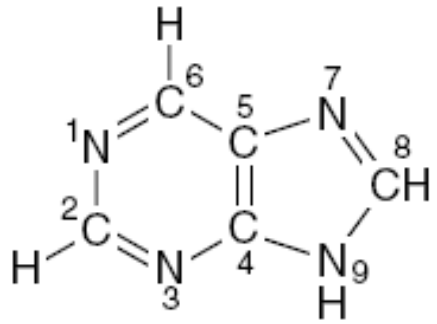
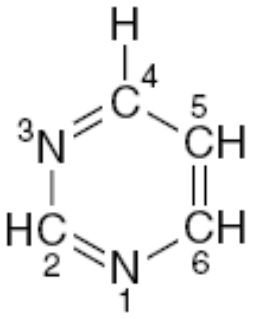
NUCLEOTIDE METABOLISM

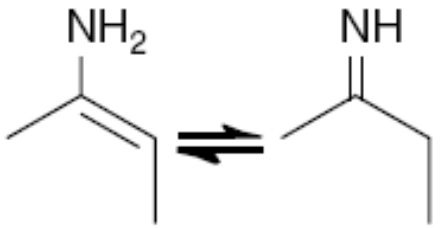


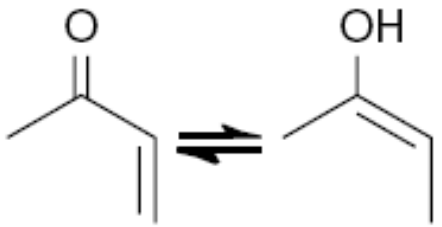
Purine



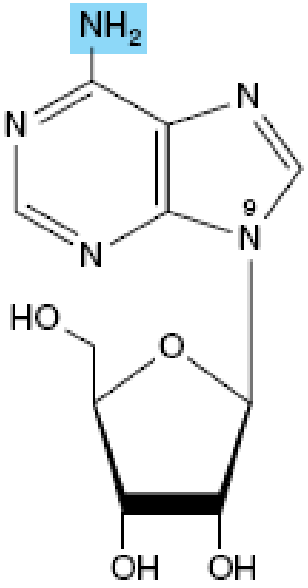
Pyrimidine

Purine and pyrimidine. The atoms are numbered according to the international system.

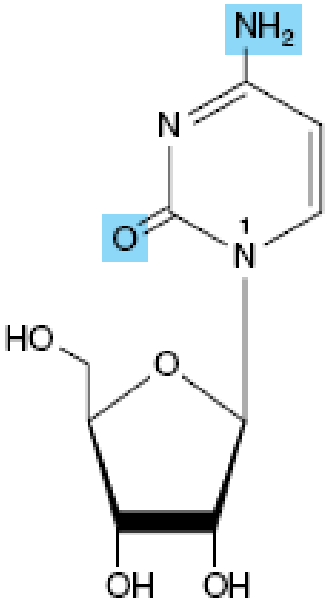




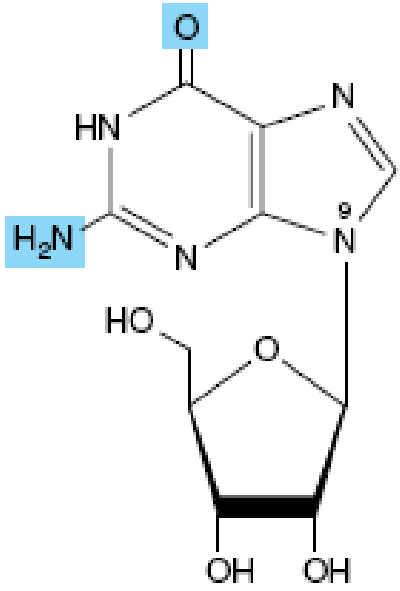
Tautomerism of the oxo and amino functional groups of purines and pyrimidines.



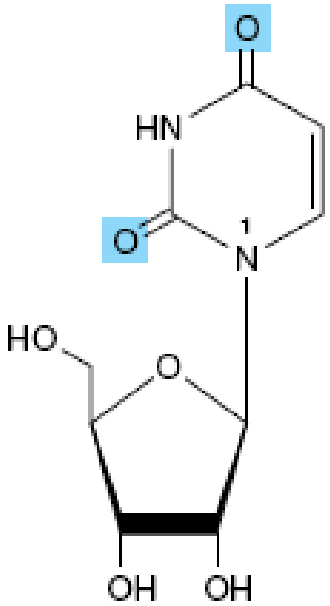
Adenosine



Cytidine

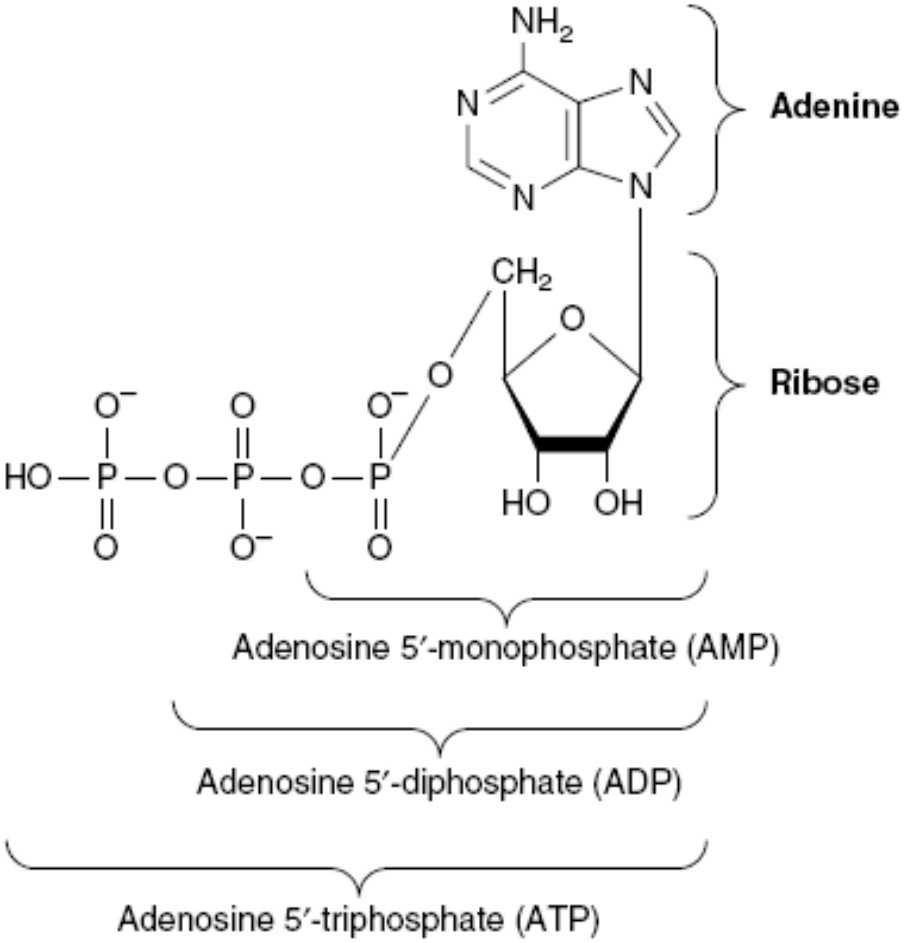


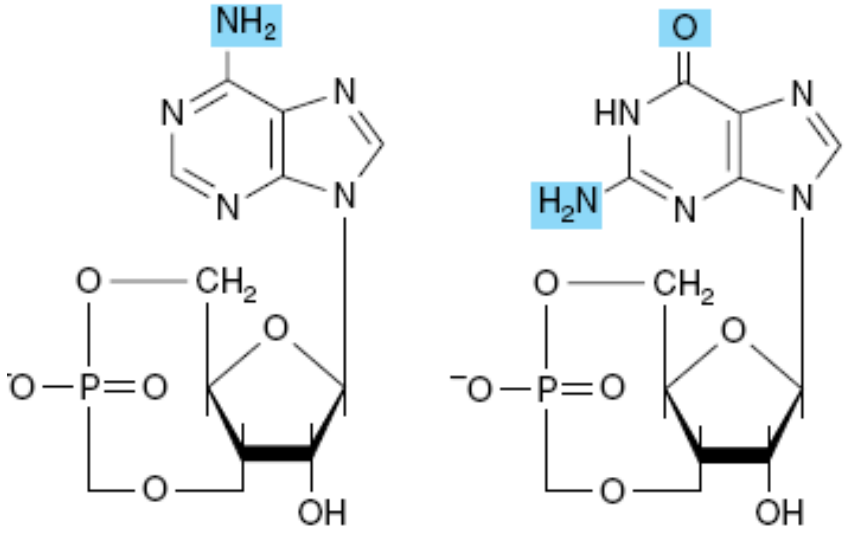
Guanosine



Uridine

Ribonucleosides, drawn as the syn conformers.

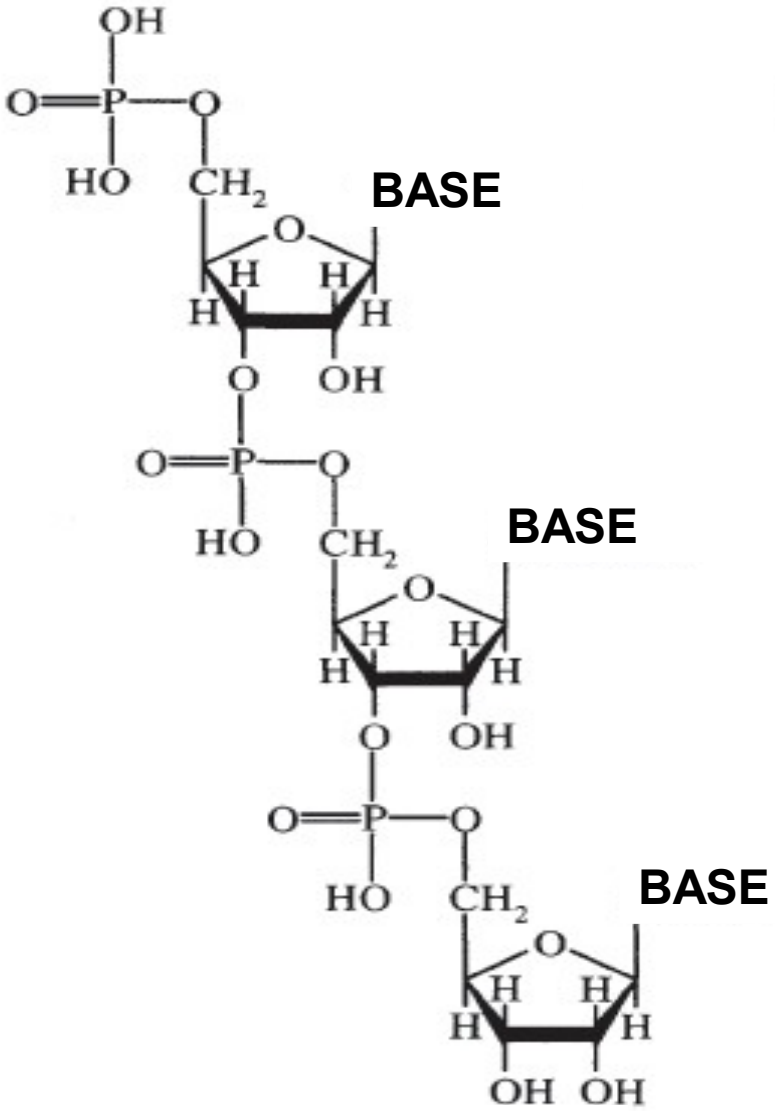




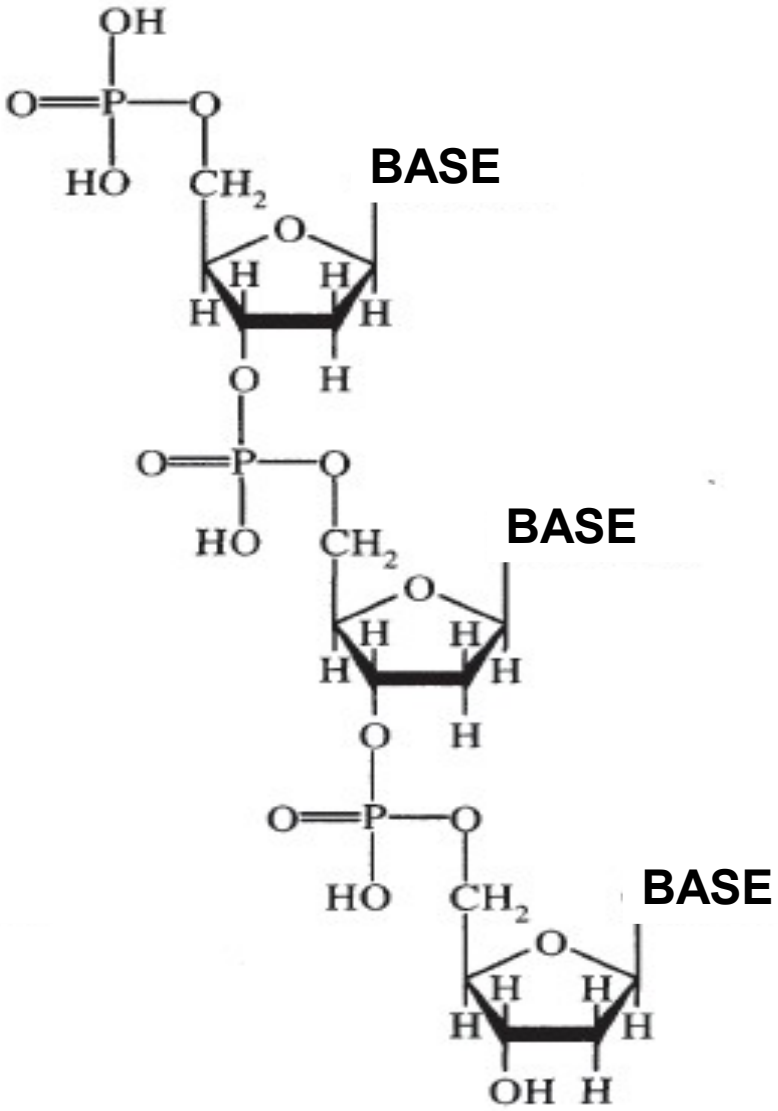
cAMP, 3′,5′-cyclic AMP, and cGMP.

POLYNUCLEOTIDES

Polynucleotides Have Primary Structure

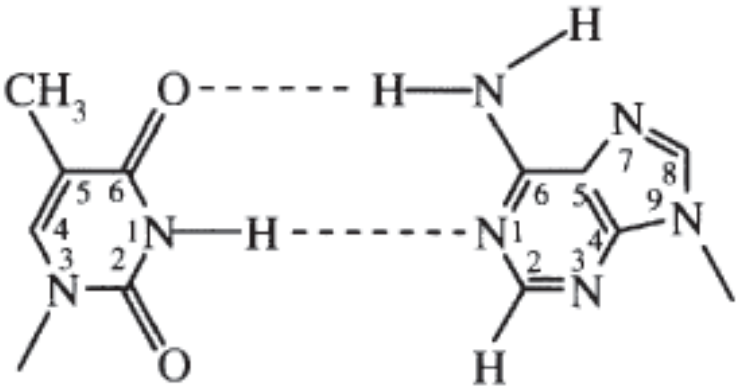


RNA



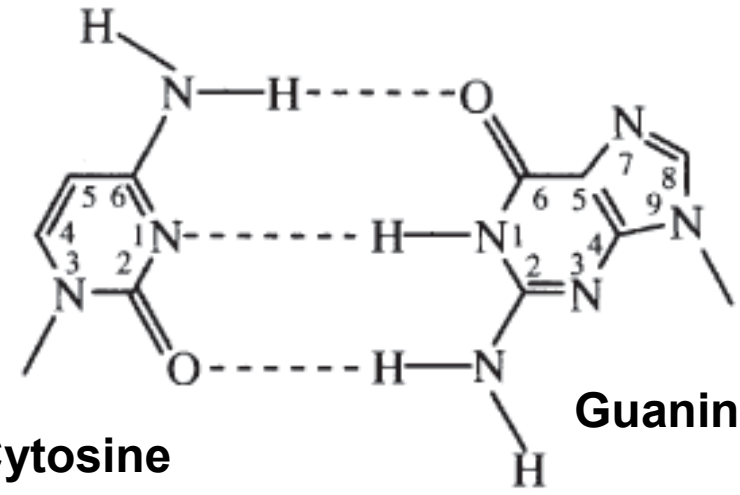
DNA

Polynucleotides Have Secondary Structure



Thymine

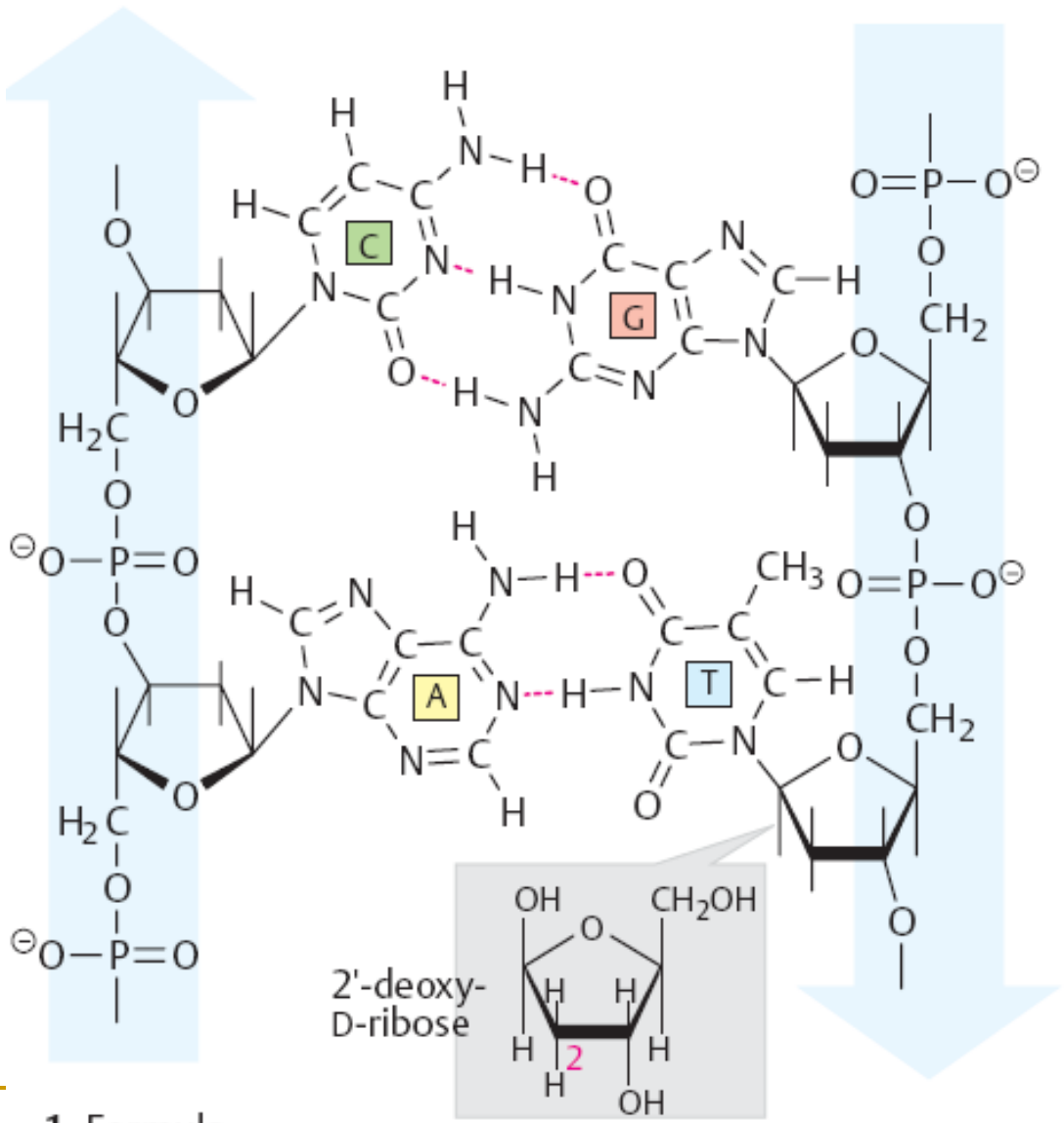
Adenine



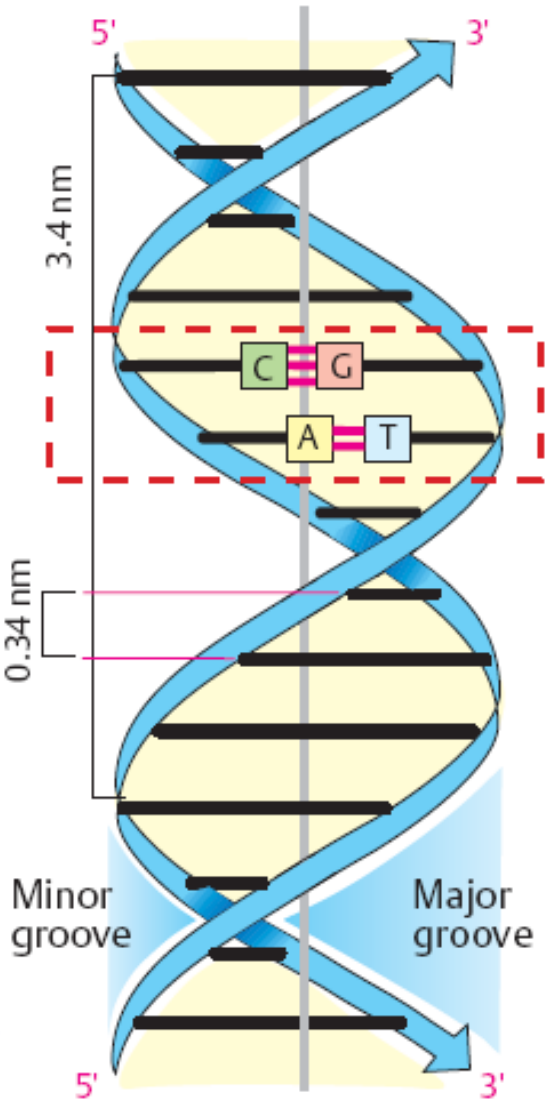
Cytosine

Guanine

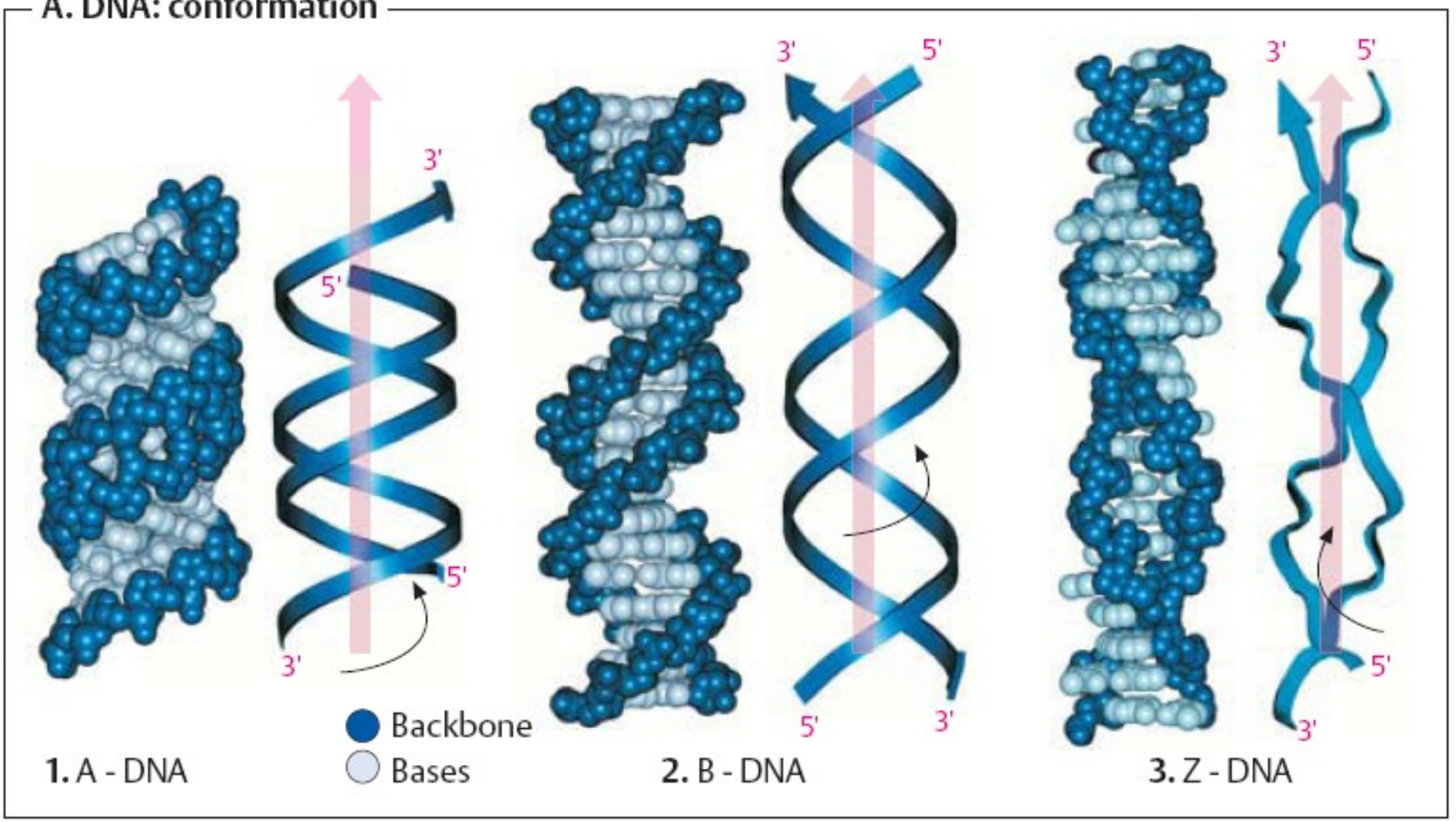
A. DNA: structure



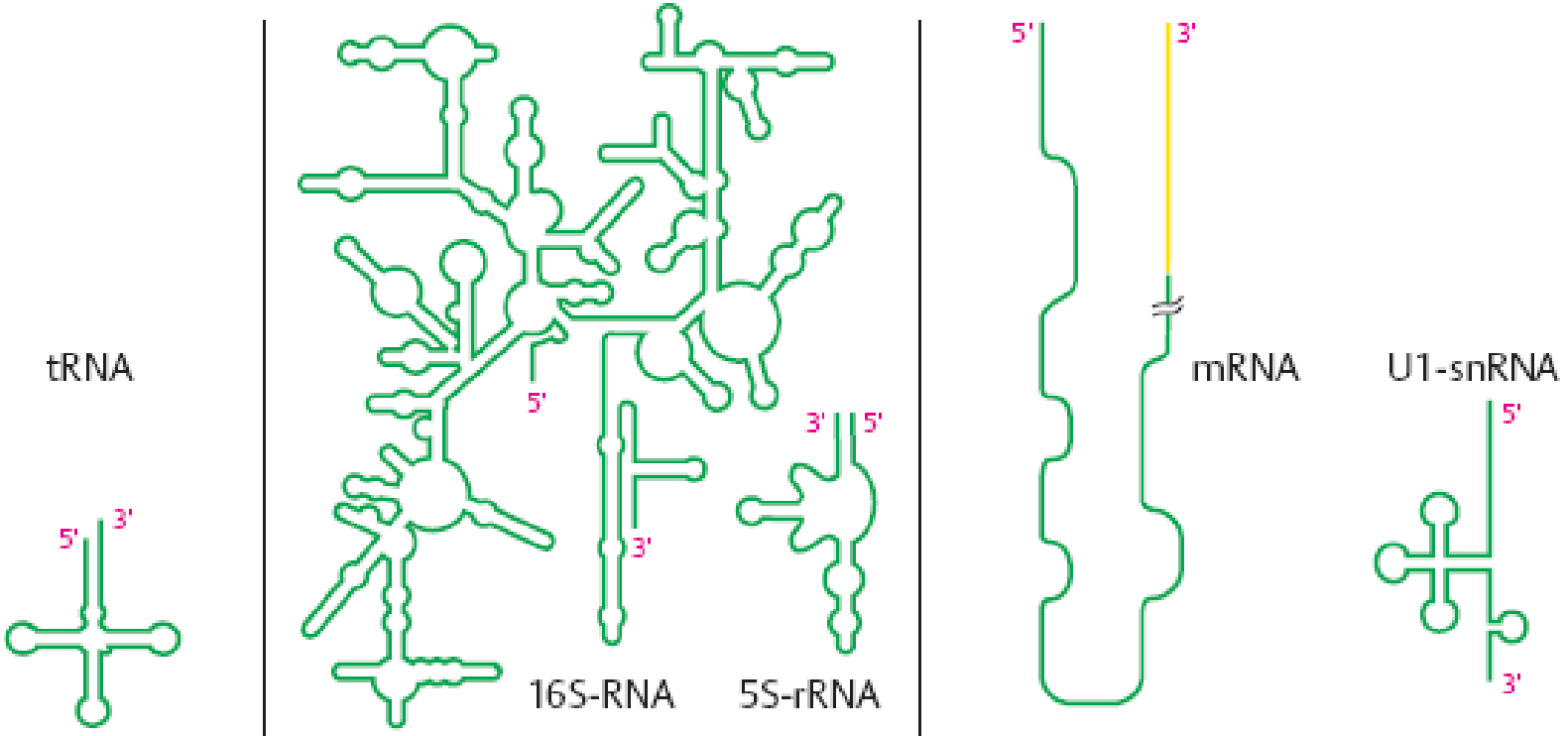
1. Formula



2. Double strand

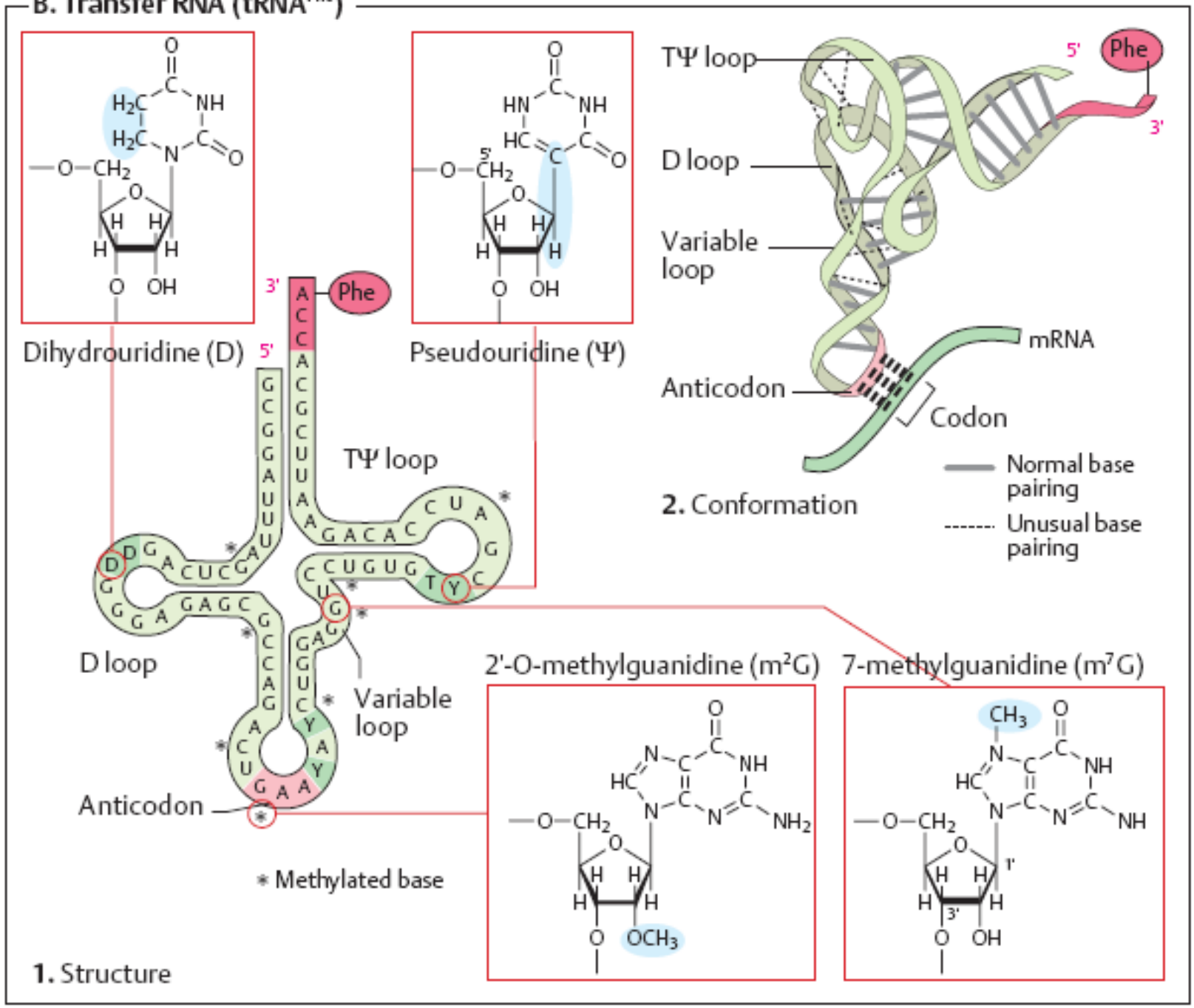

A. DNA: conformation
3'
5'
5'
3'
3'
5'
5'
3'
3'
5'
5'
3'
Backbone
Bases
1. A - DNA
2. B - DNA
3. Z - DNA

A. Ribonucleic acids (RNAs)

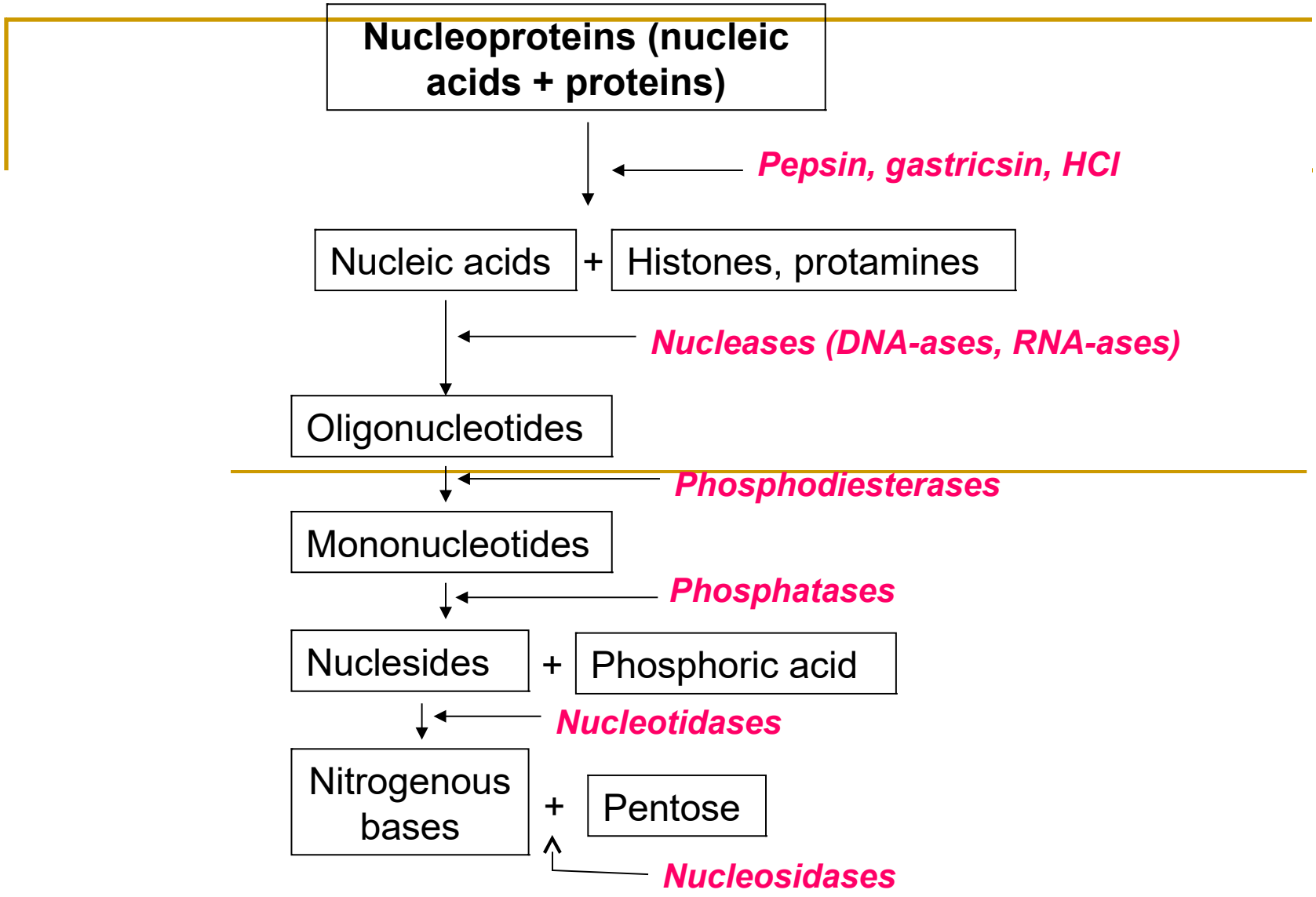


tRNA	rRNA	Type	mRNA	snRNA
>50	4	Species per cell	> 1000	~ 10
74 - 95	120 - 5000	Length (b)	400 - 6000	100 - 300
10-20%	80%	Proportion	5%	< 1%
Long	Long	Lifespan	Short	Long
Translation	Translation	Function	Translation	Splicing

Small nuclear RNAs (snRNAs) are involved in the splicing of mRNA precursors. They associate with numerous proteins to form "spliceosomes."


B. Transfer RNA (tRNA^Phe)
Dihydrouridine (D)
Pseudouridine (Ψ)
3'
Phe
5'
TΨ loop
D loop
Variable loop
Anticodon
mRNA
Codon
Normal base pairing
Unusual base pairing
2. Conformation
2'-O-methylguanidine (m²G)
7-methylguanidine (m⁷G)
* Methylated base
1. Structure

DECOMPOSITION OF NUCLEIC ACIDS IN INTESTINE AND TISSUE

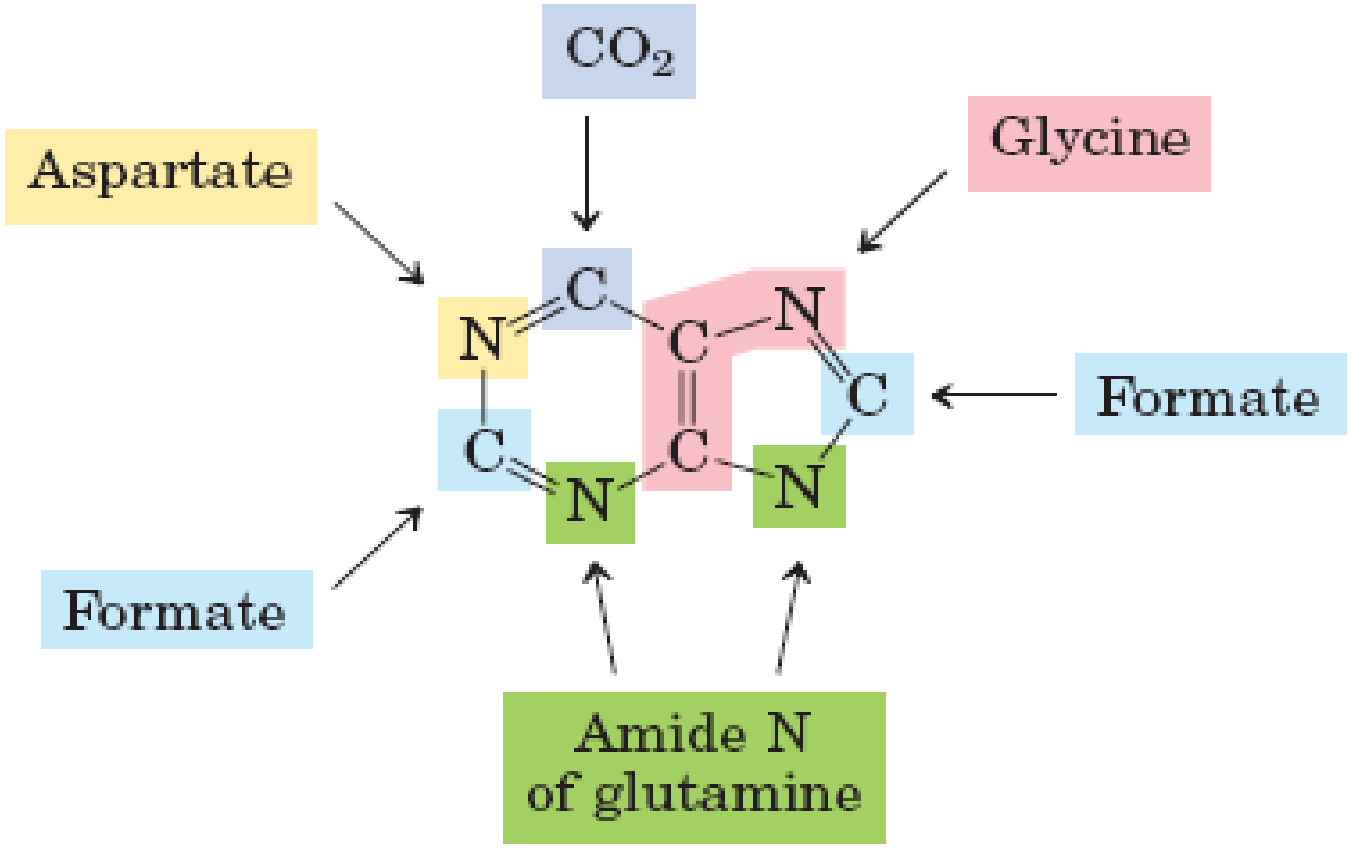


FATES OF NITROGENOUS BASES, PENTOSES AND PHOSPHORIC ACIDS IN THE ORGANISM

Nitrogenous bases → *oxidation to the end products*

Pentoses → *oxidation with energy formation;*
synthesis of nucleotided;
synthesis of hexoses;
synthesis of coenzymes

Phosphoric acid → *phosphorilation;*
ATP synthesis;
synthesis of phospholipids;
buffer systems;
constituent of bones, cartilages



Origin of the ring atoms of purines.

This information was obtained from isotopic experiments with 14C- or 15N-labeled precursors.

Formate is supplied in the form of *N*10-formyltetrahydrofolate.

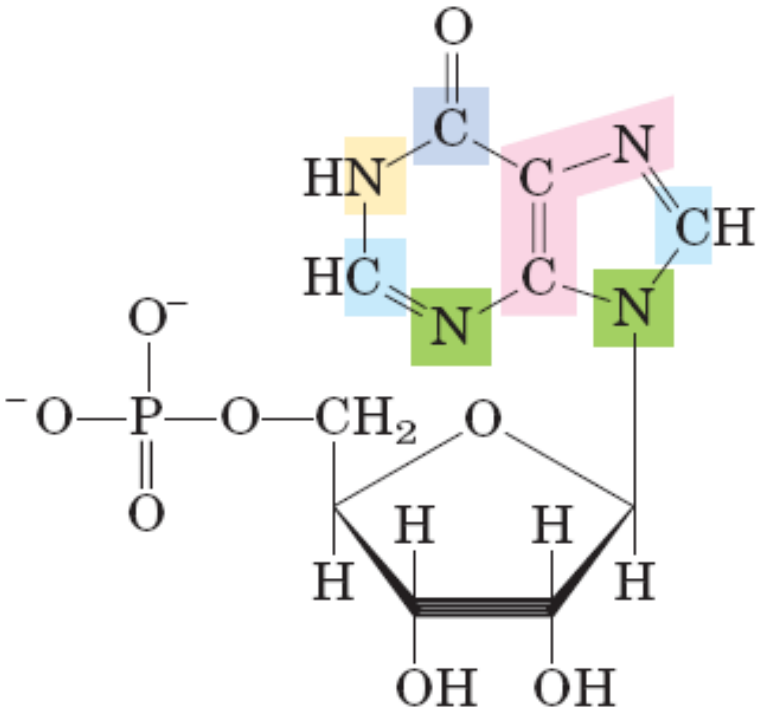
Synthesis of Purine Nucleotides

Two ways of biosynthesis:

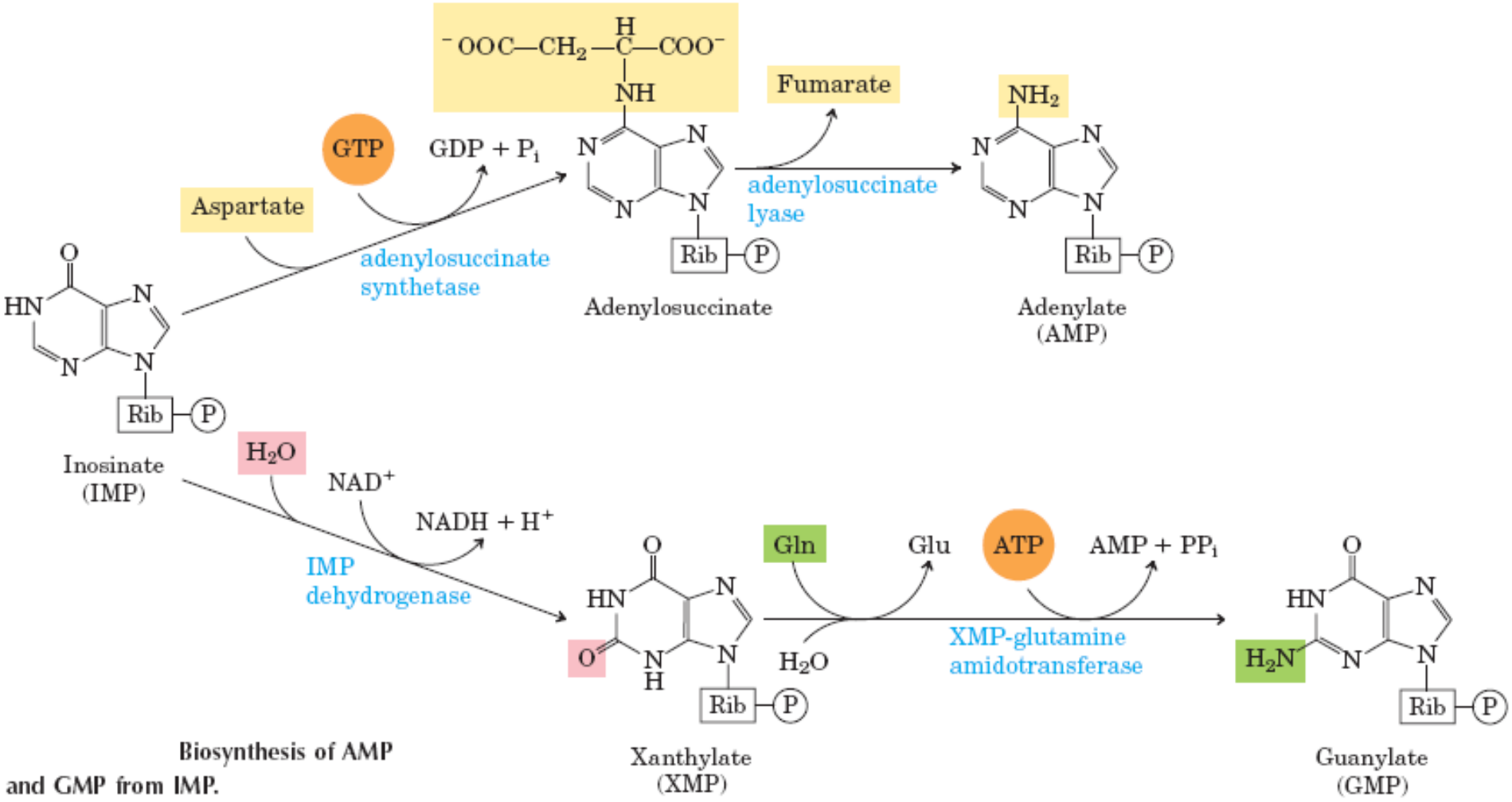
-de novo – formation of purine nucleotides from simple acyclic precursors (in liver)

-salvage (reserve) pathway – using of purine bases formed in the decomposition of nucleotides (in the out-of-liver tissues)

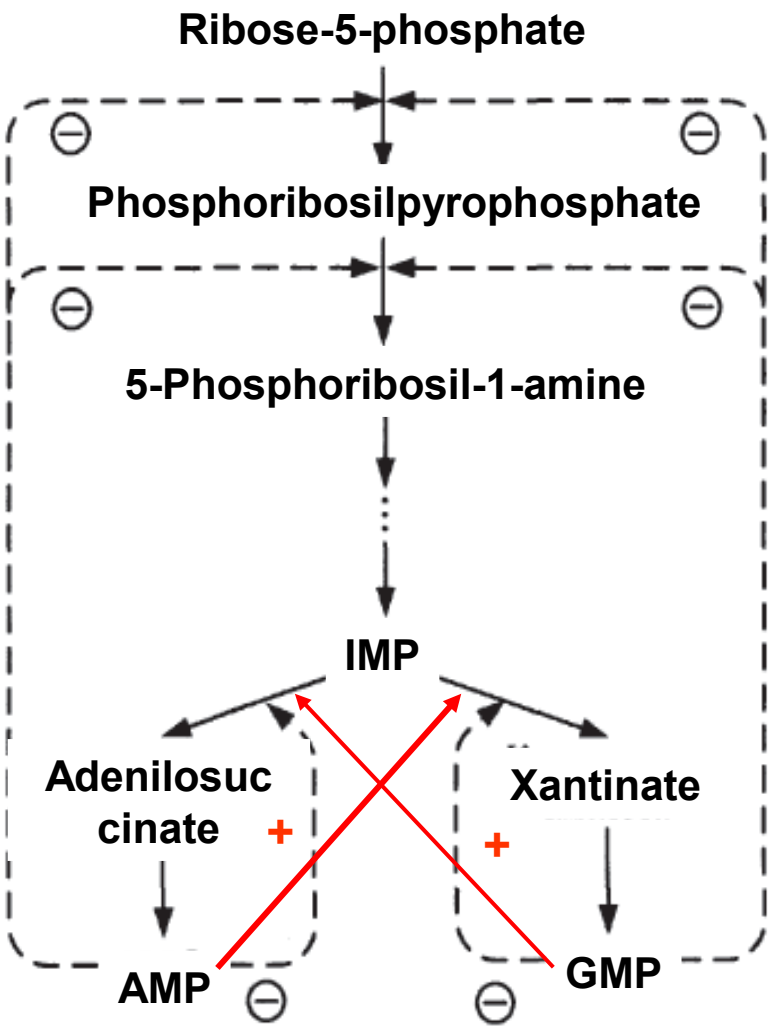
The first intermediate with a complete purine ring is **inosinate (IMP).**



Inosinate (IMP)

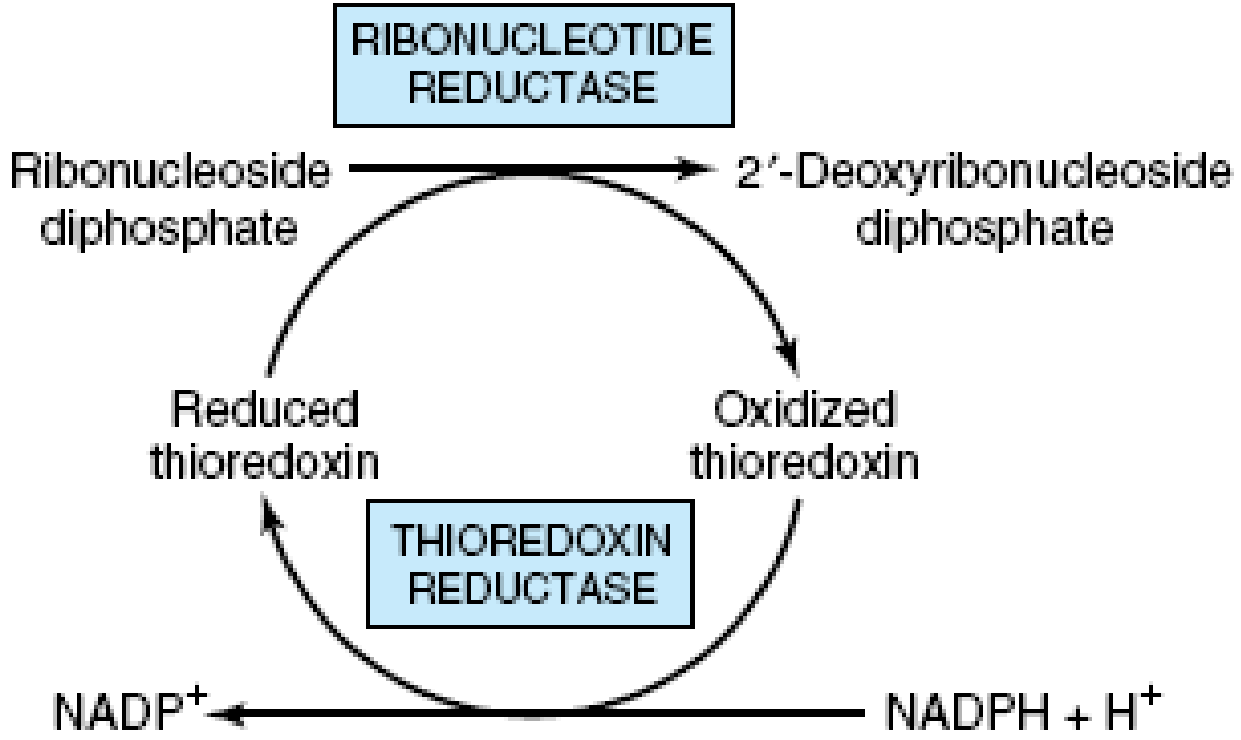


Biosynthesis of AMP and GMP from IMP.

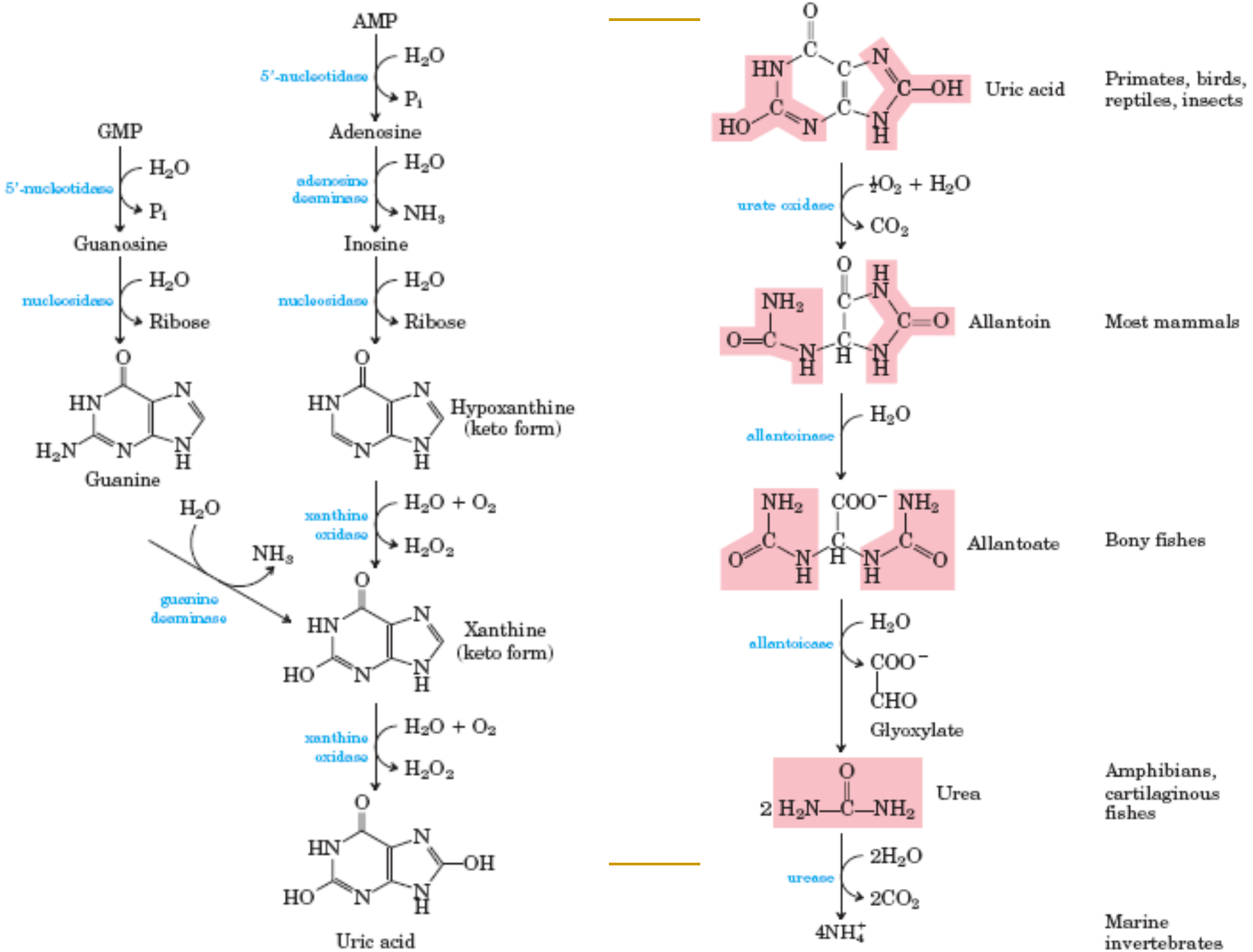


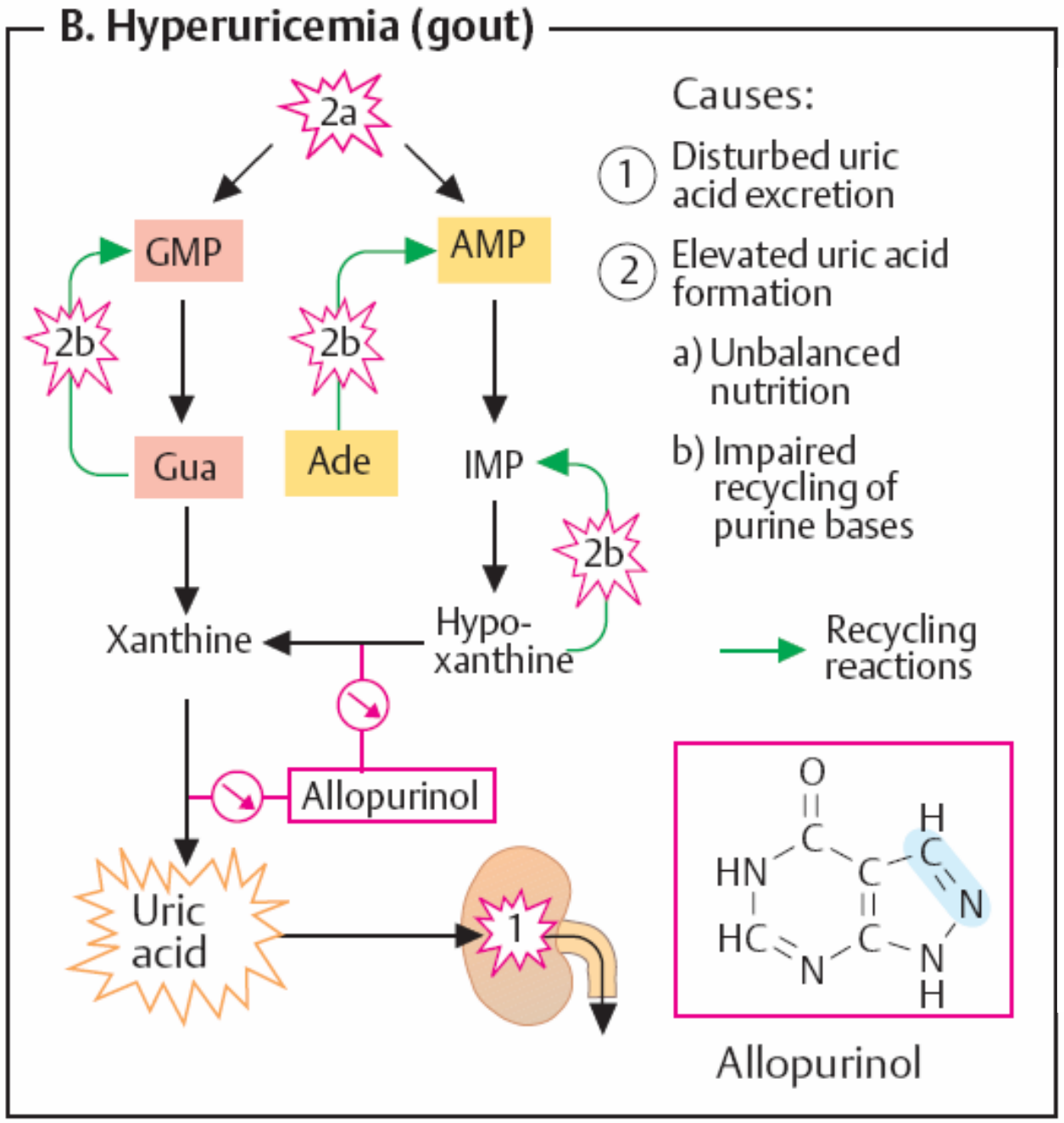
Regulatory mechanisms in the biosynthesis of adenine and guanine nucleotides

Regulation of these pathways differs in other organisms.



Reduction of ribonucleoside diphosphates to 2′-deoxyribonucleoside diphosphates.


AMP
5′-nucleotidase
H_2O
P_i
Adenosine
adenosine deaminase
H_2O
NH_3
Inosine
nucleosidase
H_2O
Ribose
Hypoxanthine (keto form)
xanthine oxidase
$H_2O + O_2$
H_2O_2
Xanthine (keto form)
xanthine oxidase
$H_2O + O_2$
H_2O_2
Uric acid
GMP
5′-nucleotidase
H_2O
P_i
Guanosine
nucleosidase
H_2O
Ribose
Guanine
H_2O
NH_3
guanine deaminase
Uric acid
Primates, birds, reptiles, insects
urate oxidase
$\frac{1}{2}O_2 + H_2O$
CO_2
Allantoin
Most mammals
allantoinase
H_2O
Allantoate
Bony fishes
allantoicase
H_2O
COO^-
CHO
Glyoxylate
Urea
Amphibians, cartilaginous fishes
urease
$2H_2O$
$2CO_2$
$4NH_4^+$
Marine invertebrates



Allopurinol, an inhibitor of xanthine oxidase.

Hypoxanthine is the normal substrate of xanthine oxidase. Only a slight alteration in the structure of hypoxanthine (shaded pink) yields the medically effective enzyme inhibitor allopurinol. At the active site, allopurinol is converted to oxypurinol, a strong competitive inhibitor that remains tightly bound to the reduced form of the enzyme.

0.5-1 g of uric acid is formed daily in the organism

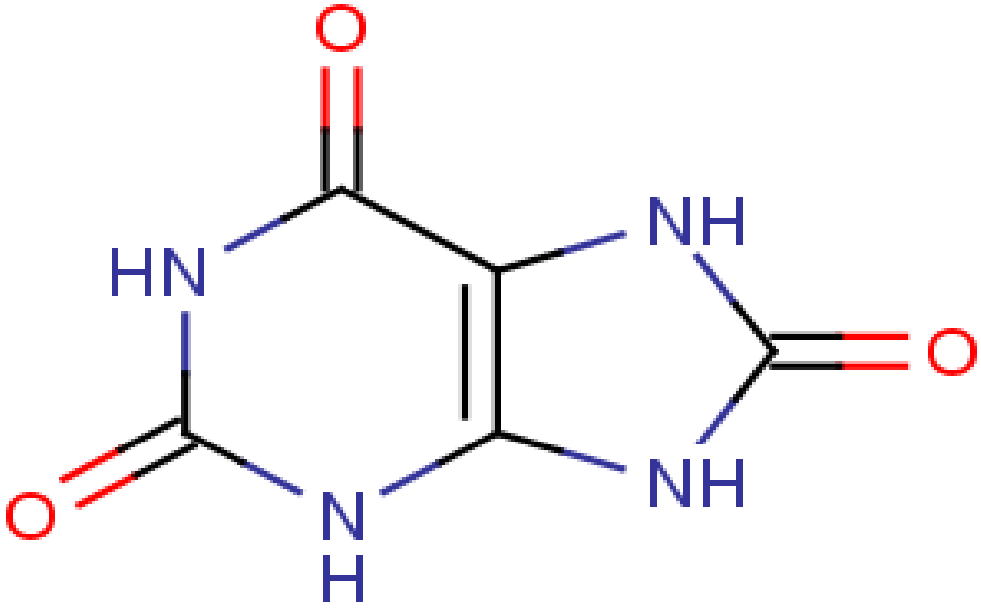
Normal concentration – 0.2-0.5 mmol/L

Uric acid – poorly soluble in water

Hyperuricemia:

-inherited (primary),

-gained (secondary).



Secondary: in radiation injury, blood diseases, tumors, toxemia, kidney diseases, alimentary (hyperconsumption of meat, coffee, tea)

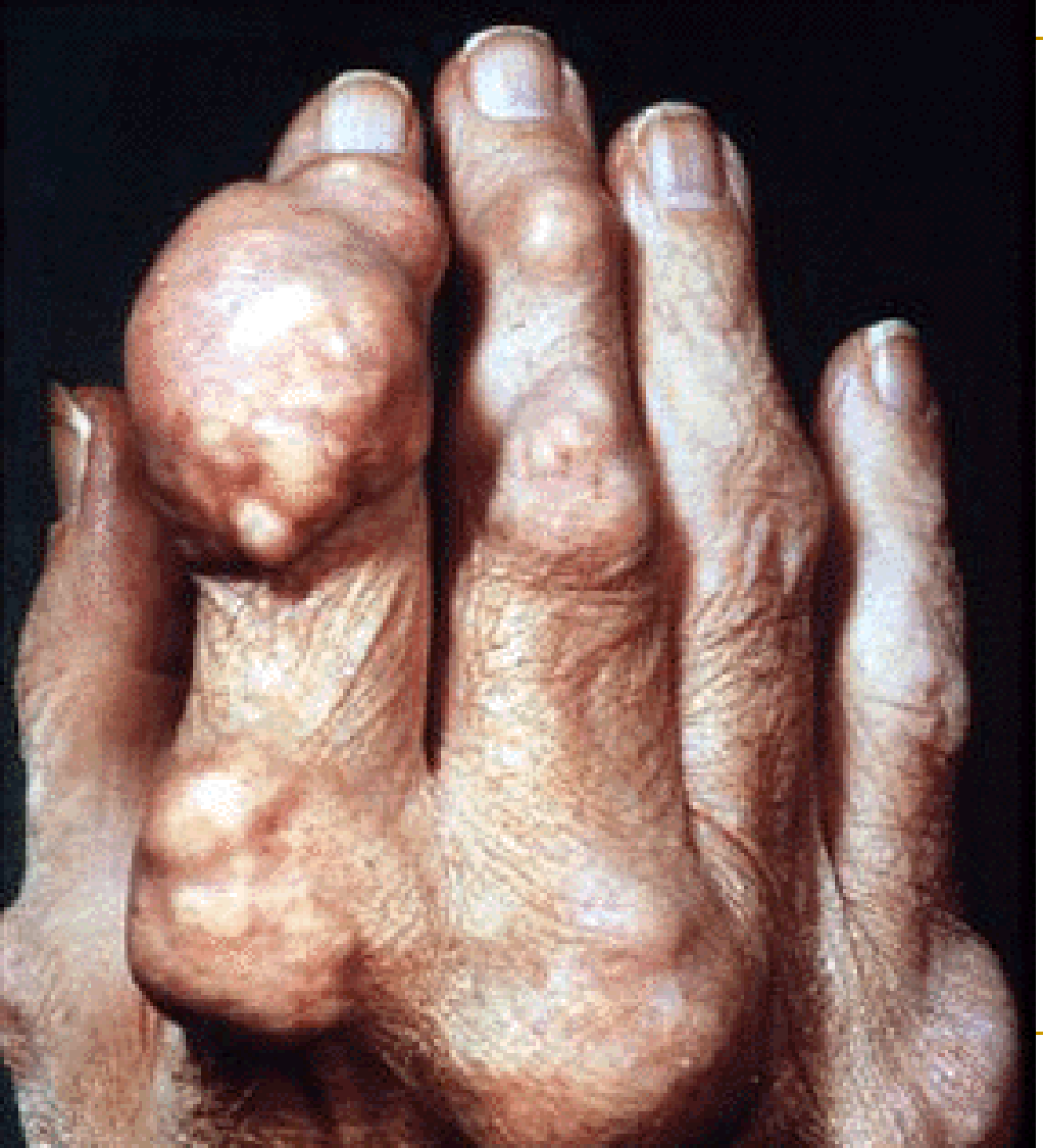
Gout – inherited disease accompanied with hyperuricemia and crystallization of uric acid and its salts in joints, cartilages and kidneys.

Symptoms:

-joints inflammation, acute pain

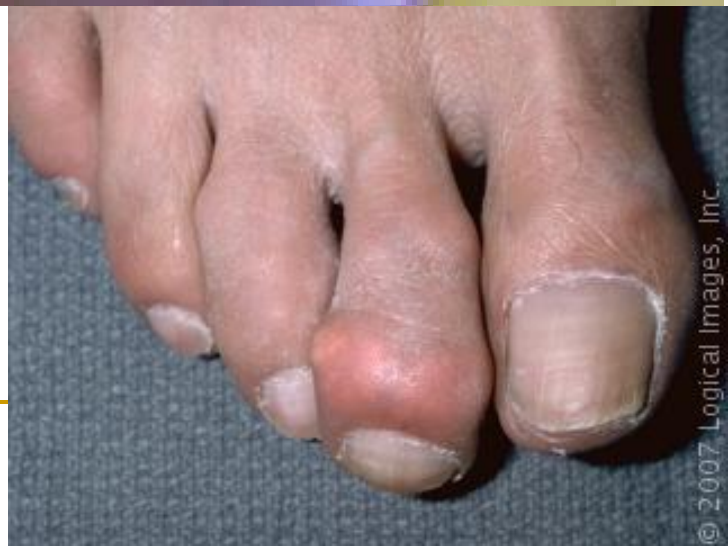
-renal stones

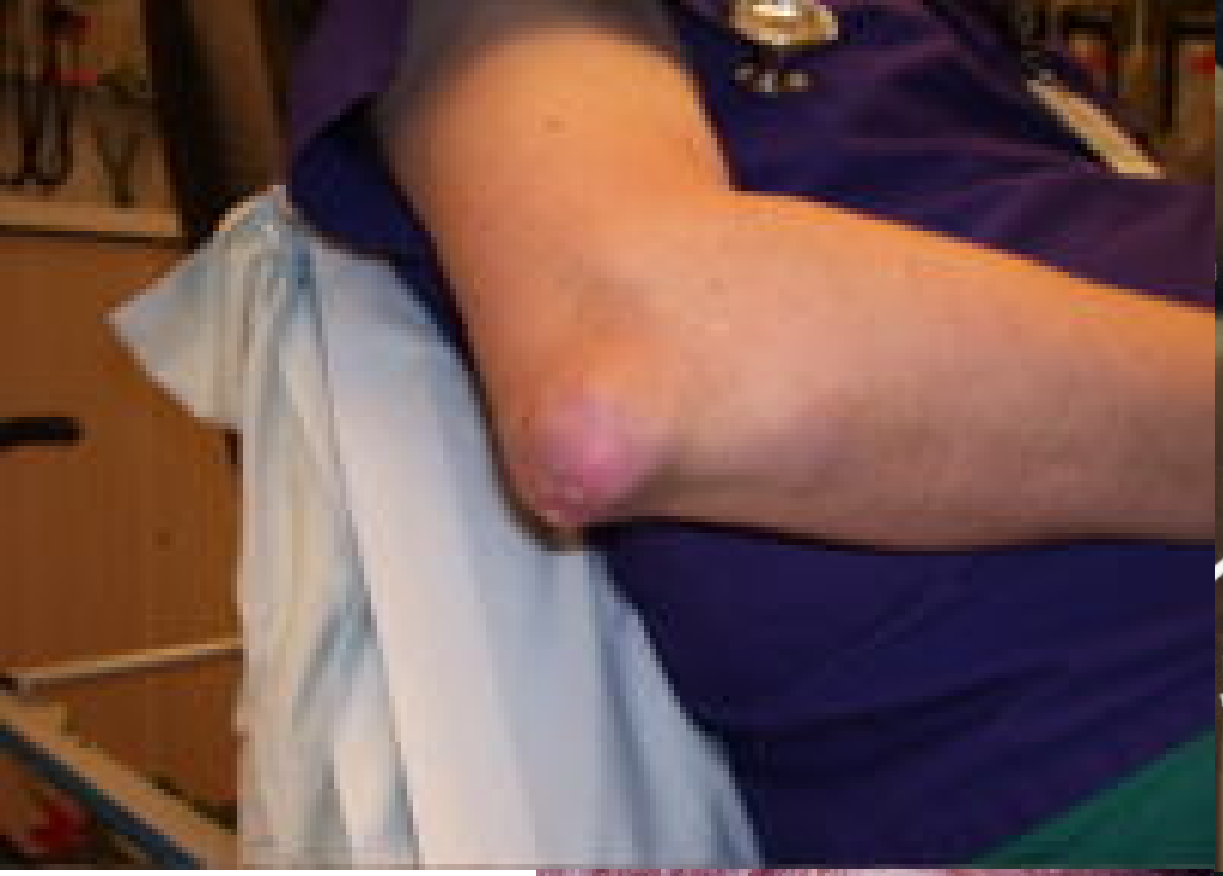
-tophuses.

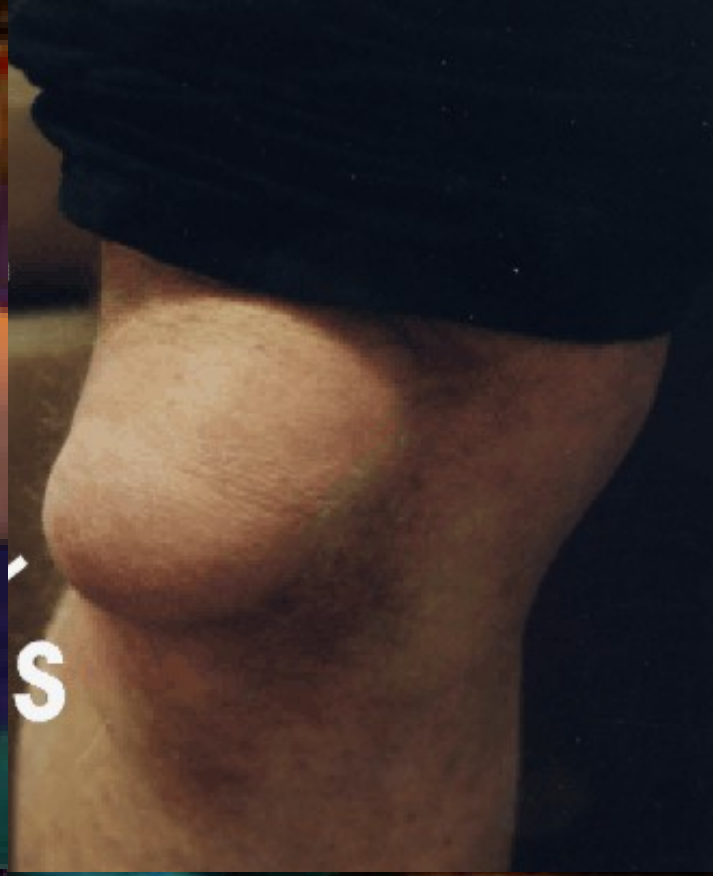


Gout: accumulation of uric acid salts in joints

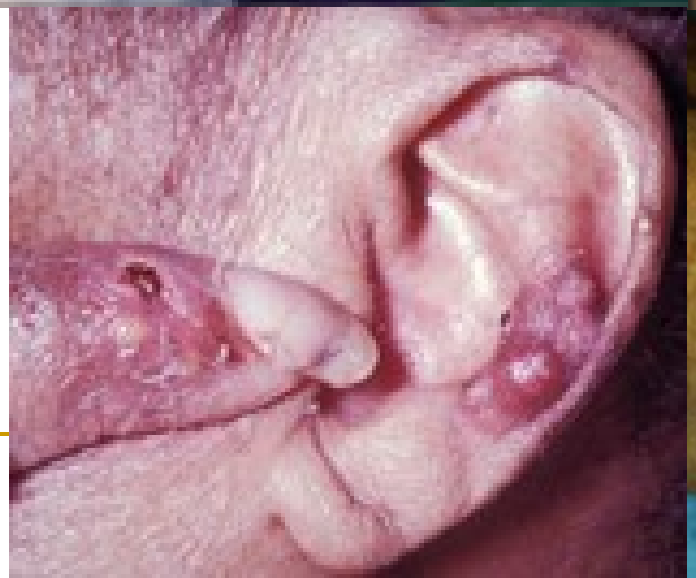
Gout: accumulation of uric acid salts in joints

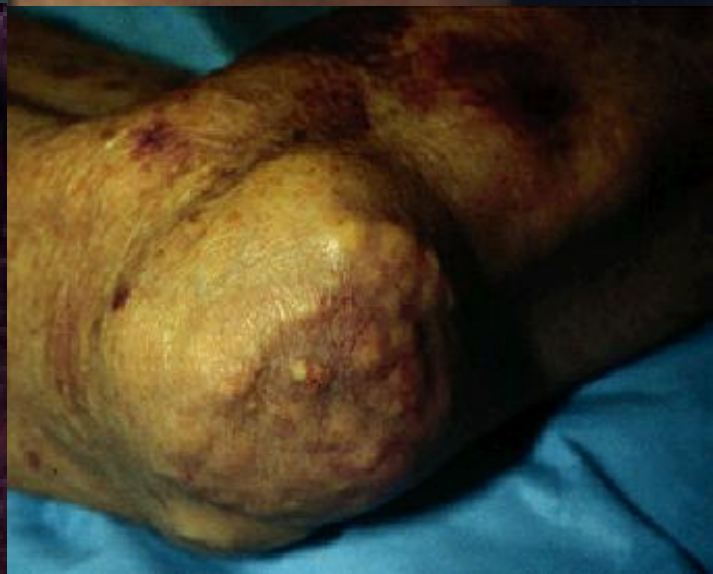






Gout: *tophuses* – accumulation of uric acid salts in cartilages, under skin.

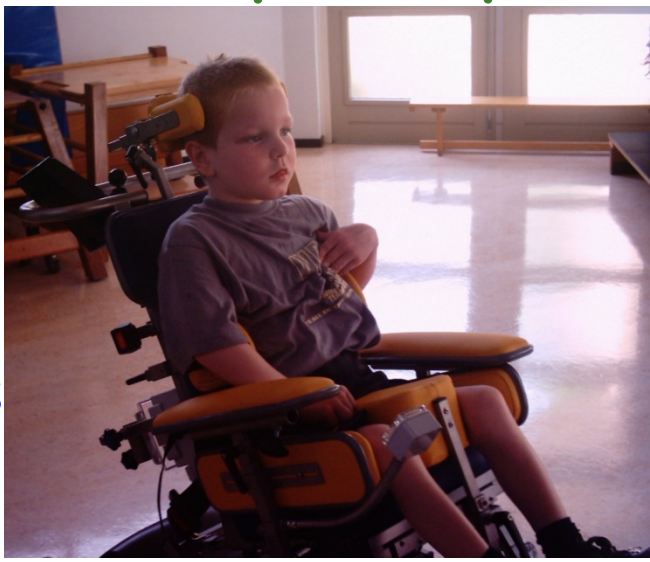




Lesch-Nyhan Syndrom: is a inherited disorder caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase. LNS is present at birth in baby boys.

Hypoxanthine and guanine are not used in the salvage pathway of purine nucleotides synthesis.

Hypoxanthine and guanine are not utilizied repeatedly but converted into uric acid.



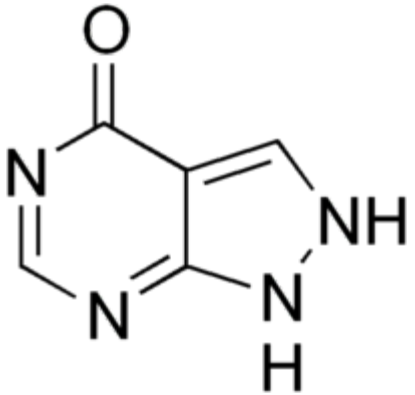
Symptoms:

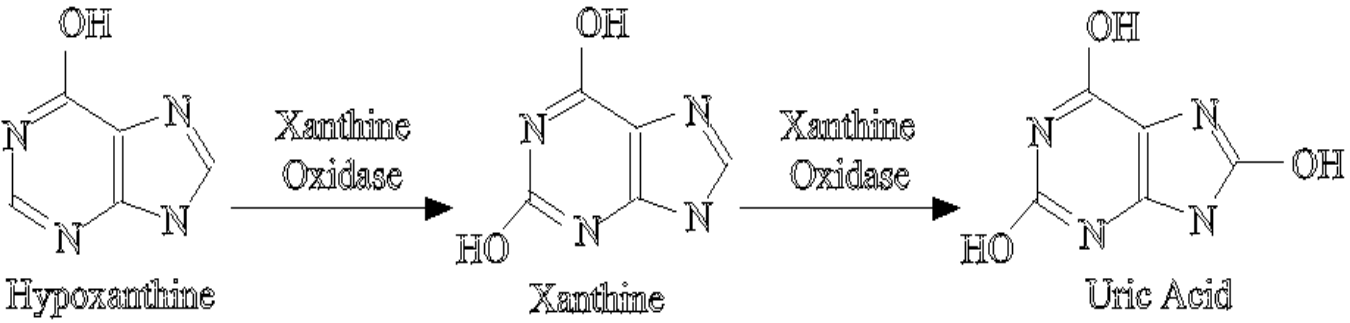
- severe gout

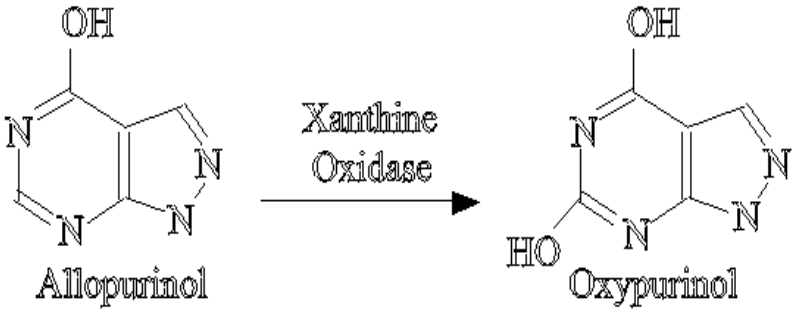
-severe mental and physical problems

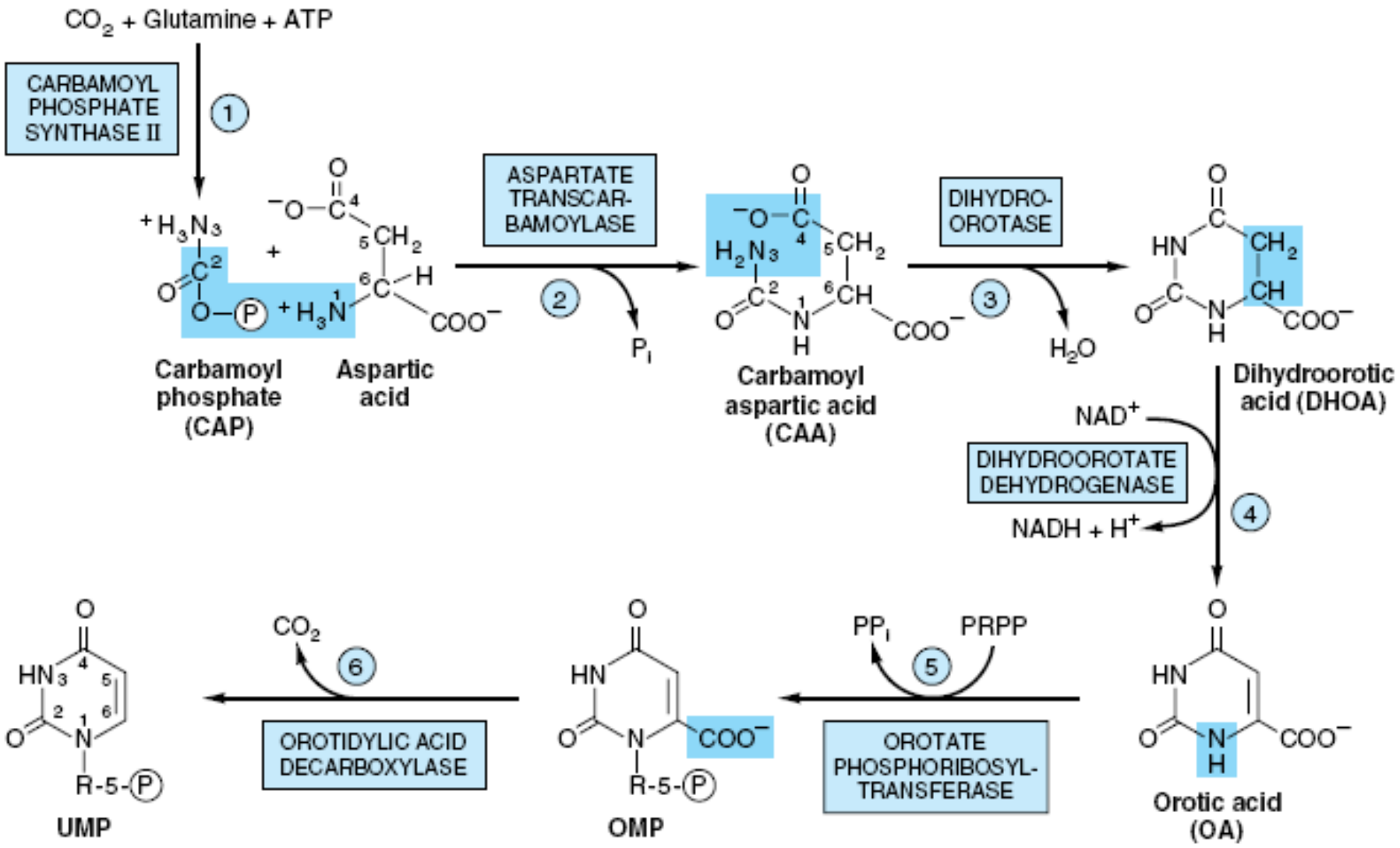
- self-mutilating behaviors

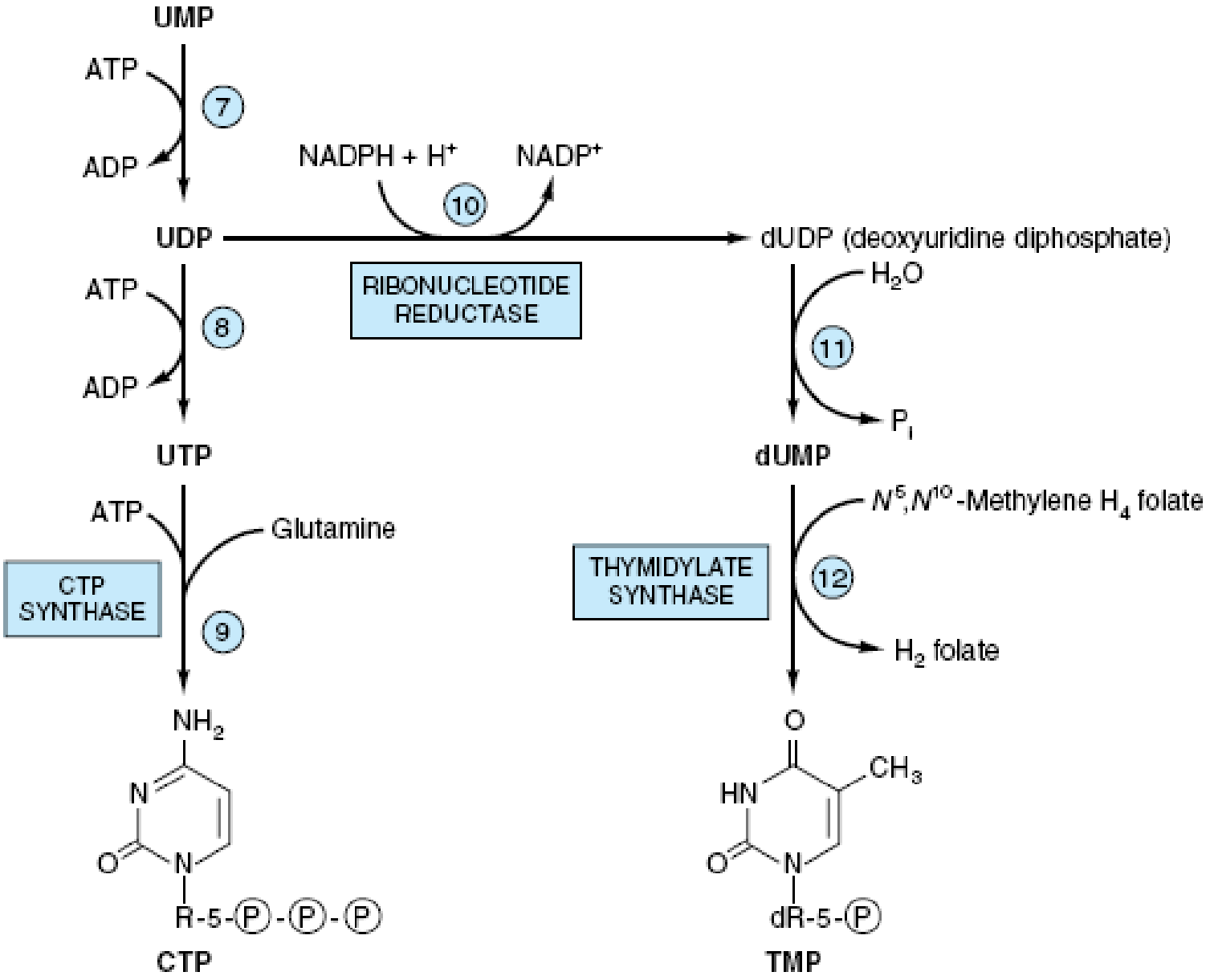
Treatment: *allopurinol* – competitive inhibitor of xanthine oxidase



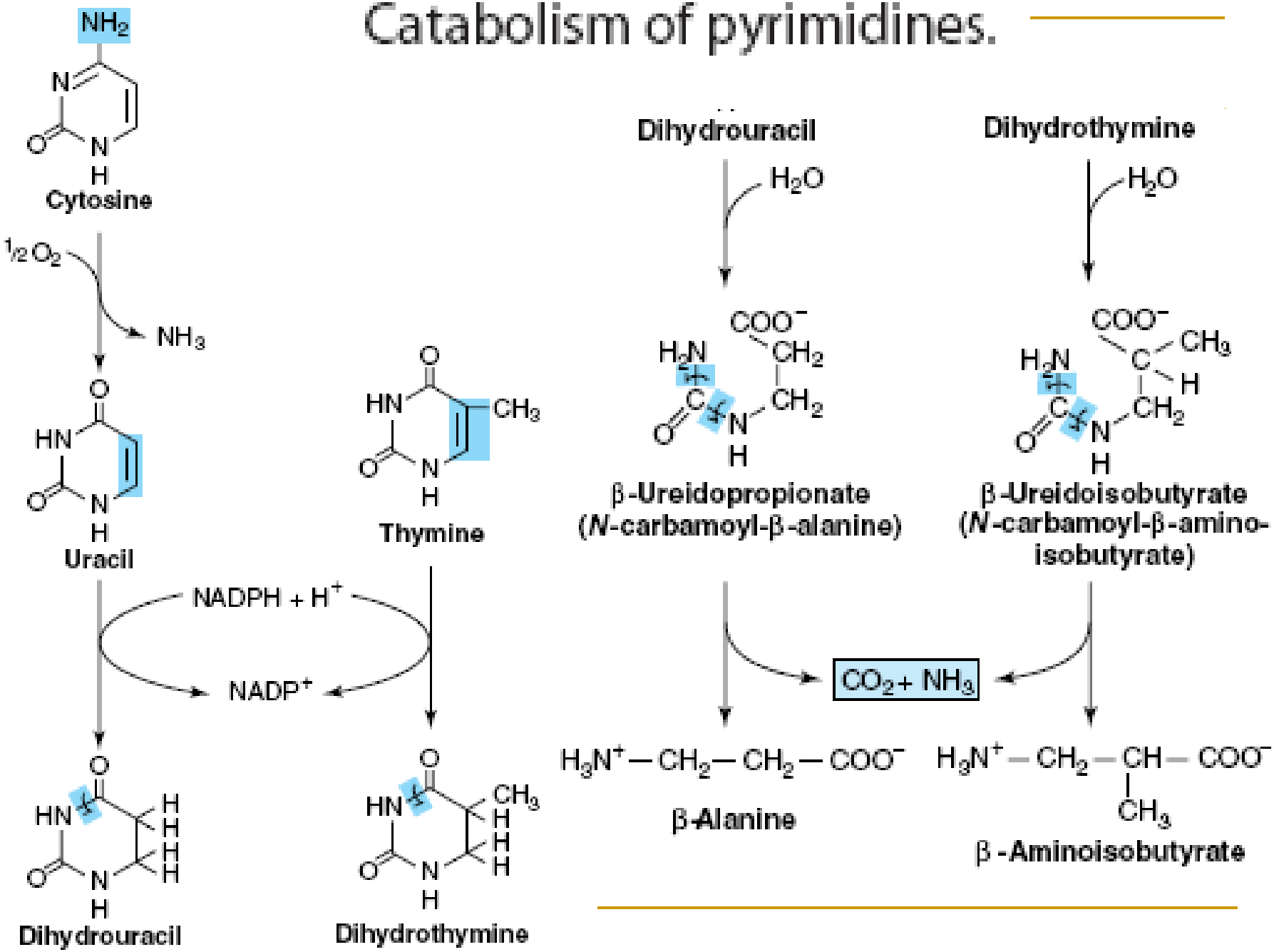





CO_2 + Glutamine + ATP
CARBAMOYL PHOSPHATE SYNTHASE II
1
Carbamoyl phosphate (CAP)
Aspartic acid
ASPARTATE TRANSCAR-BAMOYLASE
2
P_i
Carbamoyl aspartic acid (CAA)
DIHYDRO-OROTASE
3
H_2O
Dihydroorotic acid (DHOA)
NAD^+
DIHYDROOROTATE DEHYDROGENASE
$NADH + H^+$
4
Orotic acid (OA)
PP_i
PRPP
5
OROTATE PHOSPHORIBOSYL-TRANSFERASE
OMP
CO_2
6
OROTIDYLIC ACID DECARBOXYLASE
UMP


UMP
ATP
7
ADP
NADPH + H+
NADP+
10
UDP
dUDP (deoxyuridine diphosphate)
RIBONUCLEOTIDE REDUCTASE
ATP
8
ADP
H2O
11
Pi
UTP
dUMP
ATP
Glutamine
CTP SYNTHASE
9
N5,N10-Methylene H4 folate
THYMIDYLATE SYNTHASE
12
H2 folate
NH2
N
O
N
R-5-P-P-P
CTP
O
HN
CH3
O
N
dR-5-P
TMP

Catabolism of pyrimidines.



OROTACIDURIA

inherited disorder of pyrimidine synthesis caused by a deficiency of the enzyme of *orotate-phosphoribosyltransferase* and *decarboxylase*.

Symptoms:

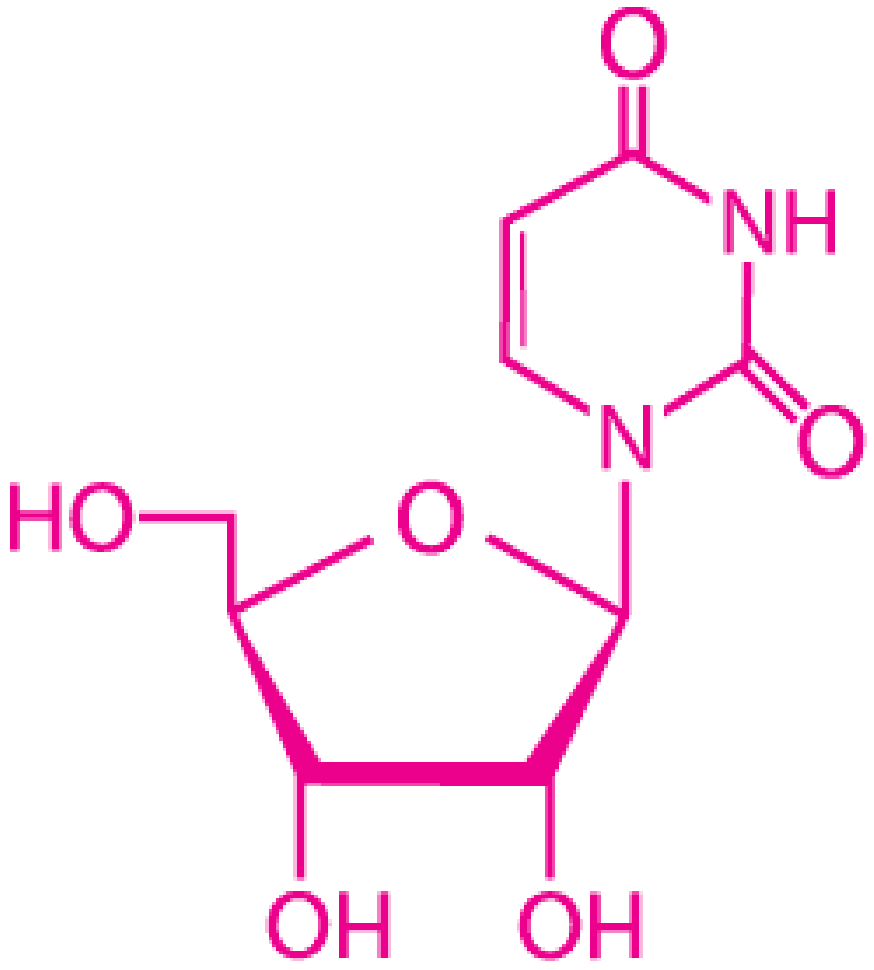
-excess of orotic acid and its excretion with urine (1.0-1.5 g)

-mental and physical retardation

-megaloblastic anemia

TREATMENT OF OROTACIDURIA

Taking of **uridin** during the whole life



Uridine

While purine deficiency states are rare in human subjects, there are numerous genetic disorders of purine catabolism. **Hyperuricemias** may be differentiated based on whether patients excrete normal or excessive quantities of total urates. Some hyperuricemias reflect specific enzyme defects. Others are secondary to diseases such as cancer or psoriasis that enhance tissue turnover.

Von Gierke's Disease

Purine overproduction and hyperuricemia in von Gierke's disease **(glucose-6-phosphatase deficiency)** occurs secondary to enhanced generation of the PRPP precursor ribose 5-phosphate. An associated lactic acidosis elevates the renal threshold for urate, elevating total body urates.

Genetic aberrations in human purine metabolism have been found, some with serious consequences.

For example, **adenosine deaminase (ADA) deficiency** leads to severe immunodeficiency disease in which T lymphocytes and B lymphocytes do not develop properly. Lack of ADA leads to a 100-fold increase in the cellular concentration of dATP, a strong inhibitor of ribonucleotide reductase