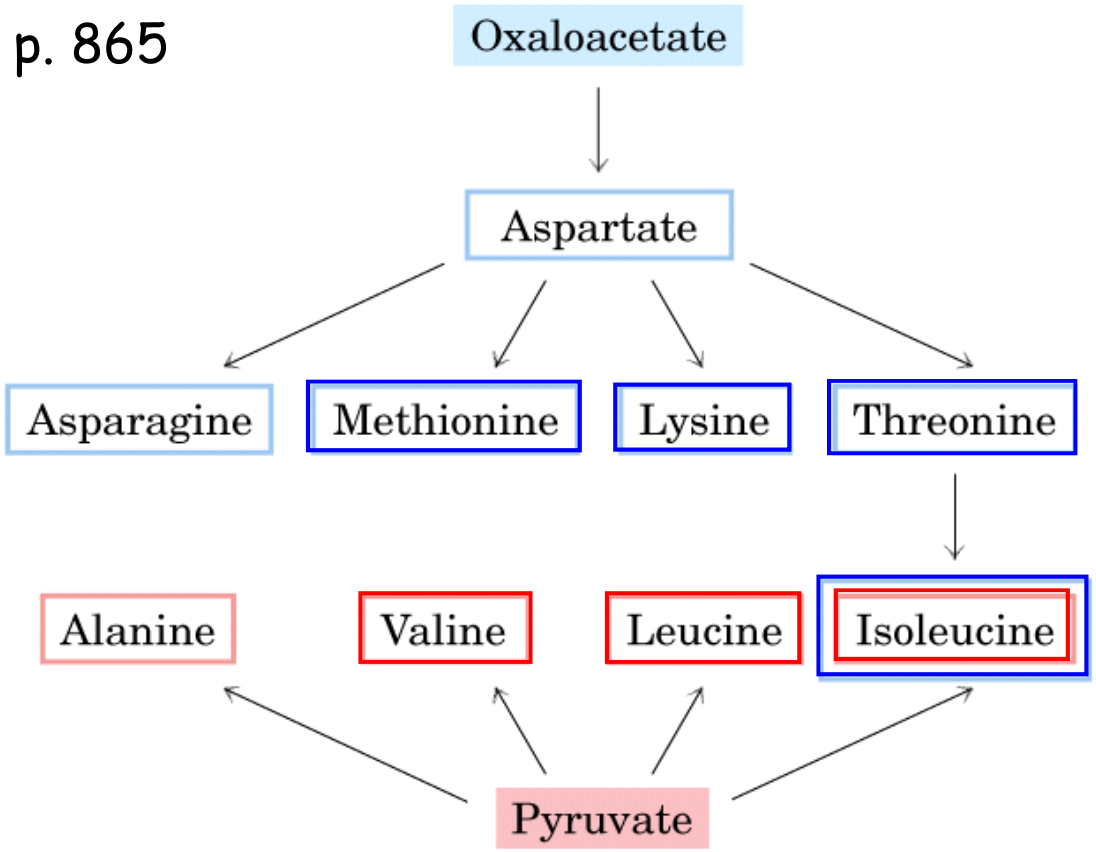
Supplement for MD

Coming back to the essentials …

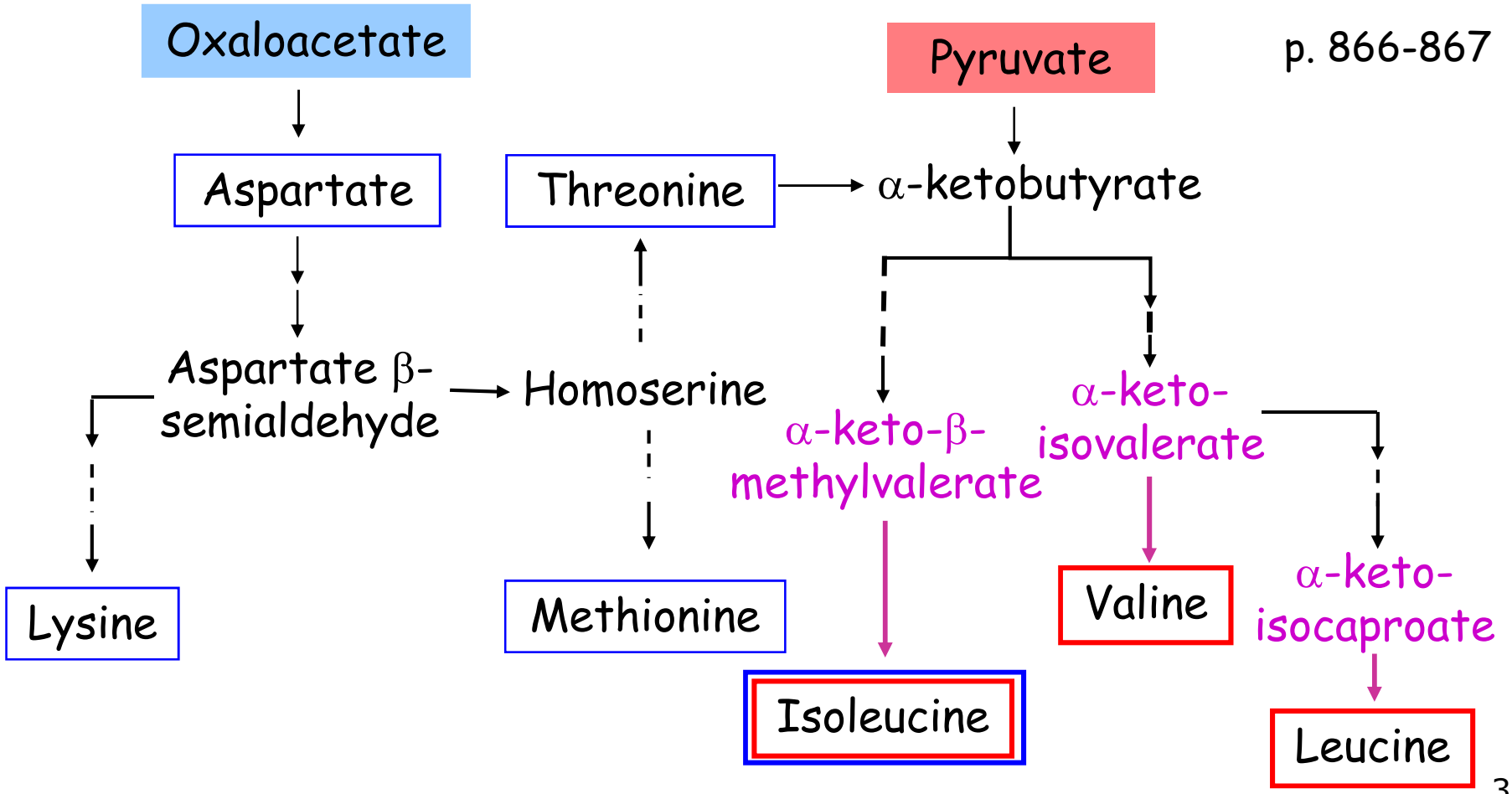
- From oxaloacetate and pyruvate
  - ✓6 essential a.a. (Fig 22-15, from bacteria)

p. 865



From OAA and pyruvate

- In bacteria (Fig 22-15 simplified)



p. 866-867

Defect in NH_4^+ removal

- Life threatening !!
- Clinical symptoms:
  - ✓ Increase [NH_4^+] in blood and urine
  - ✓ Nausea and illness after ingestion of proteins
  - ✓ Gradual mental retardation if not treated
- Treatment Low-protein diets
  - ✓ Treatments (e.g. Fig 18-13)
    - Aromatic acids benzoate + Gly → hippurate
    - Phenylacetate + Gln → phenylacetylglutamine
    - Reduce blood NH_4^+
  - ✓ Supplemented with mixtures of α-keto acids
    - From Concepts in Biochemistry, 2nd ed., p.541
    - Pick up excess NH_4^+
    - Can be converted to essential a.a.
    - α-keto-β-methylvalerate, α-ketoisovalerate, α-ketoisocaproate
    - (Ile) (Val) (Leu)

Heme biosynthesis

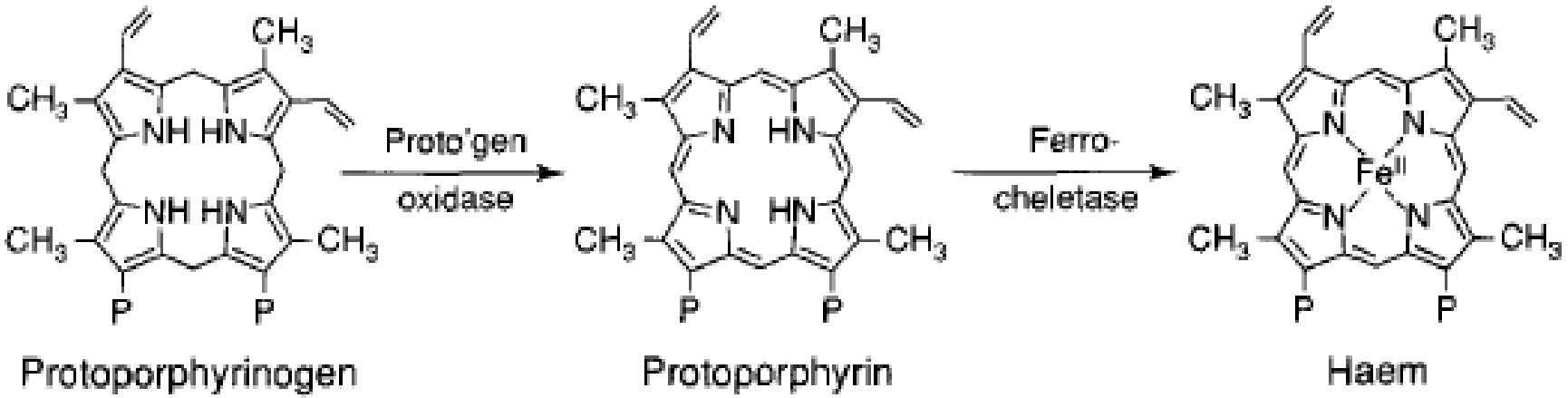
- Fig. 22-23a, 22-24
- TIBS 21 – June 1996
- Harper's 26th ed. Ch32

- 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



George III

- Acute intermittent porphyria (AIP)
- Box 22-1, p.857

喬治三世

生於1738年，1760年繼位，1820年殁

喬治三世是漢諾威諸君主中第一位在英國出生的。1760年，他的祖父喬治二世辭世後他繼承了王位，並很快對國事樂此不疲。與他的兩位先王不一樣，他認為自己是一個英格蘭人，臣民對他簡樸而直截了當的作風也深為愛戴。他晚年病體纏身，苦不堪言，1811年，他的兒子被封為攝政親王。他在位時間很長，經歷了翻天覆地的變化，整個時期現稱為"工業革命"；不過人們一提起他，首先想到的是1783年美國殖民地的丟失。

"農夫喬治"

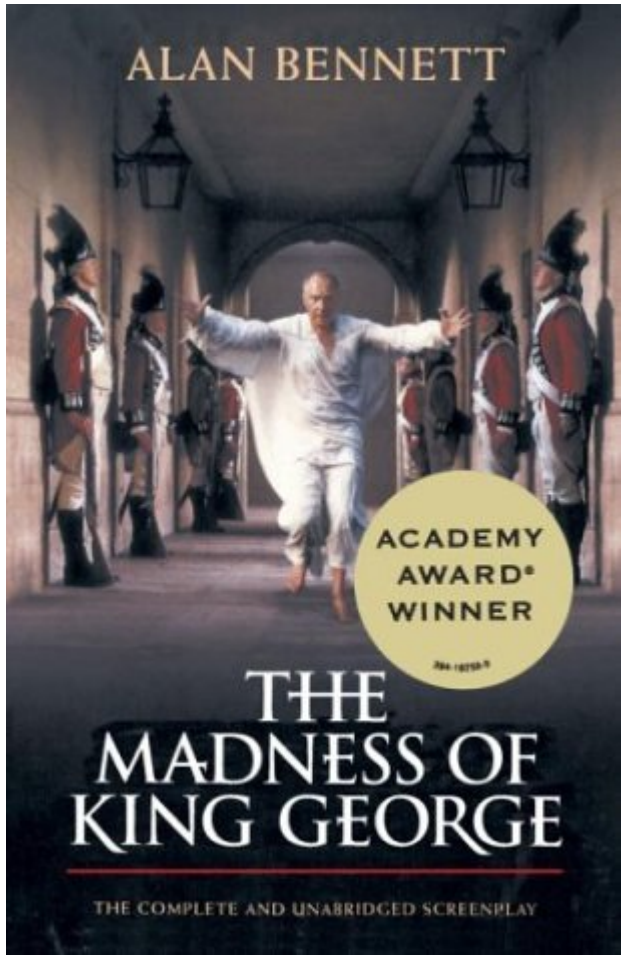
喬治一貫認為自己是一個平常人。他不辭勞苦，對朝政極其用心。他年輕的時候，對[illegible]關注，喜歡[illegible]夫交談，喬治"的綽號。

精神病

1788年起，喬治患了周期性精神恍惚症，被關起來。但是現代研究表明，他沒有發瘋，只是患了卟啉病。

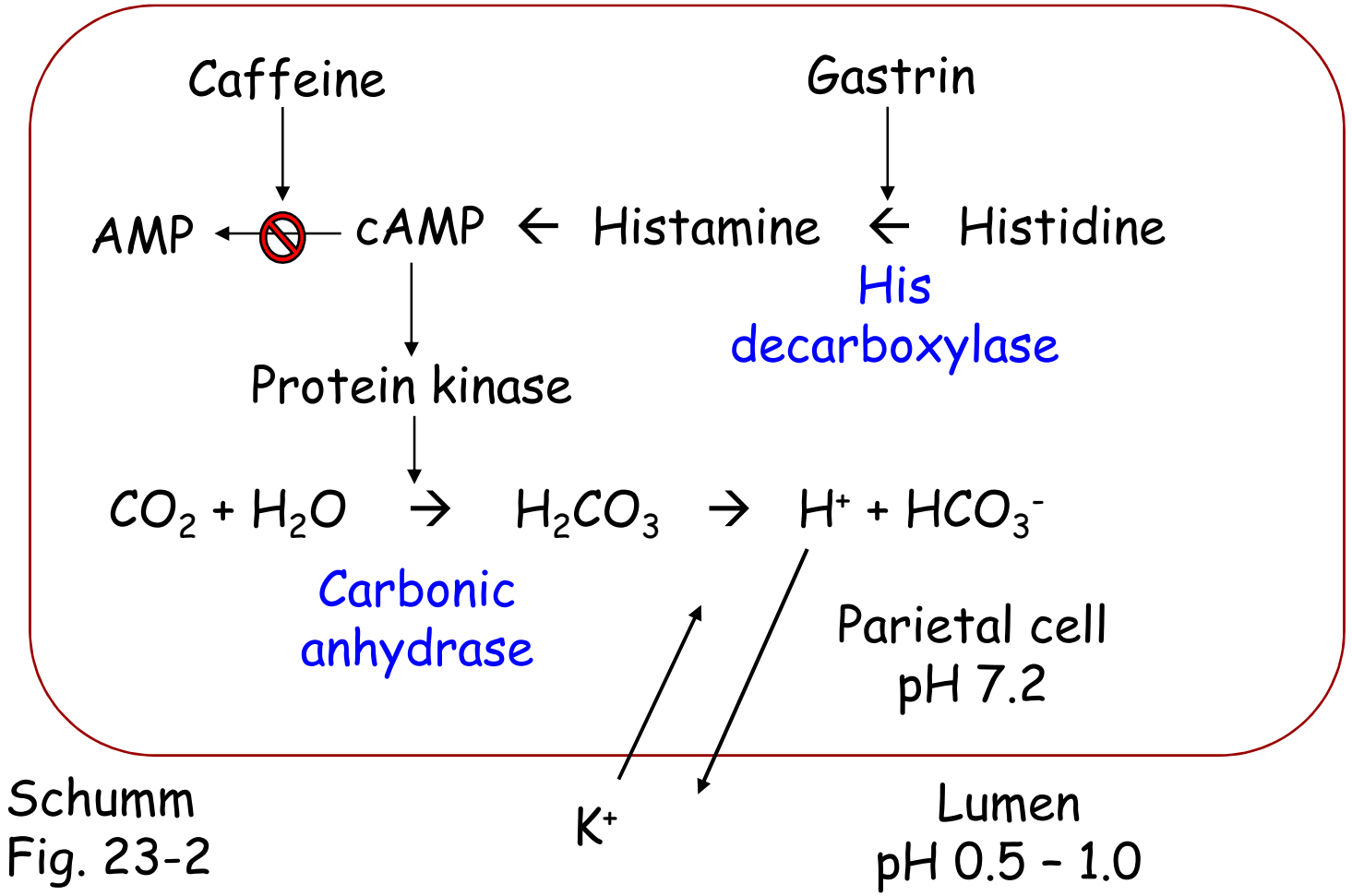
More on porphyrin …

- TIBS 21 – June 1996
  - ✓ The Madness business of King George III and porphyria
- Scientific American: Dec. 16, 2002
  - ✓ Born to the purple: the story of porphyria
  - ✓ New light on medicine [Therapy]
- Harper's 26th ed. Ch32
  - ✓ Only 16 B5 pages…



Gastric acid (HCl) secretion

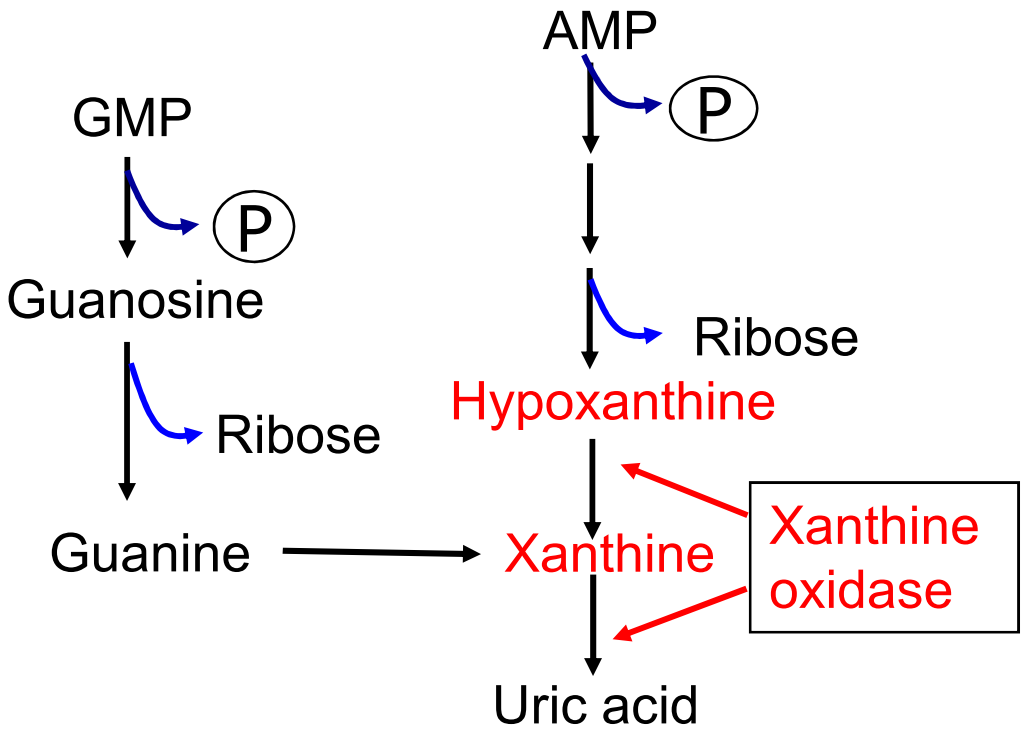
- H^+ is produced by the parietal cells of the stomach



Schumm Fig. 23-2

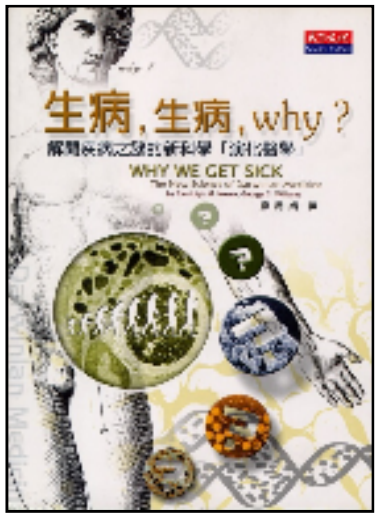
Problem 16 (Ch 22), p.898

- Allopurinol is used to treat chronic gout
  - ✓ Patients treated with allopurinol sometimes develop xanthine stones in the kidneys
  - ✓ The incidence of kidney damage is much lower than in untreated gout.
- Solubility in urine
  - ✓ Uric acid: 0.15 g/L
  - ✓ Xanthine: 0.05 g/L
  - ✓ Hypoxanthine: 1.4 g/L



生病，生病，Why？

- Why we get sick？
  - ✓ The new science of Darwinian medicine
- 演化醫學
  - ✓ Uric acid
  - ✓ Antioxidant
  - ✓ Aging
  - ✓ Gout
  - ✓ Longevity



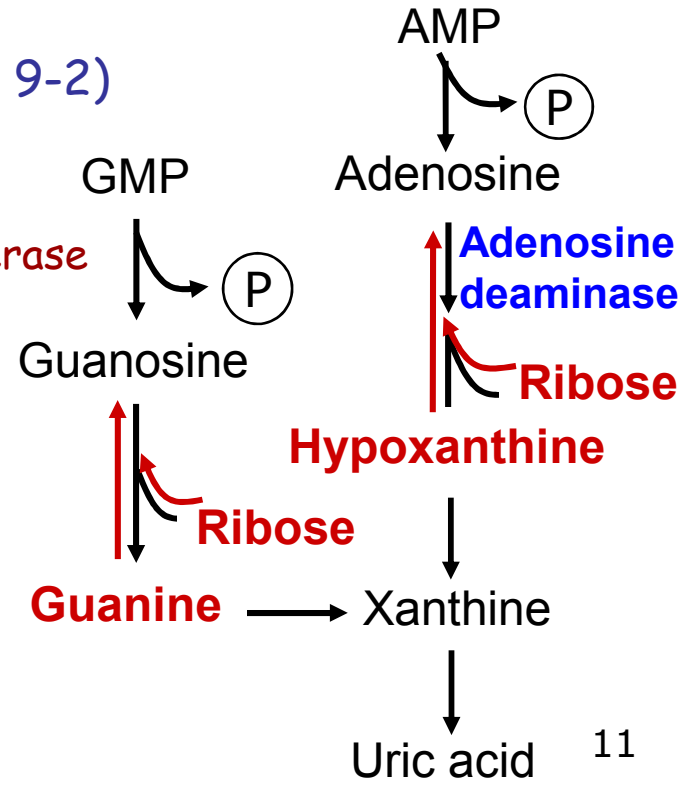
Purine catabolism
Fig 22-45 right

Uric acid	Primates, birds, reptiles, insects
↓	
Allantoin	Most mammals
↓	
Allantoate	Bony fishes
↓	
Urea	Amphibians, cartilaginous fishes
↓	
NH_4^+	Marine invertebrates

Genetic defect

P. 893

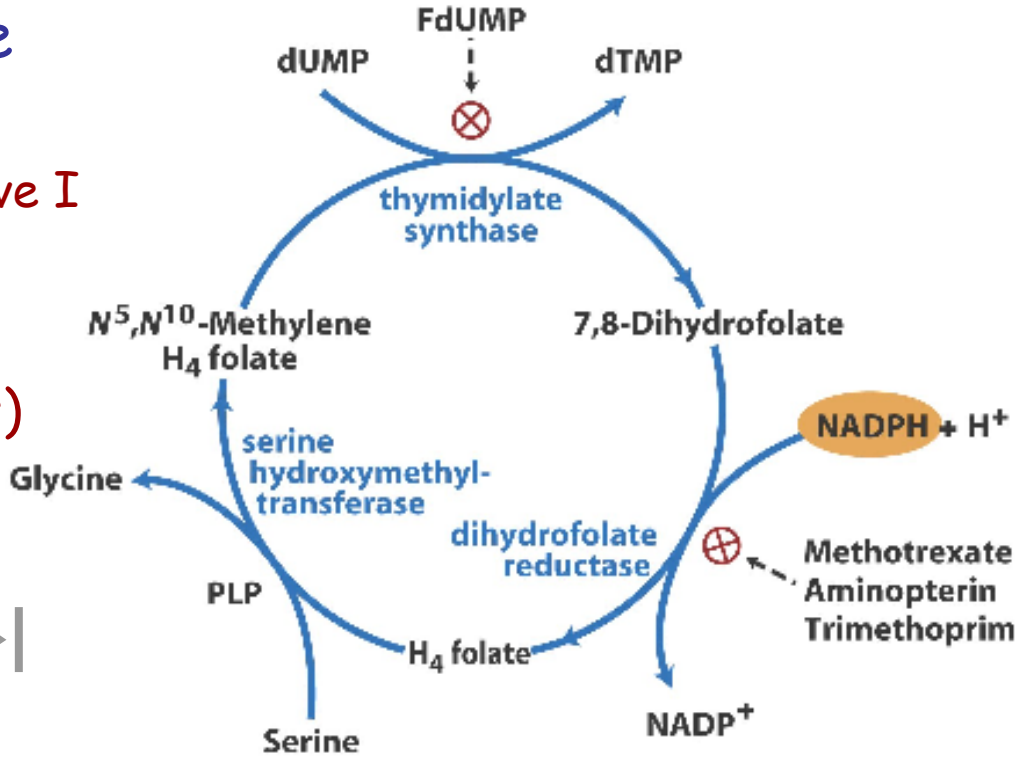
- Adenosine deaminase (ADA) deficiency
  - ✓ 100-fold increase in the cellular [dATP]
  - ✓ Inhibit ribonucleotide reductase (Fig 22-42)
  - ✓ A general deficiency of other dNTPs
  - ✓ T and B lymphocytes do not develop properly
  - ✓ Severe immunodeficiency disease
  - ✓ A sterile "bubble" environment
  - ✓ Targets for human gene therapy trials (Box 9-2)
- Lesch-Nyhan syndrome
  - ✓ Deficiency of purine salvage enzyme
    - Hypoxanthine-guanine phosphoribosyltransferase
  - ✓ [PRPP] ↑ and de novo synthesis [purine] ↑
  - ✓ [uric acid] ↑
  - ✓ Gout-like tissue damage
  - ✓ Damage to CNS



Targets of chemotherapy

- The only cellular pathway for dT synthesis
  - ✓ Thymidylate synthase
    - Fluorouracil → FdUMP (mechanism-based inhibitor)
  - ✓ Dihydrofolate reductase
    - Methotrexate
      - Folate analog, competitive I
    - Aminopterin
      - Competitive I
    - Trimethoprim (antibiotics)
      - Higher affinity for bacterial enzyme

Fig 22-49



P. 894-896