Biosynthesis

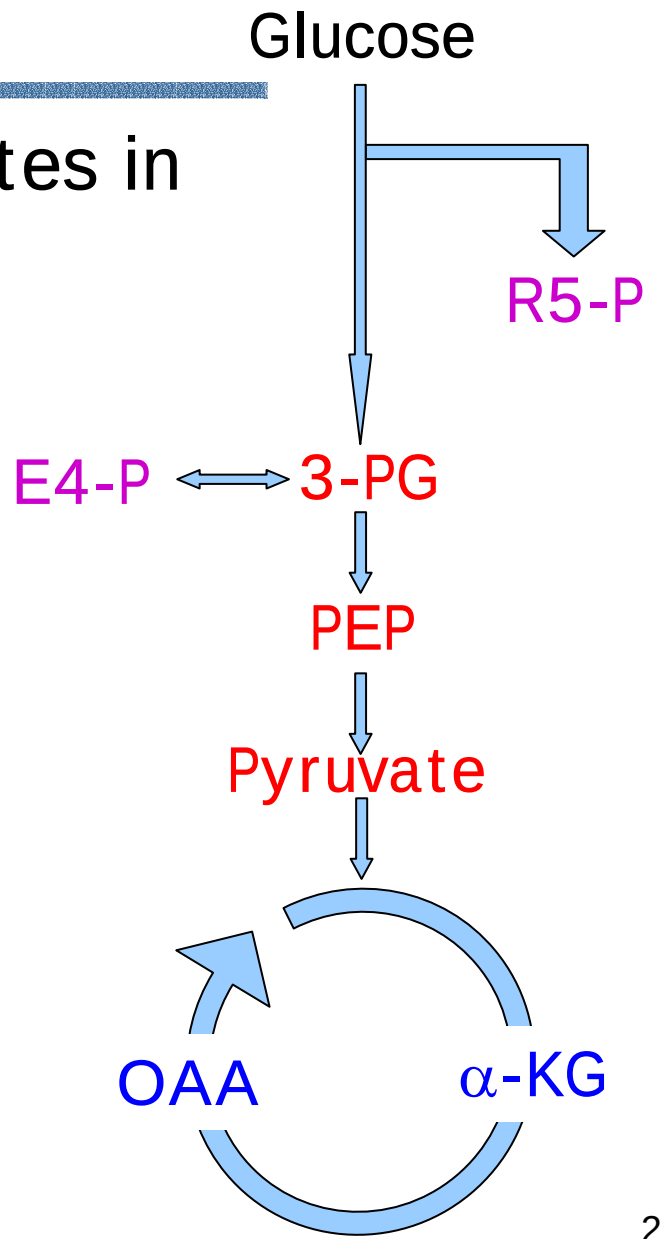
Amino acids,

N-containing molecules

Nucleotides

Biosynthesis of A.A.

- All C derived from intermediates in
  - ✓ Glycolysis
    - 3-Phosphoglycerate (3PG)
    - Phosphoenolpyruvate (PEP)
    - Pyruvate
  - ✓ The citric acid cycle
    - α-Ketoglutarate
    - Oxaloacetate
  - ✓ The pentose phosphate pathway
    - Ribose 5-phosphate
    - Erythrose 4-phosphate
- N enters these pathways as
  - ✓ Glu (aminotransferase)
  - ✓ Gln (amidotransferase)



Precursors of amino acids

- Table 22-1

Amino Acid Biosynthetic Families, Grouped by Metabolic Precursor

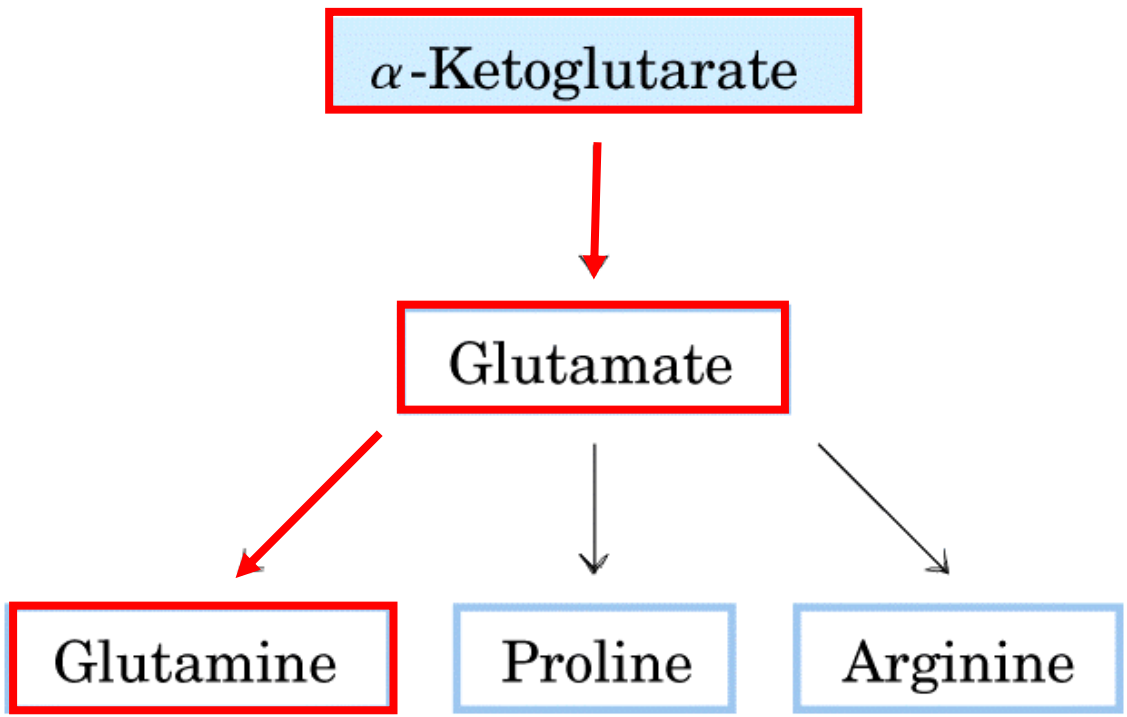
α-Ketoglutarate	**Pyruvate**
Glutamate	Alanine
Glutamine	Valine†
Proline	Leucine†
Arginine*	
	Phosphoenolpyruvate and erythrose 4-phosphate
3-Phosphoglycerate	Tryptophan†
Serine	Phenylalanine†
Glycine	Tyrosine‡
Cysteine	
	Ribose 5-phosphate
Oxaloacetate	Histidine†
Aspartate	
Asparagine	
Methionine†	
Threonine†	
Lysine†	
Isoleucine†	

p. 827

α-ketoglutarate

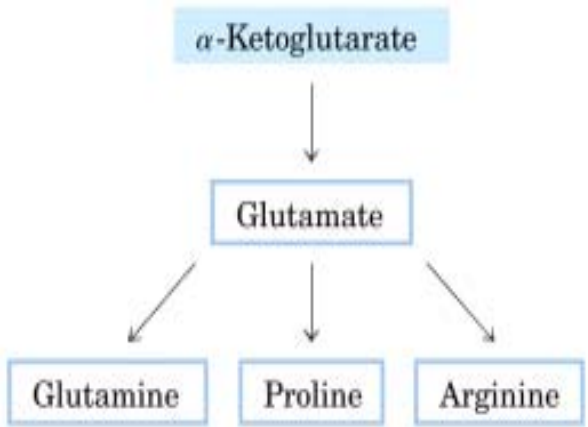
- Transamination
  - ✓ Aminotransferase
- Glutamine synthetase (requires ATP)

p. 829



α-ketoglutarate → Arg

- Arg (in mammals)



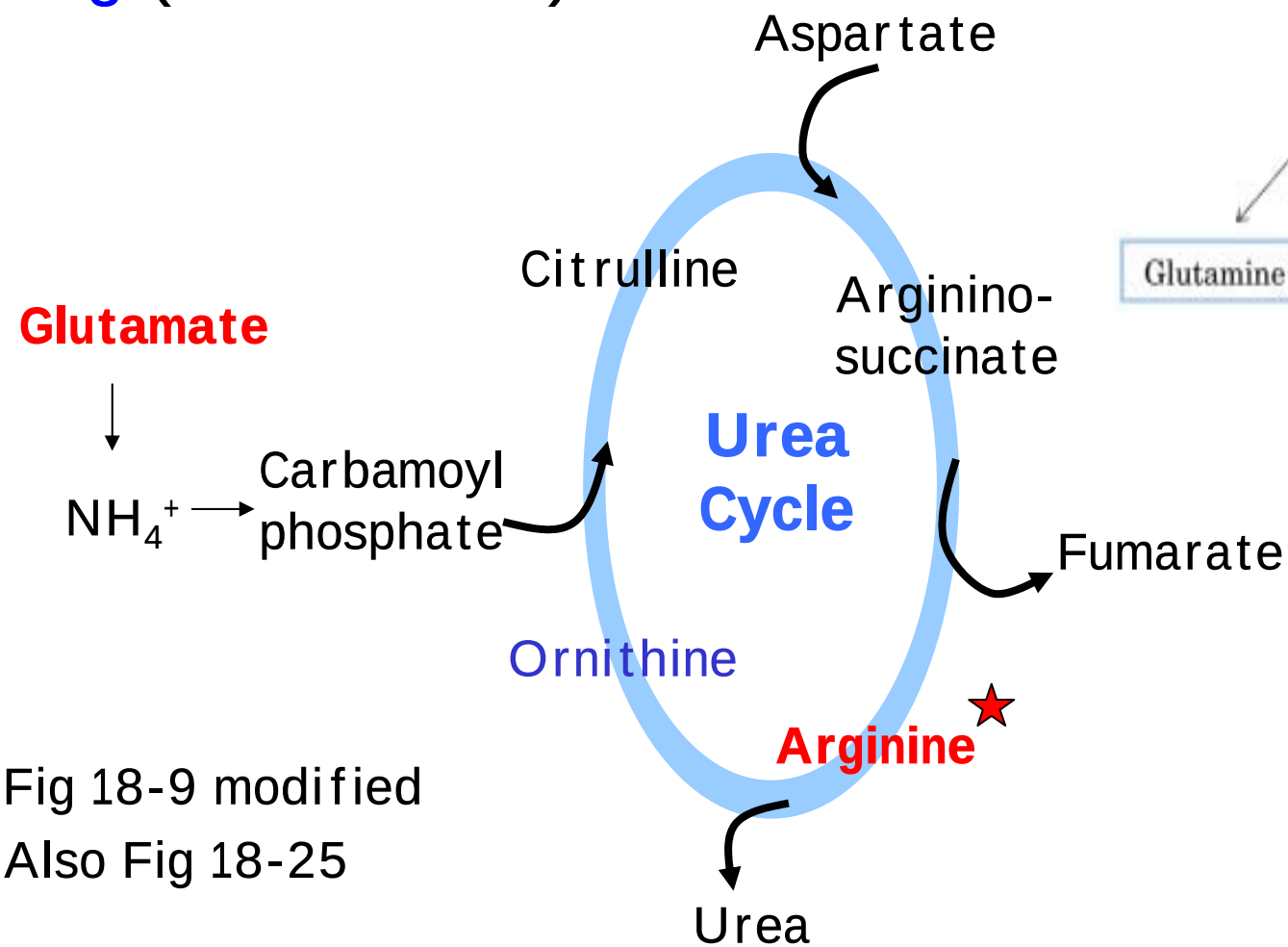


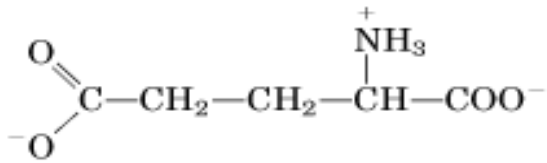
Fig 18-9 modified

Also Fig 18-25

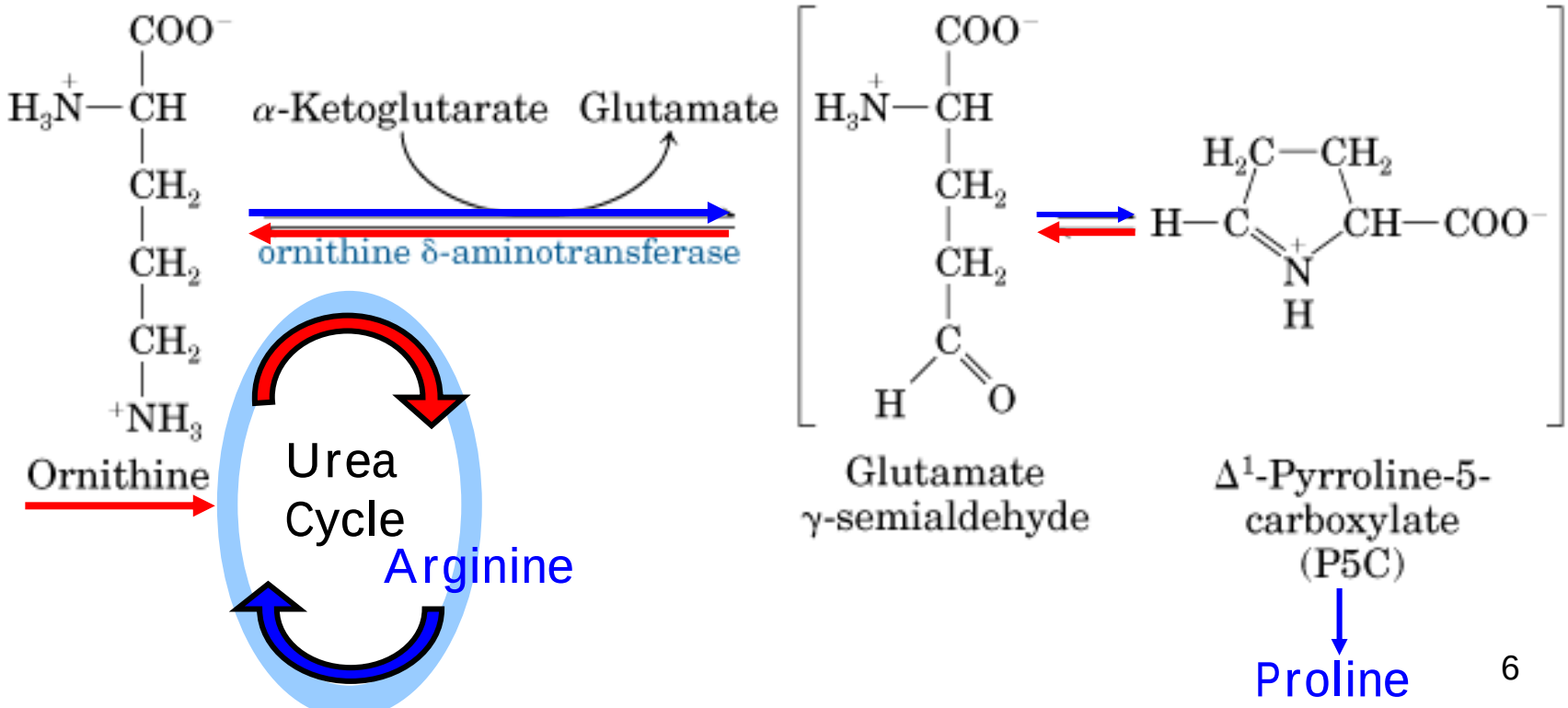
Arg ←→ Pro

Fig 22-10, 11

- In mammals
  - ✓ Glu → Pro
    - Spontaneous cyclization
  - ✓ Glu → Arg
  - ✓ Arg ←→ Pro



Glutamate



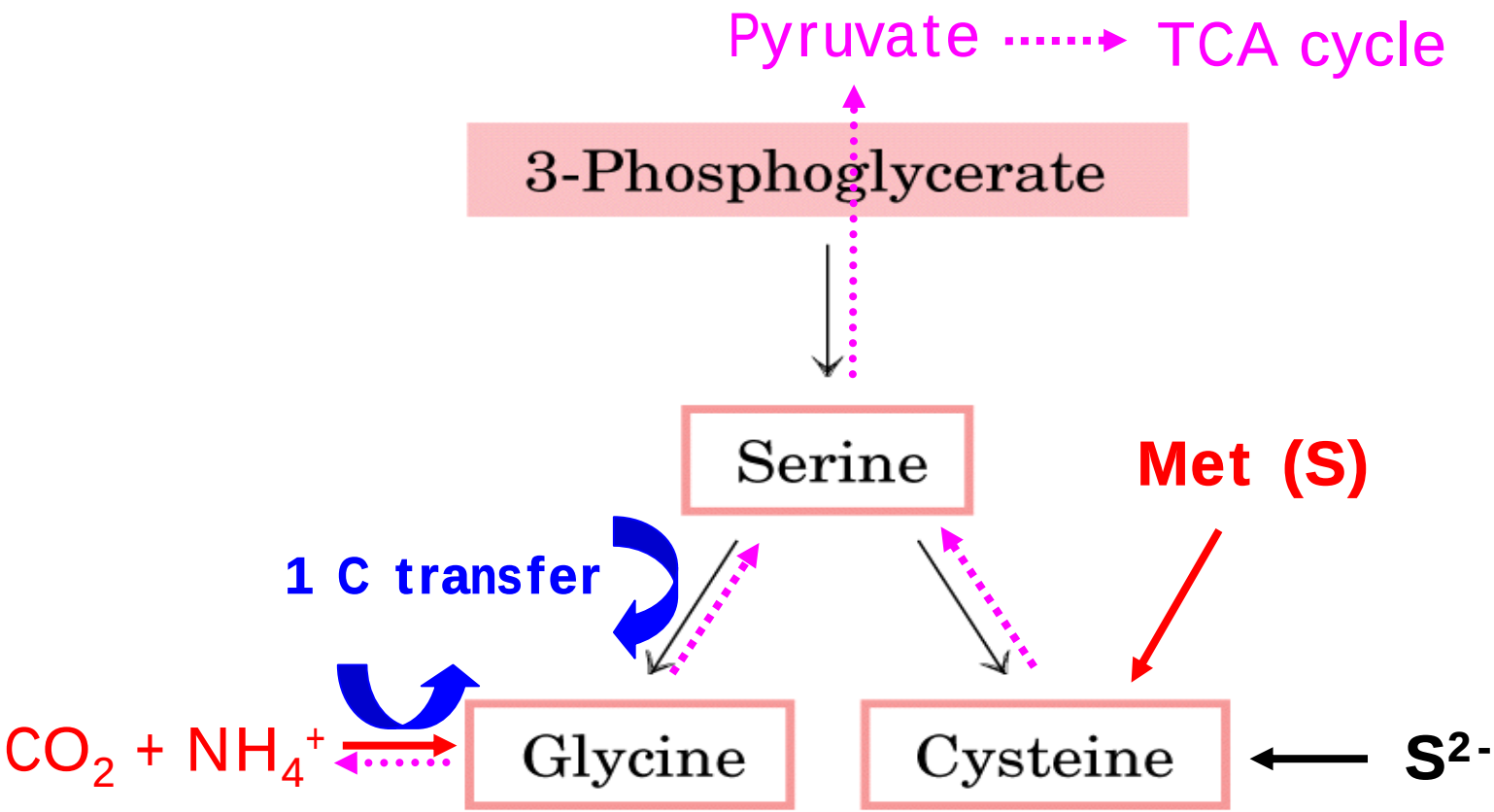
Glutamate γ-semialdehyde

Δ¹-Pyrroline-5-carboxylate (P5C)

Proline

3-phosphoglycerate → Ser

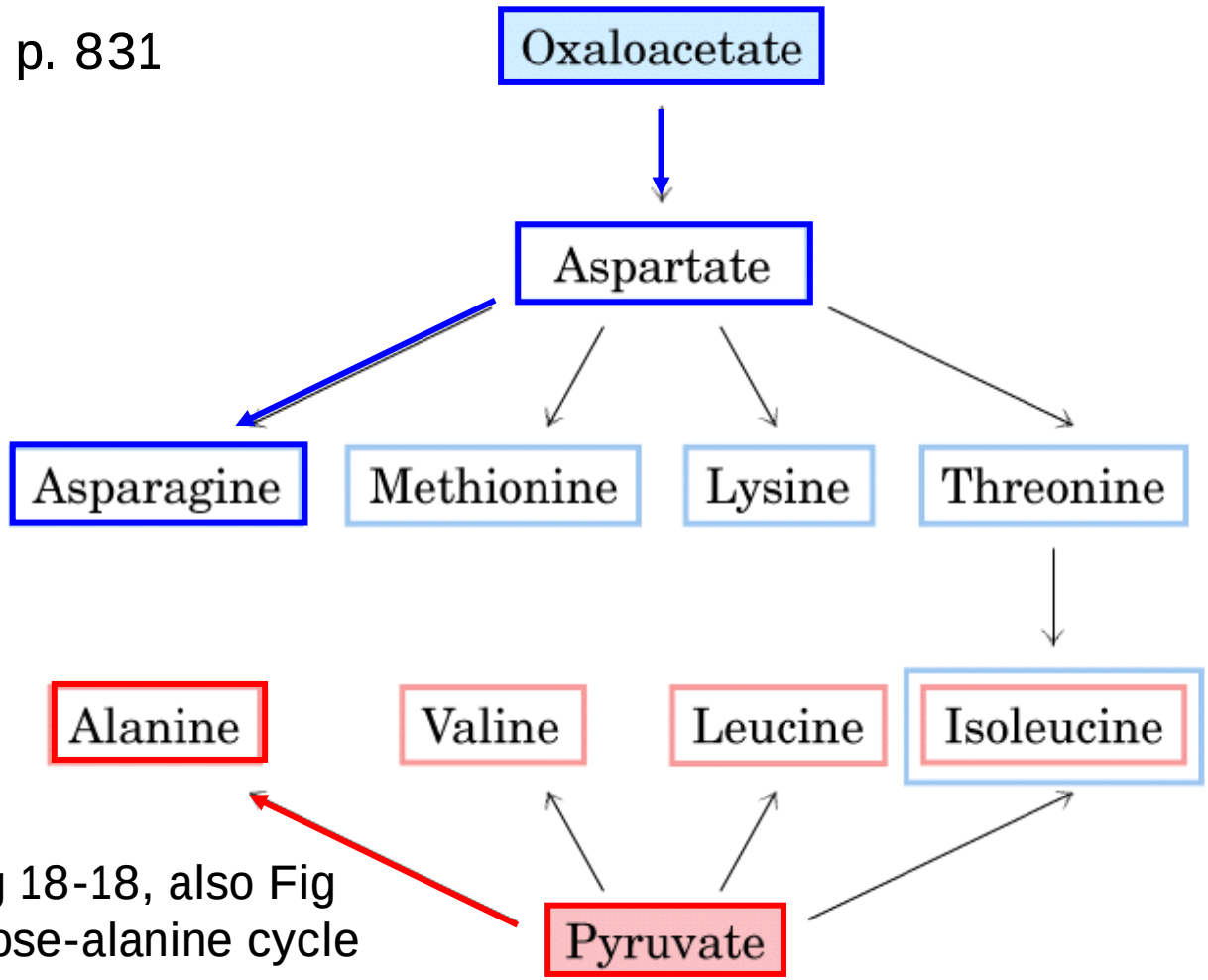
- Gly (2C)
  - ✓ From Ser (3C)
  - ✓ From CO_2, NH_4^+
- Cys
  - ✓ C-skeleton from Ser
  - ✓ S from Met (in mammals)



Next:

- From oxaloacetate and pyruvate
  - ✓ 3 nonessential a.a. (same pathway in all organisms)

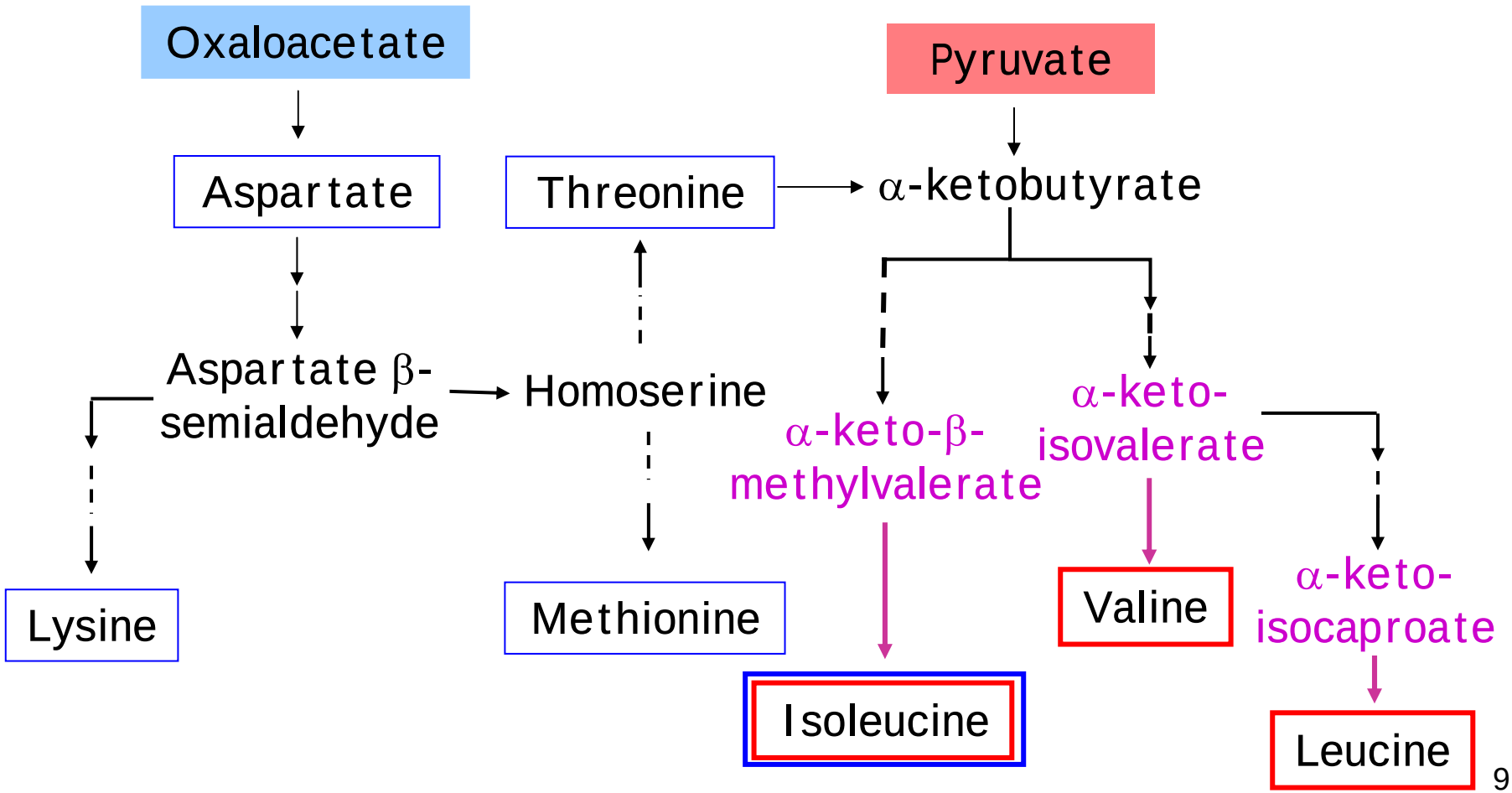
p. 831



Review Fig 18-18, also Fig 18-8, glucose-alanine cycle

BCAA and their keto acids

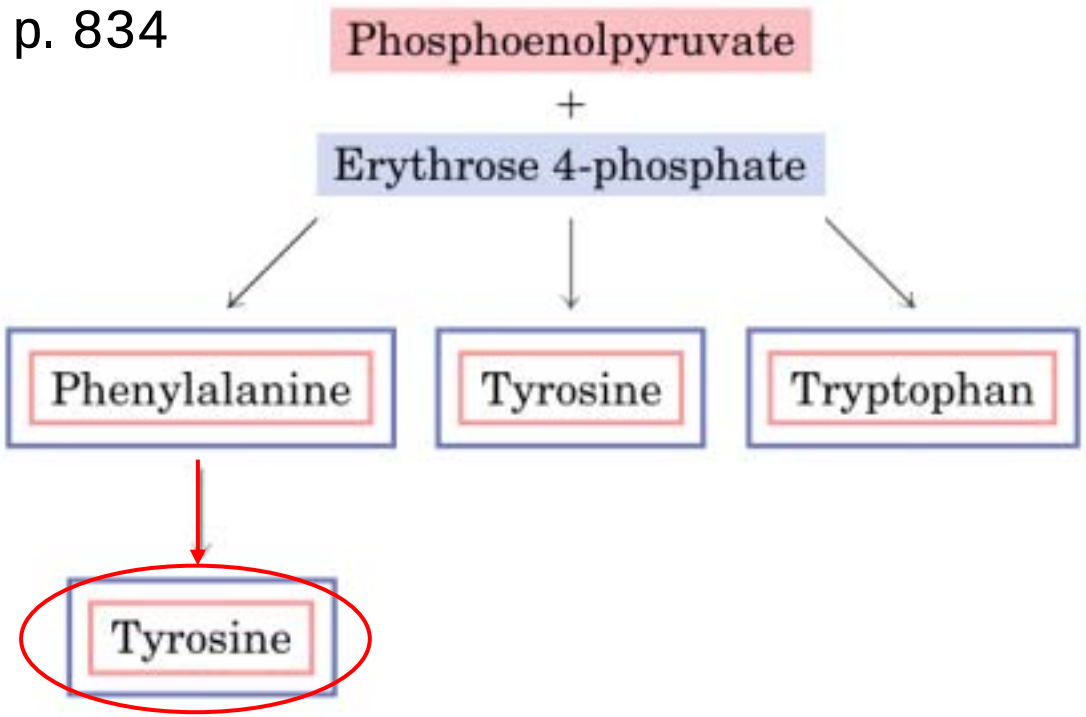
- In bacteria (Fig 22-15 simplified)
- Keto acids as diet supplement for N elimination defect



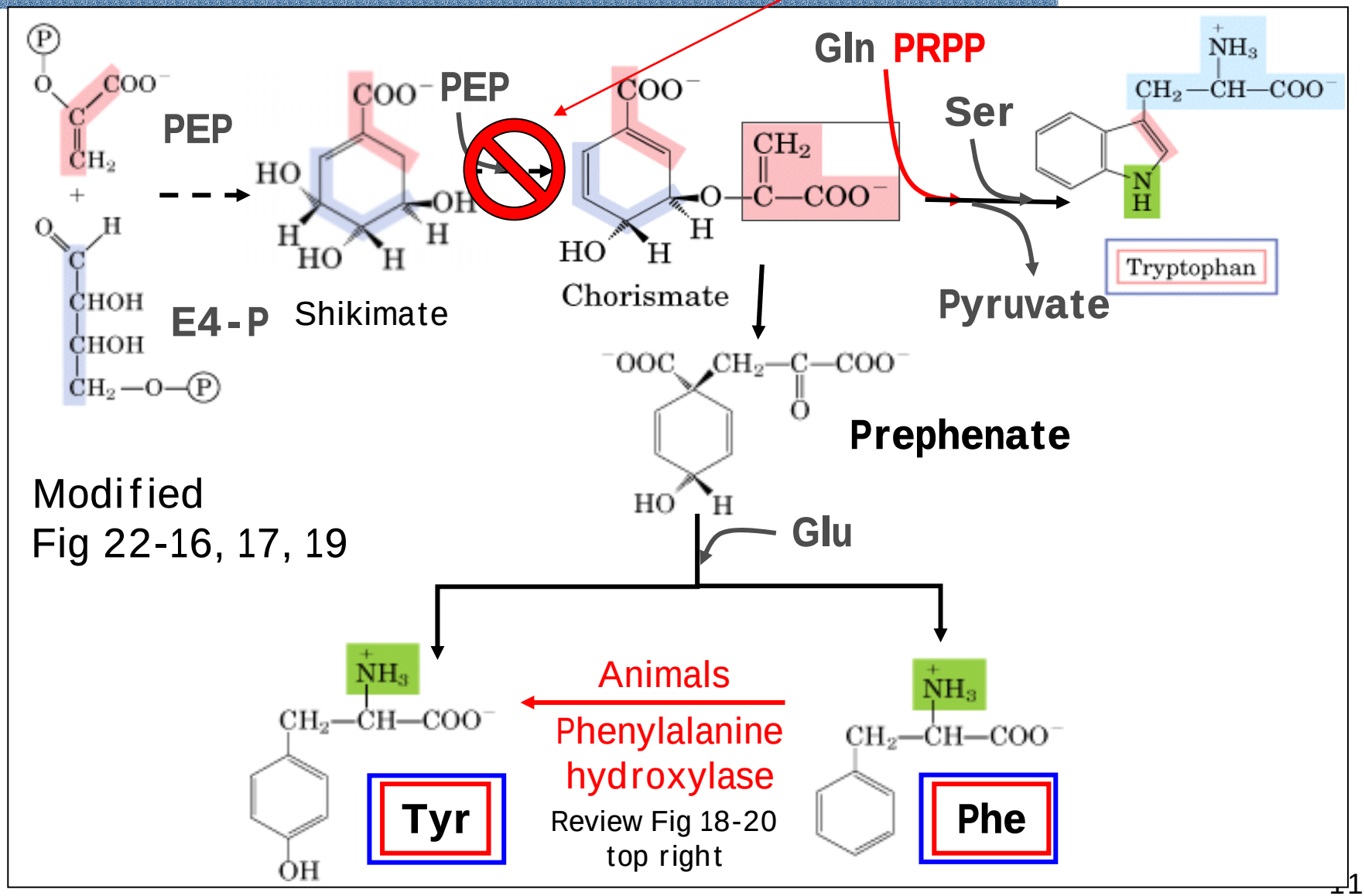
Aromatic a.a.:

- Phe, Tyr, Trp
  - ✓ From PEP and E4-P in bacteria and plants
  - ✓ Key intermediates: shikimate and chorismate:

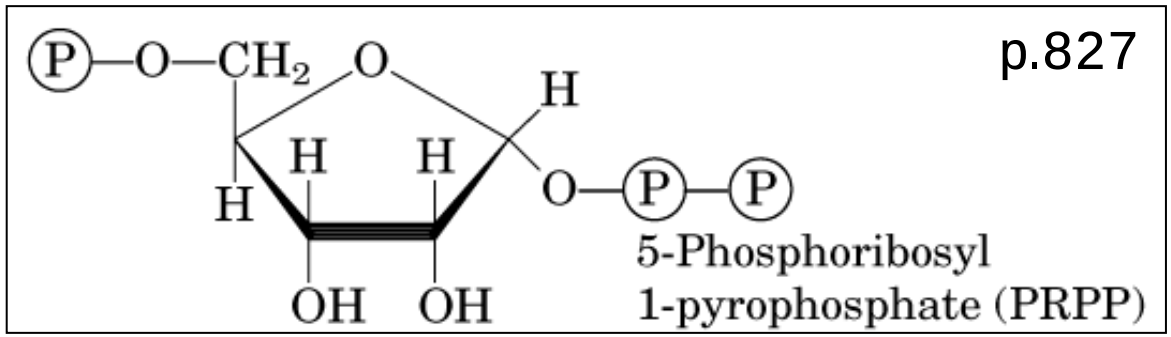
p. 834



Trp, Phe, and Tyr



PRPP

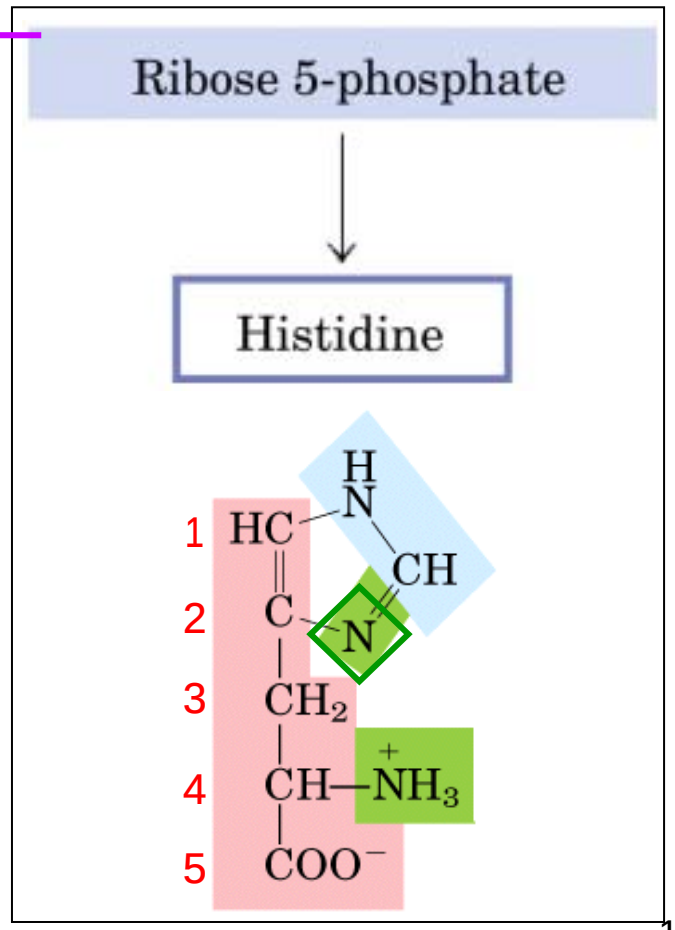


- Ⓟ = PO_4^{3-}
- PRPP = 5-phosphoribosyl-1-pyrophosphate
- Ribose 5-phosphate (from pentose phosphate pathway)
- R5-P + ATP → PRPP + AMP
- An important intermediate in several a.a. (Trp and His) and nucleotide synthesis.

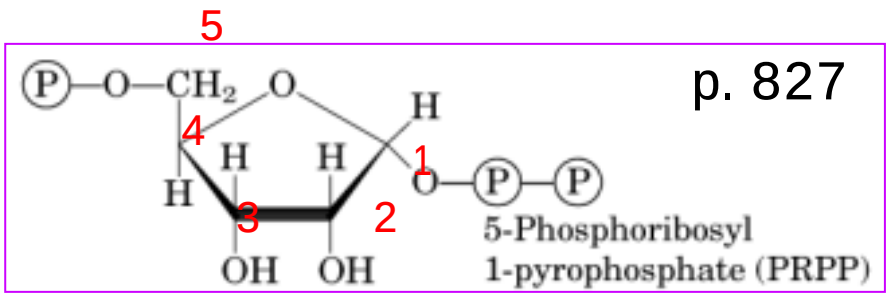
His biosynthesis

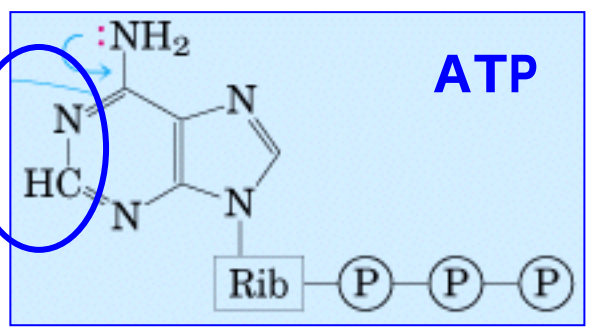
- In plants and bacteria (Fig 22-20)
- Derived from 3 precursors:
  - ✓ PRPP (5 C)
  - ✓ Purine ring of ATP (1 N, 1 C)
    - ATP as a metabolite, not as fuel
  - ✓ Gln, Glu (2 N)

p. 838



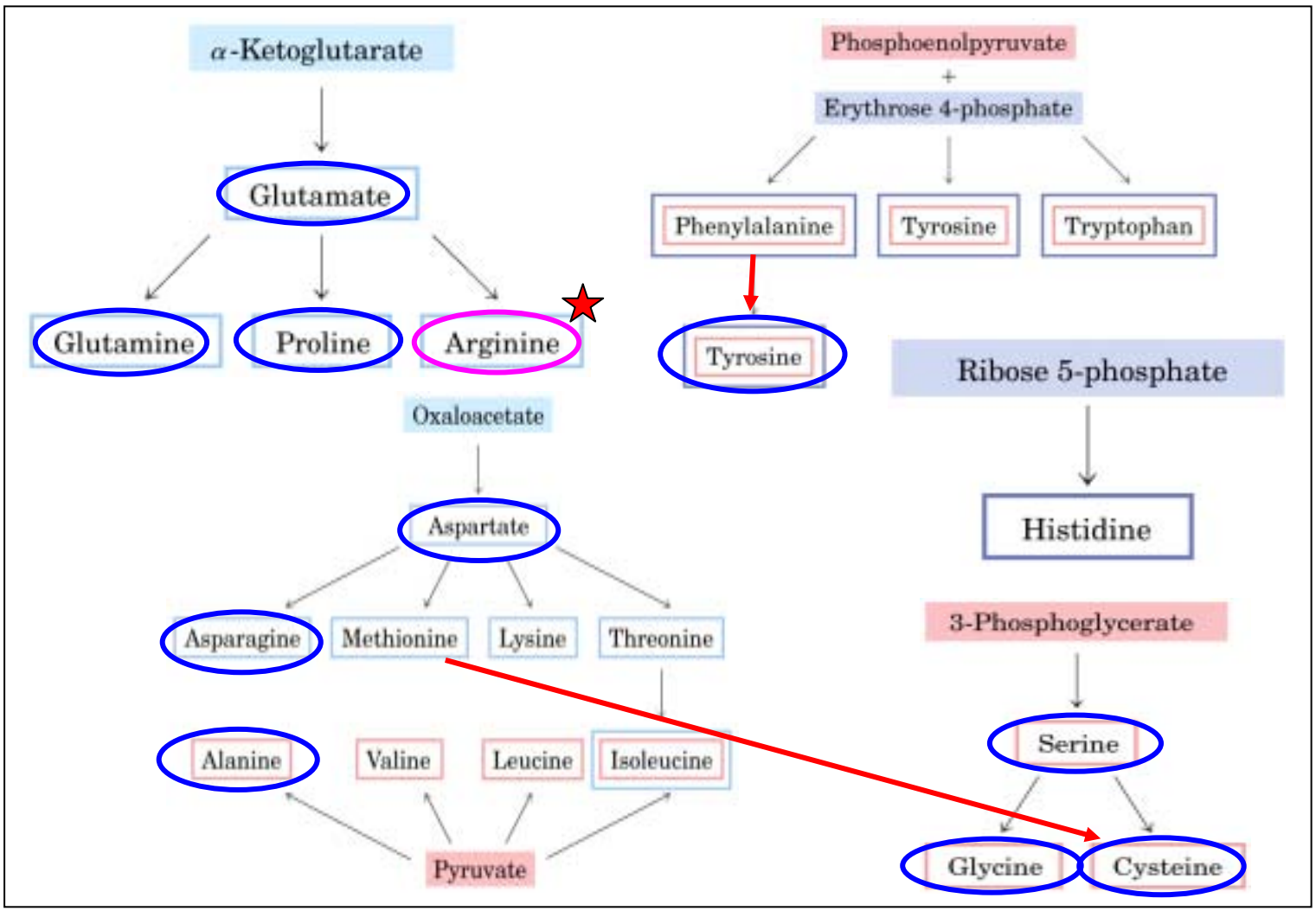
p. 827





A.A. biosynthesis

- 10 (+1) nonessential a.a. in human



Gln synthetase (I)

- Concerted inhibition
  - ✓Multiple allosteric inhibitors (I)
    - One I → partial inhibition
    - Multiple Is → ***more than additive***
    - All (8) → shut down
  - ✓Continuous adjustment of Gln levels to match immediate metabolic requirements

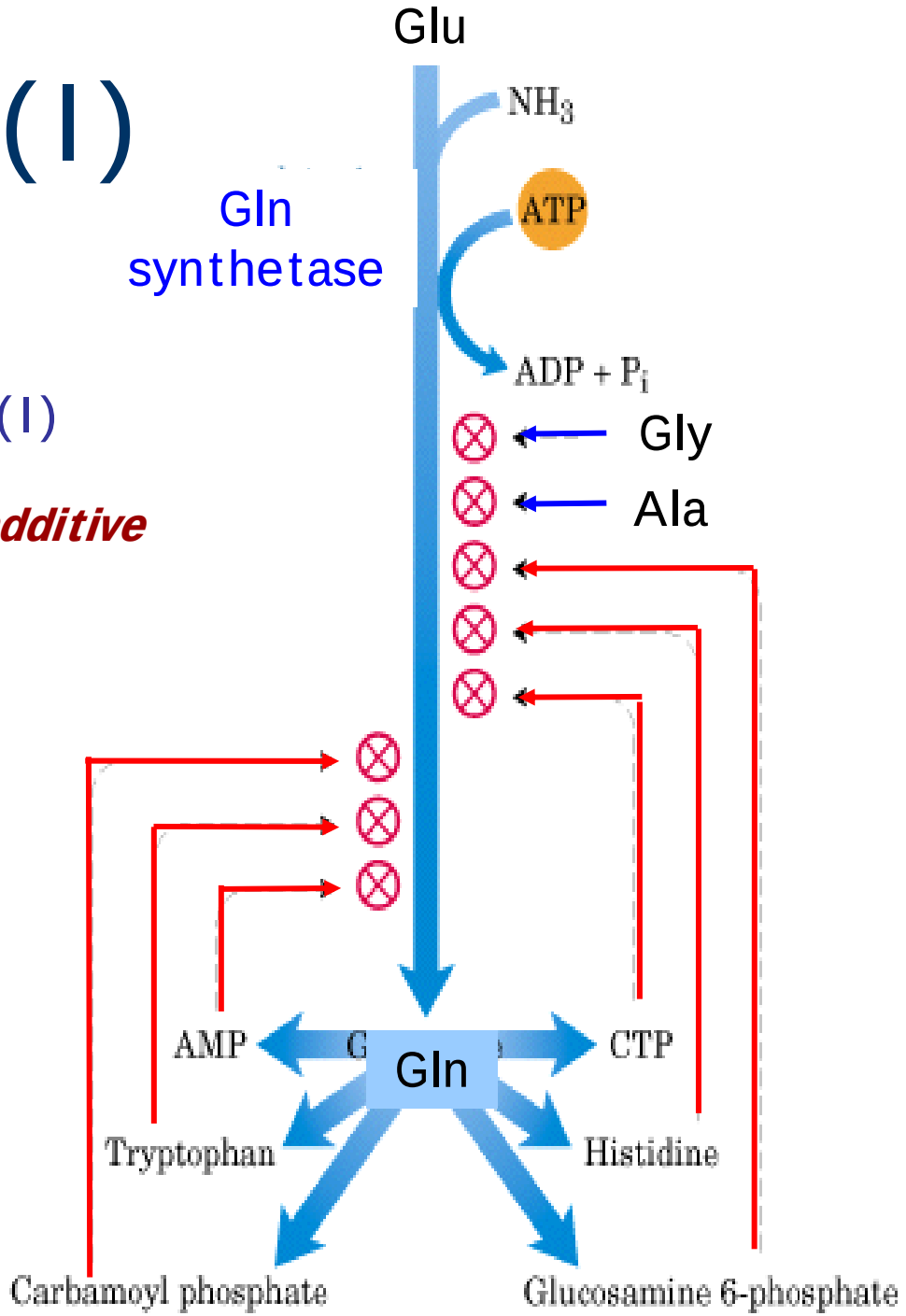
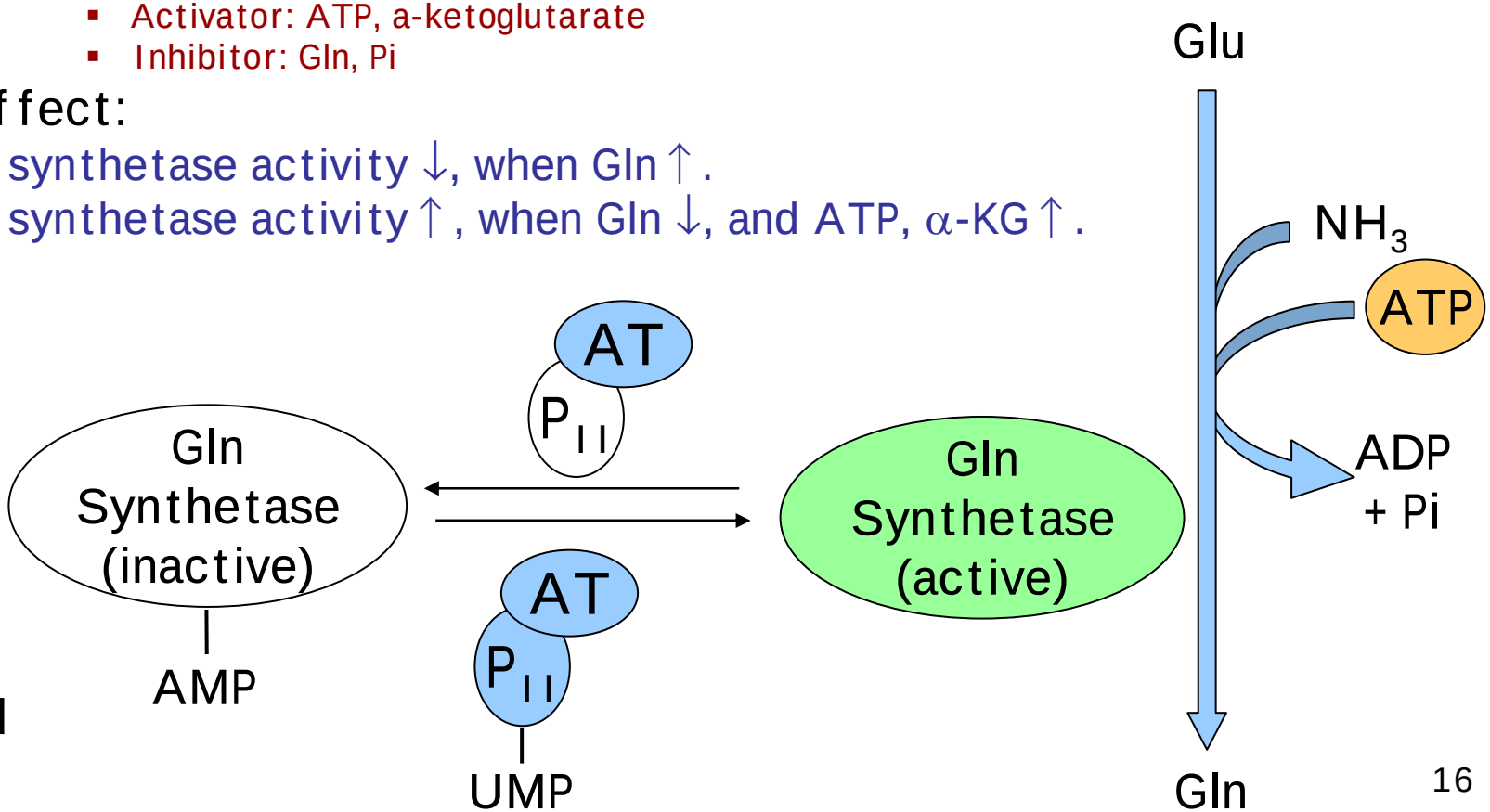


Fig 22-6
p. 824

Gln synthetase (I I) p. 825

- Covalent modification (Fig 22-7)
  - ✓Adenylation (-AMP to Tyr) of each subunit
  - ✓Adenyltransferase (AT) + P_{II}-UMP
    - Uridylylation (-UMP to Tyr)
    - Uridylyltransferase (UT) → allosteric enz.
      - Activator: ATP, a-ketoglutarate
      - Inhibitor: Gln, Pi
- Net effect:
  - ✓Gln synthetase activity ↓, when Gln ↑.
  - ✓Gln synthetase activity ↑, when Gln ↓, and ATP, α-KG ↑.



Modified Fig 22-7

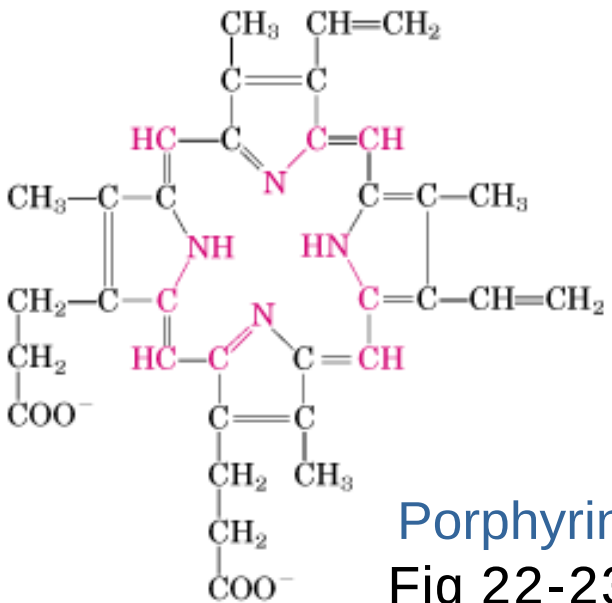
A.A derived molecules

p. 841

- Porphyrins
- Creatine and Glutathione
- D-amino acids
- Biological amines
- Nitric oxide

Synthesis of heme

- Porphyrin precursors: *glycine* + succinyl-CoA
- Feedback inhibited by heme product
- Congential erythropoietic porphyria (Box 22-1):
  - ✓ Porphyrin precursor accumulation, excreted in urine (red)
  - ✓ Deposited in skin (light sensitive)
  - ✓ Fluorescent teeth under UV
  - ✓ Often anemia (insufficient heme produced)



Porphyrin
Fig 22-23

Porphyrin + Fe = Heme (Fig 7-2b)

Heme biosynthesis

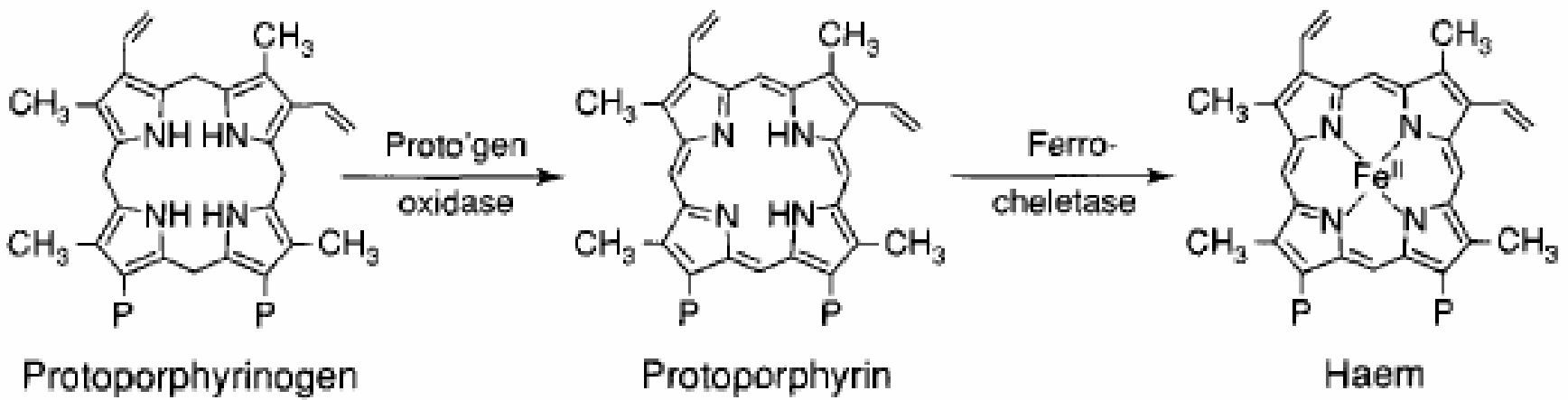
- Fig. 22-23
- TIBS 21 – June 1996
- Harper's 26th ed. Ch32

- Gly + succinyl-CoA → aminolevulinate (ALA)
  1) 2 x ALA → Porphobilinogen (PBG)
  2) 4 x PBG → Preuroporphyrinogen
  3) → Uroporphyrinogen III
  4) → Coproporphyrinogen III

  } Cytosol

  5) → Protoporphyrinogen
  6) → Protoporphyrin (Color, fluorescent)
  7) → Heme

  } Mitochondria



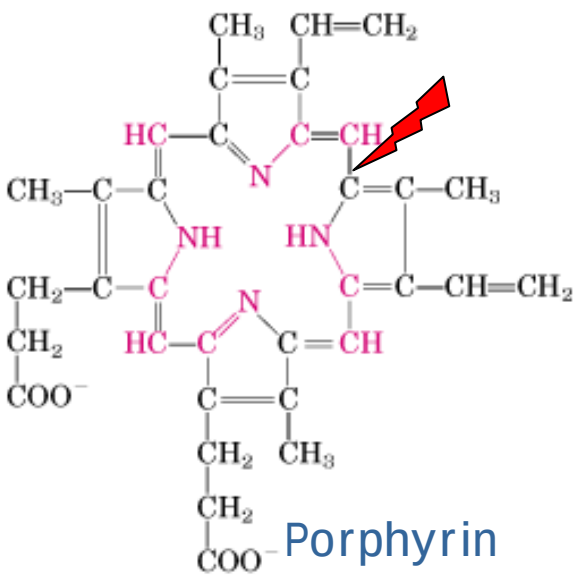
Heme breakdown

p. 842

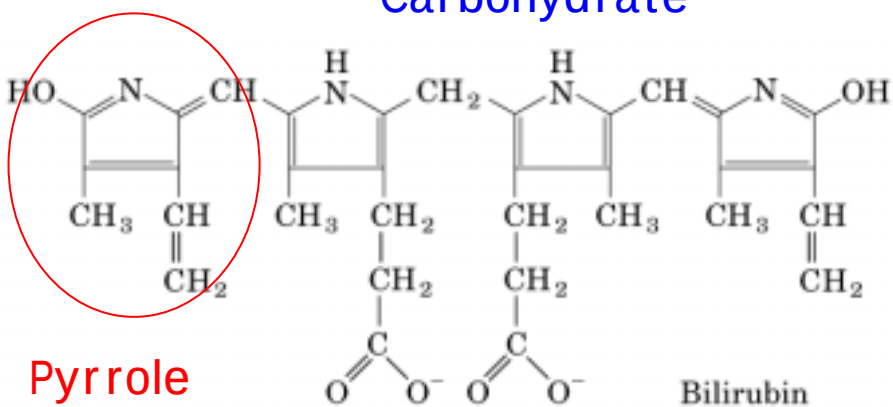
- Hb = globin (protein) + Fe + bilirubin (in spleen)
- *Bilirubin* (reddish-yellow pigment), insoluble
  - ✓ Transported to liver by serum albumin
  - ✓ Transformed to bile pigments (add glucuronide, becomes soluble) in liver
  - ✓ Excreted in the bile
- Impaired liver function or blocked bile secretion:
  - ✓ Bile leak into the blood
  - ✓ Yellowing of the skin and eyeballs
  - ✓ Jaundice

- Bilirubin (insoluble)
- Bilirubin diglucuronide (soluble)

Carbohydrate



Porphyrin



Pyrrole
(5-membered ring)

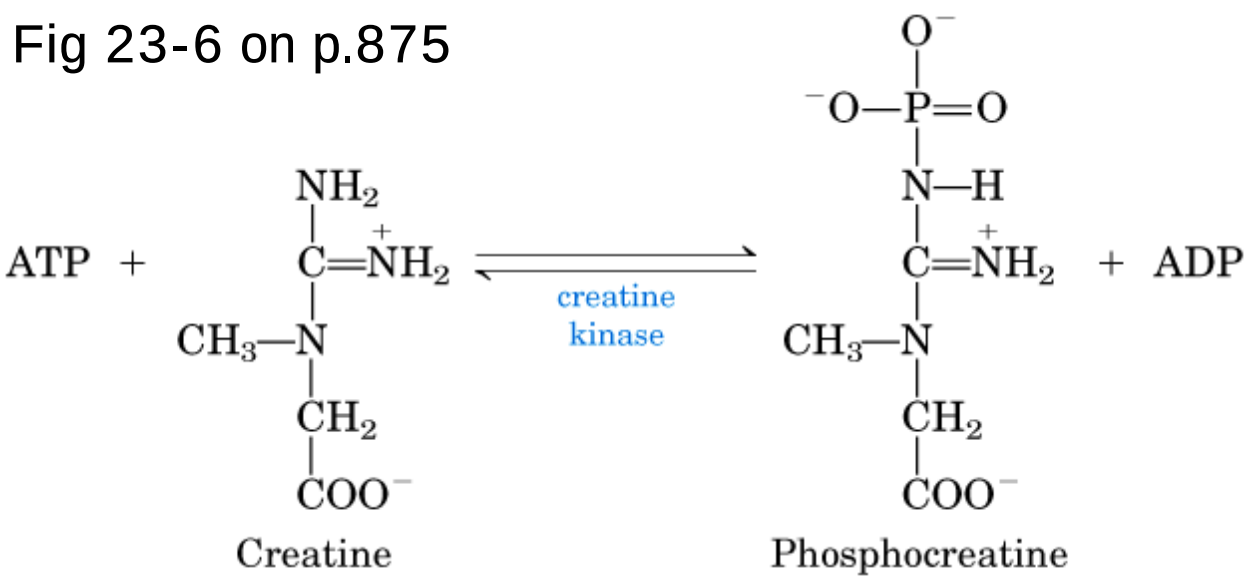
Bilirubin

Creatine and phosphocreatine

p.842, 874-5

- Creatine (Cr) = Gly + Arg + Met (adoMet)
- Creatine + ATP → Phosphocreatine (creatine kinase)
- Phosphocreatine (PCr) = Creatine phosphate (CrP)
  - ✓ Very high [PCr] in skeletal muscle (10 x of [ATP])
  - ✓ Source of Ⓟ for ATP synthesis from ADP
  - ✓ PCr as a phosphoryl reservoir (energy buffer)

Fig 23-6 on p.875



In resting muscle:

[ATP] = 4 mM

[ADP] = 0.013 mM

[CP] = 25 mM

[Cr] = 13 mM

Energy sources for muscle

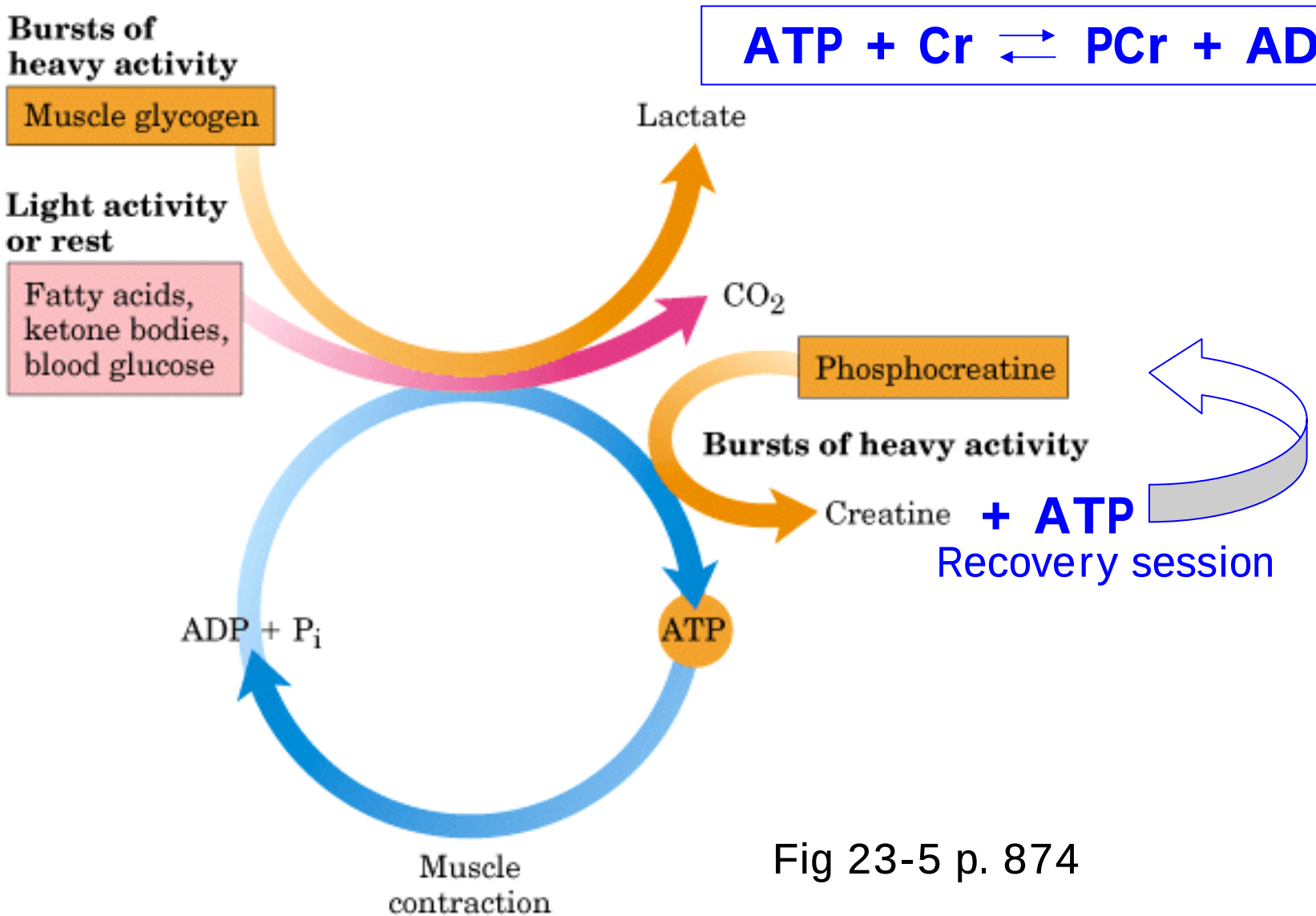


Fig 23-5 p. 874

Biological amines (I)

- A.A. are converted to amines by decarboxylation (requiring PLP as a cofactor, Fig 18-6, 22-27)
- Catecholamines (Tyr)
  - ✓ Dopamine, norepinephrine, epinephrine
  - ✓ Affects blood pressure
  - ✓ Parkinson's disease: underproduction of dopamine
  - ✓ Schizophrenia: overproduction of dopamine
- γ-aminobutyric acid (GABA) (Glu)
  - ✓ An inhibitory neurotransmitter (NT)
  - ✓ Epileptic seizures: underproduction of GABA
  - ✓ GABA analogs: treatment of epilepsy and hypertension
- Serotonin (Trp)
  - ✓ Neurotransmitter

Fig 22-27 p. 844

More amines …

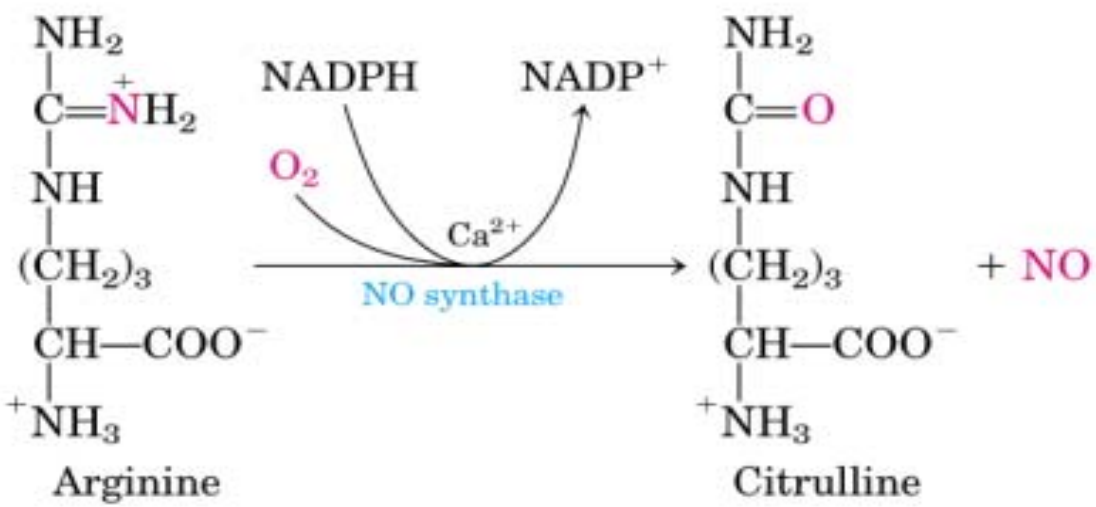
p. 845

- Histamine (His)
  - ✓ Vasodilator in animal tissue, involved in allergy
  - ✓ Stimulate stomach acid secretion
    - Cimetidine (Tagamet)
    - Structural analog of histamine = histamine receptor antagonist
    - Promoting healing of duodenal ulcers by inhibiting gastric acid secretion

Nitric oxide (NO)

- Derived from Arg, by NO synthase (NOS)
- Unstable gas, diffuse through membranes
  - ✓ Muscle relaxant (p.449)
    - Cardiac muscle: heart disease and nitroglycerine
    - Smooth muscle: erectile dysfunction and Viagra
  - ✓ Regulating blood pressure
  - ✓ Neurotransmission
  - ✓ Blood clotting

Fig 22-29 or p.449



Nucleotides

Biosynthesis
and
Degradation

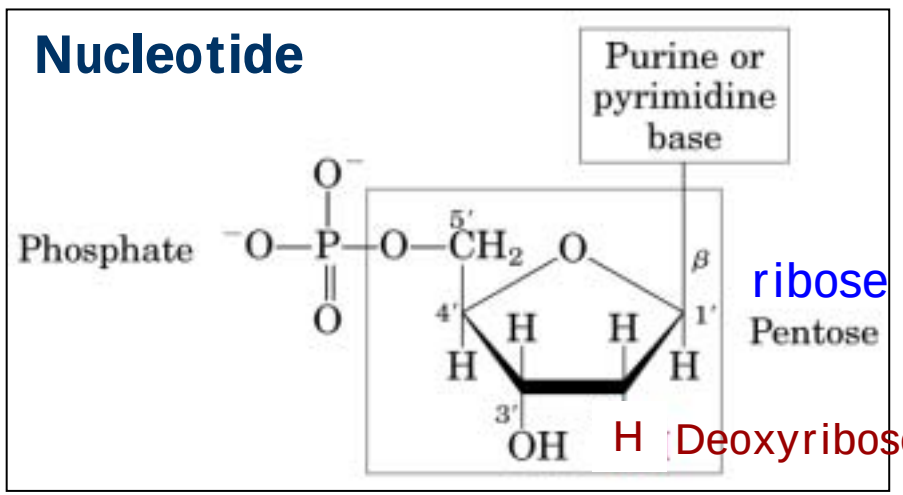
p.848

Introduction

- Nucleic acid 核酸
  - ✓DNA (deoxyribonucleic acid)
    - 5' → 3'
  - ✓RNA (ribonucleic acid)
    - Messenger RNA (mRNA)
    - Ribosomal RNA (rRNA)
    - Transfer RNA (tRNA)
- Nucleotides 核苷酸
  - ✓A, T, C, G
  - ✓A, U, C, G

dA, dT, dC, dG

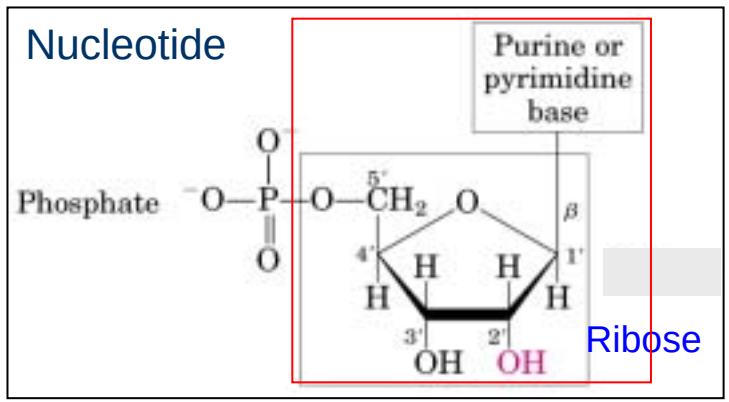
Fig 10-1 on p.325



Nucleotides Synthesis

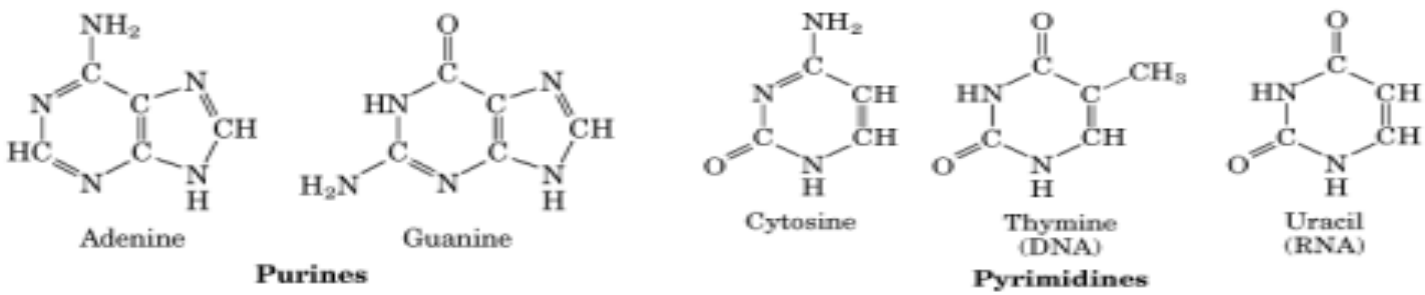
Fig 10-2 on p.326

Nucleotide vs. nucleoside



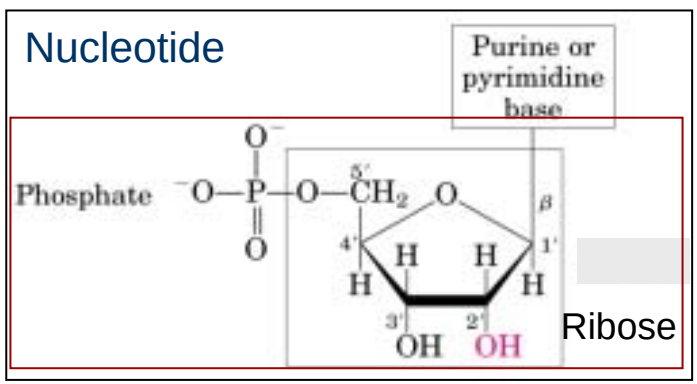
- Purine
  - ✓ Adenylate (A)
  - ✓ Guanylate (G)
- Pyrimidine
  - ✓ Cytidylate (C)
  - ✓ Thymidylate (T)
  - ✓ Uridylate (U)
- de novo pathways
  - ✓ From small molecules readily available in cells
  - ✓ A.A., ribose 5-phosphate, CO_2, and NH_3
  - ✓ The bases are *not* intermediates in this pathway
- Salvage pathways
  - ✓ Recycle the free bases and nucleosides released from nucleic acid breakdown

Bases



Purine synthesis (I)

- A (AMP), G (GMP)
- Adding functional groups *one by one* onto a preexisting ribose phosphate → inosinate (IMP)
- Fig 22-31:
  - ✓ **PRPP**, Gln, **Gly**, **1-C**, Gln, CO_2, **Asp**, **1-C** → IMP
  - ✓ In steps 8-9, Asp has an analogous role in the urea cycle



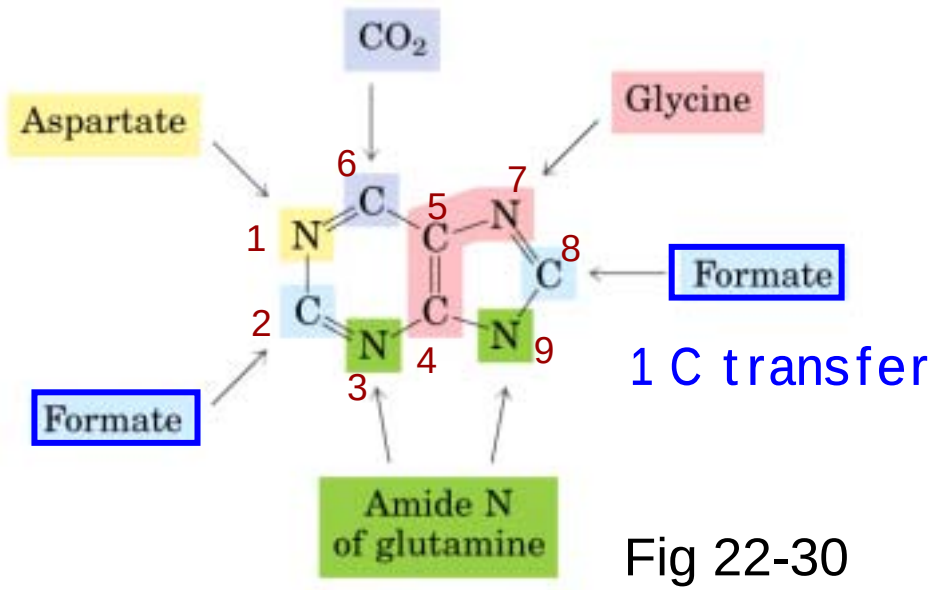
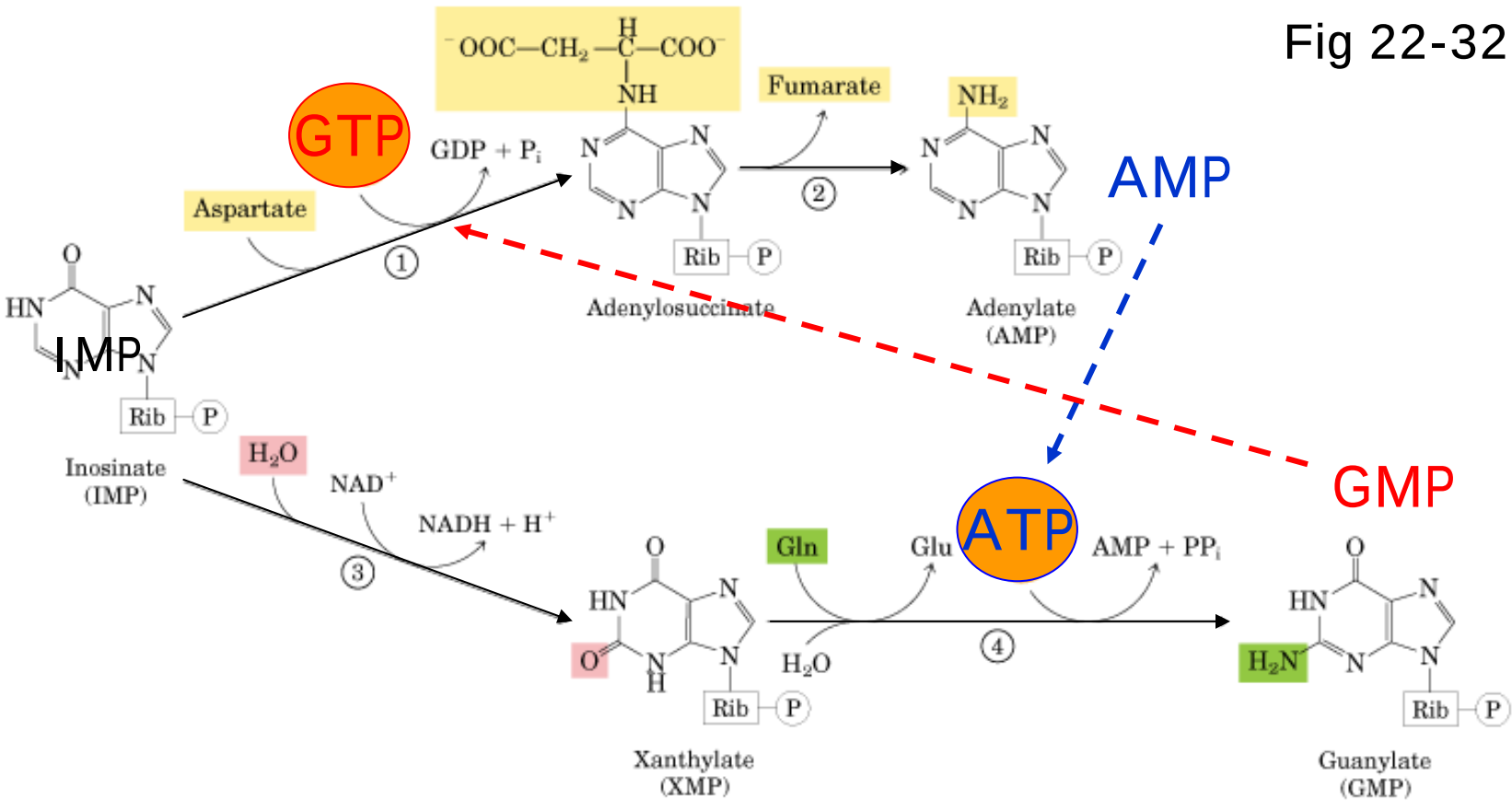


Fig 22-30

Purine synthesis (II)

- IMP (inosinate, inosine monophosphate)
  - ✓ IMP + Asp → AMP (GTP → GDP + Pi)
  - ✓ IMP → oxidized IMP + Gln → GMP (ATP → AMP + PPi)

Fig 22-32



Purine regulations

Harper 26th, Ch 34

- Regulated by
  - ✓ The pool size of PRPP
  - ✓ Feedback inhibition of PRPP-glutamyl amidotransferase by AMP and GMP

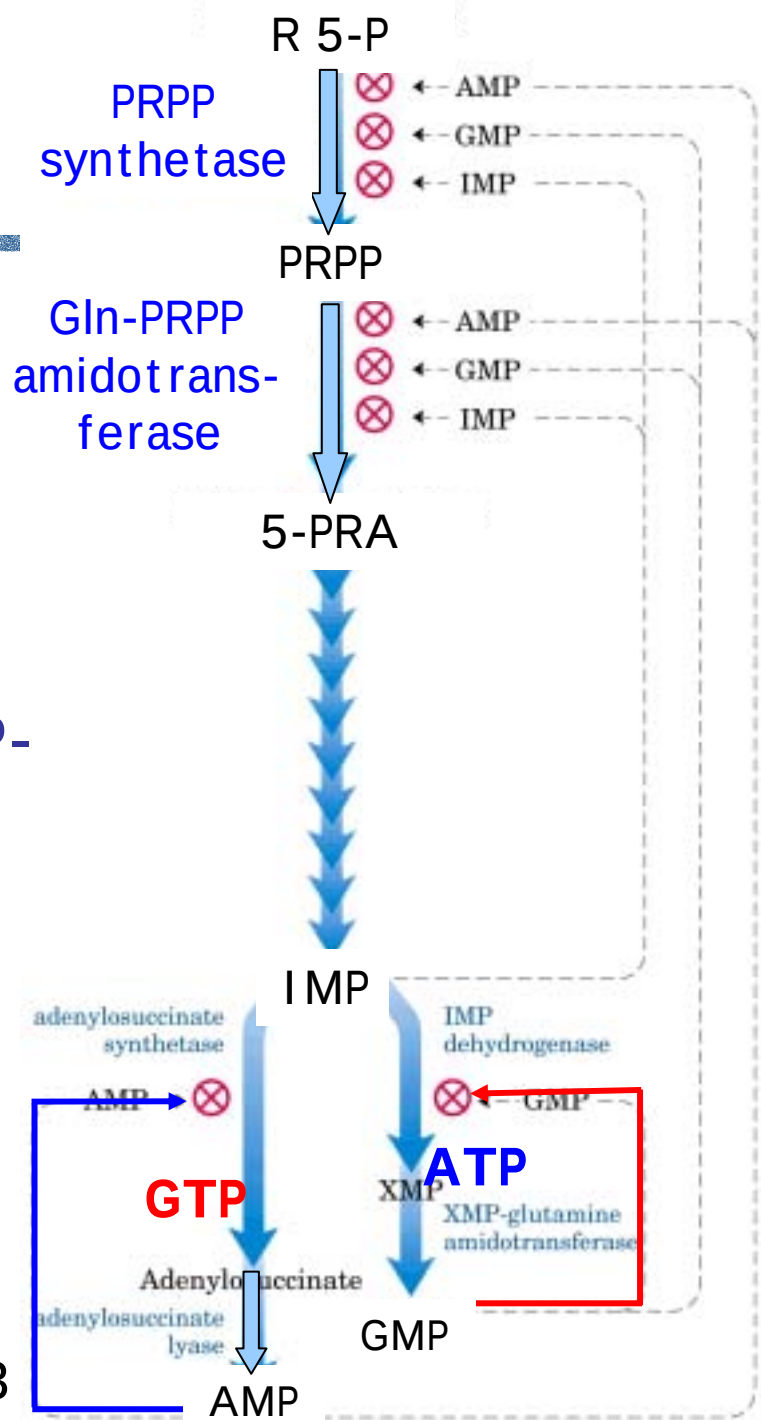
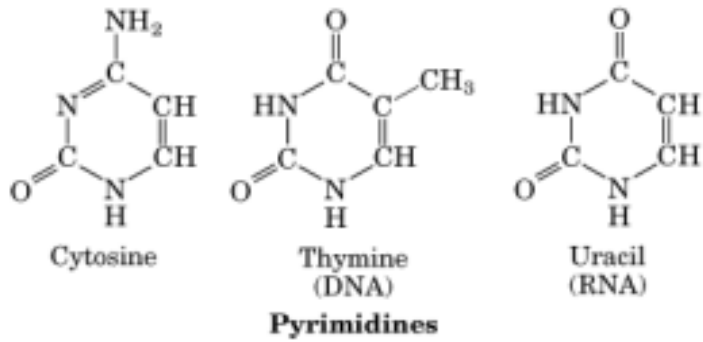


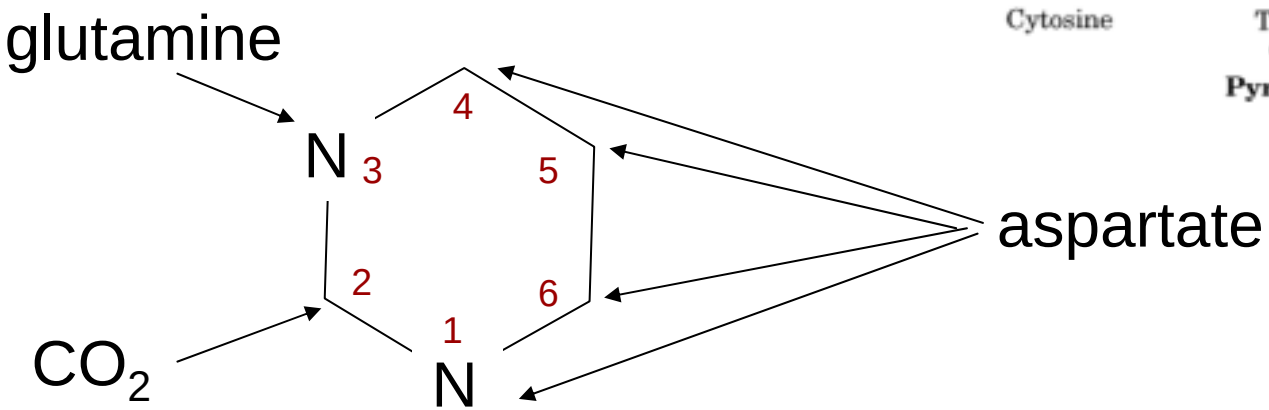
Fig 22-33

Pyrimidine synthesis (I)

p. 853-854

- U (UMP), C (CMP), T (dTMP)
- The ring (orotate) structure is *synthesized first, then attached to PRPP*. (Fig 22-34, center)



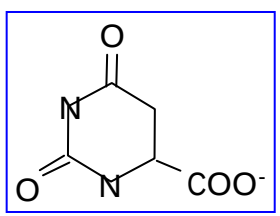


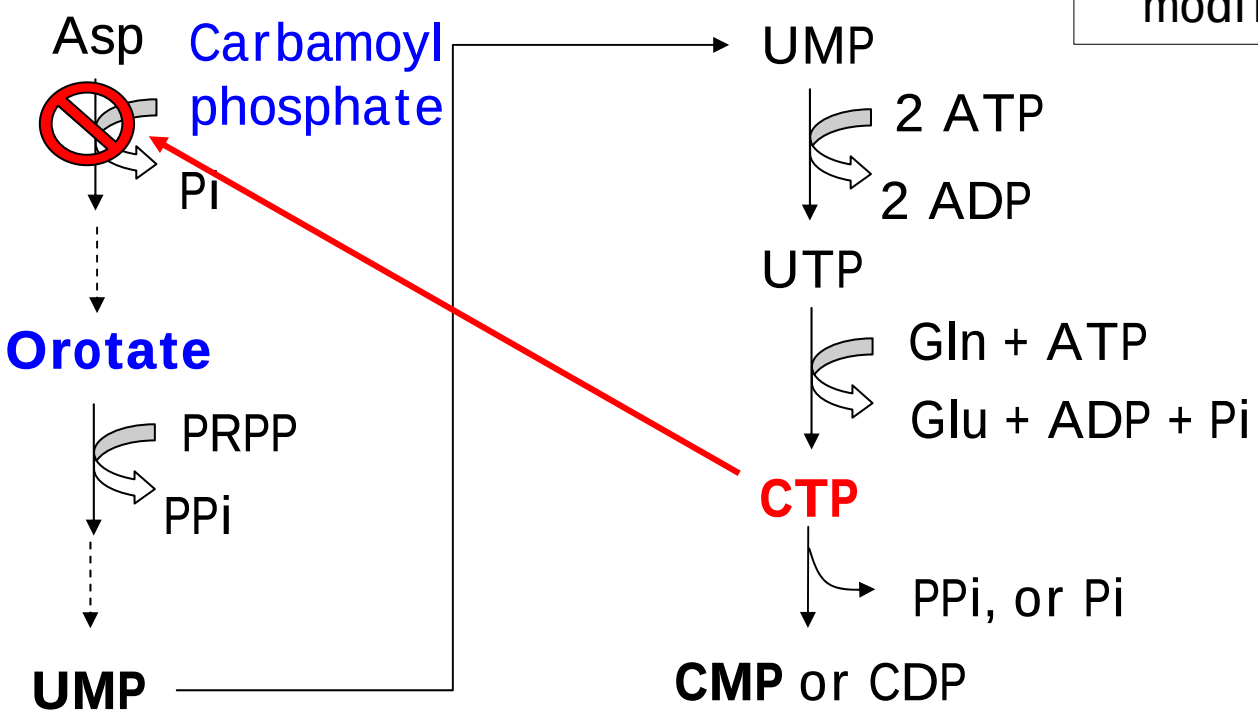
Source of the atoms of the pyrimidine ring.

Pyrimidine synthesis (II)

- Ribonucleotides: U, C
  - ✓ **Carbamoyl phosphate**, aspartate → → → orotate
  - ✓ Orotate + PRPP → → UMP
  - ✓ UMP → UTP + Gln → CTP → CDP, CMP
  - ✓ Regulated by feedback inhibition
    - Carbamoyl phosphate synthetase II (cytosolic isoform)

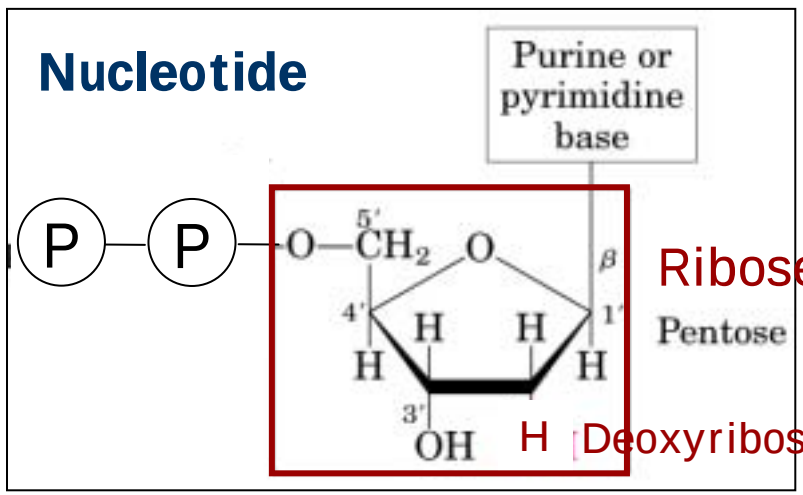
Fig 22-34 modified





Deoxyribonucleotide synthesis

- Precursors: ribonucleotides p. 856
  - ✓ Reduction only occur at the level of ribonucleoside diphosphate by ribonucleotide reductase
  - ✓ AMP → ADP → dADP → dAMP
  - ✓ GMP → GDP → dGDP → dGMP
  - ✓ CMP → CDP → dCDP → dCMP
  - ✓ UMP → UDP → dUDP → ? → dTMP



Synthesis of dTMP

- Thymidylate (dTMP) is derived from dUMP
  - ✓ Thymidylate synthase
    - Fluorouracil → FdUMP (mechanism-based inhibitor)
  - ✓ Dihydrofolate reductase
    - Methotrexate (competitive inhibitor)
    - Aminopterin
    - Fig 22-42, 22-47, 22-48

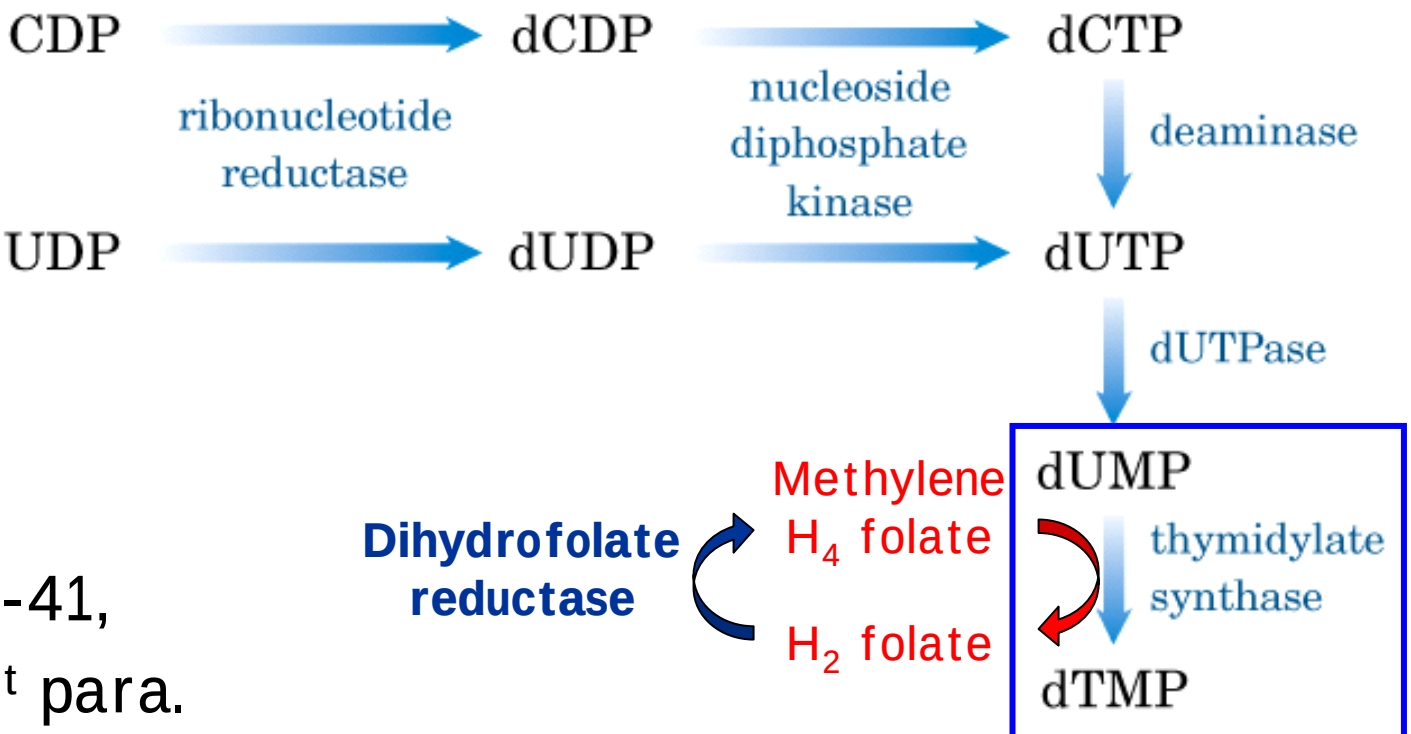


Fig 22-41,
p. 860 1st para.

Nucleotide salvage (p. 862)

- Purine salvage
  - ✓ One-step reaction
  - ✓ The purine bases (adenine, guanine) + PRPP → AMP, GMP
- Pyrimidine salvage
  - ✓ Two-step reaction
  - ✓ The pyrimidine bases (uracil, cytocine) + ribose → nucleosides (uridine, cytidine)
  - ✓ Nucleosides (uridine, cytidine) + Pi → nucleotides (UMP, CMP)

Nucleotide degradation

p. 861

- Release bases can be salvaged for reuse
- Pyrimidine degradation
  - ✓ NH_4^+ → urea
  - ✓ Produce all soluble compounds (Fig 22-44).
  - ✓ β-aminoisobutyrate, methylmalonylsemialdehyde (intermediate of Val catabolism)
- Purine degradation
  - ✓ Uric acid (low solubility)
    - Gout
    - Allopurinol (xanthine oxidase inhibitor)

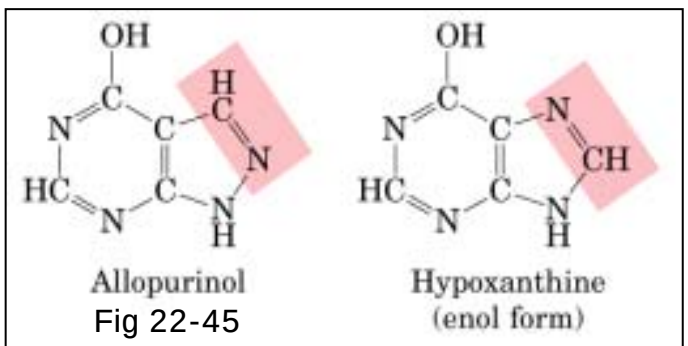
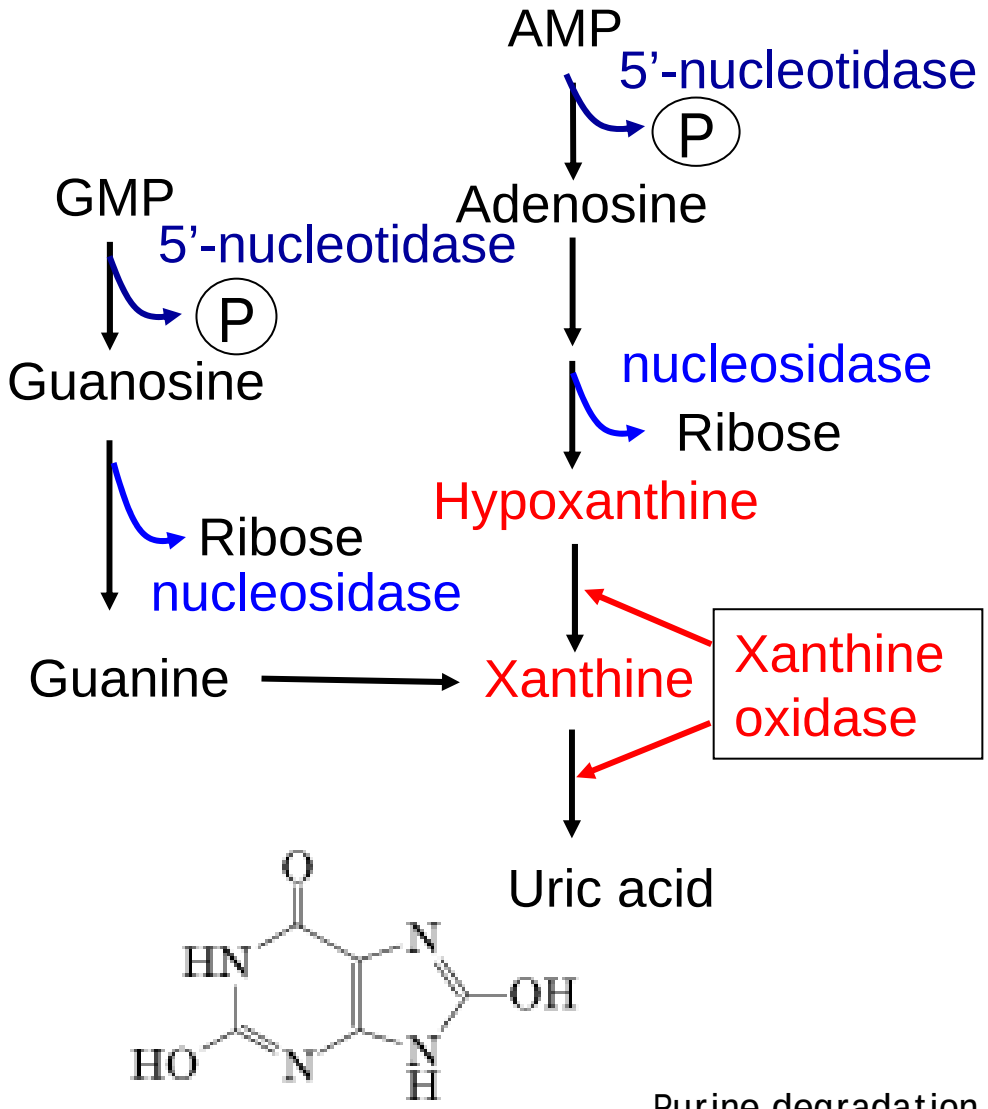


Fig 22-45



Purine degradation
Fig 22-43 left modified

Inhibitors and anticancer drugs

- Growing cells need to synthesize both DNA and RNA.
  - ✓ Drugs inhibiting nucleotide biosynthesis affect not only tumor cells but normal ones as well.
    - Side effects of cancer chemotherapy
    - Stem cells: require DNA and RNA synthesis
    - Inhibits the formation of erythrocytes, lymphocytes, cells of the intestinal epithelium, and hair-forming cells.
- Most tumor cells possess a more active salvage pathway than do normal cells.
  - ✓ Drugs entering metabolism via the salvage pathways obtain a higher conc. in tumor cells and have a therapeutic advantage.
    - Gln analogs → inhibit glutamine amidotransferases
      - Azaserine
      - Acivicin

p. 863