



Glycogen Metabolism



By Maja Słobodzian

Contents of Presentation

1. Fast Vs Fed State
 - a. Hormones involved
2. Gluconeogenesis Overview
3. Glycolysis
4. Glycogenesis
5. Relevant Clinical Correlations
 - a. Glycogen-Storage Disorders

Fasting Vs Fed

High Blood Glucose
Surplus? Store it!

Dominant Hormone
Insulin

Pathways
Glycogenesis
Glycolysis

Low Blood Glucose
Brain NEEDS Glucose - Dig
into stores

Dominant Hormone
Glucagon
(Glucose-is-gone)

Pathways
Glycogenolysis
Gluconeogenesis

Gluconeogenesis

Moving Glucose IN TO the Blood

Gluconeogenesis (Reverse Glycolysis!)

- Glucose is created from non-carbohydrate sources in the liver (sometimes the kidney!)
- Gluconeogenesis is stimulated by glucagon and norepinephrine, and inhibited by insulin.

There are **three** general substrates that glucose can be drawn from:

1. Pyruvate/Lactate (muscles)
2. Triglycerides (adipose)
3. Proteins (glucogenic amino acids)

Remember that in order to make 1 glucose, we need 2 PYRUVATE!

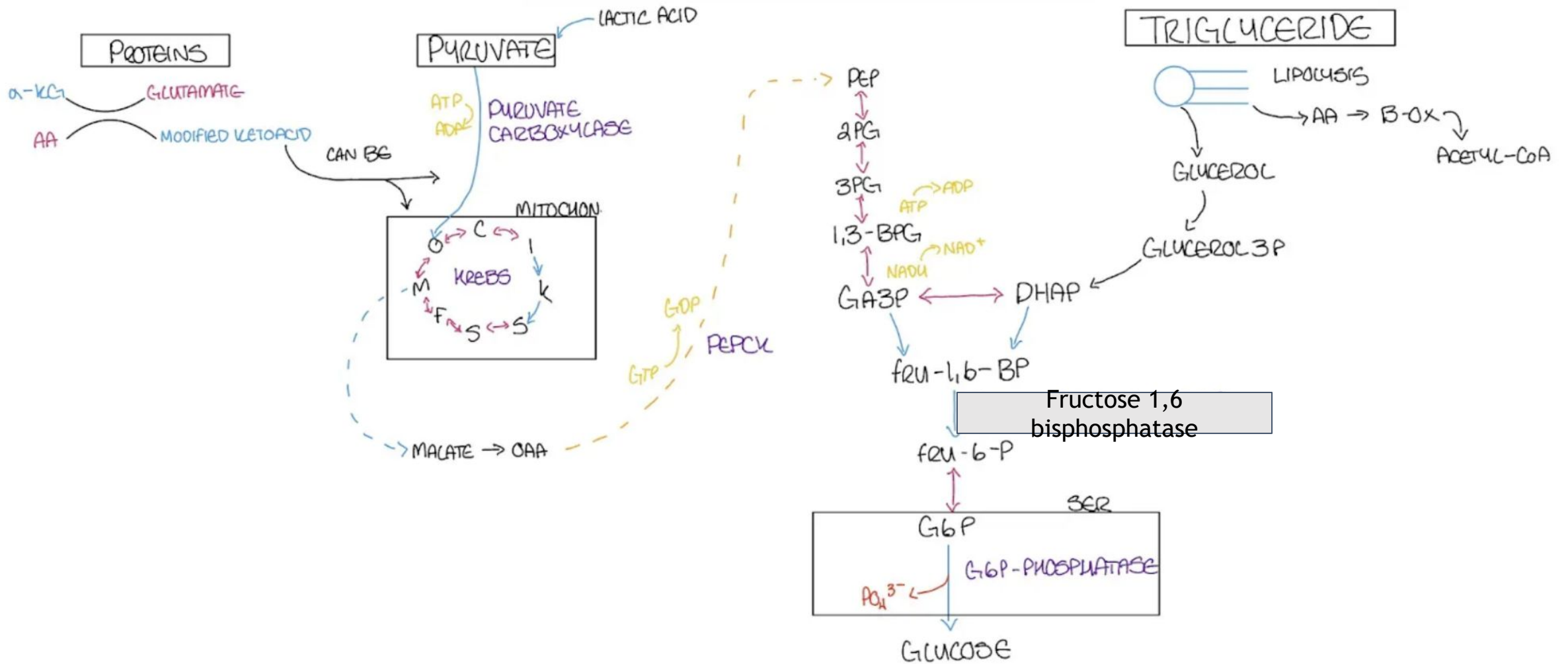
Gluconeogenesis

There are four key (**IRREVERSIBLE!!!!**) enzymes that you have to know!

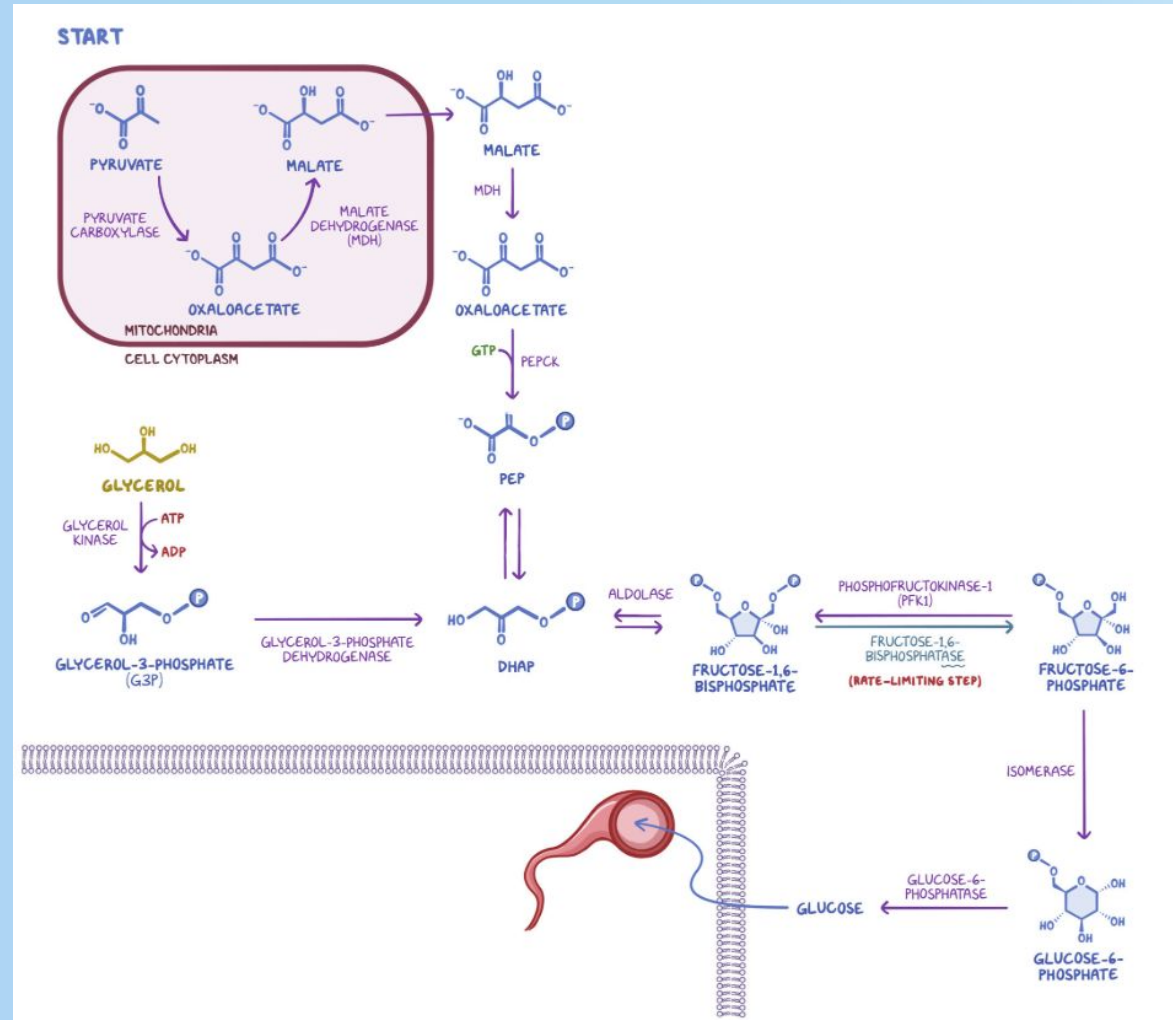
1. Pyruvate Carboxylase
 - a. During conversion of pyruvate to oxaloacetate
2. PEPCK
 - a. During conversion of oxaloacetate to PEP
3. **Fructose-1,6-Bisphosphatase**
 - a. During conversion of fructose-1,6-bisphosphate to fructose-6-phosphate
4. Glucose-6-Phosphatase
 - a. During conversion of G6P to Glucose

Rate-Limiting!

Gluconeogenesis



Gluconeogenesis



Pyruvate as a Substrate

Pyruvate for gluconeogenesis first comes from dehydrogenation of lactate, which accumulates in the muscles.

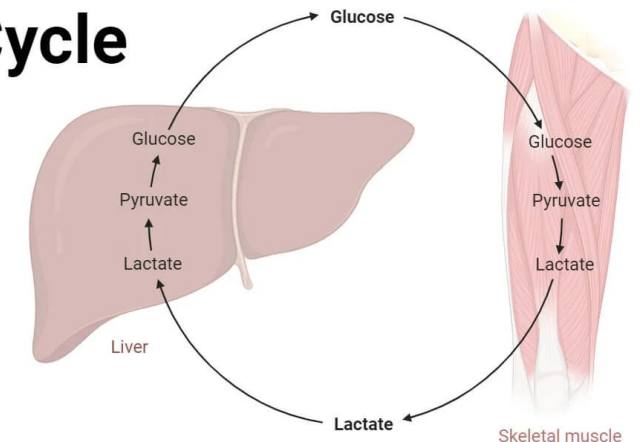
Lactate is quickly converted into pyruvate by lactate dehydrogenase using 1 NAD^+ , and is moved out of the muscle, into the bloodstream, to the liver.

High amounts of lactate in the muscle is sub-optimal and leads to acidosis.

This is called the **Cori Cycle!**



Cori Cycle



Pyruvate as a Substrate

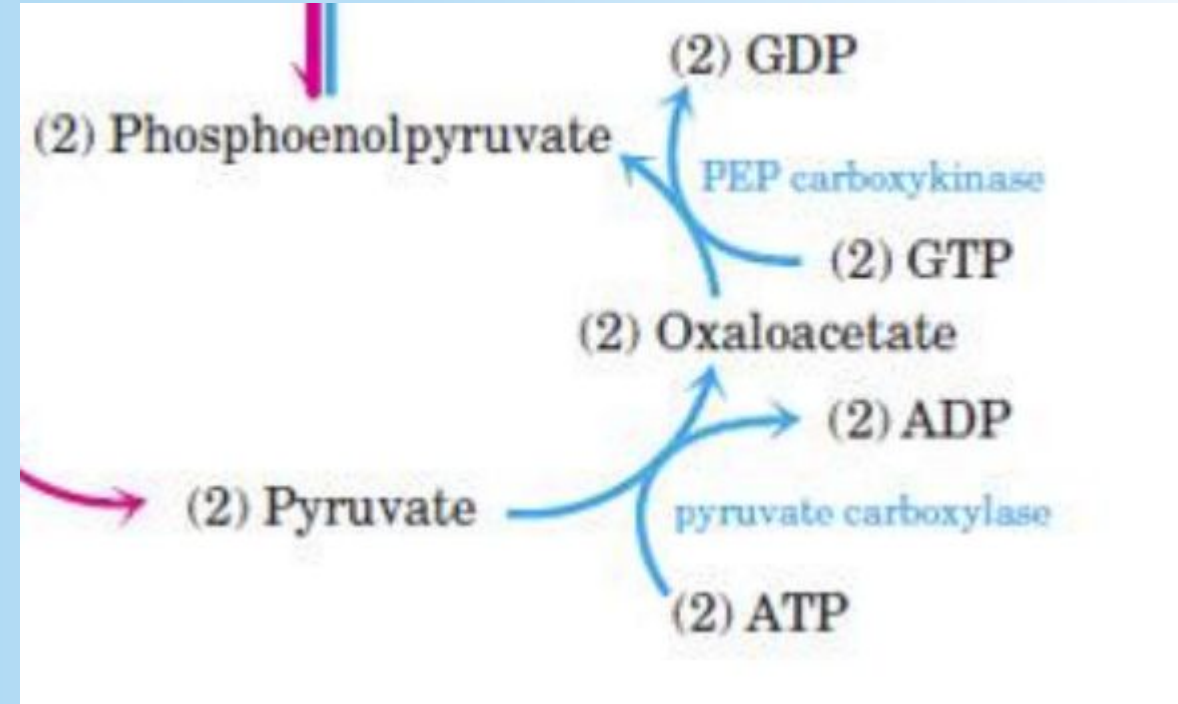
Pyruvate goes through a largely similar process, where there are **two irreversible reactions** with two key enzymes that will eventually produce PEP!

1. Pyruvate Carboxylase

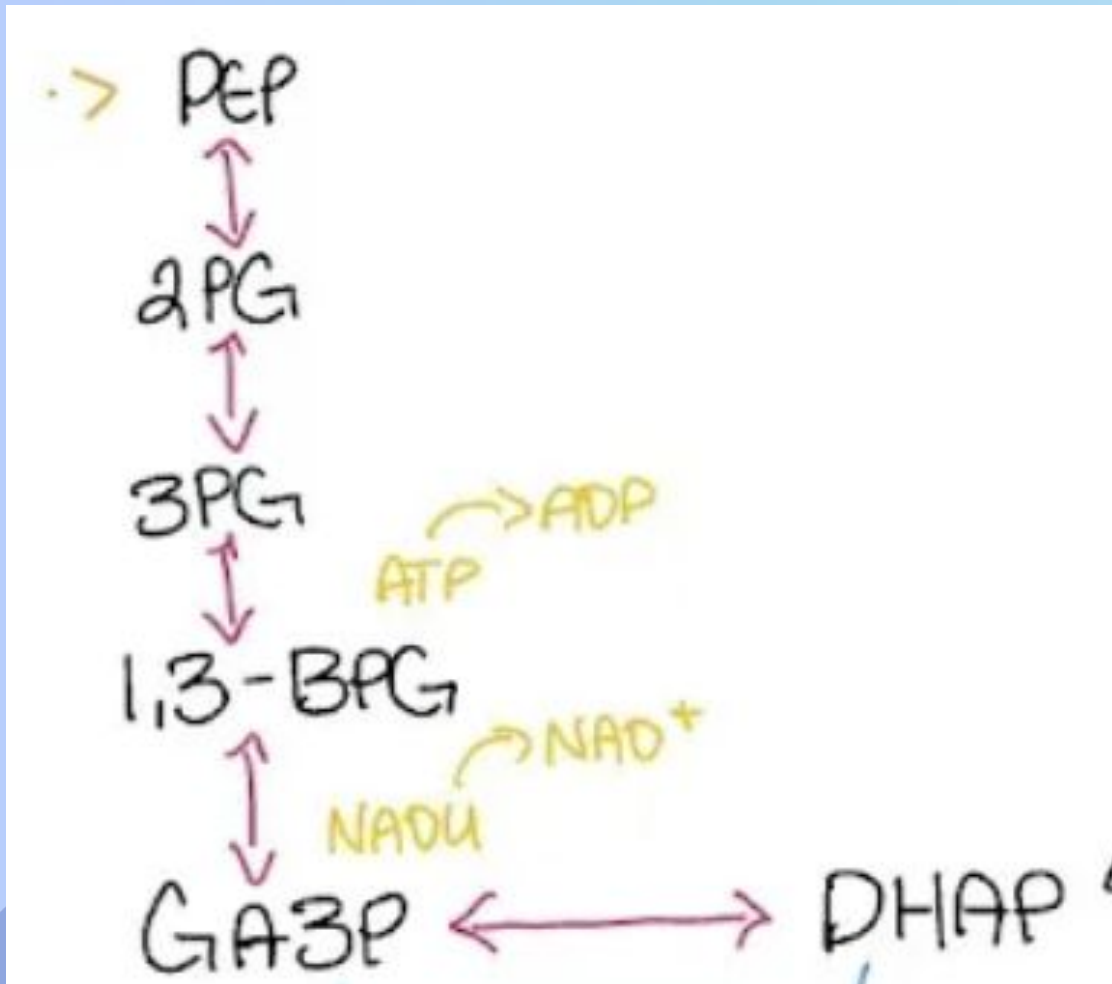
Requires 1 **ATP**

2. PEP Carboxykinase (PEPCK)

Requires 1 **GTP**



PEP

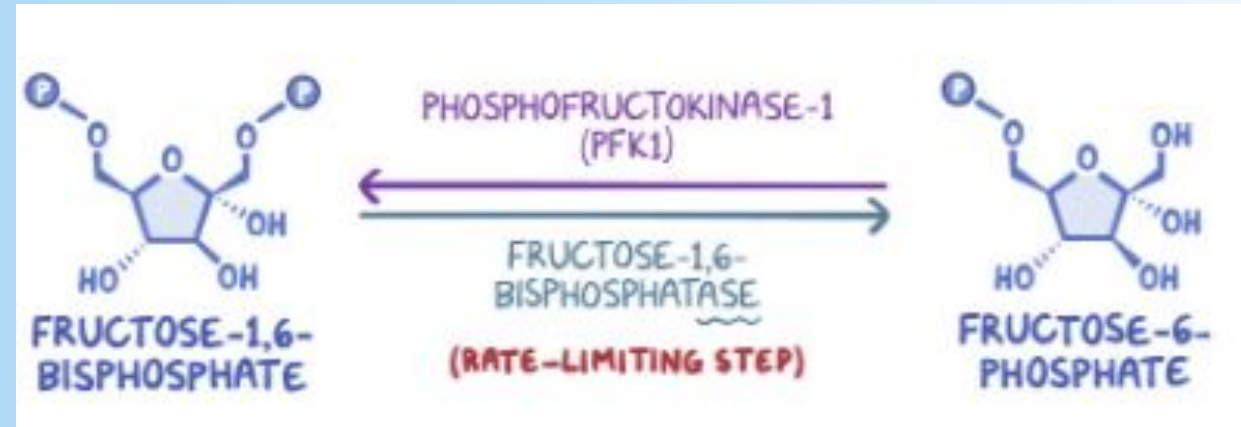


All reactions that PEP goes through up to GA3P are reversible, with a total of 1 ATP and 1 NADH being used as energy sources.

Gluconeogenesis - Final Steps

Now we have GA3P or DHAP which can both be converted to **Fructose-1,6-Bisphosphate** via aldolase.

We've finally found our rate limiting reaction! **Irreversibly**, **F-1,6-Bisphosphatase** acts on F1,6BP to form **Fructose-6-Phosphate (F6P)**!



Inhibitors

Everything HIGH ENERGY

- ATP
- Insulin
- Acetyl-CoA
- Fructose-2,6-BP

Stimulators

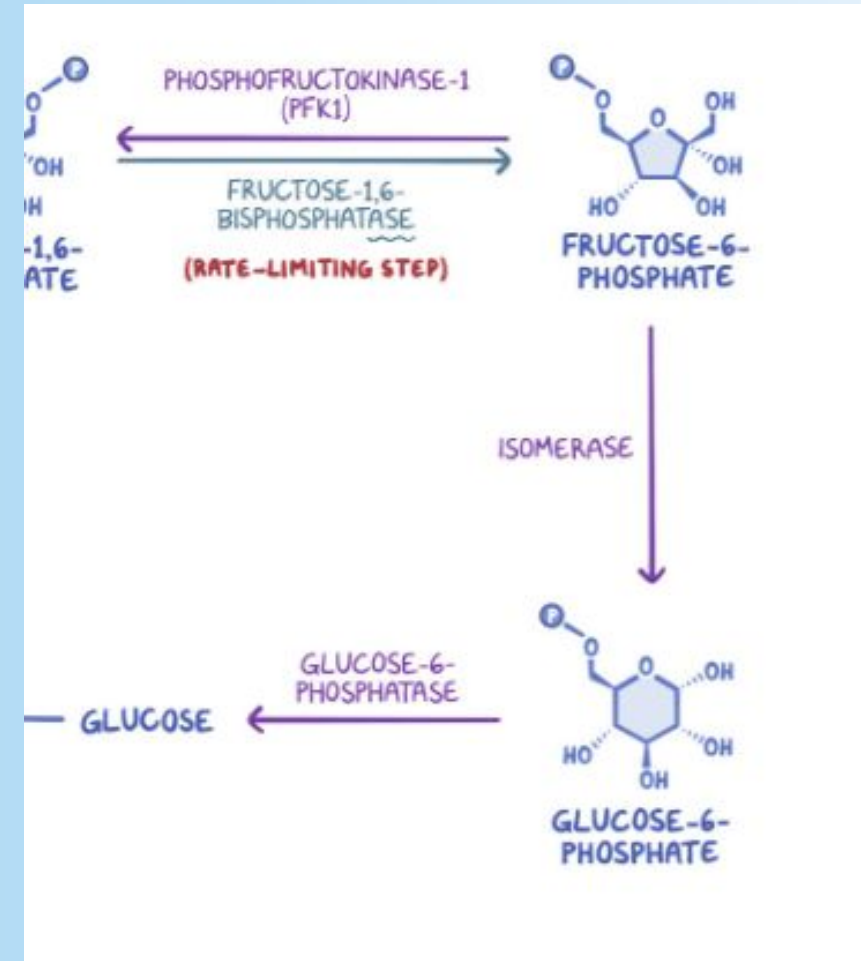
- Glucagon
- Norepi
- Epi

Gluconeogenesis - Final Steps!

Finally, F6P is converted to Glucose-6-Phosphate (G6P).

G6P is then acted on irreversibly by G6Pase (which removes a Pi) to form glucose!

Glucose is transported out of the cell and into the blood vessels through a GLUT transporter - the type varies on what tissue you're in!



Summary - Gluconeogenesis

- Tissue Locations: Liver (almost all!), epithelium of kidney, intestine
- Cell Location: Mitochondria, cytoplasm, SER
- Three Main Substrates: Pyruvate, Glucogenic AA, & Triglycerides
- 4 Key Enzymes, 1 Rate Limiting:
 - Pyruvate Carboxylase
 - PEPCK
 - **F16BPase**
 - G6 Phosphatase
- Main goal: create glucose from non-carbohydrate sources
 - Need 2 pyruvate to form one glucose



Glycogenesis

Moving Glucose OUT OF the Blood

Glycogenesis

Glycogen is a giant tree of glucose, linked by glycosidic bonds, found and stored in the skeletal muscle and liver.

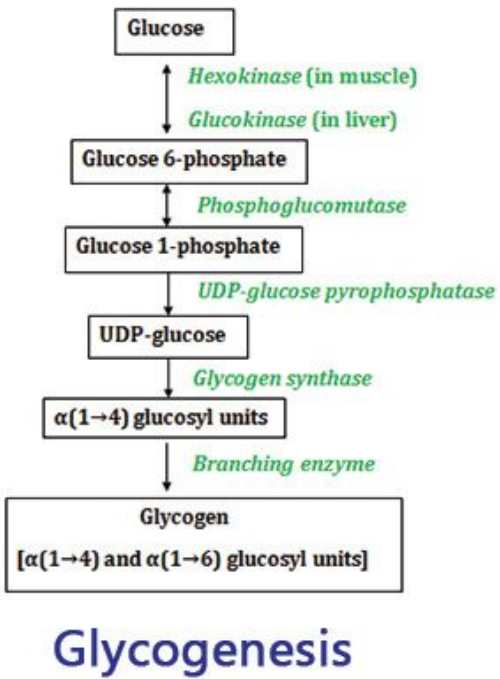
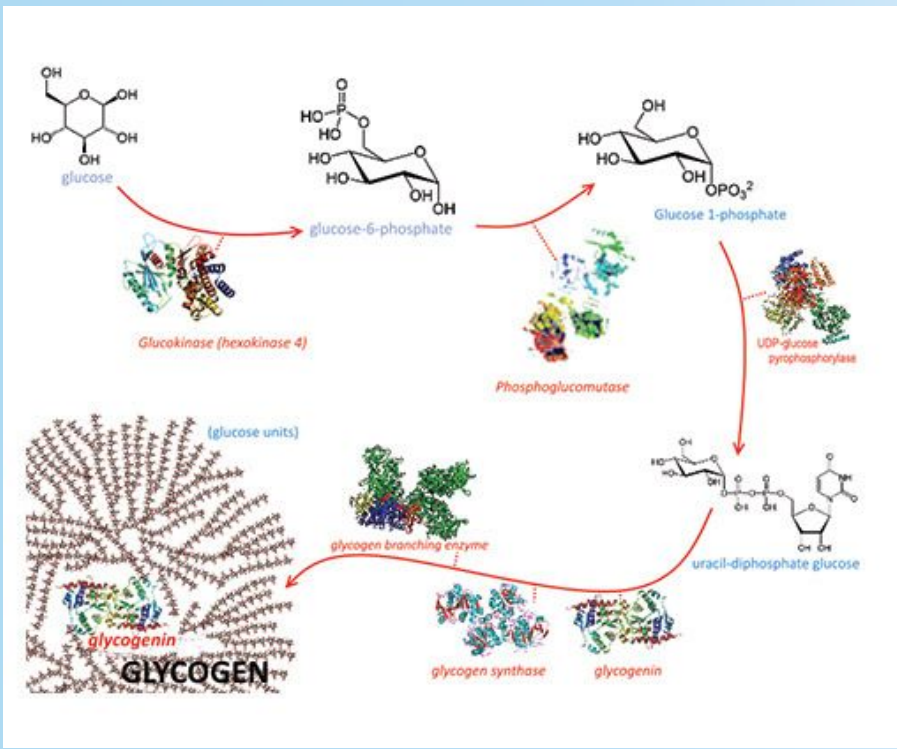
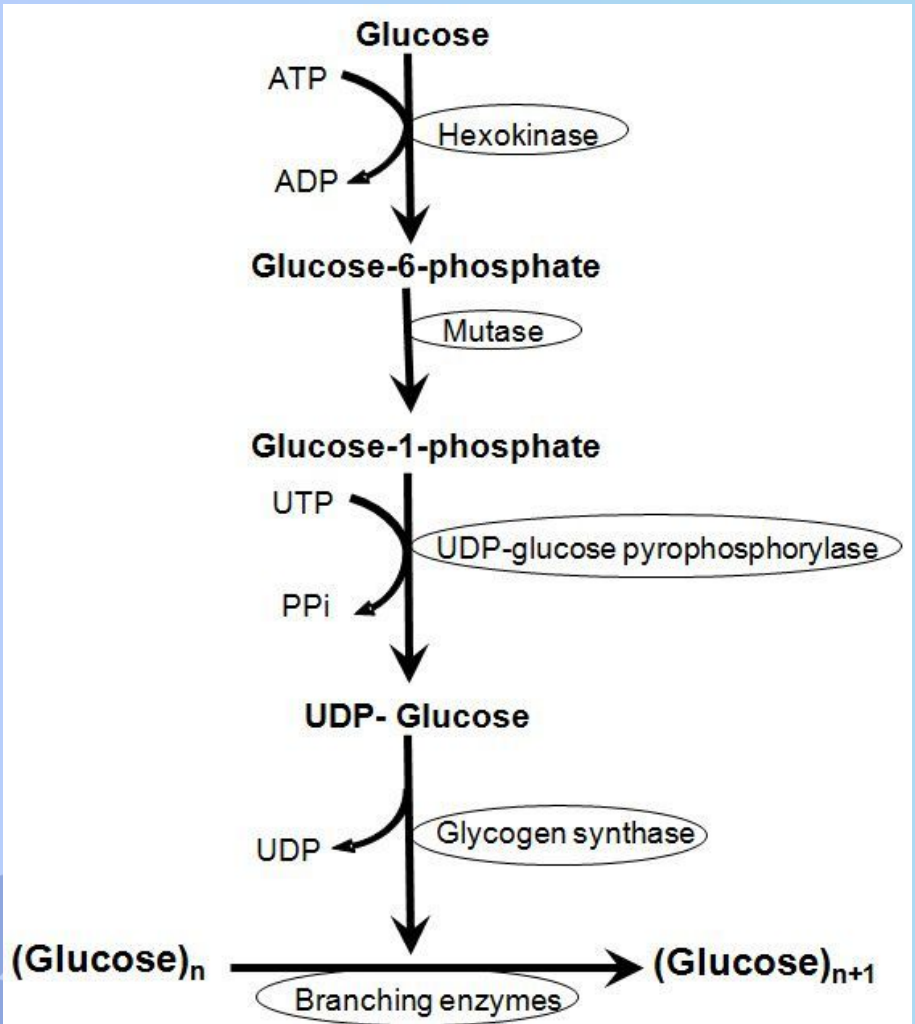
The liver stores glycogen so as to be able to keep blood glucose in homeostasis, and the muscles store it for extra energy.

TABLE 18-1 Storage of Carbohydrate in a 70-kg Person

	Percentage of Tissue Weight	Tissue Weight	Body Content (g)
Liver glycogen	5.0	1.8 kg	90
Muscle glycogen	0.7	35 kg	245
Extracellular glucose	0.1	10 L	10



Glycogenesis



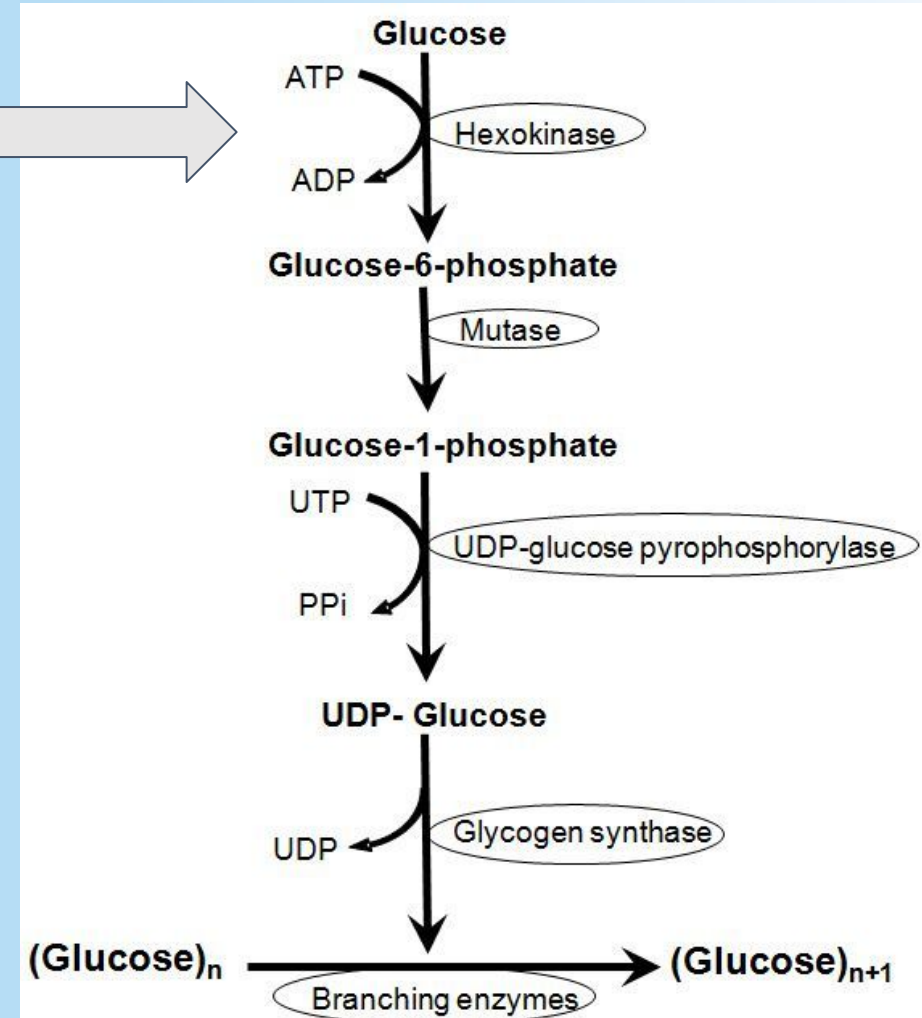
Use a diagram that works for you!

Preparing Glucose

First, glucose enters the cell via a GLUT transporter

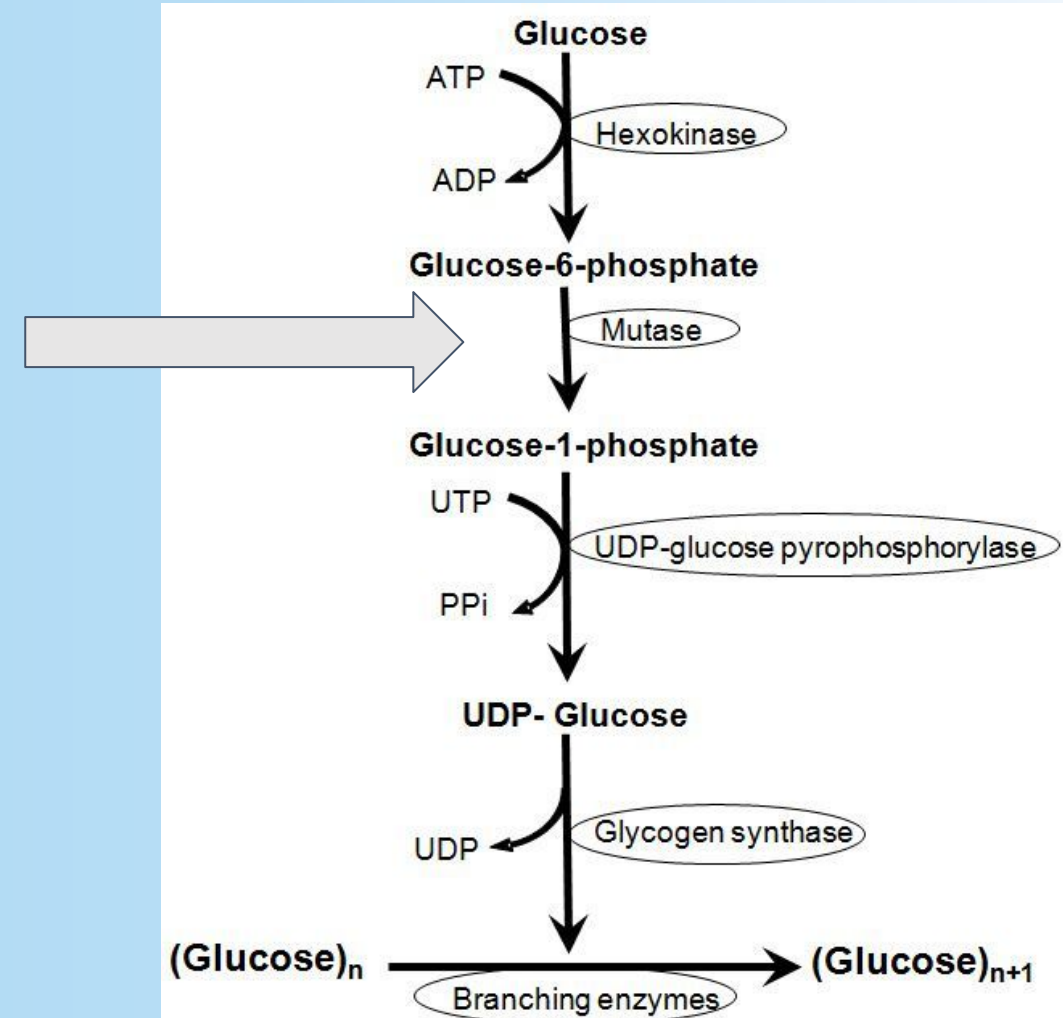
- type 2 - liver
- type 4 - muscles

Immediately, **glucokinase** (liver) or **hexokinase** (muscles) acts on this glucose and throws a phosphate from one ATP molecule on to our glucose - this yields G6P (remember her?)



Step 1

Glucose-6-phosphate is acted on by the enzyme mutase, which moves the phosphate from the 6th carbon to the first, creating glucose-1-phosphate



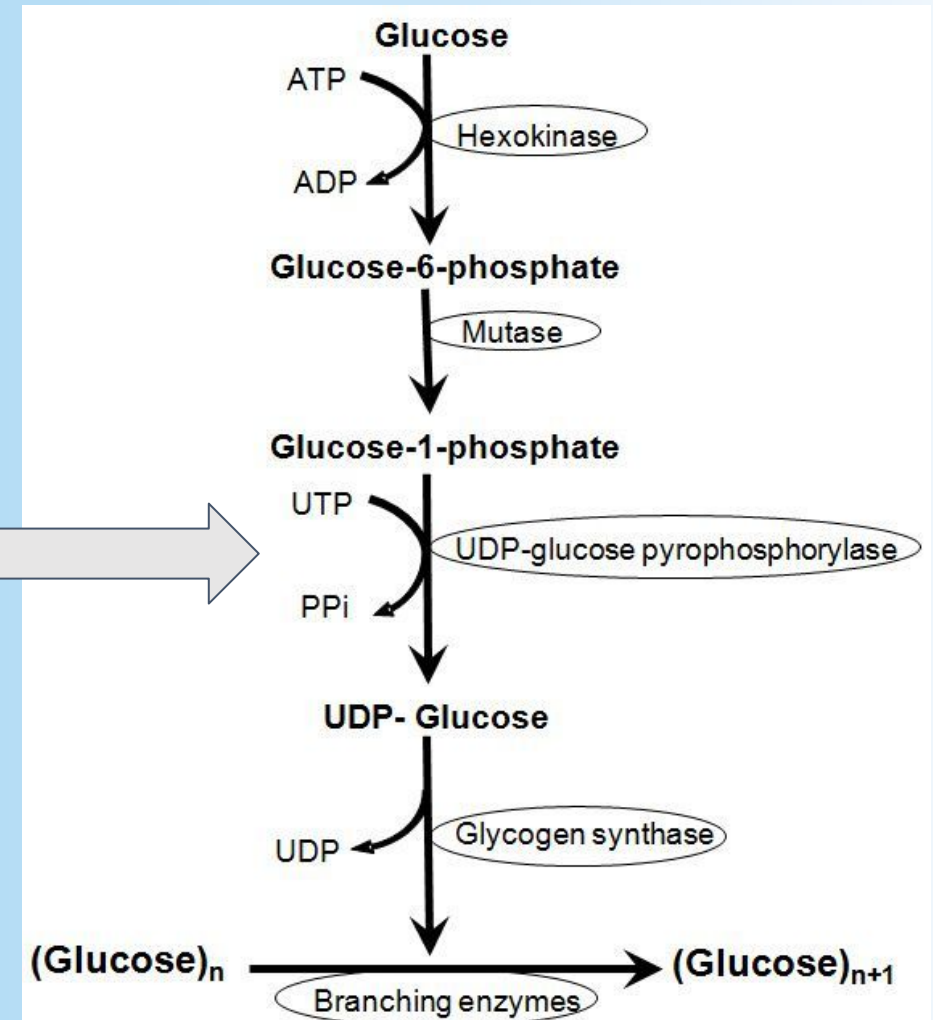
Step 2

G1P undergoes an exogenic reaction (negative delta G) where Uridine triphosphate (UTP) is converted to UDP.

UTP first has 2 of its phosphates removed. Those 2 phosphates form **pyrophosphate**.

Pyrophosphate is split by pyrophosphatase, splitting them into 2 inorganic phosphates.

This reaction releases enough energy to fuel the rest of our pathway - this is called **chemical coupling!**

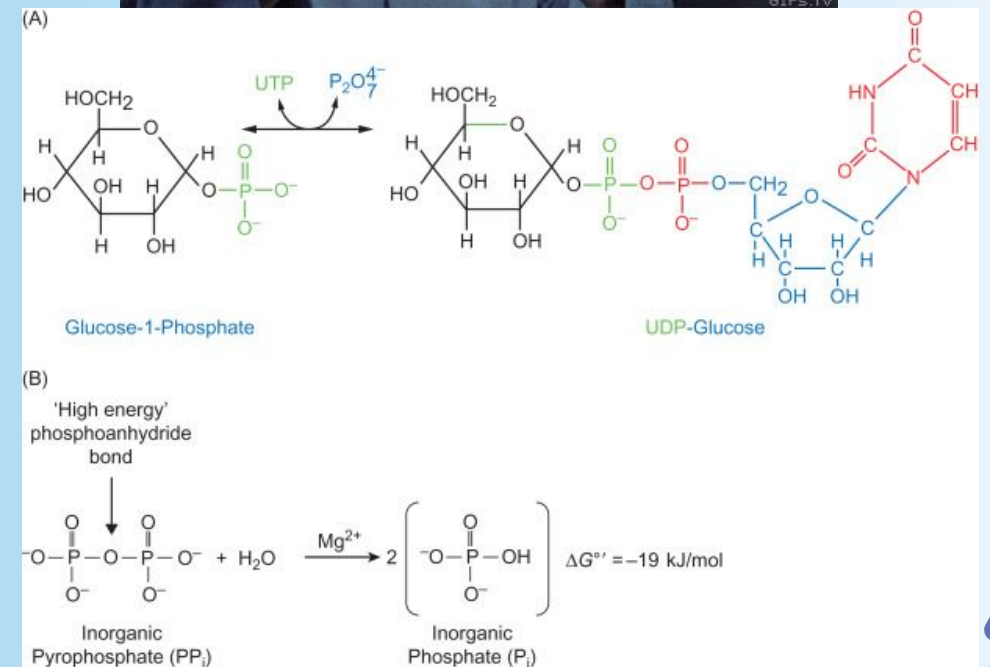


Step 3 - Autoglucosylation

In order to build a glycogen tree, there has to be a root or a point of origin; for us, it's **glycogenin**.

Glycogenin is a protein and an enzyme all rolled into one.

Basically, glycogenin wants to have a lot of glucose, but it needs to start the process itself - so it **autoglucosylates** and adds a glucose to itself.

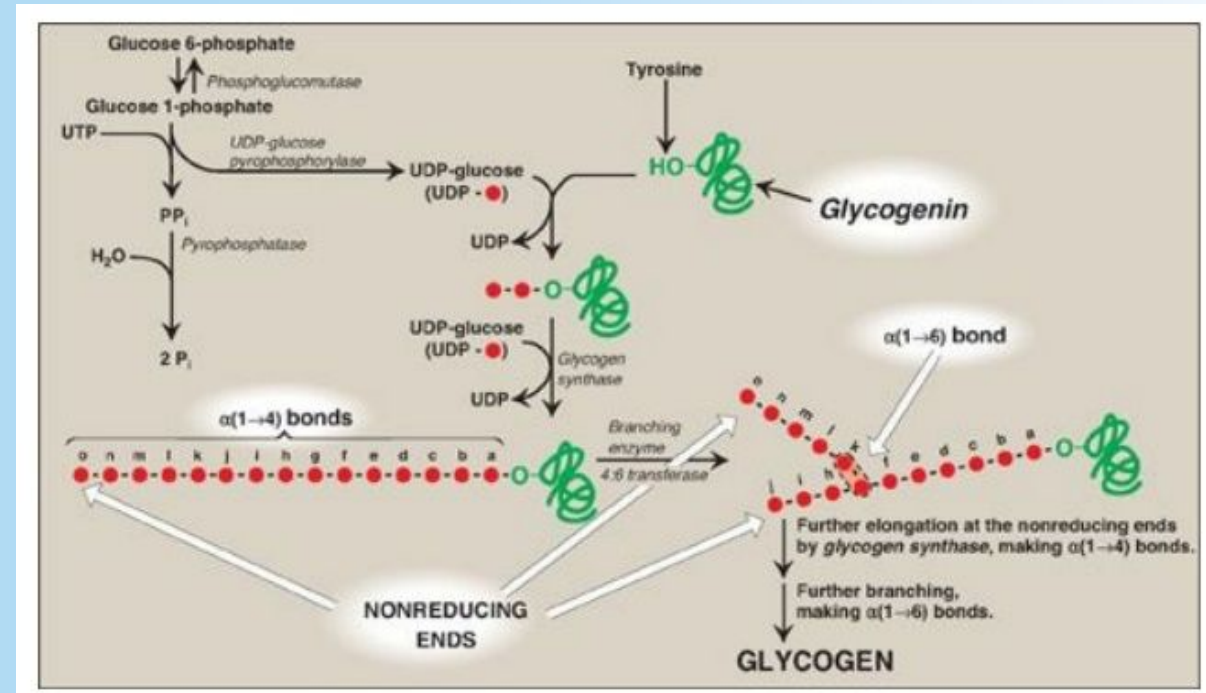


Step 4 - Building the Tree

Once the **glucogenin primer** has been formed, its time for our key rate-limiting enzyme, **Glycogen Synthase**, to do its work!

Glycogen synthase takes **UDP-glucose**, knocks the **UDP** off, and tosses the glucose on to the existing glycogen branch, always attaching glucose so that **C1** of the new glucose forms a glycosidic bond with the **C4** of the existing glucose chain.

This forms an **alpha-1,4 glycosidic bond**!



Note!

Glycogen synthase is **only active when its dephosphorylated!** The reason why glycogen synthase is a rate limiting enzyme is because it can be phosphorylated and made inactive.

Step 5 - Branching

Glycogen chains eventually have to branch and break off the original chain, because one super long chain is inconvenient and hard to utilize. For this task, we have **Branching enzyme!**

Branching enzyme transfers a portion of the original chain (portion must have at least 6 glucose linked) to a neighbouring chain, linking them together with an alpha-1,6 glycosidic bond. the place of linkage is called the branch point.

In order to continually branch, there must be at least 11 glucose attached.

Glycogenesis Summary

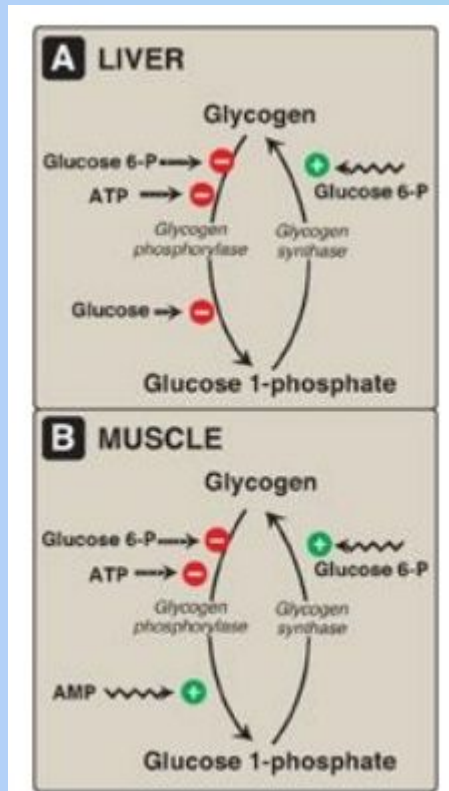
- Location: Liver and muscles
- Takes place during fed state!
- Enzymes (most relevant)
 - Glycogen Synthase - elongates chain, is the rate limiting enzyme
 - Alpha-1,4 glycosidic bonds
 - Branching Enzyme - shorten chain, makes branches
 - Alpha -1,6 glycosidic bonds

Glycogenolysis

Moving Glucose IN TO the Blood

Glycogenolysis

Glycogenolysis is a metabolic pathway that takes place during the fasting state of the body, stimulated by increased levels of glucagon, epinephrine, and norepinephrine in response to hypoglycemia.



Breaking Branches

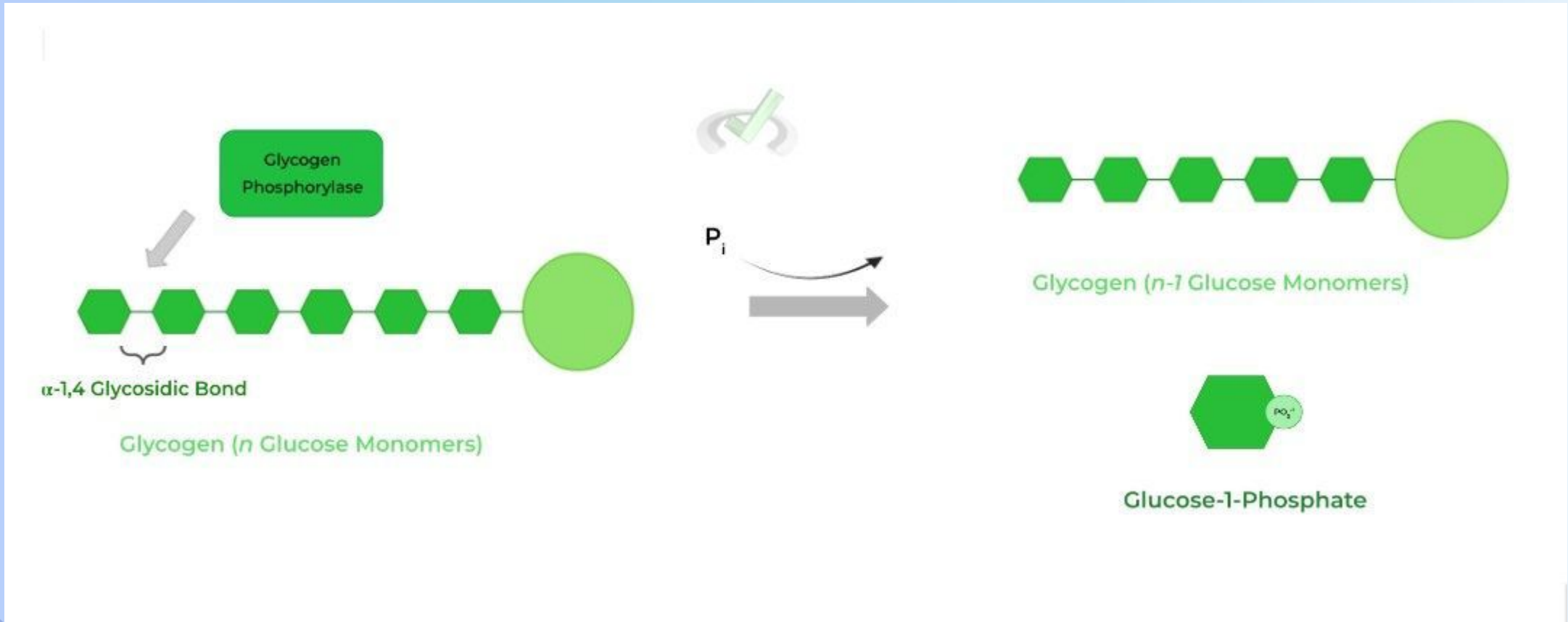
There are two enzymes at work during glycogenolysis.

1) Glycogen Phosphorylase

- Adds phosphates to glucose residues (just like how we got rid of them during glycogenesis!)
- Breaks the alpha-1,4 glycosidic bonds
- But only breaks bonds up to 4 carbons before the branch point!!!



Glycogen Phosphorylase



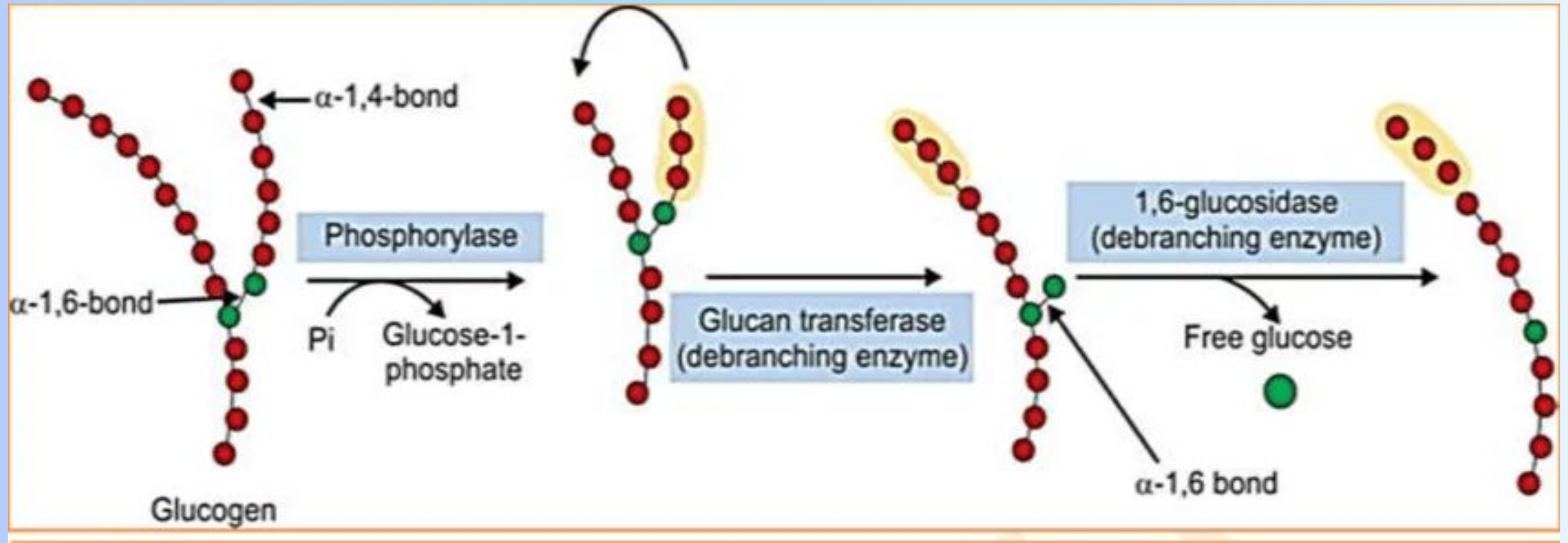
Breaking Branches

2) Debranching Enzyme

- Breaks alpha-1,4GB before the branch point
- Stops until there are three glucose molecules attached to the branch point
- Relocates the three residues to another strand
- Breaks the alpha-1,6 GB at the branch point



Debranching Enzyme



Regulation

Glycogen Phosphorylase

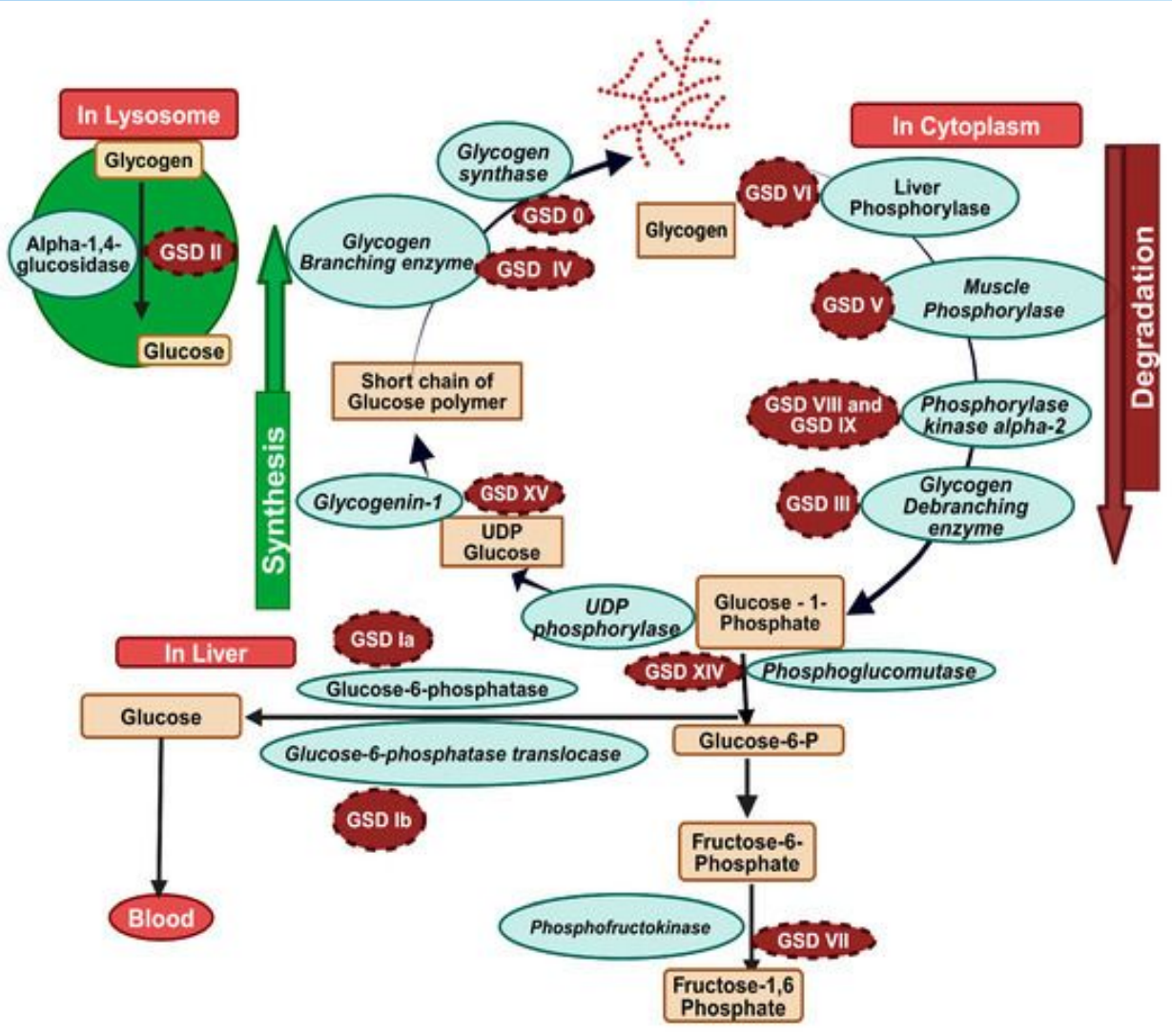
- Glycogenolysis
- Phosphorylation: **increases** activity
- **Stimulated by**
 - Epi, norepi, glucagon, Ca^{2+}
 - In muscles: AMP
- **Inhibited by**
 - ATP, G6P
 - In the liver: free glucose

Glycogen Synthase

- Glycogenesis
- Phosphorylation: **reduces** activity
- **Stimulated by**
 - insulin
- **Inhibited by**
 - Epi, norepi, glucagon

Glycogen Storage Disorders

Glycogen Storage Disorders

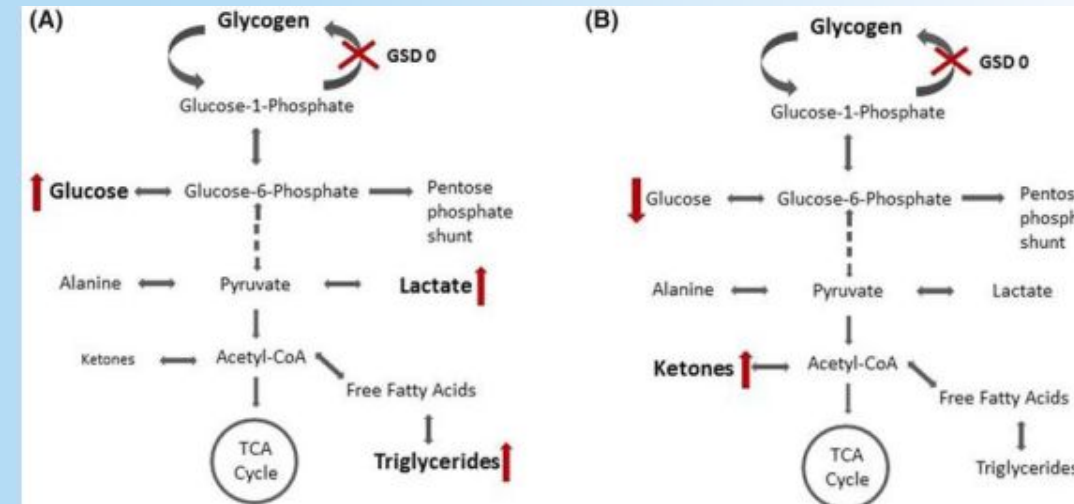


Glycogen Storage Disorders

Type 0: Lewis' Disease

- **Glycogen Synthase deficiency**
- Decreased amount of **structurally normal glycogen** in the liver
- Manifestations
 - Fasting Hypoglycemia, High blood Ketones, Increased fatty acids and lactate
 - LOW levels of alanine

These manifestations are due to limited glycogen stores and inadequate gluconeogenesis. Excess glucose is converted to lactate via glycolysis



Glycogen Storage Disorders

Type 1: Von Gierke Disease

- **G6P-Phosphatase deficiency**

- Autosomal recessive cause
- Build up of G6P, no glucose produced
- Is split into two subtypes

1a: deficiency of G6P-Phosphatase

1b: Deficiency in translocase

- Manifestations
 - Hepatomegaly - glycogen and fat accumulate in the liver
 - No glucose? hypoglycemia
 - Hyperuricemia, hyperlipidemia - problems with catabolism in liver

Glycogen storage disease type 1 Clinical features

GSD1a/GSD1b

Short stature - delayed puberty
Liver and kidney enlargement
Fasting hypoglycemia
Hyperlipidemia and hyperuricemia

Chronic renal disease

Liver adenoma
Osteoporosis

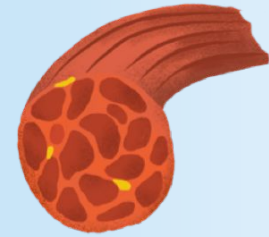
GSD1b

Neutropenia/Neutrophil dysfunction
Recurrent infections

Inflammatory bowel disease



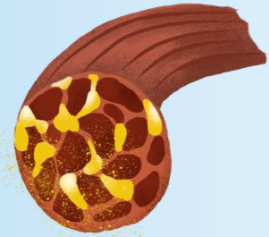
Glycogen Storage Disorders



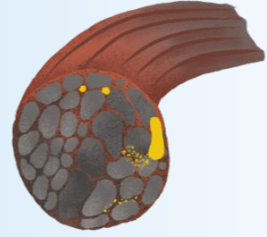
Lysosomes begin to fill with glycogen within muscle fibers



Glycogen buildup increases, causing lysosomes to enlarge



Lysosomes rupture, releasing glycogen and waste matter into the cell



Muscle fibers become damaged and lose function

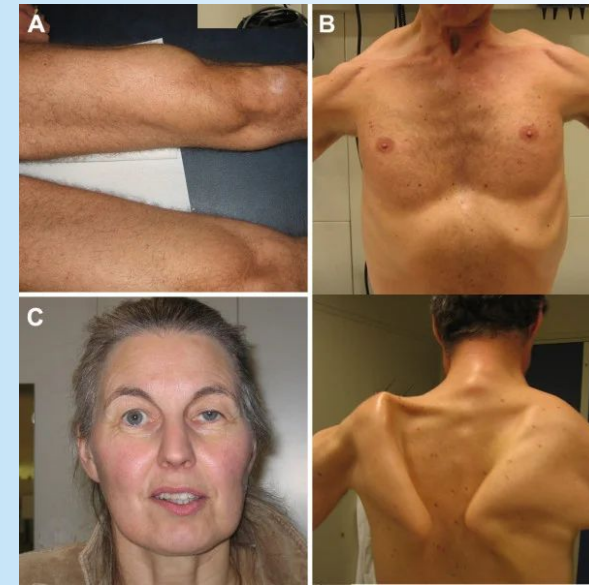
Type 2: Pompe Disease

- **Debranching Enzyme deficiency**

- Lysosomal alpha-glucosidase deficiency
- Autosomal recessive, both parents are carriers
- Most fatal disease
- Glycogen accumulates within the cells, cannot be broken down in lysosomes
 - accumulates in cardiac and nerve tissue

Clinical manifestations

- Muscle atrophy + increasing weakness
- Cardiomegaly
- Can present in neonates, infants, or childhood-adulthood



Glycogen Storage Disorders

Type 3: Cori Disease

- **Debranching enzyme deficiency**
- No conversion of glycogen polymers to glucose
 - Limit dextrose accumulates in the cytoplasm
- Abnormal glycogen structure are deposited in
 - Liver - hepatomegaly
 - Muscles - atrophy
 - Heart
- Presents during **infancy** - failure to thrive, hypoglycemia



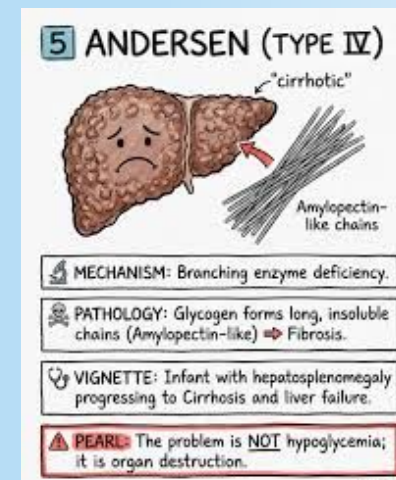
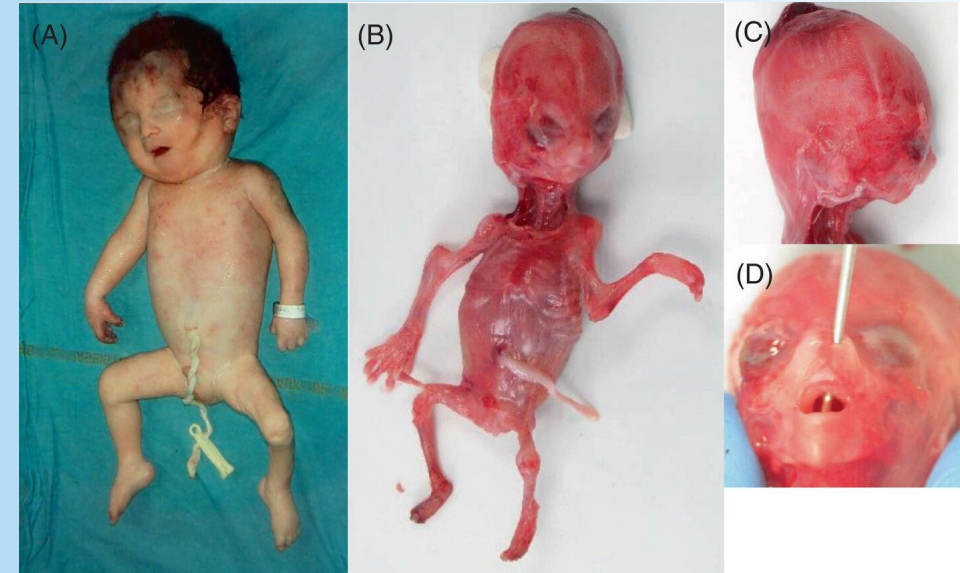
Glycogen Storage Disorders

Type 4: Andersen Disease

- **Branching enzyme deficiency**
- Autosomal recessive
- Long unbranched chains of glucose accumulate in the liver
 - The more branches, the more soluble glycogen is
 - When the solubility is low, glycogen precipitates in the liver

Clinical manifestations

- **Liver cirrhosis**
- **Hepatosplenomegaly**
- **In infants: failure to thrive**



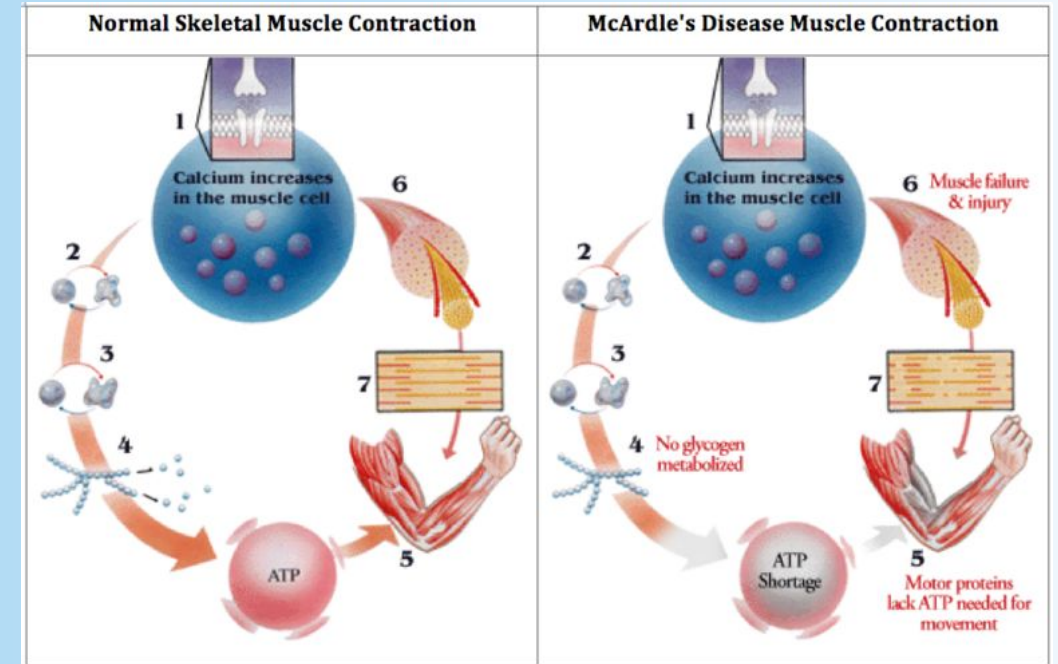
Glycogen Storage Disorders

Type 5: McArdle Disease - M for Muscle

- **Myophosphorylase Deficiency**
- Autosomal recessive
- Glycogen cannot be converted to G1P
- G1P & glycogen accumulate in the muscle

Clinical manifestations

- Muscle cramps & hypoglycemia during exercise
- myoglobinuria - breakdown of skeletal muscle, rhabdomyolysis



Glycogen Storage Disorders

Type 6: Hers Disease - H for Hepatic

- **Liver Glycogen phosphorylase deficiency**
- Autosomal Recessive/X-linked recessive
- Glycogen can't be broken down

Clinical manifestations

- **Hepatomegaly**
- Fasting hypoglycemia



Figure 1. Child from the first case at 5 years of age, prominent abdomen is observed due to hepatomegaly previously described

Glycogen Storage Diseases

Type	Deficient Enzyme
I – Von Gierke	Glucose -6- Phosphate
II - Pompe	Lysosomal α 1,4 glycosidase
III - Cori	Debranching Enzyme
IV - Anderson	Branching Enzyme
V - McArdle	Muscle Glycogen Phosphorylase
VI - Hers	Hepatic Glycogen Phosphorylase

@ Versatile Player Corey Anderson Made History.

www.dentaldevotee.blogspot.com



**Good Luck on Your Exam! You're Going to
Crush it! 💕💕**