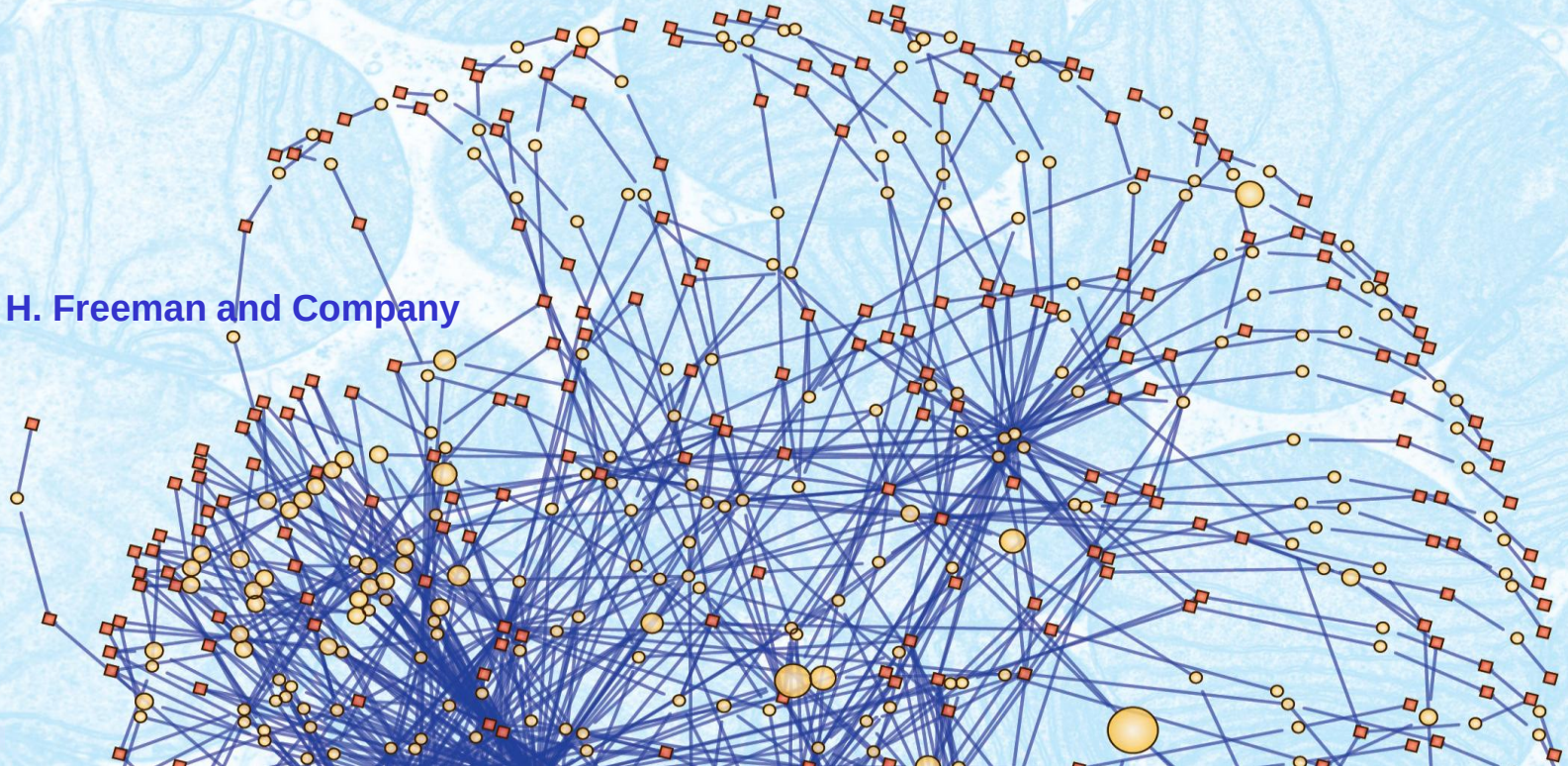
Lehninger

SIXTH EDITION

# Principles of Biochemistry

David L. Nelson | Michael M. Cox

## 14| Glucose Utilization and Biosynthesis



# Central Importance of Glucose

- Glucose is an excellent fuel
  - Yields good amount of energy upon oxidation ($\Delta G_{\text{complete oxidation}} = -2840$ kJ/mol)
  - Can be efficiently stored in the polymeric form
  - Many organisms and tissues can meet their energy needs on glucose only

- Glucose is a versatile biochemical precursor
  - Bacteria can use glucose to build the carbon skeletons of:
    - All the amino acids
    - Membrane lipids
    - Nucleotides in DNA and RNA
    - Cofactors needed for the metabolism

# Four Major Pathways of Glucose Utilization

- Storage
  - Can be stored in the polymeric form (starch, glycogen)
  - When there's excess energy
- Glycolysis
  - Generates energy via oxidation of glucose
  - Short-term energy needs
- Pentose Phosphate Pathway
  - Generates NADPH via oxidation of glucose
  - For detoxification and the biosynthesis of lipids and nucleotides
- Synthesis of Structural Polysaccharides
  - For example, in cell walls of bacteria, fungi, and plants

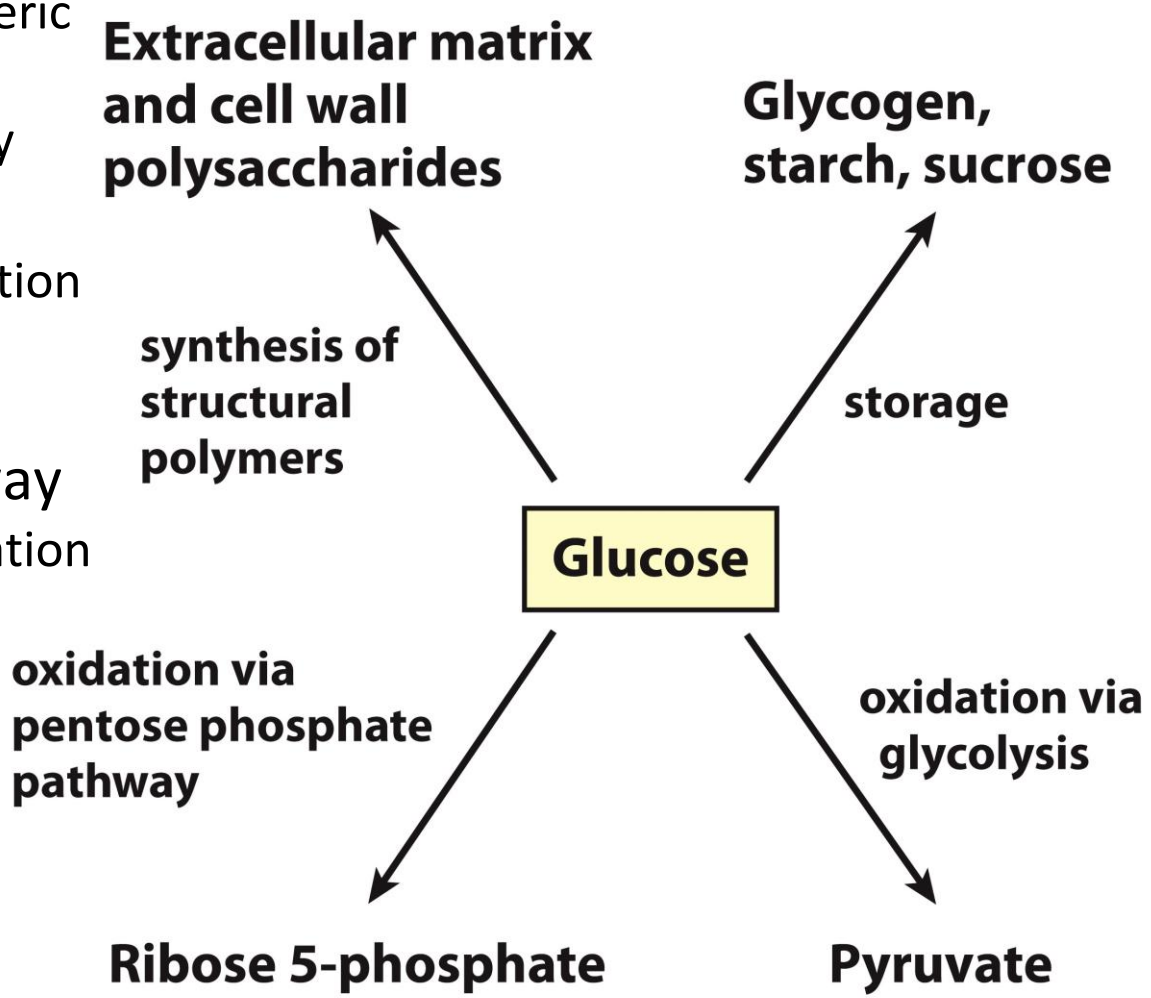



Figure 14-1
*Lehninger Principles of Biochemistry*, Sixth Edition

# Glycolysis: Importance

- Almost universal central pathway of glucose catabolism
- Sequence of enzyme-catalyzed reactions by which glucose is converted into pyruvate
  - Pyruvate can be further aerobically oxidized
  - Pyruvate can be used as a precursor in biosynthesis

- Some of the oxidation-free energy is captured by the synthesis of ATP and NADH

- Research of glycolysis played a large role in the development of modern biochemistry
  - Understanding the role of coenzymes
  - Discovery of the pivotal role of ATP
  - Development of methods for enzyme purification
  - Inspiration for the next generations of biochemists

# The 2 phases of glycolysis

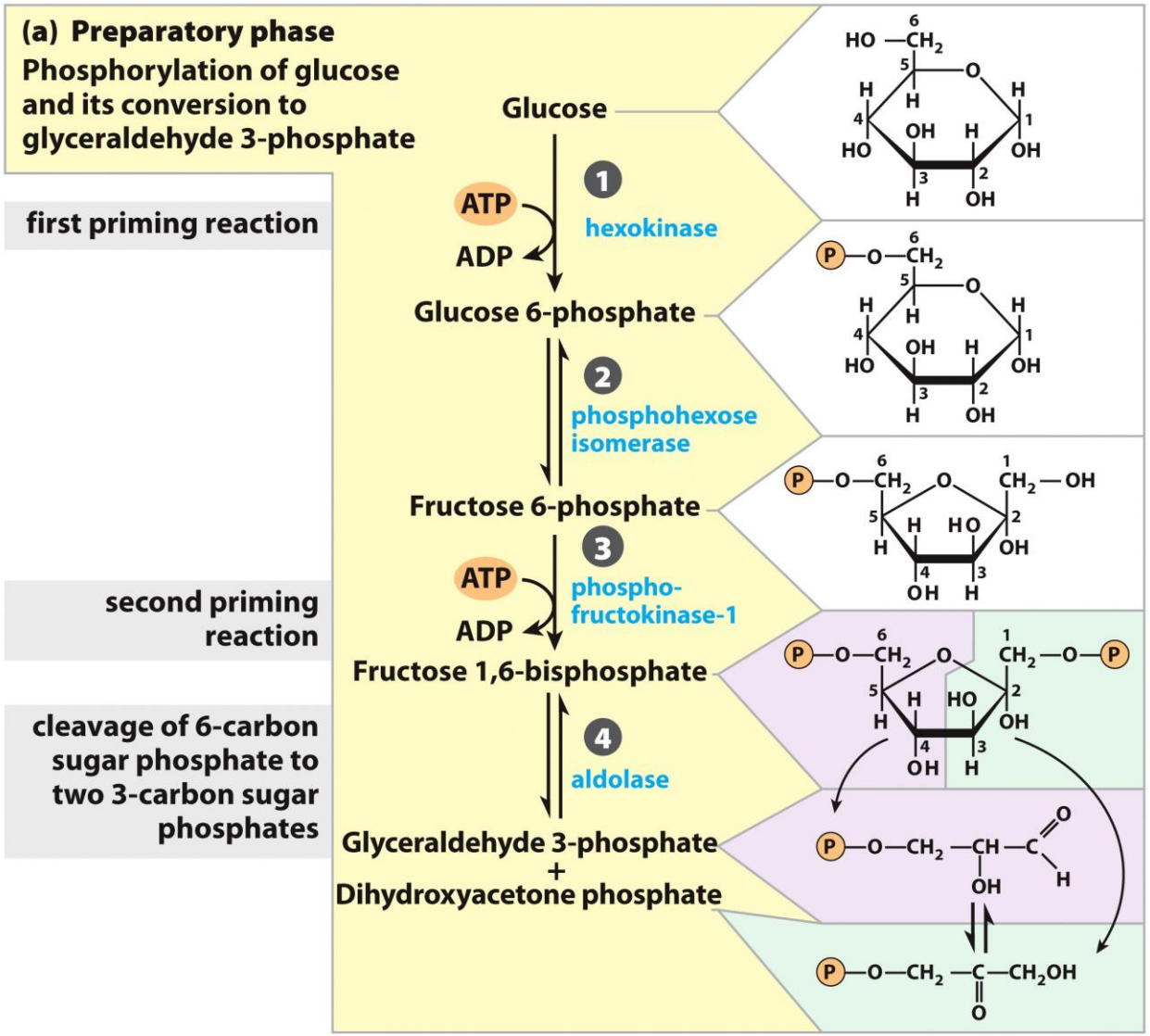
- In the evolution of life, glycolysis probably was one of the earliest energy-yielding pathways
- It developed before photosynthesis, when the atmosphere was still anaerobic

- Thus, the task upon early organisms was:
  How to extract free energy from glucose anaerobically?
- The solution:
  - First: Activate it by phosphorylation
  - Second: Collect energy from the high-energy metabolites
- Glycolysis is a sequence of 10 reactions, 5 are preparatory and 5 are energy-yielding

# Glycolysis: The Preparatory Phase

2 ATP molecules are used to raise the free energy of the intermediates

*For **each molecule of glucose** that passes through the preparatory phase, **two molecules of glyceraldehyde 3-phosphate** are formed.*




The "*lysis*" step of glycolysis

**Figure 14-2 part 1**
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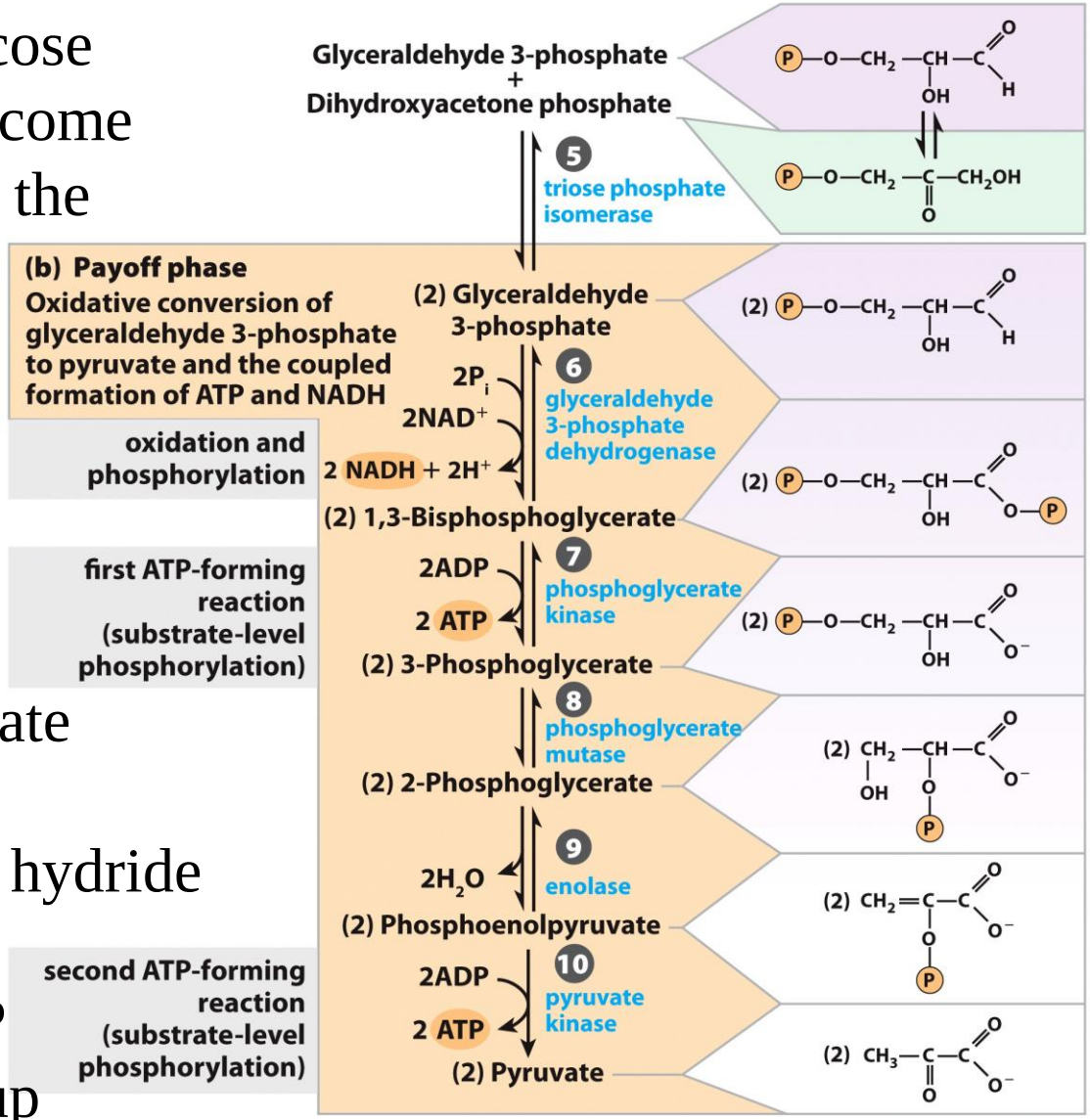
# Glycolysis: The Payoff Phase

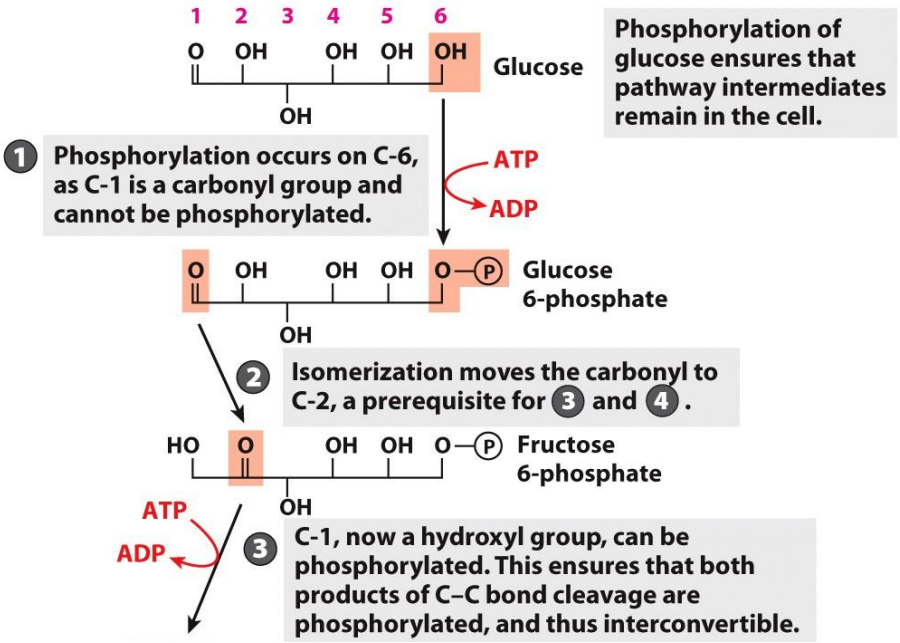
4 ATP are produced per glucose
2 ATP/glucose is the net outcome
Energy is also conserved by the formation of 2 NADH molecules

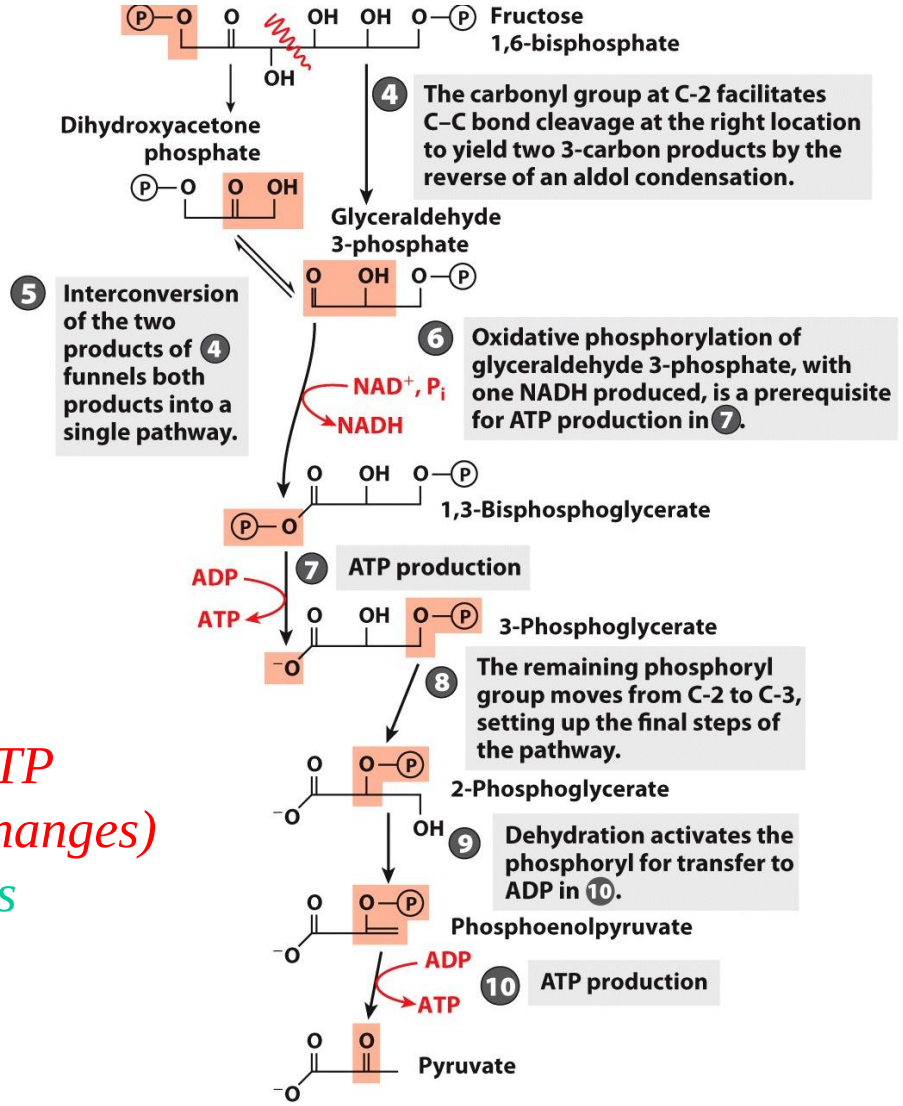
3 types of chemical transformations:

1. Breakage of glucose backbone to yield pyruvate (6C → 2x 3C)
2. Formation of NADH by hydride transfer to $NAD^+$
3. Phosphorylation of ADP by high phosphoryl group potential compounds to make ATP



# Chemical Logic of Glycolysis




- *How is the formation of NADH and ATP coupled to glycolysis? (Free energy changes)*
- *Why are phosphorylated intermediates important in glycolysis?*

# Glycolysis: Fates of Pyruvate

- In most organisms pyruvate is metabolized via one of three catabolic routes:

1. *Citric acid cycle:* pyruvate is oxidized and decarboxylated to release $CO_2$ (the electrons that are moving go through ETC in mito and are used to make ATP; aerobic conditions)
2. *Lactic acid fermentation:* after vigorous exercise, [$O_2$] in muscles is low (**hypoxia**) NADH cannot be reoxidized to $NAD^+$ for glycolysis to continue → pyruvate is reduced to lactate accepting electrons from NADH (regenerating $NAD^+$). Certain tissues (RBC and retina) ferment pyruvate into lactate even under aerobic conditions
3. *Alcohol fermentation:* some yeasts and plants can ferment pyruvate into ethanol and $CO_2$ (important for beverage production and baking)

- Pyruvate also some anabolic fates (can produce a.a. alanine or fatty acids)

# Fates of Pyruvate

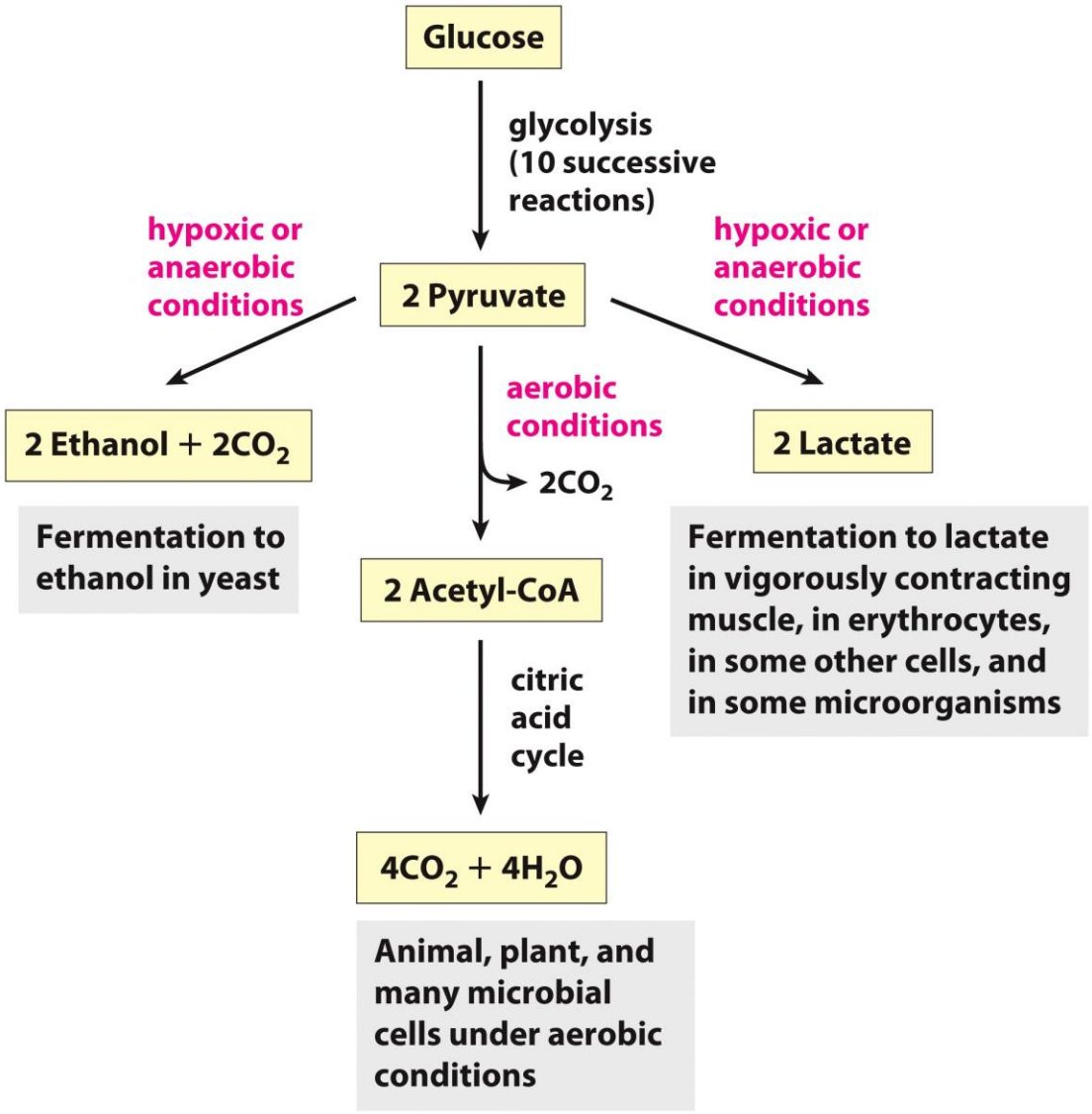



**Figure 14-4**
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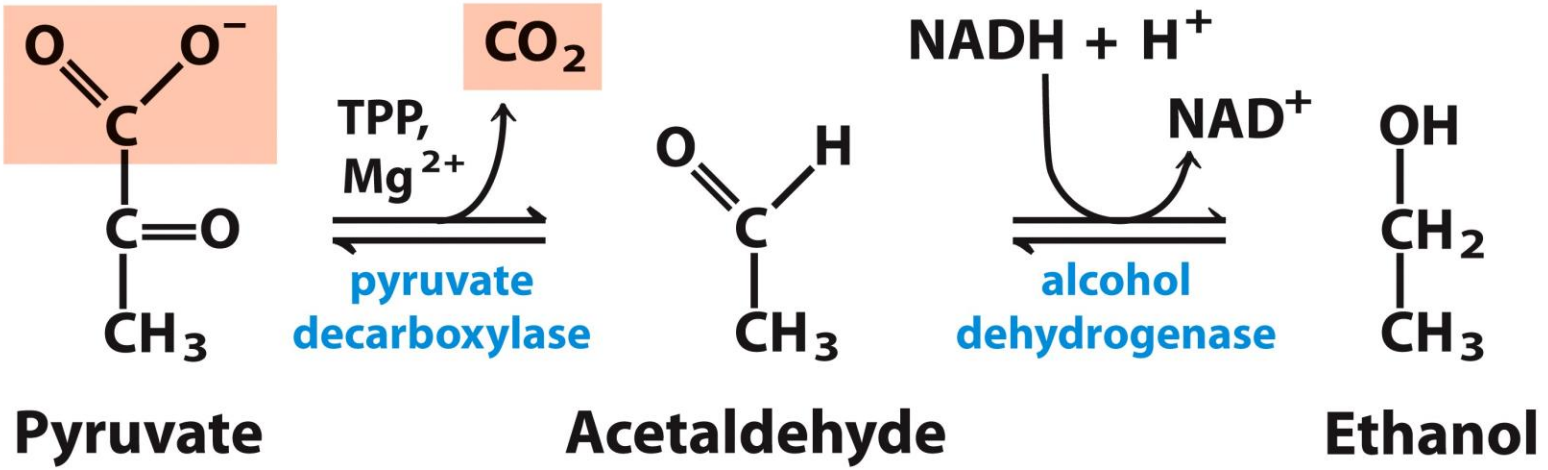
# Anaerobic Glycolysis: Fermentation

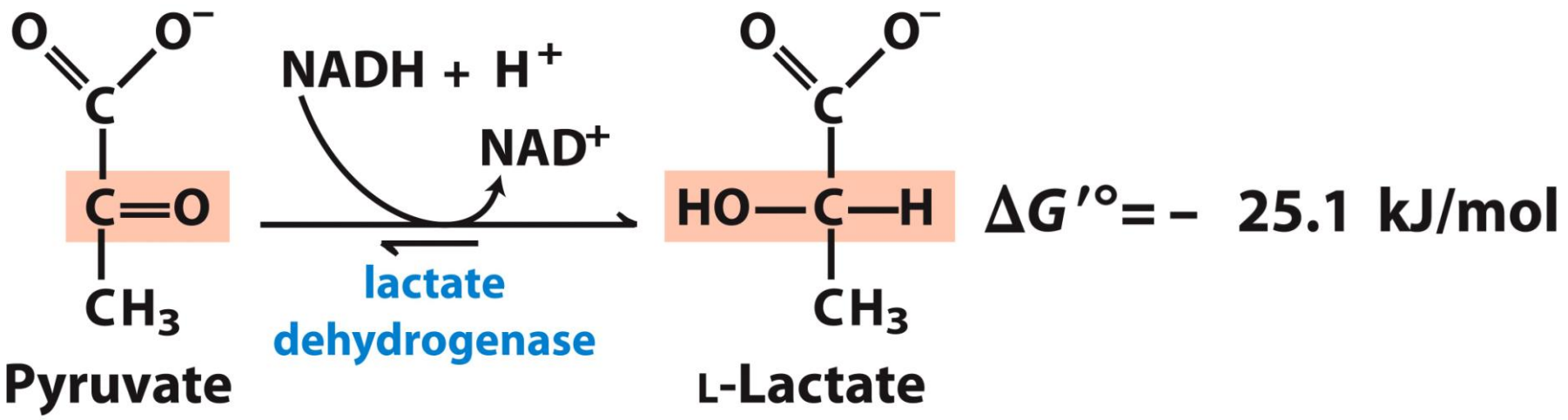
- *Generation of energy (ATP) without consuming oxygen or $NAD^+$*
- No net change in oxidation state of the sugars
- Reduction of pyruvate to another product
- Regenerates $NAD^+$ for further glycolysis under anaerobic conditions
- The process is used in the production of food from beer to yogurt to soy sauce

# Yeast undergo Ethanol Fermentation




- Two-step reduction of pyruvate to ethanol, irreversible
- Humans do not have *pyruvate decarboxylase*
- Humans do express *alcohol dehydrogenase* for ethanol metabolism
- $CO_2$ produced in the first step is responsible for:
  - carbonation in beer
  - dough rising when baking bread
- Both steps require cofactors
  - Pyruvate decarboxylase: $Mg^{2+}$ and thiamine pyrophosphate (TPP)
  - Alcohol dehydrogenase: $Zn^{2+}$ and NADH

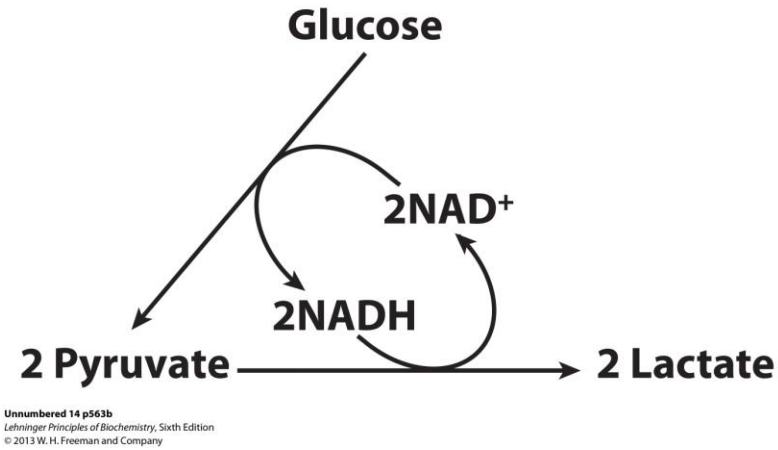
# Animals undergo lactic acid fermentation




- Reduction of pyruvate to lactate, reversible
- Equilibrium favors lactate formation
- During strenuous exercise, lactate builds up in the muscle
  - Generally less than 1 minute (even most toned athletes cannot sprint at highest speeds for more than a minute!)
- The acidification of muscle prevents its continuous strenuous work

# Lactic Acid Fermentation

- *No net change in $NAD^+$ or NADH levels*




- Lactate can be transported to the liver to be converted to glucose (the Cori cycle)
- Requires a recovery time
  - High amount of oxygen consumption to fuel gluconeogenesis
  - Restores muscle glycogen stores
  - Heavy breathing is required to replenish oxygen to repay the "oxygen debt"

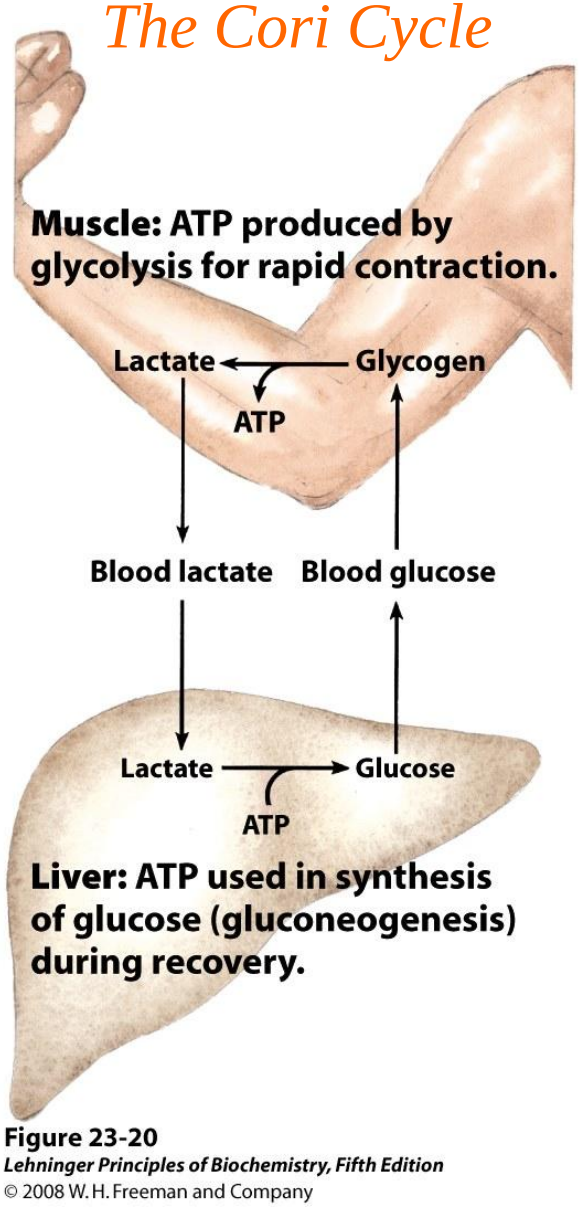



**Figure 23-20**
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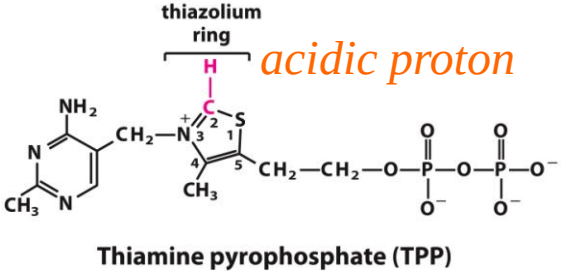
# TPP is a common acetaldehyde carrier




- Coenzyme derived from vitamin $B_1$ (thiamine)
- Lack of $B_1$ → *beriberi* (swelling, pain, paralysis and death)
- Cleavage of bonds adjacent to carbonyl groups
- Thiazolium ring of TPP stabilizes carbanion intermediates by providing an electrophilic structure into which the carbanion electrons can be delocalized by resonance "electron sinks"

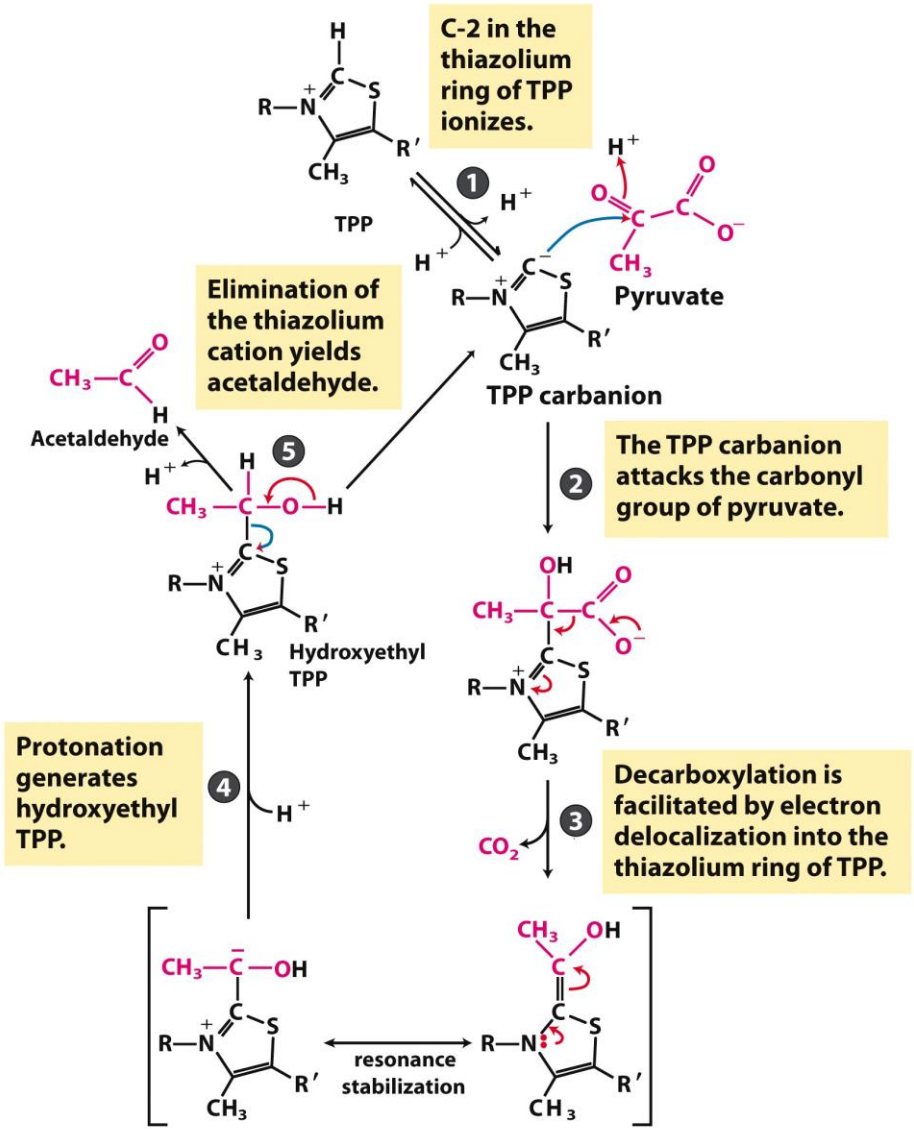
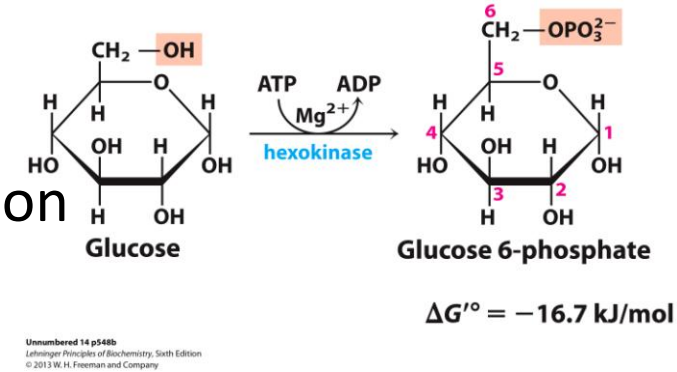



**Figure 14-15c**
*Lehninger Principles of Biochemistry*, Sixth Edition

# The Preparatory Phase

# Step 1: Phosphorylation of Glucose

- Rationale
  - Traps glucose inside the cell
  - Lowers intracellular glucose concentration to allow further uptake

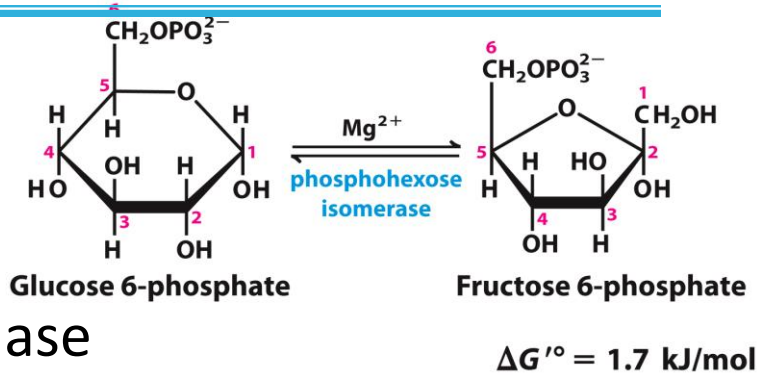



- This process uses the energy of ATP
- The first "priming" reaction
- Hexokinase in eukaryotes, and glucokinase in prokaryotes and liver (**isozymes**: 2 or more enzymes encoded in different genes but catalyze the same reaction)
- Soluble cytosolic enzyme (like all other glycolytic enzymes)
- Nucleophilic oxygen at C6 of glucose attacks the last ($\gamma$) phosphate of ATP
- ATP-bound $Mg^{2+}$ facilitates this process by shielding the negative charges on ATP

- Highly thermodynamically favorable/irreversible
  - Regulated mainly by substrate inhibition

# Step 2: Phosphohexose Isomerization

- Rationale
  - C1 of fructose is easier to phospho-rylate by PFK
  - Allows for symmetrical cleave by aldolase




- An aldose (glucose) can isomerize into a ketose (fructose) via an *enediol* intermediate
- The isomerization is catalyzed by the active-site glutamate, via general acid/base catalysis

- Slightly thermodynamically unfavorable/reversible
  - Very small positive $\Delta G'^{o}$ indicates that the reaction can proceed readily in either direction
  - Product concentration kept low to drive forward

# Mechanism of Phosphohexose Isomerase

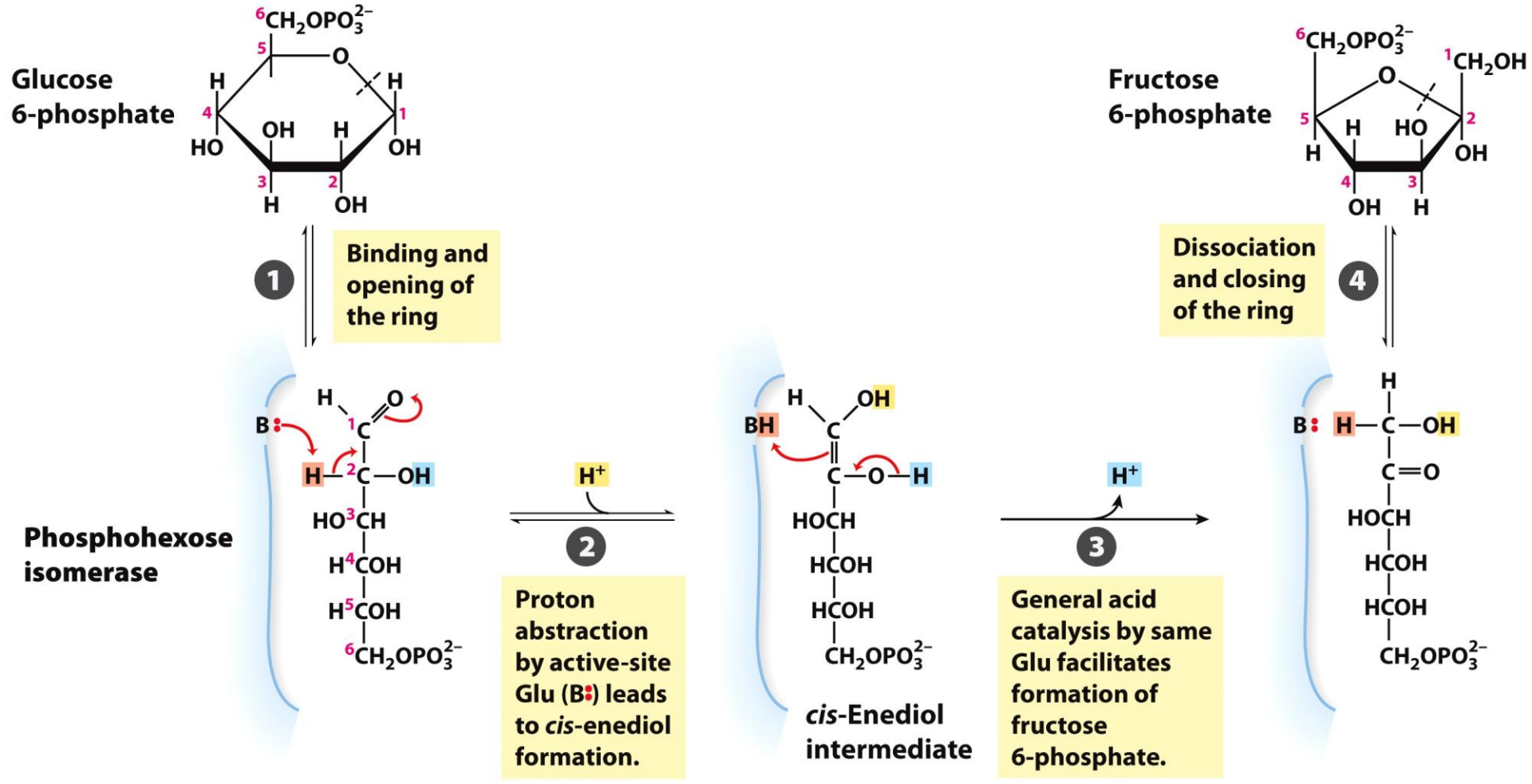



**Figure 14-5**
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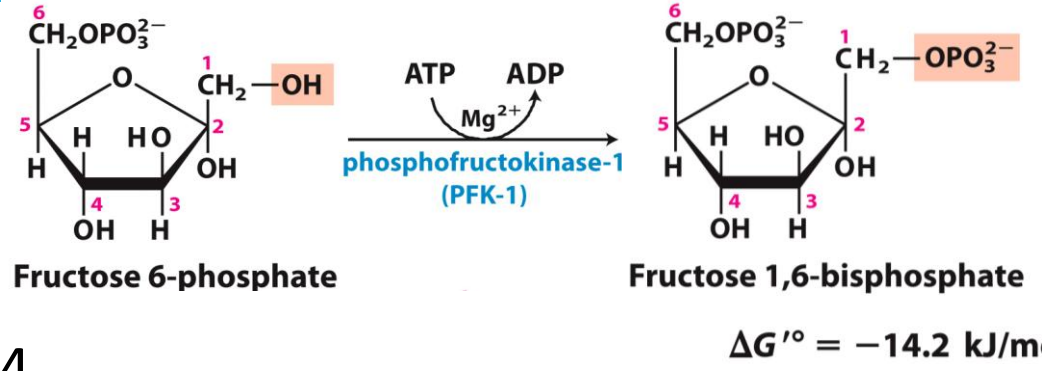
# Step 3: 2nd Priming Phosphorylation

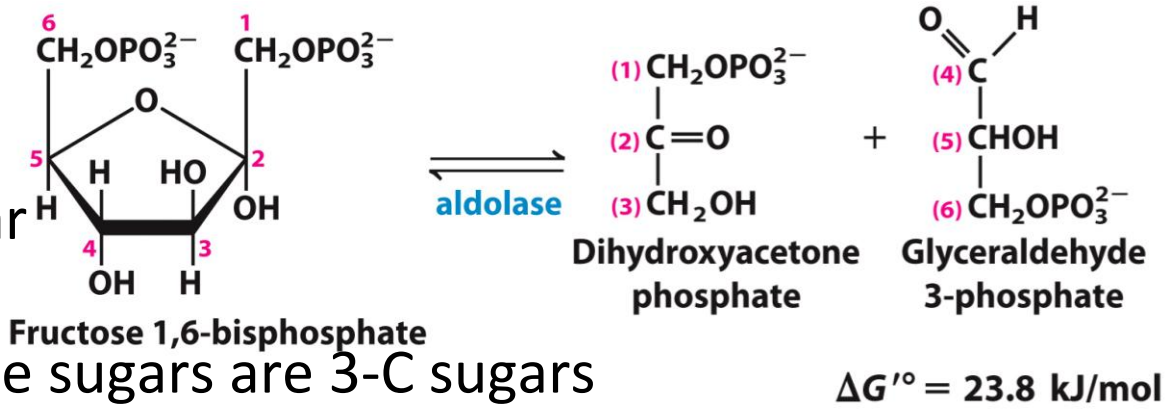



- Rationale
  - Further activation of glc
  - Allows for 1 phosphate/ 3-carbon sugar after step 4
- First Committed Step of Glycolysis
  - fructose 1,6-bisphosphate is committed to become pyruvate and yield energy whereas g-6-p and f-6-p have other possible fates
- This process uses the energy of ATP

- Highly thermodynamically favorable/irreversible
- Phosphofructokinase-1 is highly regulated
  - By ATP, ADP, AMP, fructose-2,6-bisphosphate, and other metabolites (detailed next chapter)
  - Do not burn glucose if there is plenty of ATP

# Step 4: Aldol Cleavage of F-1,6-bP

- Rationale
  - Cleavage of a 6-C sugar into two 3-C sugars
  - High-energy phosphate sugars are 3-C sugars

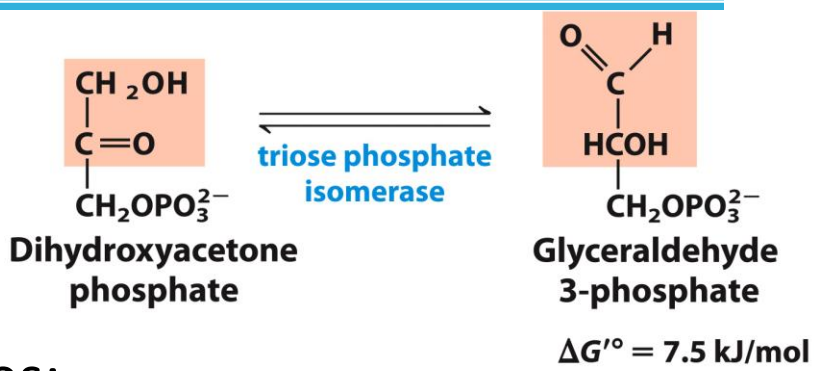



- The reverse process is the familiar aldol condensation
- Animal and plant aldolases employ covalent catalysis
- Fungal and bacterial aldolases employ metal ion catalysis

- Thermodynamically unfavorable/reversible
  - The actual free energy change is small and therefore the reaction is readily reversible. It is small because the concentration of the reactant is kept low
  - GAP concentration kept low to pull reaction forward
- *What is the mechanism of aldolase (class I)?*

# Step 5: Triose Phosphate Interconversion

- Rationale:
  - Allows glycolysis to proceed by one pathway



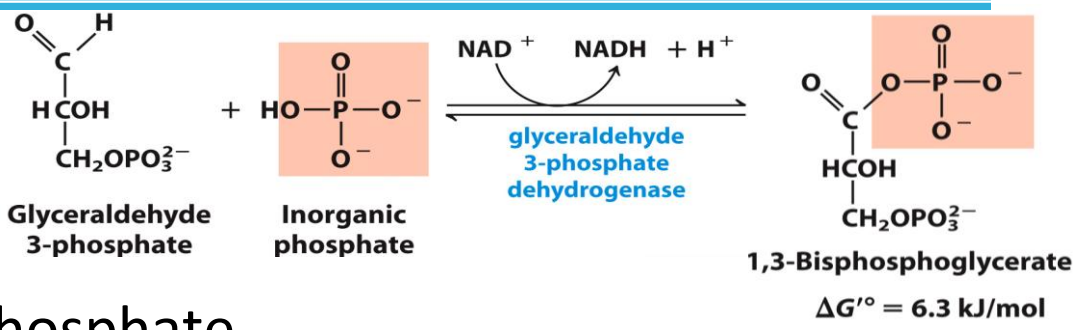

- Aldolase creates two triose phosphates:
  - Dihydroxyacetone Phosphate (DHAP)
  - Glyceraldehyde-3-Phosphate (GAP)
- Only GAP is the substrate for the next enzyme
- DHAP must be converted to GAP

- Similar mechanism as phosphohexose isomerase
- Completes preparatory phase

- Thermodynamically unfavorable/reversible
  - GAP concentration kept low to pull reaction forward

# The Payoff Phase

# Step 6: Oxidation of GAP



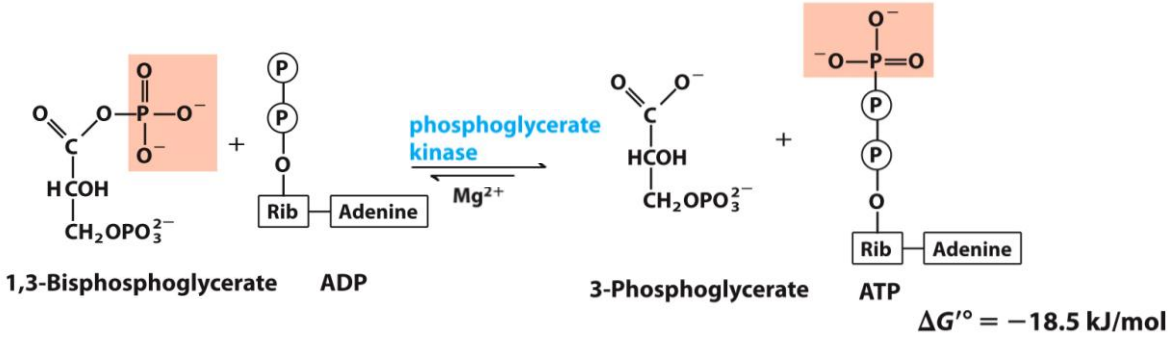

- Rationale:
  - Generation of a high-energy phosphate cpd
  - Incorporates inorganic phosphate
  - **Which allows for net production of ATP via glycolysis!**

- First energy-yielding step in glycolysis
- Oxidation of aldehyde with $NAD^+$ gives NADH and an **acyl phosphate** (very high $\Delta G'^{o} = -49.3$ kJ/mol)
- Active site cysteine
  - Forms high-energy thioester intermediate
  - Subject to inactivation by oxidative stress

- Thermodynamically unfavorable/reversible
  - Coupled to next reaction to pull forward
- *GAPDH mechanism (self study)*

# Step 7: 1st Production of ATP

- Rationale:
  - Substrate-level phosphorylation to make ATP




- 1,3-bisphosphoglycerate is a high-energy compound
  - can donate the phosphate group to ADP to make ATP
- The enzyme is named after the reverse reaction
- **Substrate-level phosphorylation**: the fprmation of ATP by group transfer from a substrate

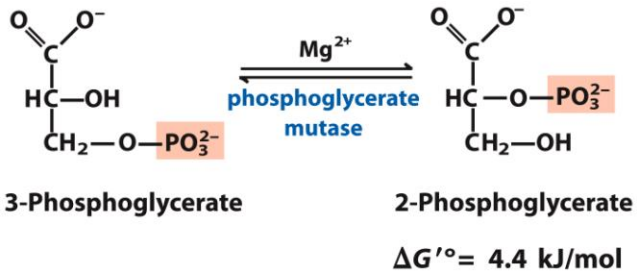
- Highly thermodynamically favorable/reversible
  - Is reversible because of coupling to GAPDH reaction
  - Steps 6 and 7 are strongly coupled·

Glyceraldehyde 3-P + ADP + $P_i$ + $NAD^+$ $\rightleftharpoons$ 3-phosphoglycerate + ATP + NADH + $H^+$

$\Delta G'^{o}$ = –12.2 kJ/mol

# Step 8: Migration of the Phosphate

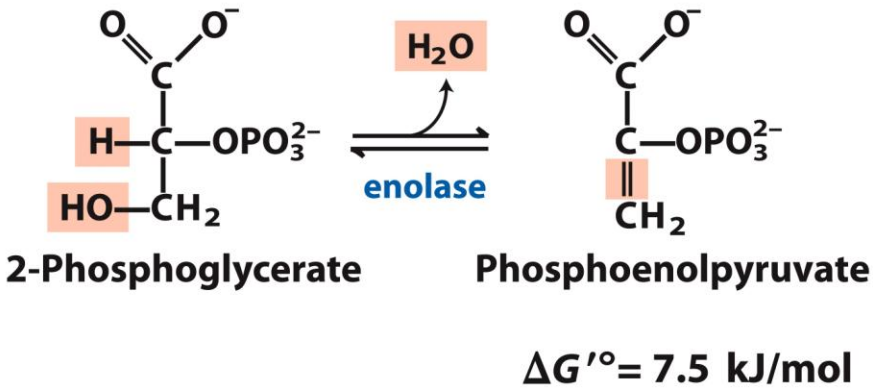
- Rationale:
  - Be able to form high-energy phosphate compound




- Mutases catalyze the (apparent) migration of functional groups
- One of the active site histidines is post-translationally modified to phosphohistidine
- Phosphohistidine donates its phosphate to O at C2 before retrieving another phosphate from O at C3
  - 2,3-bisphosphoglycerate intermediate
  - Note that the phosphate from the substrate ends up bound to the enzyme at the end of the reaction
- Thermodynamically unfavorable/reversible
  - Reactant concentration kept high by PGK to push forward

# Step 9: Dehydration of 2-PG to PEP

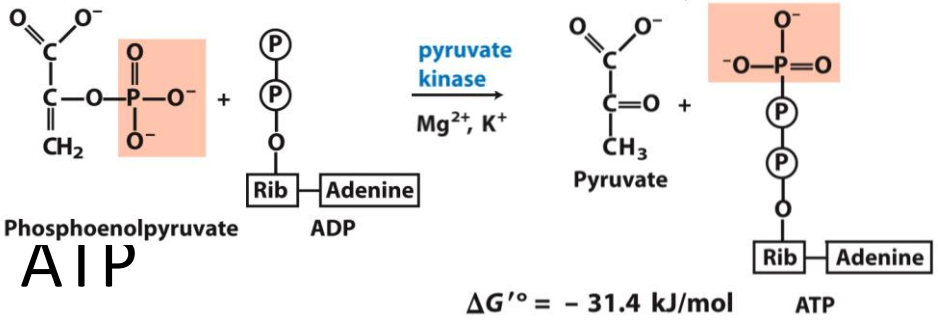
- Rationale
  - Generate a high-energy phosphate compound




- 2-Phosphoglycerate is not a good enough phosphate donor ($\Delta G'^{o} = -17.6$ kJ/mol; $\Delta G'^{o}_{PEP} = -61.9$ kJ/mol)

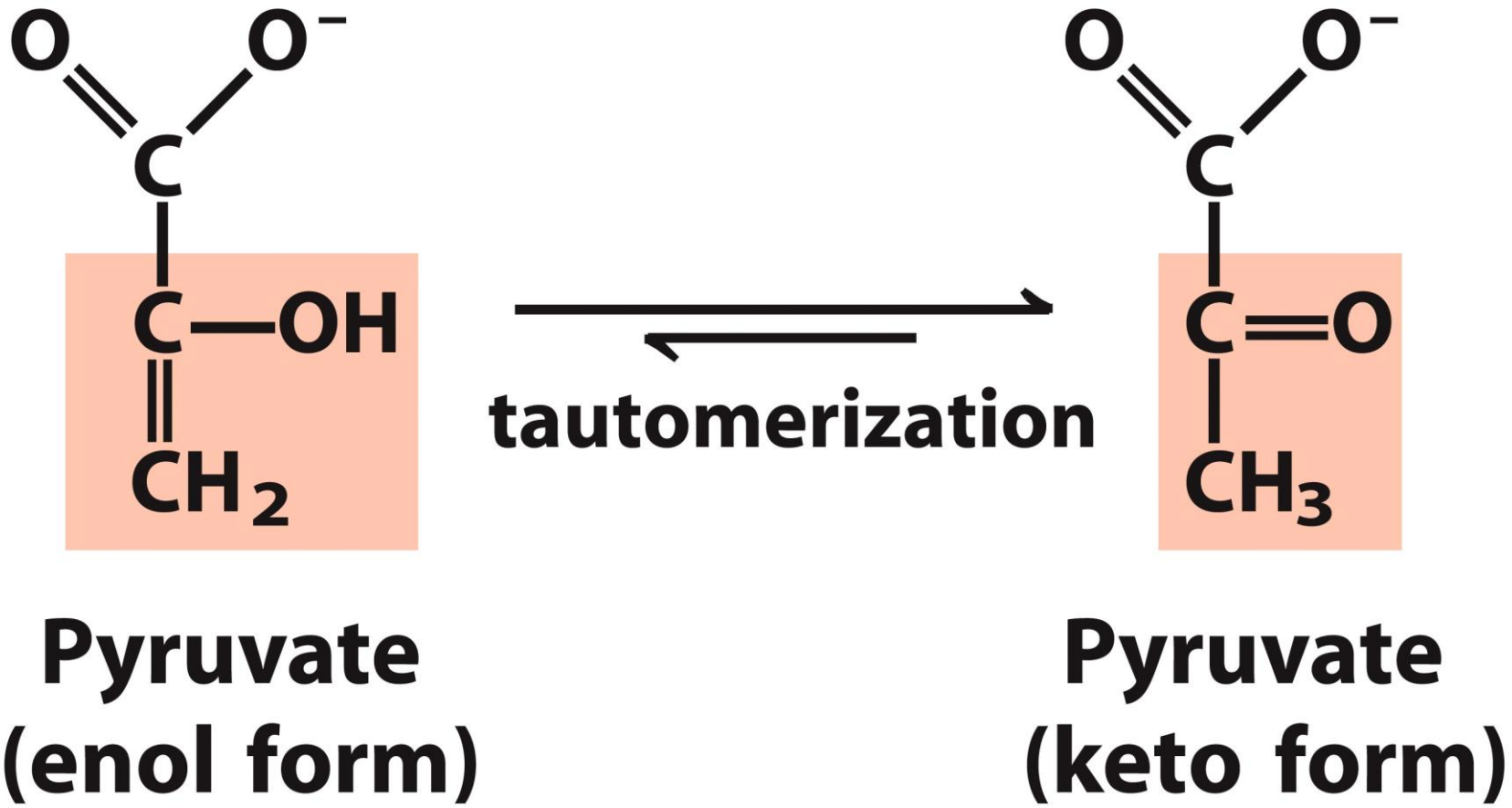
- Slightly thermodynamically unfavorable/reversible
  - Product concentration kept low to pull forward

# Step 10: 2nd Production of ATP




- Rationale
  - Substrate-level phosphorylation to make ATP
  - Net production of 2 ATP/glucose
- Loss of phosphate from PEP yields an enol that tautomerizes into ketone
- Tautomerization
  - effectively lowers the concentration of the reaction product
  - drives the reaction toward ATP formation
- Pyruvate kinase requires divalent metals ($Mg^{2+}$ or $Mn^{2+}$) for activity
- Highly thermodynamically favorable/irreversible
  - Regulated by ATP, divalent metals, and other metabolites

# Pyruvate Tautomerization Drives ATP Production

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*Lehninger Principles of Biochemistry*, Sixth Edition

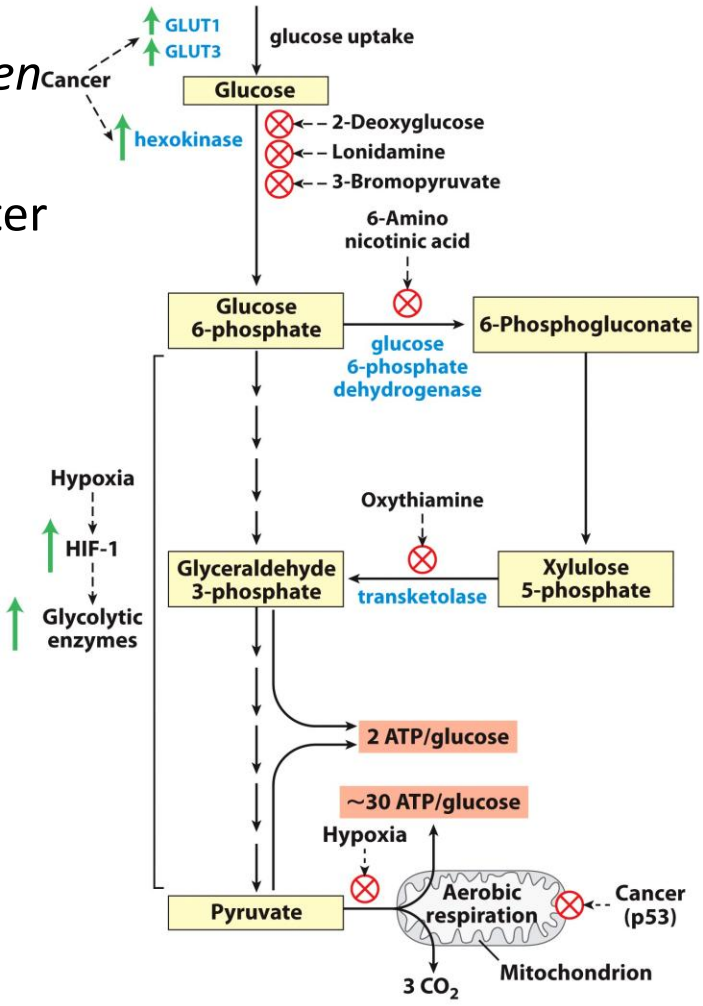
# Summary of Glycolysis

$$Glucose + 2\ NAD^+ + 2\ ADP + 2\ P_i \rightarrow 2\ Pyruvate + 2\ NADH + 2\ H^+ + 2\ H_2O + \mathbf{2\ ATP}$$

- Used:
  - 1 glucose; 2 ATP; 2 $NAD^+$
- Made:
  - 2 pyruvate
    - Various different fates
  - 4 ATP
    - Used for energy-requiring processes within the cell
  - 2 NADH
    - Must be reoxidized to $NAD^+$ in order for glycolysis to continue
- Glycolysis is heavily regulated
  - Ensure proper use of nutrients
  - Ensure production of ATP only when needed
  - Under anaerobic conditions, both the rate and the total amount of glucose consumption are many times greater than with oxygen present, **why???**

# Glycolysis occurs at elevated rates in tumor cells

- ***Warburg effect:*** tumor cells carry out glycolysis at a much higher rate than normal cells *even when oxygen is available (~10x)*
- In general, the more aggressive the tumor, the greater is its rate of glycolysis
- HIF-1 (hypoxia-inducible transcription factor) stimulates the production of at least 8 glycolytic enzymes and glucose transporters when the oxygen supply is limited
- HIF-1 also stimulates the production of VEGF (which stimulates angiogenesis)
- Overreliance of tumors on glycolysis suggests a possibility for anticancer therapy: deplete ATP from cancer cells by blocking glycolysis
- PET scans take advantage of the high uptake of glucose by tumor cells. Used to pinpoint cancers




**Box 14-1 figure 1**
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# Glucose uptake is deficient in type 1 Diabetes Mellitus

- Glucose uptake into cells is mediated by GLUT family
- GLUT1 & GLUT2 (hepatocytes) and GLUT3 (brain neurons) are always present in the plasma membrane of these cells
- GLUT4 (skeletal and cardiac muscles and adipose) only move to the plasma membrane in response to an insulin signal
- Patients with type 1 DM have too few β cells in the pancreas (cannot synthesize enough insulin) → heart, muscles and fat tissues cannot uptake glucose → hyperglycemia (after carb-rich meals)
- Fat cells turn to fat metabolism to provide alternative energy → formation of ketone bodies
- In untreated type 1 DM ketoacidosis is common and is life-threatening
- Reversed by insulin injection

# Feeder Pathways for Glycolysis

Many carbs are metabolized by glycolysis

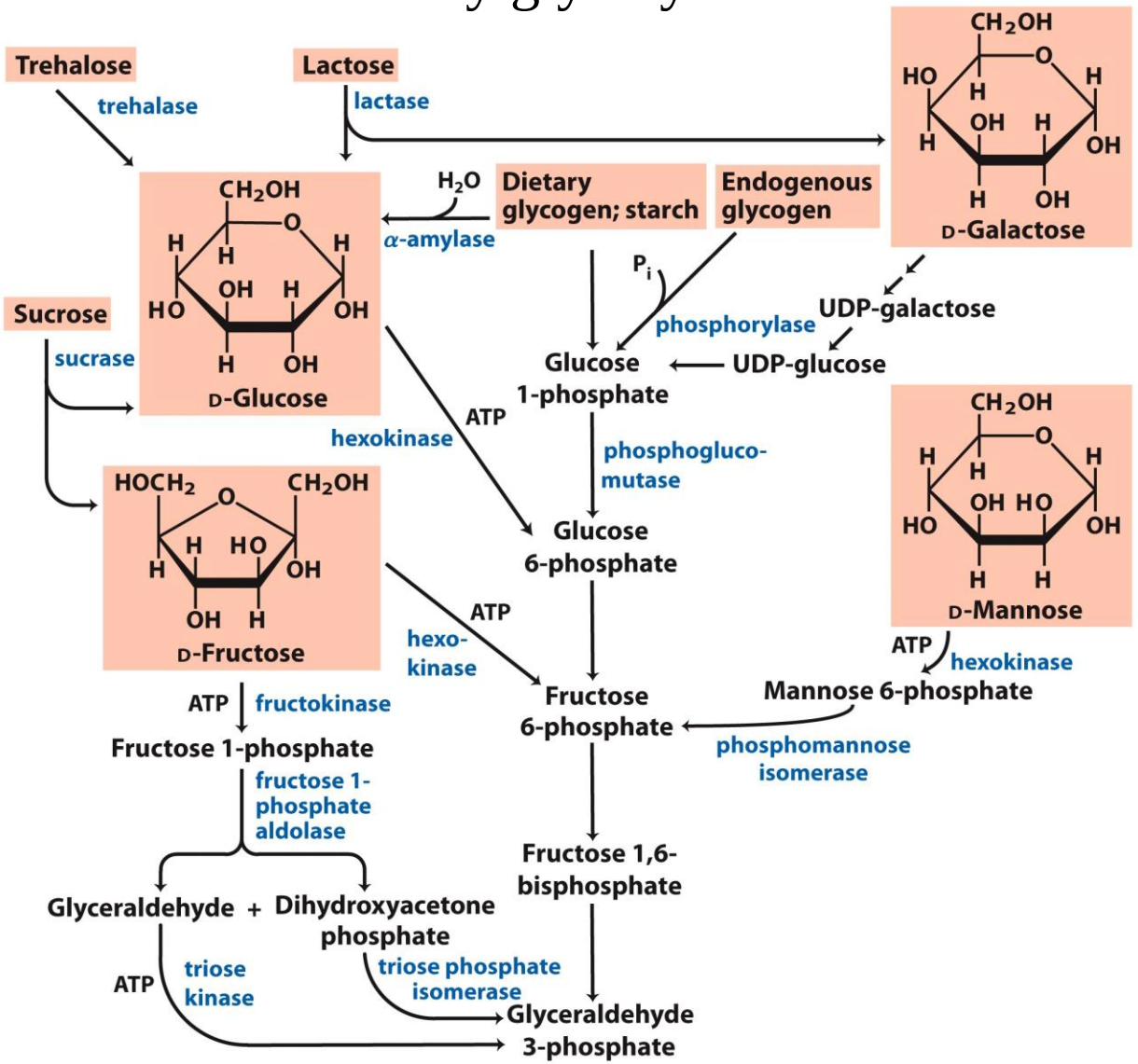


**Figure 14-11**
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# Feeder Pathways for Glycolysis

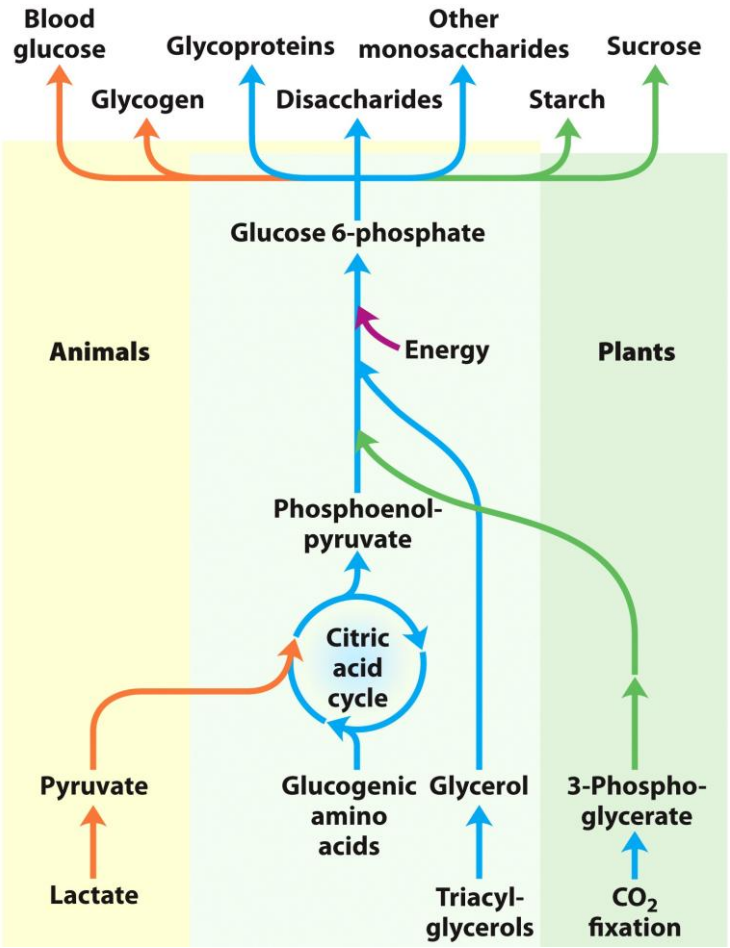
- Glucose molecules are cleaved from endogenous glycogen by glycogen phosphorylase (*phosphorolysis*)
  - Yielding glucose-1-phosphate
- Dietary starch and glycogen are cleaved by α-amylase to produce oligosaccharides and subsequently maltose and maltotriose in the small intestine, by pancreatic α-amylase (*hydrolysis*)
- Disaccharides are hydrolyzed
  - Lactose: glucose and galactose *(lactose intolerance?)*
  - Sucrose: glucose and fructose
  - Fructose, galactose, and mannose enter glycolysis at different points

# Gluconeogenesis: Precursor for Carbohydrates

- Brain and nerve cells, RBC, renal medulla, testes an embryonic tissue use only glucose as the energy source
  - 120 g of glucose daily (brain)

- Synthesizing glucose from noncarbohydrate precursors – ***gluconeogenesis***

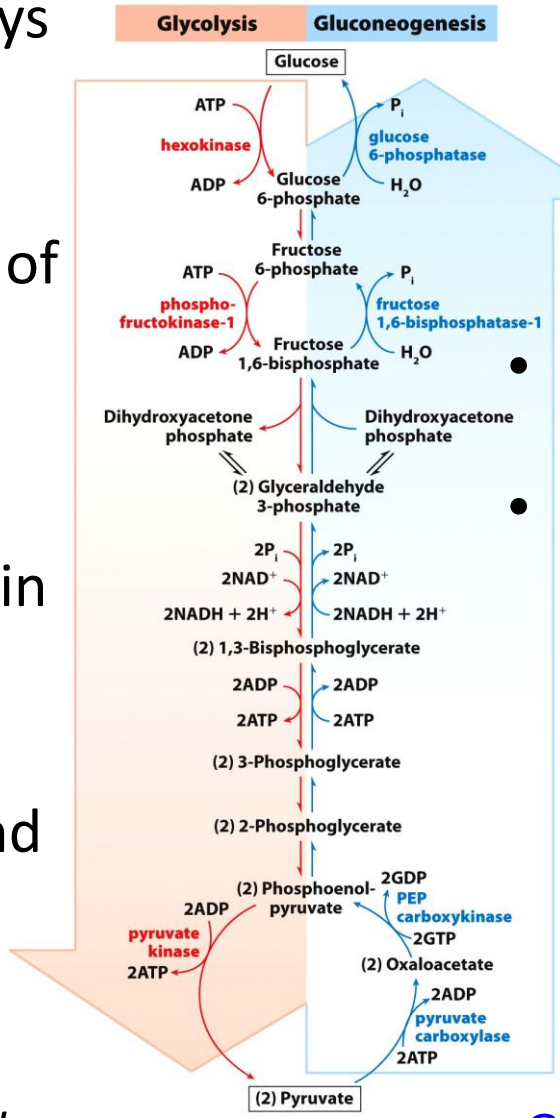
- In mammals, occurs in the liver (mainly) and in renal cortex




*Notice that mammals cannot convert fatty acids to sugars.*

# Glycolysis vs. Gluconeogenesis

- Not identical pathways running in opposite directions
- 7 of the 10 reactions of gluconeogenesis are the reverse of glycolysis
- Both are irreversible in cells
- Both occur in the cytosol (reciprocal and coordinated regulation)



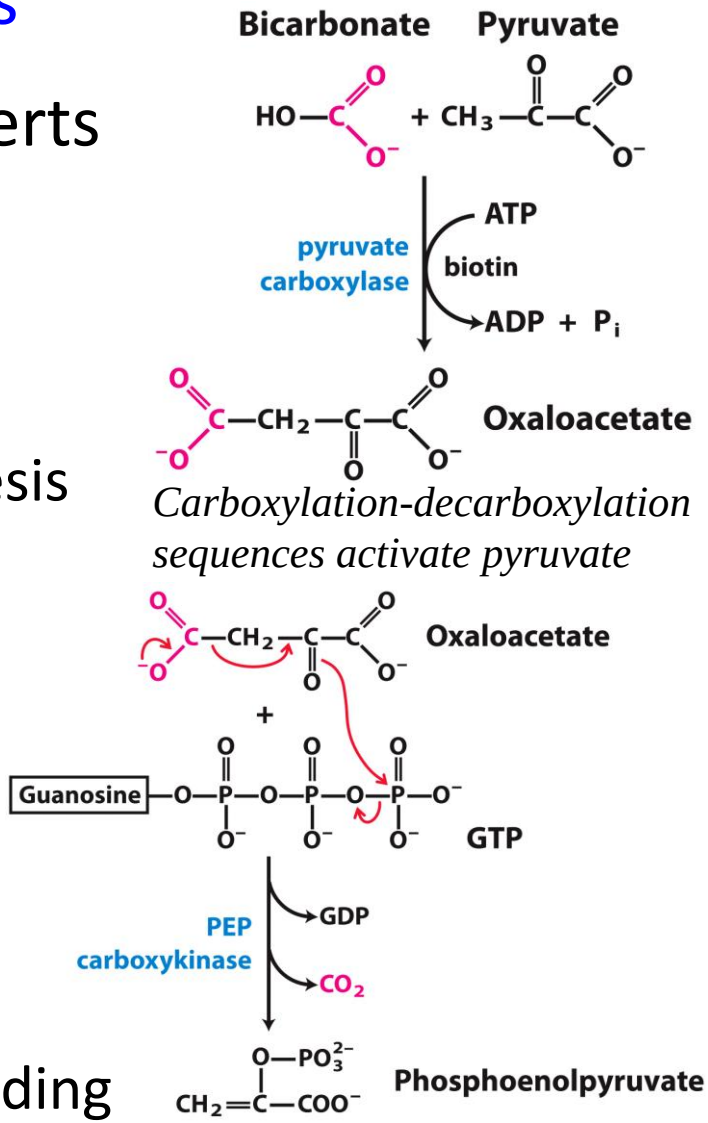

- Opposing pathways that are both thermodynamically favorable
  - Operate in opposite direction
    - end product of one is the starting cpd of the other
- Reversible reactions are used by both pathways
- Irreversible reaction of glycolysis must be bypassed in gluconeogenesis
  - Highly thermodynamically favorable, and regulated
  - Different enzymes in the different pathways
  - Differentially regulated to prevent a futile cycle

*Glycolysis occurs mainly in the muscle and brain.*

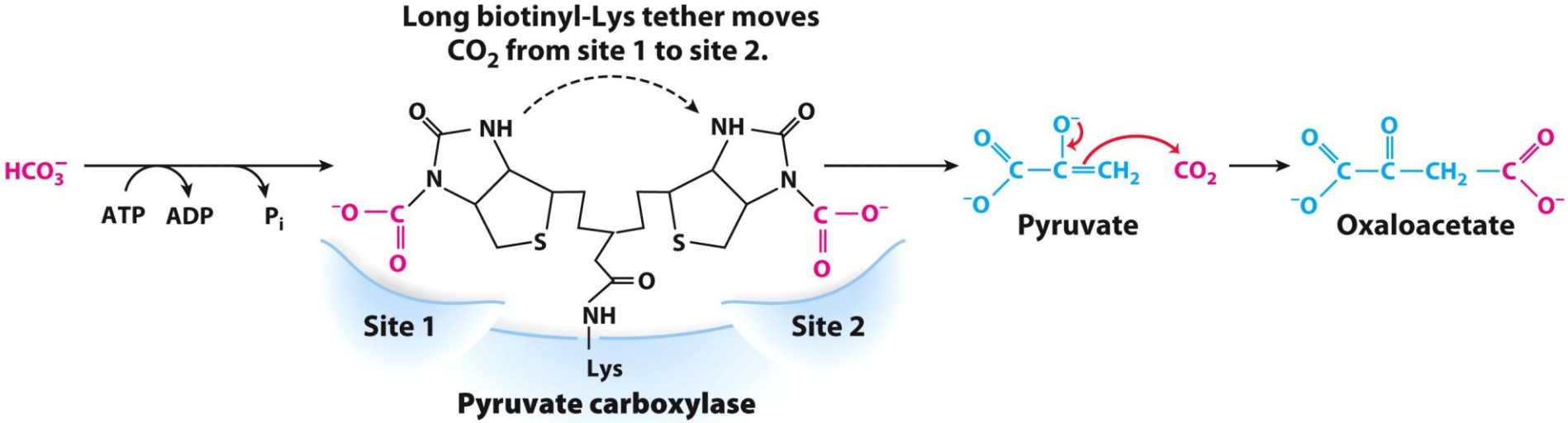
*Gluconeogenesis occurs mainly in the liver.*

# Pyruvate to Phosphoenolpyruvate

- Requires two energy-consuming steps
- First step, pyruvate carboxylase converts pyruvate to oxaloacetate
  - Carboxylation using a biotin cofactor
  - Requires transport into mitochondria
  - First regulatory enzyme in gluconeogenesis (acetyl CoA is +ve effector)
- Second step, phosphoenolpyruvate carboxykinase converts oxaloacetate to PEP
  - Phosphorylation from GTP and decarboxylation
  - Occurs in mitochondria or cytosol depending on the organism



# Biotin is a $CO_2$ Carrier




- Biotin is covalently attached to the enzyme through an amide linkage to the ε-amino group of a Lys residue
- The reaction occurs in two phases (at two different sites):
- At catalytic site 1, bicarbonate ion is converted to $CO_2$ at the expense of ATP. $CO_2$ reacts with biotin, forming carboxybiotinyl-enzyme
- The long arm carries the $CO_2$ of carboxybiotinylenzyme to catalytic site 2 on the enzyme surface, where $CO_2$ is released and reacts with the pyruvate, forming oxaloacetate
- The general role of flexible arms in carrying reaction intermediates between enzyme active sites

# Malate dehydrogenase

- No transporter of oxaloacetate in mitochondria
- OA must be reduced to malate by mitochondrial malate dehydrogenase using NADH

$$OA + NADH + H^+ \leftrightarrow \text{L-malate} + NAD^+$$

- Very low [OA] makes the $\Delta G \sim 0$ despite the high $\Delta G'^o$
- In cytosol, L-malate is reoxidized producing NADH

$$\text{L-malate} + NAD^+ \rightarrow OA + NADH + H^+$$

- $[NADH]/[NAD^+]_{mito} > [NADH]/[NAD^+]_{cyto}$ $10^5$x
  cytosolic NADH is consumed in gluconeogenesis, glucose production cannot continue unless NADH is available. Moving malate from mito to cytosol moves also NADH equivalents to allow the process to occur

# Overall bypass reaction

- OA + GTP ←→ PEP + $CO_2$ + GDP (PEP carboxykinase)
- Reversible under cellular conditions: formation of one high energy phosphate is balanced by the hydrolysis of another
- Pyruvate + ATP + GTP + $HCO_3^-$ ←→ PEP + $CO_2$ + ADP + GDP + $P_i$ $\Delta G'^o$ = 0.9 kJ/mol
- $\Delta G$ for the reaction ~ –25 kJ/mol because the actual cellular [PEP] is very low ➔ the reaction is irreversible in vivo

# Additional bypasses

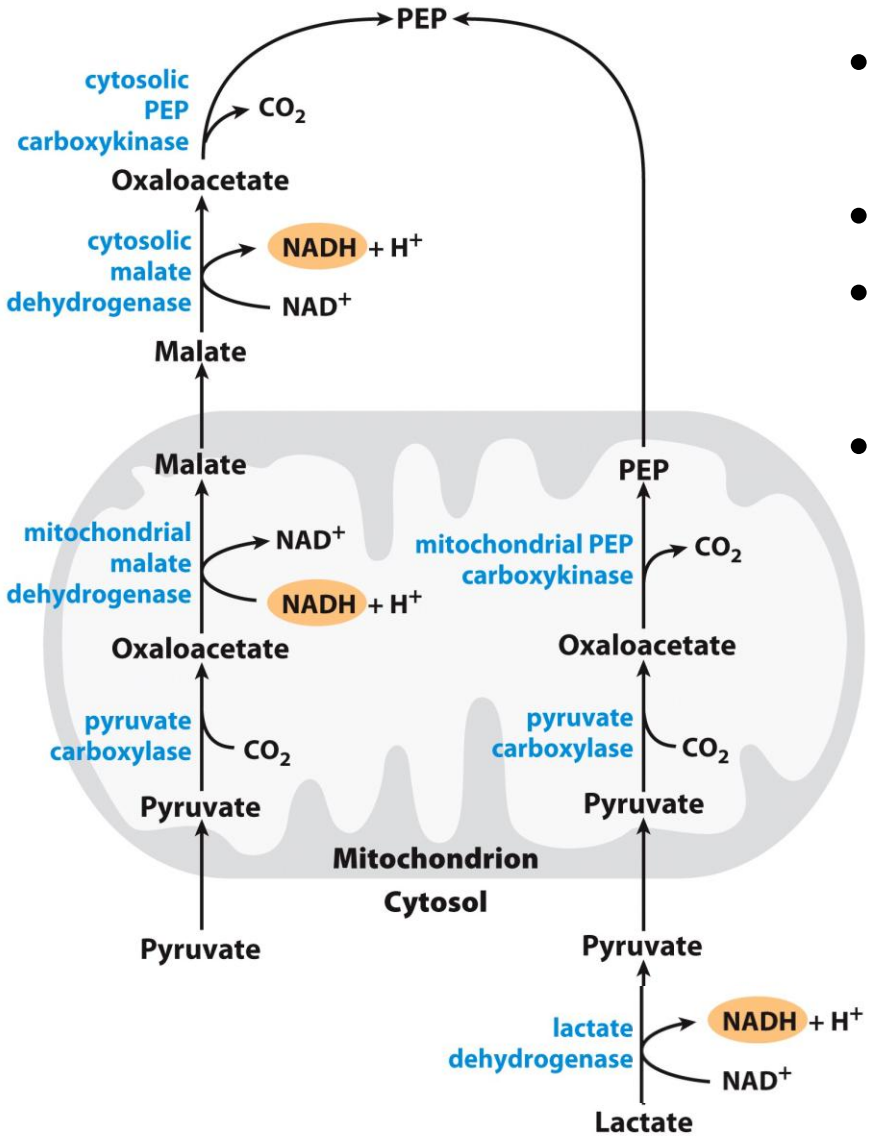



**Figure 14-20**
*Lehninger Principles of Biochemistry*, Sixth Edition


- RBC and anaerobic muscle cells, lactate predominates
- Converted to pyruvate by LDH
- Produces NADH in the cytosol, no need for malate conversion
- OA is decarboxylated by mito PEP carboxykinase and PEP is exported from mito

# Additional Bypasses

- Catalyze reverse reaction of opposing step in glycolysis
- Are irreversible themselves

- Fructose 1,6-bisphosphate → Fructose 6-Phosphate
  - By fructose bisphosphatase-1 (FBPase-1)
  - Coordinately/oppositely regulated with PFK
  - A hydrolysis reaction with $\Delta G'^{o} = -16.3$ kJ/mol

- Glucose 6-phosphate → Glucose
  - By glucose 6-phosphatase
  - A hydrolysis reaction with $\Delta G'^{o} = -13.8$ kJ/mol
  - Enzyme found in hepatocytes, renal medulla and intestinal epithelial cells, NOT anywhere else (*if it were found everywhere, … what do you expect would happen?*)

# Gluconeogenesis is expensive

2 Pyruvate + 4 ATP + 2 GTP + 2 NADH + 2 $H^+$ + 4 $H_2O$ →
Glucose + 4 ADP + 2 GDP + 6 $P_i$ + 2 $NAD^+$

- Costs 4 ATP, 2 GTP, and 2 NADH
- Not the reversal of the conversion of pyr to glc
- But physiologically necessary to ensure irreversibility
- Also, there's a need to keep pyruvate inside the cell instead of secreting it outside. Pyruvate has the potential to make more than 10 ATP per full oxidation of pyruvate

- Brain, nervous system, and red blood cells generate ATP ONLY from glucose

# Precursors for Gluconeogenesis

- Glucose can be produced from all intermediates of the CAC (citrate, isocitrate, $\alpha$-KG, succinyl-CoA , succinate, fumarate and malate) since all of them can undergo oxidation to OA

- Also, most a.a. can undergo transformations to pyruvate or CAC intermediate, and therefore has the potential to make glucose: i.e. ***glucogenic***
  - Only Leu and Lys are non-glucogenic
  - Ala and Gln are particularly important glucogenic a.a. in mammals

# Precursors for Gluconeogenesis

- Animals can produce glucose from sugars or proteins and parts of fat (triacylglycerol)
  - Sugars: pyruvate, lactate, or oxaloacetate
  - Protein: from glucogenic a.a.
  - Glycerol: the breakdown product of fats can be used after a two step reaction. *Glycerol kinase* phosphorylates it and the oxidation of the central C yields dihydroxyacetone phosphate (an intermediate in gluconeogenesis)

- Animals cannot produce glucose from fatty acids
  - Product of fatty acid degradation is acetyl-CoA
  - Cannot have a net conversion of acetyl-CoA to oxaloacetate (2 C that enter the CAC are removed as $2CO_2$)
    - Plants, yeast, and many bacteria can do this (the glyoxylate cycle), thus producing glucose from fatty acids

# Pentose Phosphate Pathway

- Glc 6-P has another catabolic fate which leads to specialized products needed by cells
- The main products are NADPH and ribose 5-phosphate
- NADPH is an electron donor
  - Reductive biosynthesis of fatty acids and steroids (liver, adipose, gonads, etc.)
  - Repair of oxidative damage esp. in cells directly exposed to $O_2$ (RBC, cornea)

- Ribose-5-phosphate is a biosynthetic precursor of nucleotides
  - Used in DNA and RNA synthesis esp. in rapidly dividing cells (skin, bone marrow, tumors, etc.)
  - Or synthesis of some coenzymes (ATP, NADH, $FADH_2$)

# Pentose Phosphate Pathway

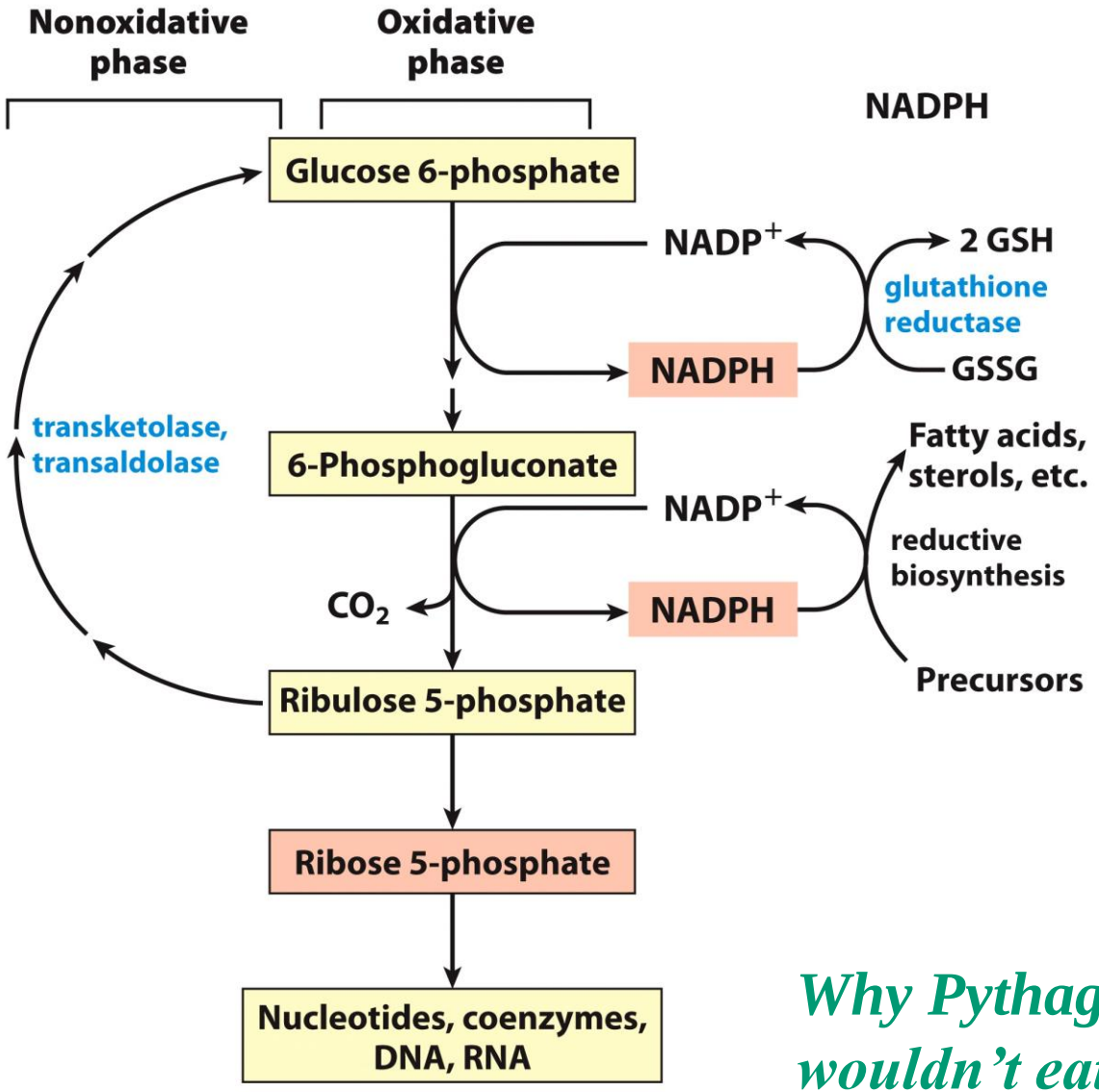



**Figure 14-21**
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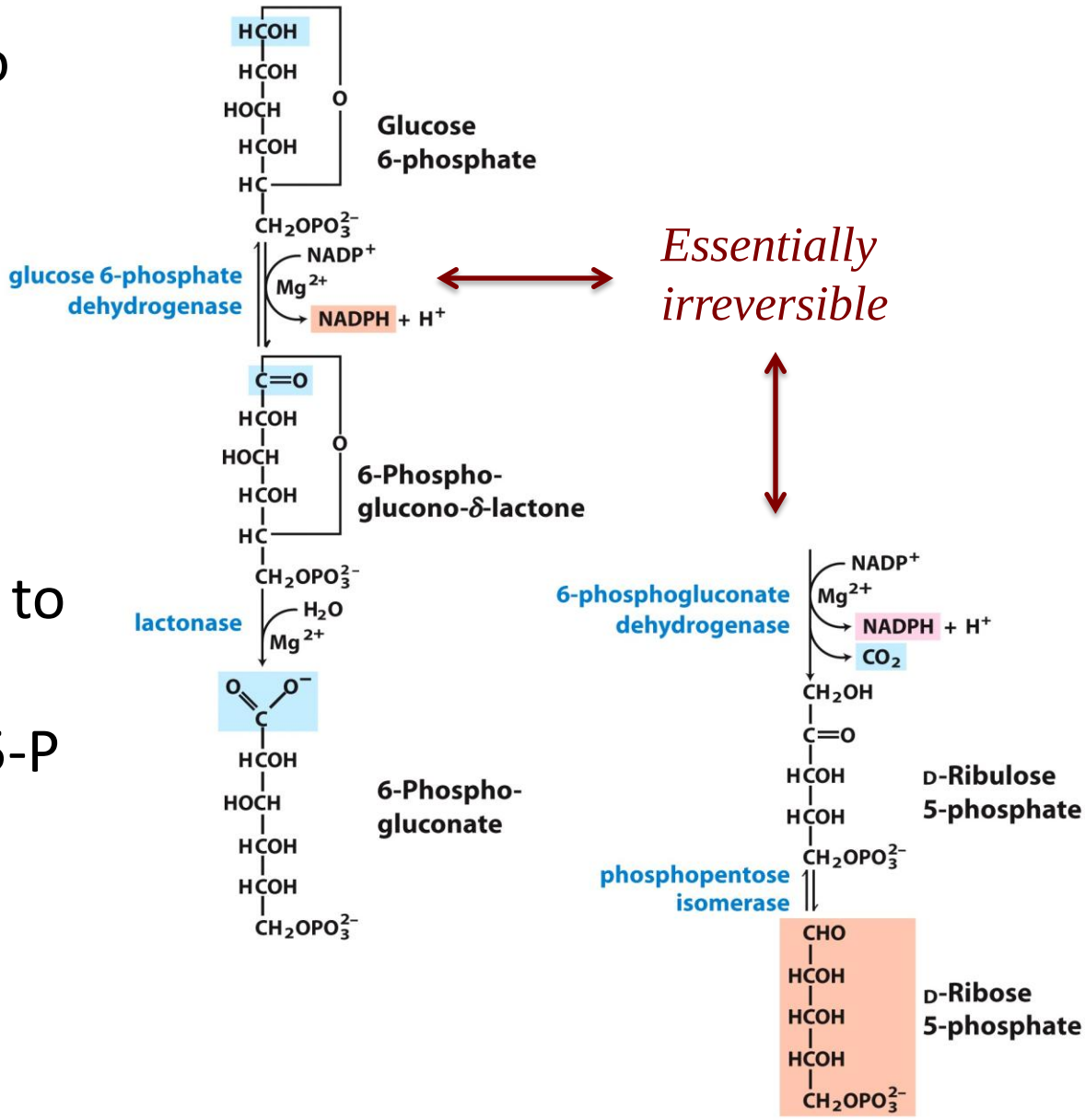
***Why Pythagoras wouldn't eat falafel???***
***Box 14-4: self check***

# Oxidative phase generates NADPH and R-5-P

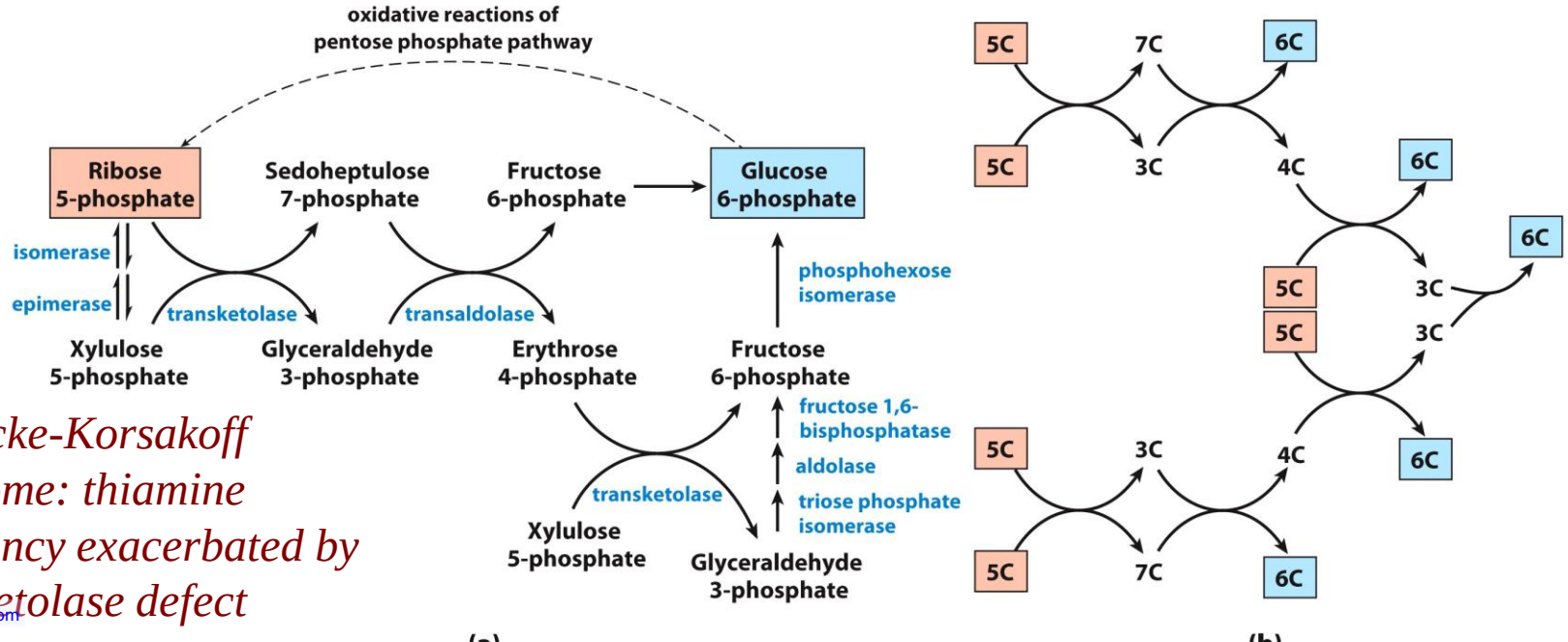
1. Oxidation of G-6-P to δ-lactone by ***G6PD***, reduction of $NADP^+$
2. Lactone hydrolysis by ***lactonase***
3. Oxidation and decarboxylation by ***6-PG dehydrogenase*** to produce ribulose 5-P
4. Formation of ribose 5-P by ***phosphopentose isomerase***

- Pentose pathway ends here in some tissues



# Non-oxidative phase regenerates G-6-P from R-5-P

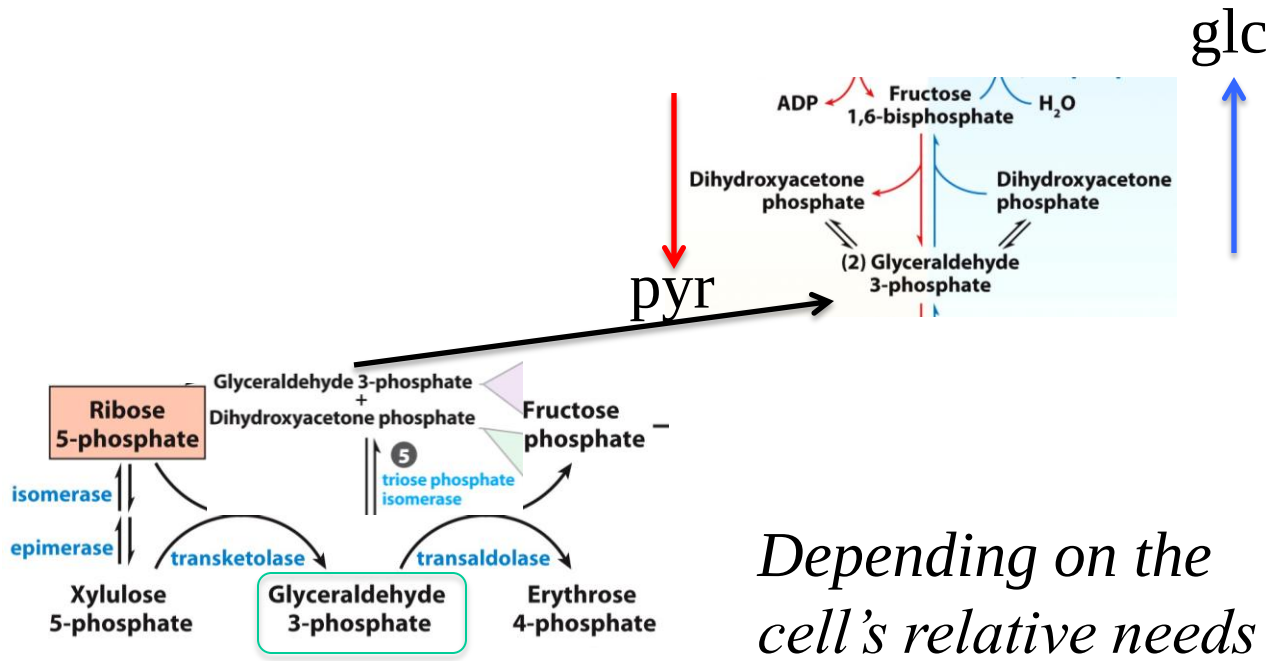
- Used in tissues requiring more NADPH than R-5-P (e.g. liver and adipose)
- Six 5-C sugar phosphates are converted into five 6-C ones, allowing continued G6P oxidation and NADPH production
- Details are not important, but remember the two key enzymes unique in this pathway: **transketolase** and **transaldolase**




*Wernicke-Korsakoff syndrome: thiamine deficiency exacerbated by transketolase defect*

# Glycolysis, gluconeogenesis and pentose phosphate pathway

- All enzymes of PP are in the cytosol
- Glycolysis, gluconeogenesis and PP are connected through several shared intermediates and enzymes:




*Depending on the cell's relative needs for NADPH, ATP and pentose phosphates*

# NADPH regulates partitioning into glycolysis vs. pentose phosphate pathway

*G6P can enter glycolysis or PP depending on the current needs to the cell and the concentration of $NADP^+$ and NADPH*

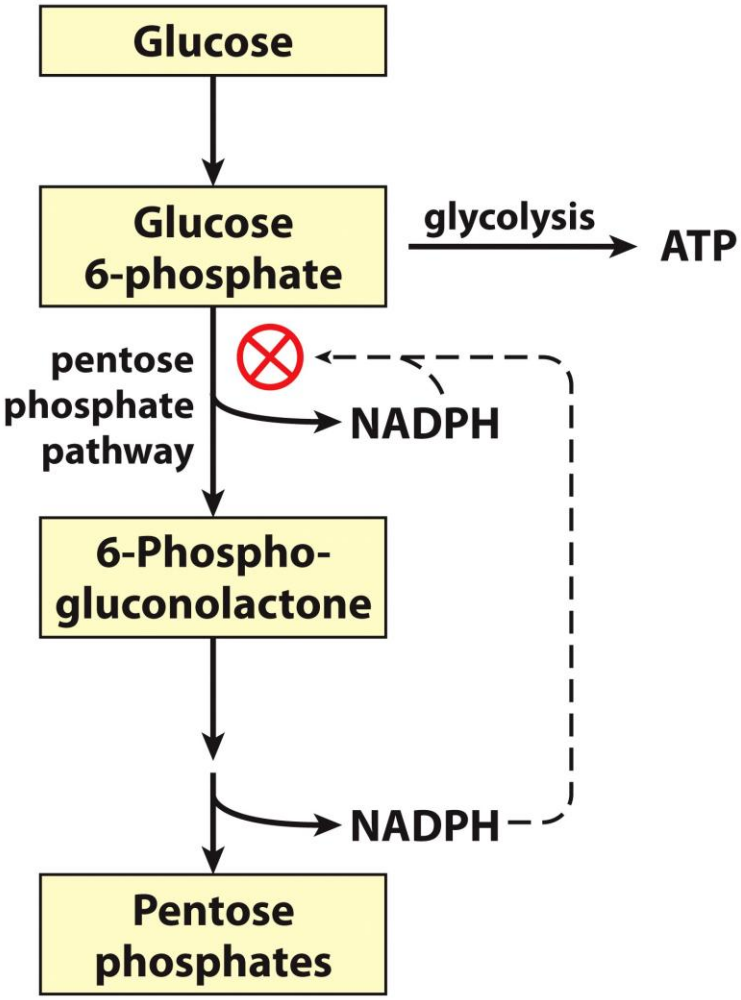



**Figure 14-28**
*Lehninger Principles of Biochemistry*, Sixth Edition

# Diabetes

- Chronic disease
- Characterized by excessive urine excretion, **polyuria**
- Greek word for “passing through” i.e. urine

- Two main forms:

***Diabetes Insipidus***

***Diabetes Mellitus***

# Diabetes Insipidus

- Insipidus means “tasteless”. Diabetes insipidus = tasteless urine
- Due to a deficiency of antidiuretic hormone (ADH, aka arginine vasopressin, AVP)
- AVP increases water resorption in kidneys
- Deficiency of AVP can be
  - **Neurogenic:** decrease in AVP release (e.g. due to alcohol intoxication or tumor)
  - **Nephrogenic:** decreased renal sensitivity to AVP (e.g. by mutations of receptors or aquaporins)
- Either neurogenic or nephrogenic → little water retention → excessive output of dilute urine → **diabetes insipidus**, **hypernatremia** (elevated $[Na^+]_{blood}$), **polyuria** (excess urine production), and **polydipsia** (thirst)
- *Has nothing to do with carbohydrate metabolism*

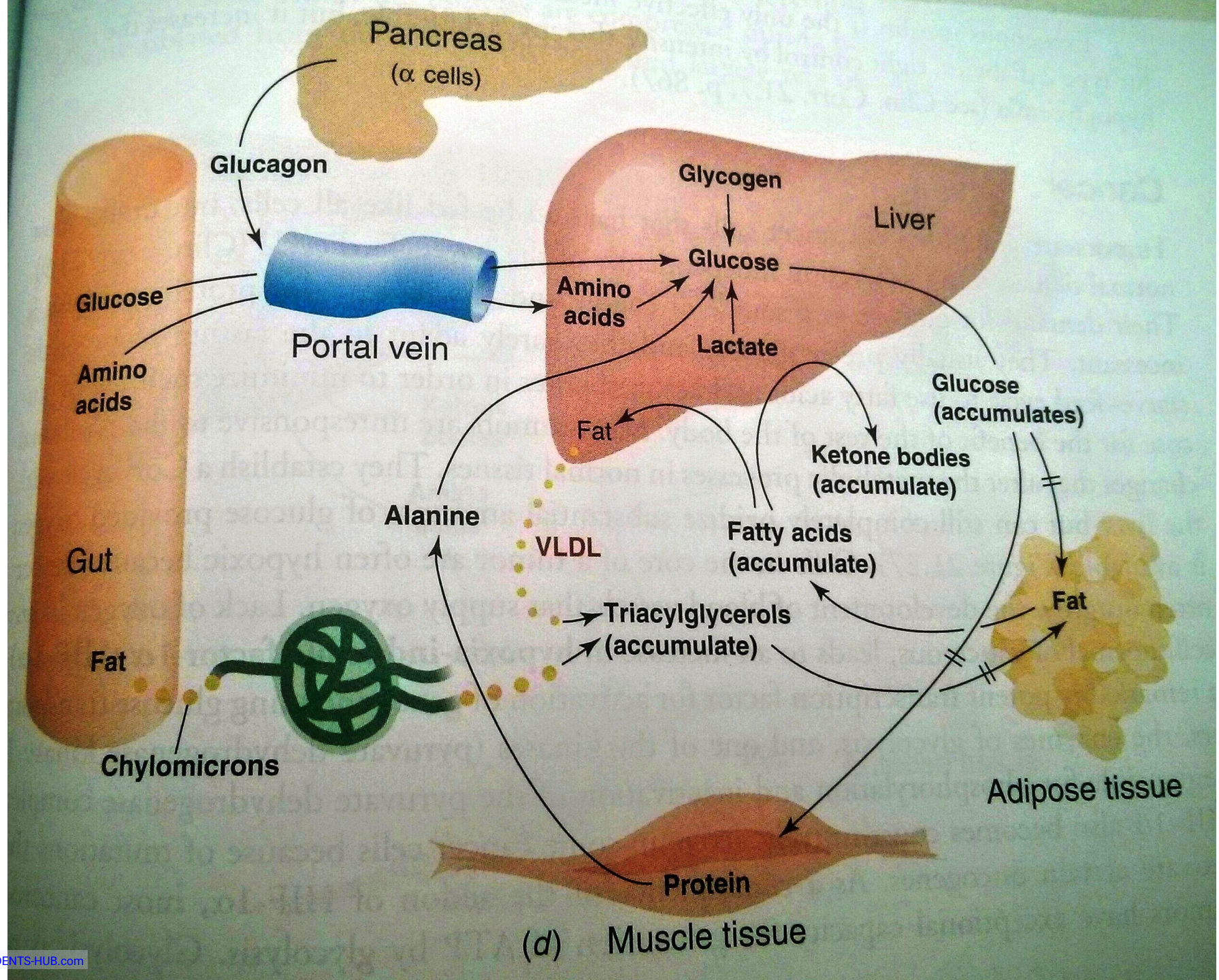
# Diabetes Mellitus

- Mellitus means “honey”. Diabetes mellitus = honey urine
- Due to defects in CHO, fats, and/or protein metabolism
- Elevated glucose in the plasma and urine
- Excessive urine excretion is due to ***osmotic diuresis*** (high blood sugar leaking into the urine and taking excess water along with it)
- Two major types:

***TYPE 1 and TYPE 2***

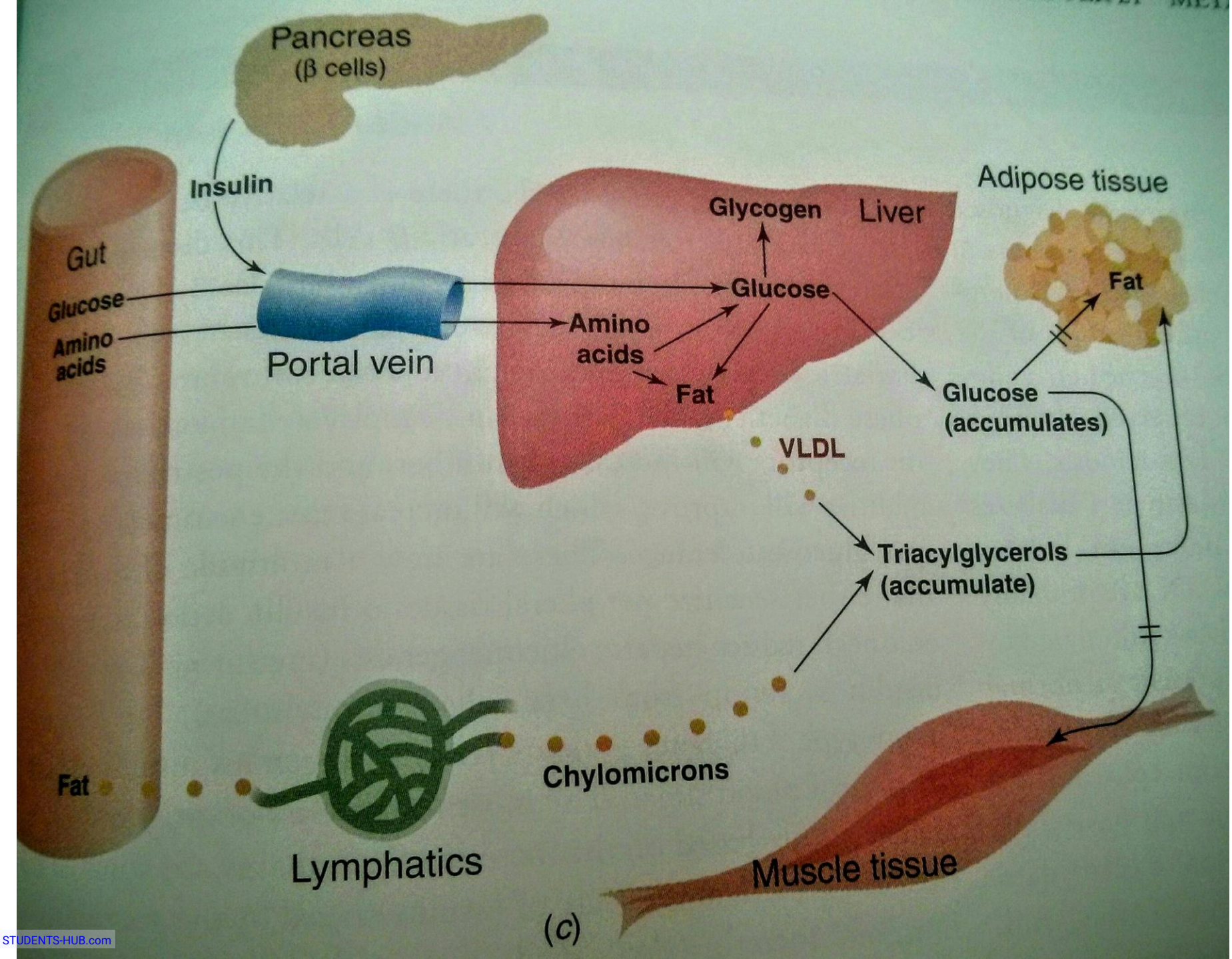
# Type 1 Diabetes Mellitus

- Usually appears in childhood
- Complete absence of insulin production from pancreas due to defective beta cell function (autoimmune)
- Inability of tissues to uptake glucose and continuous gluconeogenesis in liver ➔ **high $[glc]_{blood}$**
- Increased lipolysis in adipose and increased beta oxidation in liver ➔ **ketoacidosis**
- Absence of insulin (TF) will induce lower lipoprotein lipase activity ➔ **hyperchylomicronemia**
- **Body is always in a starved state**
- Exogenous insulin is the only effective medication which doesn't cure it but alleviates clinical symptoms. Must keep changing the dose to match nutritional states



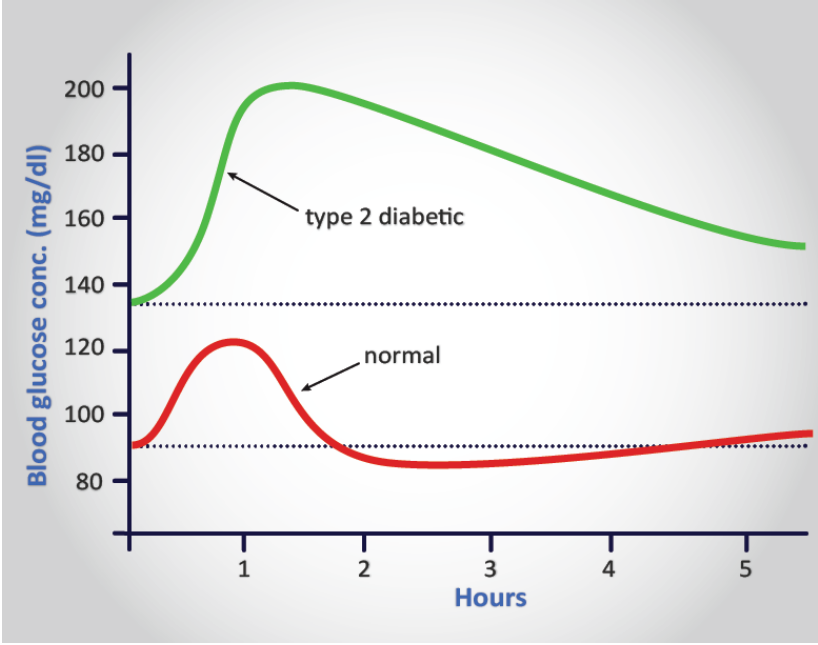
# Type 2 Diabetes Mellitus

- β cell failure and insulin resistance in obese diabetic patients
- Insufficient production of insulin to promote glucose uptake into tissues or to block gluconeogenesis in liver ➔ **hyperglycemia**
- **Ketoacidosis** ***rarely*** develops of (enough insulin is present to prevent uncontrolled release of fatty acids from adipocytes)
- **Hypertriacylglycerolemia** occurs (increase in VLDL without hyperchylomicronemia because fatty acids are combined in the liver to form TAGs and VLDL)
- Note that concurrent lipogenesis and gluconeogenesis should never occur, yet they occur in type 2 DM because of the ***state of mixed insulin resistance*** and its effects on different pathways (more on that in later chapters)
- To treat: (1) diet and exercise (2) **metformin** (inhibitor of gluconeogenesis) and (3) **insulin injections** (most effective despite insulin resistance)



# Type 2 Diabetes Mellitus diagnosis

- OGTT for diagnosis (measuring $[glc]_{blood}$ every 30-60 min for 2-4 h after ingesting 100 g carbohydrate)
- Normal individuals → $[glc]_{blood}$ returns to normal in 2 h
- Diabetics → $[glc]_{blood}$ starts high and remains high for longer periods
- An abnormal OGTT does not mean diabetes in all cases
- Common cold can contribute to abnormal reading
- Fasting blood sugar of more than 126 mg/dL is a better indication of the occurrence of diabetes



# Question 1
# Due: NEXT WEEK (jstiban@birzeit.edu)

- **Please solve questions:**

1. **14 (Arsenate poisoning)**
2. **16 (Niacin)**
3. **18 (Clinical symptoms of enzyme deficiency)**
4. **25 (Ethanol affects blood glucose)**
5. **28 (Phloridzin)**

*For written answers, I prefer to have them typed in Word. I can accept the assignment in one file sent to my email. For answers that require solving mathematically, you can either type them or write them down and scan them.*