Author(s): Dr. Robert Lyons, 2009

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M1 Renal:

Nucleotide Metabolism

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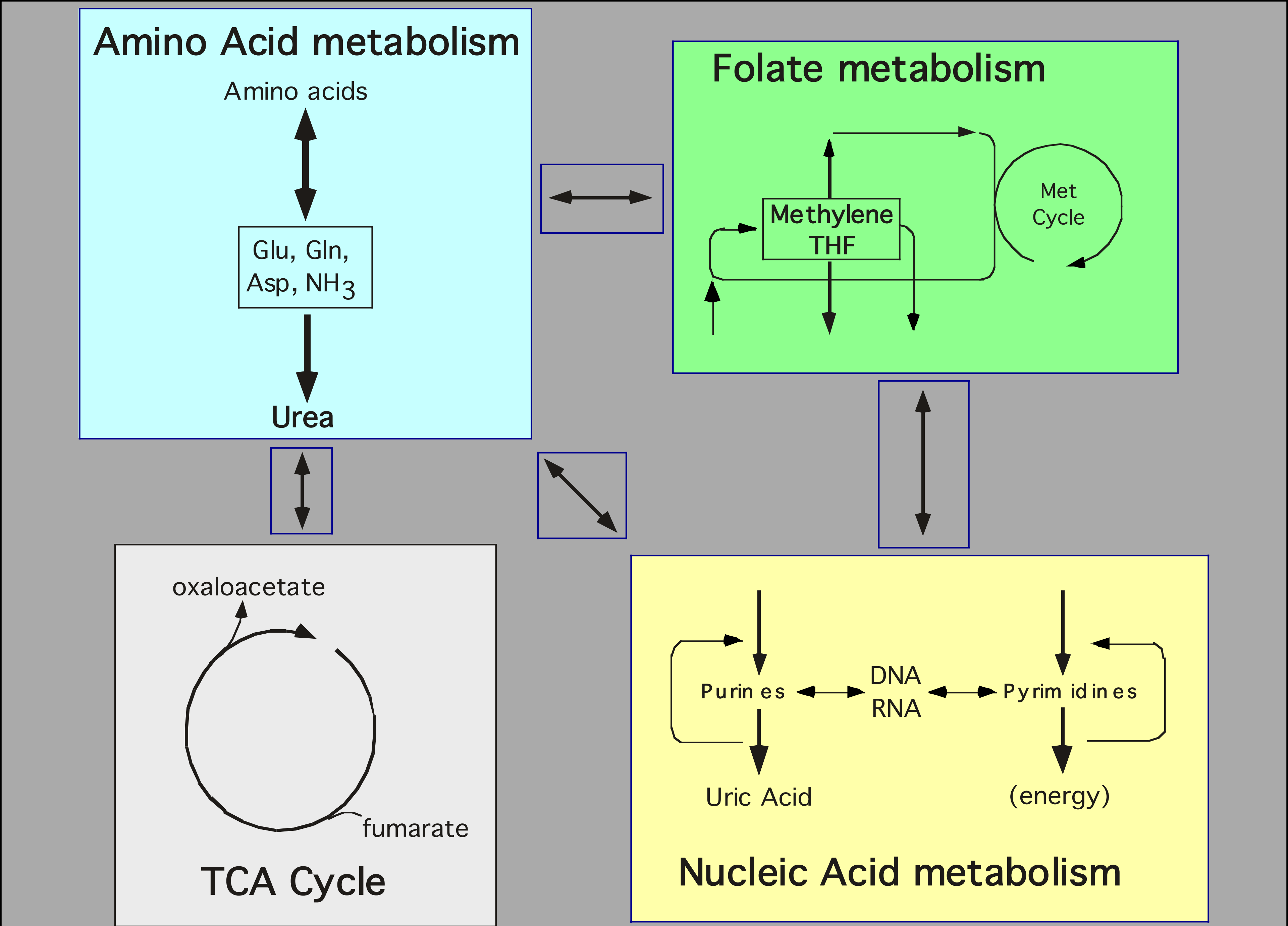
Assistant Professor, Biological Chemistry
Director, DNA Sequencing Core

Web: http://seqcore.brcf.med.umich.edu/mcb500

Fall 2008

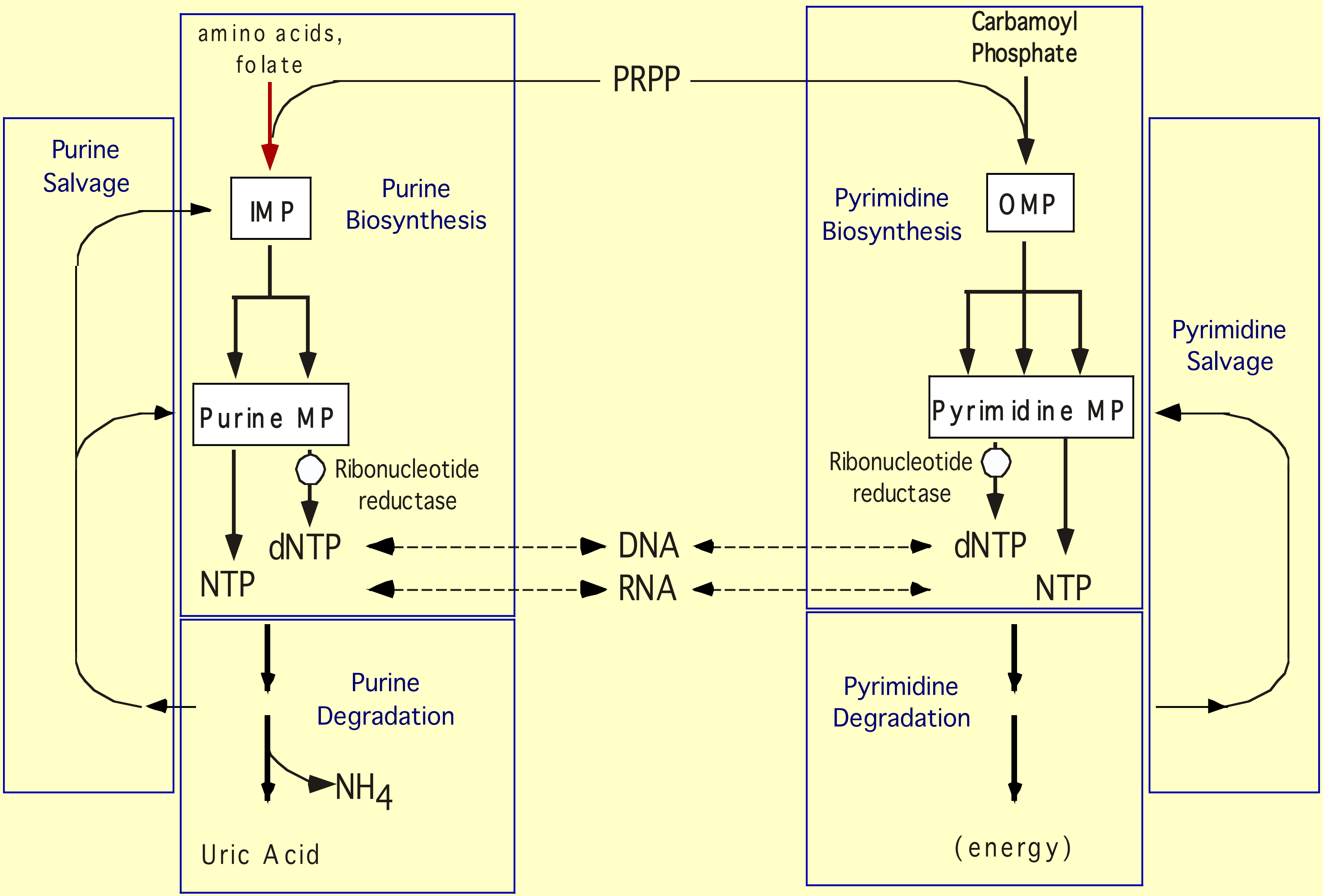
University of Michigan Medical School



Amino Acid metabolism
Amino acids
Glu, Gln, Asp, NH_3
Urea
Folate metabolism
Methylene THF
Met Cycle
oxaloacetate
fumarate
TCA Cycle
Purines
DNA
RNA
Pyrimidines
Uric Acid
(energy)
Nucleic Acid metabolism

Nucleic Acid metabolism

Click on any blue rectangle to see details.



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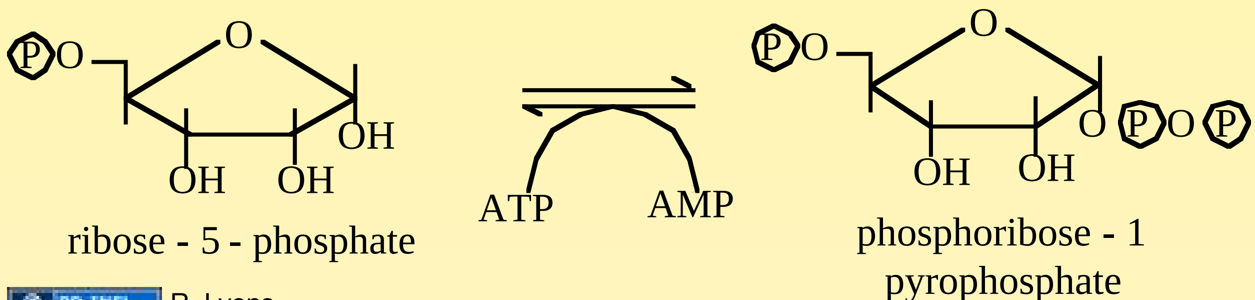
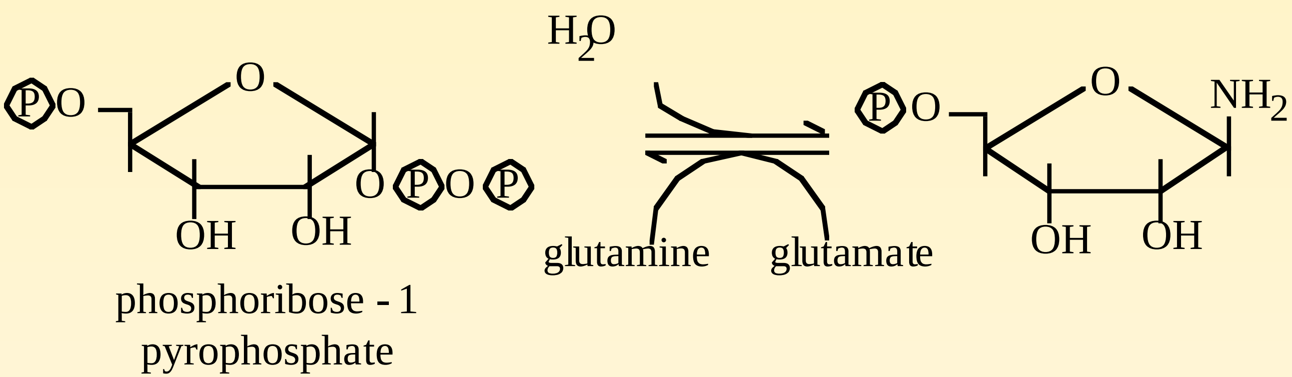
Formation of PRPP: Phosphoribose pyrophosphate

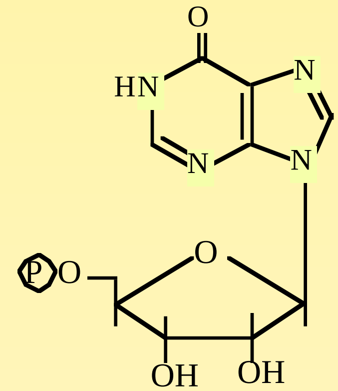


PRPP Use in Purine Biosynthesis:



The First Purine: Inosine Monophosphate

(folates are involved in this synthesis)



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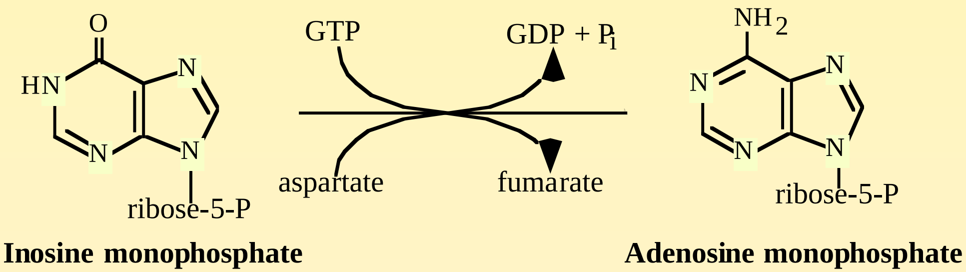
Conversion to Adenosine:



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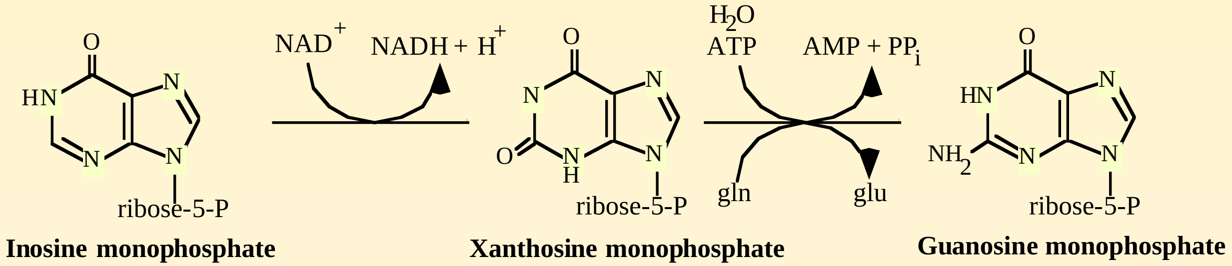
Conversion to Guanosine:



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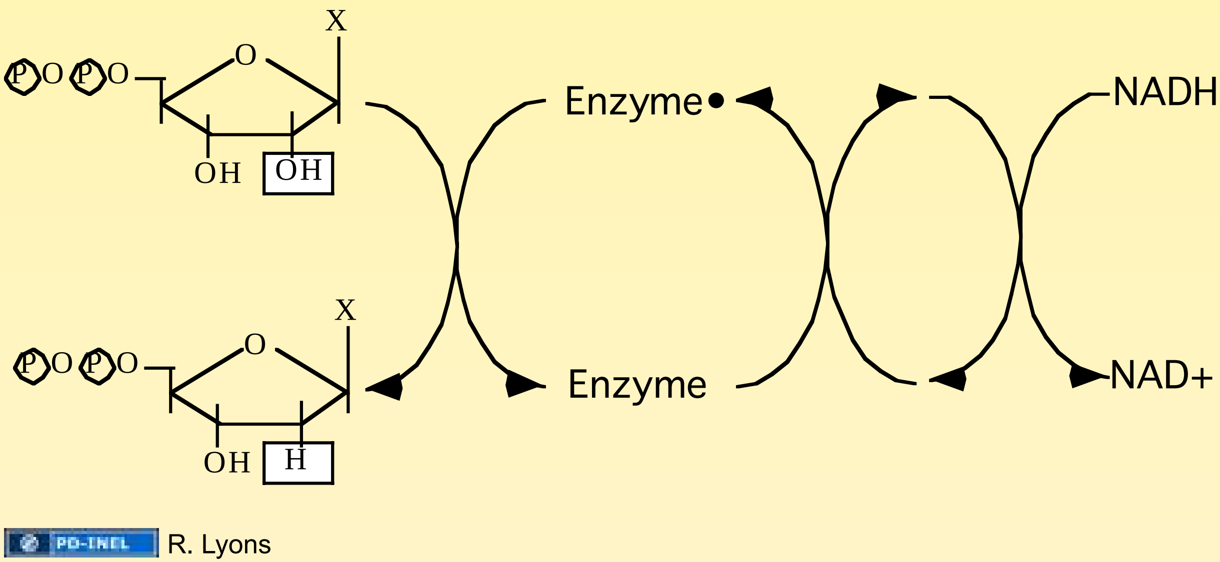
Nucleoside Monophosphate Kinases

AMP + ATP <--> 2ADP (adenylate kinase)

GMP + ATP <---> GDP + ADP (guanylate kinase)

- similar enzymes specific for each nucleotide
- no specificity for ribonucleotide vs. deoxyribonucleotide

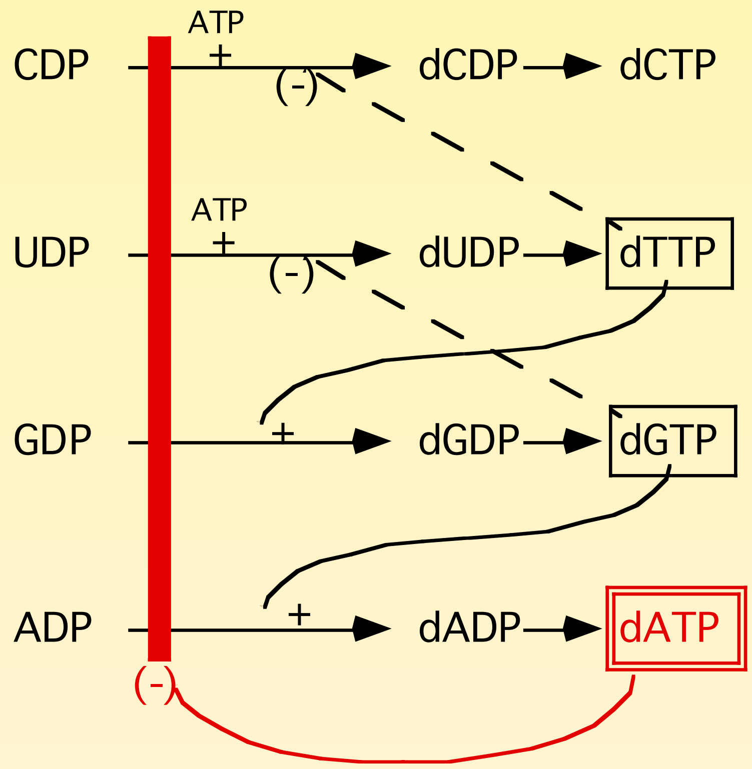
Ribonucleotide Reductase



Hydroxyurea inhibits this enzyme: chemotherapeutic use

$$HONH-\overset{\overset{\displaystyle O}{||}}{C}-NH_2$$

Regulation of Ribonucleotide Reductase



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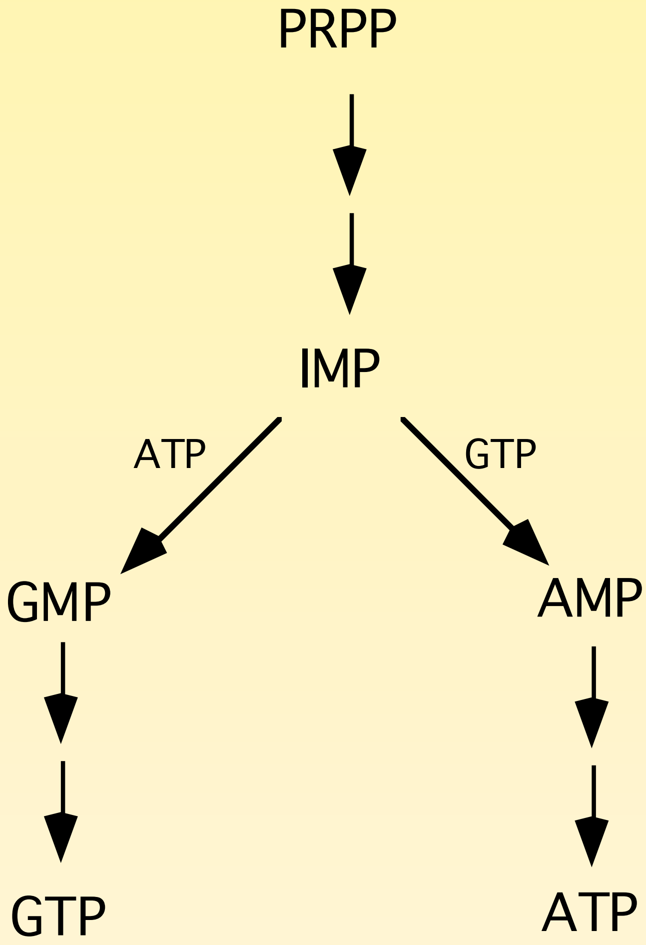
Nucleoside Diphosphate Kinase

$$N_1DP + N_2TP \ \text{<-->}\ N_1TP + N_2DP$$

$$dN_1DP + N_2TP \ \text{<-->}\ dN_1TP + N_2DP$$

- No specificity for base
- No specificity for ribo vs deoxy

Feed-forward regulation by PRPP



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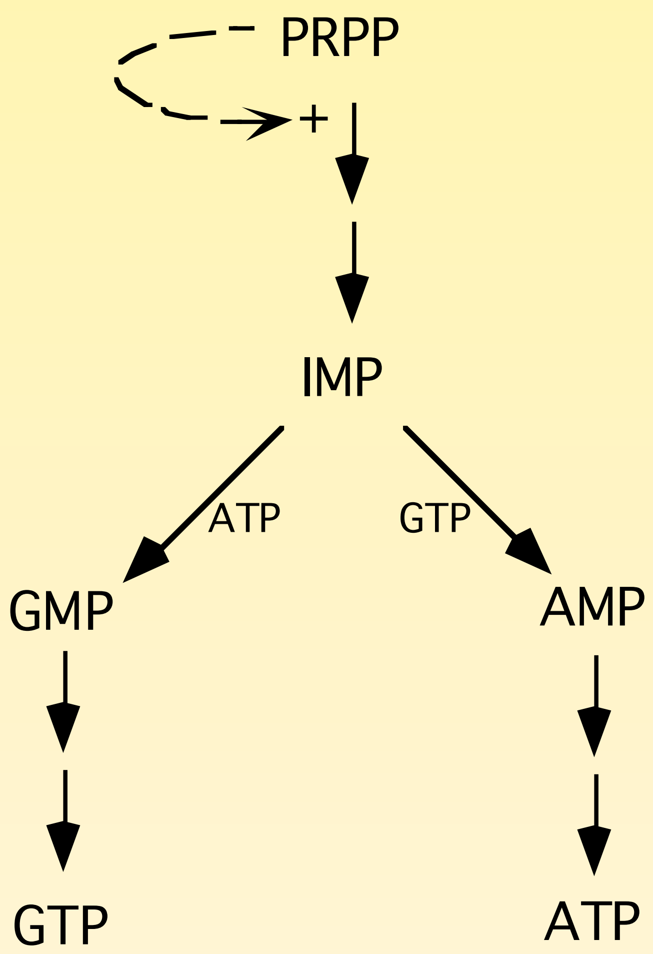
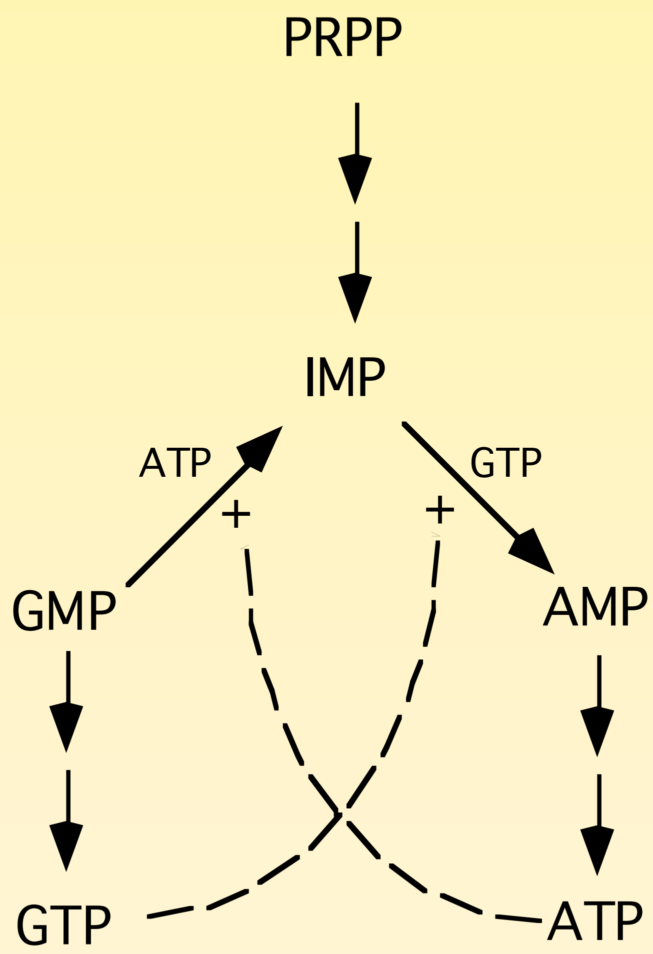
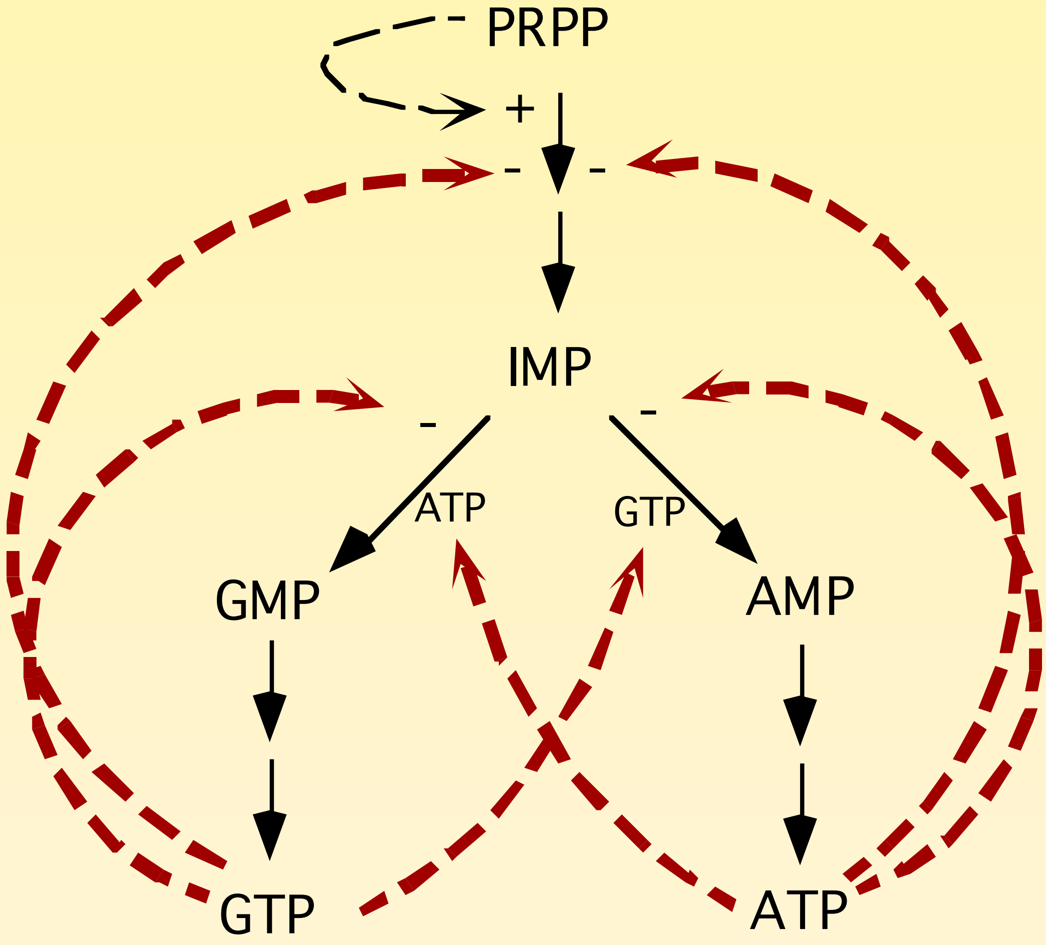
Feed-forward regulation by PRPP



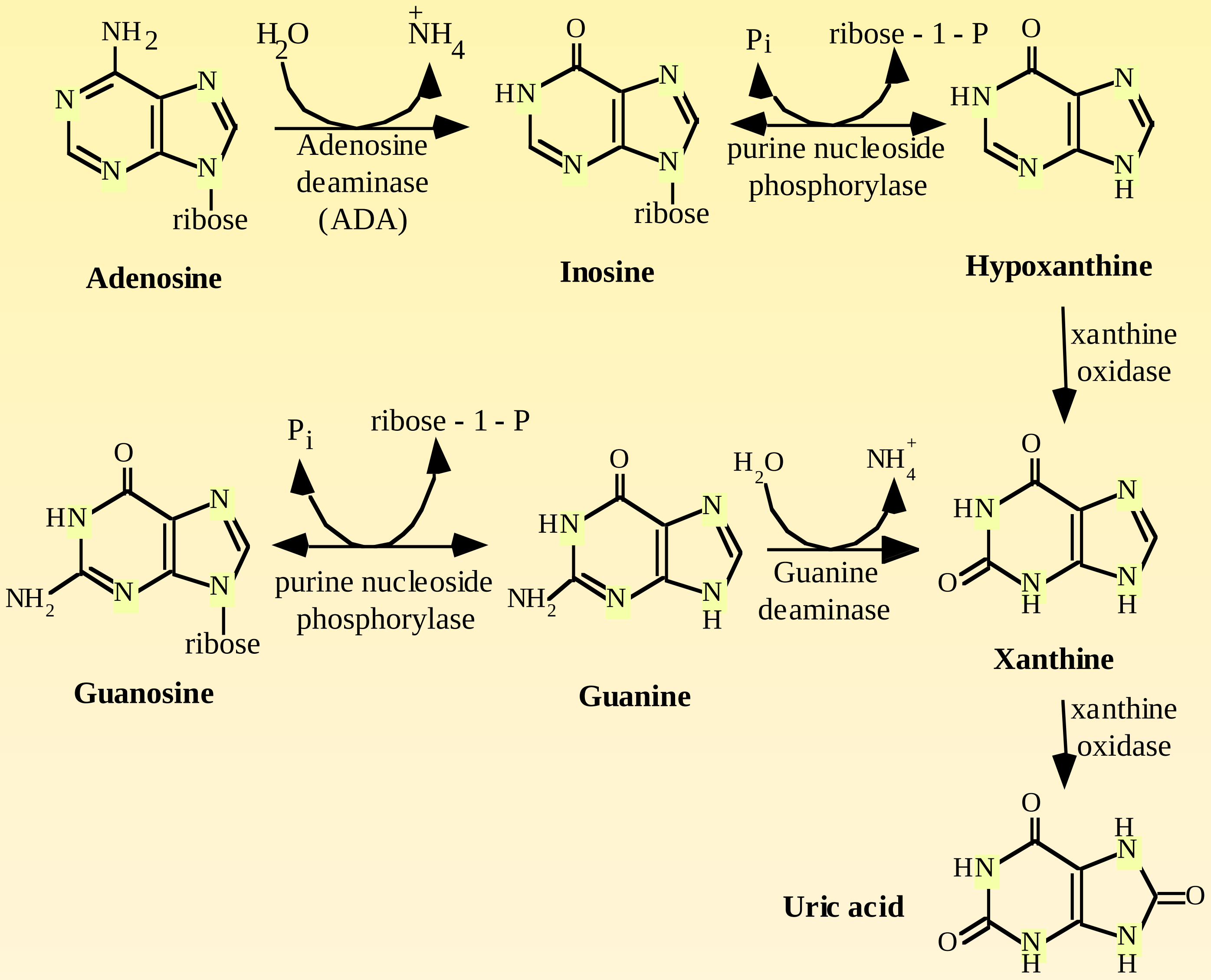
Feed-forward regulation by PRPP



Feed-forward regulation by PRPP



Degradation of the Purine Nucleosides:



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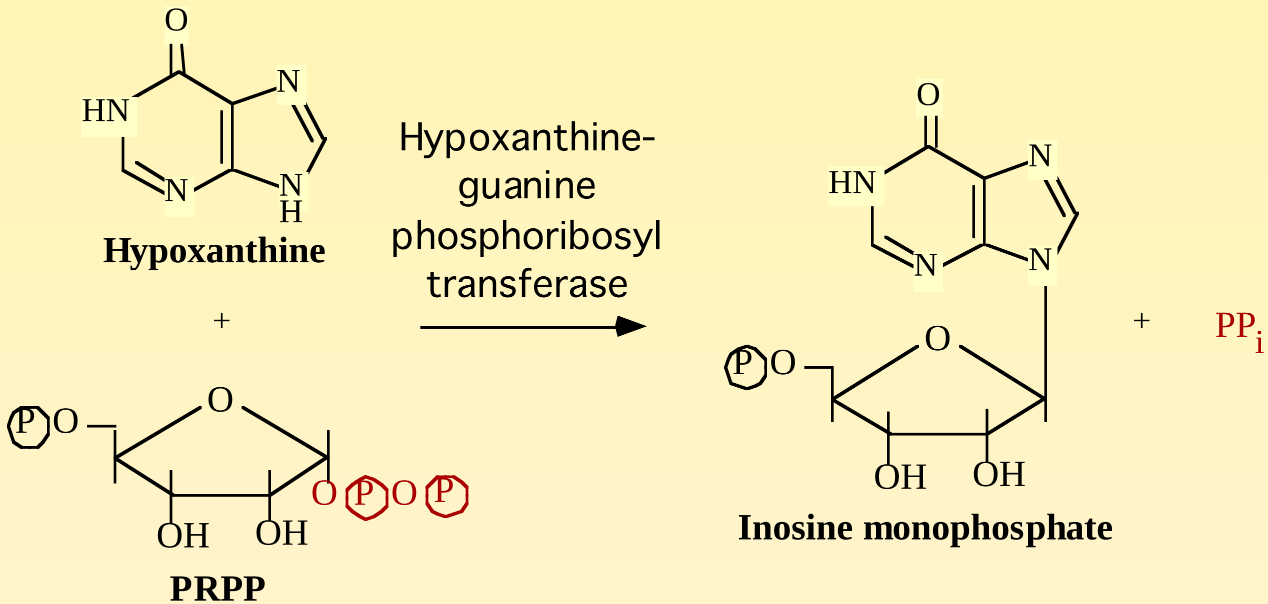
“Salvage” Pathways for Purine Nucleotides



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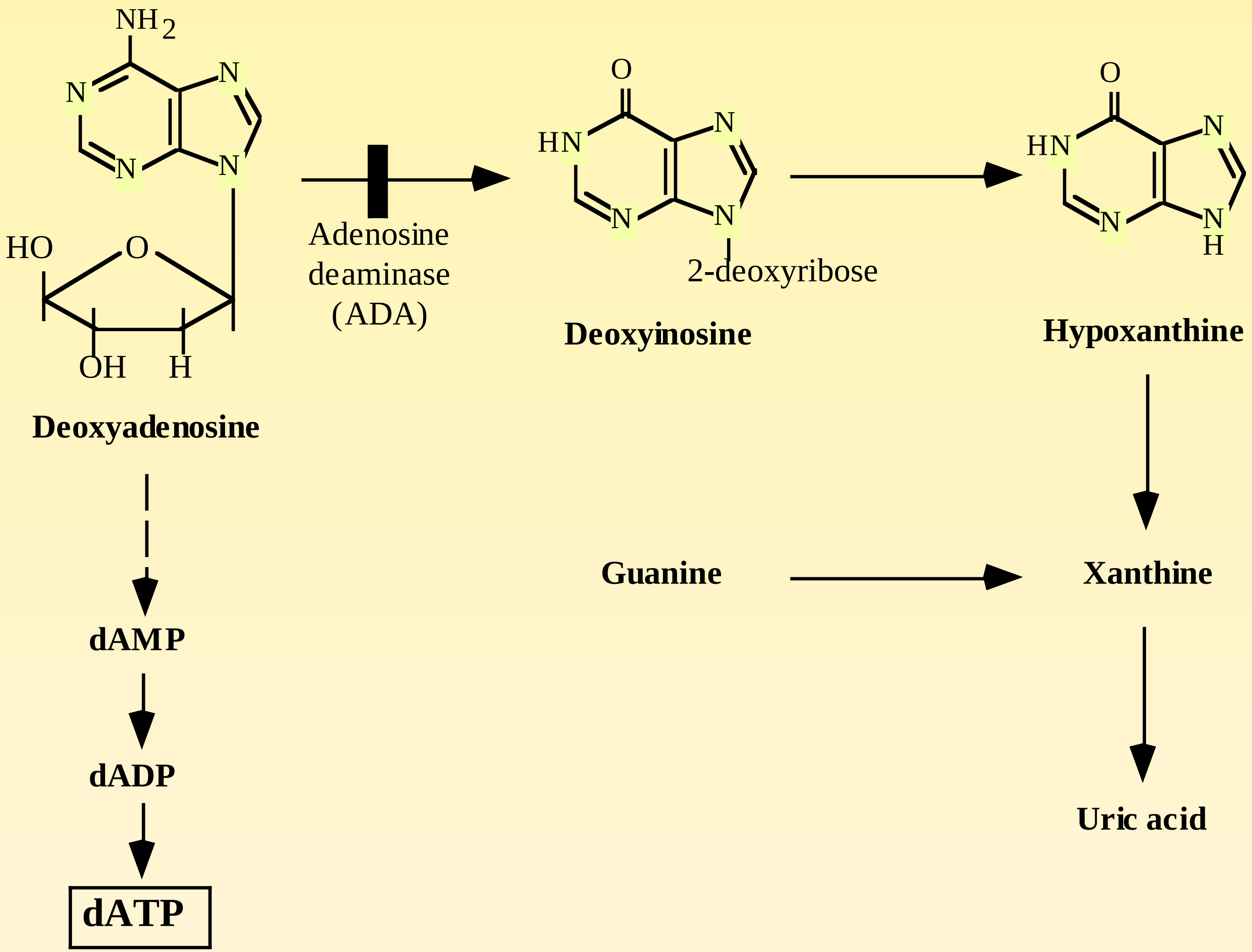
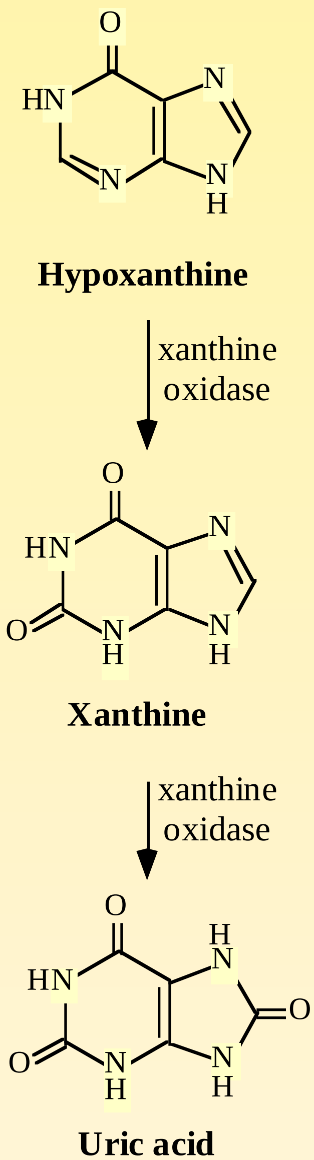
APRT - Adenine phosphoribosyl transferase - performs a similar function with adenine.

Adenosine Deaminase Deficiency:





Gout: deposition of urate crystals in joints, "tophi" in cooler periphery

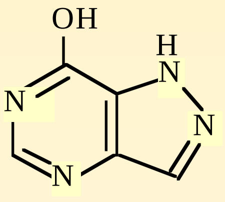
Hyperuricemia can be caused by:

Accelerated degradation of purines:

- Accelerated synthesis of purines
- Increased dietary intake of purines

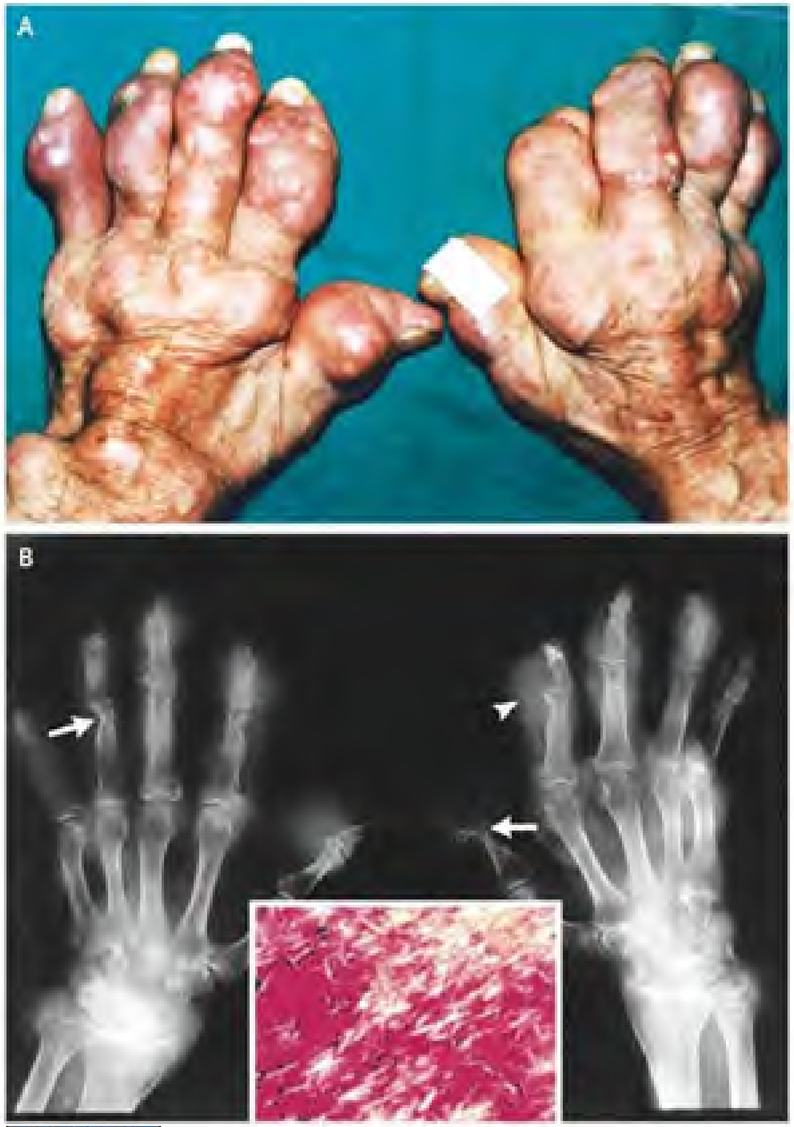
Impaired renal clearance of uric acid

Allopurinol inhibits xanthine oxidase and reduces blood uric acid levels:



Allopurinol

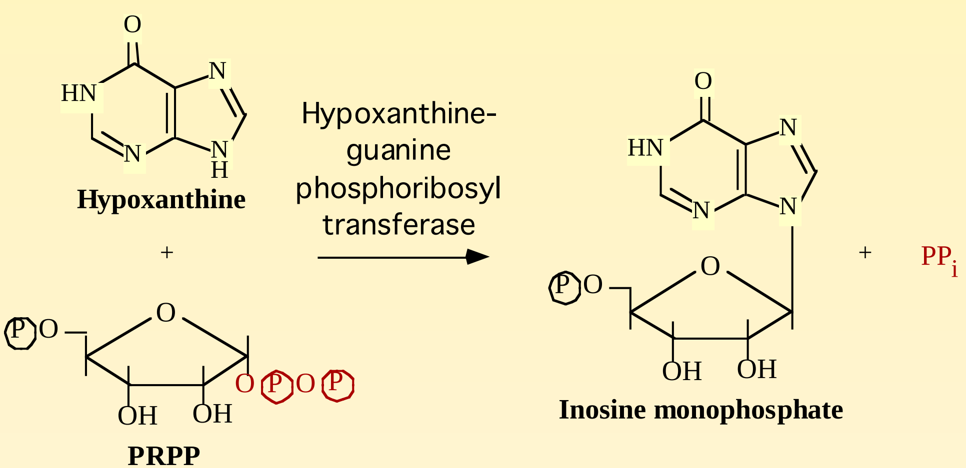
An 80-year-old man with a 30-year history of gout, this patient had been treated intermittently to reduce his serum urate levels.



PD-INEL The New England Journal of Medicine

Lesch-Nyhan Syndrome: Defective HGPRT

- hyperuricemia
- spasticity
- mental retardation
- self-mutilation behavior



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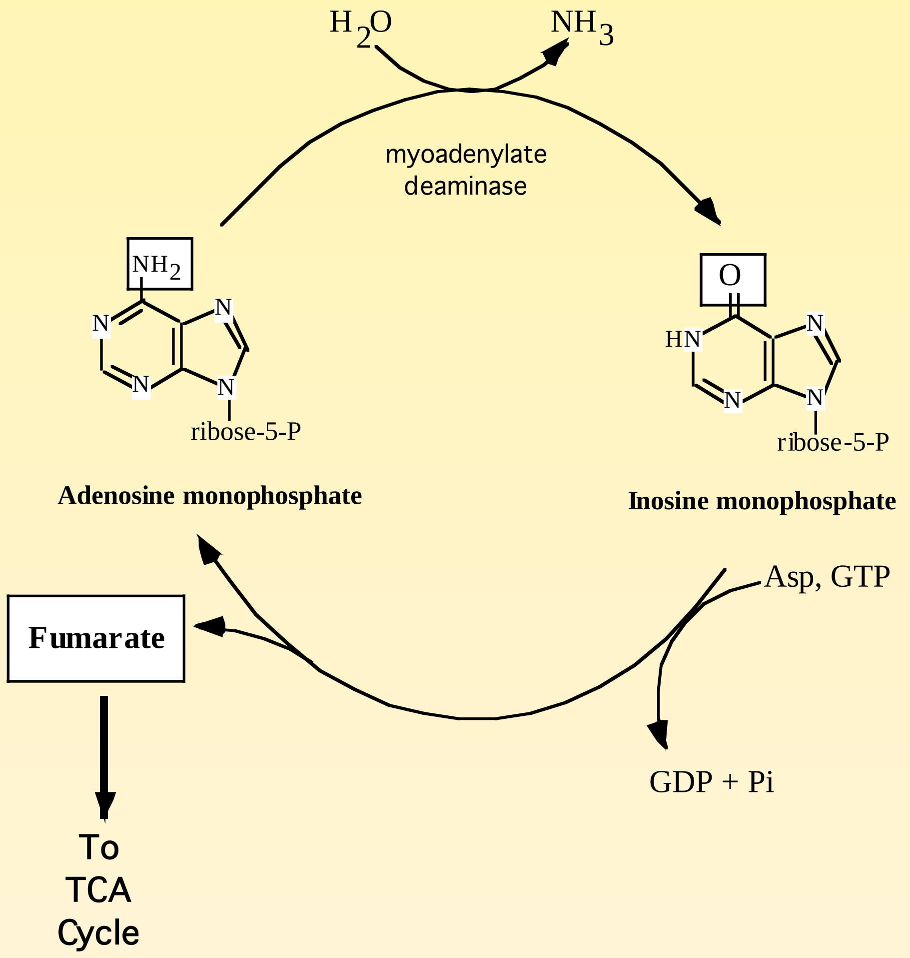
A defect in APRT does NOT have similar consequences

Myoadenylate Deaminase 'Fills' the TCA Cycle in Muscle



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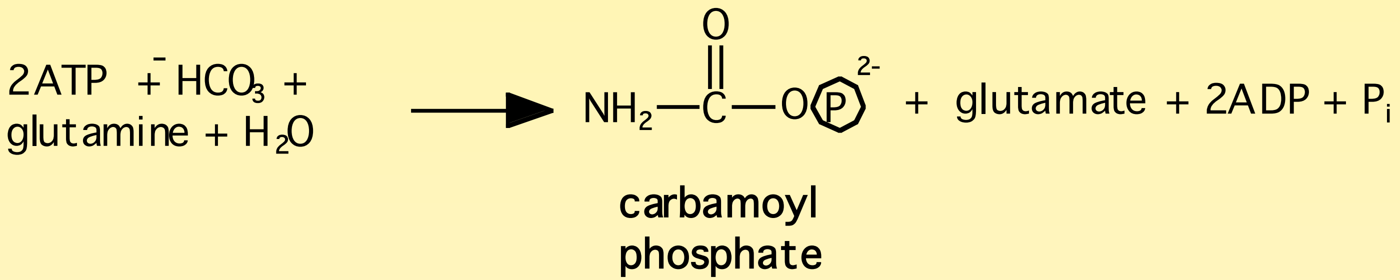
Carbamoyl phosphate synthetase II - a *cytoplasmic* enzyme…



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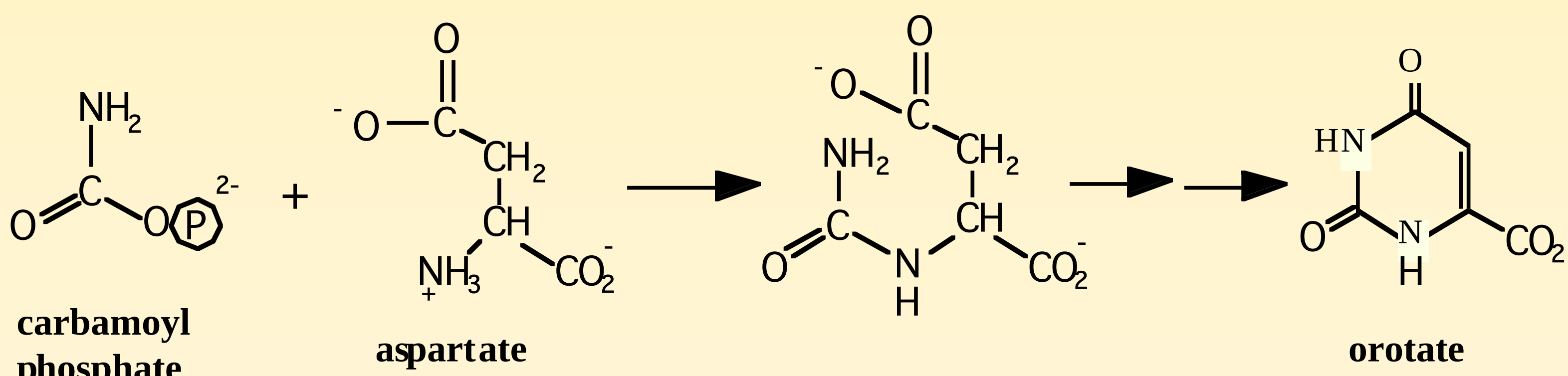
…used for pyrimidine synthesis



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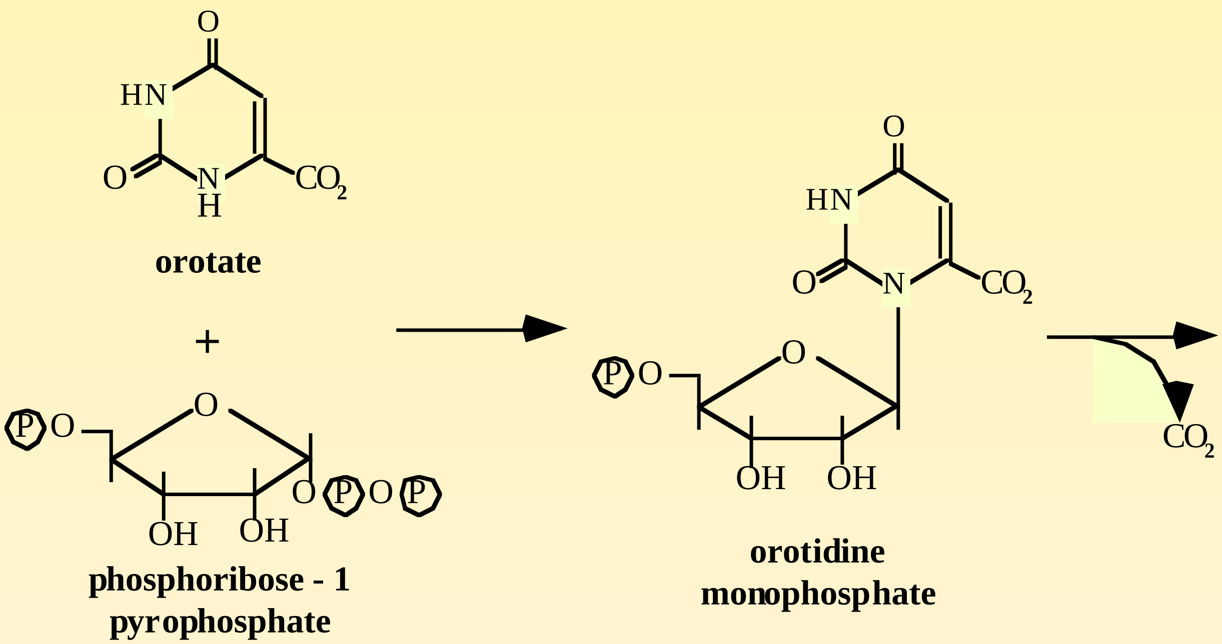
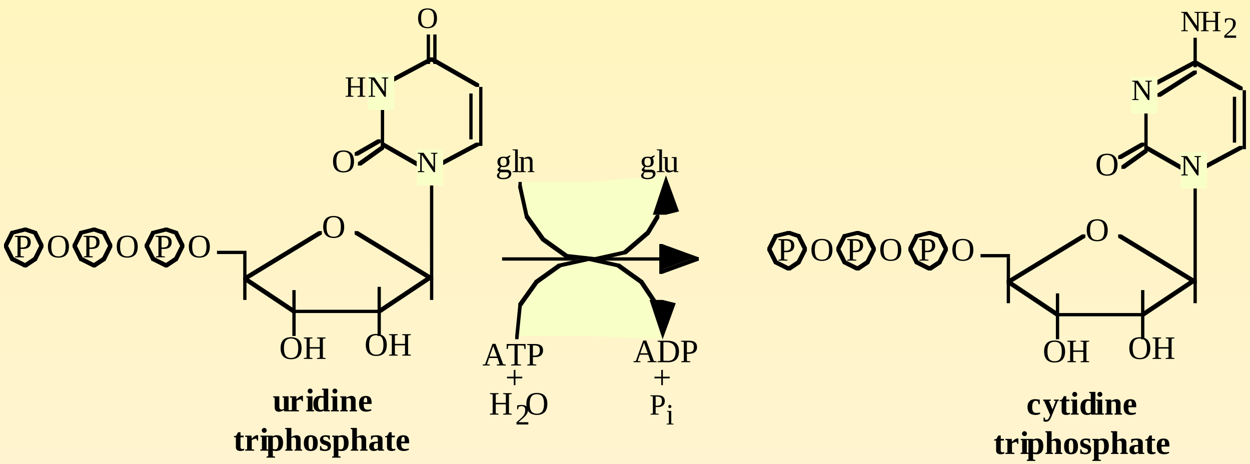
Orotate is linked to PRPP to form Uridine monophosphate:

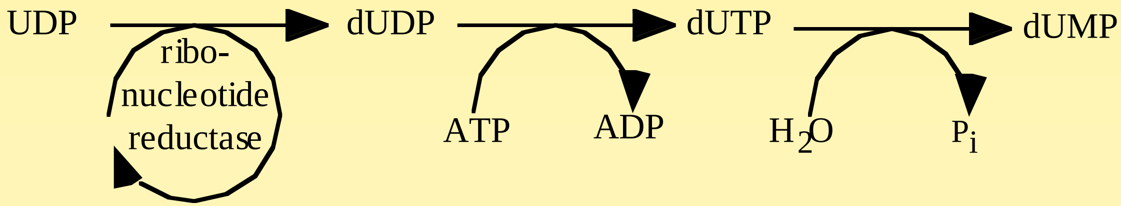


Newly-synthesized uridine monophosphate will be phosphorylated to UDP and UTP, as described for the purine nucleotides.

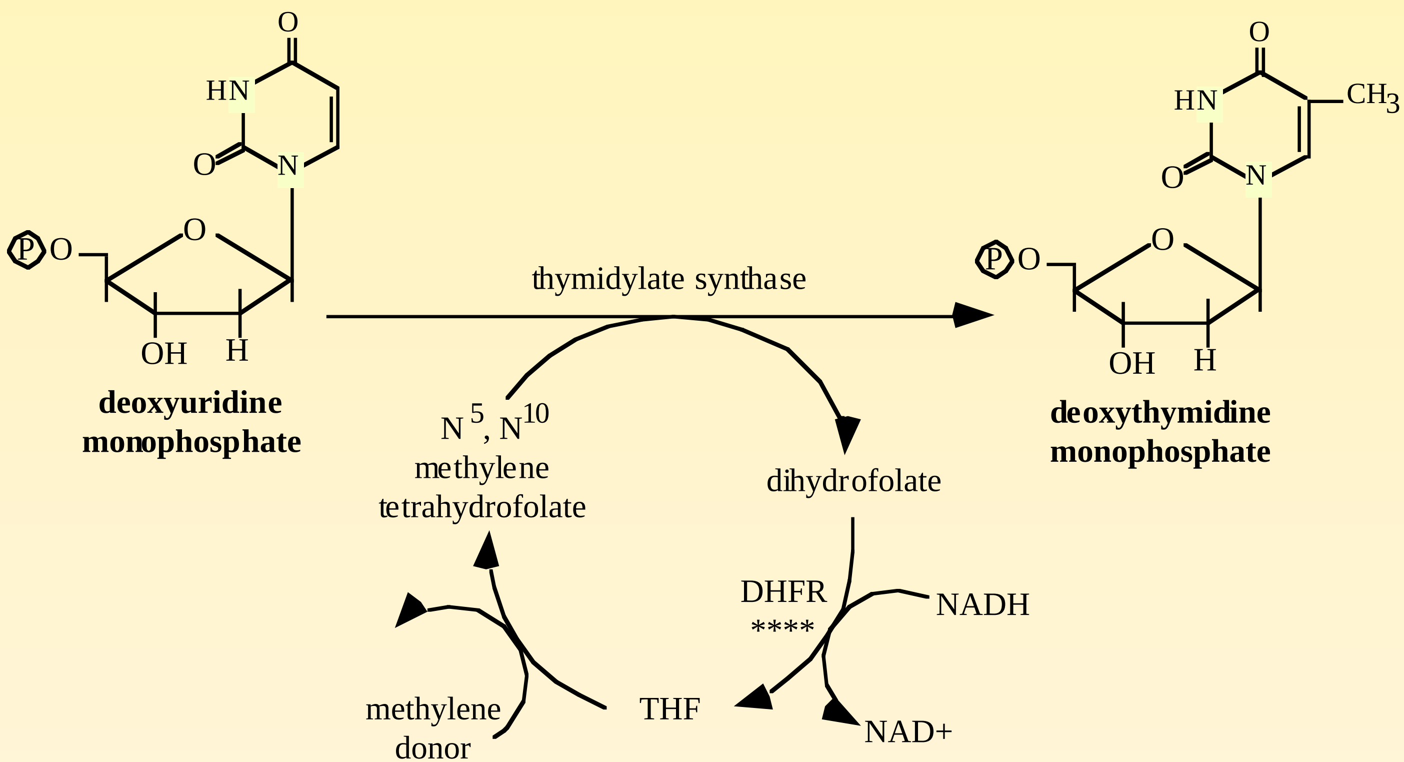
UTP can be converted to CTP by CTP Synthetase:



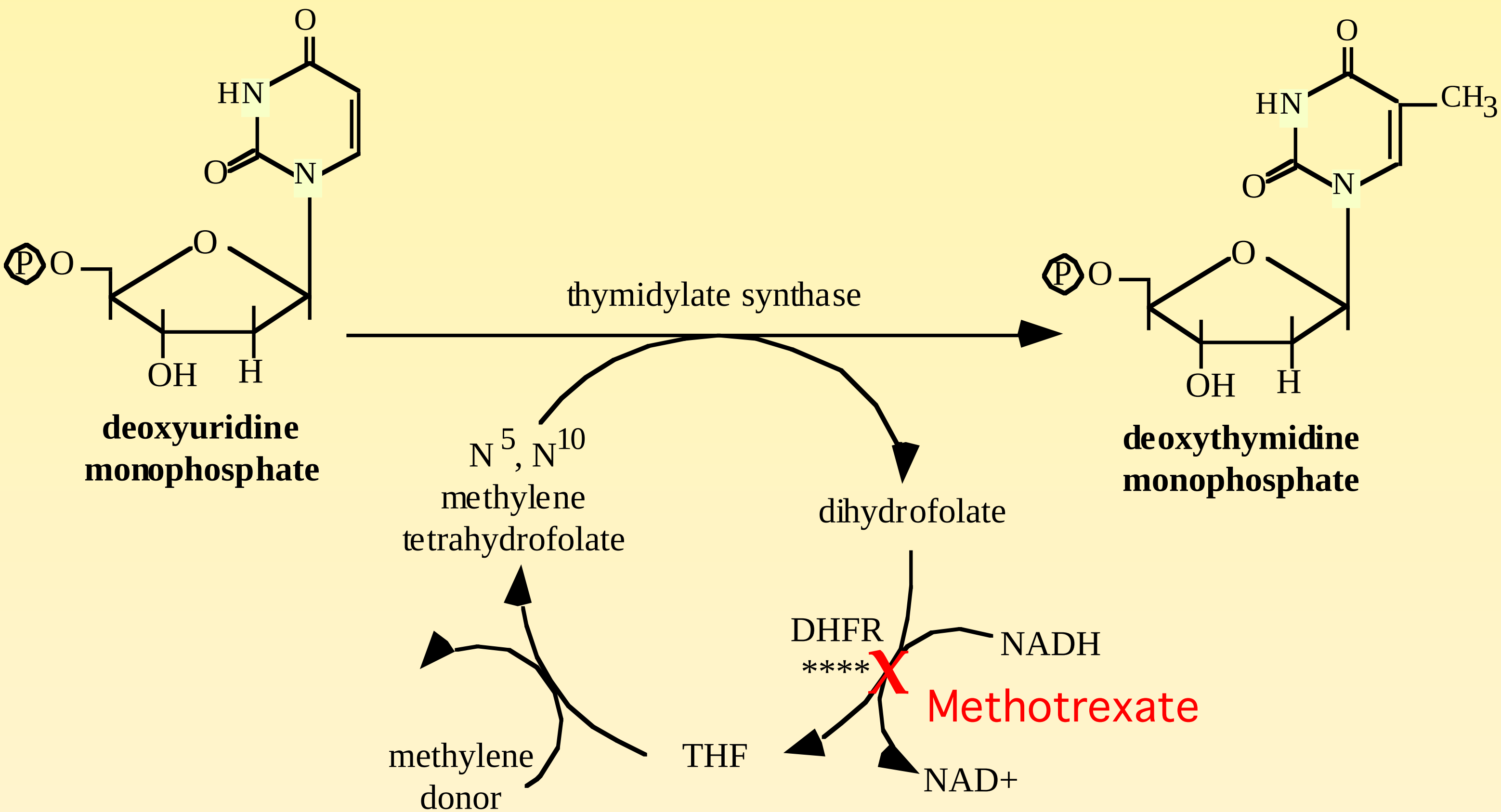
Some UDP is converted to dUDP via ribonucleotide reductase.



The Thymidylate Synthase Reaction:



Methotrexate Inhibits Dihydrofolate Reductase:



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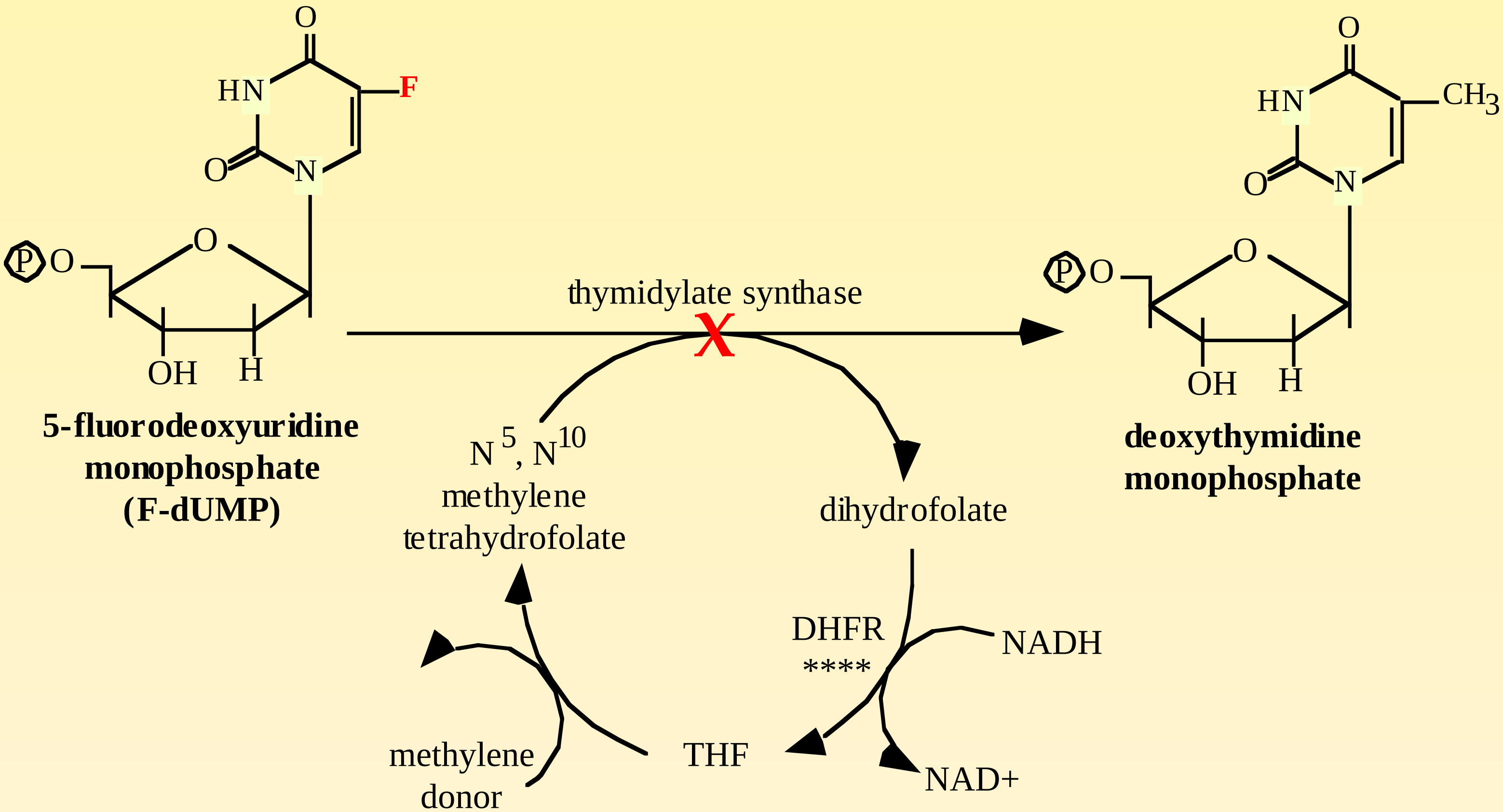
Dihydrofolate builds up, levels of THF become limiting, thymidylate synthase is unable to proceed. Follow it with a dose of Leucovorin, a.k.a. formyl-THF.

FdUMP Inhibits The Thymidylate Synthase Reaction:



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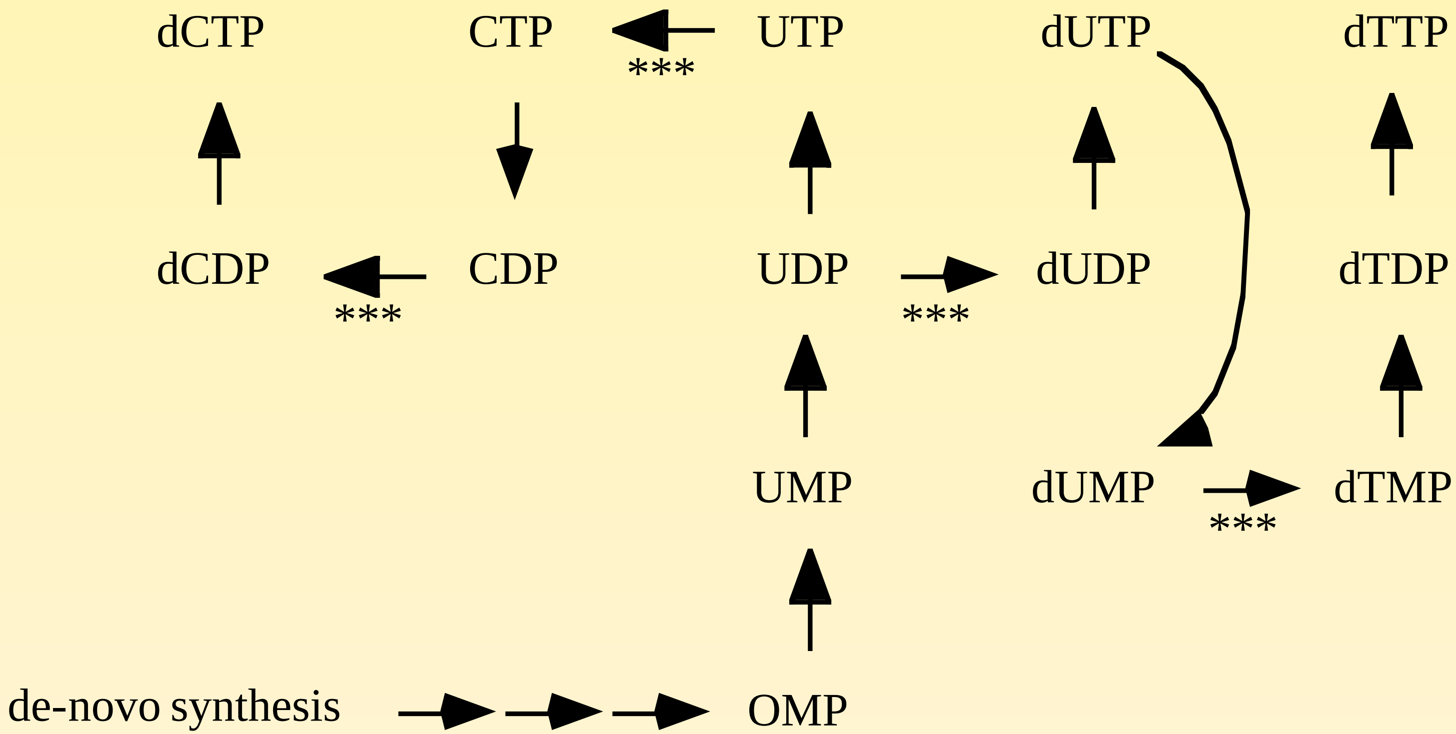
Complicated Pathways for Pyrimidine Production:



This figure is primarily a study aid; you do not need to memorize it or reproduce it. The information here merely summarizes material from previous sections.

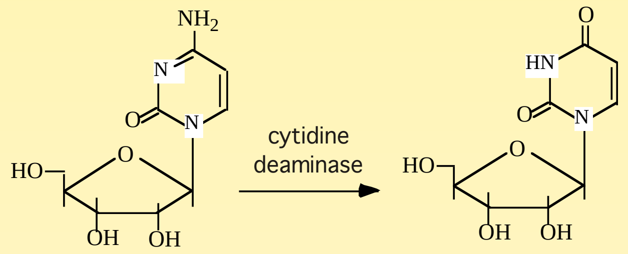
Pathologies of pyrimidine nucleotide biosynthesis:

Orotic acidurea due to OTC deficiency - please review your Urea Cycle notes.

Hereditary orotic acidurea - deficiency of the enzyme that convert orotate to OMP to UMP. Not common.

Pyrimidine degradation:

Cytidine deaminase converts cytidine to uridine



Cytidine **Uridine**

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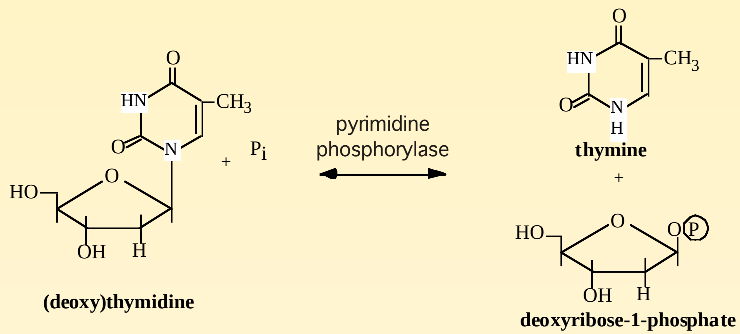
A phosphorylase removes the sugar



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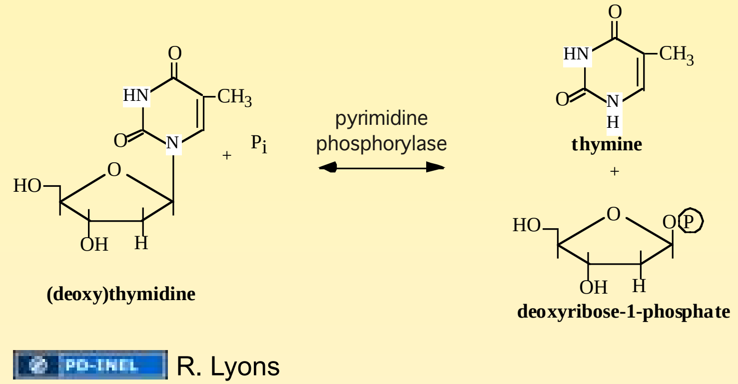
Degradation of the base proceeds (products are unimportant here)

Pyrimidines can be salvaged as well:

Enzyme: Pyrimidine nucleoside phosphorylases

Thymine + deoxyribose-1-phosphate --> thymidine
(NOT thymidine monophosphate!)

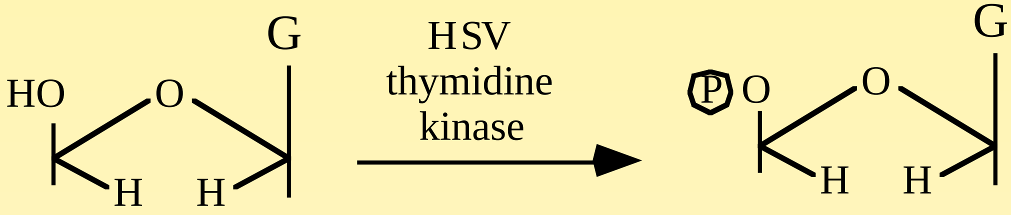


Enzyme: Thymidine kinase - adds the monophosphate back

Thymidine + ATP --> thymidine monophosphate

Herpes Simplex Virus carries its own tk gene

Certain drugs act via the pyrimidine salvage pathway:



Acyclovir **AcycloGMP**

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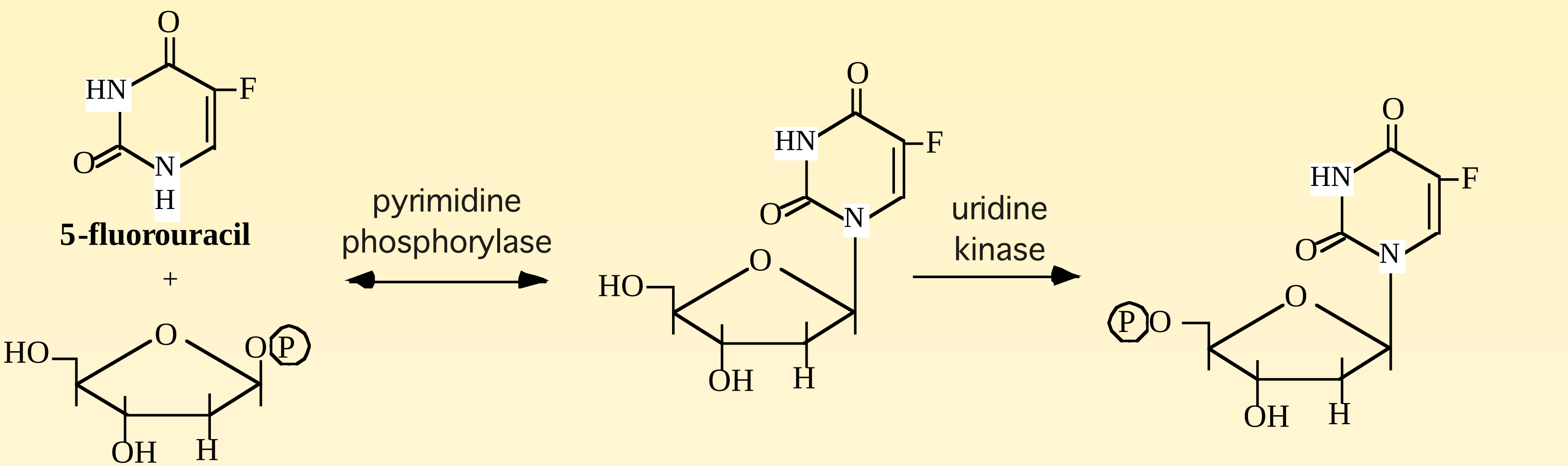

deoxyribose-1-phosphate **fluorodeoxyuridine** **fluorodeoxyuridine monophosphate (FdUMP)**

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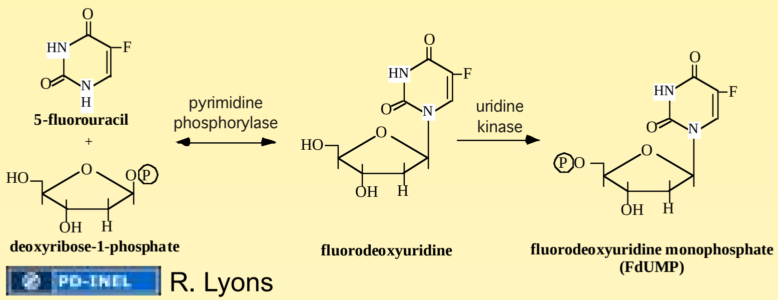
5-FU efficacy depends on rate of degradation vs activation



5-FU --> --> FdUMP

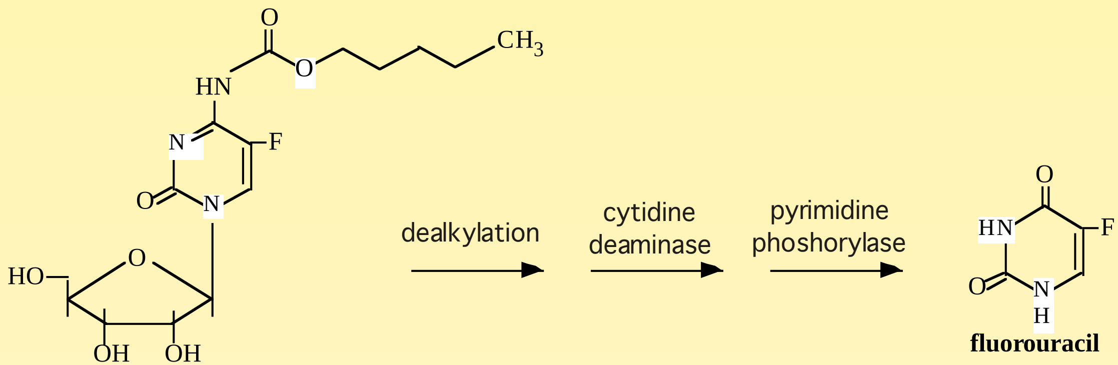
+ methylene-THF + Thymidylate Synthase

--> inactivation of TS

Degradation
(via dihydropyrimidine dehydrogenase, DPD

DPD inhibitors can potentiate 5FU activity

Capecitabine mode of action:



capecitabine

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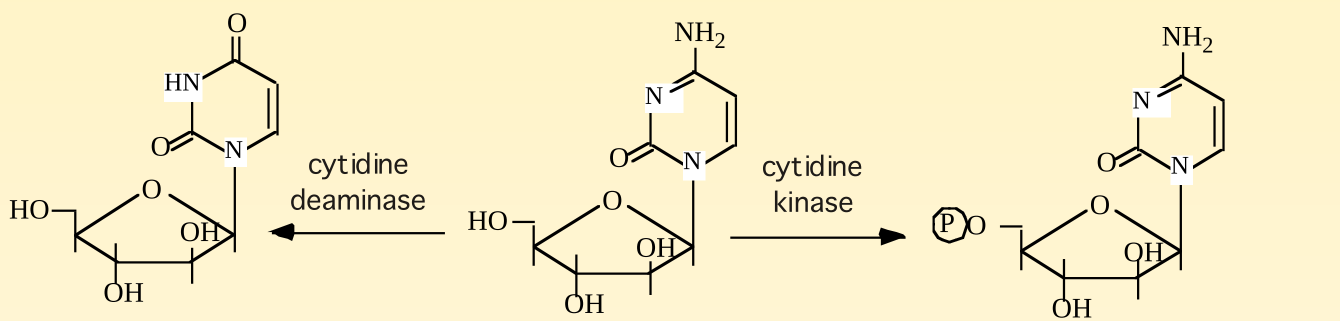
Cytosine arabinoside (araC) activation and inactivation:



Uridine arabinoside (INACTIVE)

Cytosine arabinoside (araC)

Cytosine arabinoside monophosphate (ACTIVE)

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