Nucleic Acid Metabolism

1. Describe the sources of carbon and nitrogen atoms of purine nucleotide. Write the pathway for de novo purine synthesis. Add a note on its regulation and inhibitors.

Definition: Purine synthesis involves sequential addition of carbon and nitrogen atoms to ribose 5′-phosphate to generate nine-membered ring (Fig. 14.1). Sources of carbon and nitrogen atoms of purine nucleotide are given in the Table 14.1.

Site: Liver.

Subcellular site: Cytosol.

Starting material: Ribose 5′-phosphate.

End product: Inosine monophosphate (IMP).

Sources of different atoms of purine ring

Atoms	Sources
N_1	Aspartate
C_2, C_8	N_{10} tetrahydrofolate
N_3, N_9	Glutamine
C_4, C_5, N_7	Glycine
C_6	CO_2

Regulators and inhibitors of purine synthesis are explained in Tables 14.2 and 14.3 respectively.

Regulation of purine synthesis		
Enzyme	**Inhibitor**	
Stimulator PRPP* synthetase	AMP‡, GMP§	–
Amidotransferase	GMP, AMP	–
Adenylosuccinate synthetase	AMP	GTP‖
IMP† dehydrogenase	GMP	–

*PRPP, phosphoribosyl pyrophosphate; †IMP, inosine monophosphate; ‡AMP, adenosine monophosphate; §GMP, guanosine monophosphate; ‖GTP, guanosine triphosphate.

Inhibitors of purine synthesis	
Inhibitor	**Mechanism of action**
Sulfonamides	PABA* analogues block folate synthesis in microbes
6-mercaptopurine	Inhibits formation of AMP and GMP from IMP
Mycophenolic acid	Inhibits IMP† dehydrogenase (used to prevent graft rejection)
Methotrexate and	Inhibits dihydrofolate reductase, reduces availability of active folate blocks purine synthesis; it is used as an anticancer agent

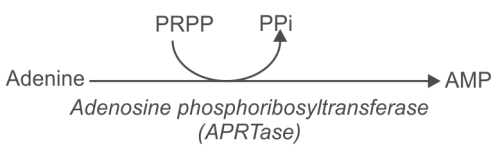
*PABA, para-aminobenzoic acid; †IMP, inosine monophosphate.

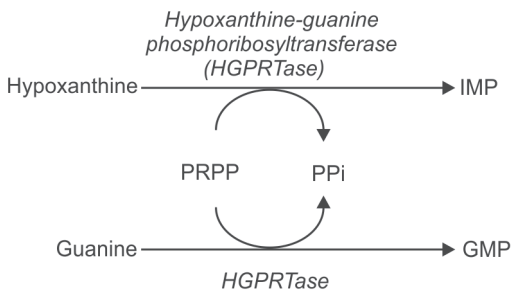
2. How are purine bases salvaged? Add a note on Lesch-Nyhan syndrome.

Definition: It involves conversion of purines, purine ribonucleosides and purine deoxyribonucleosides to corresponding mononucleotides.

Reactions:

i. Phosphoribosylation of free purines.





ii. Phosphorylation of purine ribonucleoside, e.g.

$$\text{Adenosine} + \text{ATP} \xrightarrow{\textit{Adenosine kinase}} \text{AMP} + \text{ADP}$$

Significance: This pathway is the source of nucleotides for erythrocytes and brain. As they lack amidotransferase, they cannot synthesize purines.

Lesch-Nyhan syndrome

Inheritance: X-linked.

Defect: Complete/partial absence of hypoxanthine-guanine phosphoribosyltransferase (HGPRTase).

Consequences

- Poor salvage of hypoxanthine and guanine leads to excessive uric acid formation
- ↓ HGPRTase → ↑ phosphoribosyl pyrophosphate (PRPP), ↓ GMP and ↓ IMP → ↑ de novo synthesis of purines; improper utilization + ↑ production of purines → ↑ degradation of purines → ↑ uric acid.

Clinical Features

- Hyperuricemia and gouty arthritis
- Urate stones
- Self-mutilation
- Mental retardation.

Treatment

Allopurinol (refer Question 3).

3. How is uric acid formed in the body? Add a note on gout.

Uric acid: It is the end product of purine catabolism (excreted in urine) (Fig. 14.2, p. 185).

Starting material: Purines.

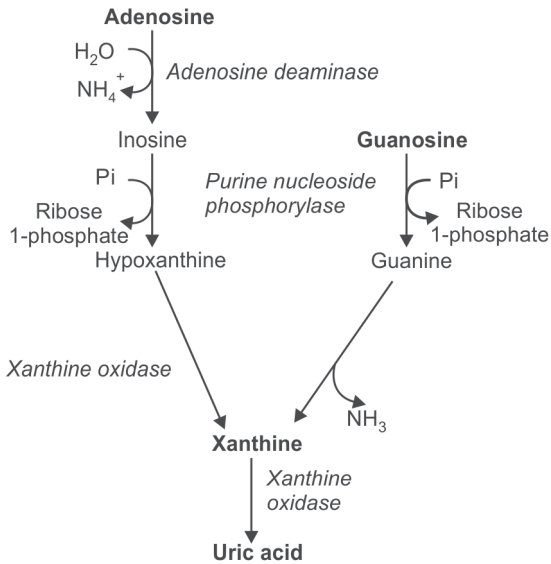
End product: Uric acid.

Gout: It is an acute inflammatory condition caused by increased production and deposition of monosodium urate crystals in the joints and soft tissues.

Causes of Primary Gout [MN: GASP]

- **G**lucose-6-phosphatase deficiency (von Gierke disease)
- **A**midotransferase not responding to feedback inhibition

- **S**alvage pathway defect (Lesch-Nyhan syndrome)
- **P**RPP synthetase not under regulation.



Steps of uric acid synthesis

Causes of Secondary Gout [MN: CRP]

- **C**ancer
- **R**enal failure
- **P**soriasis.

Clinical Features

Red, tender, swollen joint in feet and hands; ↑ uric acid → sodium urate crystals deposited in the joints → joint inflammation → gouty arthritis.

Treatment

- Allopurinol: Inhibits xanthine oxidase → ↓ uric acid production
- Probenecid → ↑ excretion of uric acid in the urine
- Non-steroidal anti-inflammatory drugs, steroids and colchicine: ↓ pain and inflammation.

4. Describe the causes and features of hyperuricemia. How is it treated?

Definition: ↑ levels of uric acid in the blood (normal level: 4–7 mg/dL).

Causes, features and treatment (refer Question 3).

5. Describe the synthesis of pyrimidine ring. Add a note on its regulation and associated disorders.

Definition: Sequential addition of nitrogen and carbon atoms to form a six-membered pyrimidine ring (Table 14.4 and Fig. 14.3, p. 187).

Sources of different atoms of pyrimidine ring

Atoms	Sources
N_3, C_2	Carbamoyl phosphate
C_4, C_5, C_6, N_1	Aspartic acid

Site: Cytosol and mitochondria.

Disorders of pyrimidine metabolism

Orotic aciduria: Refer Question 7.

6. Write a note on severe combined immunodeficiency (SCID).

Inheritance: Autosomal recessive.

Cause: Adenosine deaminase and purine nucleoside phosphorylase deficiency → ↑ dATP and dGTP → (–) ribonucleotide reductase → ↓ DNA synthesis → decreased proliferation of B and T lymphocytes → severe immune deficiency [(–) = inhibition].

Clinical features: Repeated life-threatening infections.

Treatment: Bone marrow transplantation and gene therapy.

7. Write briefly about orotic aciduria.

Definition: ↑ excretion of orotic acid in the urine.

Inheritance: Autosomal recessive.

Types and causes

- **Type I orotic aciduria:** Deficiency of enzyme orotate phosphoribosyltransferase and orotidylate decarboxylase
- **Type II orotic aciduria:** Deficiency of orotidylate decarboxylase.

Clinical features: ↑ orotic acid in urine, megaloblastic anemia and failure to thrive.

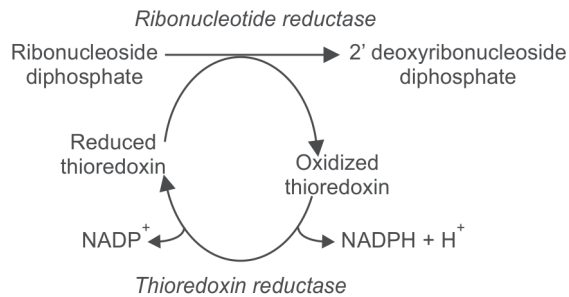
Treatment: Oral uridine/cytidine → (–) enzymes in the pyrimidine synthesis pathway.

- **Urea cycle disorder:** Ornithine transcarbamoylase deficiency (type II hyperammonemia) → ↑ carbamoyl phosphate → enters cytosol → ↑ orotic acid production
- **Allopurinol:** Competes with orotate phosphoribosyltransferase to inhibit the phosphoribosylation of orotate, which may lead to orotic aciduria.

8. Explain the synthesis of deoxyribonucleotides.

Purine and pyrimidine ribonucleotides undergo reduction at the 2′ carbon to give rise to respective deoxyribonucleotides in the presence of enzyme ribonucleotide reductase complex.

- Site: Actively dividing cells
- Requirements: Thioredoxin, thioredoxin reductase, NADPH
- General reaction:



Specific Reactions

CDP → 2′dCDP → 2′dCTP
UDP → 2′dUDP → 2′dTTP
GDP → 2′dGDP → 2′dGTP
ADP → 2′dADP → 2′dATP

Key Points

Folic acid: It is required for purine synthesis. Folate deficiency → impaired DNA synthesis → megaloblastic anemia and neural tube defects.

Methotrexate: (–) dihydrofolate reductase → used as an anticancer agent.

5'-fluorouracil: (–) thymidylate synthase → anticancer agent.

Lesch-Nyhan syndrome: X-linked recessive disorder with defect in hypoxanthine-guanine phosphoribosyltransferase (HGPRTase).

Normal plasma uric acid level: 3–7 mg/dL.

Gout: It is an acute inflammatory condition caused by increased production and deposition of monosodium urate crystals in the joints and soft tissues.

Allopurinol (competitive and also suicide inhibitor): Inhibits xanthine oxidase, thereby decreases the production of uric acid.

Severe combined immunodeficiency (SCID): Autosomal recessive disorder caused due to deficiency of adenosine deaminase and purine nucleoside phosphorylase, leading to dysfunctional T and B lymphocytes.

Carbamoyl phosphate synthetase II (CPS II): It is a cytosolic enzyme required for pyrimidine synthesis.

Orotic aciduria: Autosomal recessive disorder $\rightarrow \uparrow$ orotic acid in urine; due to deficiency of enzyme orotate phosphoribosyltransferase and orotidylate decarboxylase.