# Nucleic acid metabolism

Nucleic acid metabolism is the process by which nucleic acids (DNA and RNA) are synthesized and degraded. Nucleic acids are polymers of nucleotides. Nucleotide synthesis is an anabolic mechanism generally involving the chemical reaction of phosphate, pentose sugar, and a nitrogenous base. Destruction of nucleic acid is a catabolic reaction. Additionally, parts of the nucleotides or nucleobases can be salvaged to recreate new nucleotides. Both synthesis and degradation reactions require enzymes to facilitate the event. Defects or deficiencies in these enzymes can lead to a variety of diseases.

Nucleotides are organic molecules that serve as the monomer units for forming the nucleic acid polymers deoxyribonucleic acid(DNA) and ribonucleic acid (RNA), both of which are essential biomolecules within all life-forms on Earth. Nucleotides are the building blocks of nucleic acids; they are composed of three subunit molecules: a nitrogenous base (also known as nucleobase), a five-carbon sugar (ribose or deoxyribose), and at least one phosphate group.

A **nucleoside** is a nitrogenous base and a 5-carbon sugar. Thus a nucleoside plus a phosphate group yields a nucleotide.
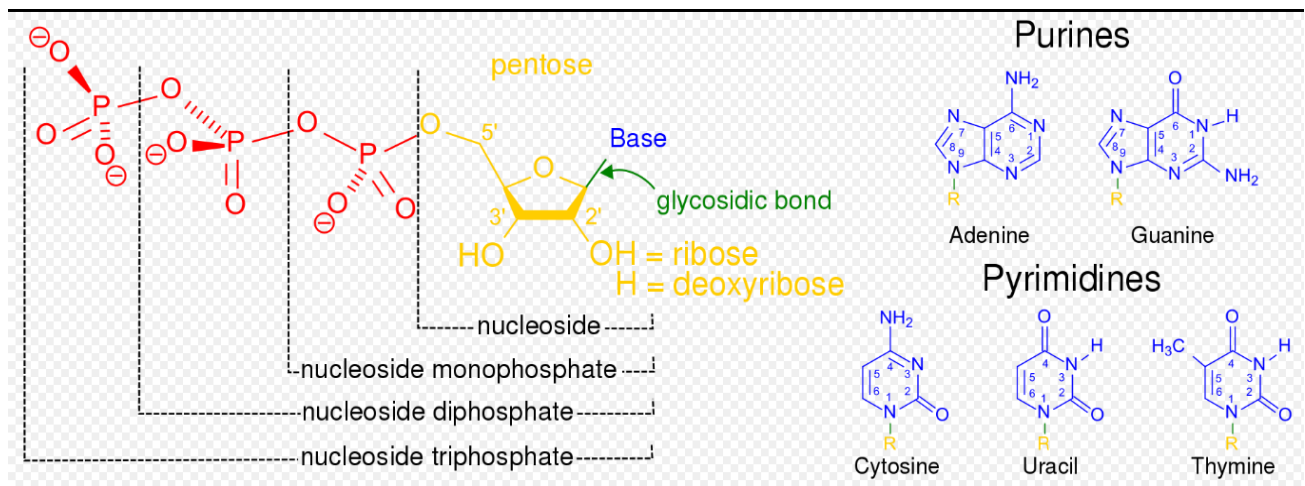
PURINES & PYRIMIDINES ARE DIETARILY NONESSENTIAL:

Human tissues can synthesize purines and pyrimidines from intermediates. Ingested nucleic acids and nucleotides, which therefore are dietary nonessential, are degraded in the intestinal tract to mononucleotides, which may be absorbed or converted to purine and pyrimidine bases. The purine bases are then oxidized to uric acid, which may be absorbed and excreted in the urine.

BIOSYNTHESIS OF PURINE NUCLEOTIDES

Purine and pyrimidine nucleotides are synthesized in vivo at rates consistent with physiologic need. Intracellular mechanisms sense and regulate the pool sizes of nucleotide triphosphates, Three processes contribute to purine nucleotide biosynthesis. These are, in order of decreasing importance:

(1) synthesis from intermediates (synthesis de novo), (2) phosphoribosylation of purines, and (3) phosphorylation of purine nucleosides.
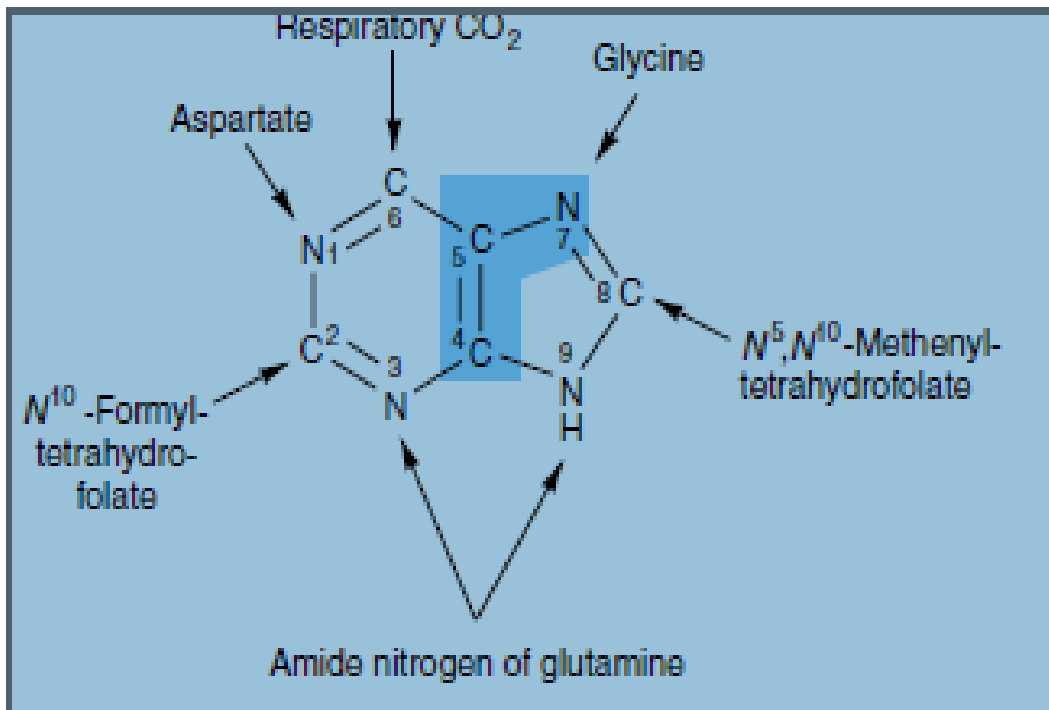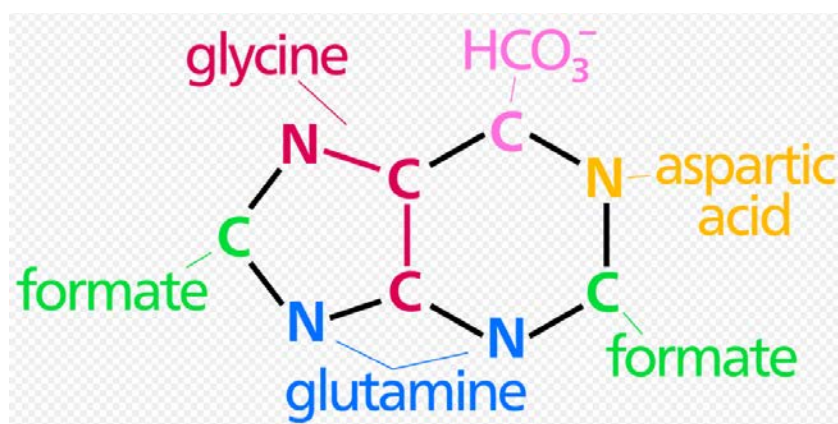

Fig 2. A)) Purine biosynthesis

Fig 2. b)) Purine biosynthesis

"SALVAGE REACTIONS" CONVERT PURINES & THEIR NUCLEOSIDES TO MONONUCLEOTIDES

Conversion of purines, their ribonucleo**sides**, and their deoxyribonucleo**sides** to mononucleo**tides** involves so called "salvage reactions" that require far less energy than de novo synthesis. The more important mechanism involves:

1- phosphoribosylation by PRPP(5-phosphoribosyl -1-pyrophosphate) of a free purine (Pu) to form a purine 5′-mononucleotide.

2- **Synthesis of 5-phosphoribosylamine:** Synthesis of 5'-phosphoribosylamine from PRPP and glutamine**.**

Synthesis of inosine monophosphate (IMP), the "parent" **purine nucleotide** :
The next nine steps in purine nucleotide biosynthesis leading to the synthesis of IMP, (whose base is hypoxanthine) are illustrated in source.
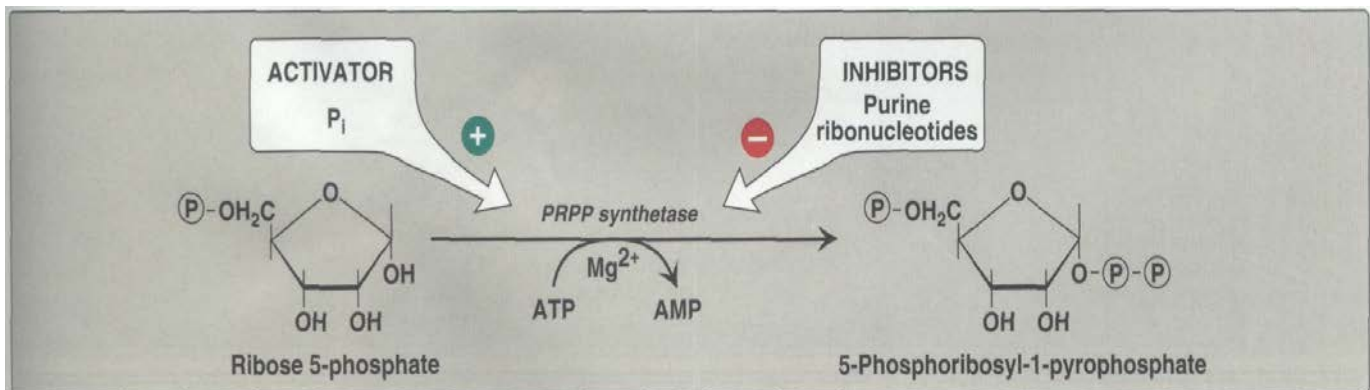

Figure 22.6
Synthesis of 5-phosphoribosyl-1-pyrophosphate (PRPP), showing the activator and inhibitors of the reaction.
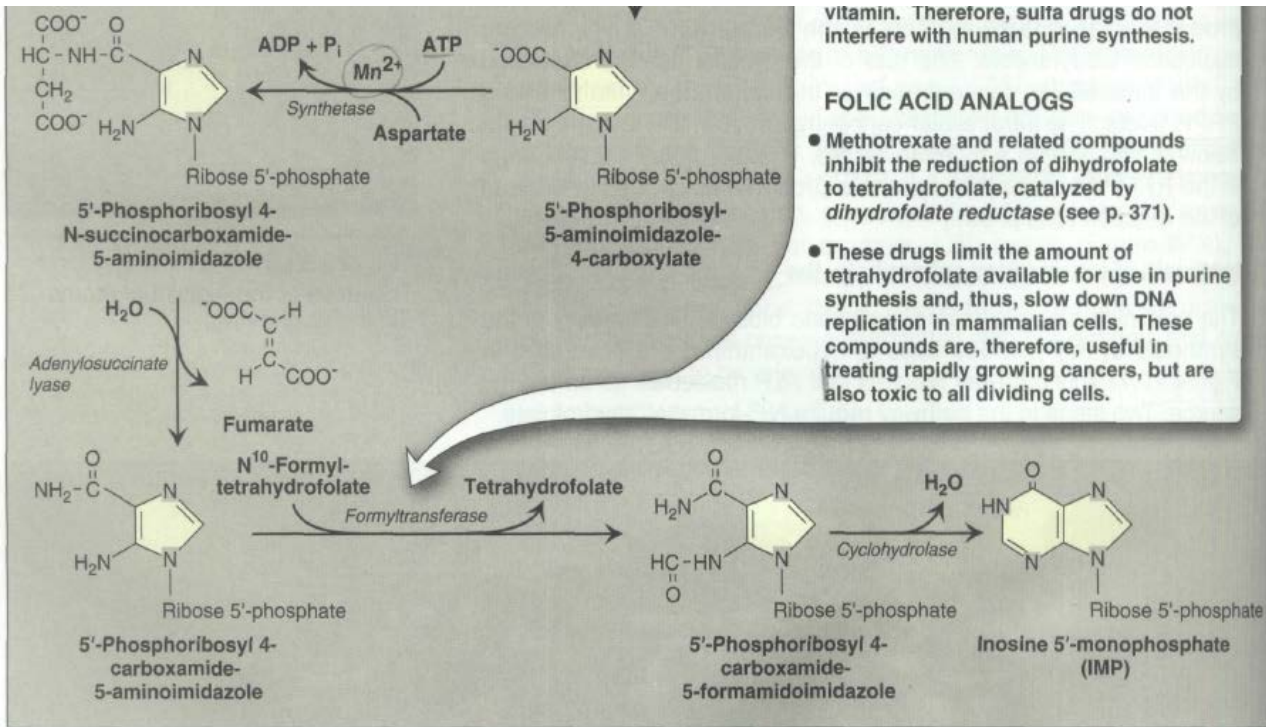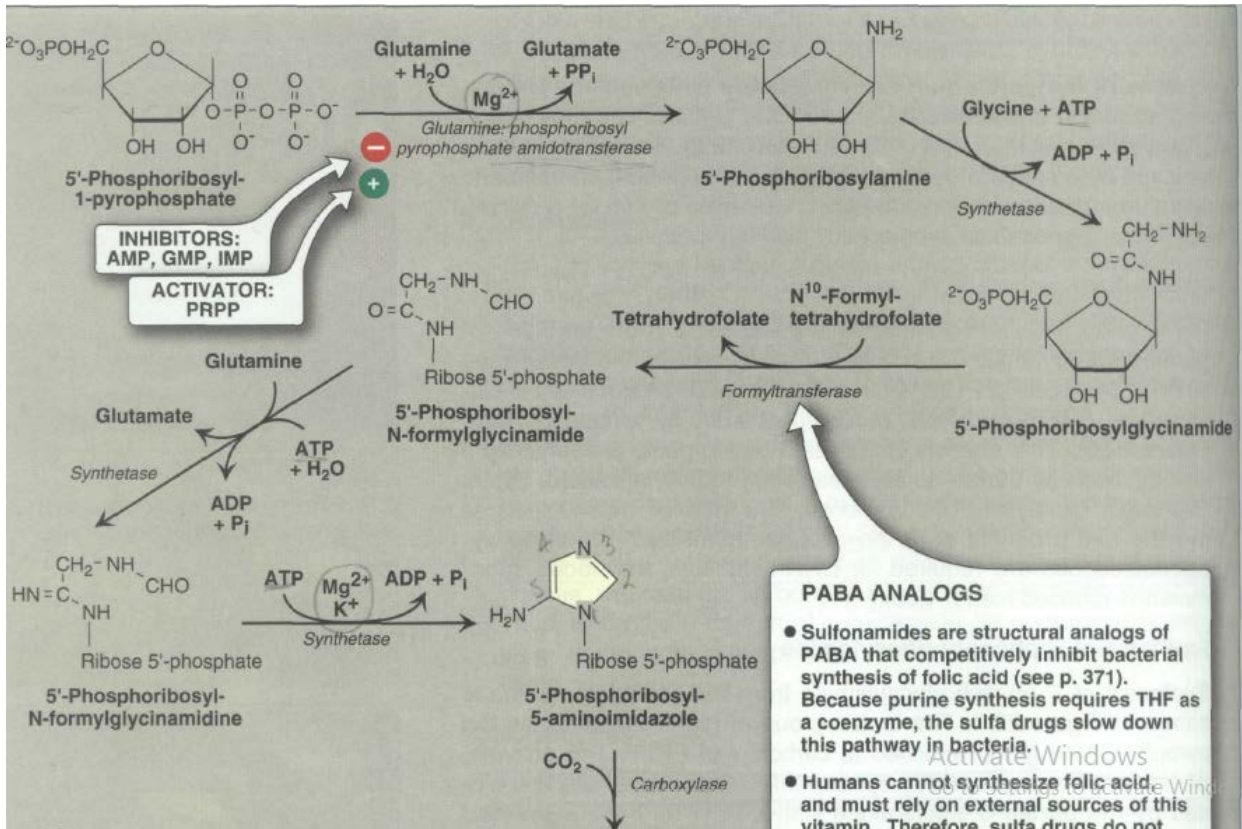
Figure (Synthesis of purine nucleotides)

$^{2-}O_3POH_2C$ O

OH   OH   O$^-$ O$^-$

O-P-O-P-O$^-$

5'-Phosphoribosyl-1-pyrophosphate

Glutamine + H$_2$O → **Glutamate + PP$_i$**

Mg^{2+}

Glutamine: phosphoribosyl pyrophosphate amidotransferase

⊖
⊕

INHIBITORS: AMP, GMP, IMP

ACTIVATOR: PRPP

$^{2-}O_3POH_2C$ O   NH$_2$

OH   OH

5'-Phosphoribosylamine

Glycine + ATP → **ADP + P$_i$**

Synthetase

CH$_2$-NH$_2$
O=C
NH

$^{2-}O_3POH_2C$ O

OH   OH

5'-Phosphoribosylglycinamide

Glutamine → **Glutamate**

Synthetase   ATP + H$_2$O → ADP + P$_i$

CH$_2$-NH
O=C   CHO
NH

Ribose 5'-phosphate

5'-Phosphoribosyl-N-formylglycinamide

Tetrahydrofolate   **N^{10}-Formyl-tetrahydrofolate**

Formyltransferase

CH$_2$-NH
HN=C   CHO
NH

Ribose 5'-phosphate

5'-Phosphoribosyl-N-formylglycinamidine

ATP Mg^{2+} K$^+$ **ADP + P$_i$**

Synthetase

N
H$_2$N   N

Ribose 5'-phosphate

5'-Phosphoribosyl-5-aminoimidazole

CO$_2$ *Carboxylase*

PABA ANALOGS

- Sulfonamides are structural analogs of PABA that competitively inhibit bacterial synthesis of folic acid (see p. 371). Because purine synthesis requires THF as a coenzyme, the sulfa drugs slow down this pathway in bacteria.
- Humans cannot synthesize folic acid and must rely on external sources of this vitamin. Therefore, sulfa drugs do not interfere with human purine synthesis.

FOLIC ACID ANALOGS

- Methotrexate and related compounds inhibit the reduction of dihydrofolate to tetrahydrofolate, catalyzed by *dihydrofolate reductase* (see p. 371).
- These drugs limit the amount of tetrahydrofolate available for use in purine synthesis and, thus, slow down DNA replication in mammalian cells. These compounds are, therefore, useful in treating rapidly growing cancers, but are also toxic to all dividing cells.

COO$^-$ O
HC-NH-C   N
CH$_2$
COO$^-$ H$_2$N   N

Ribose 5'-phosphate

5'-Phosphoribosyl 4-N-succinocarboxamide-5-aminoimidazole

ADP + P$_i$ Mn^{2+} **ATP**

Synthetase

Aspartate

$^-$OOC   N
H$_2$N   N

Ribose 5'-phosphate

5'-Phosphoribosyl-5-aminoimidazole-4-carboxylate

H$_2$O $^-$OOC   H
C=C
H   COO$^-$

Adenylosuccinate lyase

Fumarate

O
NH$_2$-C   N
H$_2$N   N

Ribose 5'-phosphate

5'-Phosphoribosyl 4-carboxamide-5-aminoimidazole

N^{10}-Formyl-tetrahydrofolate   **Tetrahydrofolate**

Formyltransferase

O
H$_2$N-C   N
HC-HN   N
O

Ribose 5'-phosphate

5'-Phosphoribosyl 4-carboxamide-5-formamidoimidazole

H$_2$O

Cyclohydrolase

O
HN   N
N   N

Ribose 5'-phosphate

Inosine 5'-monophosphate (IMP)

Figure 22.7
Synthesis of purine nucleotides, showing the inhibitory effect of some structural analogs.

4- Conversion of IMP to AMP and GMP

The conversion of IMP to either AMP or GMP uses a two-step, energy-requiring pathway (Figure 22.8). Note that the synthesis of AMP requires GTP as an energy source, whereas the synthesis of GMP requires ATP.
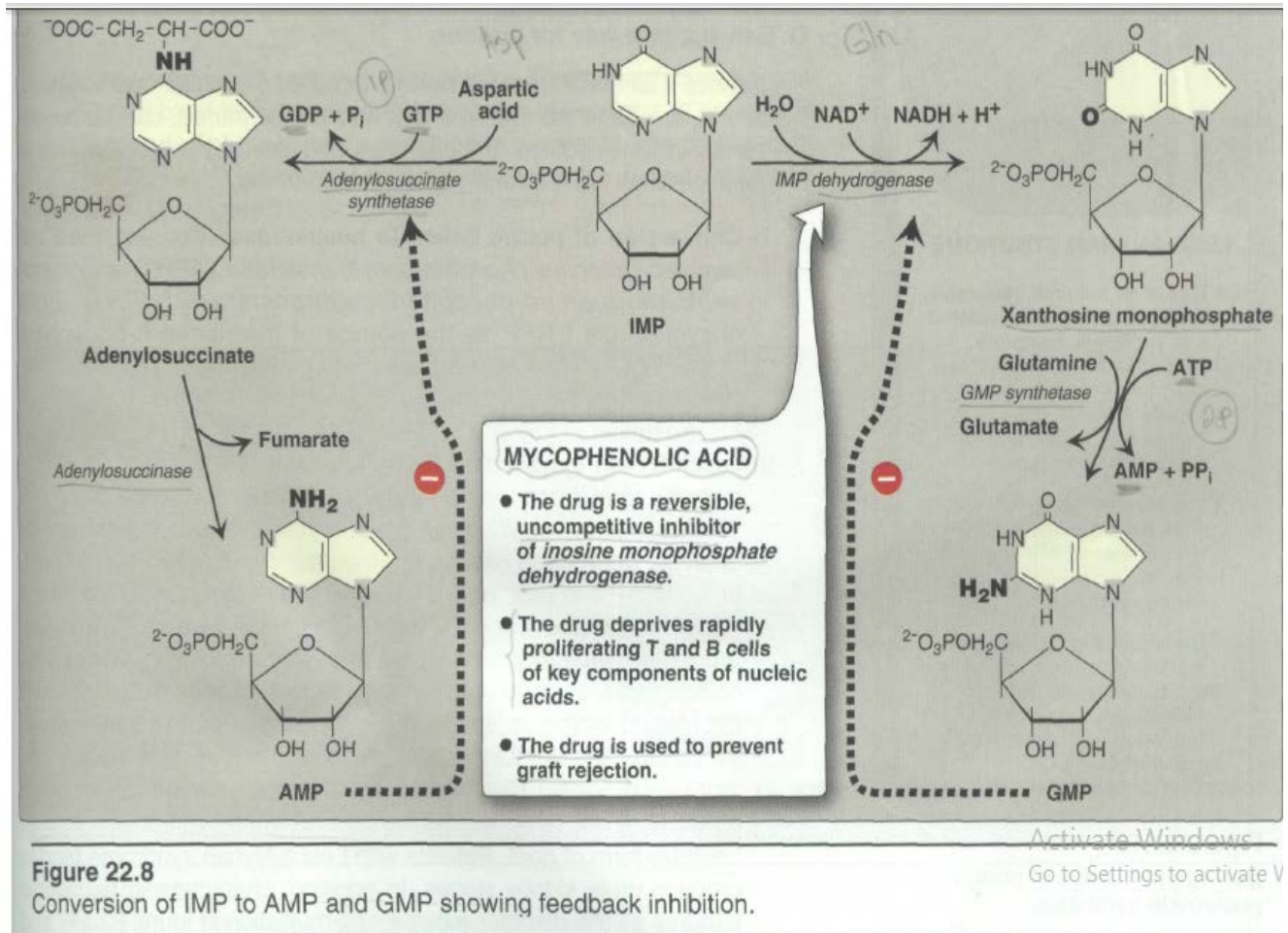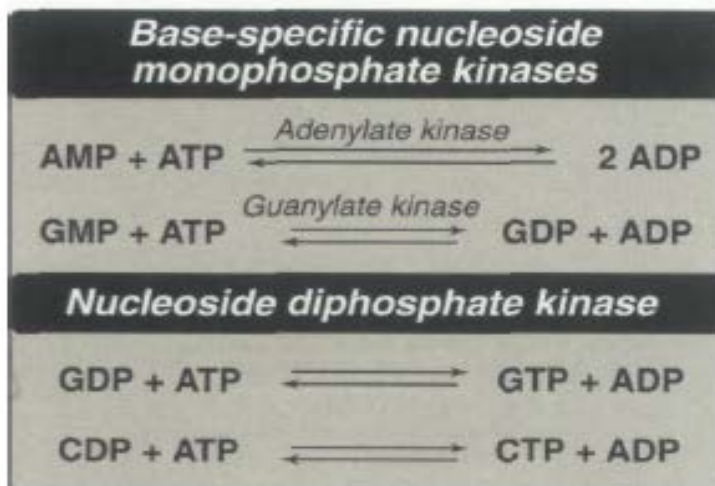

Figure 22.8
Conversion of IMP to AMP and GMP showing feedback inhibition.

Conversion of nucleoside monophosphates to nucleoside diphosphates and triphosphates:

Nucleoside diphosphates (NDP) are synthesized from the corresponding nucleoside monophosphates (NMP) by **base-specific nucleoside monophosphate kinases** (Figure 22.9). [Note: These kinases do not discriminate between ribose or deoxyribose in the substrate.] ATP is generally the source of the transferred phosphate, because it is present in higher concentrations than the other nucleoside triphosphates.

Figure 22.9
Conversion of nucloside mono-
phosphates to nucleoside
diphosphates and triphosphates.

Salvage pathway for purines

Purines that result from the normal turnover of cellular nucleic acids, or that are obtained from the diet and not degraded, can be reconverted into nucleoside triphosphates and used by the body. This is referred to as the "salvage pathway" for purines.

1. Conversion of purine bases to nucleotides: Two enzymes are involved: *adenine phosphoribosyltransferase* and *hypoxanthine-guanine phosphoribosyltransferase*

Both enzymes use PRPP as the source of the ribose 5-phosphate group. The release of pyrophosphate makes these reactions irreversible (Figure 22.10).
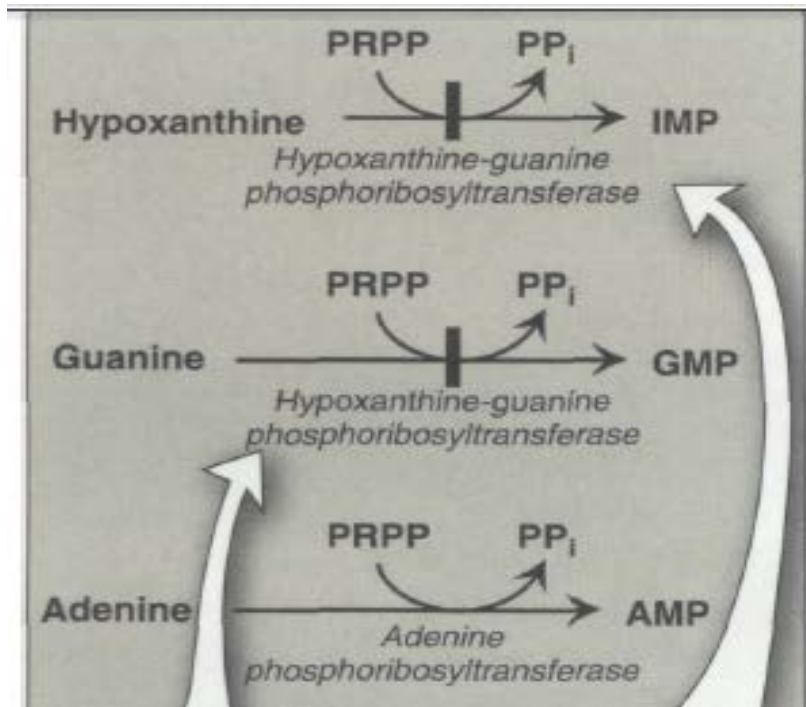
Synthesis of deoxy ribonucleotides:

The nucleotides required for DNA synthesis, however, are 2` Deoxyribonucleotides which are produced from ribonucleoside diphosphates by the enzyme *ribonucleotide reductase.*

A. Ribonucleotide reductase

Ribonucleotide reductase {ribonucleoside diphosphate reductase) that is specific for the reduction of nucleoside diphosphates (ADP, GDP, CDP, UDP) and to their deoxy-forms (dADP,dGDP, dCDP, and dUDP) The immediate donors of the hydrogen atoms needed for the reduction of the 2'-hydroxyl group are two sulfhydryl groups on the enzyme itself, which, during the reaction, form a disulfide bond.
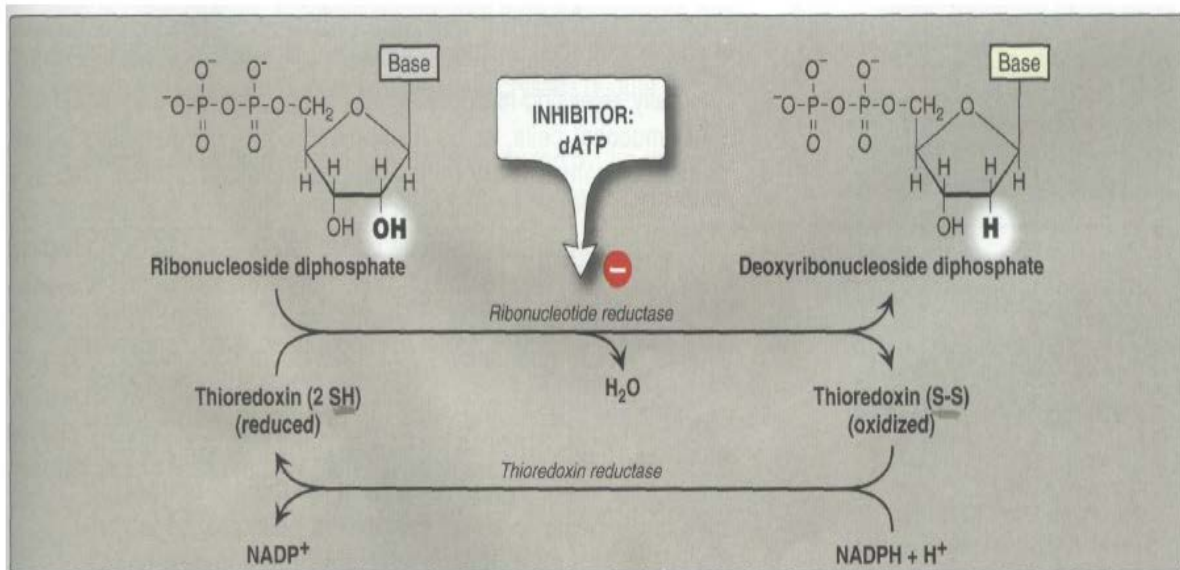
Figure 22.12
Conversion of ribonucleotides to deoxyribonucleotides.

DEGRADATION OF PURINE NUCLEOTIDES

Degradation of dietary nucleic acids occurs in the small intestine, where a family of pancreatic enzymes hydrolyzes the nucleotides to nucleosides and free bases. Inside cells, purine nucleotides are sequentially degraded by specific enzymes, with **uric acid** as the end product of this pathway. [Note: Mammals other than primates oxidize uric acid further to allantoin, which, in some animals other than mammals, may be further degraded to urea or ammonia.]

A. Degradation of dietary nucleic acids in the small intestine

Ribonucleases and deoxyribonucleases, secreted by the pancreas, hydrolyze RNA and DNA primarily to oligonucleotides. Oligonucleotides are further hydrolyzed by pancreatic phosphodiesterases, producing a mixture of 3'- and 5'-mononucleotides. A family of nucleotidases removes the phosphate groups hydrolytically, releasing nucleosides that may be absorbed by the intestinal mucosal cells, or be further degraded to free bases before uptake. [Note: Dietary purines and pyrimidines are not used to a large extent for the synthesis of tissue nucleic acids. Instead, the dietary purines are generally converted to uric acid by intestinal mucosal cells. Most of the uric acid enters the blood, and is eventually excreted in the urine. For this reason, individuals with a tendency toward gout should be careful about consuming foods such as organ meats, anchovies, sardines, or dried beans, which contain high amounts of nucleic acids. The remainder of the dietary purines are metabolized by the intestinal flora.] A summary of this pathway is shown in Figure
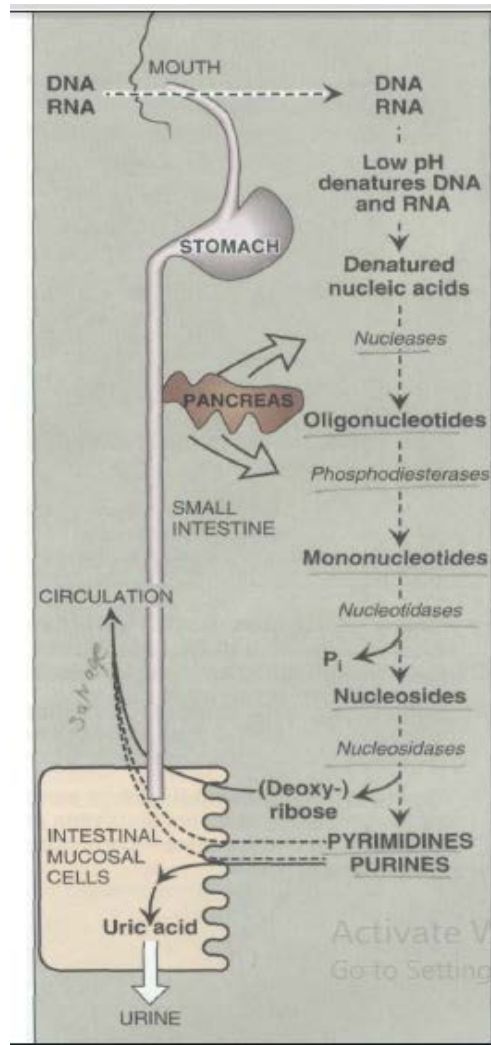
B. Formation of uric acid

A summary of the steps in the production of uric acid and genetic diseases associated with deficiencies of specific degradative enzymes

[1] An amino group is removed from AMP to produce IMP or from adenosine to produce inosine (hypoxanthine ribose) by AMP or adenosine deaminase.

[2] IMP and GMP are converted into their nucleoside forms—inosine and guanosine—by the action of 5'-nucleotidase.

[3] *Purine nucleoside phosphorylase* converts inosine and guanosine into their respective purine bases, hypoxanthine and guanine.

[4] Guanine is deaminated to form xanthine.

[5] Hypoxanthine is oxidized by *xanthine oxidase* to xanthine, which is further oxidized by *xanthine oxidase* to uric acid, the final product of human purine degradation. Uric acid is excreted in the urine.

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VI. PYRIMIDINE SYNTHESIS AND DEGRADATION

Unlike the synthesis of the purine ring, in which the ring is constructed on a preexisting ribose 5-phosphate, the pyrimidine ring is synthesized before being attached to ribose 5-phosphate, which is donated by PRPP. The sources of the atoms in the pyrimidine ring are **glutamine**, CO_2, and **aspartic acid** (Figure 22.19). [Note: Glutamine and aspartic acid are thus required for both purine and pyrimidine synthesis.]

A. Synthesis of carbamoyl phosphate
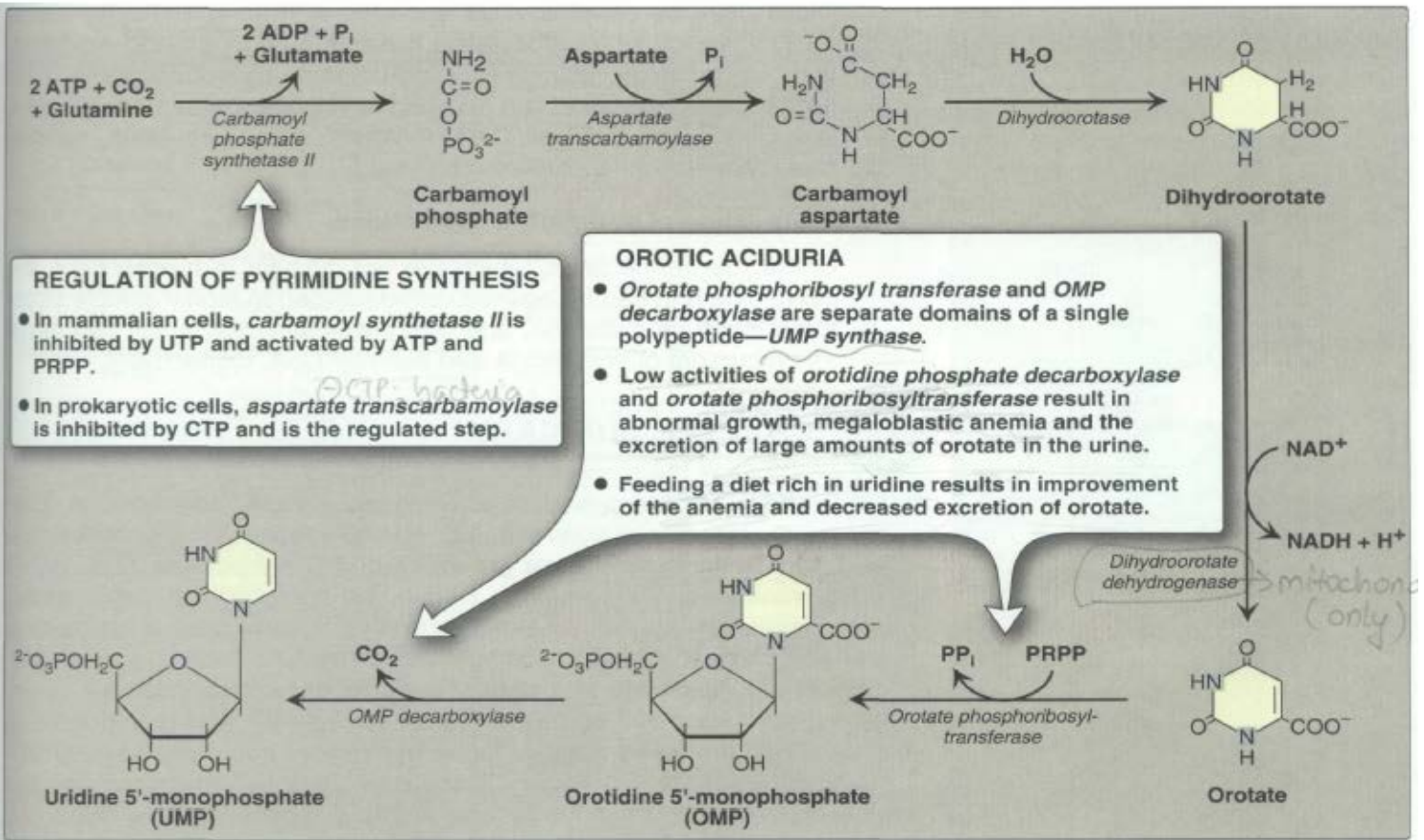
The regulated step of this pathway in mammalian cells is the synthesis of carbamoyl phosphate from **glutamine** and CO_2, catalyzed by *carbamoyl phosphate synthetase II (CPS II)*. CPS II is inhibited by UTP (the end-product of this pathway, which can be converted into the other Pyrimidine nucleotides
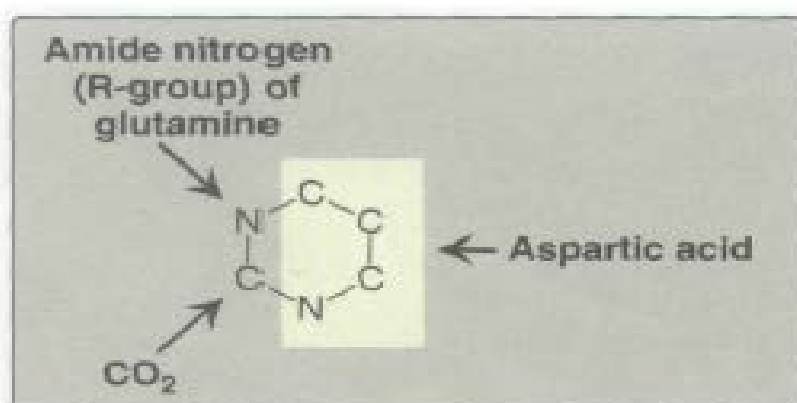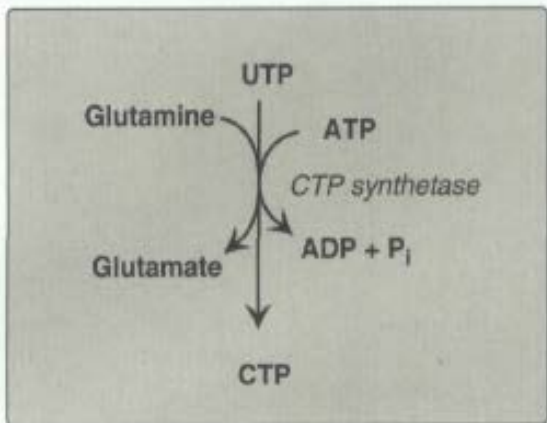

Figure 22.19
Sources of the individual atoms in the pyrimidine ring.

Figure 22.21
De novo pyrimidine synthesis.

The figure contains the following labeled elements and text:

$2\ ATP + CO_2 + Glutamine$ → (via Carbamoyl phosphate synthetase II, releasing $2\ ADP + P_i + Glutamate$) → Carbamoyl phosphate

Carbamoyl phosphate → (Aspartate transcarbamoylase, with Aspartate, releasing P_i) → Carbamoyl aspartate

Carbamoyl aspartate → (Dihydroorotase, releasing H_2O) → Dihydroorotate

Dihydroorotate → (Dihydroorotate dehydrogenase, NAD^+ → $NADH + H^+$) → Orotate *mitochondria (only)*

Orotate → (Orotate phosphoribosyl-transferase, PRPP → PP_i) → Orotidine 5'-monophosphate (OMP)

Orotidine 5'-monophosphate (OMP) → (OMP decarboxylase, releasing CO_2) → Uridine 5'-monophosphate (UMP)

REGULATION OF PYRIMIDINE SYNTHESIS
- In mammalian cells, *carbamoyl synthetase II* is inhibited by UTP and activated by ATP and PRPP.
- In prokaryotic cells, *aspartate transcarbamoylase* is inhibited by CTP and is the regulated step.

⊖CTP: bacteria

OROTIC ACIDURIA
- *Orotate phosphoribosyl transferase* and *OMP decarboxylase* are separate domains of a single polypeptide—*UMP synthase*.
- Low activities of *orotidine phosphate decarboxylase* and *orotate phosphoribosyltransferase* result in abnormal growth, megaloblastic anemia and the excretion of large amounts of orotate in the urine.
- Feeding a diet rich in uridine results in improvement of the anemia and decreased excretion of orotate.

Figure 22.22
Synthesis of CTP from UTP.

UTP → (CTP synthetase, Glutamine → Glutamate, ATP → $ADP + P_i$) → CTP

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Salvage of pyrimidines

Few pyrimidine bases are salvaged in human cells. However, the pyrimidine nucleosides **uridine** and **cytidine** can be salvaged by *uri-dine-cytidine kinase,* **deoxycytidine** can be salvaged by *deoxycytidine kinase,* and **thymidine** can be salvaged by the enzyme *thymidine kinase.* Each of these enzymes catalyzes the phosphorylation of a nucleoside(s) utilizing ATP, and forming UMP,CMP, dCMP, and TMP.

Degradation of pyrimidine nucleotides

Unlike the purine rings, which are not cleaved in human cells, the pyrimidine ring can be opened and degraded to highly soluble structures, such as β-alanine, and β-aminoisobutyrate, which can serve as precursors acetyl CoA and succinyl CoA, respectively.
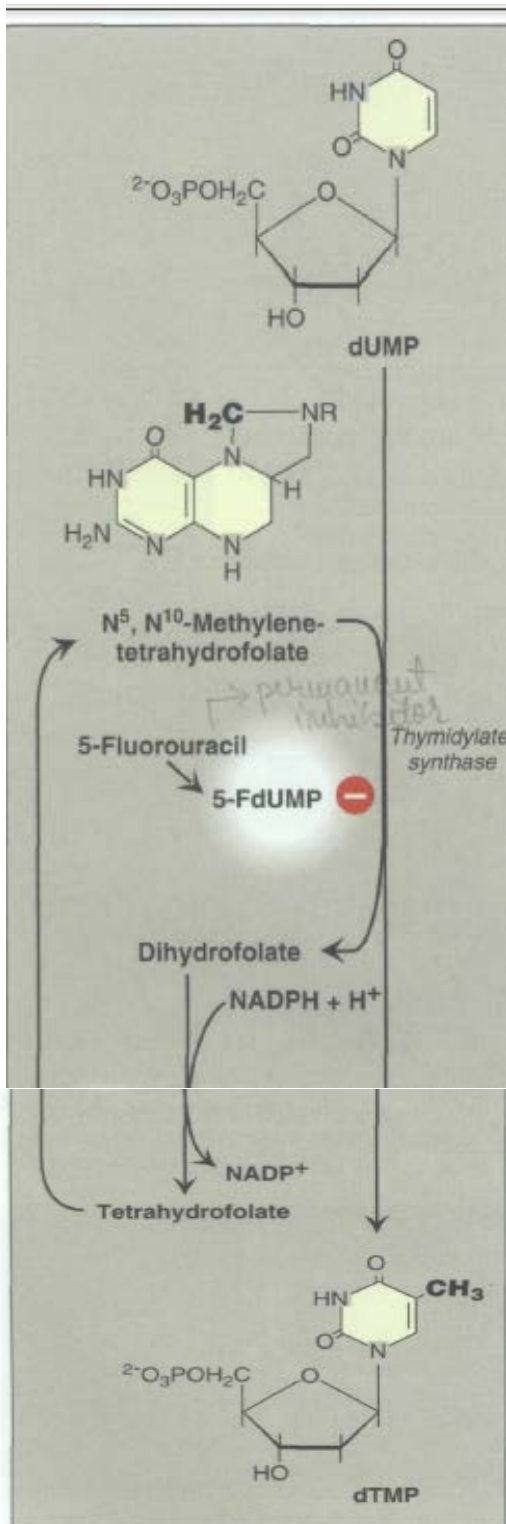
Figure 22.23
Synthesis of dTMP from dUMP, illustrating sites of action of antineoplastic drugs.