Biochemistry

Metabolism

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Pentose phosphate path (PPP)

Gerhild van Echten-Deckert

Tel. 73 2703
E-mail: g.echten.deckert@uni-bonn.de
www.limes-institut-bonn.de

Utilization of glycogen

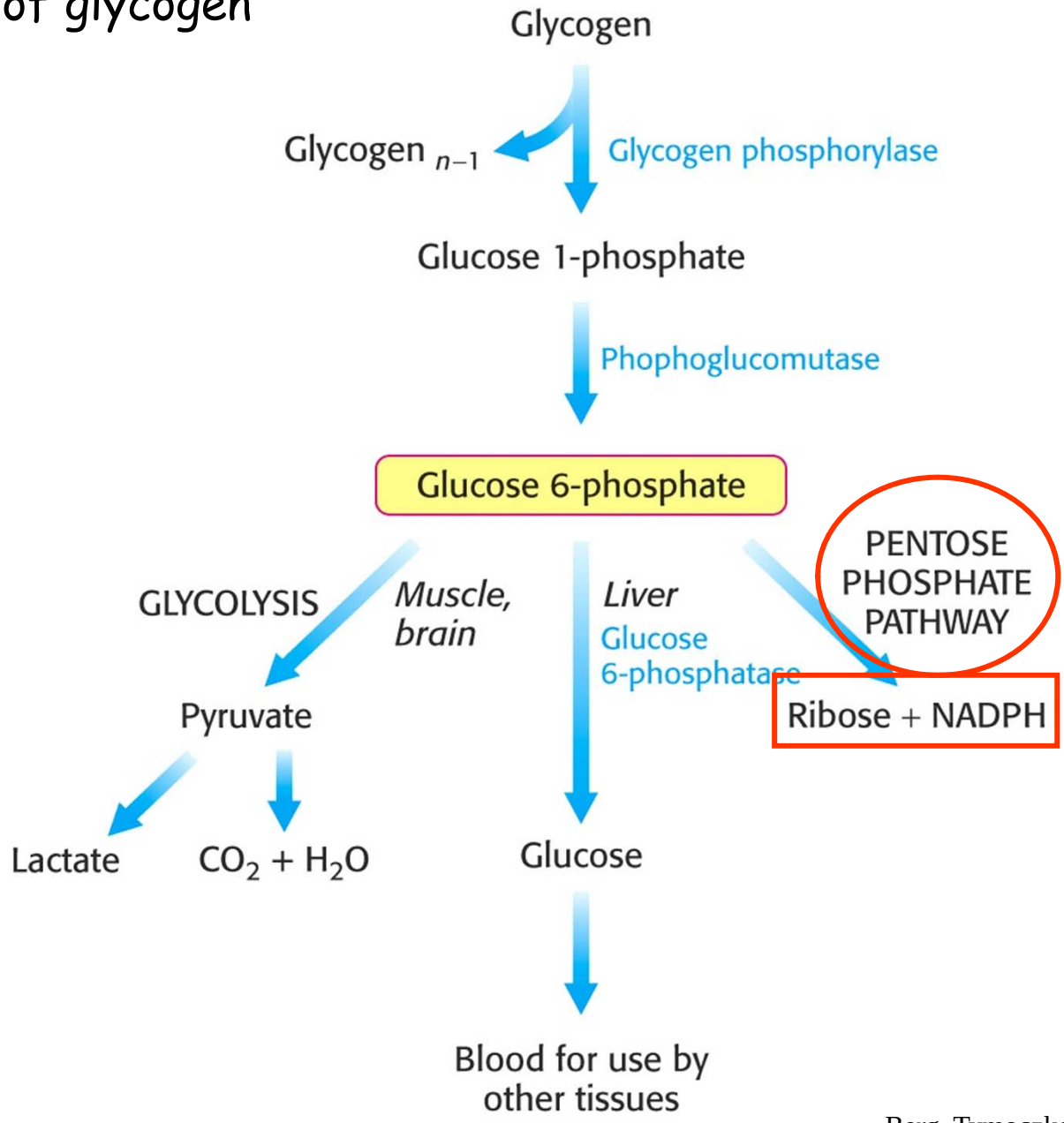

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TABLE 20.2 Pathways requiring NADPH

Synthesis

Fatty acid biosynthesis

Cholesterol biosynthesis

Neurotransmitter biosynthesis

Nucleotide biosynthesis

Detoxification

Reduction of oxidized glutathione

Cytochrome P450 monooxygenases

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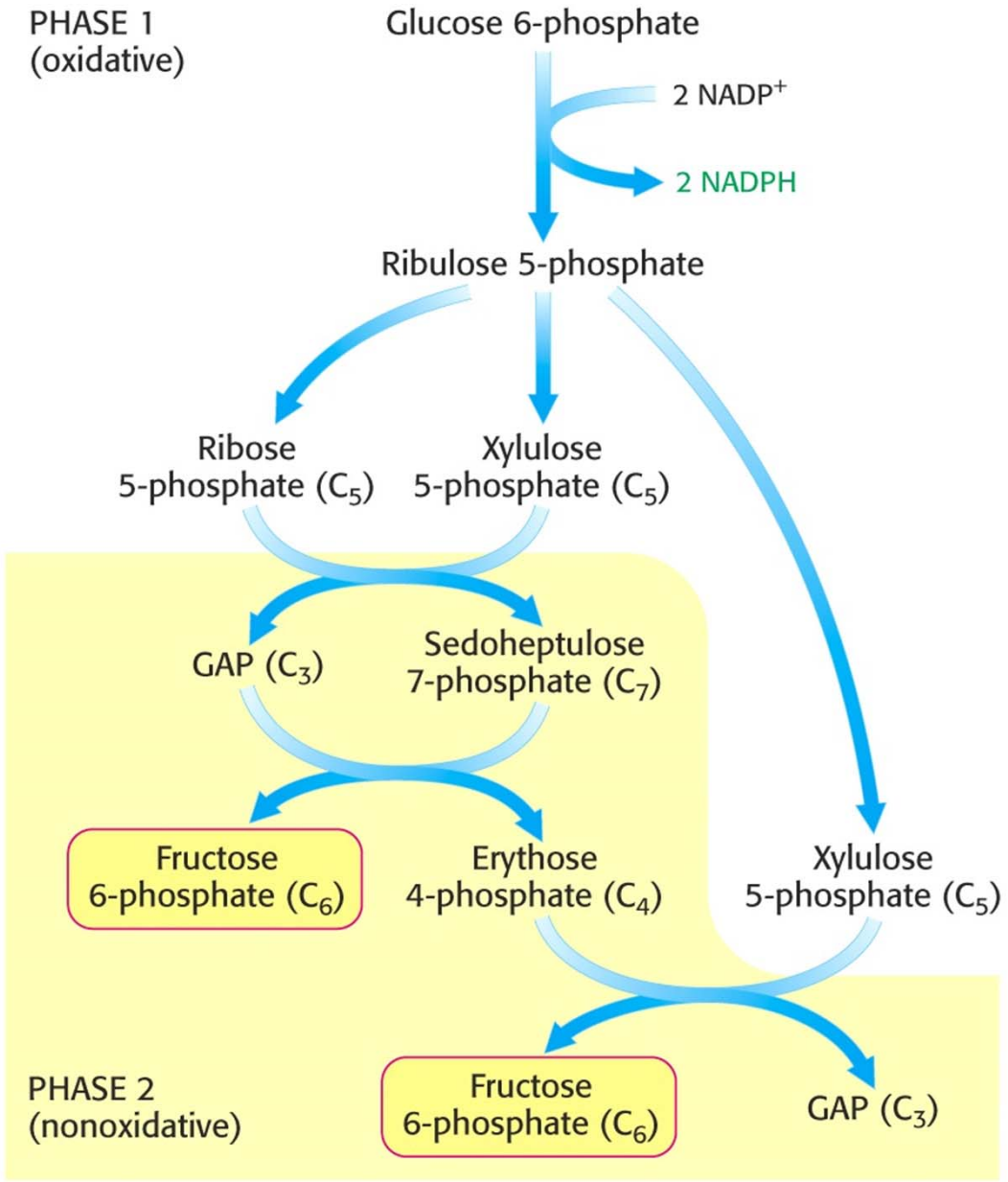
TABLE 20.4 Tissues with active pentose phosphate pathways

Tissue	Function
Adrenal gland	Steroid synthesis
Liver	Fatty acid and cholesterol synthesis
Testes	Steroid synthesis
Adipose tissue	Fatty acid synthesis
Ovary	Steroid synthesis
Mammary gland	Fatty acid synthesis
Red blood cells	Maintenance of reduced glutathione

The pentose phosphate pathway
(localized to the cytosol)

- Conversion of G6P into pentose phosphate
- Generation of NADPH

Phase 2
(redistribution and transfer)



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Regulation of glucokinase (hexokinase IV) by sequestration in the nucleus

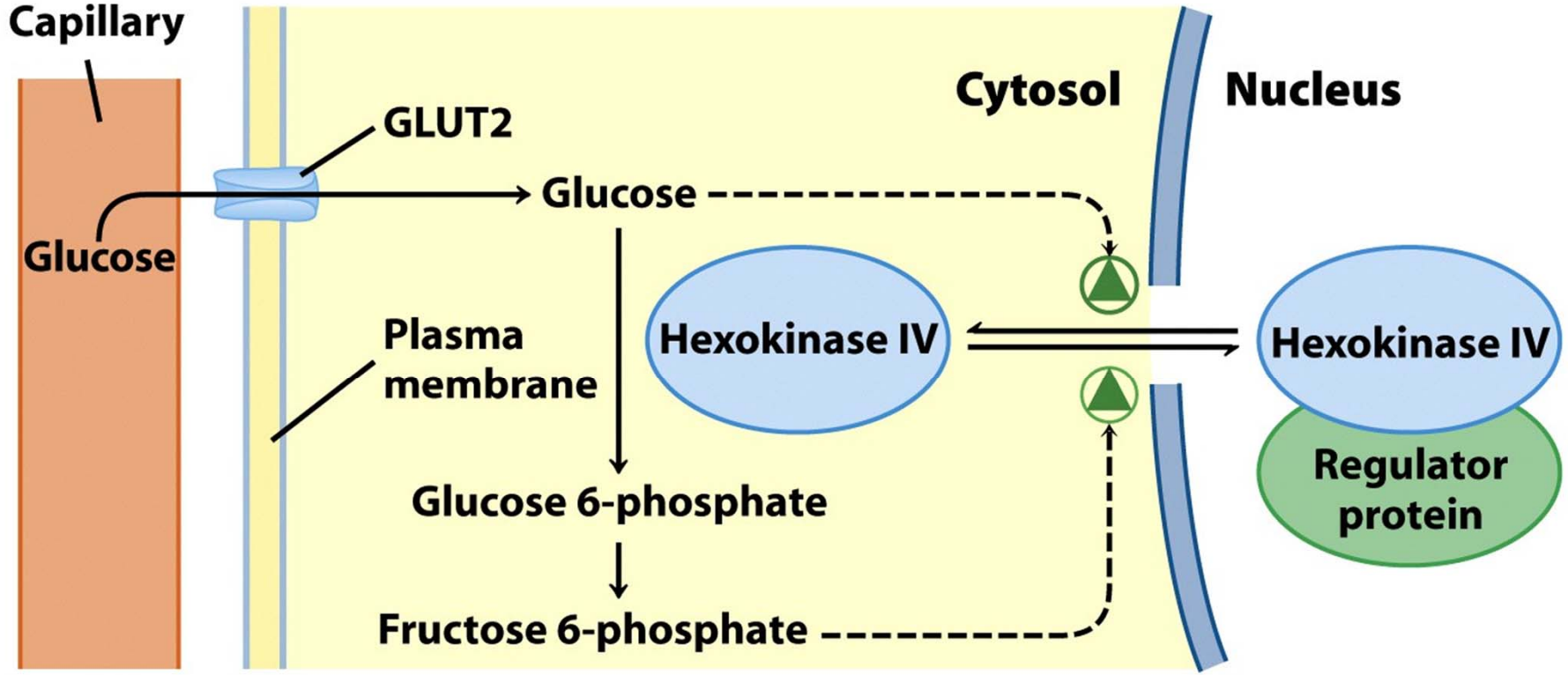

Figure 15-13
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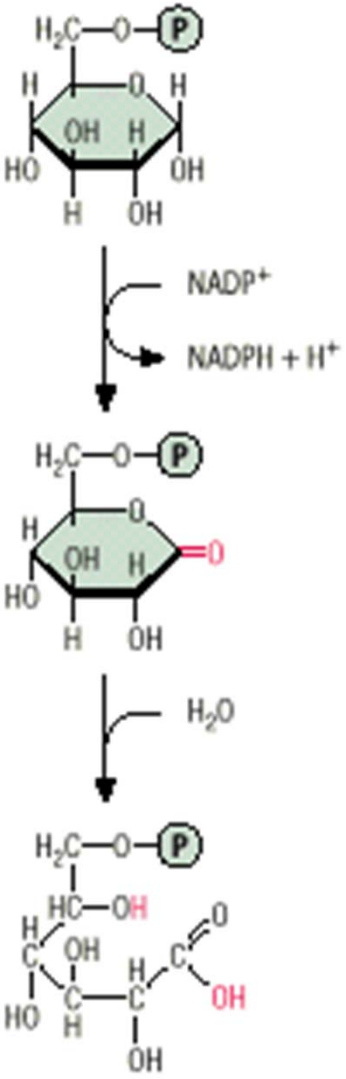
Remember glucokinase (hexokinase IV) is not inhibited by G6P whereas its accumulation completely inhibits all other hexokinases (I-III). In the liver where 30 % of Glc is metabolized via PPP, F6P competes with Glc which after a carbohydrate-rich meal enters hepatocytes via GLUT2 and activates the enzyme.

The pentose phosphate pathway

1. Phase: oxidative decarboxylation of G6P yielding ribulose5P



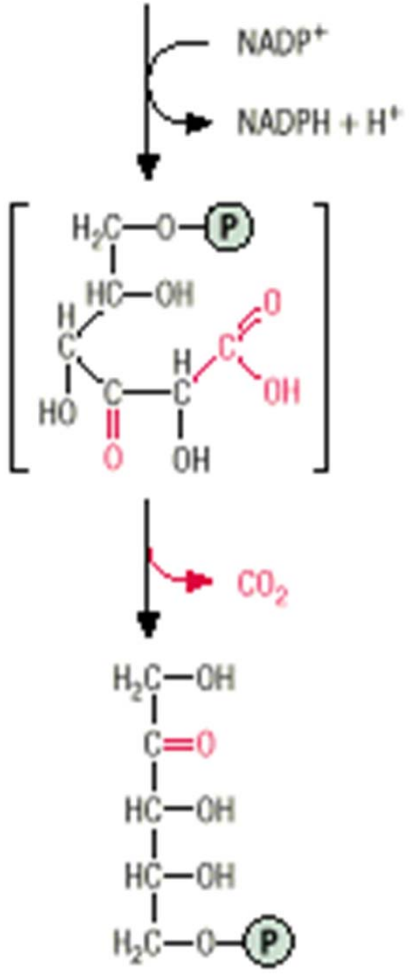
Glucose-6-phosphate

G6P-DH (rate limiting, controlled by [NADP+])

6-phosphoglucono-lactone

6-phosphogluconolactonase

6-phosphogluconate



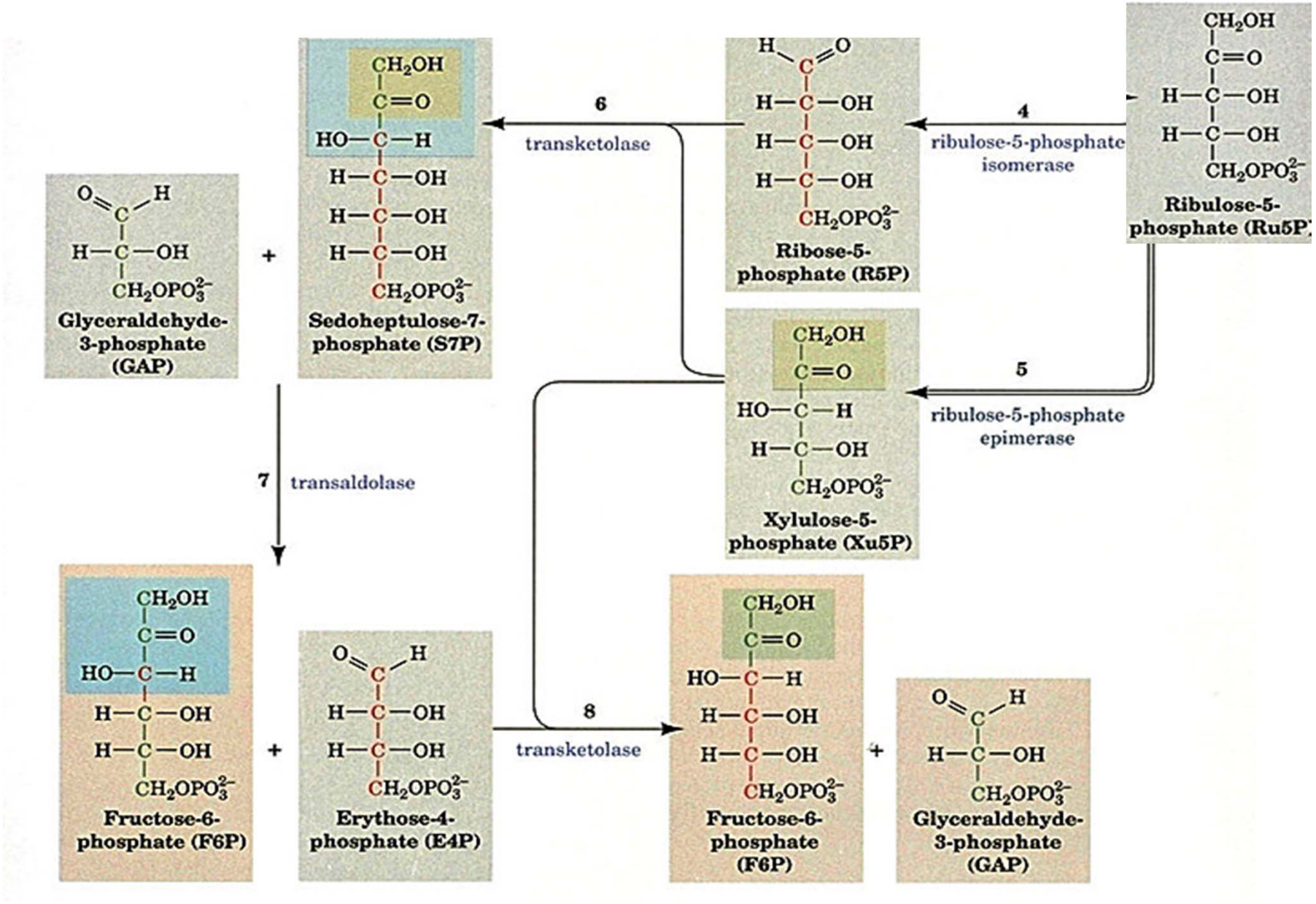
6-phosphogluconate-DH

β-keto acid intermediate

Ribulose 5-phosphate

Biochemie u. Pathobiochemie.
Löffler & Petrides

2. **Phase:** redistribution and transfer



Biochemistry. Voet & Voet

Mechanism of transketolase

(Role of TPP in cleaving the C2-C3 bond of the ketose and addition of the C2-unit to the aldose)

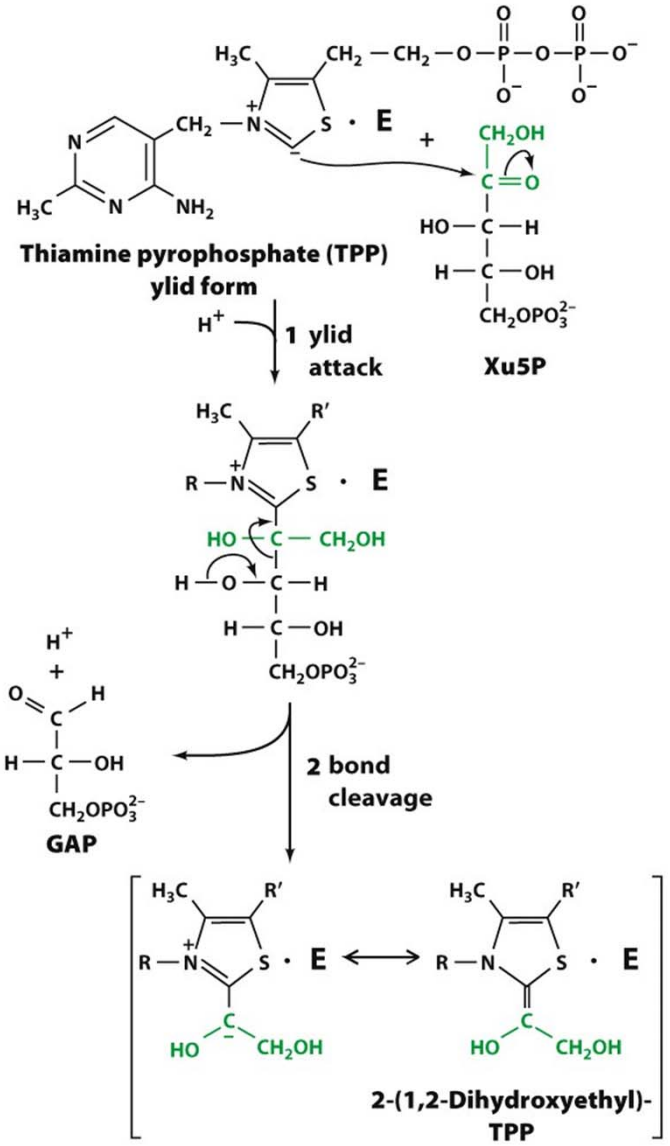


Figure 23-30 part 1

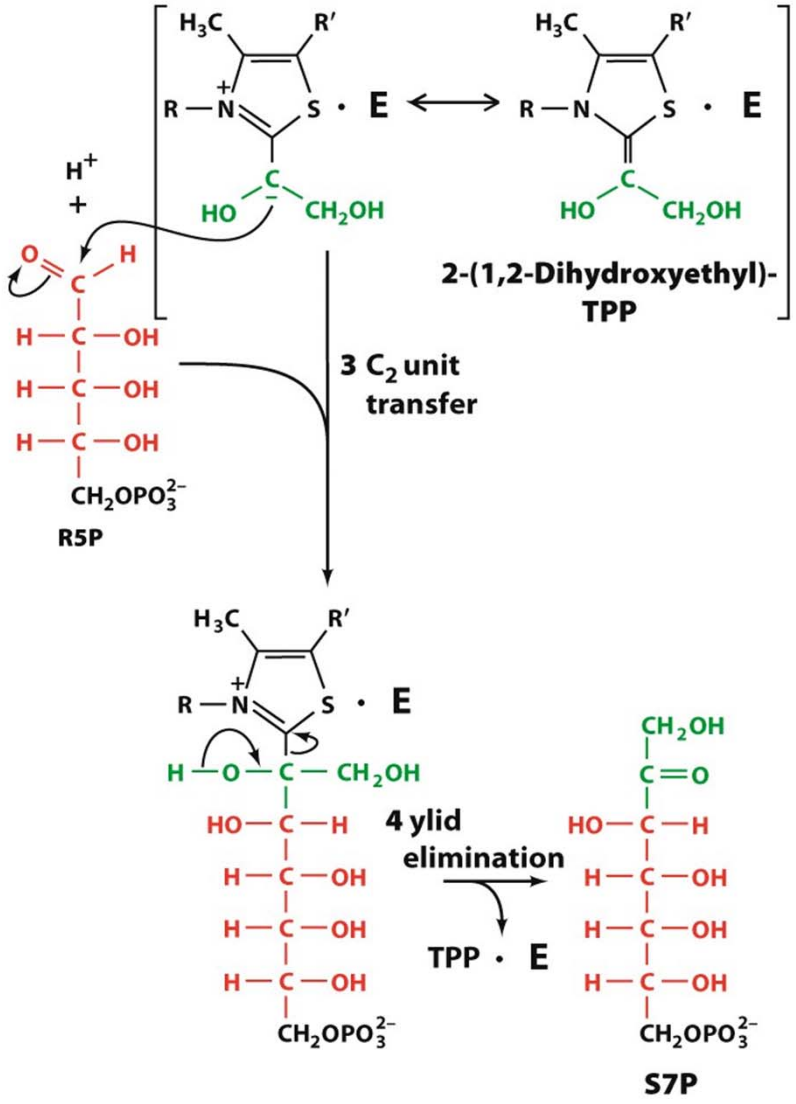


Figure 23-30 part 2

Biochemistry. Voet & Voet

Mechanism of transaldolase

The essential role of a Lys-residue, that forms a protonated Schiff base with S7P to facilitate an aldol cleavage between C3 and C4 that eliminates E4P. The C3 unit is added to GAP forming F6P.

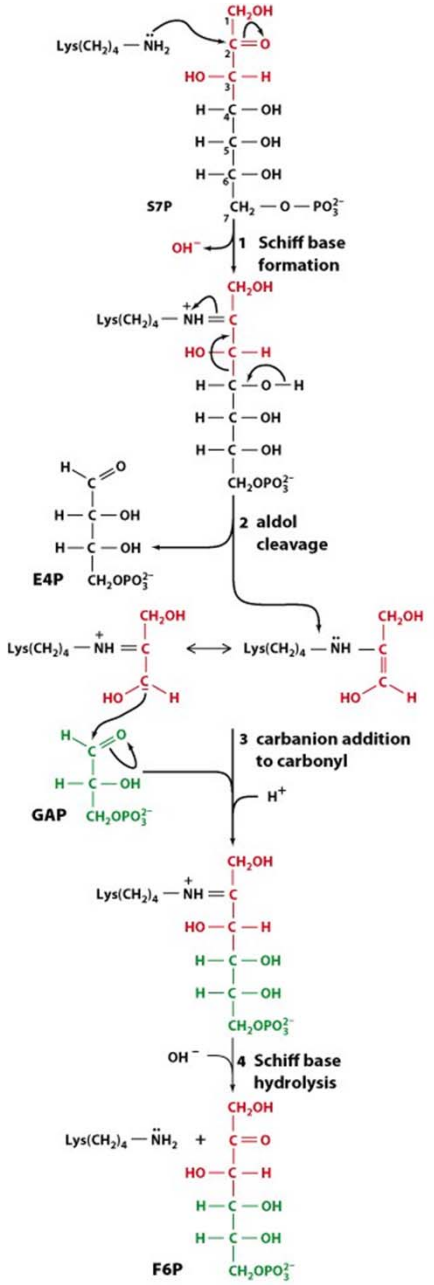


Figure 23-31

Biochemistry. Voet & Voet

Oxidative phase:

$3G6P+6NADP^{+}+3H_2O\rightarrow$
$6NADPH+6H^{+}+3CO_2+3Ru5P$

Rearrangement phase:

$3Ru5P \leftrightarrow R5P+2Xu5P$

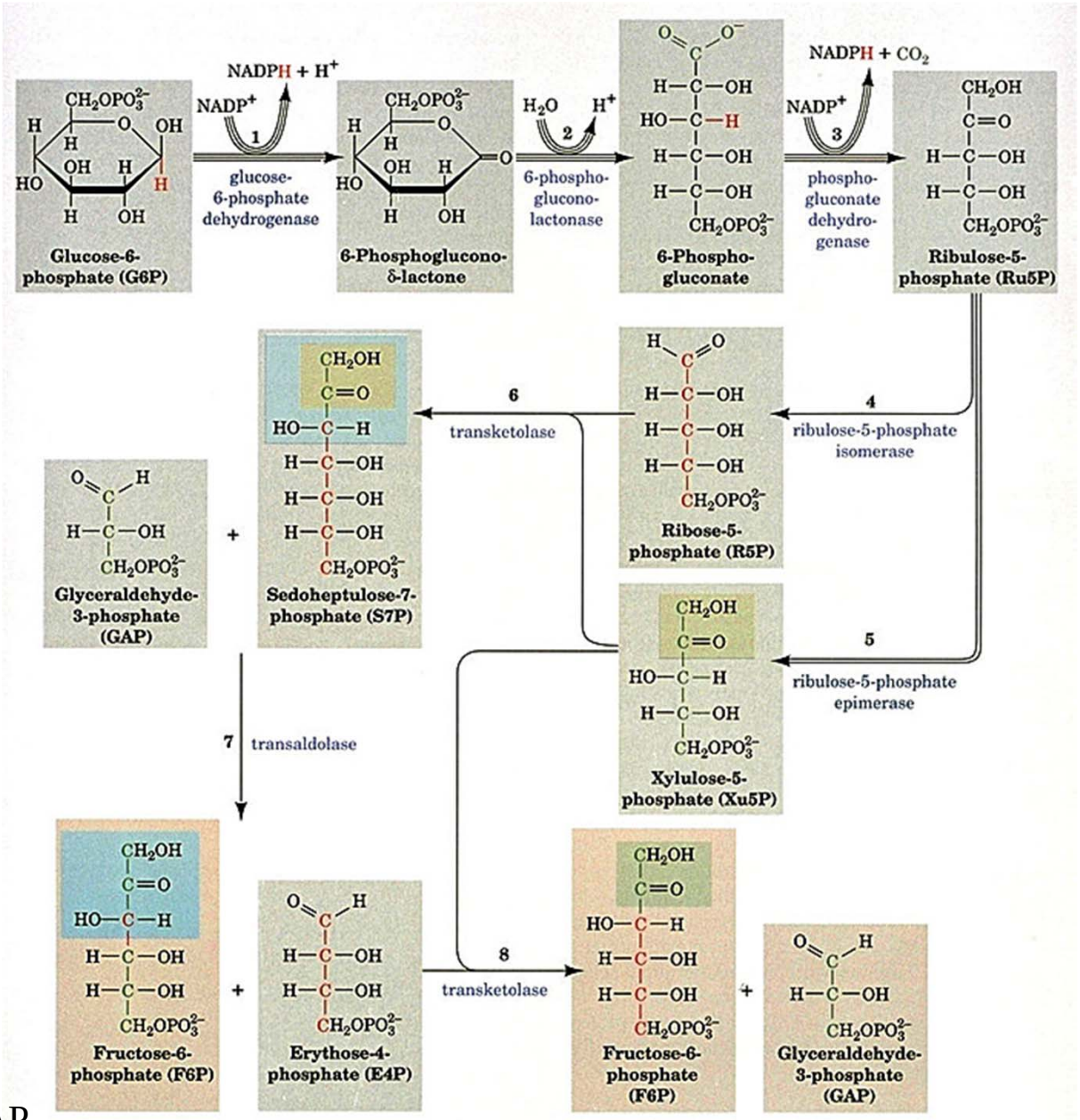
Transfer phase:

$R5P+2Xu5P \leftrightarrow 2F6P+GAP$

Overall:

$3G6P+6NADP^{+}+3H_2O\rightarrow$

$6NADPH+6H^{+}+3CO_2+2F6P+GAP$



Biochemistry. Voet & Voet

TABLE 20.3 **Pentose phosphate pathway**

Reaction	Enzyme
Oxidative phase	
Glucose 6-phosphate + $NADP^+$ $\longrightarrow$ 6-phosphoglucono-δ-lactone + NADPH + H^+	Glucose 6-phosphate dehydrogenase
6-Phosphoglucono-δ-lactone + H_2O $\longrightarrow$ 6-phosphogluconate + H^+	Lactonase
6-Phosphogluconate + $NADP^+$ $\longrightarrow$ ribulose 5-phosphate + CO_2 + NADPH	6-Phosphogluconate dehydrogenase
Nonoxidative Phase	
Ribulose 5-phosphate $\rightleftharpoons$ ribose 5-phosphate	Phosphopentose isomerase
Ribulose 5-phosphate $\rightleftharpoons$ xylulose 5-phosphate	Phosphopentose epimerase
Xylulose 5-phosphate + ribose 5-phosphate $\rightleftharpoons$ sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate	Transketolase
Sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate $\rightleftharpoons$ fructose 6-phosphate + erythrose 4-phosphate	Transaldolase
Xylulose 5-phosphate + erythrose 4-phosphate $\rightleftharpoons$ fructose 6-phosphate + glyceraldehyde 3-phosphate	Transketolase

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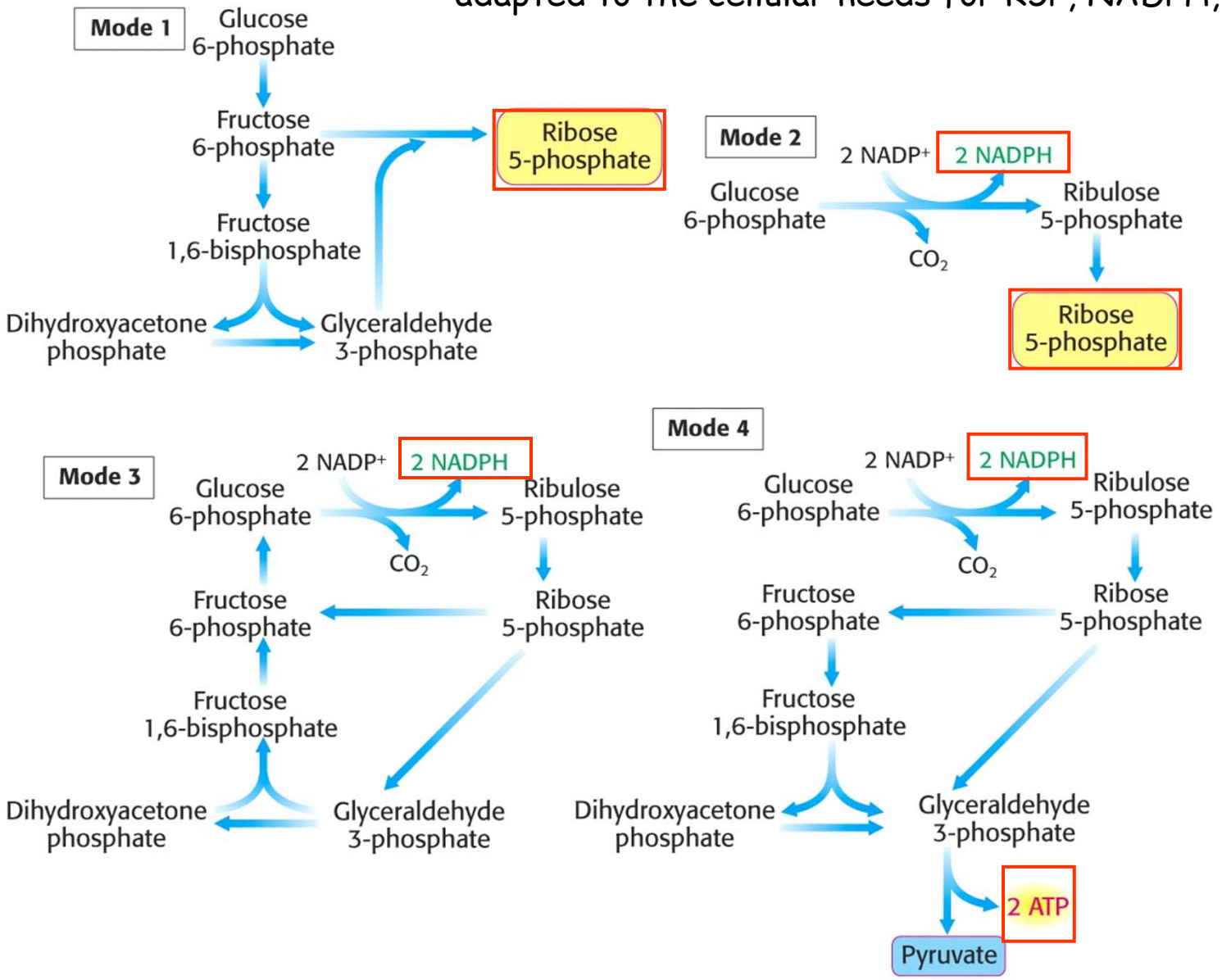
The reactions of the pentose phosphate pathway are adapted to the cellular needs for R5P, NADPH, ATP



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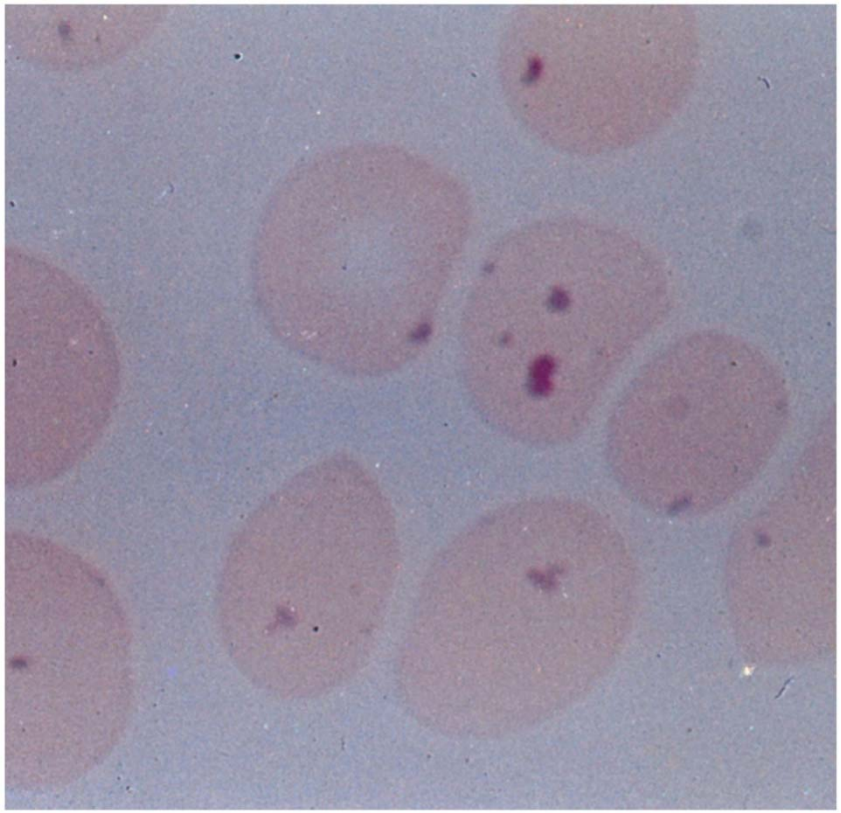
A deficiency of G6P-DH is the most common enzymopathy affecting hundreds of millions of people

- discovered due to hemolytic anemia induced by the antimalarial drug pamaquine in some patients

- inherited on the X chromosome

- oxidative damage of red blood cells (GSH)

- the incidence of the most common G6P-DH deficiency (10fold reduction of catalytic activity) is 11% among Afro-Americans (African heritage). Such high frequency suggests some advantages for certain environmental conditions: Protects against infection with *Plasmodium falciparum* and/or *Plasmodium malariae*



Light micrograph of red blood cells with Heinz bodies

The Cori cycle

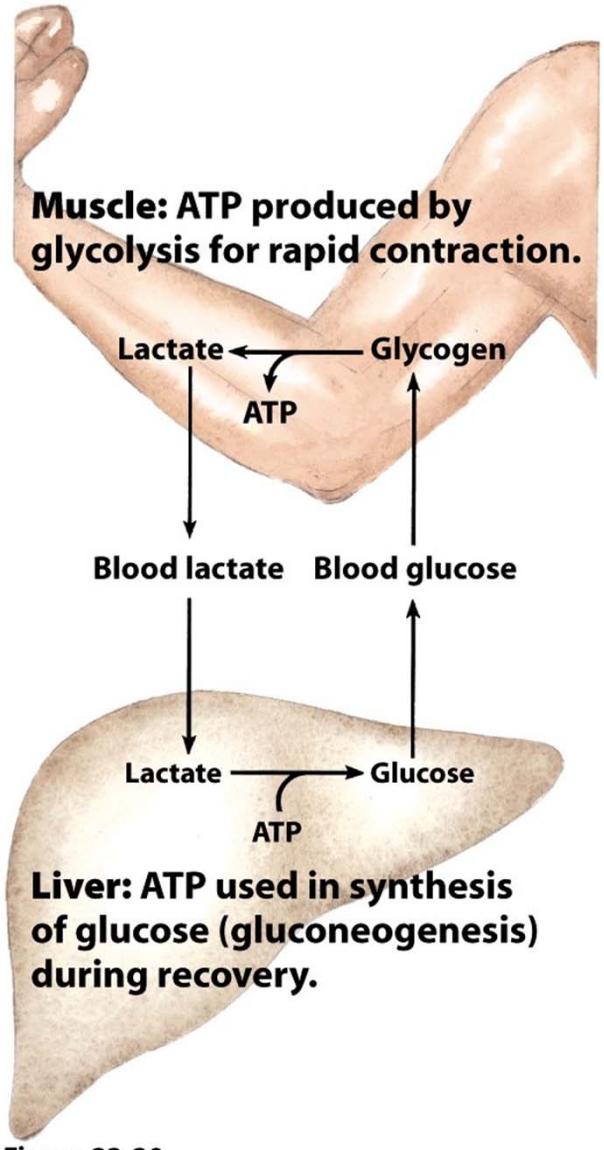


Figure 23-20
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Glucose-alanine cycle

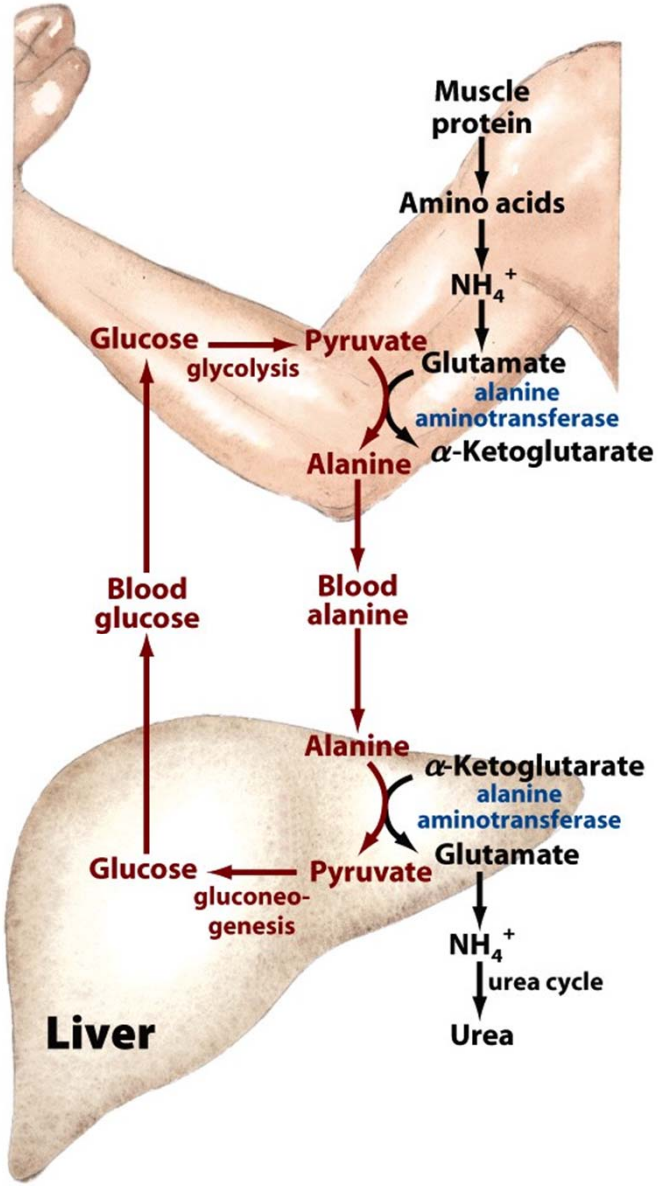

Figure 18-9
Lehninger Principles of Biochemistry, Fifth Edition

Lactic Acidosis

- Elevated concentrations of lactate in the plasma, termed lactic acidosis, occur when there is a collapse of the circulatory system, such as in **myocardial infarction**, **pulmonary embolism**, and **uncontrolled hemorrhage**, or when an individual is in **shock**.

- Failure to bring adequate amounts of oxygen to the tissues results in impaired oxidative phosphorylation and decreased ATP synthesis.

- To survive, the cells use **anaerobic glycolysis** as a backup system for generating ATP, producing lactic acid as the end product.
  - Production of even meager amounts of ATP may be life-saving during the period required to reestablish adequate blood flow to the tissues.

- The excess oxygen required to recover from a period when the availability of oxygen has been inadequate is termed the **oxygen debt**.