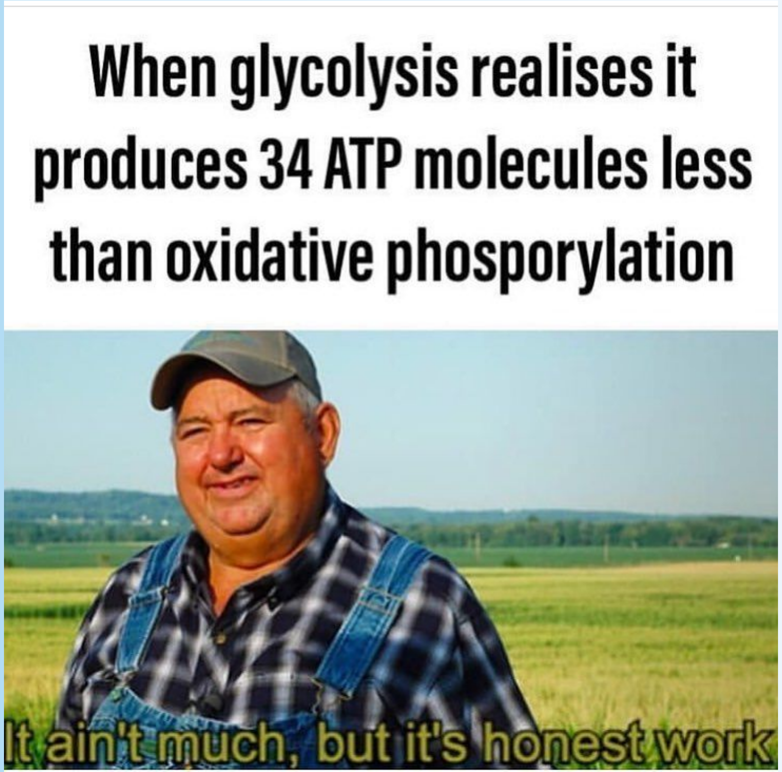
Glycolysis & Pentose Phosphate Pathway

Karolina Orocz

SCAN ME

BIOCHEMISTRY

GLYCOLYSIS



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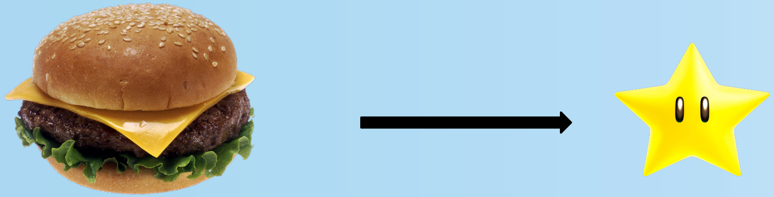
What is glycolysis?

When our body breaks down **glucose** into **pyruvate**



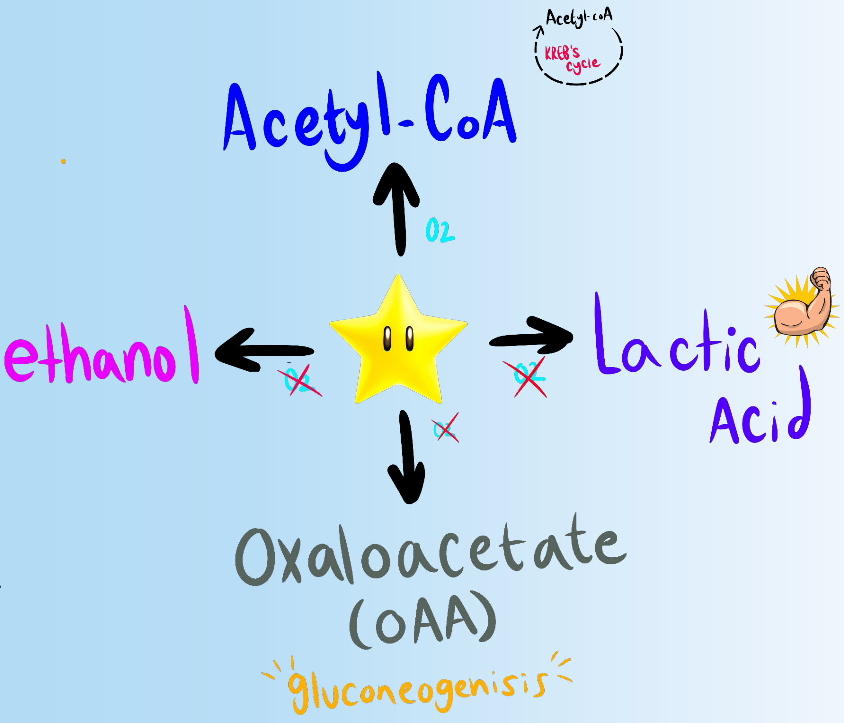
Why do we love pyruvate?

Pyruvate can be turned into substrates like…

- ★ **Acetyl-CoA**
  - for Krebs cycle
  - via pyruvate dehydrogenase enzyme complex (PDC)
- ★ **Oxaloacetate**
  - for gluconeogenesis
  - via pyruvate carboxylase

Or give off byproducts like…

- Lactic acid
  - happens in cells without mitochondria or that lack of oxygen
  - via lactate dehydrogenase
- Ethanol
  - happens in yeast & bacteria
  - via pyruvate carboxylase



When & where does glycolysis occur?

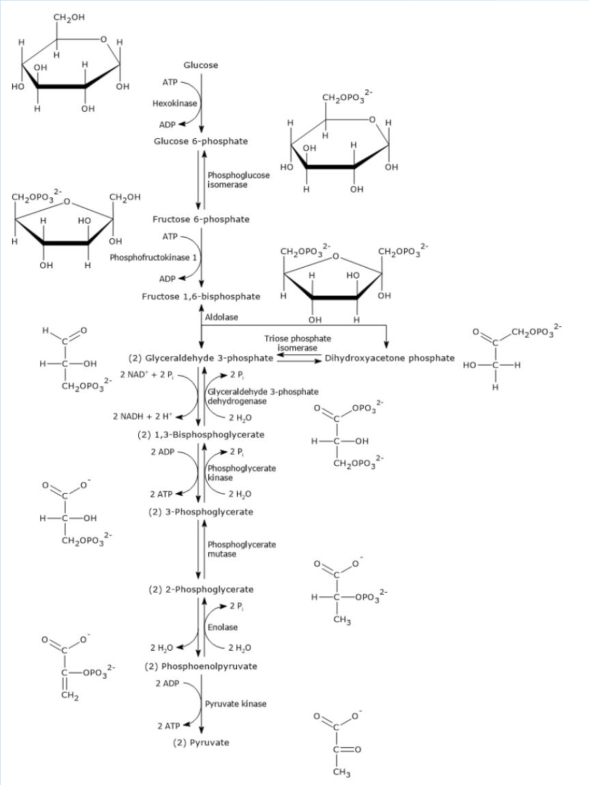
When:

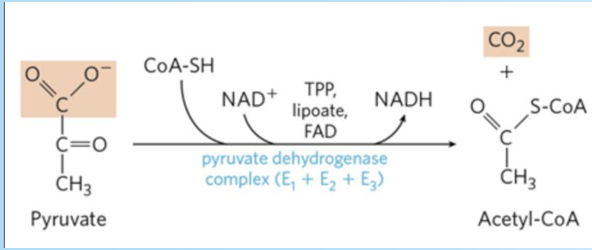
- You just ate
- You need ATP *and* have sufficient glucose in your body
  - Example: working out
  - No glucose? Ketolysis!
- Insulin is circulating in the body
  - During the “Fed” state
  - Especially affects liver

Where:

- Most cells *except* RBCs!
  - RBCs do Pentose phosphate pathway (PPP)
- Cell cytosol

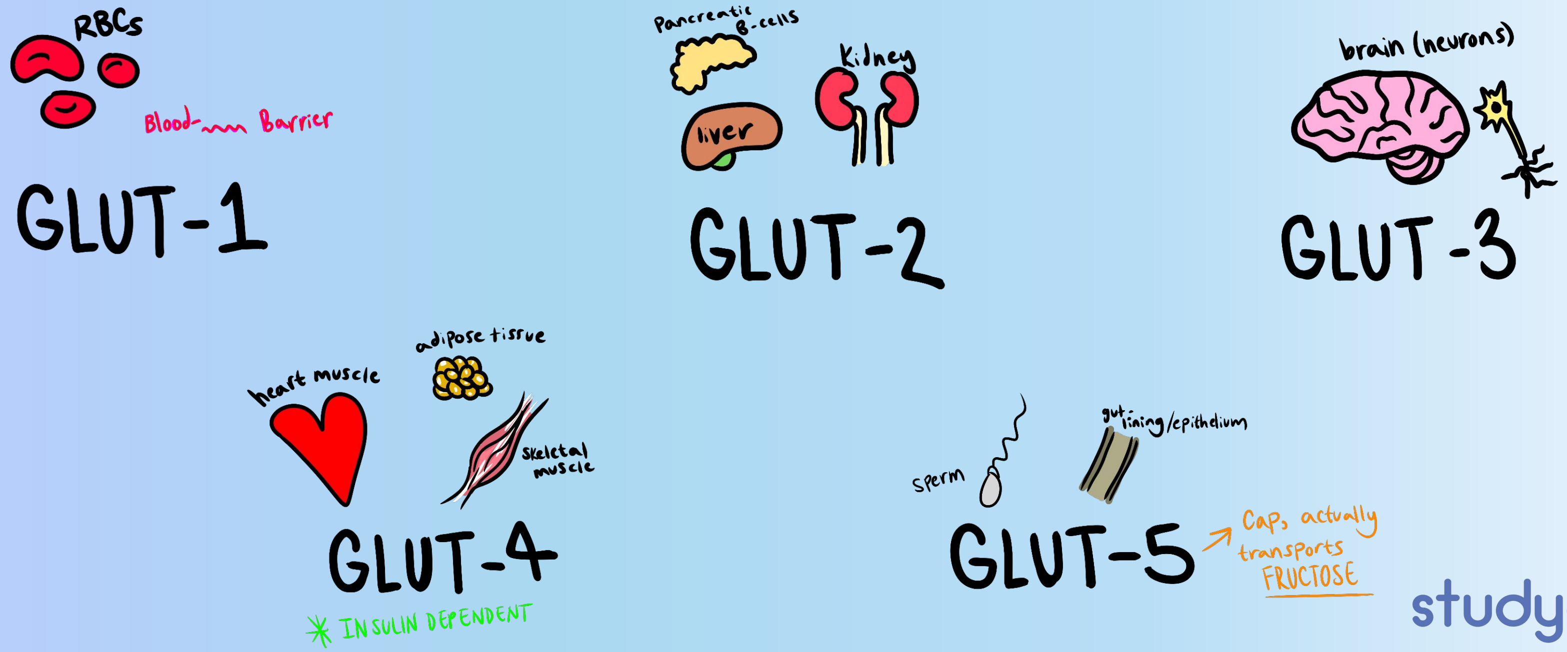
Let’s start!


Glucose
ATP
Hexokinase
ADP
Glucose 6-phosphate
Phosphoglucose isomerase
Fructose 6-phosphate
ATP
Phosphofructokinase 1
ADP
Fructose 1,6-bisphosphate
Aldolase
Triose phosphate isomerase
(2) Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
2 NAD+ + 2 Pi
2 NADH + 2 H+
Glyceraldehyde 3-phosphate dehydrogenase
2 Pi
2 H2O
(2) 1,3-Bisphosphoglycerate
2 ADP
2 ATP
Phosphoglycerate kinase
2 Pi
2 H2O
(2) 3-Phosphoglycerate
Phosphoglycerate mutase
(2) 2-Phosphoglycerate
Enolase
2 Pi
2 H2O
2 H2O
(2) Phosphoenolpyruvate
2 ADP
Pyruvate kinase
2 ATP
(2) Pyruvate

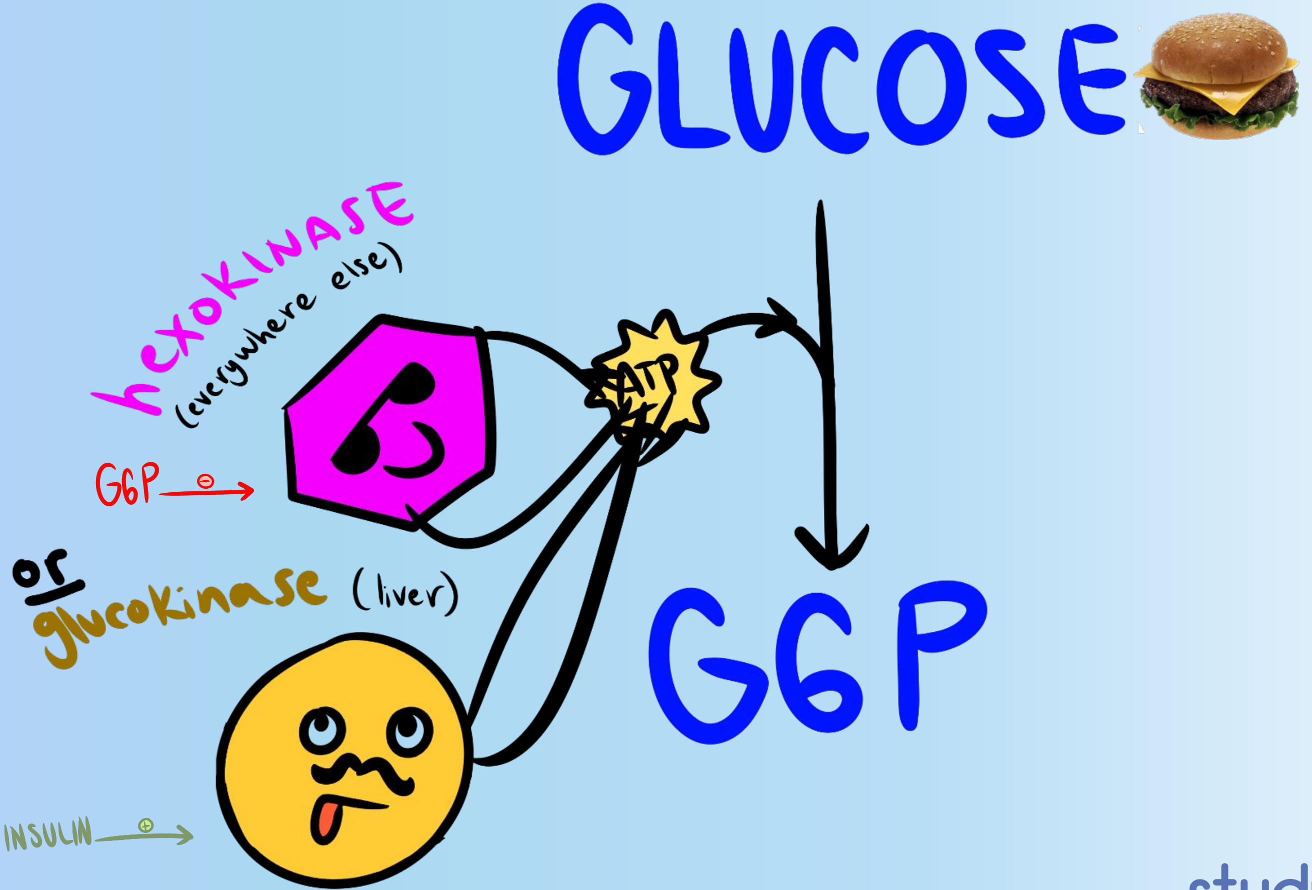

CoA-SH
NAD+
TPP, lipoate, FAD
NADH
pyruvate dehydrogenase complex (E1 + E2 + E3)
CO2
+
S-CoA
Pyruvate
Acetyl-CoA

Step 0: How do we get glucose into the cell?

Glucose Transporters! (GLUTs)

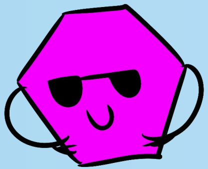


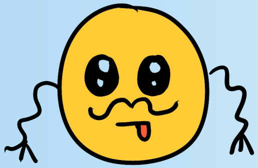
Step 1:



★ G6P: Glucose-6-phosphate

IRREVERSIBLE REACTION





Enzyme:	**Hexokinase**	**Glucokinase**
Where:	Most tissues	Liver
Km	Low Km *High affinity towards glucose – converts glucose at low concentrations*	High Km *Low affinity towards glucose – converts glucose only at high concentrations*
Effect of G6P	Negative feedback	None
Effect of insulin	None	Stimulated

Step 2:

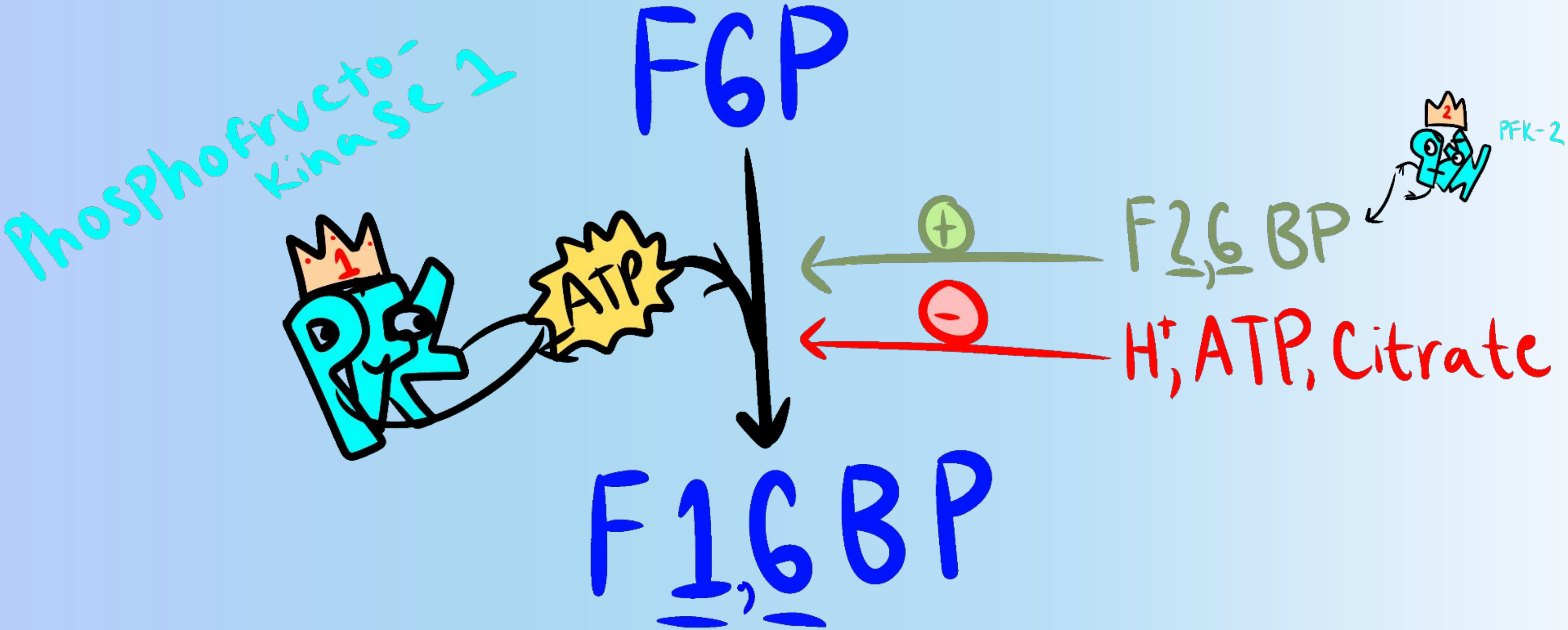
G6P

↕

F6P

★ F6P: Fructose-6-phosphate

Step 3: MAIN RATE-LIMITING STEP



★ F1,6BP: Fructose 1, 6 bisphosphate

IRREVERSIBLE REACTION

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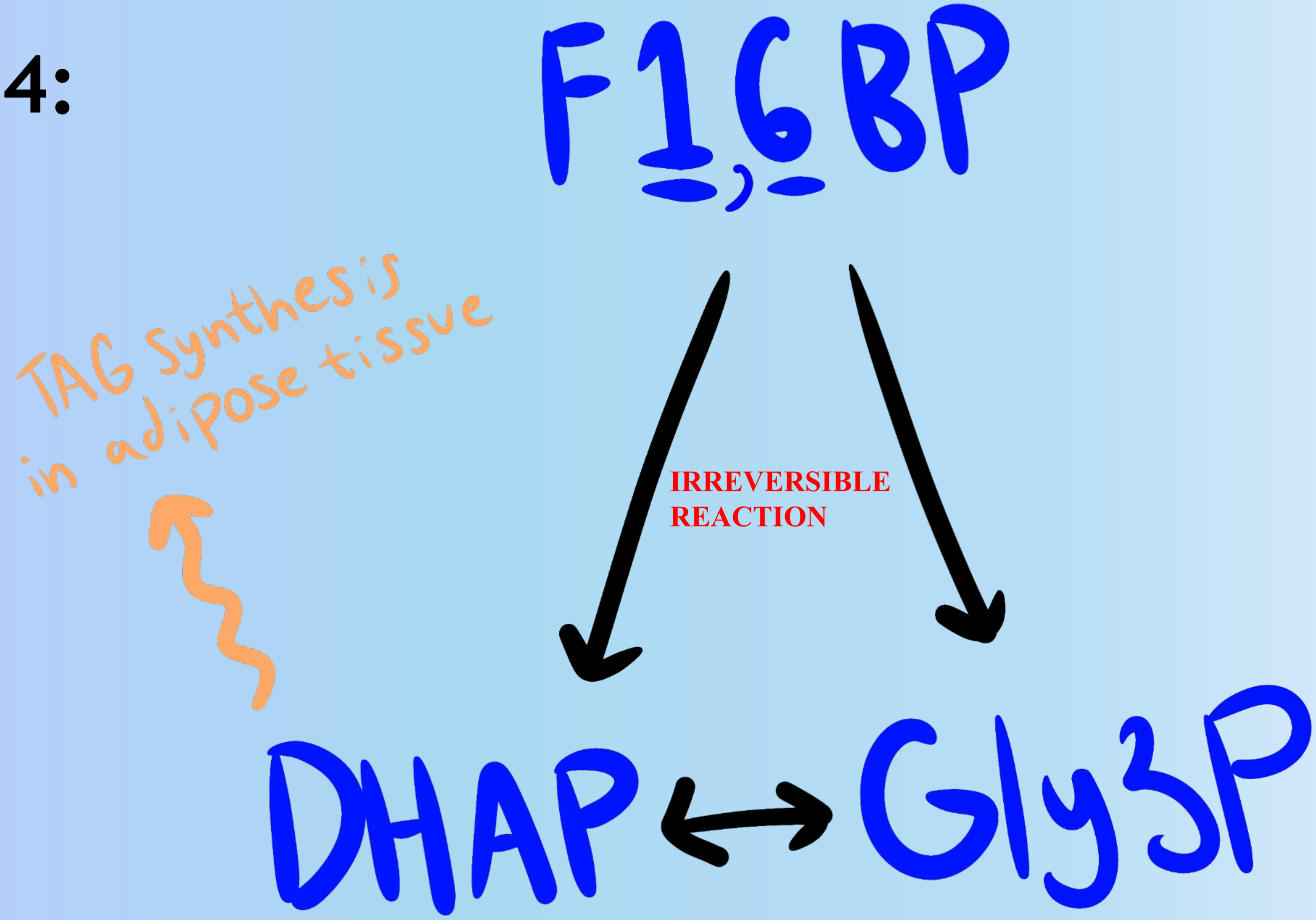
Step 4:



★ DHAP: Dihydroxyacetone phosphate

★ Gly3P: Glyceraldehyde 3 phosphate

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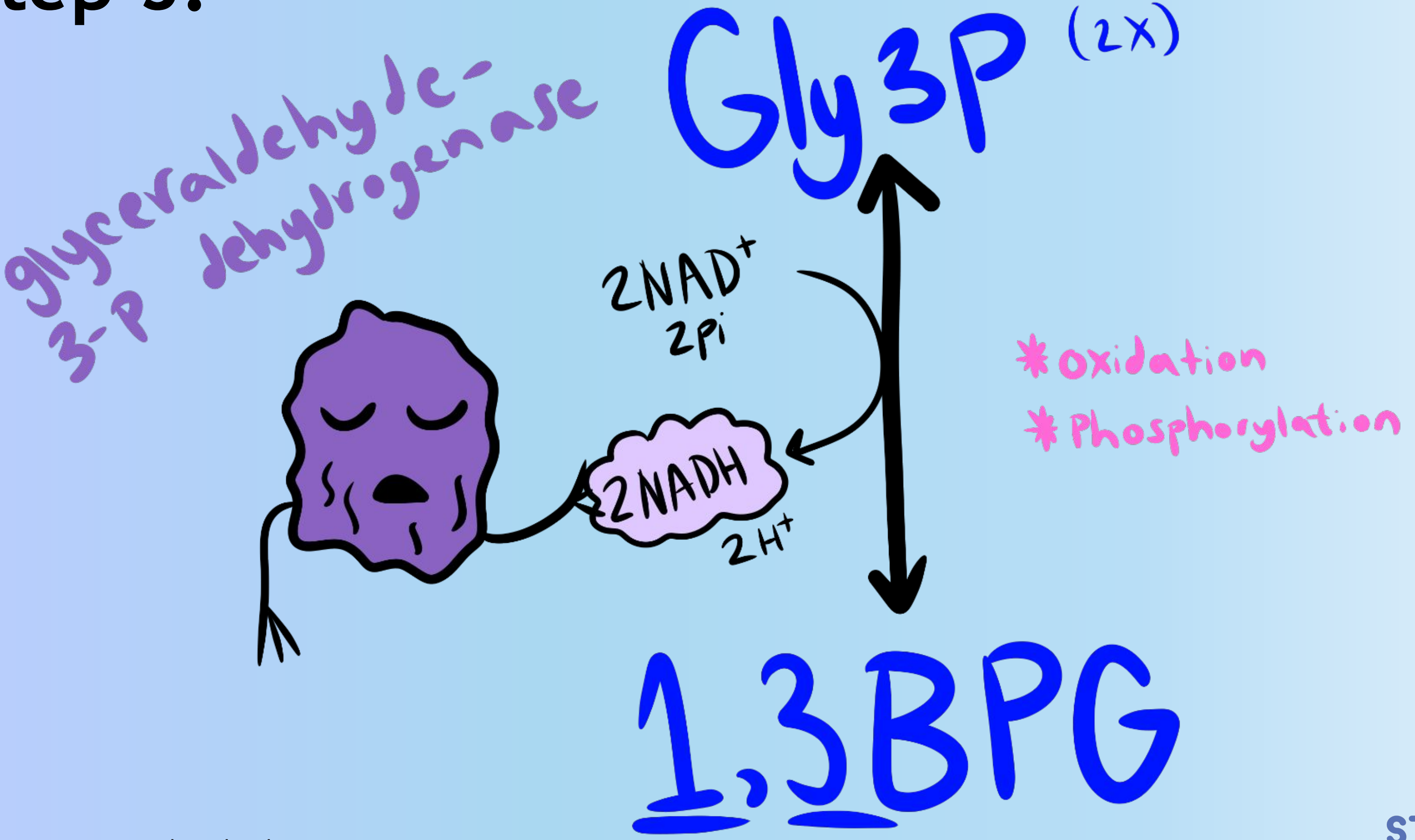
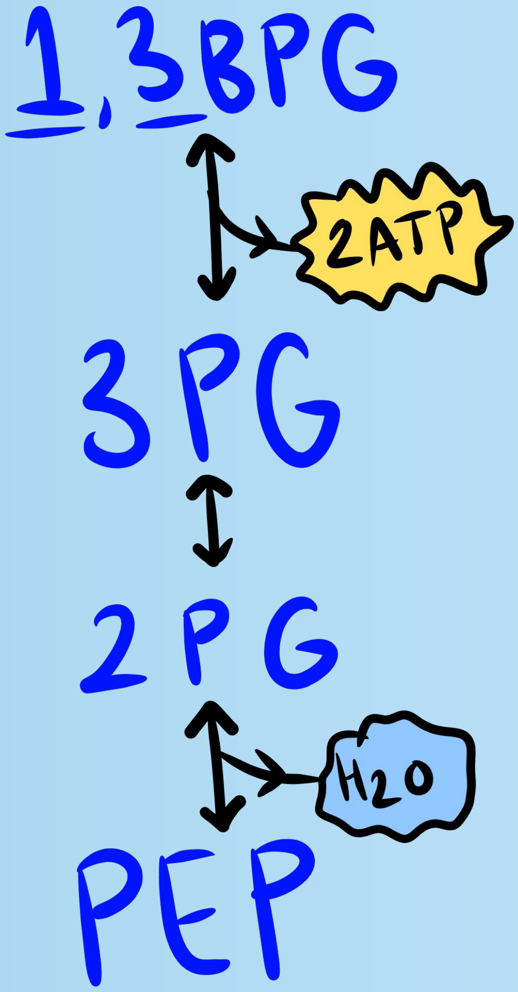
Step 5:



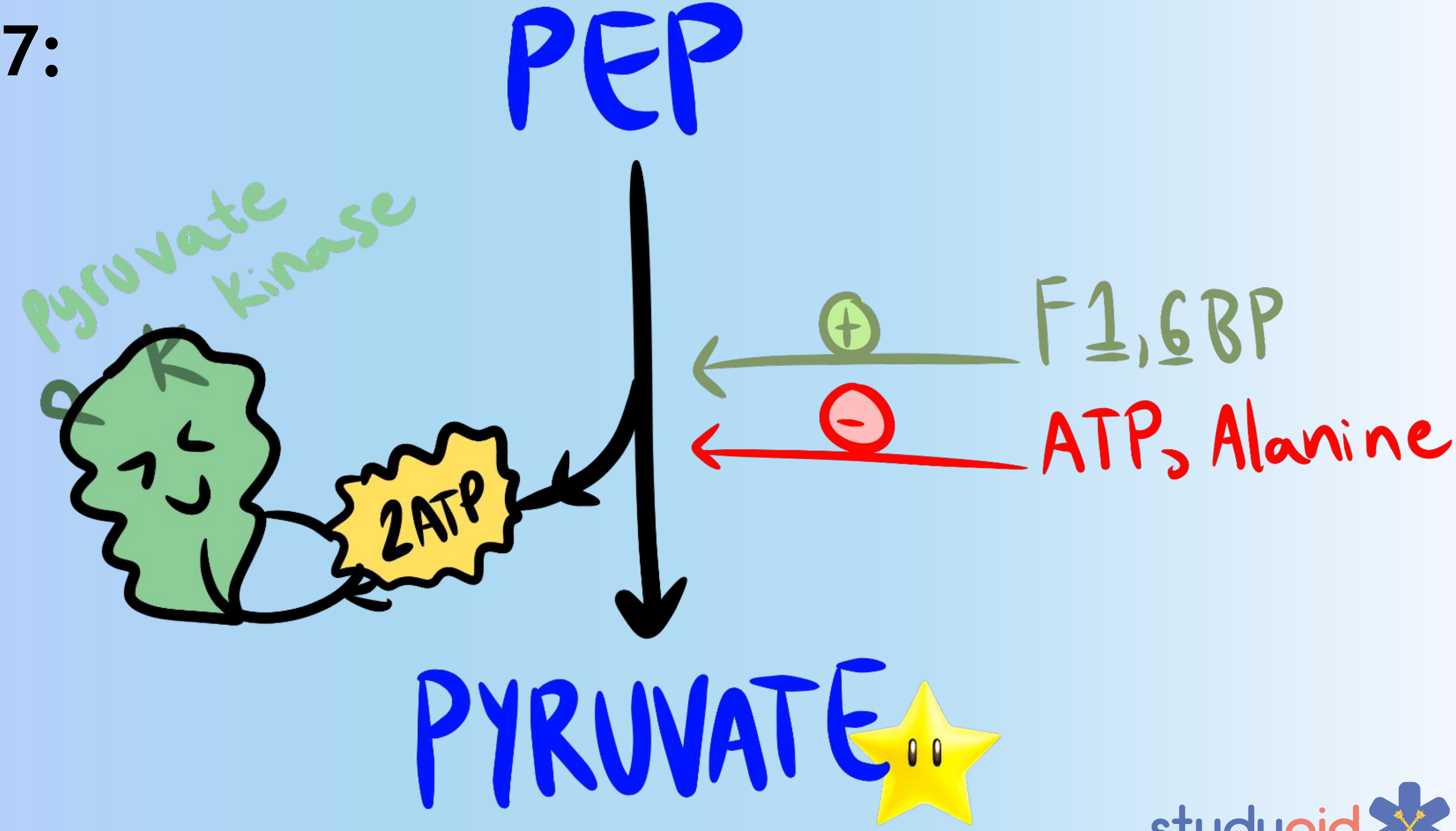
★ 1,3BPG: 1,3 Biphosphoglycerate

Step 6:



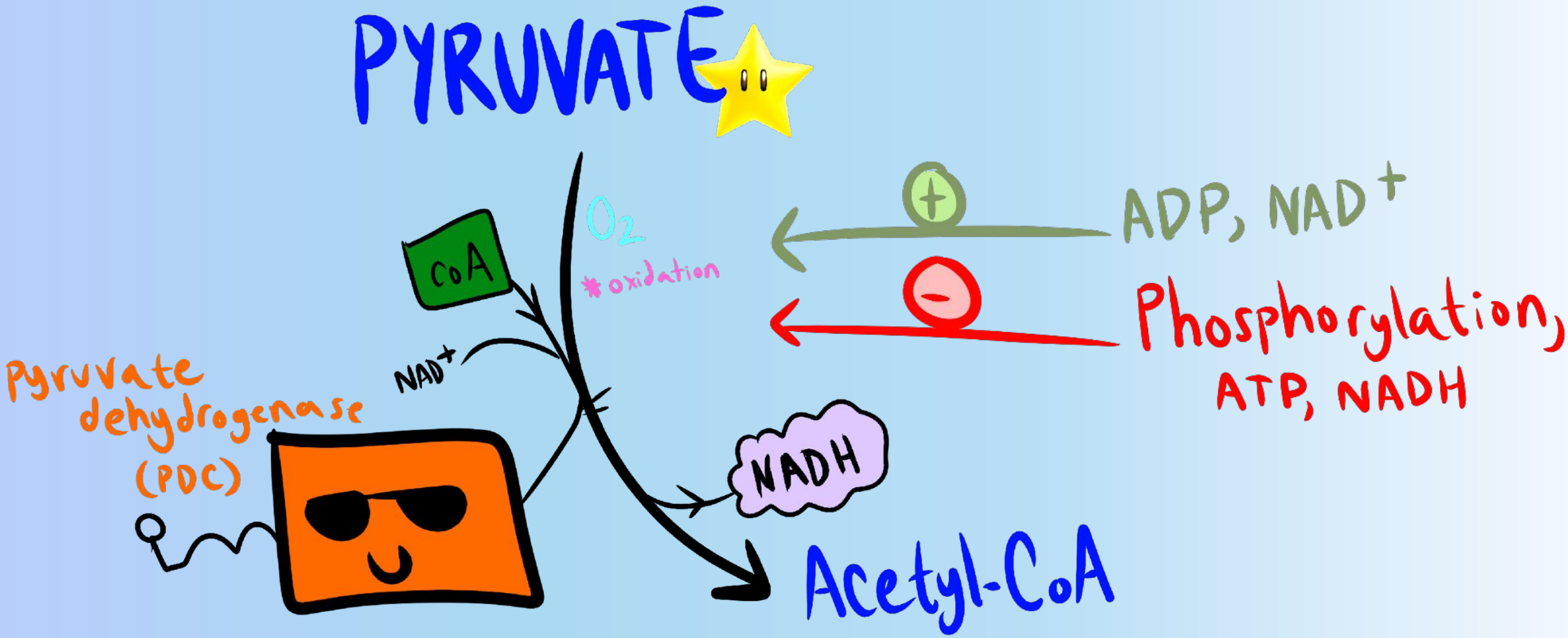
- ★ 3PG: 3 Phosphoglycerate
- ★ PEP: Phosphoenolpyruvate

Step 7:



IRREVERSIBLE REACTION

One of the endings…

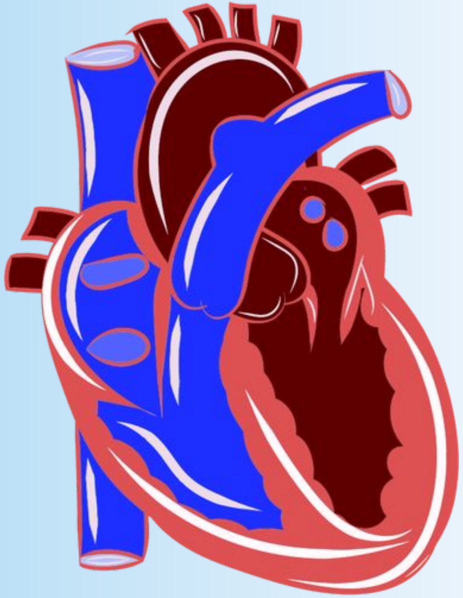


IRREVERSIBLE REACTION

Clinical correlation: Myocardial infarction

Normally the heart needs lots of ATP & O2 to run!

- **95%** of ATP: mitochondrial oxidative phosphorylation
  - aerobic process: needs O2 to run!
- **5%** of ATP: glycolysis
  - anaerobic



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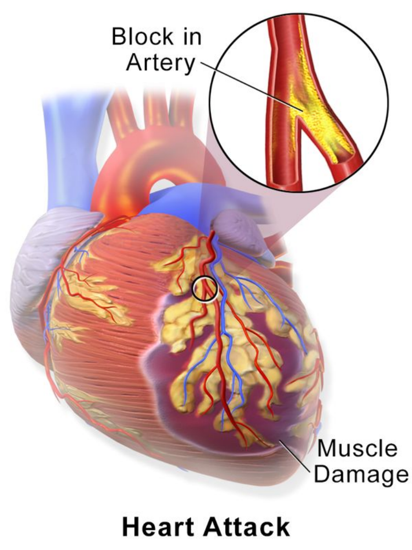
When myocardial infarction happens, there is not enough O2 getting to the heart!



- No O2 ⇒ mitochondrial oxidative phosphorylation can't happen
  - MUCH LESS ATP MADE
- **Glycolysis takes over: GOOD AT FIRST, THEN A PROBLEM**
  - Doesn’t make a lot of ATP
  - Anaerobic conditions ⇒ converts pyruvate → lactic acid & H+
    - Damages the heart even further!
    - Buildup of these byproducts start to inhibit glycolysis from happening ⇒ even less ATP made

Treatment?
Reprefuse the heart with O2 & good circulation ASAP!

The problem…

When reprefuse the heart, fatty acid oxidation (FA breakdown into acetyl-CoA) takes overs

- Decreases Kreb's cycle & electron transport chain activity
- Keeps glycolysis activity high
- High levels of H+ & lactic acid remain ⇒ decreased cardiac efficiency & more damage

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Glycolysis high yield Recaps!

- Remember which enzymes have *irreversible* reactions:
  - Hexokinase/Glucokinase
  - Phosphofructokinase-1
  - Pyruvate Kinase
  - PDC
- Remember what molecules activate and inhibit…
  - Hexokinase/Glucokinase
  - Phosphofructokinase-1
  - Pyruvate Kinase
  - PDC
- INSULIN is the glycolysis hormone
- **Glycolysis NET profit: (not including pyruvate —> Acetyl-CoA conversion)**
  - 2 pyruvate
  - 2 ATP
  - 2 NADH

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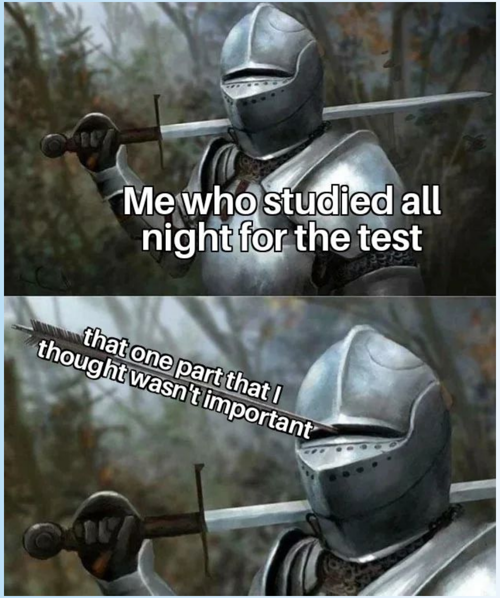
Pentose Phosphate Pathway (PPP)



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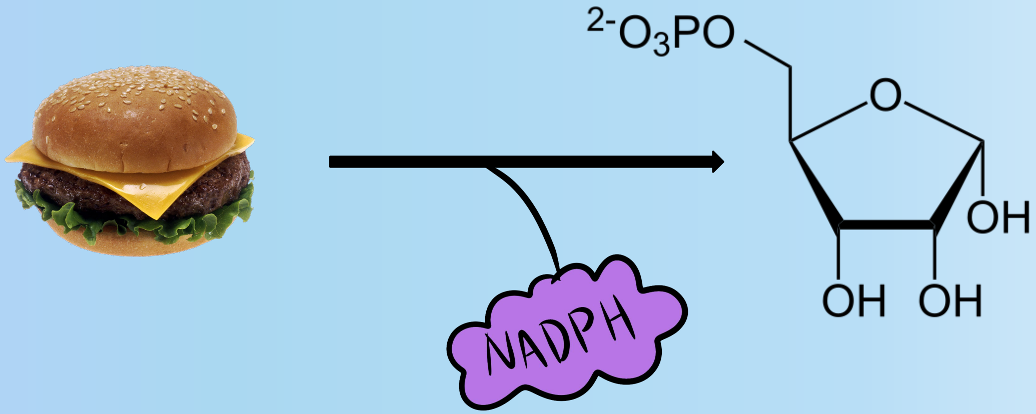
What is PPP?

An alternative way to break down glucose;

Along the way you make NADPH, and at the end you make Ribose-5-Phosphate



When & where does PPP occur?

When:

- Need **NADPH** to power:
  - Cholesterol synthesis
  - Fatty acid synthesis
  - Riddance of ROS via glutathione
- Need **Ribose-5-Phosphate** to help synthesize:
  - DNA/RNA/ATP
  - NAD+/FAD/CoA
- Insulin is circulating in the body

Where:

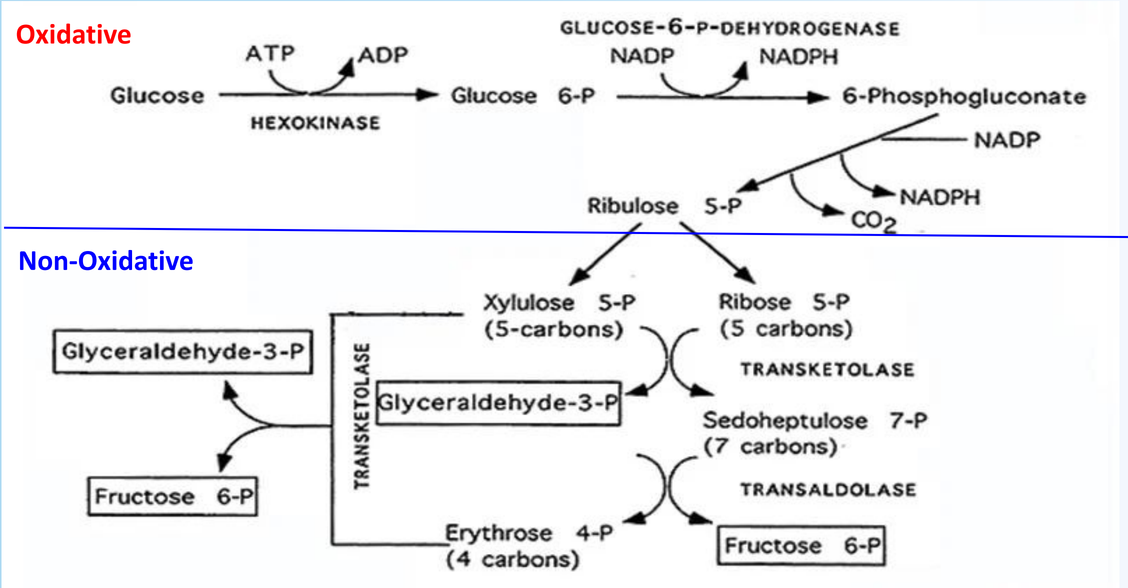
- Red blood cells
  - Cells without mitochondria
- Liver cells
- Cell cytosol (like glycolysis)

PPP is divided into…

1) **Oxidative phase**
   a) Oxidation: when you break down a molecule and lose at least one electrons
   b) Irreversible
   c) Aerobic (O2)
   d) Makes NADPH & Ribose-5-P

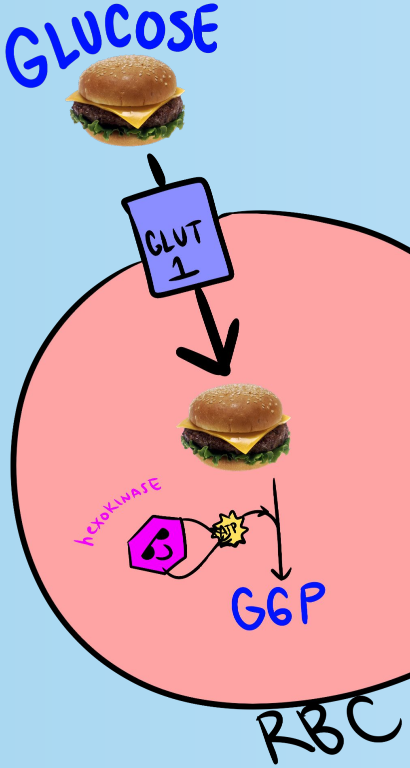
2) **Non-Oxidative phase**
   a) Reversible
   b) Anaerobic (No O2)
   c) ONLY makes Ribose-5-P

Let’s start!

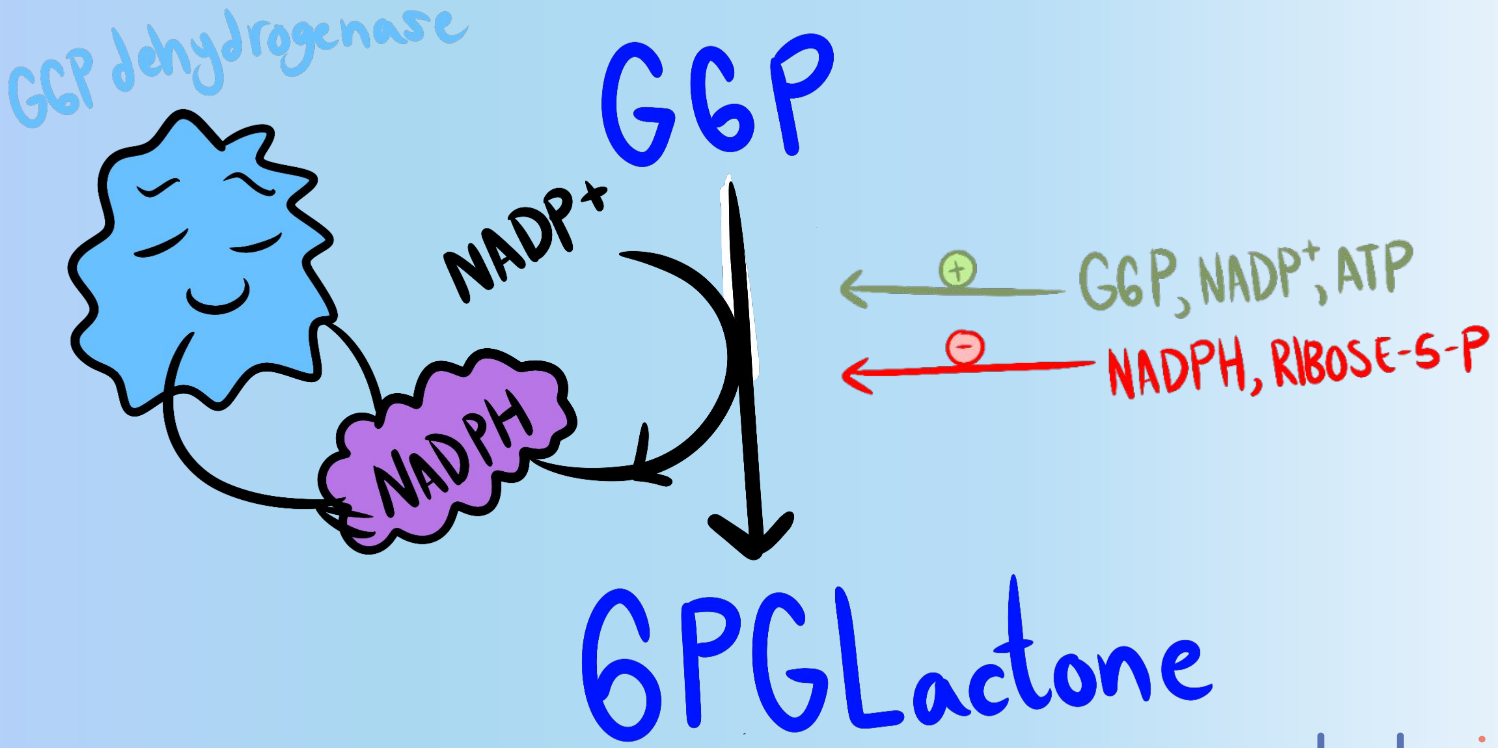


Oxidative
GLUCOSE-6-P-DEHYDROGENASE
ATP
ADP
NADP
NADPH
Glucose
HEXOKINASE
Glucose 6-P
6-Phosphogluconate
NADP
NADPH
Ribulose 5-P
CO_2
Non-Oxidative
Xylulose 5-P
(5-carbons)
Ribose 5-P
(5 carbons)
Glyceraldehyde-3-P
TRANSKETOLASE
Glyceraldehyde-3-P
TRANSKETOLASE
Sedoheptulose 7-P
(7 carbons)
TRANSALDOLASE
Fructose 6-P
Erythrose 4-P
(4 carbons)
Fructose 6-P

Step 0: Incoming glucose & glycolysis again?

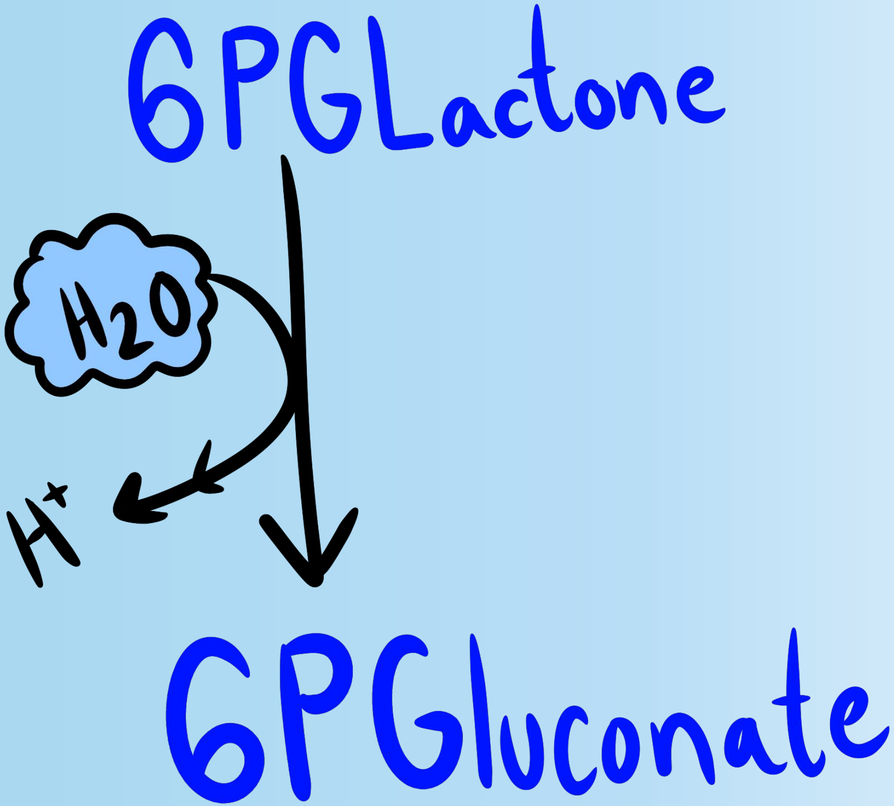


Step 1: RATE LIMITING STEP



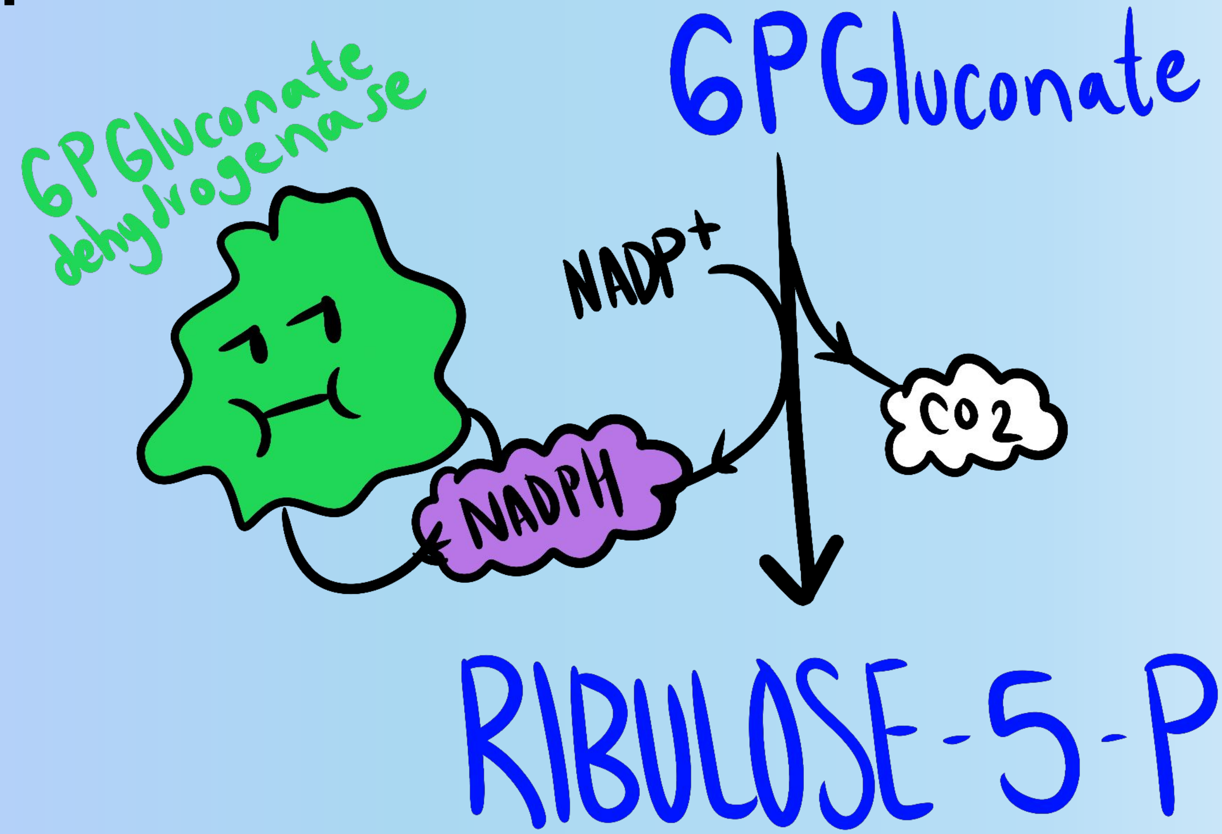
★ 6PGLactone: 6-phosphoglucolactone

Step 2:

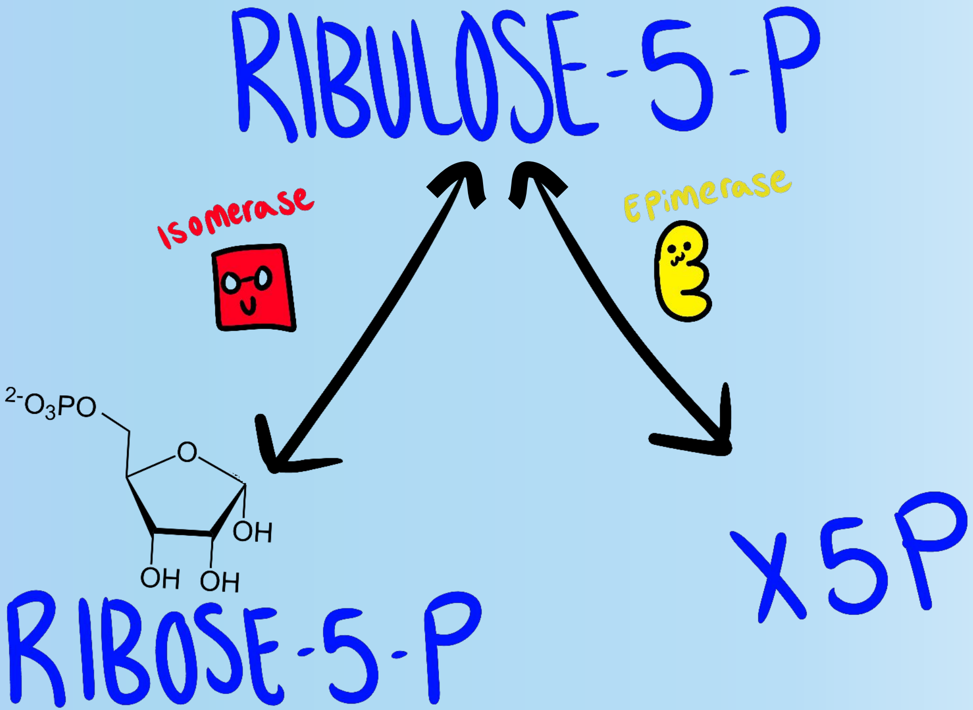


★ 6PGluconate: 6-phosphogluconate

Step 3:

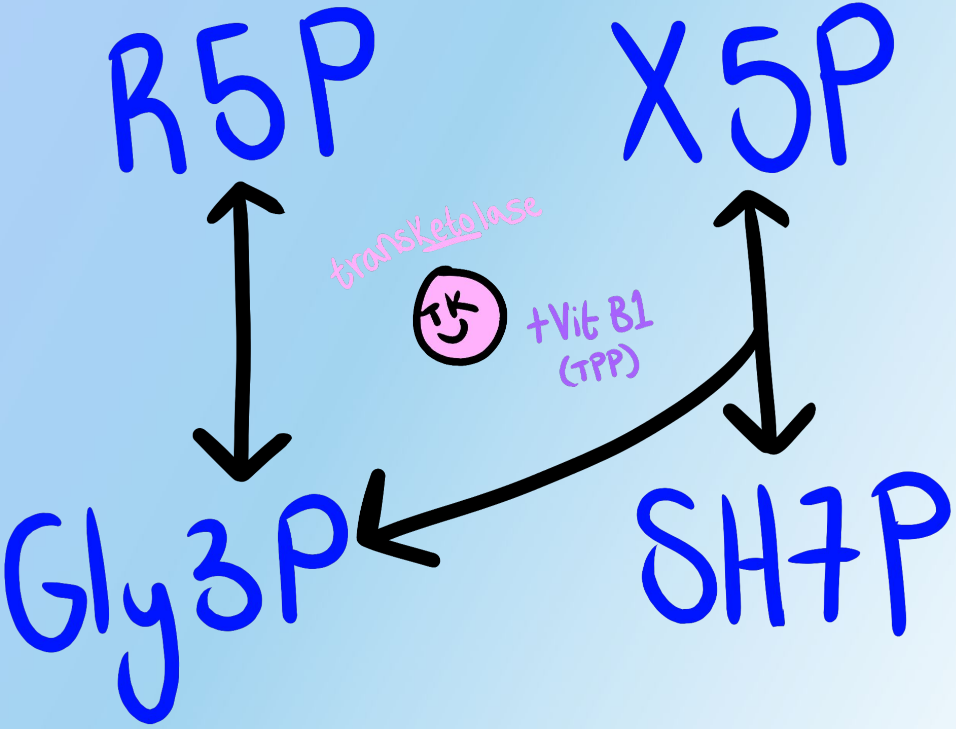

6PGluconate
6PGluconate dehydrogenase
NADP+
NADPH
CO2
RIBULOSE-5-P

Step 4:



★ X5P: Xylulose-5-phosphate

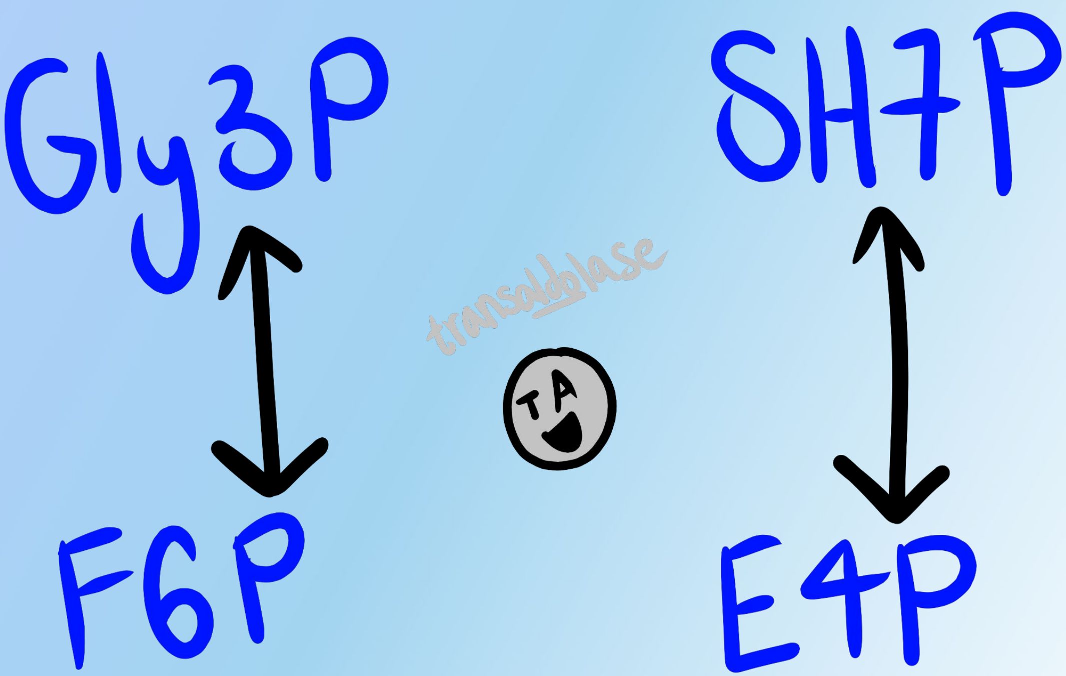
Step 5:



★ Gly3P: Glyceraldehyde-3-phosphate

★ SH7P: Sedoheptulose-7-phosphate

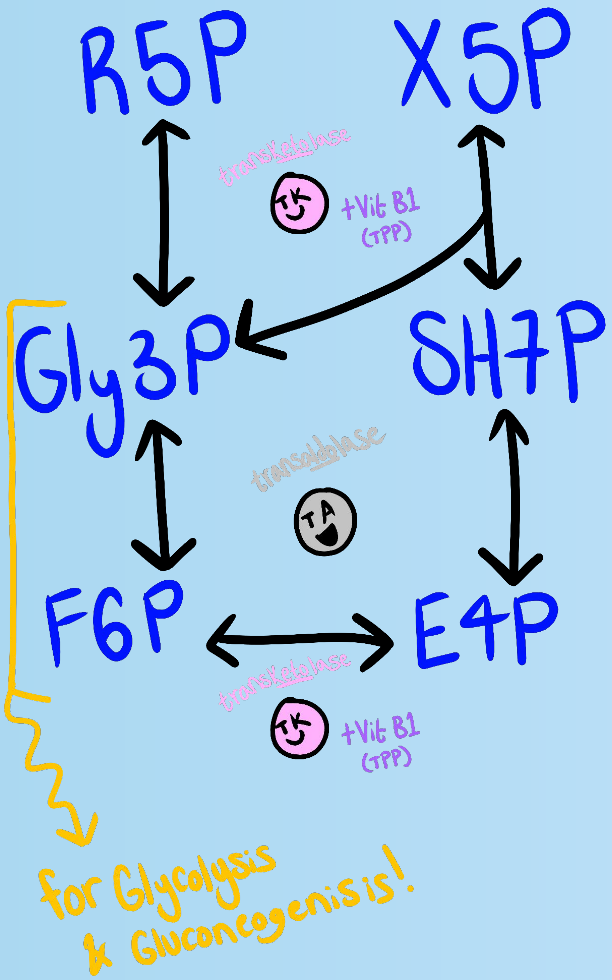
Step 6:



★ F6P: Fructose-6-phosphate

★ E4P: Erythrose-4-phosphate

Step 7:


R5P
X5P
transketolase
TK
+Vit B1
(TPP)
Gly3P
S H7P
transaldolase
TA
F6P
E4P
transketolase
TK
+Vit B1
(TPP)
for Glycolysis
& Gluconeogenisis!

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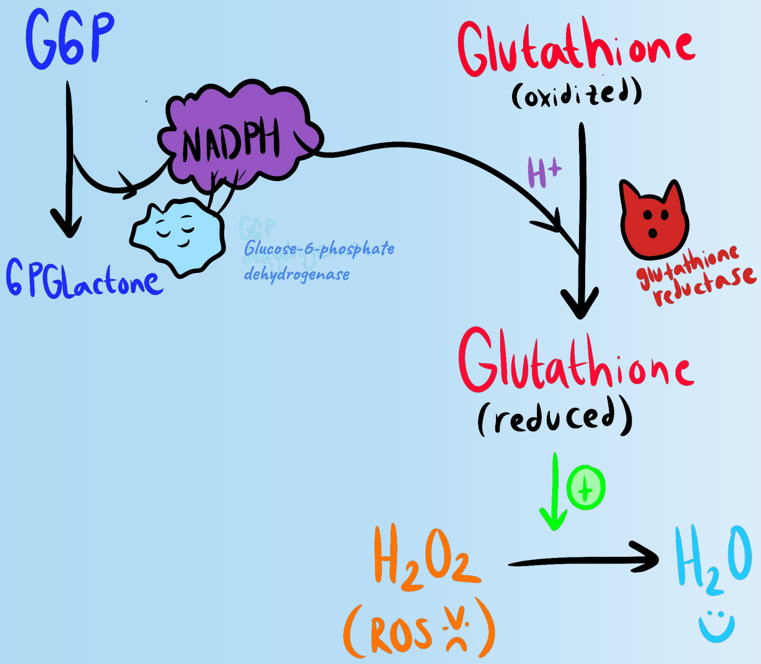
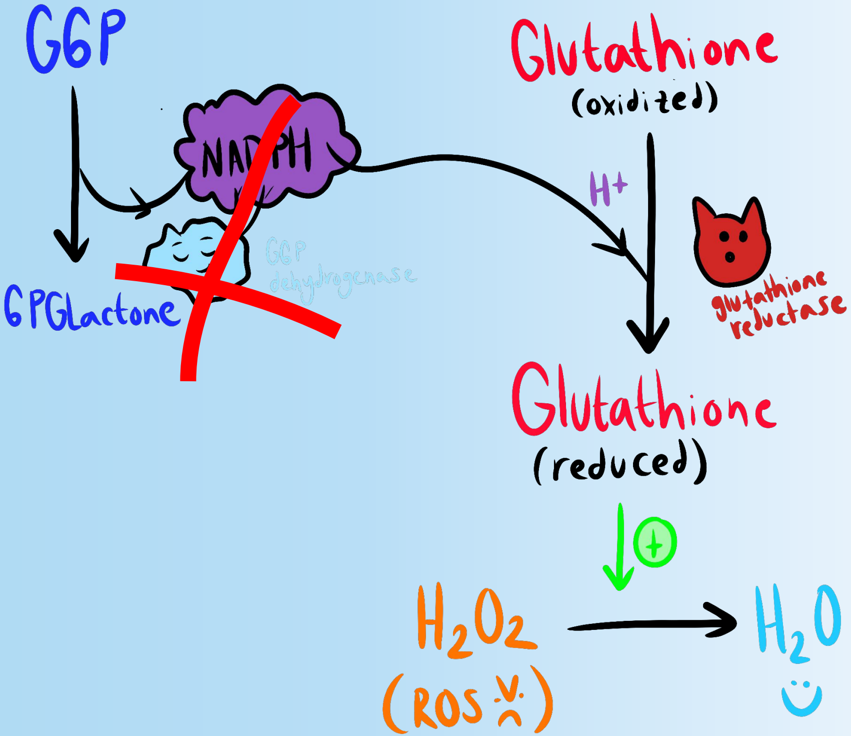
Clinical correlation: Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Normal Conditions:
In a RBC, G6P Dehydrogenase helps Glutathione Reductase do its job by donating a H+ from NADPH; Reduced glutathione helps convert H2O2, a damaging reactive oxygen species, into a harmless water molecule



G6P dehydrogenase deficiency:

- No NADPH to reduce glutathione
- No reduced glutathione to convert H2O2 into water
- H2O2 buildup = RBC gets damaged
- Hemolytic anemia



PPP High Yield Recaps!

- Remember where and when PPP occurs
- Remember the differences between the oxidative and non-oxidative stage
- Remember the rate-limiting step
- Remember that the non-oxidative stage can make substrates for glycolysis & gluconeogenesis
- Remember about G6PD deficiency
- **PPP NET profit:**
    - 2 NADPH
    - 1 CO2
    - 1 Ribose-5-phosphate

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