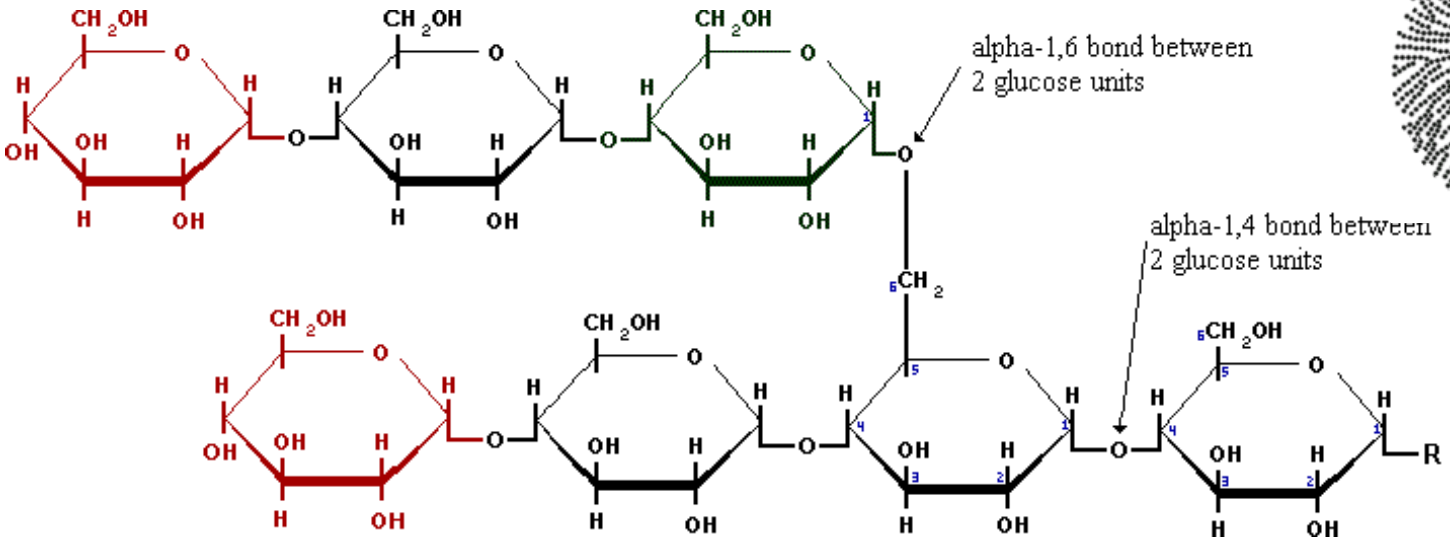
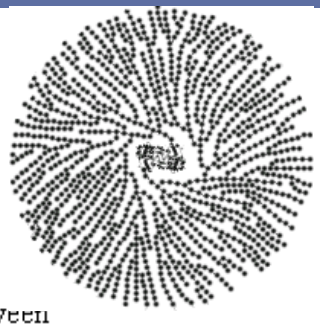
GLYCOGEN STORAGE DISEASES

Glycogen

- Glycogen is a branched-chain polymer of glucose and serves as a dynamic but limited reservoir of glucose, mainly in skeletal muscle and liver.

- There are a number of different enzymes involved in glycogen synthesis, utilization and breakdown within the body.



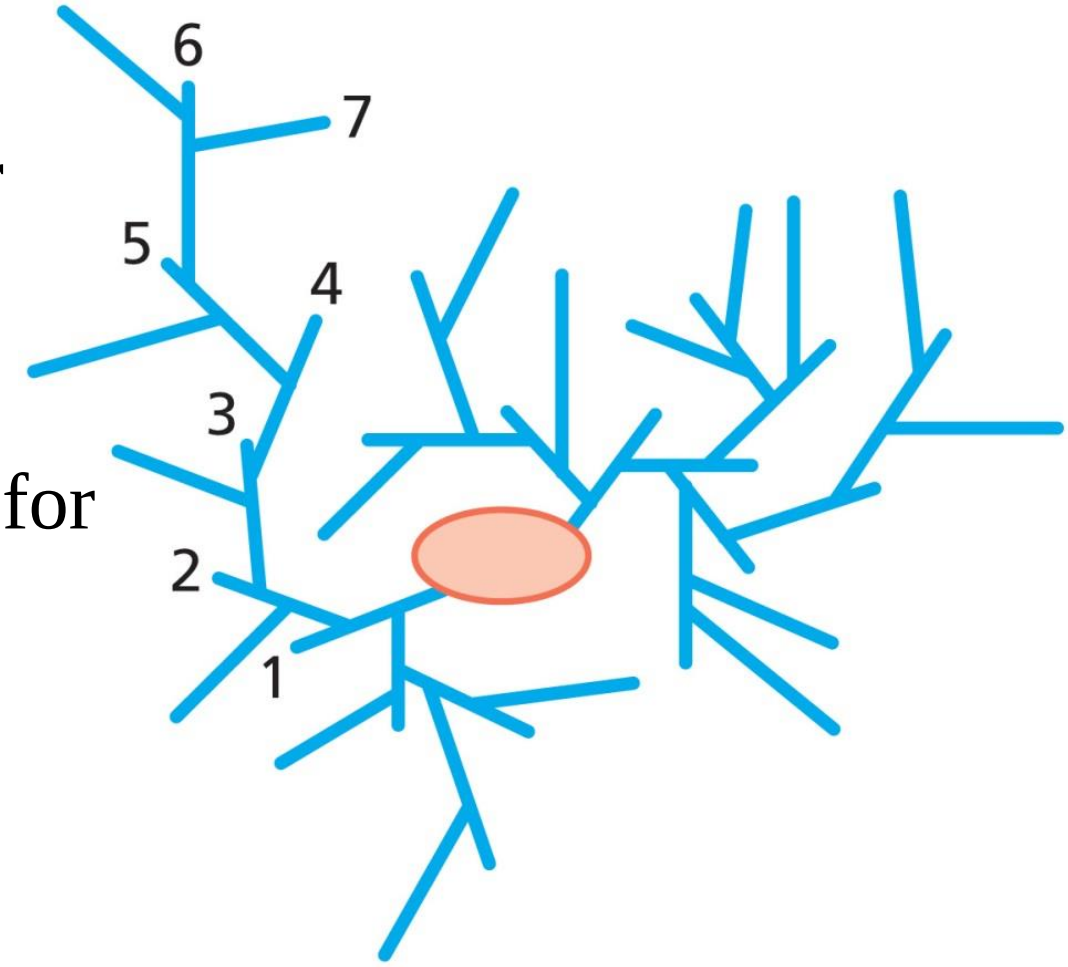


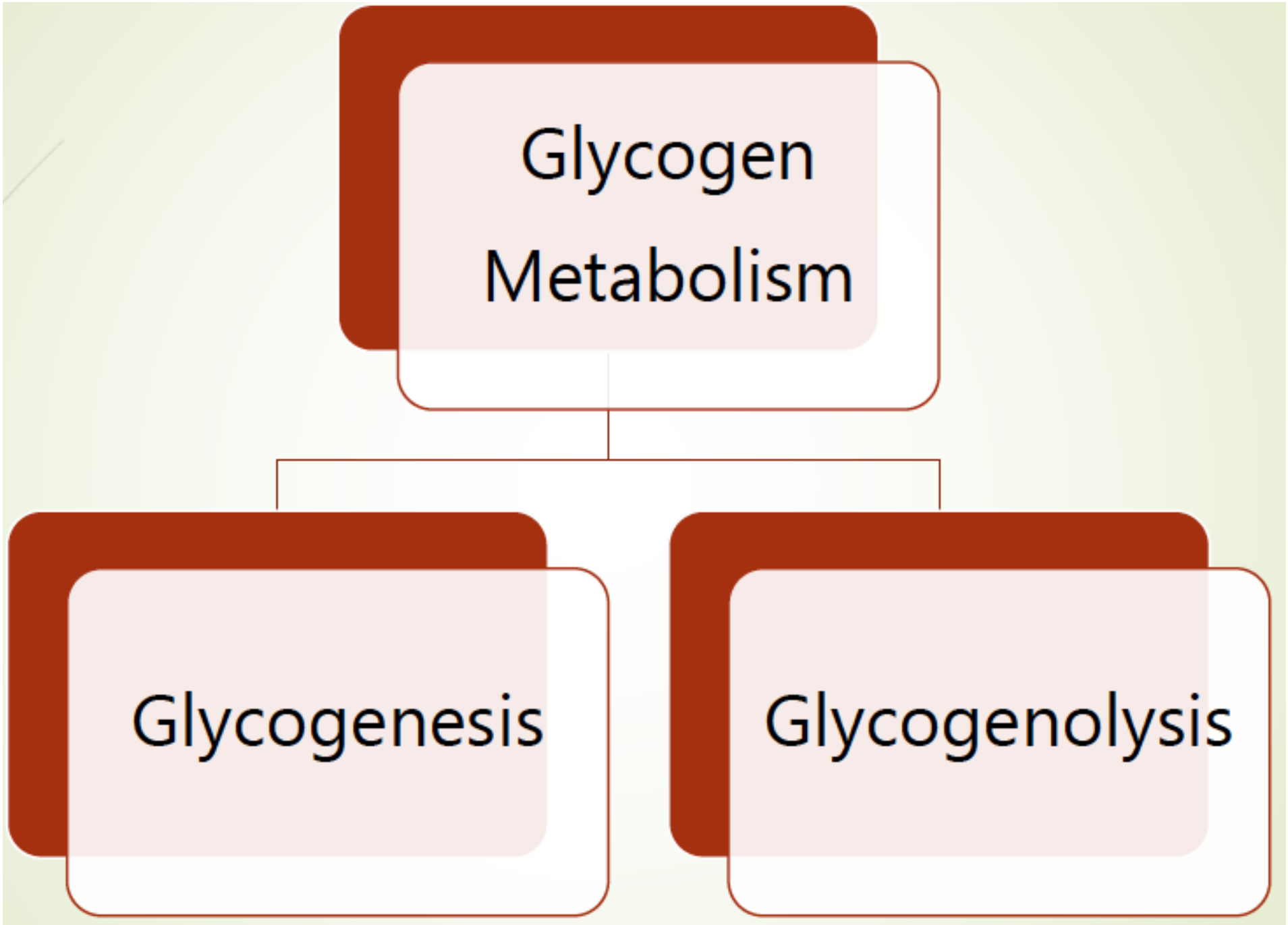
Glycogen is a polymer of glucose residues linked by

- α(1→4) glycosidic bonds, linear chains
- α(1→6) glycosidic bonds, at branch points

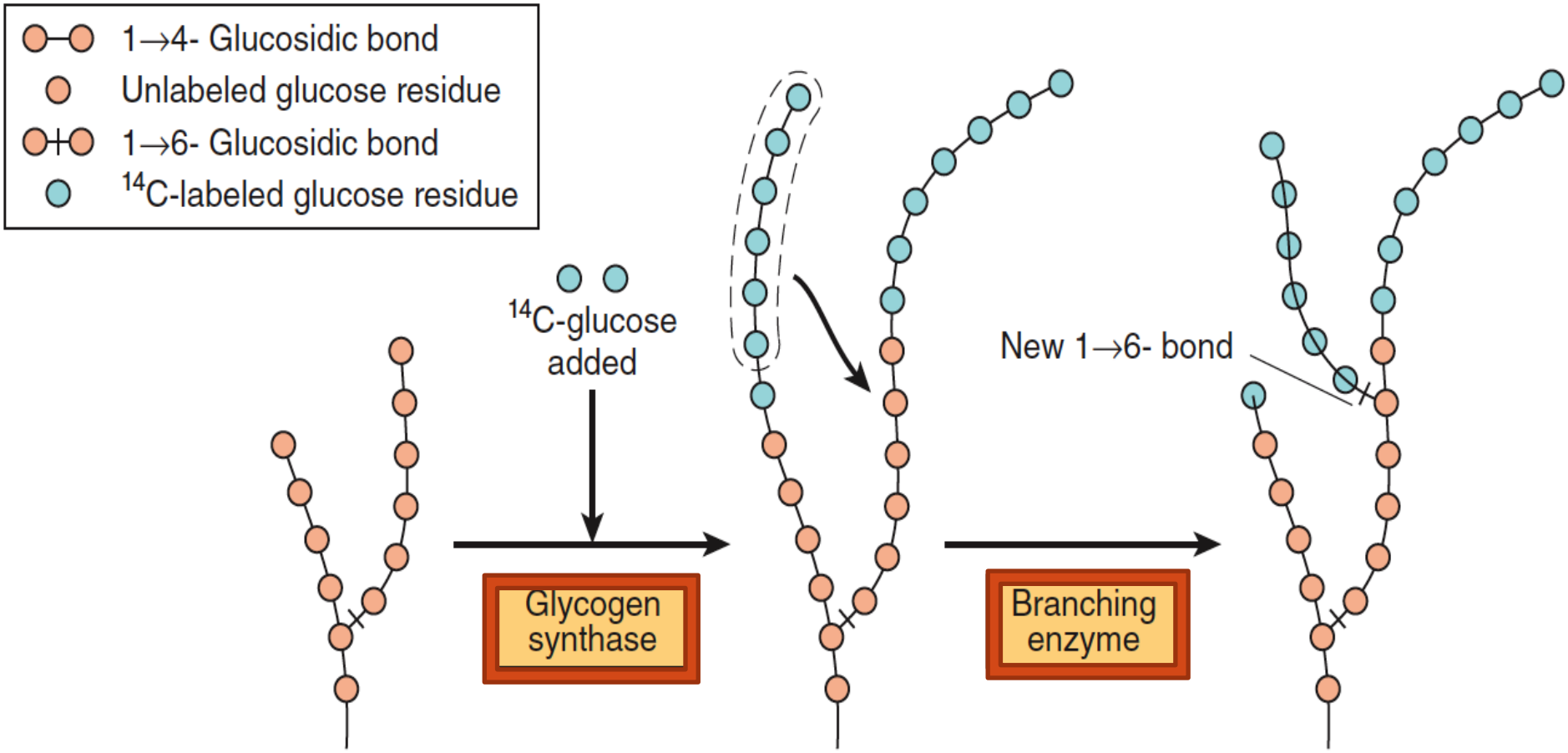
Glycogen

- Storage molecule
- Primer necessary for synthesis
- Very large!
- Multiple ends allow for quick synthesis and degradation

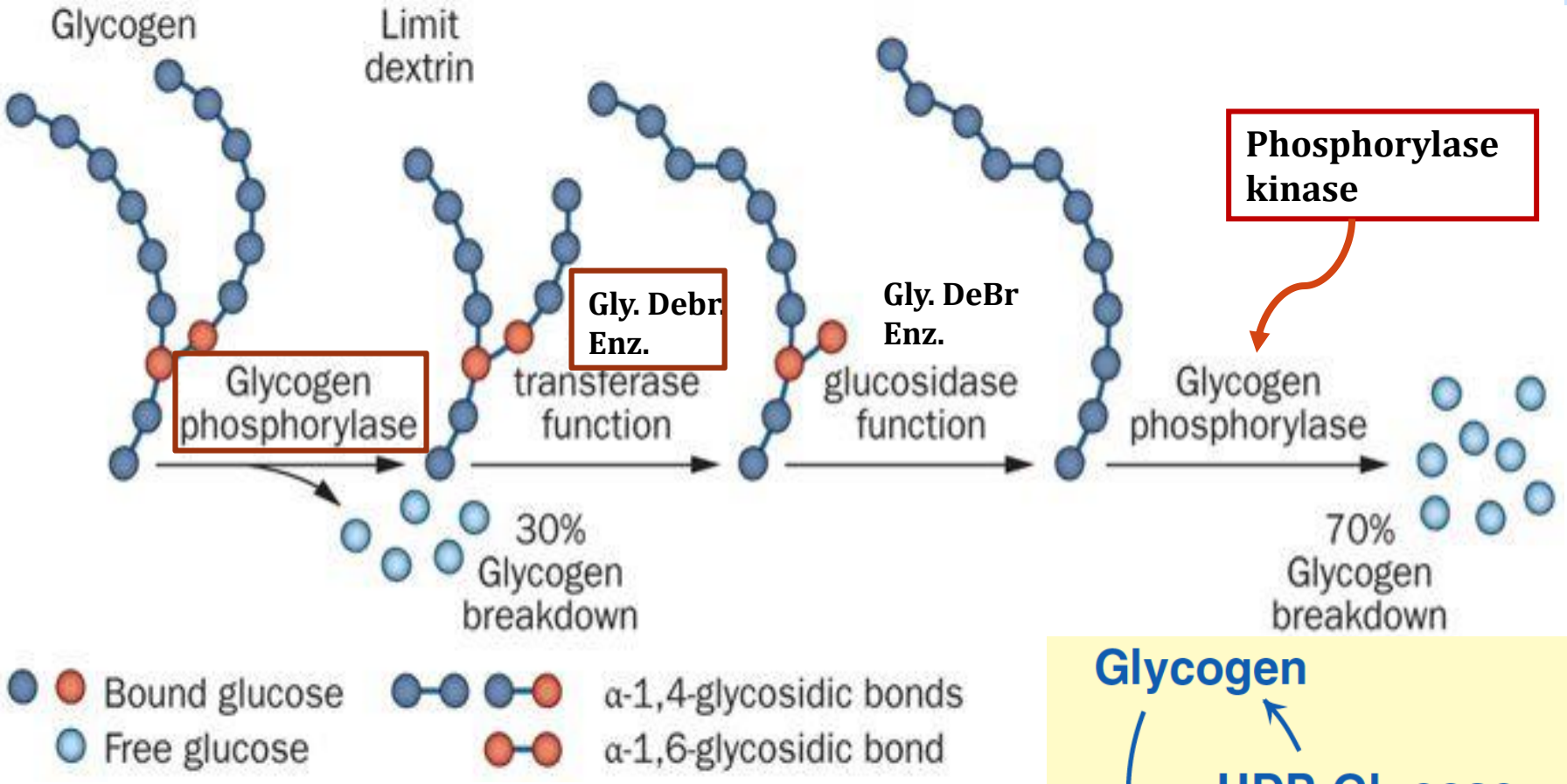



Glycogen Metabolism
Glycogenesis
Glycogenolysis

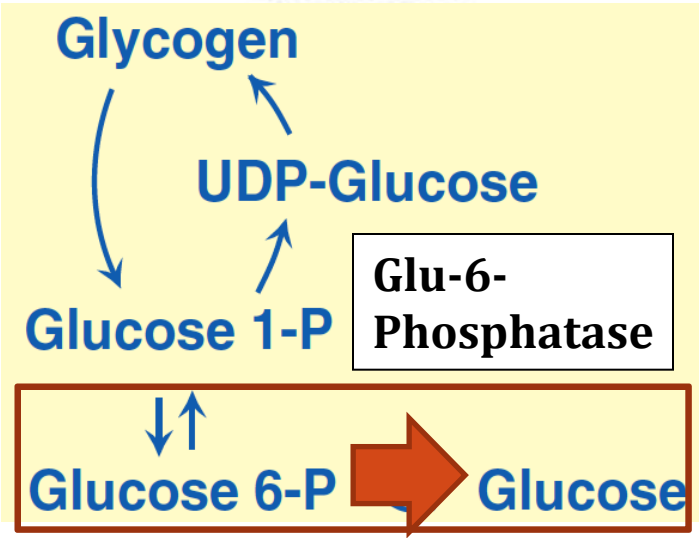
Glycogenesis (Glycogen synthesis)



Glycogenolysis (Glycogen breakdown)



Gly. Debr. Enz. = Glycogen De-branching Enzyme (AGL)



Lysosomal degradation of glycogen

- A small amount of glycogen is continuously degraded by lysosomal enz, ***α(1→4)-glucosidase*** (acid maltase).

- However, a deficiency of this enz causes accumulation of glycogen in vacuoles in the cytosol, resulting in the serious glycogen storage disease type II (Pompe disease)

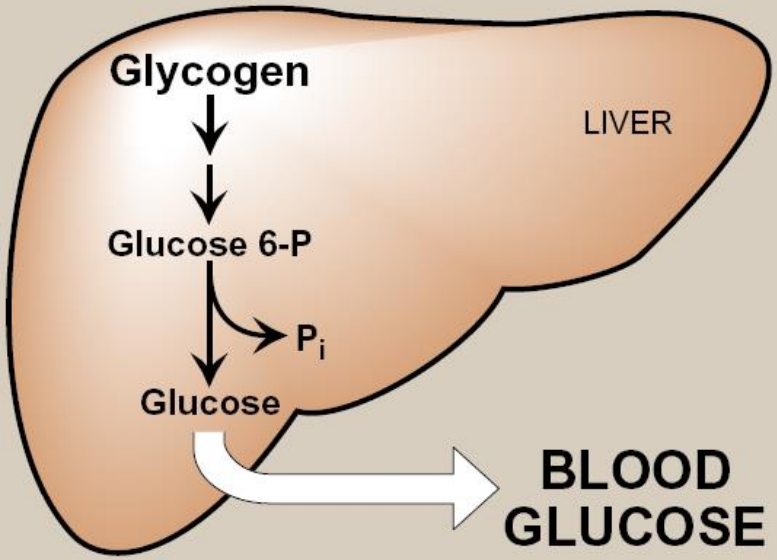
Functions of Glycogen

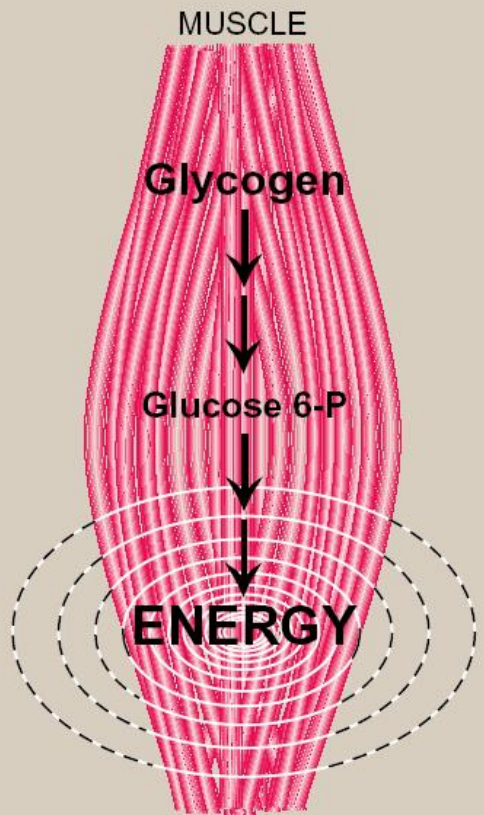
- In liver – The synthesis and breakdown of glycogen is regulated to maintain blood glucose levels.
- In muscle - The synthesis and breakdown of glycogen is regulated to meet the energy requirements of the muscle cell.

Remember!

•Liver contains Glu 6-phosphatase.

•Muscle does not have this enzyme.





GLUCOGEN STORAGE DISEASE

Glycogen storage diseases are a group of inherited disorders characterized by metabolic defects concerned with the glycogen synthesis and degradation – collectively referred to as **GLUCOGEN STORAGE DISEASE**

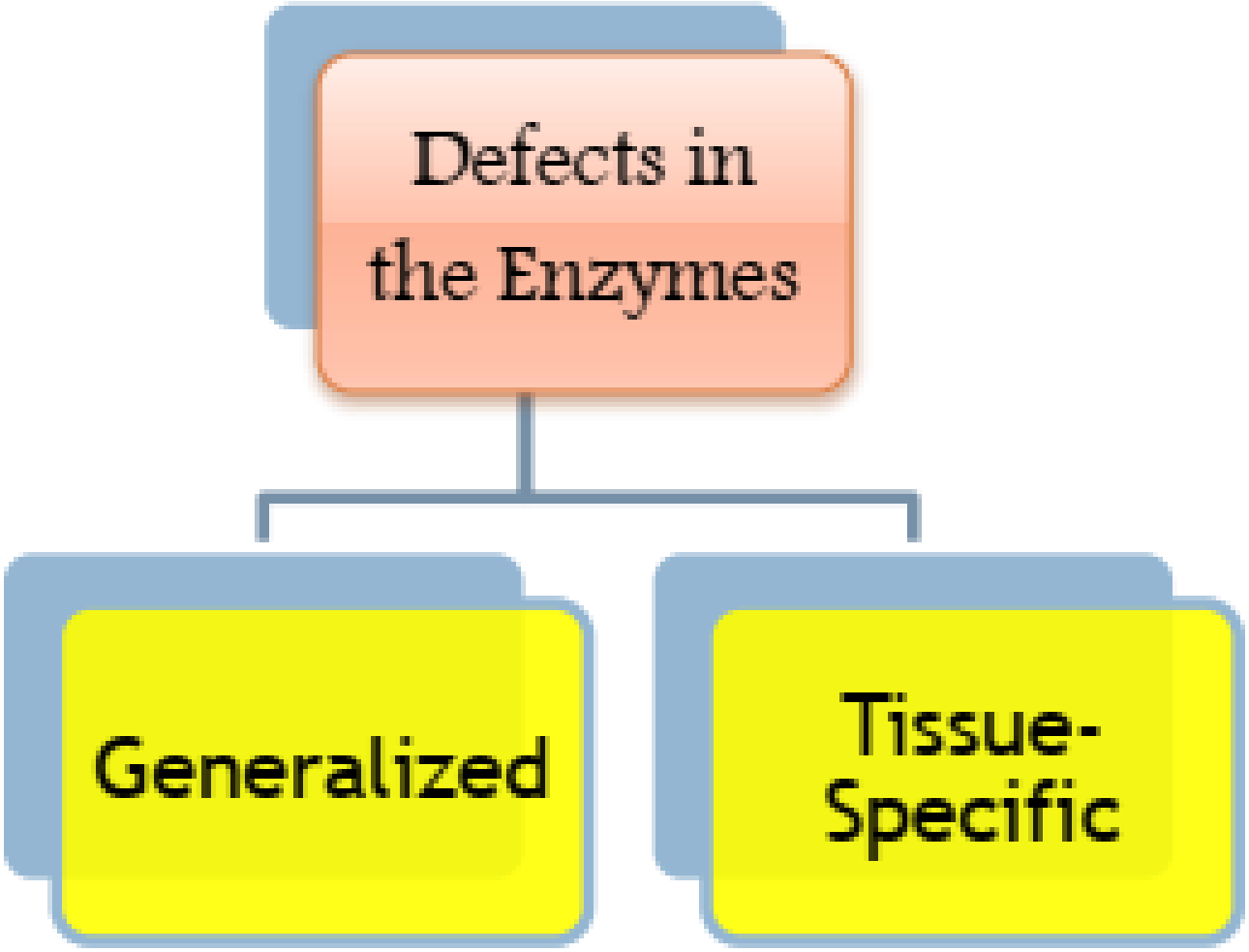
GLUCOGEN STORAGE DISEASE

Deficient mobilization of glycogen or deposition of abnormal forms of glycogen, leading to liver damage and muscle weakness; some glycogen storage diseases result in early death.

GSD

- Mostly confined to liver and muscle.
- But some cause more generalized pathology and affect tissues such as the kidney, heart and bowel.
- The classification of glycogen storage disorders is based on:
  - the enzyme deficiency and
  - the affected tissue

GSD due to?



Glycogen Storage Disorders (GSDs)

GSDs arise in enzymatic defects of:

- Glycogen synthesis: glycogen synthase, branching enzyme
- Glycogenolysis: tissue specific phosphorylases, debranching enzyme, lysosomal glucosidase
- Glycolysis: phosphofructokinase
- **Glycogenosis vs Glycogenesis???**

Glycogen Storage Disorders (GSDs)

- Disruption of glycogen metabolism also affects other biochemical pathways as the body seeks alternative fuel sources.

- Accumulation of abnormal metabolic by-products can damage other organs.

Inheritance patterns

- Mostly Autosomal recessive (I, II, III, IV, V, VII, some IX).
  - Both parents are carriers.
  - Chance of sibling being affected is 1 in 4.
- X-linked (some IX)

Type	Name	Enzyme Deficiency	Clinical Features
0	—	Glycogen synthase	Hypoglycemia; hyperketonemia; early death
Ia	Von Gierke disease	Glucose-6-phosphatase	Glycogen accumulation in liver and renal tubule cells; hypoglycemia; lactic acidemia; ketosis; hyperlipemia
Ib	—	Endoplasmic reticulum glucose-6-phosphate transporter	As type Ia; neutropenia and impaired neutrophil function leading to recurrent infections
II	Pompe disease	Lysosomal $\alpha_1 \rightarrow 4$ and $\alpha_1 \rightarrow 6$ glucosidase (acid maltase)	Accumulation of glycogen in lysosomes: juvenile onset variant, muscle hypotonia, death from heart failure by age 2; adult onset variant, muscle dystrophy
IIIa	Limit dextrinosis, Forbe or Cori disease	Liver and muscle debranching enzyme	Fasting hypoglycemia; hepatomegaly in infancy; accumulation of characteristic branched polysaccharide (limit dextrin); muscle weakness
IIIb	Limit dextrinosis	Liver debranching enzyme	As type IIIa, but no muscle weakness
IV	Amylopectinosis, Andersen disease	Branching enzyme	Hepatosplenomegaly; accumulation of polysaccharide with few branch points; death from heart or liver failure before age 5
V	Myophosphorylase deficiency, McArdle syndrome	Muscle phosphorylase	Poor exercise tolerance; muscle glycogen abnormally high (2.5%-4%); blood lactate very low after exercise
VI	Hers disease	Liver phosphorylase	Hepatomegaly; accumulation of glycogen in liver; mild hypoglycemia; generally good prognosis
VII	Tarui disease	Muscle and erythrocyte phosphofructokinase 1	Poor exercise tolerance; muscle glycogen abnormally high (2.5%-4%); blood lactate very low after exercise; also hemolytic anemia
VIII		Liver phosphorylase kinase	Hepatomegaly; accumulation of glycogen in liver; mild hypoglycemia; generally good prognosis
IX		Liver and muscle phosphorylase kinase	Hepatomegaly; accumulation of glycogen in liver and muscle; mild hypoglycemia; generally good prognosis
X		cAMP-dependent protein kinase A	Hepatomegaly; accumulation of glycogen in liver

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe disease	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori disease	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen disease	Branching enzyme (α-1,4 $\longrightarrow$ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle disease	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers disease	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

Glycogen Storage Disease Type 0

Type	Name	Enzyme Deficiency	Clinical Features
0	—	Glycogen synthase	Hypoglycemia; hyperketonemia; early death

(Glycogen Synthase Deficiency)

GSD 0 is caused by a deficiency of glycogen synthase (GS), a key-enzyme of glycogen synthesis. Consequently, patients with GS deficiency have decreased liver glycogen concentration, resulting in fasting hypoglycemia.

Ketotic Hypoglycemia without Hepatomegaly

TABLE 21.1 Glycogen-storage diseases

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe disease	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori disease	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen disease	Branching enzyme (α-1,4 $\longrightarrow$ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle disease	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers disease	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.

TABLE 21.1 Glycogen-storage diseases

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.

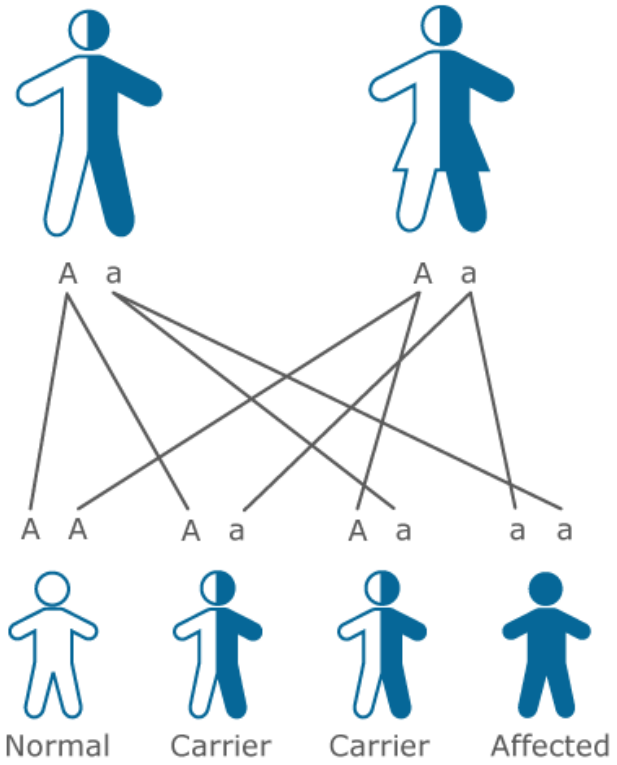
GSD-I

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.

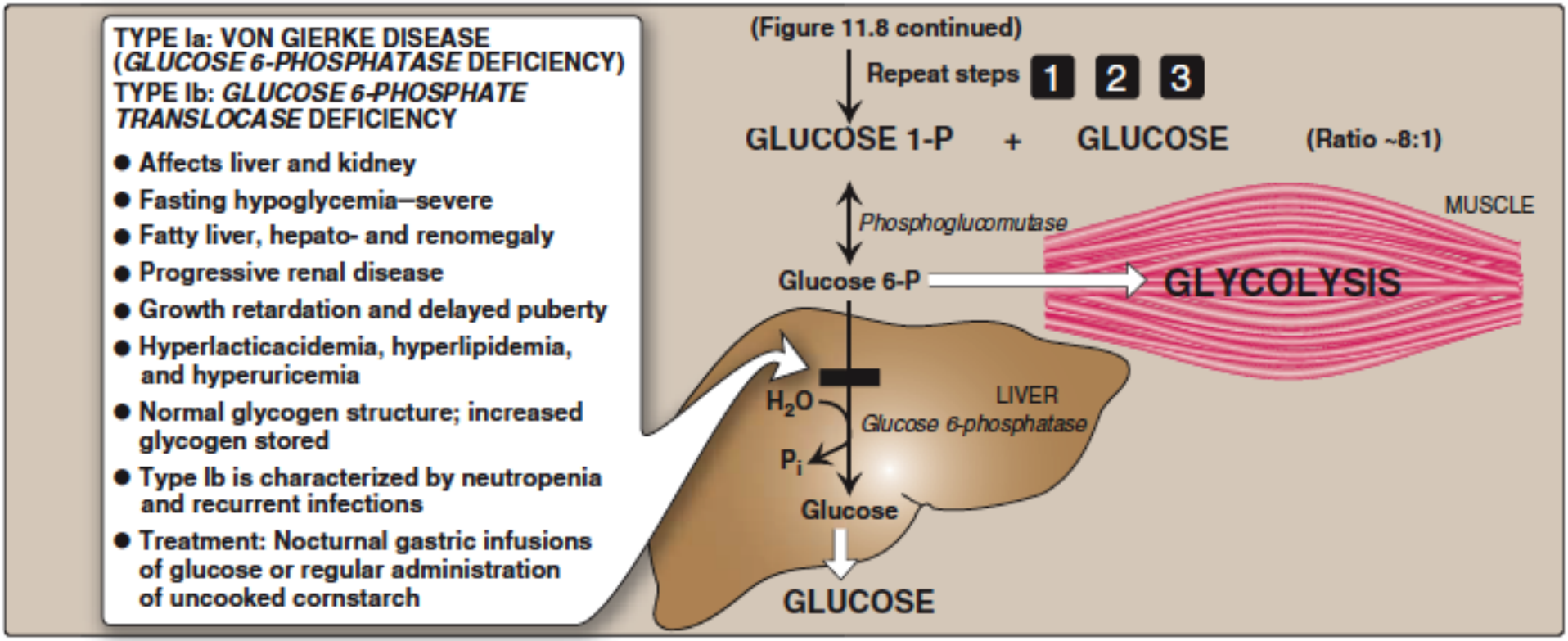
Type	Name	Enzyme Deficiency	Clinical Features
Ia	Von Gierke disease	Glucose-6-phosphatase	Glycogen accumulation in liver and renal tubule cells; hypoglycemia; lactic acidemia; ketosis; hyperlipemia
Ib	—	Endoplasmic reticulum glucose-6-phosphate transporter	As type Ia; neutropenia and impaired neutrophil function leading to recurrent infections

- **Type I is the most common (25% of all GSD).**

Autosomal Recessive Disease



GSD-I


TYPE Ia: VON GIERKE DISEASE (GLUCOSE 6-PHOSPHATASE DEFICIENCY)
TYPE Ib: GLUCOSE 6-PHOSPHATE TRANSLOCASE DEFICIENCY
Affects liver and kidney
Fasting hypoglycemia—severe
Fatty liver, hepato- and renomegaly
Progressive renal disease
Growth retardation and delayed puberty
Hyperlacticacidemia, hyperlipidemia, and hyperuricemia
Normal glycogen structure; increased glycogen stored
Type Ib is characterized by neutropenia and recurrent infections
Treatment: Nocturnal gastric infusions of glucose or regular administration of uncooked cornstarch
(Figure 11.8 continued)
Repeat steps 1 2 3
GLUCOSE 1-P + GLUCOSE (Ratio ~8:1)
Phosphoglucomutase
MUSCLE
Glucose 6-P
GLYCOLYSIS
LIVER
H2O
Glucose 6-phosphatase
Pi
Glucose
GLUCOSE

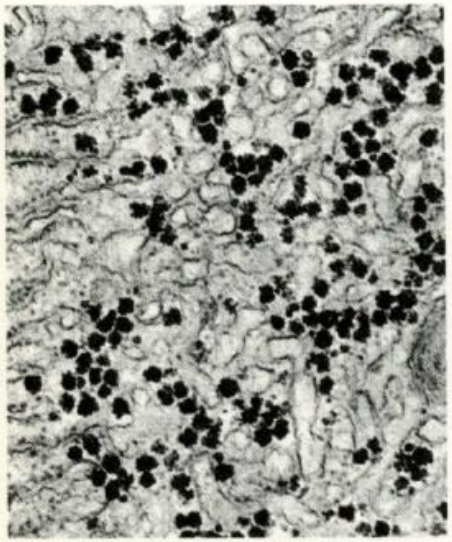
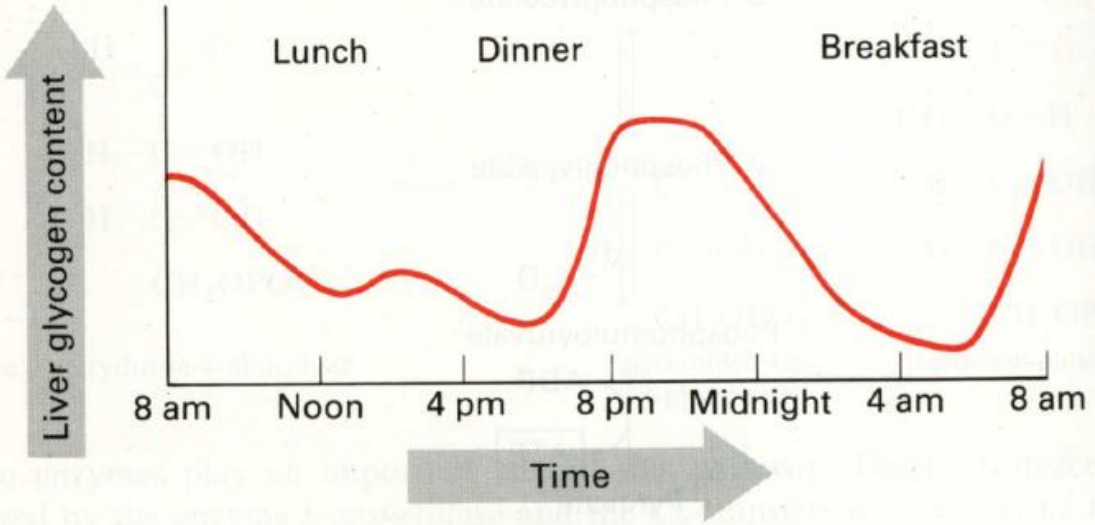


FIGURE 29–9 Electron micrographs showing glycogen granules (darkly stained material) in liver cells.

FIGURE 29–10 Variation of liver glycogen levels between meals.



GSD-I

serum apolipoprotein E

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.

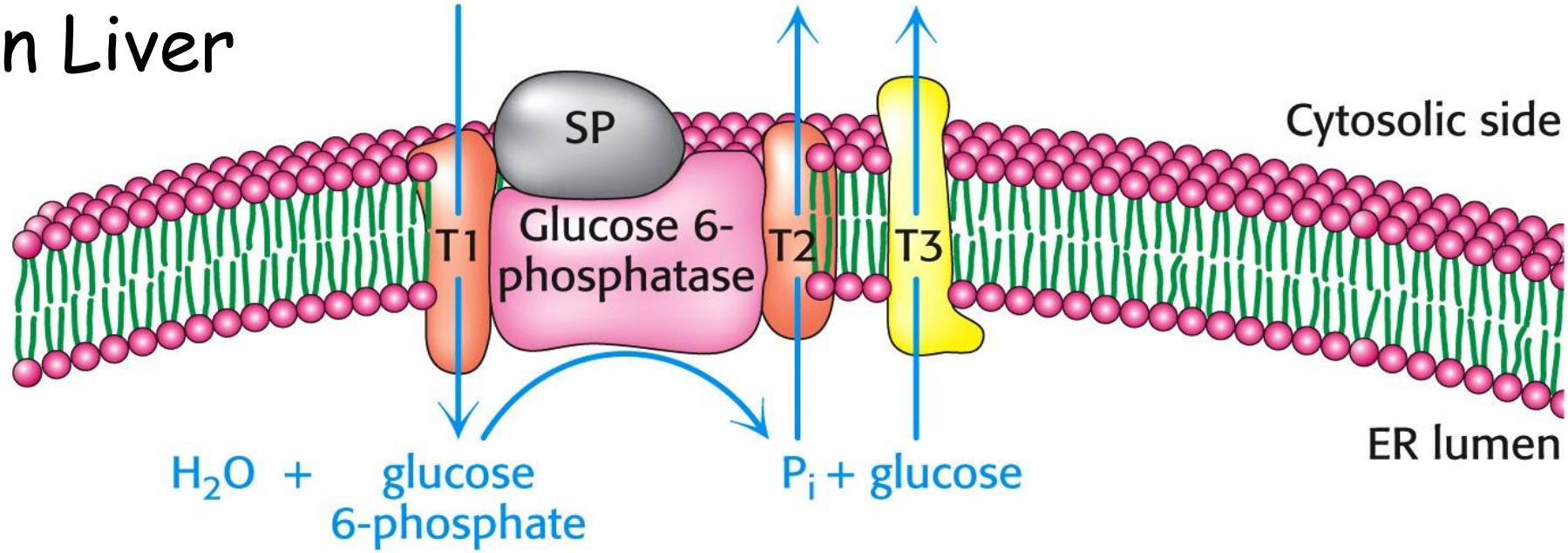
4 types

Type	Name	Enzyme Deficiency	Clinical Features
Ia	Von Gierke disease	Glucose-6-phosphatase	Glycogen accumulation in liver and renal tubule cells; hypoglycemia; lactic acidemia; ketosis; hyperlipemia
Ib	—	Endoplasmic reticulum glucose-6-phosphate transporter	As type Ia; neutropenia and impaired neutrophil function leading to recurrent infections

I-c

I-d

In Liver



- T1 transports glucose 6-phosphate into the lumen of the ER.
- T2 and T3 transport Pi and glucose, respectively, back into the cytosol.
- Glucose 6-phosphatase is stabilized by a Ca2+-binding protein (SP).

4 TYPES:

Type-Ia = Glucose 6 phosphatase Deficiency

Type-Ib = T1 transporter Deficiency

Type-Ic = T2 transporter Deficiency

Type-Id = T3 transporter Deficiency

Presentation

- Liver cannot release stored glucose
  - hepatomegaly
  - severe hypoglycemia
- Body must rely on fat/protein catabolism for energy
  - hyperlipidemia
  - hyperuricemia
  - lactic acidosis
- Normal glycogen structure

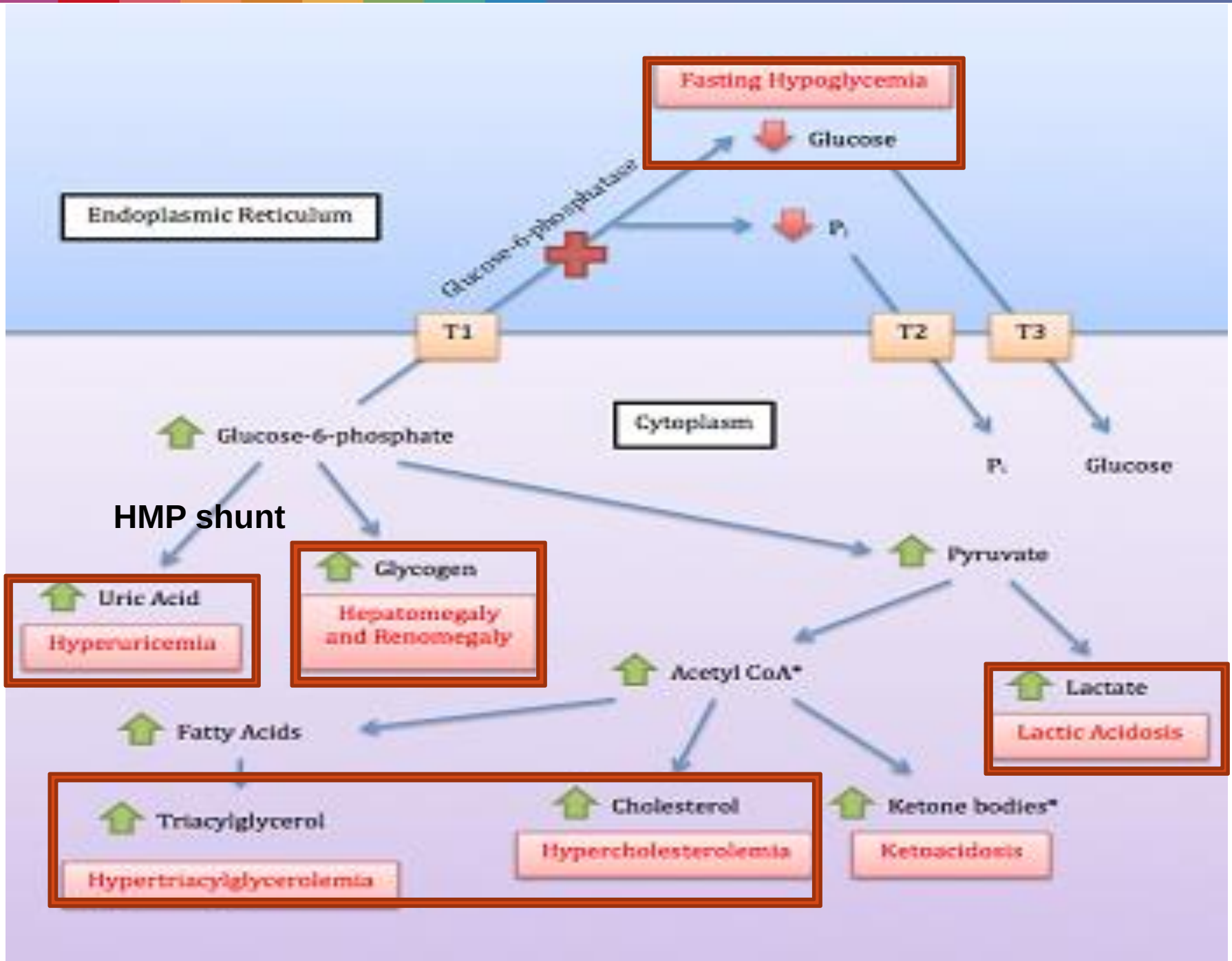
Presentation

Patients typically present by 6 months of age with fasting hypoglycemia or hepatomegaly, and are found to have protuberant abdomen, stunted growth, and doll-like facies

GSD type I is characterized by:

- Growth retardation and delayed puberty,
- Associated with poor metabolic control, particularly chronic metabolic acidosis – interferes with growth hormone activity

➢ If both parents carry the defective gene related to this condition, each of their children has a 25% chance of developing the disease


Fasting Hypoglycemia
Glucose
Endoplasmic Reticulum
Glucose-6-phosphatase
Pi
T1
T2
T3
Glucose-6-phosphate
Cytoplasm
Pi
Glucose
HMP shunt
Pyruvate
Uric Acid
Hyperuricemia
Glycogen
Hepatomegaly and Renomegaly
Acetyl CoA*
Lactate
Lactic Acidosis
Fatty Acids
Triacylglycerol
Hypertriacylglycerolemia
Cholesterol
Hypercholesterolemia
Ketone bodies*
Ketoacidosis

Lysosomal degradation of glycogen

- A small amount of glycogen is continuously degraded by lysosomal enz, ***α(1→4)-glucosidase*** (acid maltase). Purpose of this pathway is unknown
- However, a deficiency of this enz causes accumulation of glycogen in vacuoles in the cytosol, resulting in the serious glycogen storage disease type II (Pompe disease)

GSD-II

Type	Name	Enzyme Deficiency	Clinical Features
II	Pompe disease **3 types**	Lysosomal $\alpha_1 \rightarrow 4$ and $\alpha_1 \rightarrow 6$ glucosidase (acid maltase)	Accumulation of glycogen in lysosomes: juvenile onset variant, muscle hypotonia, death from heart failure by age 2; adult onset variant, muscle dystrophy

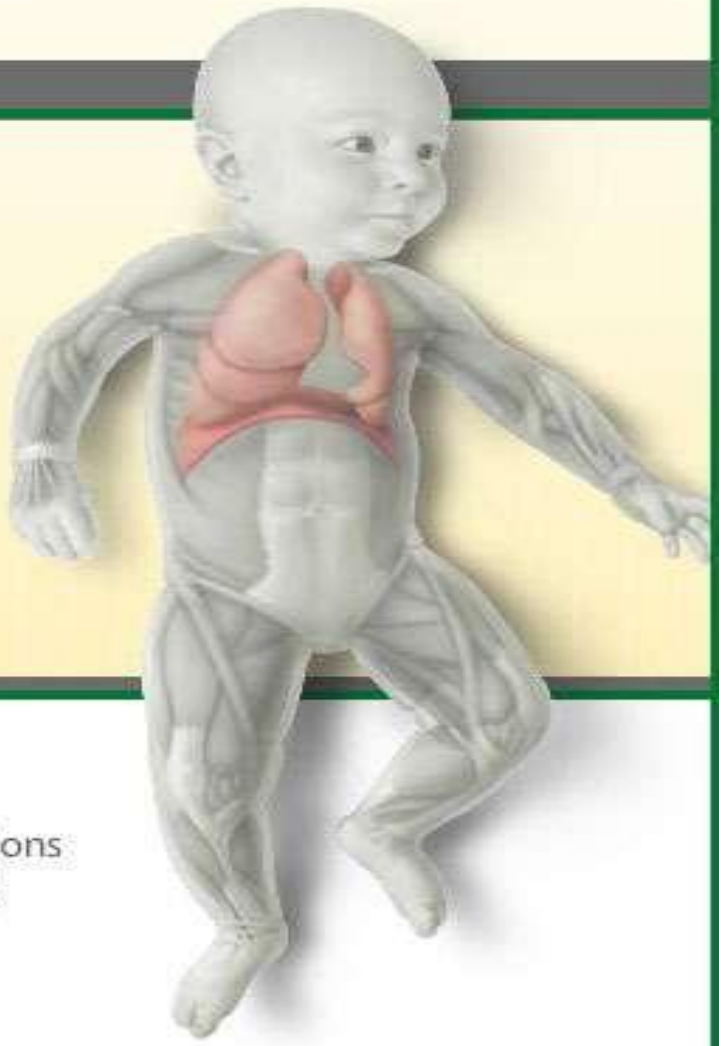
Infantile, Juvenile, Adult

→In the infantile form, infants seem normal at birth, but within a few months they develop muscle weakness, trouble breathing, and an enlarged heart. Cardiac failure and death usually occur before age 2, despite medical treatment.

→The juvenile and adult forms of GSD II affect mainly the skeletal muscles in the body's limbs and torso. Decreased muscle strength and weakness developed

SYMPTOMS IN INFANTS
with Pompe disease

- Gastrointestinal
- Cardiac
- Respiratory
- Musculoskeletal



RESPIRATORY

- Frequent respiratory infections
- Sleep disordered breathing
- Progression to respiratory insufficiency
- Premature death due to cardiorespiratory failure

Treatment :

Enzyme replacement therapy using recombinant human α-glucosidase has been used successfully

Danon Disease

- **Danon Disease** or **GSD II-b**, or **pseudo-Pompe disease**, is an X-linked dominant lysosomal storage disease due to deficiency of LAMP-2 (**L**ysosomal **A**ssociated **M**embrane **P**rotein **2**).
- Starts after the first decade, extremely rare, affects cardiac and skeletal muscle.
- Acid maltase activity is normal, muscle biopsy shows vacuolar myopathy with vacuoles containing glycogen and cytoplasmatic degradation products

GSD-III

Type	Name	Enzyme Deficiency	Clinical Features
IIIa	Limit dextrinosis, Forbe or Cori disease	Liver and muscle debranching enzyme	Fasting hypoglycemia; hepatomegaly in infancy; accumulation of characteristic branched polysaccharide (limit dextrin); muscle weakness
IIIb	Limit dextrinosis	Liver debranching enzyme	As type IIIa, but no muscle weakness

2 types

Pan-deficiency of the enzyme – GSD III-a
or
Muscle-specific retention of glycogen debranching enzyme, ABSENT IN LIVER – GSD III-b.

Lacks Debranching enzyme

Remember:

- **C**ori = **C**an't **C**atabolize branches - alpha 1,6 glucosidase defective
- Liver cannot break down glycogen past a branch point

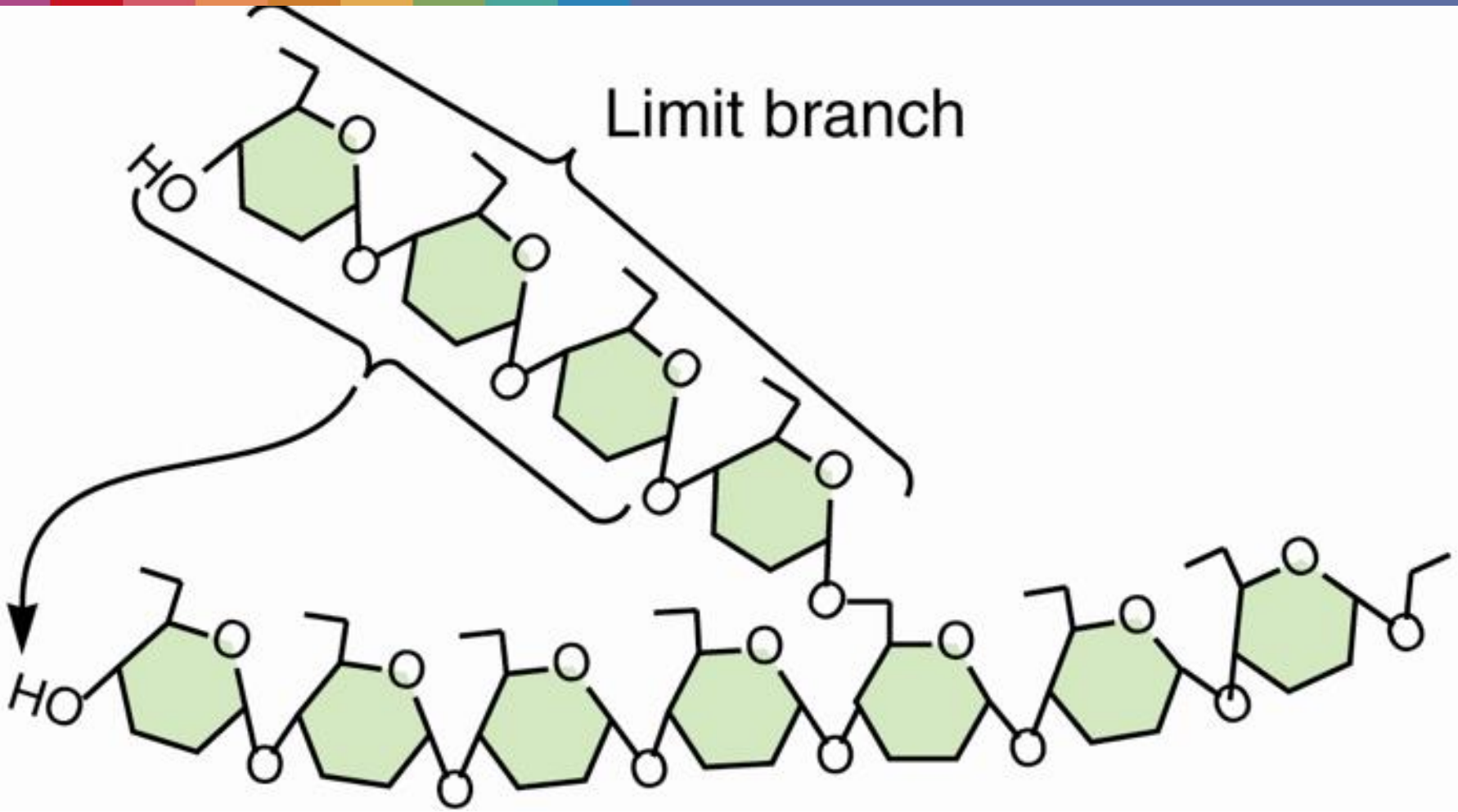
- Abnormal glycogen structure – short outer glycogen chains

GSD III

Although the enzyme is found in all tissues, clinical manifestations generally are non-myopathic.

Presentation

- Hepatomegaly, few with liver cirrhosis and hepatocellular carcinoma
- Moderate progressive myopathy
- Hypoglycemia
- History may consists of infant seizures and growth retardation.
- Vigorous exercise is not associated with cramping, tenderness, or myoglobulinuria.



Limit dextrin is the remaining polymer produced after hydrolysis of glycogen. Without glycogen debranching enzymes, limit dextrinosis abnormally accumulates

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe disease	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori disease	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen disease	Branching enzyme (α-1,4 ⟶ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle disease	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers disease	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

GSD-IV

Type	Name	Enzyme Deficiency	Clinical Features
IV	Amylopectinosis, Andersen disease	Branching enzyme	Hepatosplenomegaly; accumulation of polysaccharide with few branch points; death from heart or liver failure before age 5

Andersen disease Lacks Branching enzyme

Remember: **ABCD**

- **A= Andersen disease**
- **B= Branching Enzyme deficient**
- **–** very long outer glycogen chains

- **C= Cori's disease**
- **D= De-branching Enzyme deficient**
- **–** short outer glycogen chains

- **Both have Abnormal glycogen structure**

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe disease	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori disease	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen disease	Branching enzyme (α-1,4 ⟶ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle disease	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers disease	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

The classical GSD4 presents around 18 months of birth:

- Failure to thrive,
- Hepatosplenomegaly,
- Liver cirrhosis .
- Leads to death by the age of 5 unless a liver transplant is performed.

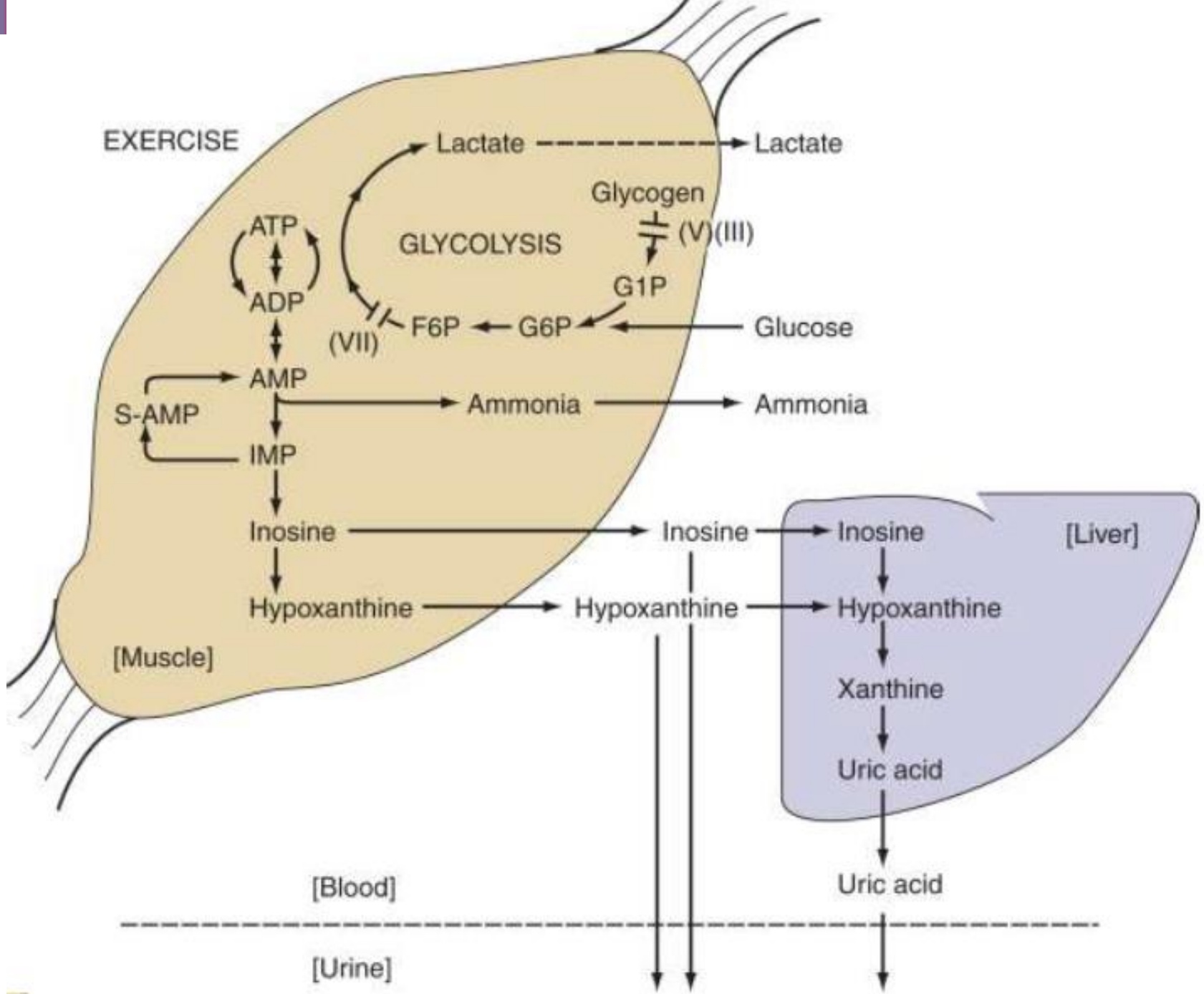
➢ A non-progressive hepatic form with a similar presentation has also been described.

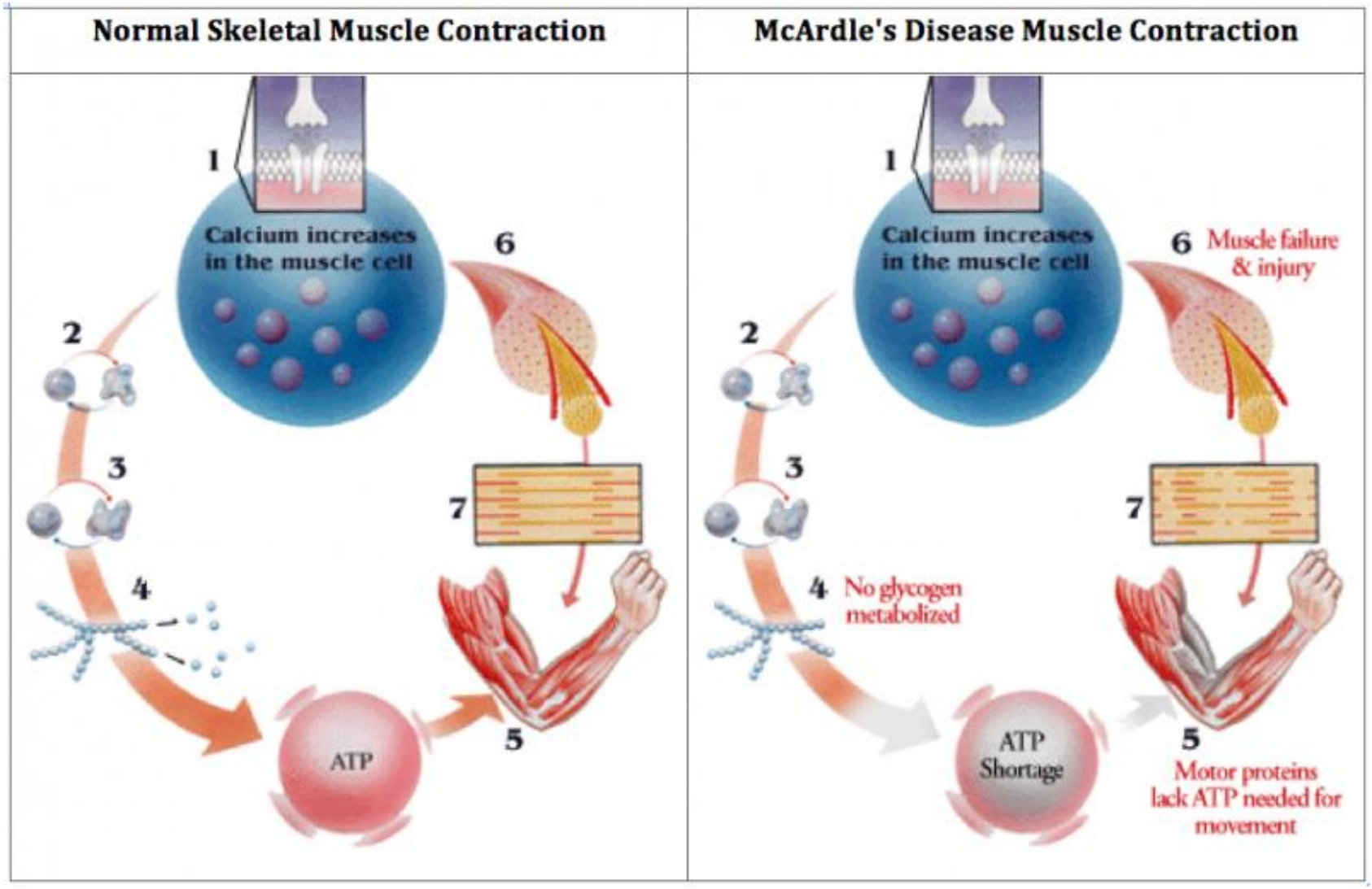
GSD-V

Type	Name	Enzyme Deficiency	Clinical Features
V	Myophosphorylase deficiency, McArdle syndrome	Muscle phosphorylase	Poor exercise tolerance; muscle glycogen abnormally high (2.5%-4%); blood lactate very low after exercise

- Lacks Muscle Phosphorylase
- Remember: **M**cArdles = **M**uscle
- Can't breakdown glycogen to glucose-1-phosphate

- **Presentation**
  - Muscle weakness/cramps upon exertion
  - Myoglobinuria
  - Normal glycogen structure


EXERCISE
Lactate
Lactate
Glycogen
(V)(III)
ATP
GLYCOLYSIS
ADP
G1P
(VII)
F6P
G6P
Glucose
AMP
S-AMP
Ammonia
Ammonia
IMP
Inosine
Inosine
Inosine
[Liver]
Hypoxanthine
Hypoxanthine
Hypoxanthine
[Muscle]
Xanthine
Uric acid
[Blood]
Uric acid
[Urine]


Normal Skeletal Muscle Contraction
McArdle's Disease Muscle Contraction
1
Calcium increases in the muscle cell
2
3
4
ATP
5
6
7
1
Calcium increases in the muscle cell
2
3
4
No glycogen metabolized
ATP Shortage
5
Motor proteins lack ATP needed for movement
6
Muscle failure & injury
7

GSD-VI

Type	Name	Enzyme Deficiency	Clinical Features
VI	Hers disease	Liver phosphorylase	Hepatomegaly; accumulation of glycogen in liver; mild hypoglycemia; generally good prognosis

- Lacks Hepatic Phosphorylase
- Remember: **H**ers = **H**epatic

- **Presentation**
  - Hepatomegaly
  - Fasting hypoglycemia – mild due to gluconeogenic compensation
  - Normal glycogen structure

GSD-VII

Type	Name	Enzyme Deficiency	Clinical Features
VII	Tarui disease	Muscle and erythrocyte phosphofructokinase 1	Poor exercise tolerance; muscle glycogen abnormally high (2.5%-4%); blood lactate very low after exercise; also hemolytic anemia

Glycogen Storage Disease Type VII(Phosphofructokinase Deficiency)

first described by Tarui

Although glucose may be available as a fuel in muscles, the cells cannot metabolize it.

Symptoms :

Muscle cramps with exercise

Anemia

Note : Symptoms can be similar to McArdle's Glycogen Storage Disease but more severe.

PFK consists of 3 subunits: muscle (M), liver (L), and platelet (P).

- Phosphofructokinase catalyzes the rate-limiting step in glycolysis.

- Phosphofructokinase deficiency leads to muscle pain and exercise-induced fatigue and weakness.
- Tarui disease resolves with rest, and, although no specific treatment exists, the condition may not progress to severe disability

Type	Name	Enzyme Deficiency	Clinical Features
0	—	Glycogen synthase	Hypoglycemia; hyperketonemia; early death
Ia	Von Gierke disease	Glucose-6-phosphatase	Glycogen accumulation in liver and renal tubule cells; hypoglycemia; lactic acidemia; ketosis; hyperlipemia
Ib	—	Endoplasmic reticulum glucose-6-phosphate transporter	As type Ia; neutropenia and impaired neutrophil function leading to recurrent infections
II	Pompe disease	Lysosomal $\alpha_1 \rightarrow 4$ and $\alpha_1 \rightarrow 6$ glucosidase (acid maltase)	Accumulation of glycogen in lysosomes: juvenile onset variant, muscle hypotonia, death from heart failure by age 2; adult onset variant, muscle dystrophy
IIIa	Limit dextrinosis, Forbe or Cori disease	Liver and muscle debranching enzyme	Fasting hypoglycemia; hepatomegaly in infancy; accumulation of characteristic branched polysaccharide (limit dextrin); muscle weakness
IIIb	Limit dextrinosis	Liver debranching enzyme	As type IIIa, but no muscle weakness
IV	Amylopectinosis, Andersen disease	Branching enzyme	Hepatosplenomegaly; accumulation of polysaccharide with few branch points; death from heart or liver failure before age 5
V	Myophosphorylase deficiency, McArdle syndrome	Muscle phosphorylase	Poor exercise tolerance; muscle glycogen abnormally high (2.5%-4%); blood lactate very low after exercise
VI	Hers disease	Liver phosphorylase	Hepatomegaly; accumulation of glycogen in liver; mild hypoglycemia; generally good prognosis
VII	Tarui disease	Muscle and erythrocyte phosphofructokinase 1	Poor exercise tolerance; muscle glycogen abnormally high (2.5%-4%); blood lactate very low after exercise; also hemolytic anemia
VIII		Liver phosphorylase kinase	Hepatomegaly; accumulation of glycogen in liver; mild hypoglycemia; generally good prognosis
IX		Liver and muscle phosphorylase kinase	Hepatomegaly; accumulation of glycogen in liver and muscle; mild hypoglycemia; generally good prognosis
X		cAMP-dependent protein kinase A	Hepatomegaly; accumulation of glycogen in liver

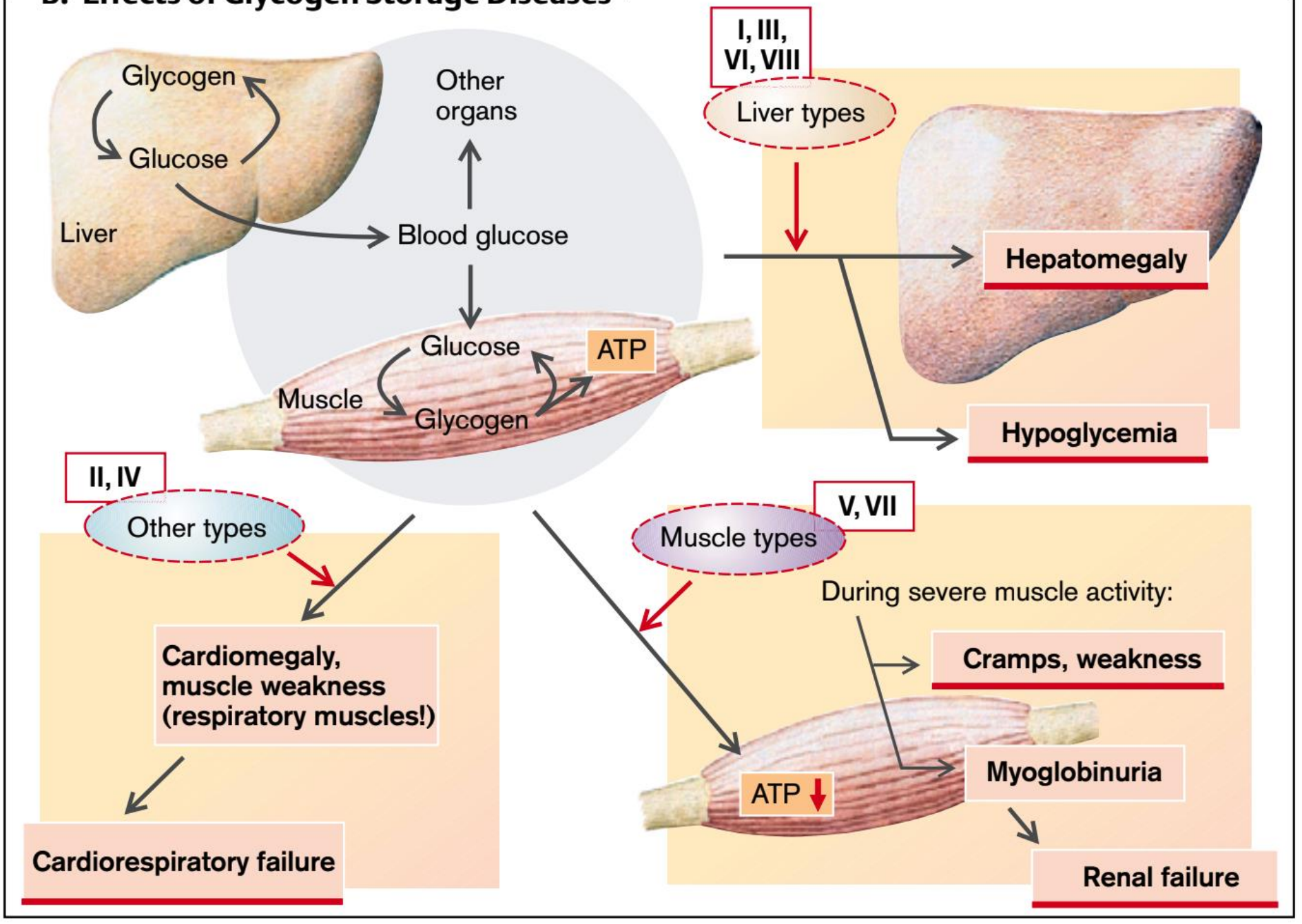
Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe disease	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori disease	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen disease	Branching enzyme (α-1,4 $\longrightarrow$ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle disease	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers disease	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

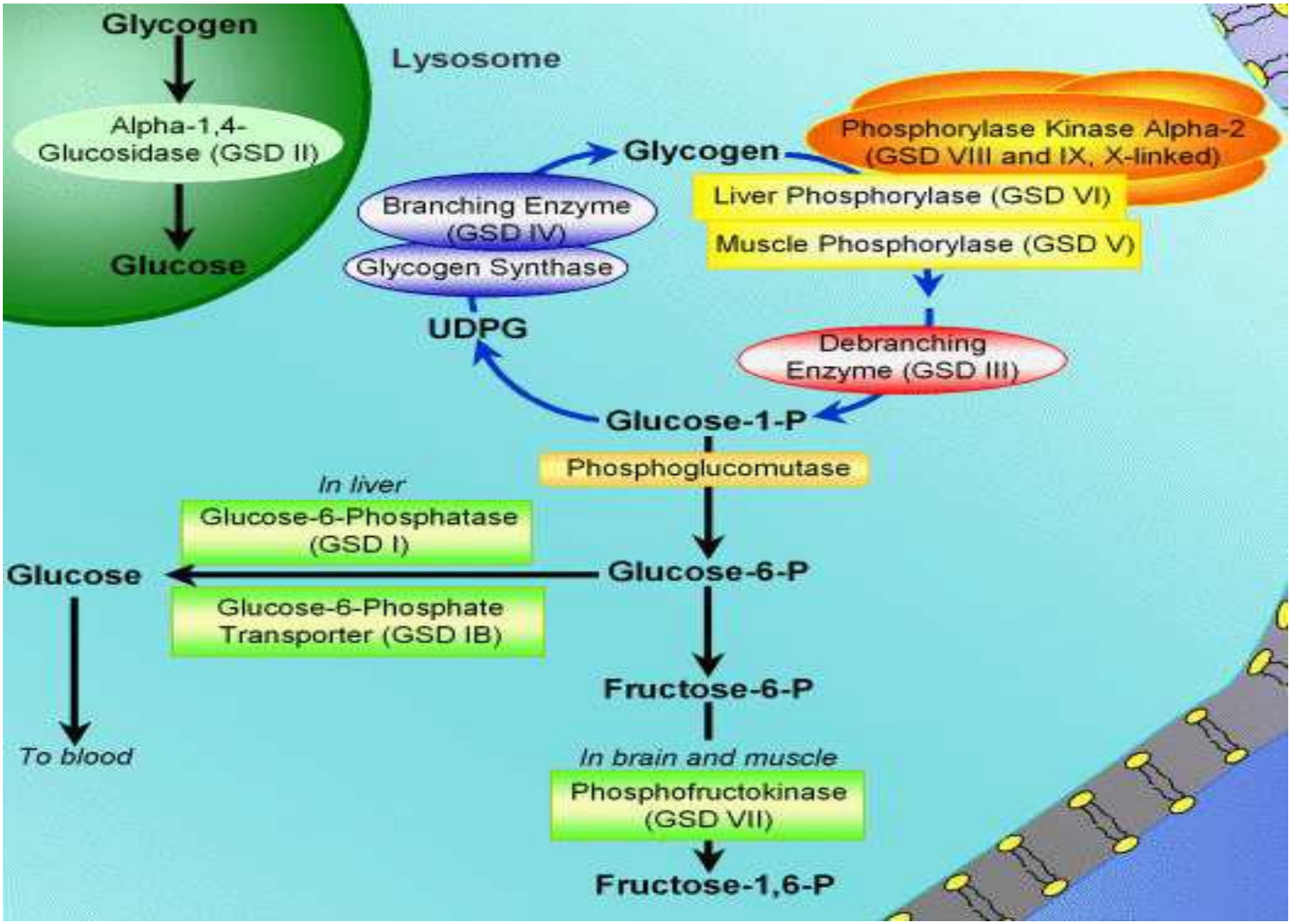
At least 14 unique GSDs

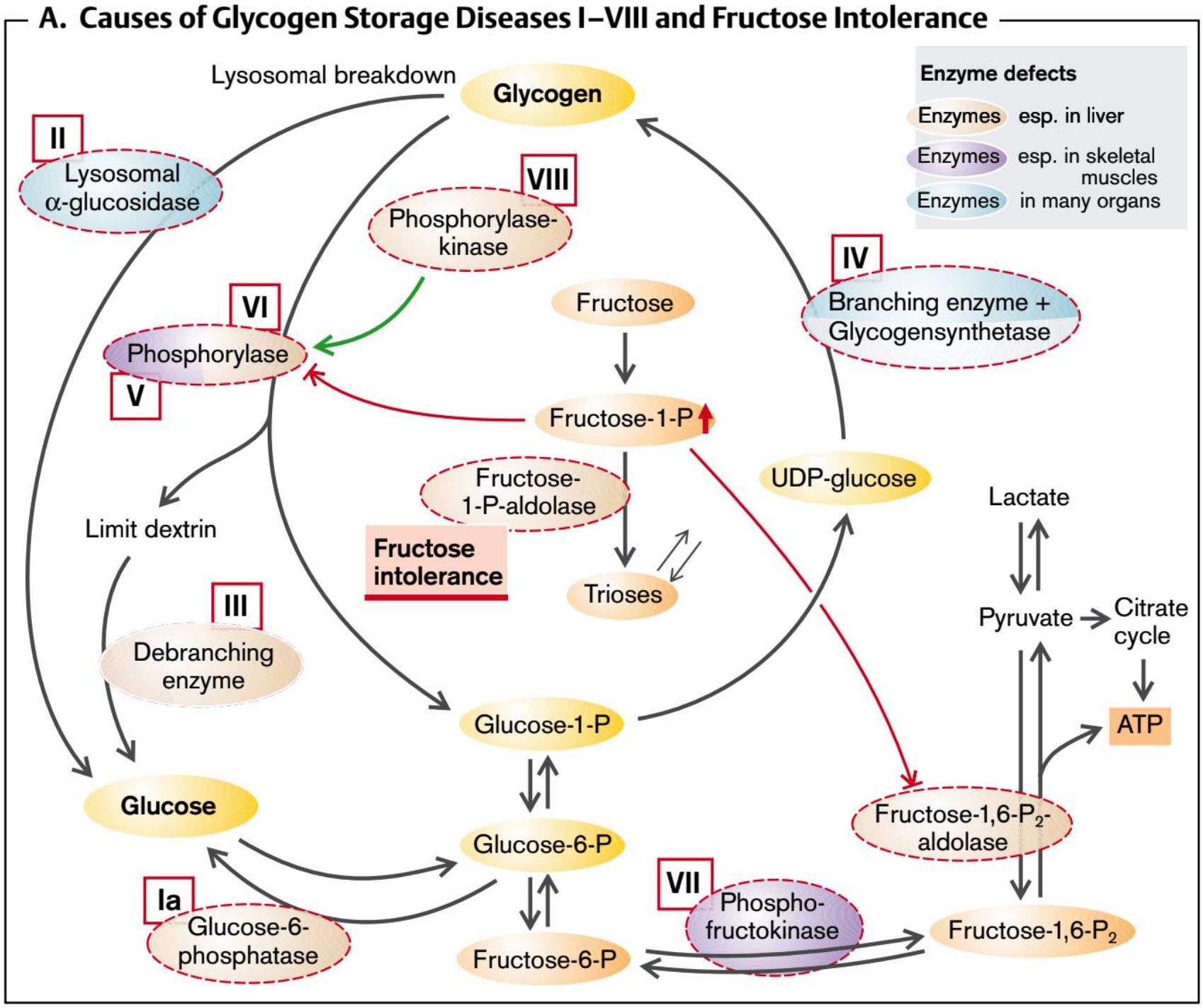
- Four cause clinically significant muscle disease:
  1. Pompe disease (GSD type II),
  2. Cori disease (GSD type IIIa),
  3. McArdle disease (GSD type V), and
  4. Tarui disease (GSD type VII).

- Von Gierke disease (GSD type Ia), causes clinically significant end-organ disease with significant morbidity.

B. Effects of Glycogen Storage Diseases




Glycogen
Lysosome
Alpha-1,4-Glucosidase (GSD II)
Glucose
Glycogen
Phosphorylase Kinase Alpha-2 (GSD VIII and IX, X-linked)
Liver Phosphorylase (GSD VI)
Muscle Phosphorylase (GSD V)
Branching Enzyme (GSD IV)
Glycogen Synthase
UDPG
Debranching Enzyme (GSD III)
Glucose-1-P
Phosphoglucomutase
In liver
Glucose-6-Phosphatase (GSD I)
Glucose
Glucose-6-P
Glucose-6-Phosphate Transporter (GSD IB)
Fructose-6-P
To blood
In brain and muscle
Phosphofructokinase (GSD VII)
Fructose-1,6-P


A. Causes of Glycogen Storage Diseases I–VIII and Fructose Intolerance
Lysosomal breakdown
Glycogen
Enzyme defects
Enzymes esp. in liver
Enzymes esp. in skeletal muscles
Enzymes in many organs
II
Lysosomal α-glucosidase
VIII
Phosphorylase-kinase
IV
Branching enzyme + Glycogensynthetase
VI
Phosphorylase
V
Fructose
Fructose-1-P
UDP-glucose
Fructose-1-P-aldolase
Fructose intolerance
Trioses
Limit dextrin
III
Debranching enzyme
Lactate
Pyruvate
Citrate cycle
ATP
Glucose-1-P
Glucose
Glucose-6-P
Fructose-1,6-P2-aldolase
Ia
Glucose-6-phosphatase
VII
Phospho-fructokinase
Fructose-6-P
Fructose-1,6-P2

Investigation

Blood tests:

- Blood glucose: hypoglycaemia is likely
- Liver function tests: monitoring for hepatic failure
- Anion gap calculation: if glucose low, this may indicate lactic acidaemia
- Urate
- Creatinine clearance
- Creatine kinase
- Full blood count

Stimulation tests

Fructose stimulation

Glucagon stimulation

Urine tests:

Myoglobinuria

Biopsy

- Of liver.
- Muscle or other tissues gives definitive diagnosis.

Thanks for your attention!