

Unless otherwise noted, the content of this course material is licensed under a Creative Commons Attribution – Share Alike 3.0 License.

Copyright 2007, Robert Lyons.

The following information is intended to inform and educate and is not a tool for self-diagnosis or a replacement for medical evaluation, advice, diagnosis or treatment by a healthcare professional. You should speak to your physician or make an appointment to be seen if you have questions or concerns about this information or your medical condition. You assume all responsibility for use and potential liability associated with any use of the material.

Material contains copyrighted content, used in accordance with U.S. law. Copyright holders of content included in this material should contact [open.michigan@umich.edu](mailto:open.michigan@umich.edu) with any questions, corrections, or clarifications regarding the use of content. The Regents of the University of Michigan do not license the use of third party content posted to this site unless such a license is specifically granted in connection with particular content objects. Users of content are responsible for their compliance with applicable law. Mention of specific products in this recording solely represents the opinion of the speaker and does not represent an endorsement by the University of Michigan.

Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.

# Amino Acid metabolism

Amino acids



Glu, Gln,  
Asp, NH<sub>3</sub>



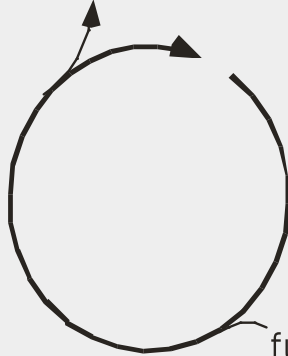
Urea

# Folate metabolism

Methylene  
THF

Met  
Cycle

oxaloacetate



fumarate

TCA Cycle

Purines

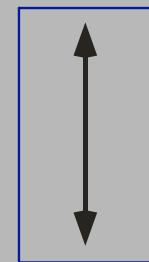
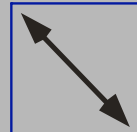
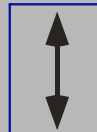
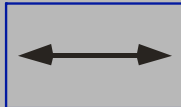
DNA  
RNA

Pyrimidines

Uric Acid

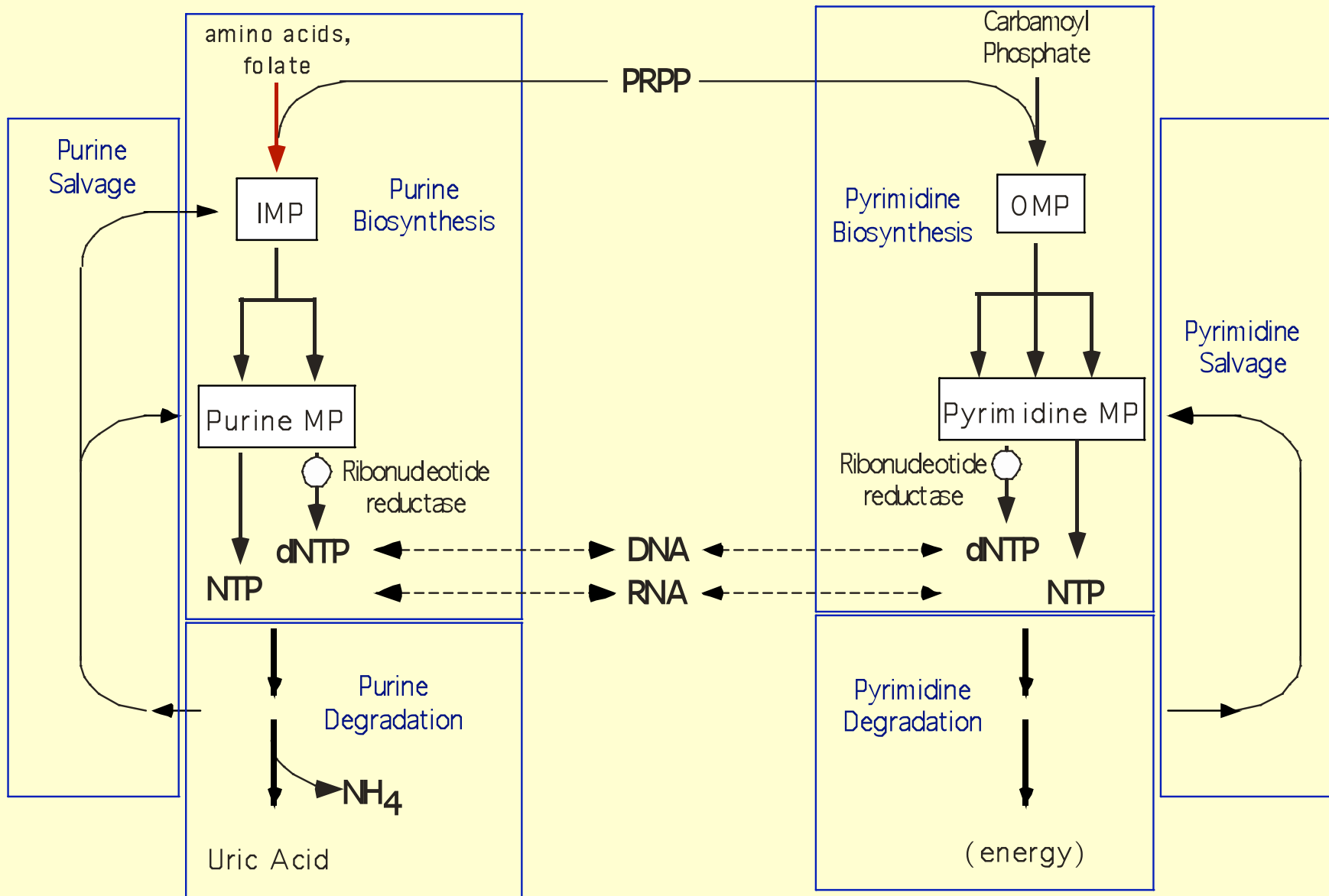
(energy)

Nucleic Acid metabolism

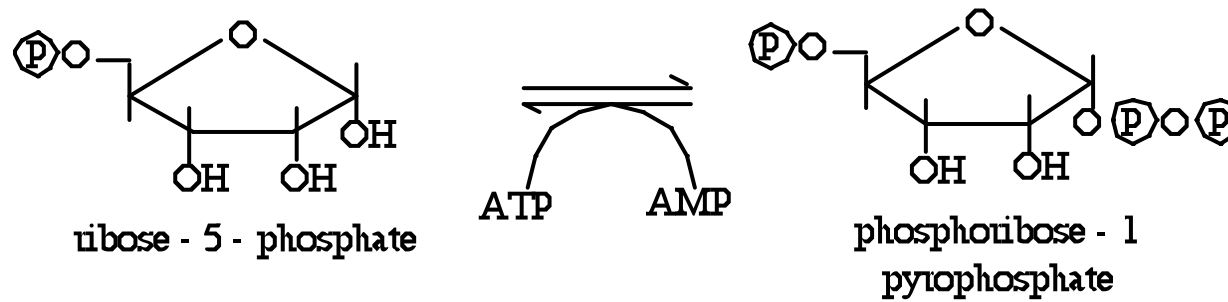


# Nucleic Acid metabolism

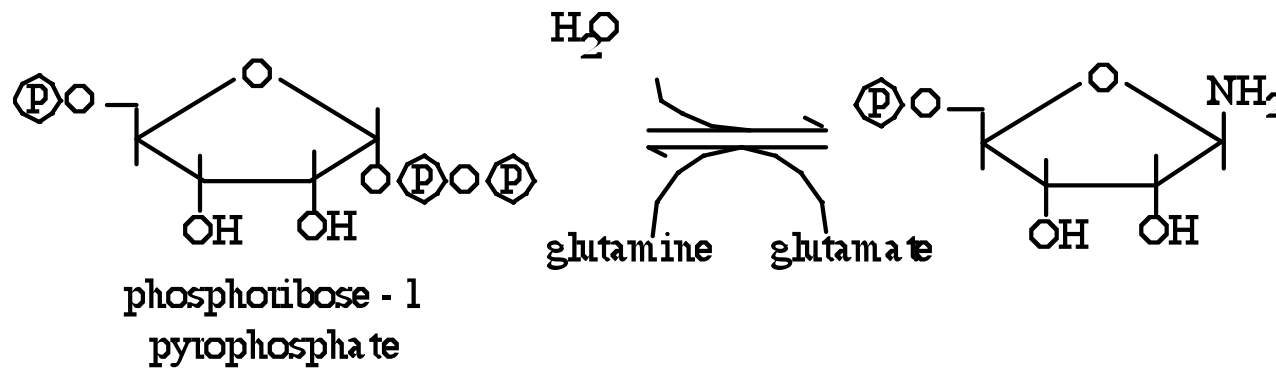
Click on any blue rectangle to see details.



## Formation of PRPP: Phosphoribose pyrophosphate

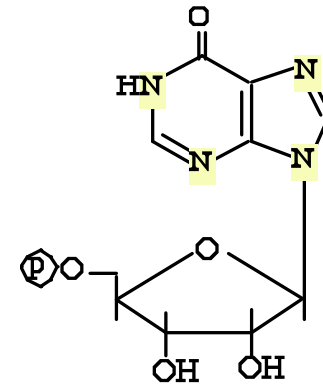


## PRPP Use in Purine Biosynthesis:

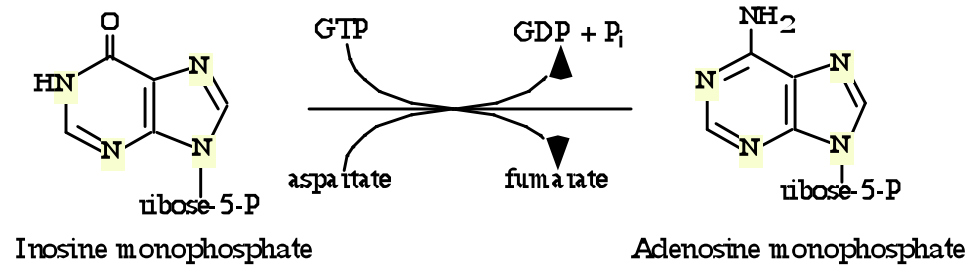


# The First Purine: Inosine Monophosphate

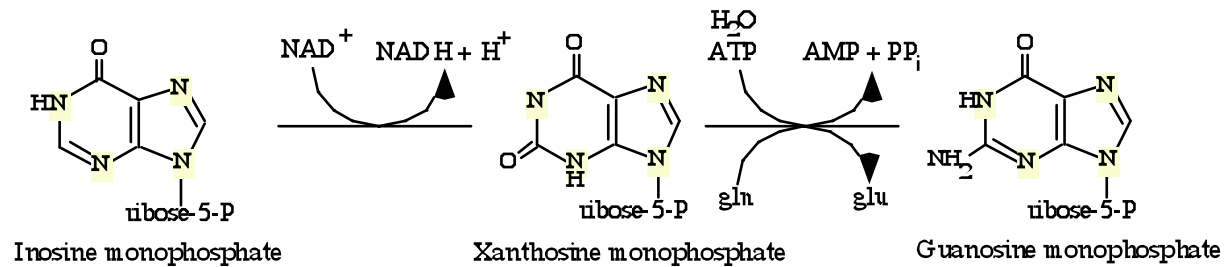
(folates are involved in this synthesis)



## Conversion to Adenosine:



## Conversion to Guanosine:

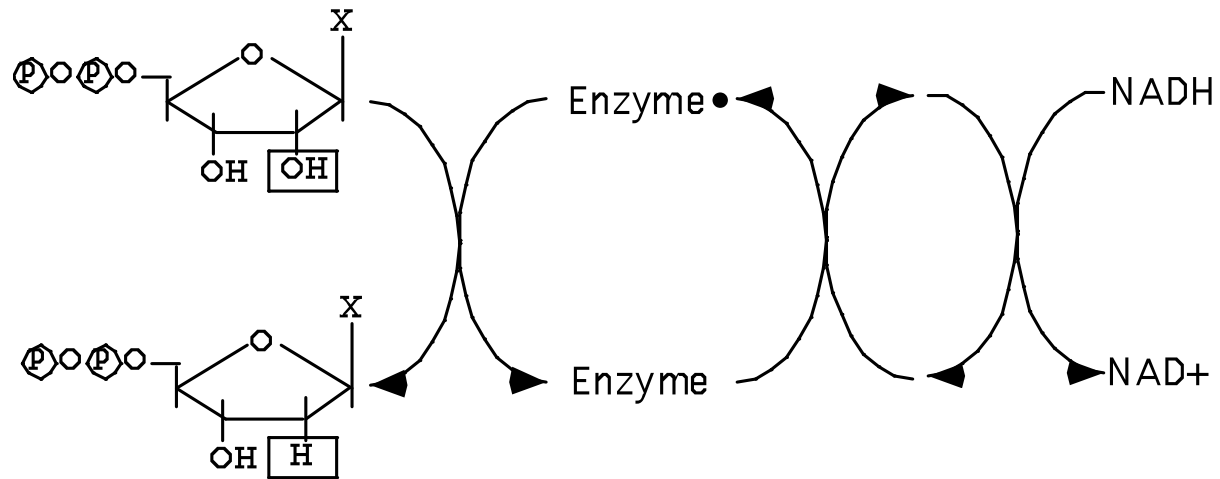


# Nucleoside Monophosphate Kinases

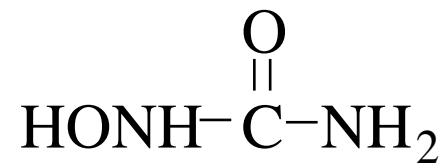


- similar enzymes specific for each nucleotide
- no specificity for ribonucleotide vs. deoxyribonucleotide

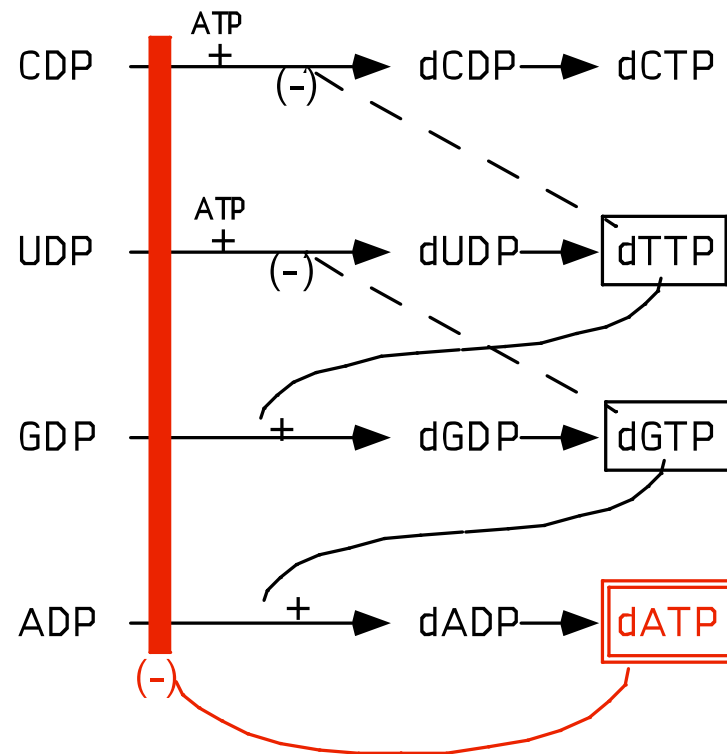
# Ribonucleotide Reductase



Hydroxyurea inhibits this enzyme: chemotherapeutic use

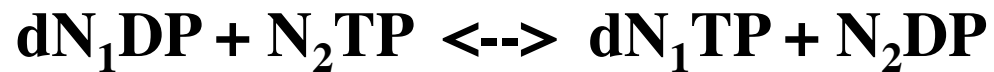
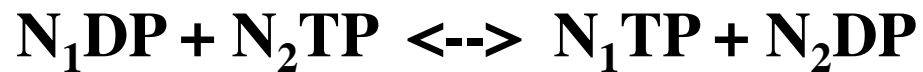


# Regulation of Ribonucleotide Reductase



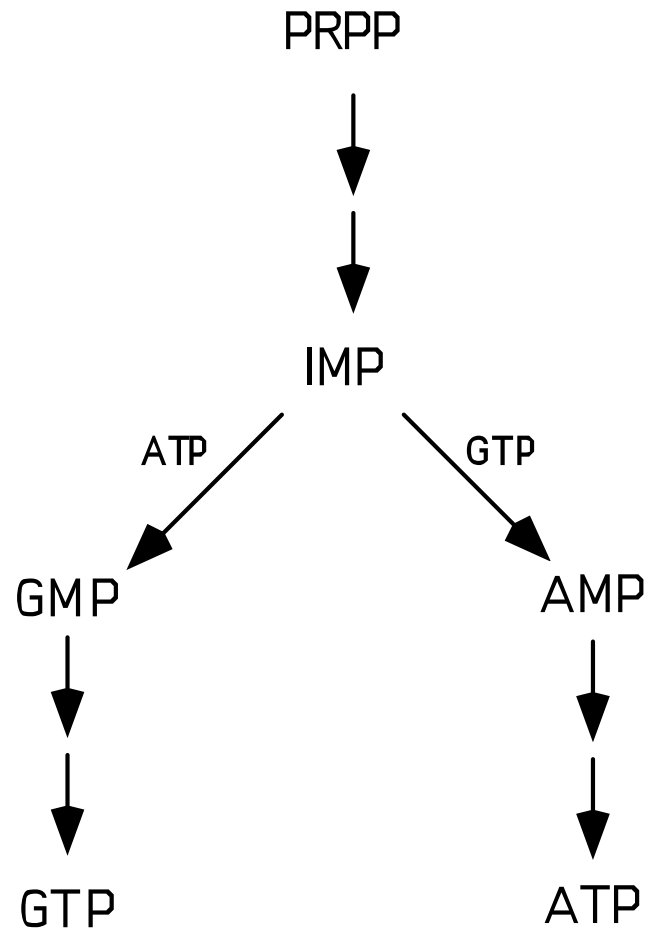


# Nucleoside Diphosphate Kinase

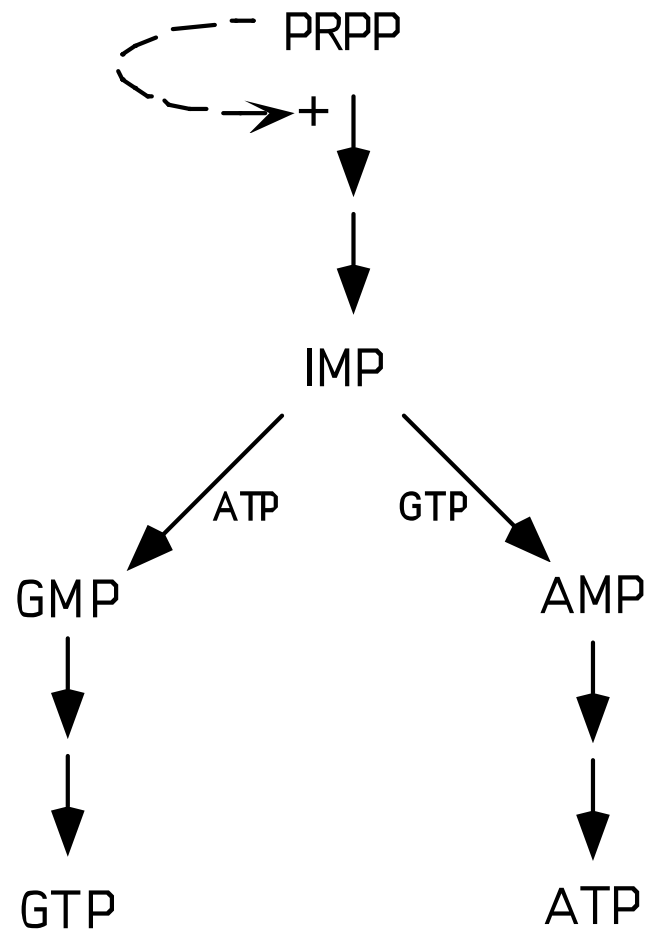


- No specificity for base
- No specificity for ribo vs deoxy

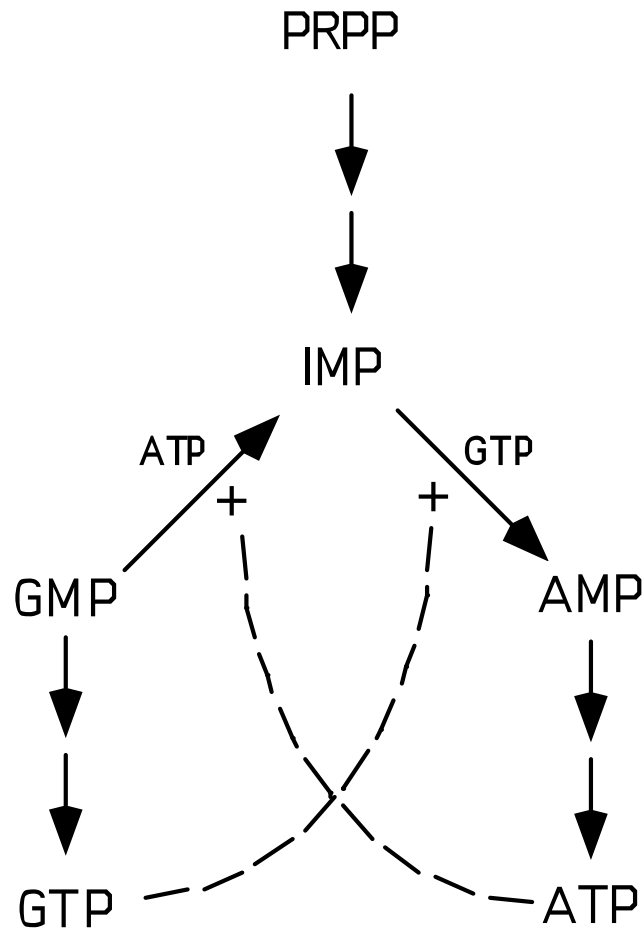
# Feed-forward regulation by PRPP



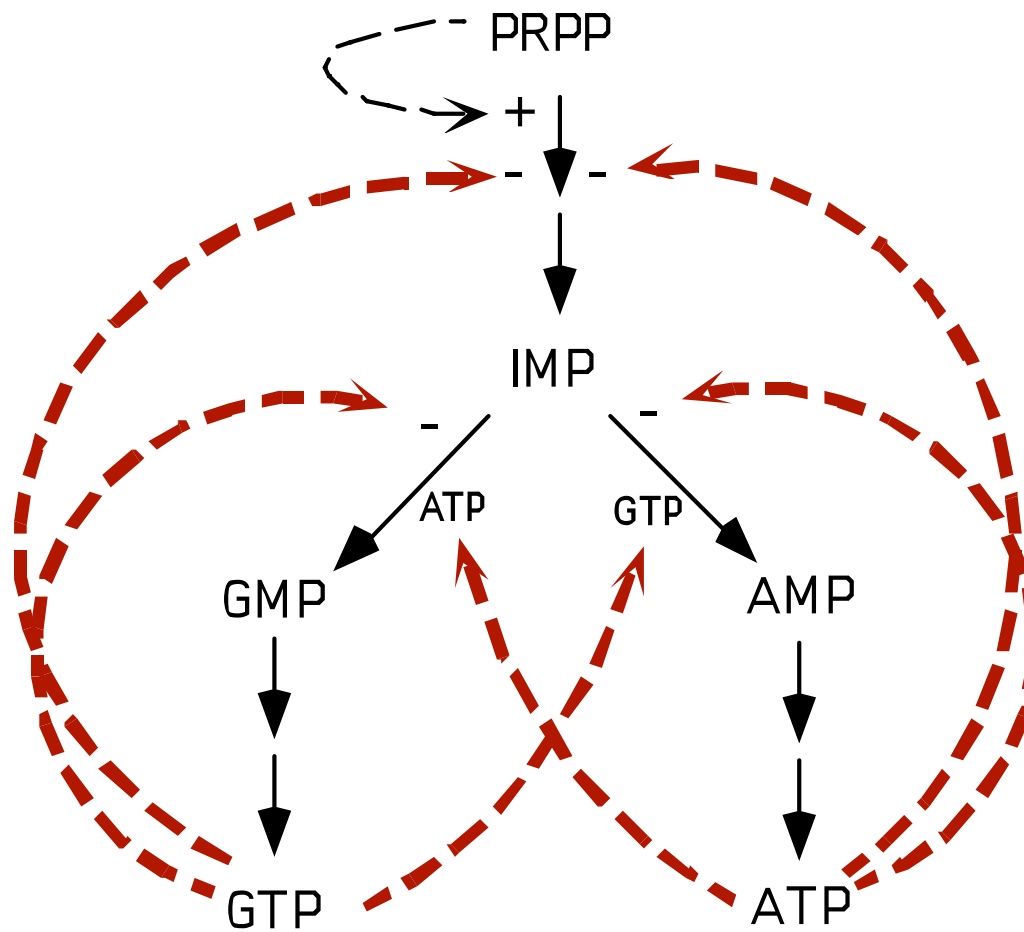
# Feed-forward regulation by PRPP



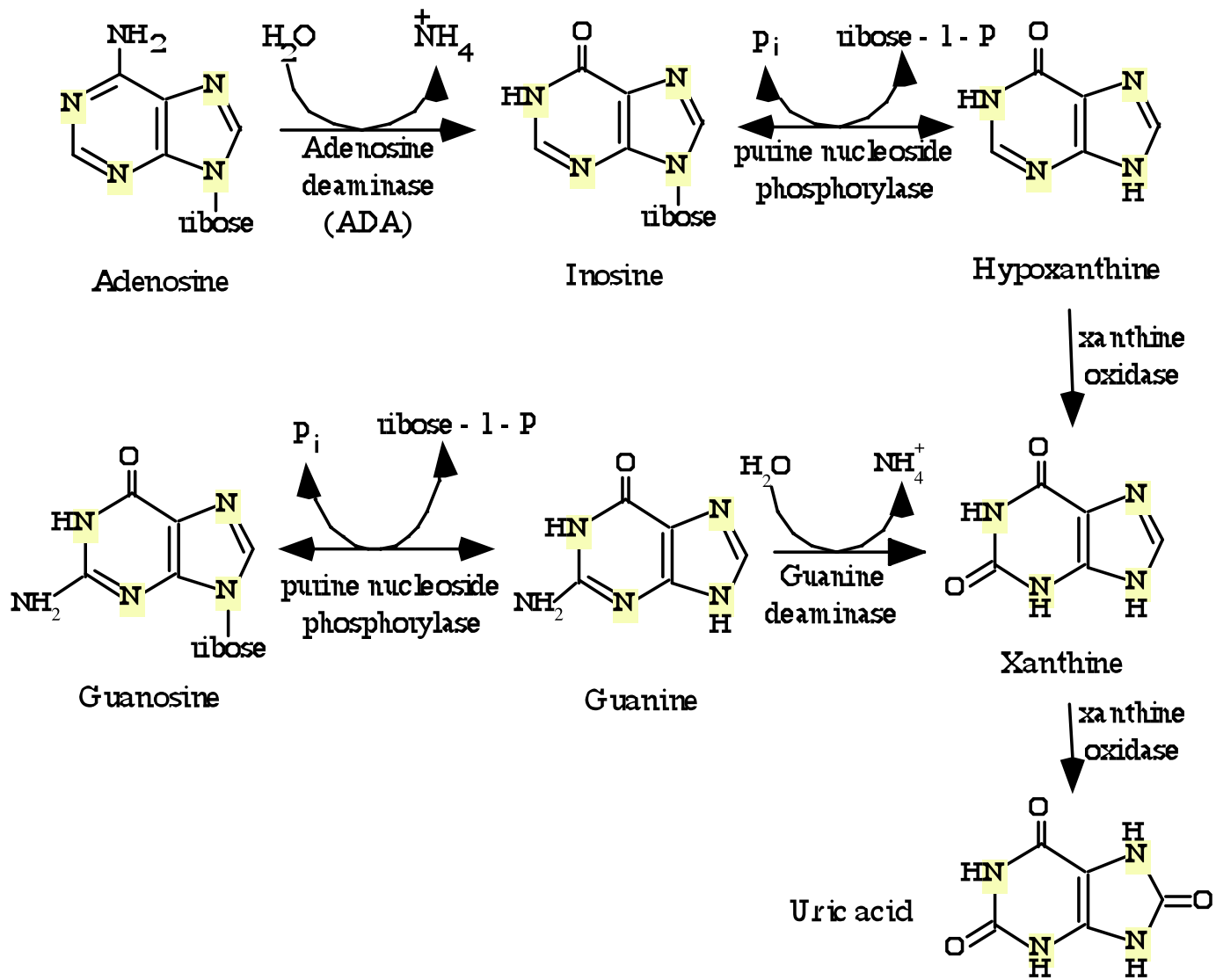
# Feed-forward regulation by PRPP



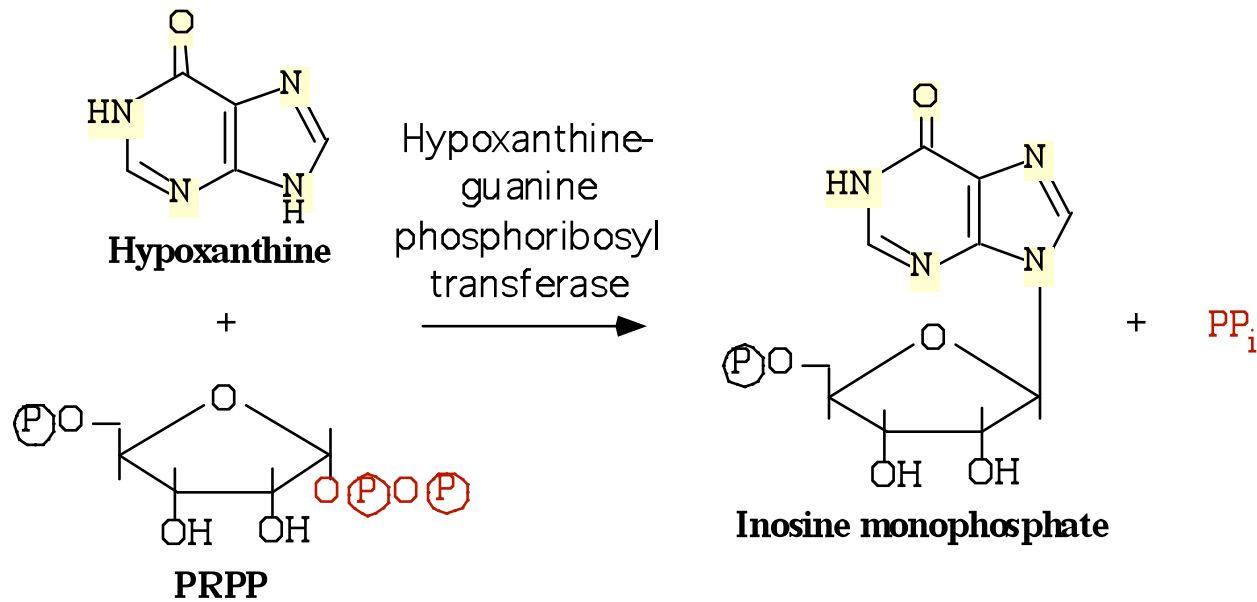
# Feed-forward regulation by PRPP



# Degradation of the Purine Nucleosides:

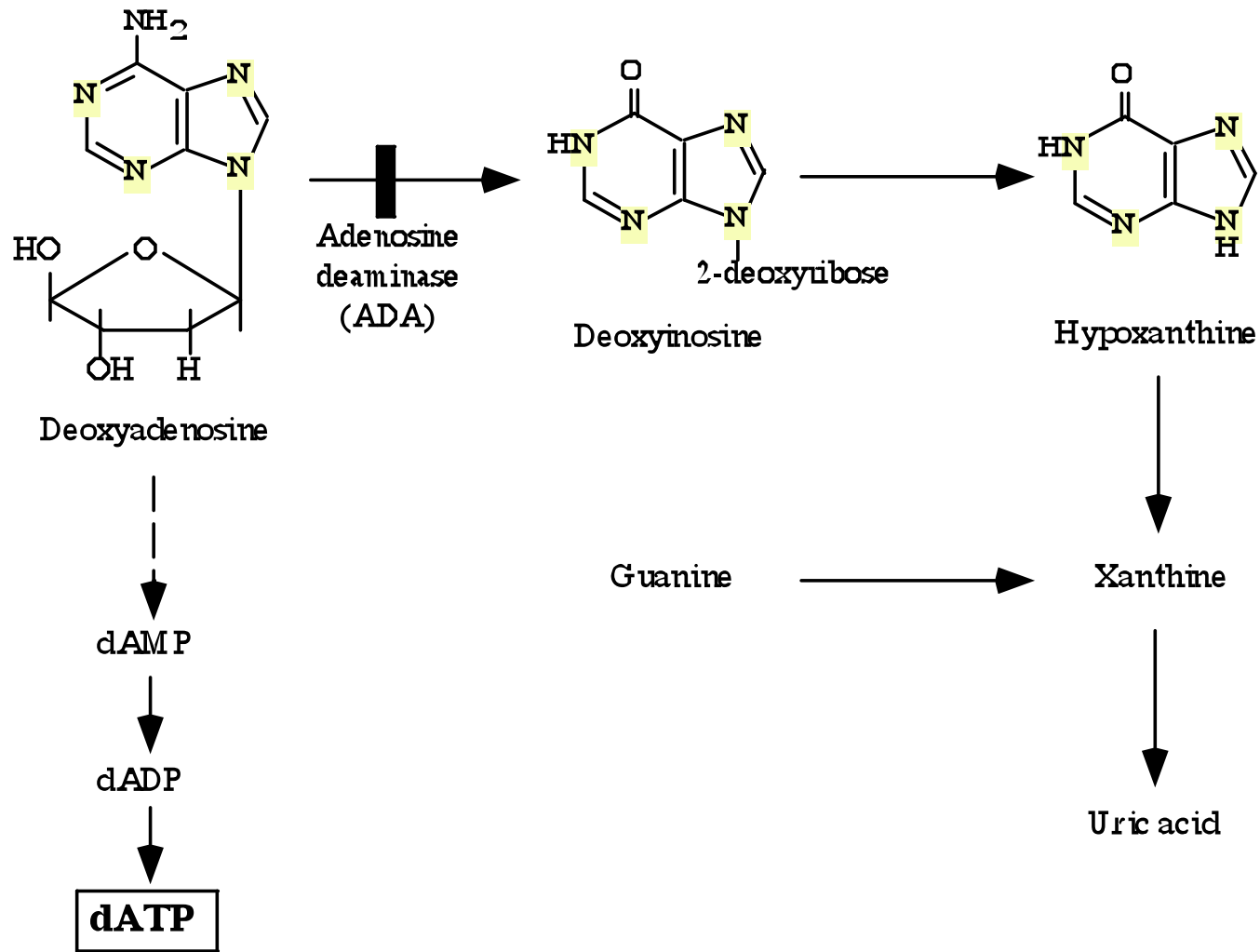


## “Salvage” Pathways for Purine Nucleotides

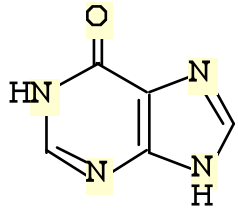


APRT - Adenine phosphoribosyl transferase - performs a similar function with adenine.

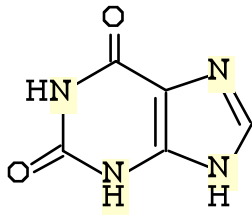
# Adenosine Deaminase Deficiency:



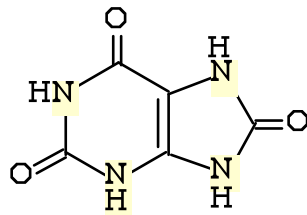
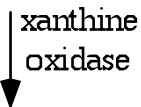




**Hypoxanthine**



**Xanthine**



**Uric acid**

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

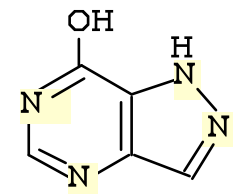
**Hyperuricemia** can be caused by:

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**

The hands of a patient with a long history of gout, including high serum urate levels

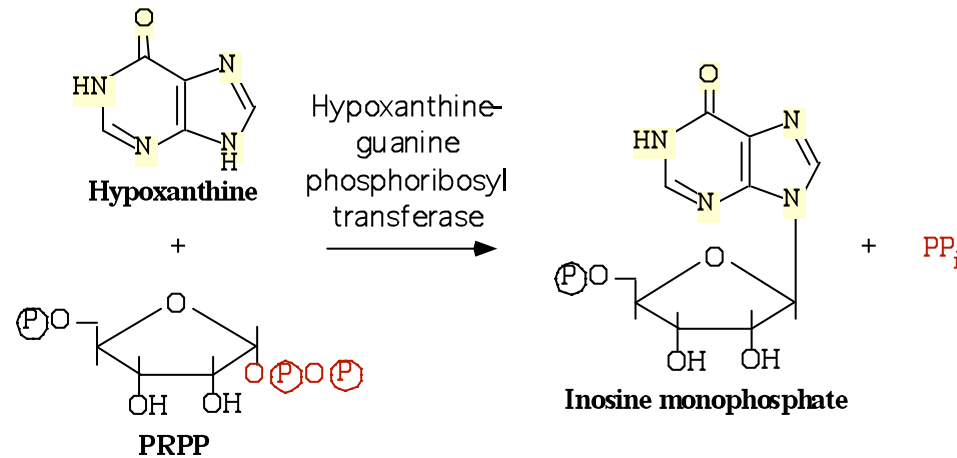


BY: Univ. of Alabama at Birmingham, Dept. of Pathology  
<http://creativecommons.org/licenses/by-nc-sa/3.0/deed.en>



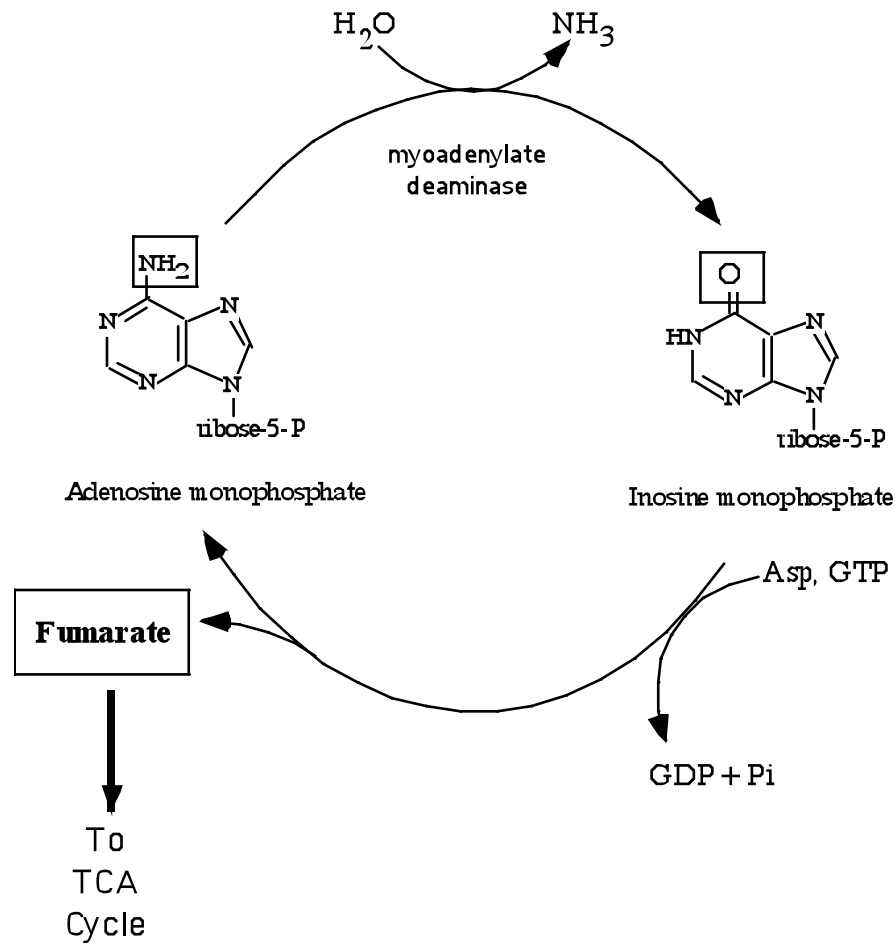
## Lesch-Nyhan Syndrome: Defective HGPRT

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

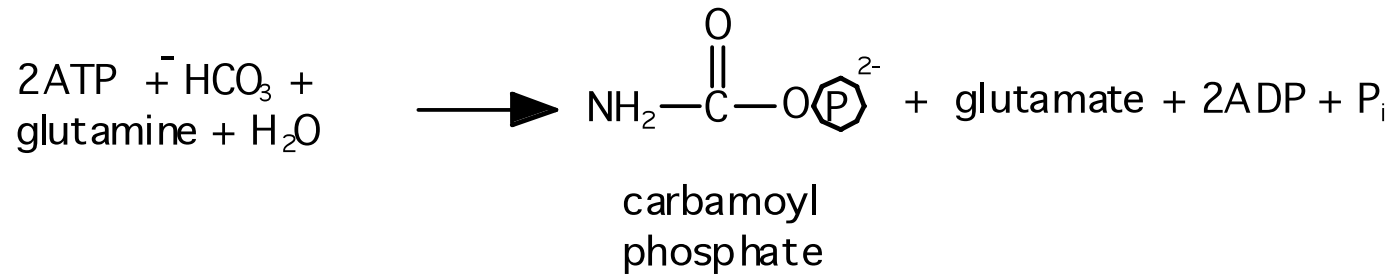


A defect in APRT does NOT have similar consequences

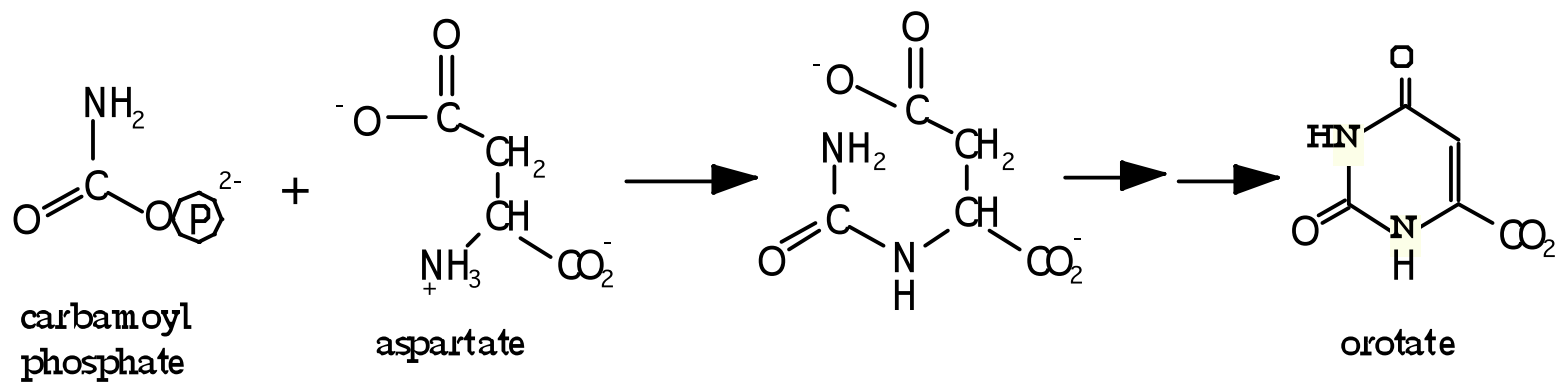
# Myoadenylate Deaminase 'Fills' the TCA Cycle in Muscle



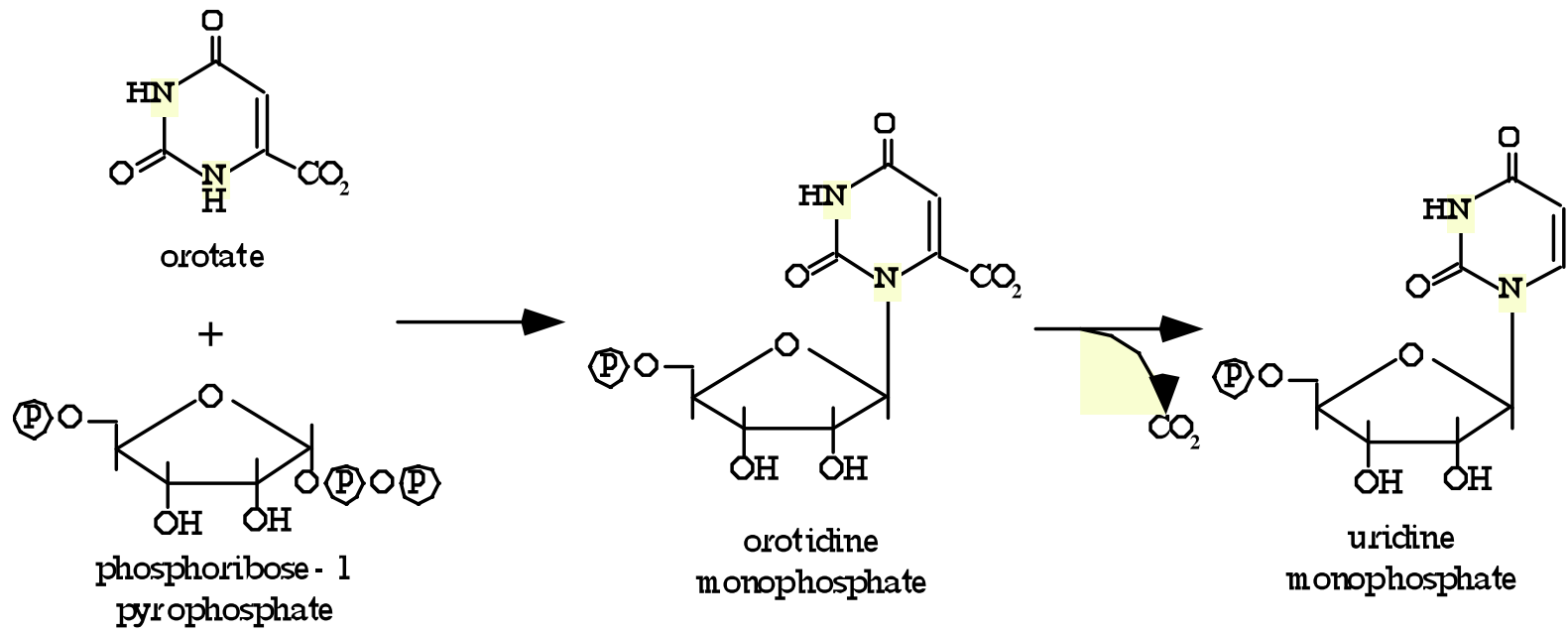
## Carbamoyl phosphate synthetase II - a *cytoplasmic* enzyme...



...used for pyrimidine synthesis

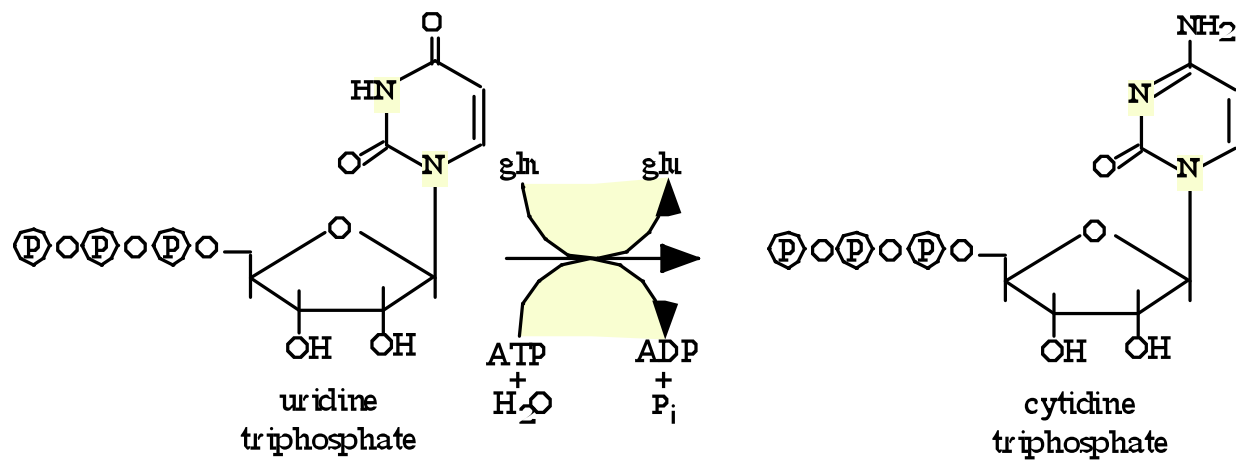


Orotate is linked to PRPP to form Uridine monophosphate:

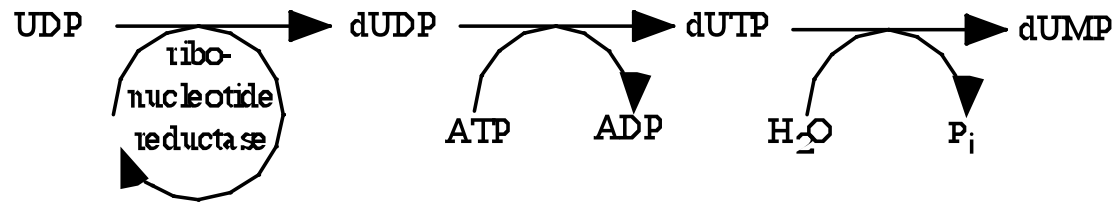


Newly-synthesized uridine monophosphate will be phosphorylated to UDP and UTP, as described for the purine nucleotides.

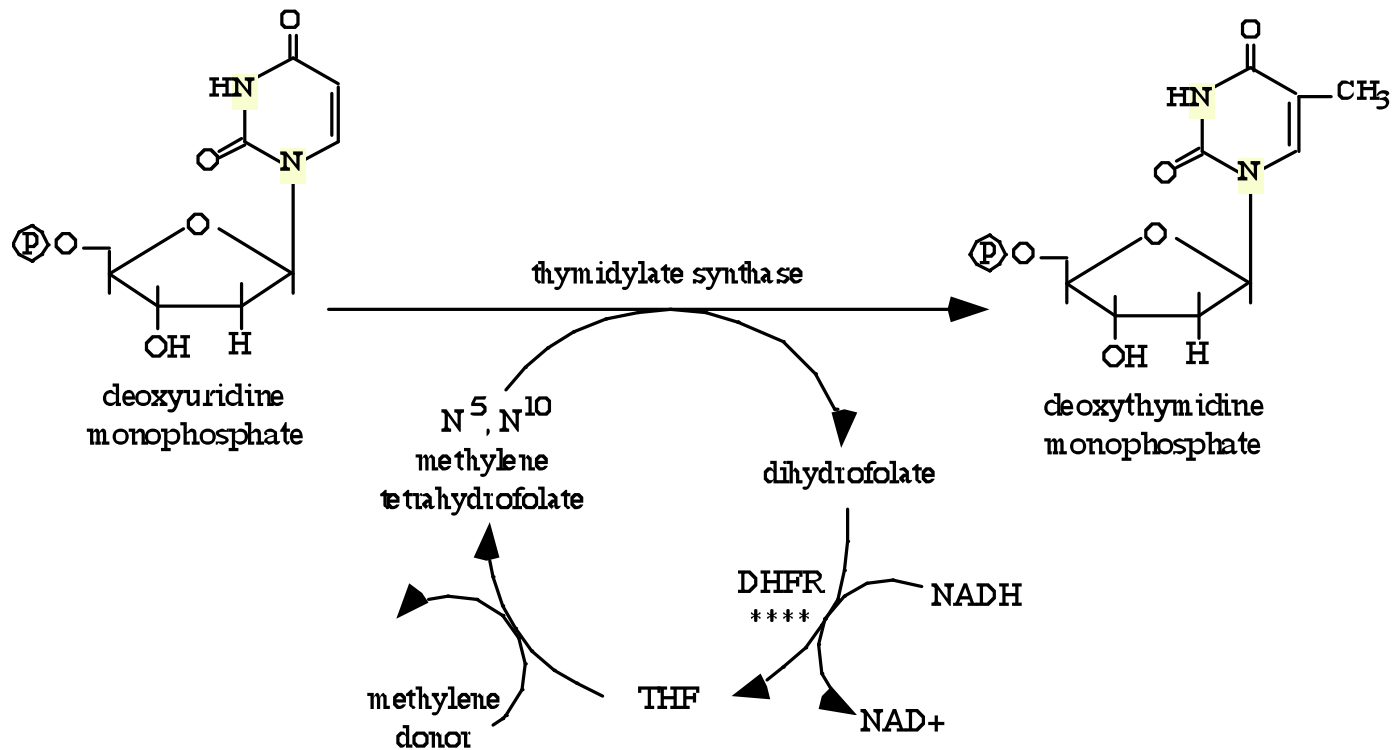
UTP can be converted to CTP by CTP Synthetase:



Some UDP is converted to dUDP via ribonucleotide reductase.

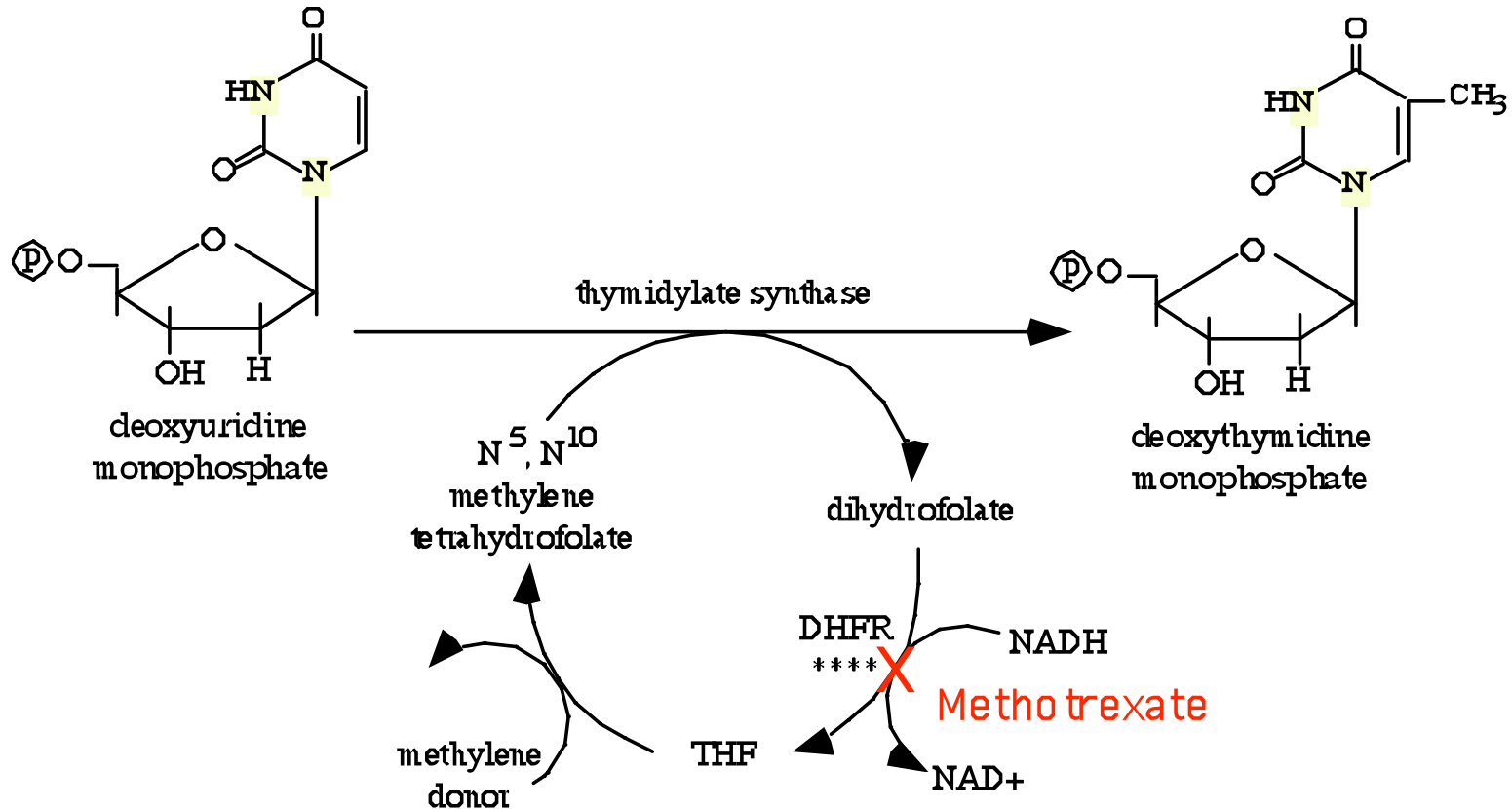


The Thymidylate Synthase Reaction:



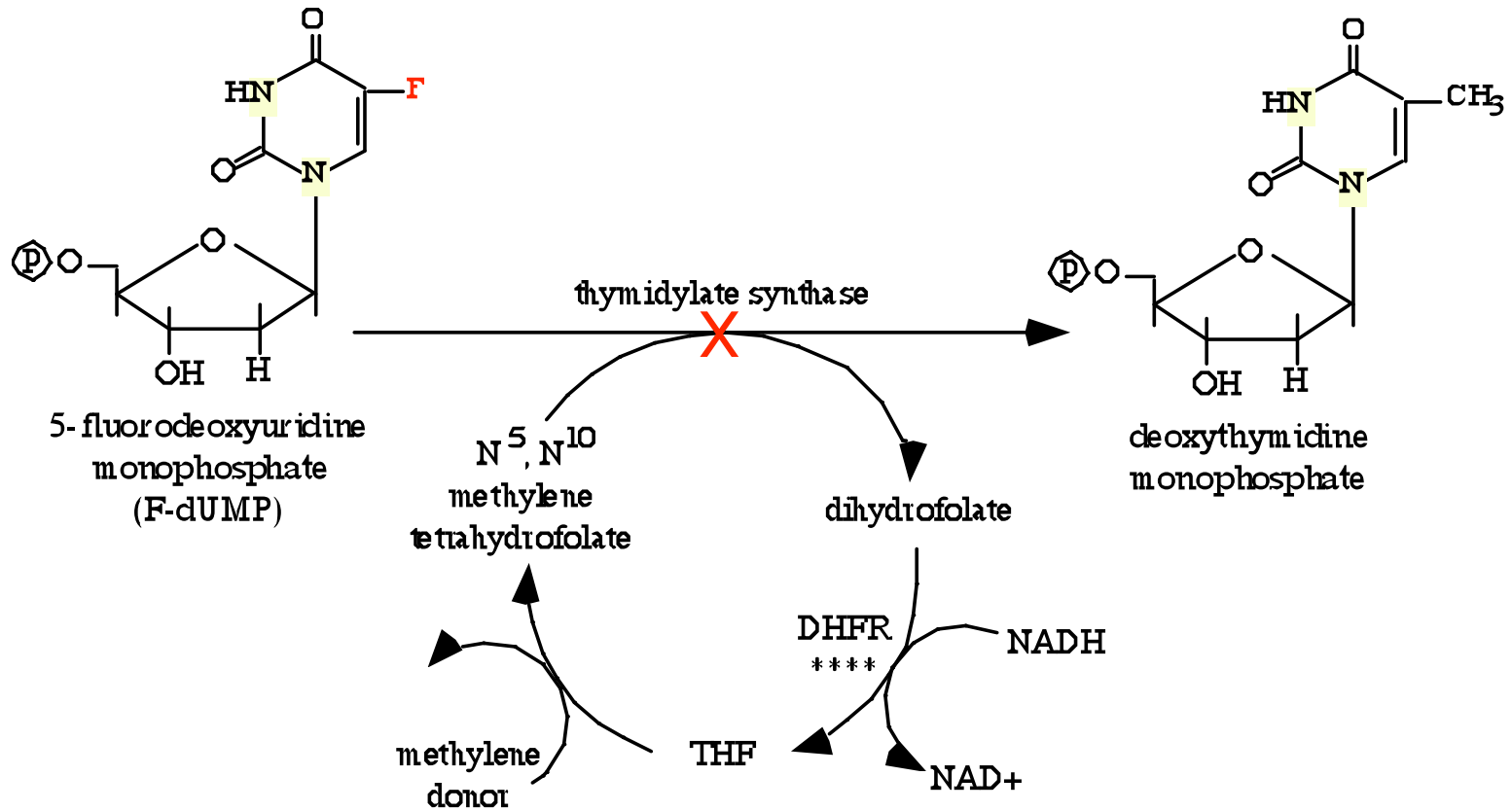


# Methotrexate Inhibits Dihydrofolate Reductase:

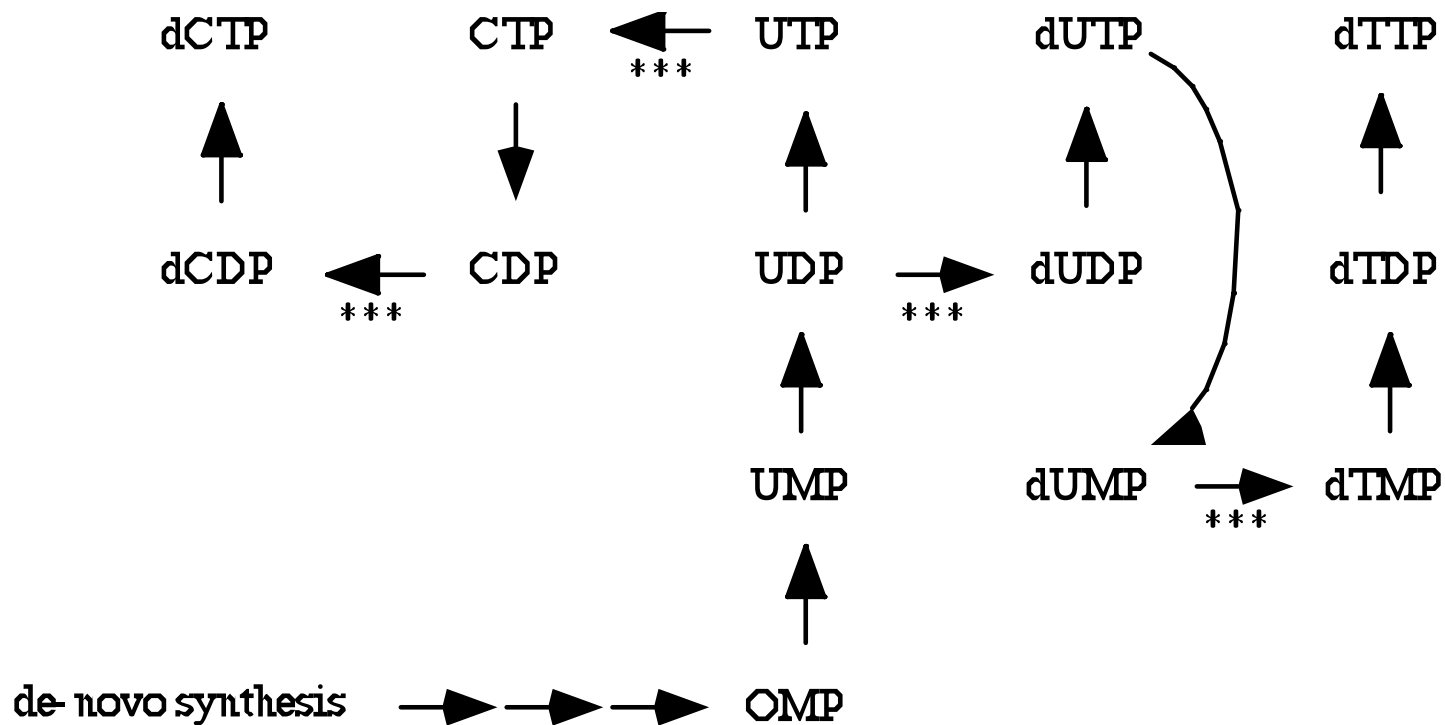


Dihydrofolate builds up, levels of THF become limiting, thymidylate synthase is unable to proceed. Follow it with a dose of Leucovorin, a.k.a. formyl-THF.

# FdUMP Inhibits The Thymidylate Synthase Reaction:



# 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.

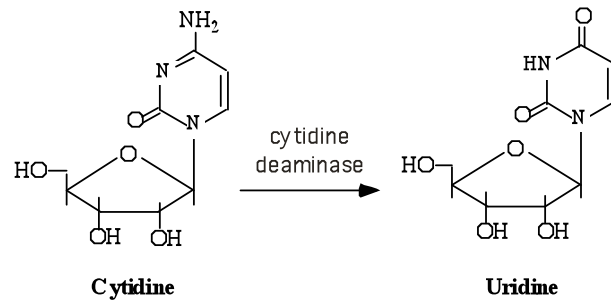
## **Pathologies of pyrimidine nucleotide biosynthesis:**

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

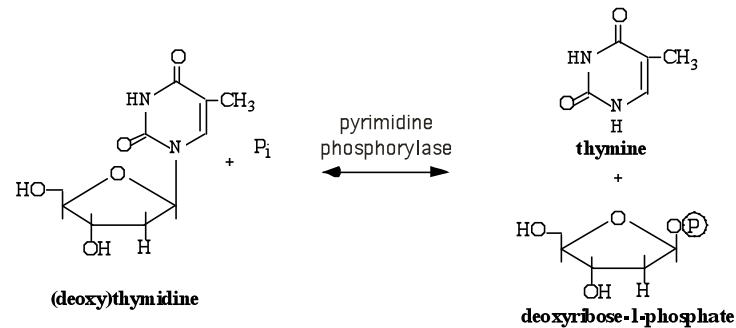
Hereditary orotic aciduria - deficiency of the enzyme that convert orotate to OMP to UMP.  
Not common.

# Pyrimidine degradation:

Cytidine deaminase converts cytidine to uridine



A phosphorylase removes the sugar

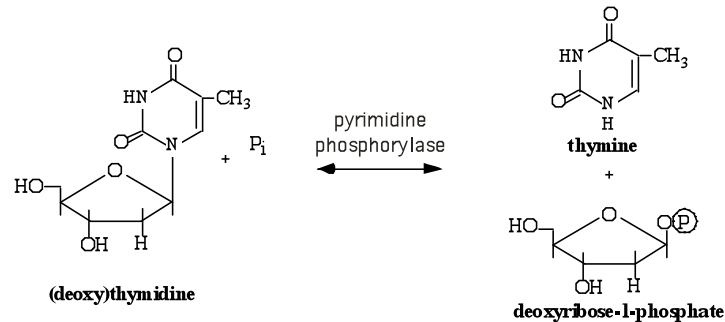


Degradation of the base proceeds (products are unimportant here)

# Pyrimidines can be salvaged as well:

Enzyme: Pyrimidine nucleoside phosphorylases

Thymine + deoxyribose-1-phosphate  $\rightarrow$  thymidine  
(NOT thymidine monophosphate!)

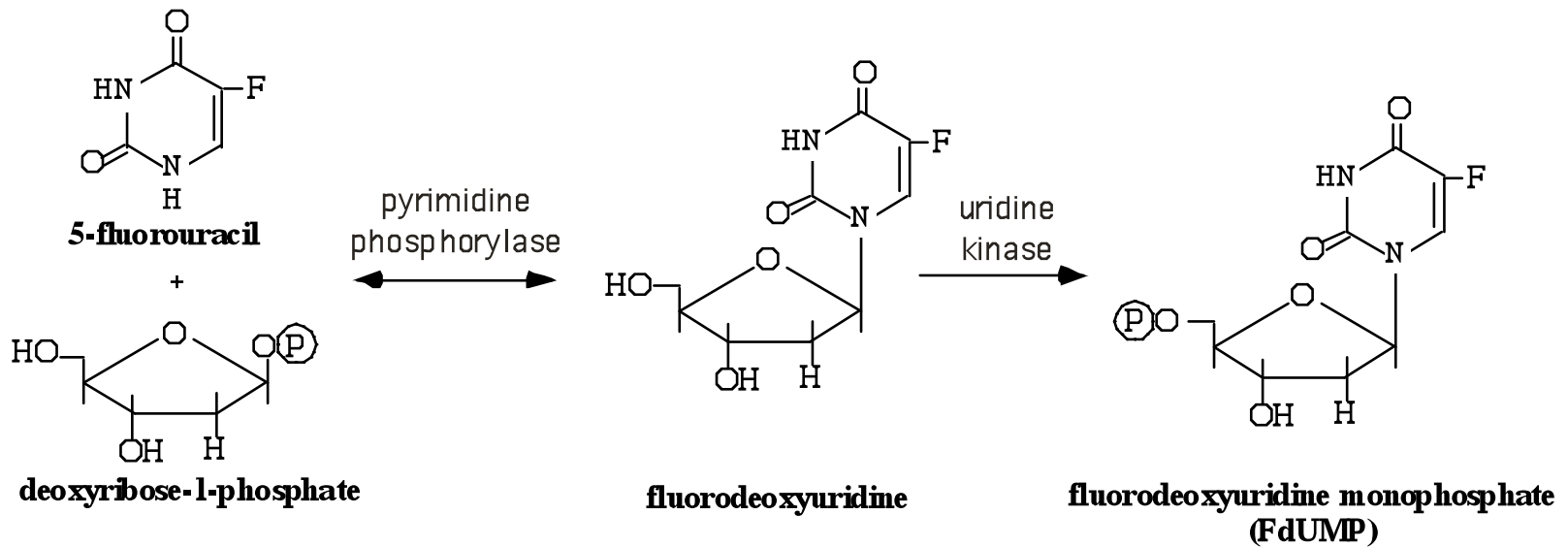
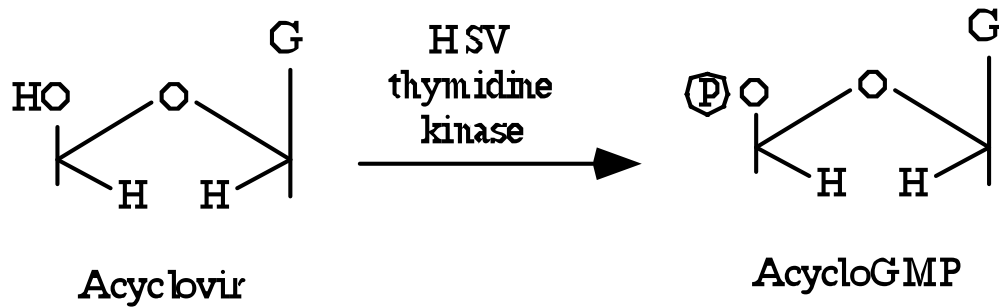


Enzyme: Thymidine kinase - adds the monophosphate back

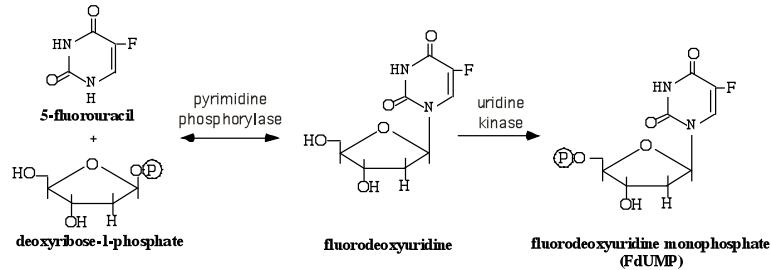
Thymidine + ATP  $\rightarrow$  thymidine monophosphate

Herpes Simplex Virus carries its own tk gene

# Certain drugs act via the pyrimidine salvage pathway:



# 5-FU efficacy depends on rate of degradation vs activation



5-FU

-->

-->

FdUMP

+ methylene-THF + Thymidylate Synthase

--> inactivation of TS



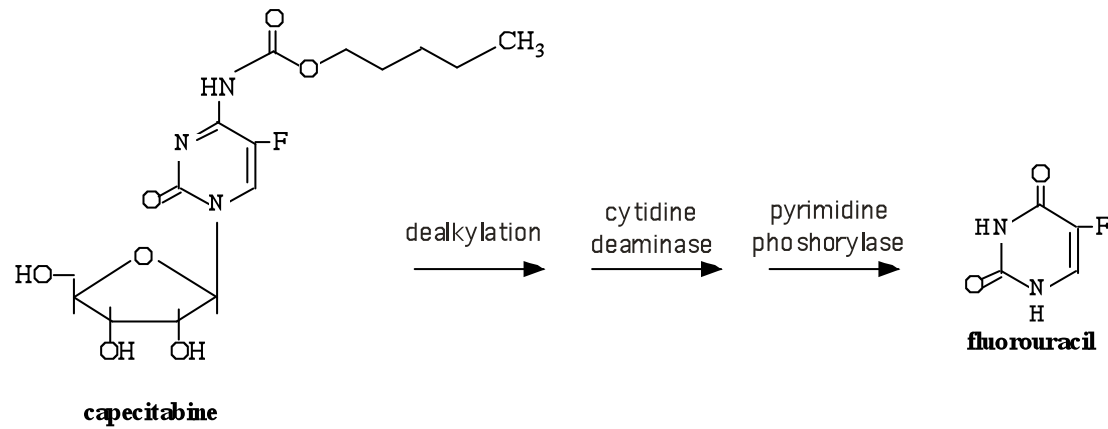
Degradation

(via dihydropyrimidine dehydrogenase, DPD)

DPD inhibitors can potentiate 5FU activity



## Capecitabine mode of action:



## Cytosine arabinoside (araC) activation and inactivation:

