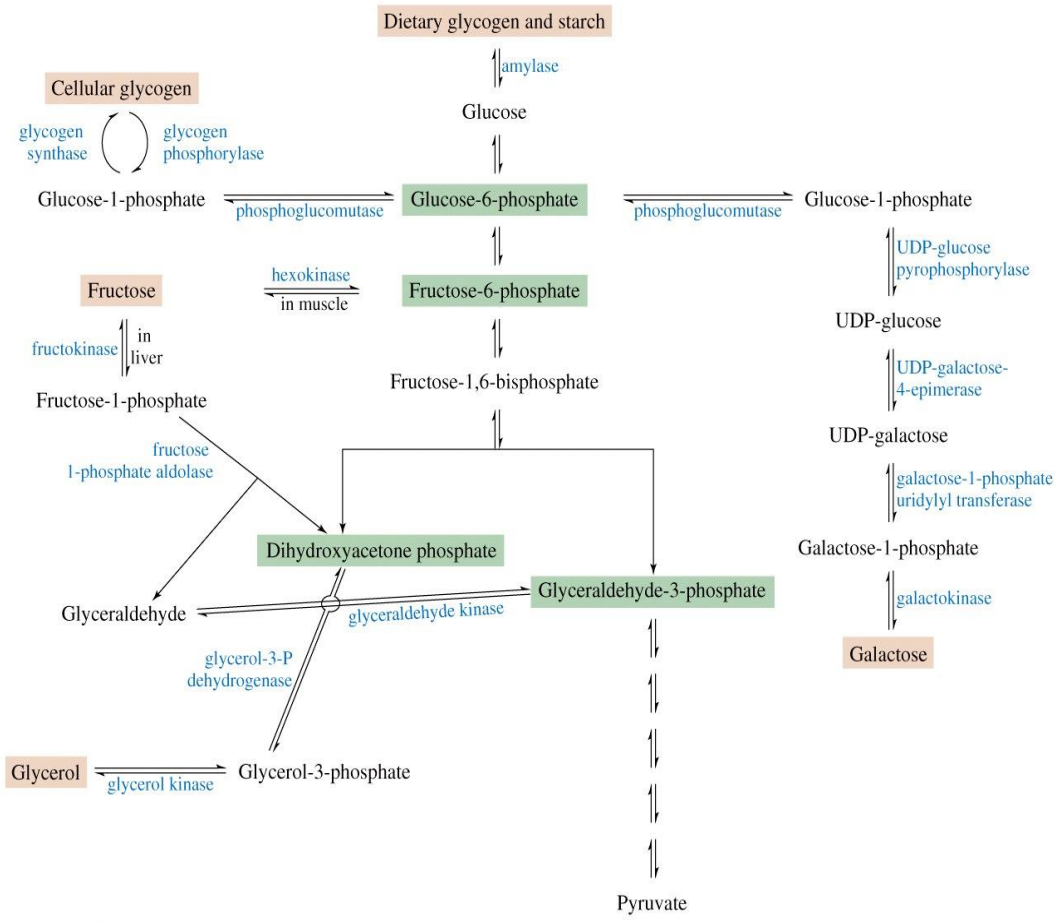


Figure 15-3 Concepts in Biochemistry, 3/e
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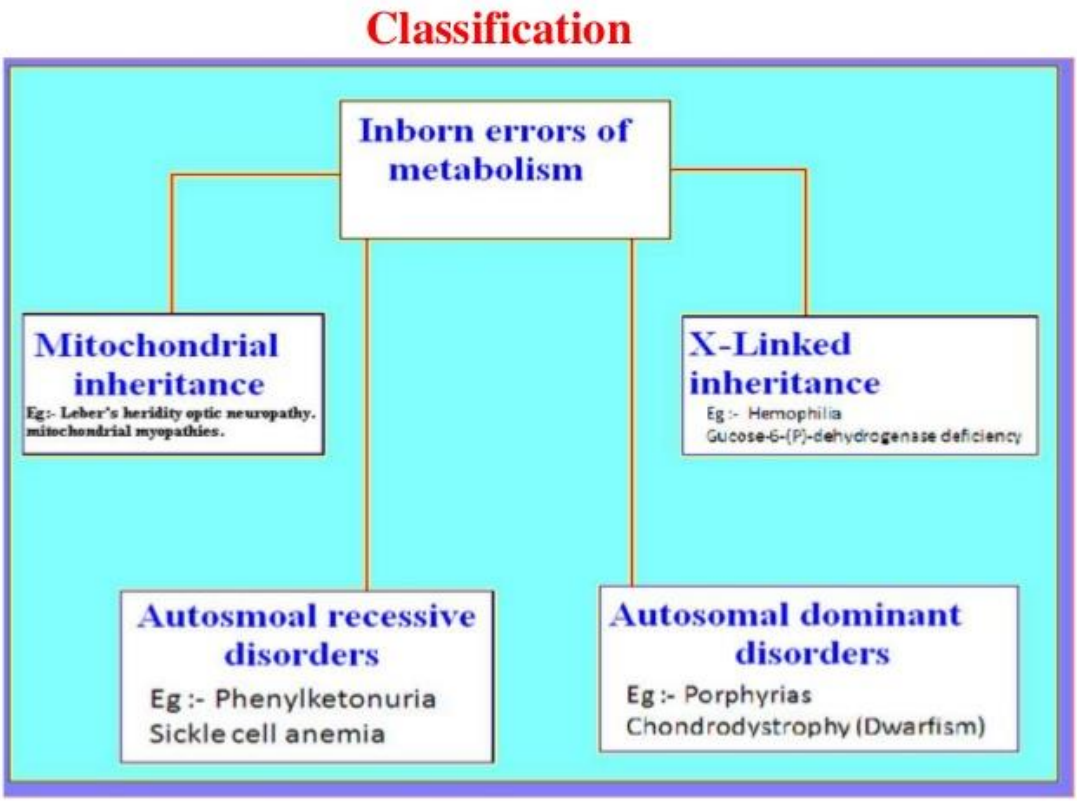
- According to Garrod's hypothesis, a genetically determined biochemical disorder in which a specific enzyme defect produces a metabolic block that may have pathologic consequences at birth **(e.g. phenylketonuria)** or in later life **(e.g. diabetes mellitus)**; also called enzymopathy and genetotrophic disease.



٤. Mitochondrial inheritance

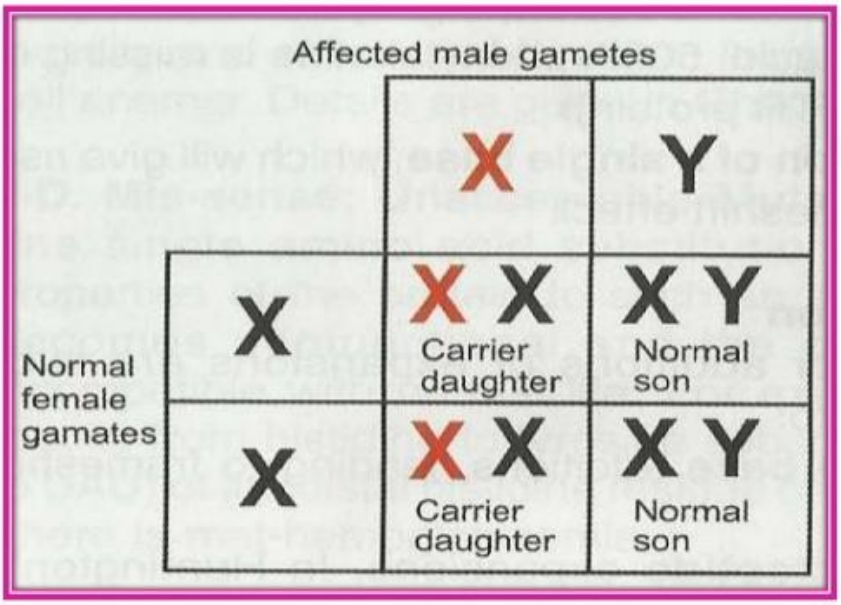
١- Leber's hereditary optic neuropathy is caused by complex-I defect in ETC, leads to blindness, cardiac conduction defects.

٢-Leigh's syndrome: - Complex I defect, leads movement disorders.

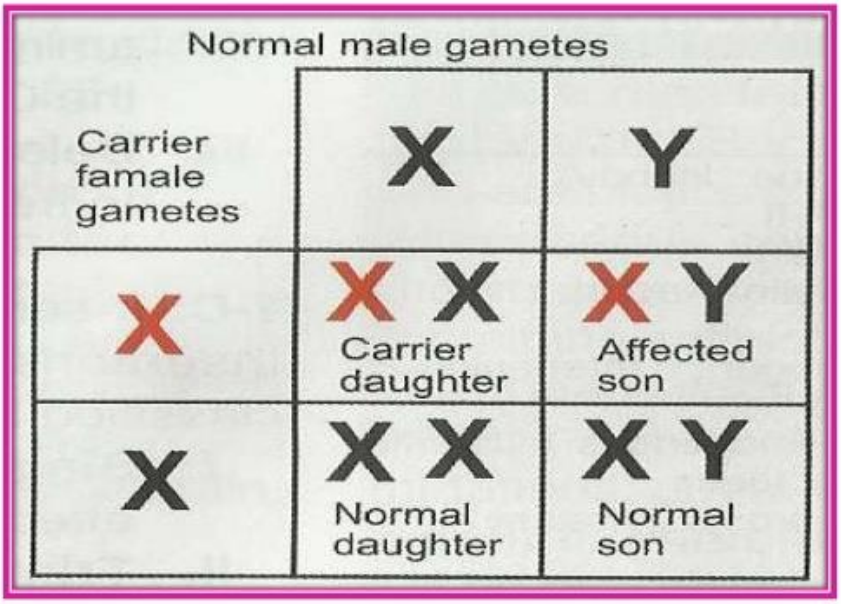
٣- Mitochondrial myopathies

Defects in mitochondrial genome will lead to mitochondrial myopathies such as myoclonic epilepsy and myopathy dementia.

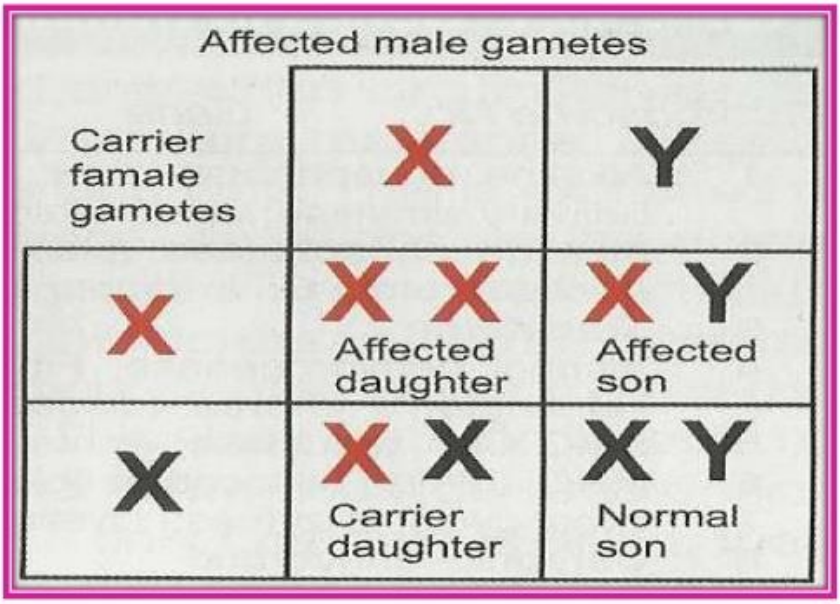
٤-Complex-I defect also causes lactic acidosis, strokes and seizures



Sex-linked recessive inheritance



Sex-linked recessive inheritance



Sex-linked recessive inheritance

٥. Categories

١) **Hemolytic anemia's caused by deficiencies of**

A. Hexokinase

B. Pyruvate kinase

C. Glucose-٦-(P)-dehydrogenase

٢) **Pyruvate dehydrogenase deficiency**.

٣) **Carbohydrate intolerance disorders**

A. Lactose intolerance.

B. Fructose intolerance.

٤) **Fructosuria**.

٥) **Galactosemia**.

٦) **Pentosuria.**

٧) **Glycogen storage disorders.**

٨) **Mucopolysaccharidoses.**

٦. Hexokinase deficiency

- This is very rare among all the hemolytic disorders.

- Glycolysis in the RBC is linked with ٢,٣-BPG production, essential for the oxygen transport.

- In the deficiency of the hexokinase, the synthesis and concentration of ٢,٣-BPG are low in RBC, so the oxygen unload to the tissues decreased, condition leads to Hemolysis.

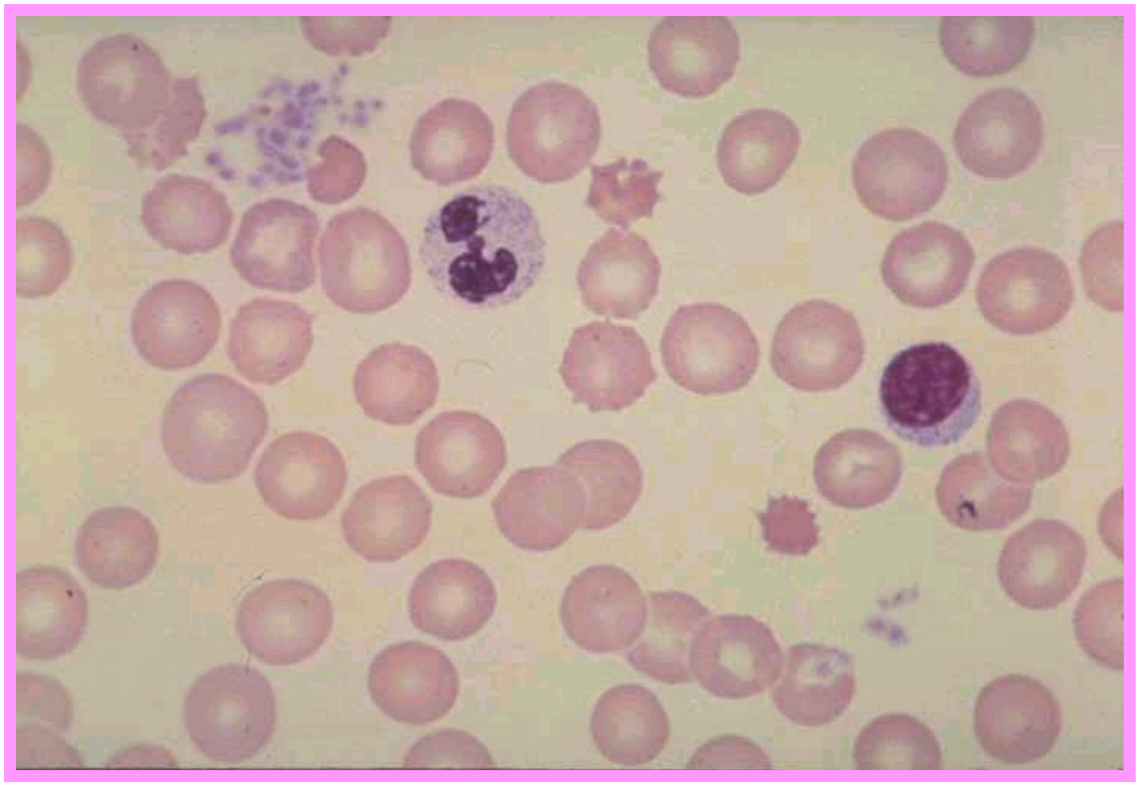
٧. Pyruvate kinase deficiency

- It is an autosomal recessive disorder and most common red cell enzymopathy after G-٦-P D deficiency.

- PK catalyses the conversion of phosphoenolpyruvate to pyruvate with the generation of ATP.

- Inadequate ATP generation leads to premature red blood cell death (Prickle cells).

- On the other hand in the patients with pyruvate kinase deficiency, the level of ٢, ٣-BPG in RBC is high, resulting in low oxygen affinity of Hb observed.



Blood film: PK deficiency: Characteristic "prickle cells" can be seen.

٨. Glucose-٦-phosphate dehydrogenase deficiency

- G-٦-PD deficiency is a X-linked recessive disorder.

- Frequency is ١ in ٥,٠٠٠ births.

- The deficiency occurs in all the cells of affected individuals but it is more severe in RBCs.

- RBCs depend only on HMP shunt for their NADPH requirement.

- G-٦PD deficiency leads impaired NADPH production, so oxidized glutathione is not converted to its reduced form.

- Low NADPH concentration also results the accumulation of methemoglobin and peroxides in RBC, causes loss of RBC membrane integrity.

- Till now it is mostly asymptomatic but when the enzyme deficient subjects exposed to severe infection, administered oxidant drugs such as

  - Anti-malarial (Primaquine)
  - Antibiotic (Sulfamethoxazole)
  - Acetanilide (Antipyretic)

- Favism :- Ingestion of Fava beans.

- Leads to → → → → Hemolytic anemia.

٩. Pyruvate dehydrogenase deficiency

- Frequency is ١ in ٢٥٠,٠٠٠ births.

- Main symptom is lactic acidosis.

- Neuronal loss in brain.

- Muscular hypotonia.

١٠. Carbohydrate intolerance disorders

١٠,١ Hereditary Lactose intolerance

- It is a rare disorder, due to the deficiency of Lactase (β-Galactosidase) enzyme.

- Diarrhea, electrolyte disturbances , prominent feature is Lactosuria (Lactose in urine).

- Milk is not digested in the individuals so milk products are preferred.

١٠,٢ Hereditary Fructose intolerance

- It is an autosomal recessive disorder.

- Incidence is ١ in ٢٠,٠٠٠.

- ١ in ٧٠ persons is carriers of abnormal gene.

- The defect is Adolase-B (fructose-١-P aldolase)

- Fructose -١(P) cannot be metabolized.

- Fructose-١(P) →×→ Glyceraldehyde + DHAP.

- It leads to accumulation of fructose-١-(P),

- Severe hypoglycemia, vomiting, hepatic failure and jaundice.

- Fructose-١-(P) allosterically inhibits liver phosphorylase and blocks glycogenolysis leading to hypoglycemia.

- Treatment- Early detection and intake of diet free from fructose and sucrose are advised to overcome fructose intolerance.

١٠,٣ Essential fructosuria :-

- Due to the deficiency of fructokinase. Fructose is not converted to fructose-١-(P).

- Fructose →→×→→Fructose-١-(P).

- This is an asymptomatic condition with excretion of fructose in urine.

١٠,٤ Galactosemia

- It is a serious autosomal recessive disorder resulting from the deficiency of galactose-١-(P) uridyltransferase, leads to accumulation of Galactose-١-(P) in the liver and becomes toxic.

- Incidence is one in ٣٥,٠٠٠ births.

Galactose -١-(P) →→×→→UDP Galactose.

- The buildup of galactose and the other chemicals can cause serious health problems like

- Swollen and inflamed liver

- Kidney failure

- Stunted physical and mental growth.

- Cataracts in the eyes

- Treatment: - Galactose free diet is preferred i.e. milk will be avoided.

١٠,٥ Essential pentosuria :

- It is a rare autosomal recessive disorder and benign condition, asymptomatic.

- Individuals do not show any ill-effects.

- Incidence is one in ٢,٥٠٠ births.

- Primarily in Jewish population.

- Lack Xylitol dehydrogenase leads to excretion of larger amounts of L-Xylulose in urine.

L-Xylulose →→×→→ Xylitol

- It is also reported after administration of drugs such as,

Aminopyrine and Antipyrine.

١١. Glycogen storage disease (GSD)

- Glycogen storage disease, also (**glycogenosis and dextrinosis**) is the result of defects in the processing of glycogen synthesis or breakdown within muscles, liver, and other cell types.

- GSD has two classes of cause: genetic and acquired.

- Genetic GSD is caused by any inborn error of metabolism (genetically defective enzymes) involved in these processes.

١١,١ Type I GSD (Von Gierke's disease)

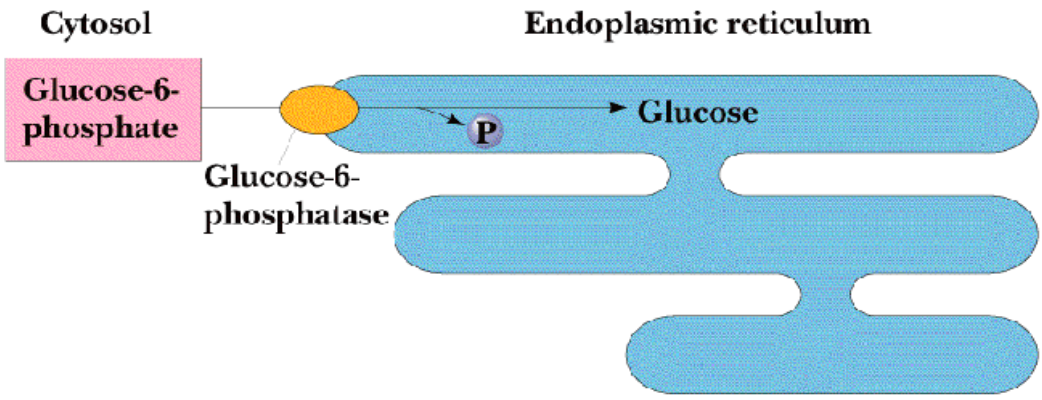
Symptoms

- Hypoglycemia, Hyperlipidemia, Hepatomegaly, Lactic acidosis, and Hyperuricemia.

- Progression: Growth failure

- Enzyme deficiency: **(glucose-٦-phosphatase)**

. This deficiency impairs the ability of the liver to produce free glucose from glycogen and from gluconeogenesis. Since these are the two principal metabolic mechanisms by which the liver supplies glucose to the rest of the body during periods of fasting, it causes severe hypoglycemia.



Treatment

- The essential treatment goal is prevention of hypoglycemia and the secondary metabolic derangements by frequent feedings of foods high in glucose or starch.

-To compensate for the inability of the liver to provide sugar, the total amount of dietary carbohydrate should approximate the ٢٤-hour glucose production rate. The diet should contain approximately ٦٥- ٧٠٪ carbohydrate, ١٠-١٥٪ protein, and ٢٠-٢٥٪ fat.

- At least a third of the carbohydrates should be supplied through the night, so that a young child goes no more than ٣–٤ hours without carbohydrate intake

Two methods have been used to achieve this goal in young children: (١) continuous nocturnal gastric infusion of glucose or starch; and (٢) night-time feedings of uncooked cornstarch.

١١,٢ GSD type II (Pompe's disease)

- It is an autosomal recessive metabolic disorder, which damages muscle and nerve cells throughout the body.
- caused by a mutation in a gene (acid alpha-glucosidase: also known as acid maltase) on long arm of chromosome ١٧. ١٣

- It is caused by an accumulation of glycogen in the lysosome.
- The build-up of glycogen causes progressive muscle weakness (myopathy) and affects various body tissues, particularly in the heart, skeletal muscles, and weakness facial and oral muscles.
- Pompes disease causes cardiomyopathy and hepatomegaly.
- **Nutrition and Weight Maintenance**
    - Because of weakened facial and oral muscles, patients of all ages, from infants to adults, may experience difficulties eating.
    - Trouble with sucking, chewing, and/or swallowing can lead to insufficient caloric intake, problems maintaining a healthy weight. Several approaches can address these issues
    - Physical therapy to help strengthen muscles
    - Modification of food texture to facilitate swallowing and reduce the risk of aspiration.
    - Carefully balanced diets to maximize nutrients and provide protein to muscles.
    - Tube feeding, most commonly in severely ill infants.
    - In ٢٠٠٦, the European Medicines Agency (EMEA) and the U.S. Food and Drug Administration (FDA) both granted marketing approval for the drug Myozyme (alglucosidase alfa) for treatment of Pompe disease.

١١,٣ Type GSD IIb (Pseudo-pompe)

Danon disease

- X-linked dominant lysosomal storage disease
- Deficiency of LAMP-٢ (lysosomal-associated membrane protein٢)
- Xq٢٤
- Maltase activity is normal

١١,٤ Type III GSD Cori disease Forbes disease

- debranching enzyme deficiency

- An autosomal recessive disorder

- Gene map locus is ١p٢١

- GSD III A affects about ٨٥٪ in both liver and muscle

- GSD III B affects only the liver.

- Symptoms

  - Swollen abdomen due to an enlarged liver
  - Growth delay during childhood
  - Low blood glucose level
  - Elevated fat levels in blood
  - Possible muscle weakness

- Diagnosis

  - Liver and muscle biopsies for abnormal glycogen and for debranching enzyme.

- Treatment

  - Continuous glucose delivery

١١. ٥ Type IV GSD (Andersen disease)

- Branching enzyme deficiency
- Formation of amylopectin-like
- Autosomal recessive
- Gene map locus is ٣p١٢
- Growth delay

- Enlarged liver
- Progressive cirrhosis
- May affect muscle and heart in late-onset type

١١.٦ GSD type V (McArdle disease)

- It is a metabolic disorder, caused by a deficiency of enzyme myophosphorylase,
- This enzyme helps break down glycogen into glucose-١- phosphate
- The onset of this disease is usually noticed in childhood, but often not diagnosed until the third or fourth decade of life.
- Symptoms include exercise intolerance with myalgia, early fatigue, painful cramps, weakness of exercising muscles and myoglobinuria.
- Myoglobinuria, the condition where myoglobin is present in urine, may result from serious damage to the muscles, or rhabdomyolysis, where skeletal muscle cells breakdown rapidly, sending their contents into the bloodstream.
- **Rhabdomyolysis** is a condition in which damaged skeletal striated muscle breaks down rapidly. Breakdown products of damaged muscle cells are released into the bloodstream; some of these, such as the protein myoglobin, are harmful to the kidneys and may lead to kidney failure.
- Oral vitamin B٦ appears to impart greater resistance to fatigue.
- No specific therapy exists, but combined aerobic exercise programs and high-protein diets may help.
- Supervised exercise programs have been recommended to lessen the risks of extended inactivity.
- Sucrose treatment is now being recommended prior to exercise.
- Progression: Renal failure due to myoglobinuria.

١١. ٧ Type VI GSD (Her's disease)

- Liver glycogen phosphorylase deficiency
- Hypoglycemia if fasting
- Hepatomegaly
- Lactic acidosis
- The signs and symptoms of GSDVI tend to improve with age

١١,٨ GSD type VII (Tarui's disease)

- Is metabolic disorder with autosomal recessive inheritance
- It is due to Phosphofructokinase deficiency.
- In this condition, a deficiency phosphofructokinase enzyme impairs the ability of cells such as erythrocytes and skeletal muscles to use carbohydrates for energy.
- Unlike most other GSD, it directly affects glycolysis.
- The disease presents with exercise-induced muscle cramps and weakness (sometimes rhabdomyolysis), myoglobinuria, as well as with haemolytic anaemia causing dark urine.
- Hyperuricemia is common.
- Myopathy occurs and leads to death in the infancy or early childhood.
- There is no cure for Tarui disease, but various treatments may alleviate symptoms and complications.
- Individuals with Tarui disease should be observant to myoglobulinuria, presenting as a dark discoloration of the urine.
- Owing to the risk of kidney damage, medical help should be sought immediately if symptoms arise. Dialysis is needed if toxic waste products accumulate owing to renal failure (uraemia).

- In Tarui’s disease, jaundice is mild and generally does not require treatment.

- High uric acid concentrations that may cause gout can be treated with drugs which lower uric acid levels in the blood.

- The effectiveness of dietary management remains unclear. It is possible that food with a high fat content (notably fatty fish) has a beneficial effect, as the glycerol in neutral fat can replace glucose as a source of energy

- It may be possible to "teach" the skeletal muscle cells to oxidise fatty acids rather than glucose to produce energy.

- Individuals with Tarui’s disease should avoid intensive muscle activity that has many negative consequences for physical and mental health.

Type VIII GSD

One of the mildest form of the glycogenoses. It is characterized by hepatomegaly, growth retardation, elevation of glutamate-pyruvate transaminase and glutamate-oxaloacetate transaminase, hypercholesterolemia, hypertriglyceridemia, and fasting hyperketosis.

Hepatic Phosphorylase Kinase Deficiency; Phosphorylase Kinase-Deficient Liver Glycogenosis; Glycogenosis type VIII. [*NB:* Also classified as GSD type VIa. GSD type IX is a variant of the recessive form of defective enzyme without brain involvement.]

Fewer than ١٠ cases have been reported, but it may be underdiagnosed because it is often asymptomatic and, when symptomatic, often classified as GSD VI.

X-linked recessive (GSD VIII) and autosomal recessive (GSD IX) types described. Gene map loci are Xp٢٢,٢-p٢٢,١ (GSD VIII) and ١٦q١٢-q١٣ (GSD IX).

Deficiency of liver phosphorylase kinase, which is required to activate liver phosphorylase. Protein phosphorylation is a major mechanism of signal transduction.

Clinical finding of hepatomegaly. Enzyme deficiency on liver biopsy.

Massive hepatomegaly in infancy that may regress later in life. Otherwise, children are normal and prognosis is good.

Check liver function.

Anesthetic management has not been described. If hepatomegaly is significant, functional residual capacity of the lungs may be reduced. Proper preoxygenation would be recommended. Case reports exist where hepatomegaly finally progressed to liver cirrhosis and formation of a hepatocellular adenoma.

No agents specifically contraindicated.

Type IX GSD

- GSD-IX
- PhK deficiency
- phosphorylase kinase deficiency

Subdivisions of Type IX

- glycogen storage disease type Ixa
- glycogen storage disease type Ixb
- glycogen storage disease type Ixc
- glycogen storage disease type Ixd

Type X GSD

It is caused by homozygous or compound heterozygous mutation in the PGAM٢ gene (٦١٢٩٣١), which encodes muscle phosphoglycerate mutase, on chromosome ٧p١٣.

▼ Clinical Features

DiMauro et al. (١٩٨١) studied a ٥٢-year-old who had onset in adolescence of exercise-induced cramps, occasional myoglobinuria, and intolerance for strenuous exercise. However, he led a relatively normal life including service in the army. Physical examination showed gouty tophi and signs of severe coronary arteriosclerosis. Muscle phosphoglycerate mutase activity was ٥ to ٧٪ of the lowest control value.

Bresolin et al. (١٩٨٣) reported a ١٧-year-old girl with recurrent myoglobinuria after intense exercise. Muscle biopsy showed increased PAS stain with twice normal glycogen concentration. PGAM٢ activity was ٦٪ of normal controls. Intermediate PGAM activities, ٣٩٪ and ٥٠٪, respectively, were found in muscle biopsies from the patient's asymptomatic parents, indicating autosomal recessive inheritance.

Additional patients were reported by Kissel et al. (١٩٨٥) and Vita et al. (١٩٩٠).

Tsujino et al. (١٩٩٣) reported a ١٧-year-old girl with GSD١٠ who complained of exercise intolerance since age ٨ years; intense exertion caused pain and cramps in the exercising muscles. During episodes of myalgia, increases of serum creatine kinase were documented but there was no pigmenturia. A brother complained of similar exercise intolerance with cramps and had persistently elevated serum creatine kinase. Tsujino et al. (١٩٩٣) also reported a ٣٠-year-old African American man with GSD١٠ who was admitted to the

hospital because of pigmenturia that appeared a few hours after he ran a race. Serum creatine kinase was greatly elevated and myoglobin was demonstrated in the urine. He developed renal failure that required hemodialysis. He had had ٢ similar episodes, at ages ٢١ and ٢٢ years, both after strenuous exercise.

Hadjigeorgiou et al. (١٩٩٩) reported a Japanese family with GSD١٠ due to a G٩٧D mutation (٦١٢٩٣١,٠٠٠٤) in the PGAM٢ gene. Two family members heterozygous for the mutation presented with exercise intolerance and muscle cramps.

▼ Inheritance

Autosomal recessive inheritance was supported by the finding of Bresolin et al. (١٩٨٣) that muscle extracts from the unaffected parents of their patient exhibited approximately ٥٠٪ of normal PGAM enzymatic activity.

▼ Molecular Genetics

In 5 patients with muscle phosphoglycerate mutase deficiency, Tsujino et al. (1993) identified 3 homozygous or compound heterozygous mutations in the PGAM2 gene (612931.0001-612931.0003). Four of the 5 patients were African American; the fifth was Italian.

Type XI GSD (Fanconi-Bickel disease)

- GLUT٢ deficiency

-Fanconi-Bickel glycogenosis (FBG)

- A rare glycogen storage disease

- Characterized by hepatorenal glycogen accumulation,

- Severe renal tubular dysfunction

- Impaired glucose and galactose metabolism.

Type XII (GSD١٢)

It is caused by homozygous mutation in the ALDOA gene (١٠٣٨٥٠), which encodes fructose-١,٦-bisphosphate aldolase A, on chromosome ١٦p١١.

▼ Description

Aldolase A deficiency is an autosomal recessive disorder associated with hereditary hemolytic anemia (Kishi et al., ١٩٨٧).

▼ Clinical Features

Beutler et al. (١٩٧٣) described a son of first-cousin parents who had nonspherocytic hemolytic anemia, mental retardation, and increased hepatic glycogen due, apparently, to deficiency of red cell aldolase. Puzzlingly, both parents had normal levels of red cell aldolase. The patient was presented again at the Birth Defects Conference in Vancouver in ١٩٧٦ (Lowry and Hanson, ١٩٧٧). He showed many dysmorphic features, some of which (ptosis, epicanthi, short neck, and low posterior hairline) were reminiscent of Noonan syndrome (١٦٣٩٥٠). The patient reported by Beutler et al. (١٩٧٣) had an unstable enzyme that became depleted in enucleated erythrocytes. Consequently, energy production was impaired and membrane stability decreased with declining ion transport activity. Hurst et al. (١٩٨٧) described a brother and sister with mental retardation, short stature, delayed puberty, hemolytic anemia, and abnormal facial appearance. The similarities to the boy reported by Beutler et al. (١٩٧٣) were striking.

Miwa et al. (١٩٨١) reported ٢ patients with red cell aldolase deficiency associated with congenital nonspherocytic hemolytic anemia. The proband was a ١٤-month-old Japanese boy whose parents were probably consanguineous. He had mild to moderate anemia that was aggravated by upper respiratory infections, ١ cm hepatomegaly, and ٢,٥ cm splenomegaly,

but showed no growth or mental retardation and did not have dysmorphic features. Red cell aldolase activity was ٦٪ of the normal mean. The enzyme was unstable with respect to heat, and Km for fructose ١,٦-diphosphate was high. The parents and other heterozygotes showed intermediate enzyme activity between that of the proband and that of normal subjects. The other affected patient reported by Miwa et al. (١٩٨١)was the ١٣-year-old nephew of the proband's maternal grandmother, and he presented with a phenotype similar to that of the proband.

Kreuder et al. (١٩٩٦) described a boy with aldolase deficiency who presented with predominantly myopathic symptoms, including muscle weakness and premature muscle fatigue. He had episodes of anemia and jaundice and was prone to episodes of rhabdomyolysis during febrile illness. Biochemical assays revealed a profound reduction in muscle and red cell aldolase levels and a decrease in thermostability of residual enzyme.

▼ Mapping

Aldolase A deficiency is caused by mutation in the ALDOA gene, which maps to chromosome ١٦p١١,٢ (Amberger, ٢٠٠٨).

▼ Molecular Genetics

Kishi et al. (١٩٨٧) studied a patient with red cell aldolase deficiency reported by Miwa et al. (١٩٨١)and identified a mutation in the ALDOA gene that resulted in an asp١٢٨-to-gly (D١٢٨G; ١٠٣٨٥٠,٠٠٠١) substitution in the protein. The patient's enzyme from red cells and from cultured lymphoblastoid cells was highly thermolabile, and the enzyme expressed in E. coli was likewise thermolabile. The parents had intermediate levels of red cell aldolase A. Southern blot analysis of genomic DNA showed that the patient was homozygous for a mutation that was heterozygous in both parents.

In a boy they reported with aldolase A deficiency, Kreuder et al. (١٩٩٦) identified a homozygous germline mutation in the ALDOA gene that resulted substitution of a negatively charged glutamic acid with a positively charged lysine at the highly conserved residue ٢٠٦ (E٢٠٦L; ١٠٣٨٥٠,٠٠٠٢).

Type XIII GSD

caused by compound heterozygous mutation in the ENO٣ gene (١٣١٣٧٠), which encodes beta-enolase, on chromosome ١٧p١٣. One such patient has been reported.

▼ Clinical Features

Comi et al. (٢٠٠١) described a ٤٧-year-old man affected with exercise intolerance, myalgias, and increased serum creatine kinase. No rise of serum lactate was observed with the ischemic forearm exercise. Ultrastructural analysis showed focal sarcoplasmic accumulation of glycogen-beta particles. He had severe deficiency of muscle enolase activity (٥٪ of control values).

▼ Molecular Genetics

In a man with GSD١٣, Comi et al. (٢٠٠١) identified compound heterozygosity for ٢ mutations in the ENO٣ gene (١٣١٣٧٠,٠٠٠١ and ١٣١٣٧٠,٠٠٠٢). Immunohistochemistry and immunoblotting detected dramatically reduced beta-enolase protein in this patient, while alpha-enolase was normally represented.

Type XIV GSD

- due to phosphoglucomutase deficiency

Type XV GSD

Glycogen storage disease type ١٥ is an extremely rare genetic glycogen storage disease reported in one patient to date. Clinical signs included muscle weakness, cardiac arrhythmia associated with accumulation of abnormal storage material in the heart and glycogen depletion in skeletal muscle.

Type ٠ GSD

- Glycogen synthase deficiency
- Depletion of liver glycogen content
- Fasting hypoglycemia
- Gene map locus of GSDa is ١٢p١٢,١.
- Gene map locus of GSDb is ١٩p١٣,٣٣.

Disorder	Enzyme	Affected Tissue
Type I (von Gierke's disease)	Glucose-6-phosphatase	**Liver, kidney, intestine**
Type II (Pompe's disease)	Lysosomal α 1,4- glucosidase (Acid maltase)	**All organs**
Type III (Cori's disease)	Amylo α 1,6- glucosidase (debranching enzyme)	**Liver, muscle, heart, leukocytes**
Type IV (Anderson's disease)	Glucosyl 4,6-transferase	**Most tissues**
Type V (Mc Ardle's disease)	Muscle glycogen phosphorylase	**Skeletal muscle**
Type VI (Her's disease)	Liver glycogen phosphorylase	**Liver**
Type VII (Tauri's disease)	Phosphofructokinase	**Skeletal muscle, erythrocytes.**

Disorder	Incidence in births (1 out of)	Chromosome location
Type I (von Gierke's disease)	1,00,000	17
Type II (Pompe's disease)	1,75,000	**17**
Type III (Cori's disease)	1,25,000	**1**
Type IV (Anderson's disease)	1 million	**3**
Type V (Mc Ardle's disease)	1 million	**11**
Type VI (Her's disease)	1 million	**14**
Type VII (Tauri's disease)	1 million	**1**

Disorder	Features
Type I (von Gierke's disease)	Hypoglycemia, Hepatomegaly, Cirrhosis, Ketosis, Hyperuricemia.
Type II (Pompe's disease)	Generalized glycogen deposit; lysosomal storage disease.
Type III (Cori's disease)	Hepatomegaly, Cirrhosis
Type IV (Anderson's disease)	Hepatomegaly, Cirrhosis
Type V (Mc Ardle's disease)	Exercise intolerance
Type VI (Her's disease)	Hepatomegaly, Hyperuricemia.
Type VII (Tauri's disease)	

Other Types of Glycogen Storage Diseases

Type of GSD	Eponym	Enzyme deficiency	Progression and Complications
GSD III	Cori's or Forbes disease	Glycogen debrancher	Hypoglycemia and myopathy
GSD IV	Andersen disease	Glycogen branching Enzyme	Liver cirrhosis, death at age ~5 years
GSD VI	Hers disease	Liver glycogen phosphorylase	Hypoglycemia and Hepatomegaly
GSD IX		Phosphorylase kinase	Delayed motor development, Growth retardation
GSD XI	Fanconi-Bickel syndrome	Glucose transporter, GLUT2	Hypoglycemia and Hepatomegaly
GSD XII	Red Cell Aldolase	Aldolase A	Exercise intolerance, and muscle cramps
GSD XIII		B-enolase	Exercise intolerance, and muscle cramps
GSD O		Glycogen synthase	Hypoglycemia

١٢. Mucopolysaccaridoses

8) Mucopolysaccharidoses

Type I – Hurler's syndrome – L-Iduronidase.

Type II – Hunter's – Iduronate sulphatase.

Type III – Sanfilippo's –N-Acetylglucosaminidase, Heparin sulphatase.

Type IV – Morquio's – Galactosamine sulphatase.

Type V – Scheie's – L-Iduronidase.

Type VI – Maroteaux-Lamy's – N-Acetyl-β-D-galactosamino-4-sulphatase.

Type VII – Sly's – β-Glucuronidase.

Overview of Carbohydrate metabolism

Enzyme Deficiency	Disease
Hexokinase Pyruvate kinase Glucose-6-(P) dehydrogenase	Hemolytic Anemia
Pyruvate dehydrogenase	Muscular hypotonia, Lactic acidosis.
Lactase Aldolase B (fructose-1-(P) aldolase)	Hereditary Lactose intolerance Hereditary fructose intolerance
Fructokinase	Essential Fructosuria
Galactose-1-(P)-Uridyl transferase Galactokinase Uridine di-(P)-galactose-4-epimerase	Galactosemia
L-Xylitol dehydrogenase	Essential Pentosuria
	Glycogen storage disorders And Mucopolysaccharidoses

١٣. Wernicke-Korsakoff syndrome

- This is a genetic disorder associated with HMP shunt. But it is not an inborn error.
- An alteration in transketolase activity that reduces affinity with TPP (a Biochemical lesion).
- Symptoms are mental disorder, loss of memory and partial paralysis.
- These symptoms manifested in chronic alcoholics, whose diets are thiamin-deficient

Clinical Cases Study

Preface

The goal of newborn screening is to identify infants that appear healthy at birth but are afflicted with treatable conditions that can cause severe illness or death. With reliable early detection, these conditions can be managed before the newborn or infant experiences serious medical complications, some of which can be irreversible.

Without newborn screening or a known previously affected individual within a family (positive family history) triggering a genetic work-up, in most cases. IEMs are identified only after a patient becomes symptomatic. Although many IEMs (milder forms) can present later in infancy, in childhood, or even in early adolescence, the acute onset in the newborn period or early infancy indicates more severe and often life-threatening forms.

Most IEMs are difficult to detect (by biochemical testing) in a healthy well-fed child. Onset of symptoms is most often associated with “metabolic stress,” i.e, prolonged fasting, increased protein intake, and illness with fever, vomiting/diarrhea, or decreased oral intake (“catabolic state”).

Birth in general (loss of maternal/placental resource of nutrition and clearance), birth complications (respiratory distress, feeding problems, infection), lack of maternal breast milk supply and increase in protein intake, can be considered metabolic stress; it typically results in a newborn at risk (affected by a severe IEM) displaying early, often nonspecific symptoms (reduced alertness/activity, decreased appetite/intake, emesis, lethargy, and unresponsiveness). When parents or providers miss these signs, the process is aggravated and can progress very quickly to coma, organ failure, and death.

Glycogen Storage Disease Symptoms

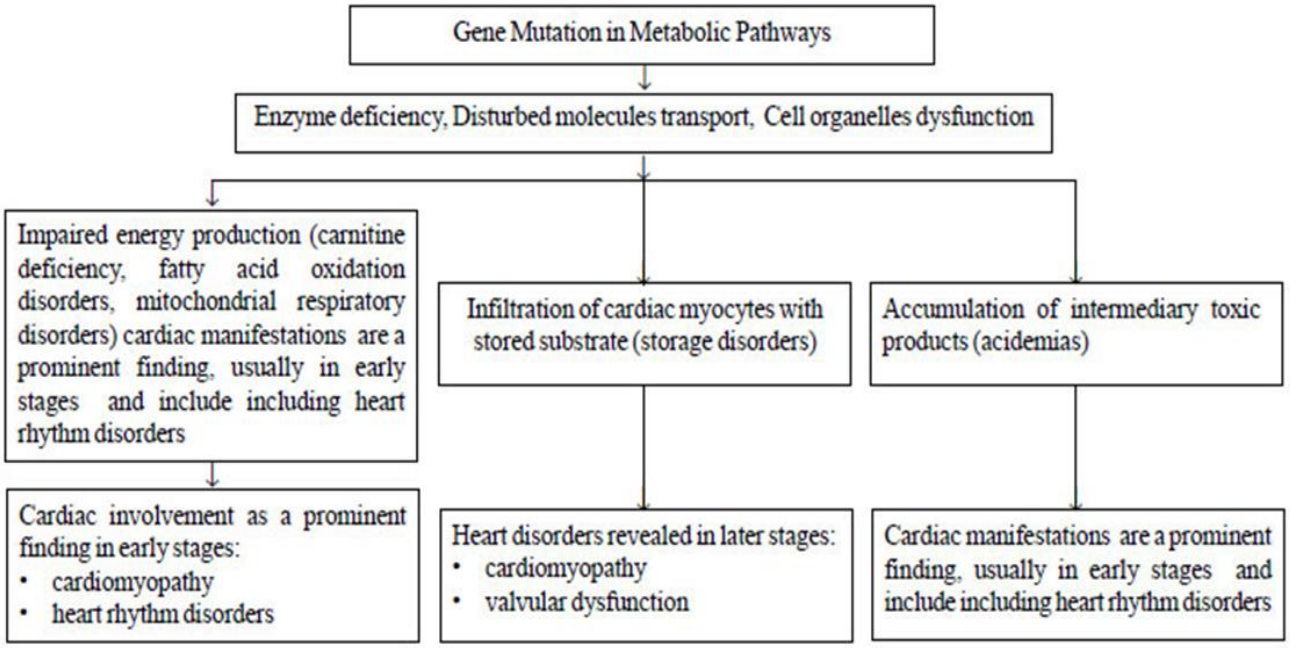


Fig. 1 Pathophysiological mechanisms of cardiac involvement in metabolic disorders.

Table I. Cardiac Manifestations in Inborn Errors of Metabolism

Disease	Prominent finding	Secondary finding(s)	Age at onset
Carnitine deficiency	Cardiomyopathy	Heart rhythm/ valvular	Neonatal to early childhood
		disorders	
Fatty acid oxidation disorder	Cardiomyopathy, heart	–	Neonatal to early
	rhythm disorders		childhood
Acidemias	Cardiomyopathy	Heart rhythm disorders	Neonatal to childhood
Glycogen storage disorders*	Cardiomyopathy, valvular	Heart rhythm disorders	Late infancy to childhood
	disorders		
Pompe	Cardiomyopathy, heart	–	Infancy to childhood
	rhythm/ valvular disorders		
Gaucher*	Cardiomyopathy, valvular	Heart rhythm disorders	Late infancy to childhood
	disorders		
Mucopolysaccharidoses*	Cardiomyopathy, valvular	Heart rhythm disorders	Late infancy to childhood
		disorders	
Congenital glycosylation disorders	Cardiomyopathy	–	Neonatal to early childhood

*Cardiac manifestations ate usually not a presenting feature.

Pathophysiology includes three basic mechanisms: (i) impaired energy production due to enzyme deficiency, disturbed transport of molecules or cellular organelles dysfunction (e.g., mitochondrial dysfunction), (ii) infiltration of cardiac myocytes with stored substrate and subsequent cellular damage, (iii) accumulation of intermediary metabolites, which exert a toxic effect on surrounding tissues and lead myocytes to apoptosis. It is noteworthy that in many cases more than one mechanisms may be involved, especially in later stages of the disease course.

Glycogen storage disease symptoms in pediatric patients depend on its type. The following is a list of common glycogen storage disease symptoms:

- Low blood sugar
- Enlarged liver
- Slow growth
- Muscle cramps

Symptoms of specific types of glycogen storage diseases include:

Type I - Von Gierke Disease

- Enlarged liver and kidneys
- Low blood sugar
- High levels of lactate, fats, and uric acid in the blood
- Impaired growth and delayed puberty
- Bone thinning from osteoporosis
- Increased mouth ulcers and infection

Type II - Pompe's Disease

- Enlarged liver and heart
- In severe cases, muscle weakness and heart problems develop
- In severe cases, infants may suffer heart failure by the age of ١٨ months
- Milder forms of type II may not cause heart problems

Type III - Cori's Disease

- Swollen abdomen due to an enlarged liver
- Growth delay during childhood
- Low blood sugar
- Elevated fat levels in blood
- Possible muscle weakness

Type IV - Anderson's Disease

- Growth delay in childhood
- Enlarged liver
- Progressive cirrhosis of the liver (which may lead to liver failure)
- May affect muscles and heart in late-onset type

Type V - McArdle's Disease

- Muscle cramps during exercise
- Extreme fatigue after exercise
- Burgundy-colored urine after exercise

Types VI, IX - Hers' Disease

- Liver enlargement occurs, but diminishes with age
- Low blood sugar

Type VII- Tarui's Disease

- Muscle cramps with exercise
- Anemia

Type VIII

- Muscle weakness
- Anemia
- Increased levels of uric acid

Glycogen Storage Disease Diagnosis

Glycogen storage disease diagnosis usually occurs in infancy or childhood as a result of the above symptoms. If your child's doctor suspects a glycogen storage diseases, he or she will ask about your child's symptoms and medical history, then perform a physical exam. The doctor will perform tests to rule out or confirm the diagnosis. These tests may include:

- Biopsy of the affected organs
- Blood tests and urine tests
- MRI scan – a test that uses magnetic waves to make pictures of the inside of the body

Glycogen Storage Disease Treatment

Glycogen storage disease treatment will depend on the type of disease and the symptoms. The following general treatment guidelines apply to people who have glycogen storage diseases that affect the liver, or types I, III, IV, and VI. Your child's doctor will develop a treatment regimen based on your child's specific symptoms.

The goal of treatment is to maintain normal blood glucose levels. This may be done with:

- A nasogastric infusion of glucose in infants and children under age two
- Dietary changes, including:

- In children over age two, frequent small carbohydrate feedings are given throughout the day. This may include uncooked cornstarch. (Uncooked cornstarch provides a steady slow-release form of glucose.)
- Elimination of foods that are high in fructose or lactose (type I only)
- Allopurinol (Aloprim, Zyloprim) may be prescribed to reduce uric acid levels in the blood. This is done to prevent gout and kidney stones.
- Type IV is sometimes treated with liver transplantation.
- The next group of glycogen storage disease treatment guidelines applies to people who have glycogen storage diseases that affect the muscles, or types V and VII. Your child's doctor will develop a treatment regimen based on your child's specific symptoms.

The goal of treatment is to avoid muscle fatigue and/or cramps induced by exercise. This is done by:

- Regulating or limiting strenuous exercise to avoid fatigue symptoms
- Improving exercise tolerance by oral intake of glucose or fructose (fructose must be avoided in people with type I), or an injection of glucagon
- Eating a high protein diet

There is no way to prevent glycogen storage diseases. However, early treatment can help control the disease once a person has it. If you have a glycogen storage disease or a family history of the disorder, you can talk to a genetic counselor when deciding to have children.

Definitions

Cellulose: A polysaccharide composed of β-D-glucopyranose units joined by a β(١→٤) glycosidic bond, which is not hydrolyzed by enzymes in the digestive tracts of humans.

Gums: Complex polysaccharides composed of arabinose, fucose, alactose, mannose, rhamnose, and xylose. Gums are soluble in water and, because of their mucilaginous nature, slowly digestible.

Hemicellulose: Polysaccharides with a random, amorphous structure that are components of plant cell walls. Unrelated to cellulose structurally, they are composed of a variety of monosaccharides, including some acidic sugars, with xylose being the most prevalent.

Insoluble fibers: Components of plant cell walls that are insoluble in water and not broken down by the body's digestive enzymes.

Lignins: Aromatic polymers formed by the irreversible dehydration of sugars. Because of their structure, they cannot be broken down by the digestive enzymes and make up part of the stool bulk.

Mucilaginous: Having a characteristic that is like the viscous and sticky nature of glue.

Pectins: One of the soluble fibers in the diet composed primarily of polymers of galacturonic acid with varying amounts of other hexose and pentose residues.

Soluble fibers: Mucilaginous fibers such as pectin and true plant gums that are soluble in water and digestible by the enzymes of the intestinal tract. By absorbing water and forming viscous gels, they decrease the rate of gastric emptying.

Clinical Cases

Case ١

The patient was a one year old boy who presented with fasting hypoglycemia and acidosis. The liver was enlarged three-fold and kidneys

two-fold. Hypoglycemia responded to oral doses of glucose but not to administered glucagon or epinephrine. During hypoglycemic episodes, lactic acid in the blood increased almost ١٠-fold higher than normal. Unlike the response in normal individuals, administration of oral galactose did not increase blood glucose concentrations but blood lactate levels were increased. Urine contained high levels of lactate. A glucose tolerance test showed normal insulin responses with a corresponding increase in blood glucose and decrease in blood lactate levels, liver glycogen stores were elevated three-fold but muscle glycogen levels were normal. Liver glycogen structure was normal. Assays for liver glucose-٤ phosphatase activity showed a ٢٠-fold lower activity per mg liver protein compared to control using either glucose-٦-phosphate or glucose- I -phosphate as a substrate.

١. What enzyme in the infant is lacking? Explain your answer.

٢. What is the metabolic reason for elevated levels of blood lactate in this patient? What are the biochemical sources of lactate?

٣. What evidence suggests that phosphoglucomutase levels in the patient were normal?

٤. Why were glycogen levels elevated in liver but normal in skeletal muscle? What symptoms. if any, would appear for this patient under exercise?

٥. What is the biochemical basis for the increase in blood glucose following oral galactose administration, and why was this response not observed in the patient?

٦. Successful treatment of the patient's symptoms was through frequent daytime feedings and administration of high-glucose formula via nocturnal nasogastric infusion.

٧. Why is this treatment successful in maintaining blood glucose concentrations and reducing blood lactate levels?

The answer, The infant is lacking the enzyme hepatic glucose-٦-phosphatase.

Case ٢

A ٤٣-year-old man of Mediterranean descent presented to his primary care provider for a routine visit. During the examination, the provider noted some mild splenomegaly and tenderness. On closer examination, some scleral icterus was noted. Subsequent labs showed marginally elevated LDH (lactate dehydrogenase), bilirubin, and slight anemia.

Which is the enzyme deficient?

a- Glycogen synthase
b- Glucose-٦-phosphate dehydrogenase
c- Debranching enzymes
d- Muscle phosphorylase
e- Glucose-٦-phosphatse

Discussion

G٦PD, or glucose-٦-phosphate dehydrogenase deficiency, is a genetic condition that makes carriers more susceptible to hemolysis and resultant jaundice. Symptoms usually only appear after a triggering event or intake of a certain food or medication. It is particularly common in people of Mediterranean and African origin and in men more often than in women. The main caution in these patients is to avoid triggers of oxidative stress, which, in extreme cases, can lead to hemolytic anemia, acute renal failure, and death. This patient was questioned regarding recent food intakes or other stressors and was found to have been drinking “several cans of beer” every night. His examination and lab values returned to normal limits, and he abstained from

alcohol intake. He was also given information on other foods and medication that he should avoid.

Case ٣

A female infant appears normal at birth but develop sign of liver disease and muscles weakness at month ٣. She had hypoglycemia, particularly at awakening, enlarged liver, ketoacidosis, blood pH ٧,٢٥, elevated ALT and AST, administration of glucagon after carbos meal, ameliorate blood glucose, but did not improve it after administration of glucagon after overnight fasting. Liver biopsy revealed increased elevated glycogen content.

١- Which is the enzyme affected?

f- Glycogen synthase
g- Branching enzyme
h- Debranching enzymes
i- Muscle phosphorylase
j- Glucose-٦-phosphatse

٢- In contrast to GSD type I, liver and skeletal muscles are involved in GSD type III.

a- True b- False

٣- Differentiating between GSD type I and III by physical examination solely, is not easy.

a- True b- False

Case ٤

A-١٤-years old high school girl is extremely conscious about her appearance. She was invited to a dance party. So, she had a full day fasting to fit in to a dress she bought in a size smaller than her actual size.

١- Which of the following tissues/organs is contributed in formation of glucose during prolonged fasting?

a- RBCs b- Liver c- Skeletal muscles d- Kidney

e- (b) and (c) f- (b) and (d) g- (c) and (d)

٢- What is the role of S.muscles in that operation?

٣- S. muscles contribute indirectly in maintenance of blood glucose level

a- True b- false

Case ٥

A ٣-months old girl had fussiness and lethargy. She was fine till mother returned to work and the baby switched from breast milk feeding to baby foods, formula, and fruit juices. The baby cried after feeding and vomited beside that she got lethargic. The baby appetite got worsened.

١- Which possible enzyme defect might lead to this case??

a- **Glucokinase b- Aldolase B c- Fructokinase d- hexokinase**

She is suffering from hereditary fructose intolerance. Mutation occurred in gene encoding aldolase B. the patient was asymptomatic till she was feeding fructose/sucrose-containing diet.

٢- Galactokinase deficiency is declined. Explain why??

a- Yes b- No

Because during breast feeding, there were no problems

٣- Treatment is by avoidance of fructose/sucrose-containing diet.

a- Yes b-No

٤- Fructokinase deficiency is ruled out. Explain why??

a- Yes b- No

There is no excessive excretion of fructose in urine

Case ٦

A ٤-year-old boy was administered in the pediatric clinics because of hepatomegaly, metabolic acidosis and growth retardation. Some of his abnormal fasting blood results were as follows:

Plasma (fasting)

Glucose ٢,٠ mmol/L (٣,٠–٥,٥)

Urate ٠,٦١ mmol/L (٠,٢٠–٠,٤٣)

Lactic acid ٣,٧ mmol/L (٠,٥–١,٥)

Cholesterol ٥,٤ mmol/L (٣,٠–٥,٠)

Triglycerides ٦,٧ mmol/L (٠,٥–١,٥)

DISCUSSION

The child has hyperlactataemia, hypoglycaemia, hyperuricaemia and hyperlipidaemia. He was later found to have von Gierke's disease (or type

I glycogen storage disease) due to glucose-٦-phosphatase deficiency. This enzyme deficiency leads to abnormalities of glycolysis and gluconeogenesis, resulting in the hypoglycaemia and lactic acidosis. The raised plasma lactic acid concentration may interfere with uric acid renal excretion, leading to hyperuricaemia.

Case ٧

A ٢-year-old black girl is being seen by the hematologist after her pediatrician found her to be severely anemic with splenomegaly and jaundice. Her mother gives a possible history of a "blood problem" in her family but doesn't know

for sure. Her hemoglobin electrophoresis was normal, and the complete blood count (CBC) revealed a normocytic anemia. The platelet and white blood cell counts are normal. On the peripheral smear, there are many bizarre erythrocytes, including spiculated cells. A diagnosis of pyruvate kinase deficiency is made.

١- **What is the biochemical mechanism for this disorder?**

٢- **How is this disorder inherited?**

٣- Why splenomegaly occurs

١- Biochemical mechanism: Pyruvate kinase deficiency usually will manifest clinical symptoms on red blood cells (RBCs) with no apparent metabolic abnormalities in other cells. Insufficient adenosine triphosphate (ATP) is produced in the red cell and its membrane is becomes distorted and removed by the spleen.

٢- Inheritance: Autosomal recessive.

٣- Insufficient pyruvate kinase activity compromises erythrocyte ATP production, leading to ionic imbalance and misshaped cell membranes. These cells are removed from the circulation by the macrophages of the spleen.

Hemolytic anemia: A pathologic condition in which there is an abnormally lowered number of circulating RBCs caused by rupture of RBCs as a result of membrane abnormalities or deficient enzyme(s) level within the red blood cell.

Case ٨

A young man with normocytic anemia, jaundice, and splenomegaly. The peripheral blood smear showed spiculated cells.

Diagnosis

was diagnosed as having RBC pyruvate kinase deficiency

١. Deficient pyruvate kinase leads to low pyruvate levels and elevated intermediates above pyruvate in the glycolytic pathway. Which of the following products may not be made in the appropriate amounts in the RBC because of the deficiency of pyruvate?

A. Glucose

B. Oxaloacetate

C. acetyl-CoA

D. Lactate

٢. In the RBCs of the patient described above, which of the following would be expected?

A. ADP to ATP ratios would be elevated above normal.

B. NADP+ would increase relative to NADPH.

C. Ribulose ٥-phosphate levels would decrease.

D. NADH to NAD+ ratios would decrease.

E. Methemoglobin levels would increase.

٣. The glycolytic pathway is a multistep process by which glucose is broken down to a three-carbon metabolite. Some of the steps are listed below:

١. Conversion of ٣-phosphoglycerate to ٢-phosphoglycerate

٢. Conversion of phosphoenolpyruvate to pyruvate

٣. Conversion of glyceraldehyde ٣-phosphate to ١,٣-bisphosphoglycerate

٤. Conversion of glucose to glucose ٦-phosphate

٥. Conversion of fructose ٦-phosphate to fructose ١,٦-bisphosphate

Which of the following is the correct order of these conversions?

A. ٤ → ٥ → ١ → ٢ → ٣

B. ٤ → ٣ → ١ → ٢ → ٥

C. ٤ → ٥ → ٣ → ١ → ٢

D. ٤ → ١ → ٣ → ٥ → ٢

E. ٤ → ٥ → ٣ → ٢ → ١

Answers

١. **D.** The RBC has no mitochondria so glucose cannot be made from pyruvate or acetyl-CoA or oxaloacetate. The RBC does have lactate dehydrogenase and conversion to lactate depends on pyruvate levels.

٢ **A.** In the RBC a deficiency of pyruvate kinase would tend to shunt glucose toward the hexose monophosphate pathway increasing ribulose ٥-P levels, and the ratio of NADP+ to NADPH would decrease. NADH to NAD+ ratios would increase as a result of lower pyruvate levels making more NADH available to reduce methemoglobin and regenerate NAD+. Pyruvate kinase deficiency, leads to elevated the ADP to ATP ratio.

٣ **C.** Glucose to glucose ٦-phosphate → fructose ٦-phosphate → fructose ١,٦-bisphosphate → glyceraldehyde ٣-phosphate → ١,٣-bisphosphoglycerate→٣-phosphoglycerate→٢-phosphoglycerate→ phosphoenolphosphate → pyruvate.

Some definition

GLUT ٥: A facilitative glucose transporter isoform present in the small intestine and other tissues that will transport fructose (and glucose to a lesser extent) across the plasma membrane.

b-Glycosidase: A bifunctional, membrane-bound enzyme located on the brush-border membrane of the small intestine. This single polypeptide enzyme has two activities, lactase and glycosylceramidase, located in different domains of the protein. It will hydrolyze lactose to glucose and galactose.

SGLT١: A sodium-dependent glucose transporter located on the luminal side of the intestinal epithelial cells. It will transport glucose and galactose across the intestinal cell using a sodium ion gradient.

SGLT٢: A sodium-dependent glucose transporter that has a high specificity for glucose and is specific to the kidney.

Sucrase-isomaltase complex: An enzyme complex comprised of two enzyme units. Both units have high α-١,٤-glucosidase activity and will hydrolyze maltose and maltotriose to glucose. The sucrase unit will also hydrolyze sucrose to fructose and glucose, whereas the isomaltase unit will hydrolyze α-١,٦ bonds found in isomaltose and the limit dextrins of starch.

Case ٩

A ٢٢-year-old soldier collapses from dehydration during maneuvers in the desert and is sent to a military hospital. Prior to enlisting, a physician observed a high level of glucose in his urine during an examination. At first, he was not allowed to enlist because he was suspected of being a diabetic. Further tests, however, determined that his insulin level was normal. A glucose tolerance test exhibited a normal pattern. Laboratory tests following his dehydration episode repeat the previous findings, but further testing of the urine reveals that only D-glucose is elevated. Other sugars were not elevated. This patient's elevated urinary glucose and his dehydration episode are caused by a deficiency in which of the following?

A. GLUT ٢

B. GLUT ٤

C. Insulin receptor

D. SGLT١

E. SGLT٢

The Answer: E.

The patient has normal levels of blood insulin and exhibits a normal glucose tolerance test. This indicates that glucose absorption from the intestine is normal as is clearance of glucose from the blood. The presence of glucose in the urine is most likely a kidney problem. Because the defect seems to involve only D-glucose and no other sugar, this points to a transporter with high specificity. The kidney has the GLUT ٢, SGLT١, and SGLT٢ transporters. GLUT ٢ and SGLT١ are present in other tissues, and a defect in these would be expected to result in more serious sequelae. SGLT٢ is a sodiumdependent glucose transporter specific to the kidney that has a high specificity for glucose. The glucose is present in the urine because of a failure to reabsorb it as a consequence of a defect in SGLT٢. This leads to a loss of water also, because it is reabsorbed with glucose.

Case ١٠

A ٧-month-old baby girl, the second child born to unrelated parents. She did not respond well to breast-feeding and was changed entirely to a formula based on cow's milk at ٤ weeks. Between ٧ and ١٢ weeks of age, she was admitted to the hospital twice with a history of screaming after feeding, but was discharged after observation without a specific diagnosis. Elimination of cow's milk from her diet did not relieve her symptoms; her mother reported that the screaming bouts were worse after the child drank juice and that she frequently had gas and a distended abdomen. Analysis of a liver needle biopsy did not reveal any liver enzyme deficiencies. Overall, the girl is thriving (weight greater than ٩٧th percentile) with no abnormal findings on physical examination.

If a biopsy of intestinal tissue were obtained from your patient and analyzed, which of the following would most likely be deficient or defective?

A. GLUT ٢

B. GLUT ٥

C. Isomaltase

D. Lactase

E. SGLT١

The Answer: B.

Because the patient's liver enzymes are normal and her symptoms seem to correlate with her intake of fruit juices, most likely her problem stems from an inability to absorb fructose. Since removal of cow's milk from her diet did not eliminate the problem, a lactase deficiency can be ruled out. GLUT ٥ is the primary transporter of fructose in the intestine and a deficiency in this transporter would lead to an inability to absorb fructose in the gut, making it a substrate for bacterial metabolism that produces various gases, including hydrogen, as well as organic acids.

Case ١١

A ٢٤-year-old African-American female presents with complaints of intestinal bloating, gas, cramps, and diarrhea following a meal including dairy products. A lactose-tolerance test confirms your suspicion that she had a deficiency of lactase in her intestine. Which of the following dairy products could you recommend that would be least likely to cause her difficulties in the future?

A. Condensed milk

B. Cottage cheese

C. Ice cream

D. Skim milk

E. Yogurt

The Answers: E.

The microorganisms that convert milk to yogurt (*Streptococcus*

salivarius thermophilus and *Lactobacillus delbrueckii bulgaricus*) metabolize most of the lactose in the milk, thus removing the source of this patient's intestinal disquietude. Yogurt is also a good source of dietary calcium.

Case ١٢

A ٣٨-year-old female presents to the clinic with complaints of alternating diarrhea and constipation. She reports some abdominal discomfort and bloating that are relieved with her bowel movement. She states that her episodes are worse in times of stress. She denies any blood in her diarrhea. She denies any weight loss or anorexia. Her physical exam is all within normal limits. She has been prescribed a cellulose-containing dietary supplement, which her doctor says will increase the bulk of her stools.

١- **What is the most likely diagnosis?**

2- **What is the biochemical mechanism of the dietary supplement's effect on the intestines?**

- **Diagnosis:** Irritable bowel syndrome.
- **Biochemical mechanism:** Cellulose-containing foods are not digestible but swell up by absorbing water and correlate with larger softer stools. The increase in dietary fiber also increases the intestinal transit time and decreases the intracolic pressure, thereby decreasing the symptoms of irritable bowel.

Clinical Correlation

Irritable bowel syndrome affects many individuals in Western countries, and it manifests as abdominal cramping and bloating in the absence of disease. It is thought to be caused by increased spasms of the intestines. Constipation with or without episodes of diarrhea may be seen. Weight loss, fever, vomiting, bloody stools, or anemia would be worrisome and should not be attributed to irritable bowel syndrome. Typically, affected patients are anxious and may be under stress. After ruling out other disease processes, a trial of fiber-containing foods, stress reduction, and avoidance of aggravating foods are effective therapies. Patients should be advised to avoid laxative use. Rarely

antispasmodic or antiperistaltic agents can be used. Notably, increased fiber in the diet may also decrease the absorption of fats and may lower the risk of colon cancer.

Case ١٣

A patient with type I diabetes mellitus has fasting and postprandial blood glucose levels that are frequently above the normal range despite good compliance with his insulin therapy. He was referred to a dietician that specialized in diabetic patients. The patient was recommended to incorporate foods high in dietary fiber. Which of the following dietary fibers would be most helpful in maintaining a normal blood glucose level?

A. Cellulose

B. Hemicellulose

C. Lignins

D. Pectins

Pectins and gums are soluble dietary fibers that absorb water and form mucilaginous gels. In doing so, they delay gastric emptying and decrease the rate at which monosaccharides such as glucose and fructose and disaccharides are absorbed by the intestinal tract. By decreasing the rate of sugar absorption, postprandial spikes in blood glucose concentration are avoided.

Dietary fiber comprises those components that are not digestible, which can be grouped into two main categories, those that are soluble and those that are insoluble in water.

The soluble fibers include pectins, gums, some hemicelluloses, and storage polysaccharides (starch and glycogen). The insoluble fibers include cellulose, most hemicelluloses, and lignins.

Case ١٤

A ٥٦-year-old male presents to your clinic for follow-up on his diabetes. He has had diabetes since the age of ١٢ and has always required insulin for

therapy. He reports feeling very tremulous and diaphoretic at ٢ AM with the blood sugars in the range of ٤٠ mg/dl, which is very low. He, however, notes that his morning fasting blood sugar is high without taking any carbohydrates. His physician describes the morning high sugars as a result of biochemical processes in response to the nighttime hypoglycemia.

١- What are the biochemical processes that govern the response to the nighttime hypoglycemia?

The case exihibits Smogyi effect

Biochemical mechanism of hypoglycemia: The low nighttime serum blood sugar stimulates the counter-regulatory hormones to try to raise the glucose level. These include epinephrine, glucagon, cortisol, and growth hormone, which affect the glucose level and raise it by the time morning comes around.
This individual has a classic manifestation of the Somogyi effect, which is fasting morning hyperglycemia in response to hypoglycemia in the early morning and late night hours. The danger is that if nighttime blood glucose levels are not measured, the physician may interpret the patient as having hyperglycemia and require even higher doses of insulin. This would be exactly the wrong treatment. The diagnosis is established by measuring a ٢ AM glucose level, and when confirmed, then the bedtime NPH insulin (intermediate to long acting) needs to be decreased.

Case ١٥

A ٢٩-year-old male presents to the emergency department with complaints of dark-colored urine, generalized fatigue, myalgia, and weakness after completing a marathon. The patient states that this was his first marathon. He has no significant medical history and denies any medications or drug use. On examination, he appears moderately ill and is afebrile with normal vital signs. Physical exam reveals diffuse musculoskeletal tenderness. Urinalysis revealed

large amounts of blood (hemoglobin and myoglobin), and serum creatine phosphokinase (CPK) was significantly elevated, as well as the potassium level. The serum lactate level was markedly elevated.

◆ What is the most likely diagnosis?

◆ What is the most appropriate treatment?

◆ What is the biochemical basis for the markedly elevated serum lactate level?

The Answer: Rhabdomyolysis

◆ Most likely diagnosis: Rhabdomyolysis (skeletal muscle cell lysis) after strenuous exercise.

◆ Treatment: Aggressive intravenous hydration to help clear the excess myoglobin from the serum, and correction of electrolyte abnormalities and treatment of kidney failure if present.

◆ Biochemical basis for elevated lactate: Nicotinamide adenine dinucleotide (NADH) levels increase because of the relative lack of oxygen for muscle, adenosine diphosphate (ADP) and adenosine monophosphate (AMP) concentrations rise in the cytoplasm, leading to an increased flux of glucose through the glycolytic pathway in the muscle, causing pyruvate levels to increase. Pyruvate is reduced by NADH to lactate in a reaction catalyzed by lactate dehydrogenase. Lactate is transported out of the muscle cell to the blood.

Case ١٦

A ٥٩-year-old male is brought to the emergency department by the EMS after a family member found him extremely confused and disoriented, with an unsteady gait and strange irregular eye movements. The patient has been known in the past to be a heavy drinker. He has no known medical problems and denies any other drug usage. On examination, he is a febrile with a pulse of ١١٠ beats per minute and a normal blood pressure. He is extremely

disoriented and agitated. Horizontal rapid eye movement on lateral gaze is noted bilaterally. His gait is very unsteady. The remainder of his examination is normal. The urine drug screen was negative and he had a positive blood alcohol level. The emergency room physician administers thiamine.

◆ What is the most likely diagnosis?

◆ What is importance of thiamine in biochemical reactions?

Answers: Thiamine deficiency

Summary: A ٥٩-year-old male with history of heavy alcohol use presents with mental confusion, ataxia, and ophthalmoplegia.

◆ Most likely diagnosis: Wernicke-Korsakoff syndrome (thiamine deficiency) often associated with chronic alcoholics.

◆ Importance of thiamine: An important water-soluble vitamin used as a cofactor in enzymatic reactions involving the transfer of an aldehyde group. Without thiamine, individuals can develop dementia, macrocytic anemia (folate deficiency), gastritis, peptic ulcer disease, liver disease, depression, nutritional deficiencies, cardiomyopathy, and pancreatitis.

Cases in brief

Case number	Disease	Probable deficiency
١	von Gierke'disease Type I GSD	Glucose-6-phosphatase
٢		Glucose-6-phphospate dehydrogenase
٣	Cori' disease Type III GSD	Debranching enzyme
٥	hereditary fructose intolerance	Aldolase B
٦	von Gierke'disease Type I GSD	Glucose-6-phosphatase
٧	Hemolytic anemia	Pyruvate kinase
٨	Hemolytic anemia	Pyruvate kinase
٩		SGLT2

١٠		GLUT 5
١٢	Irritable bowel syndrome	
١٤	Smogyi effect	
١٥	Rhabdomyolysis	
١٦	Wernicke-Korsakoff syndrome	TPP

Questions Models

I discuss the relationship between HMP and Favism

II What are the symptoms of

a- Galactosemia **b- Type I GSD**

c- Pompe's syndrome **d- GSD type V**

III Don't choose the true answers but choose the best ones

١- G٦PD deficiency is **.....** genetic disorder

a- X-linked recessive c- X-linked dominant

b- Autosomal recessive d- autosomal dominant

٢- Glycogen Storage Disorders (GSD) has.....types

a- ١٢ b- ٢٥ c- ١٥ d- none

٣- Type I constitute ..... % of all GSD

a-١٢ b- ٢١ c- ٢٥ d- none

٤- von Gierke disease is type... **.....** GSD.

a- type I b- type IV c- type II d- none

٥- von Gierke disease is due to deficiency of ....

a- Pyruvate kinase c- G٦PD

b- Hexokinase d- glucose ٦ phosphatase

٦- Cori disease is due to ..... deficiency.

a- Pyruvate kinase c- debranching enzyme

b- Hexokinase d- glucose ٦ phosphatase

III Which of followings is (T) and which is (F)

١- In G٦PD deficiency, Arg is changed to Leu at position ٤٥٩. ( )

٢- Hyperglycemia occurs in NDM. ( )

٣- Hypoglycemia occurs in von Gierke disease. ( )

٤- ٢,٣ phosphoglycerate increase oxygen affinity for hemoglobin. ( )

٥- Enlarged liver is due to glucose-٦-phosphatase deficiency. ( )

٦- Danon disease (GSD IIb) is pseudo-Pompe disease. ( )

IV Complete the followings

١- The most common disorder of RBCs is……..

٢- Neonatal diabetes mellitus is due to ……..

I. Mark the followings by (T) or by (F).

١-In Glucose transporter (SGLT-١), glucose enters downhill ( )

٢- ٢nd most common form of hemolytic anemia is due to deficiency in pyruvate kinase. ( )

٣- RBCs depend on aerobic glycoylsis for its need of energy. ( )

٤- Dyspenea and tachycardia are symptoms of PK deficiency. ( )

٥- Formation of amylopectin-like molecules occur in branching enzyme deficiency. ( )

٦- ٣ isoforms of glycogen phosphorylase, Brain /heart, liver and muscle.

٧- GSD II is a lysosomal storage disorder. ( )

٨- GSD III is a lysosomal disorder caused by the deficiency of lysosomal enzyme, acid phosphatase (α-glucosidase) ( )

٩- Danon disease (GSD IIb) is pseudo-Pompe disease. ( )

١٠- In pseudo-Pompe disease acid phosphatase is deficient. ( )

١١- In galactosemia, Galactose-١-phosphate uridyltransferase (GALT) is deficient. ( )

١٢- Pentosuria is due to deficiency of xylitol dehydrogenase and/or L-xylulose reductase. ( )

١٣ -In Glucose transporter (SGLT-١), glucose enters downhill ( )

١٤- ٢nd most common form of hemolytic anemia is due to deficiency in pyruvate kinase. ( )

١٥- RBCs depend on aerobic glycoylsis for its need of energy. ( )

١٦- In G٦PD deficiency, Arg is changed to Leu at position ٤٥٩. ( )

١٧- Hyperglycemia occurs in NDM. ( )

١٨- Hypoglycemia occurs in von Gierke disease. ( )

١٩- ٢,٣ phosphoglycerate increase oxygen affinity for hemoglobin. ( )

٢٠- Dyspenea and tachycardia are symptoms of PK deficiency. ( )

٢١- Enlarged liver is due to glucose-٦-phosphatase deficiency. ( )

٢٢- Formation of amylopectin-like molecules occur in branching enzyme deficiency. ( )

٢٣- isoforms of glycogen phosphorylase, Brain /heart, liver and muscle.

٢٤- GSD II is a lysosomal storage disorder. ( )

٢٥- GSD III is a lysosomal disorder caused by the deficiency of lysosomal enzyme, acid phosphatase (α-glucosidase) ( )

٢٦- Danon disease (GSD IIb) is pseudo-Pompe disease. ( )

٢٧- In Danon disease acid maltase is deficient. ( )

٢٨- In GSD IIb acid phosphatase is deficient. ( )

٢٩- In pseudo-Pompe disease acid phosphatase is deficient. ( )

II. Don't choose the correct answers but choose the best ones.

١- Cori disease is due to …….deficiency.

c- Pyruvate kinase c- debranching enzyme

d- Hexokinase d- glucose ٦ phosphatase

٢- Type VII GSD is due to ……..deficiency.

a- Pyruvate kinase c- debranching enzyme

b- Hexokinase d- PFK

٣- Forbes disease is due to **……** deficiency.

a- Pyruvate kinase c- debranching enzyme

b- Hexokinase d- glucose ٦ phosphatase

٤- Andersen disease is due to …… deficiency.

a- debranching enzyme c- pyruvate kinase

b- branching enzyme d- glucose ٦ phosphatase

٥- Type ٠ is due to …….. deficiency.

a- debranching enzyme c- glycogen synthase

b- branching enzyme d- glucose ٦ phosphatase

٦- Type V is due to **……** deficiency.

a- myophosphorylase c- glycogen synthase

b- branching enzyme d- glucose ٦ phosphatase

٧- Lactase deficiency in small intestine results in……..

a) lactose intolerance
b) Sucrase intolerance
c) impairment of digestion of lactose into glucose and galactose
d) increased osmotic pressure
e) dehydration in tissues
f) diarrhea
g) constipation
h) distention and abdominal cramps
i) increased fermentation of lactose by bacteria
j) a, c, d, e, f, h and i
k) b, c, g, h and i

٨- According to Garrod's hypothesis,……..

a) There is a product deficiency
b) There is a product excess
c) There a substrate excess
d) There a substrate deficiency
e) a and c
f) b and d

٧- Type IV GSD is due to **branching Enzyme** deficiency

a- - debranching enzyme c- pyruvate kinase

b- branching enzyme d- glucose ٦ phosphatase

٨- Andersen disease is due to **branching Enzyme** deficiency

c- debranching enzyme c- pyruvate kinase

d- branching enzyme d- glucose ٦ phosphatase

٩- Type ٠ is due to **Glycogen Synthase** deficiency

c- debranching enzyme c- glycogen synthase

d- branching enzyme d- glucose ٦ phosphatase

١٠- Type V is due to **myophosphorylase** Deficiency**.**

c- myophosphorylase c- glycogen synthase

d- branching enzyme d- glucose ٦ phosphatase

١١- GSD II is caused by the deficiency of lysosomal enzyme, **acid phosphatase**.

a- myophosphorylase c-acid phosphatase

b- branching enzyme d- glucose ٦ phosphatase

III. Complete the followings

١- Serum C-peptide is used to diagnosis of …….

٢-ICA is used to diagnosis of …….

٣- Deficiency of liver fructokinase leads to …….

٤- Deficiency of aldolase B is known as …….

٥- Type I constitute …….. % of all GSD

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