Nucleotide Metabolism

By Jessica Shuster

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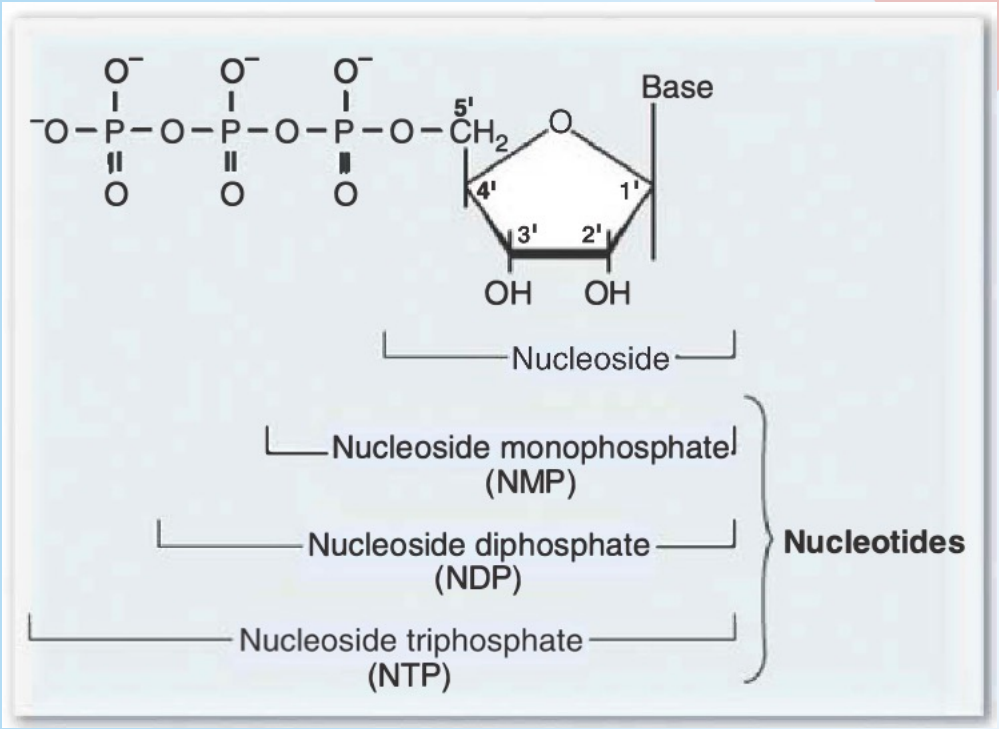
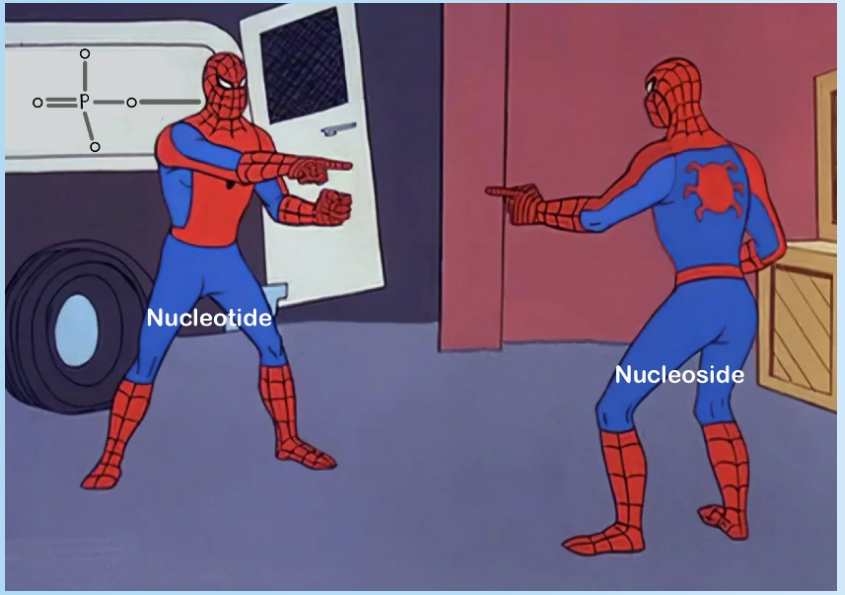
Overview of Nucleotides

- Components
  - Nitrogenous base (purine/pyrimidine)
  - Pentose sugar (ribose/deoxyribose)
  - Phosphate group(s)

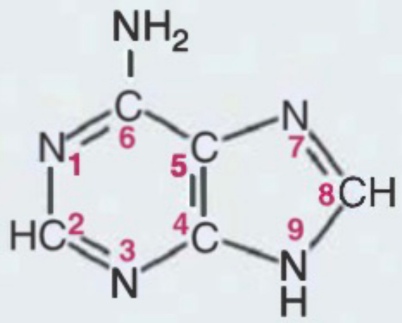
- Functions
  - Building blocks of DNA/RNA
  - Coenzymes (NAD+, FAD)
  - Energy transfer (ATP, GTP)
  - Second messengers (cAMP, cGMP)
  - Allosteric regulators (ATP, ADP, AMP)



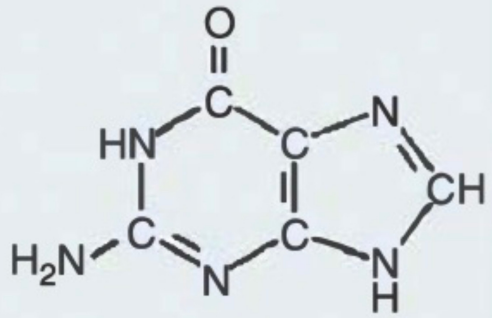


Structure of Purines and Pyrimidines

Purines



Adenine (A)

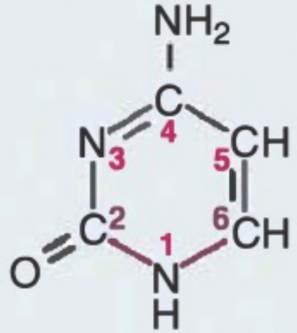


Guanine (G)

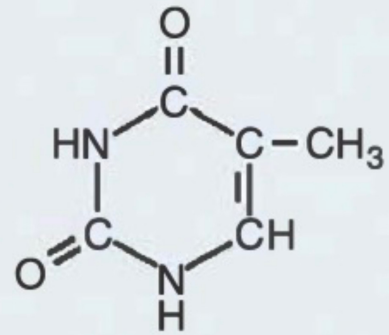
Pure As Gold

CUT the pyramid

Pyrimidines



Cytosine (C)



Thymine (T)

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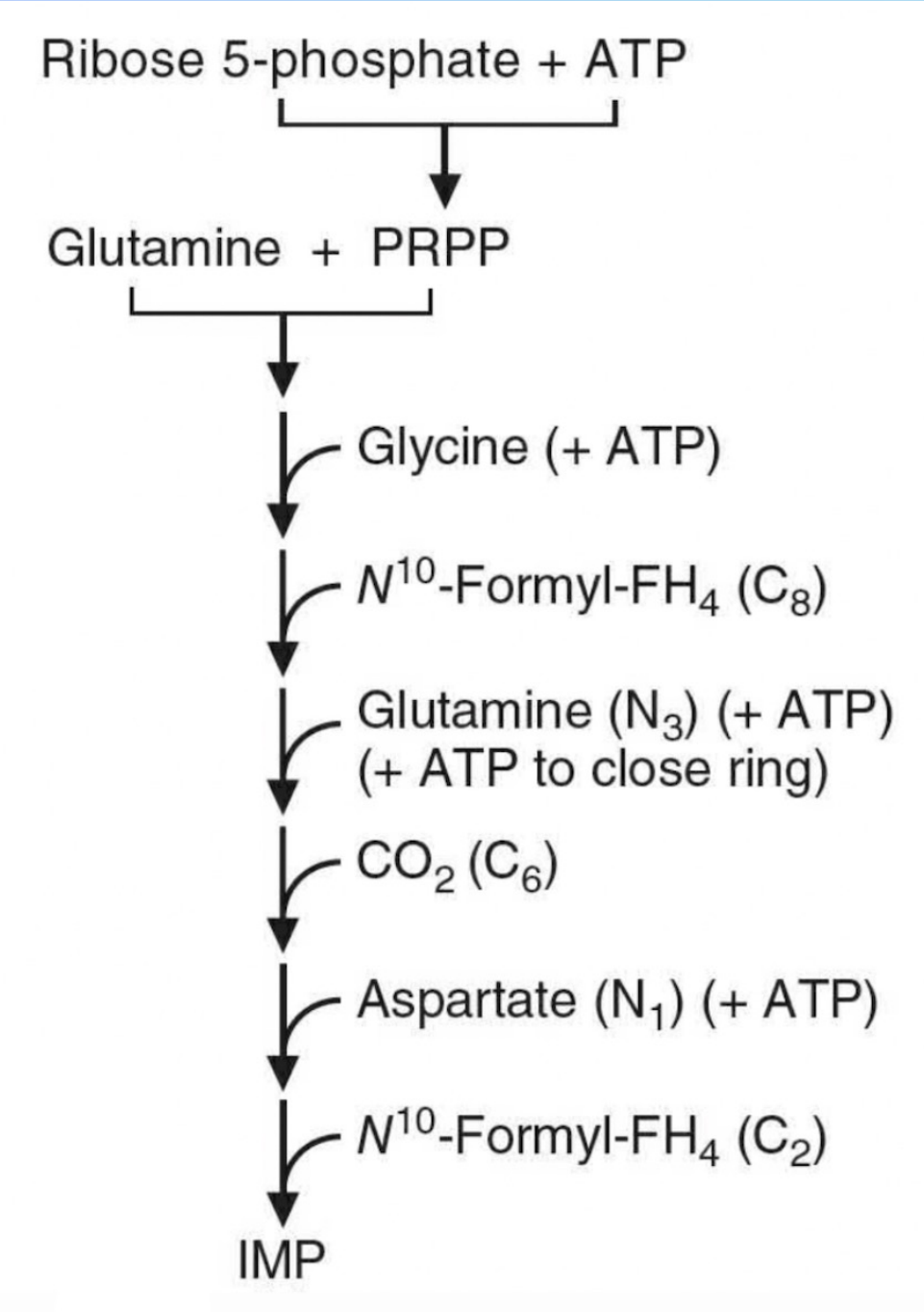

De Novo Purine Biosynthesis

- Uses **amino acids** as precursors to produce nucleotides
- Occurs primarily in the **liver**
- Requires at least **six high-energy bonds (ATP)** per purine molecule synthesized
- Goal is to create **inosine monophosphate (IMP)**, and IMP turns into adenine or guanine
- 11 step process !

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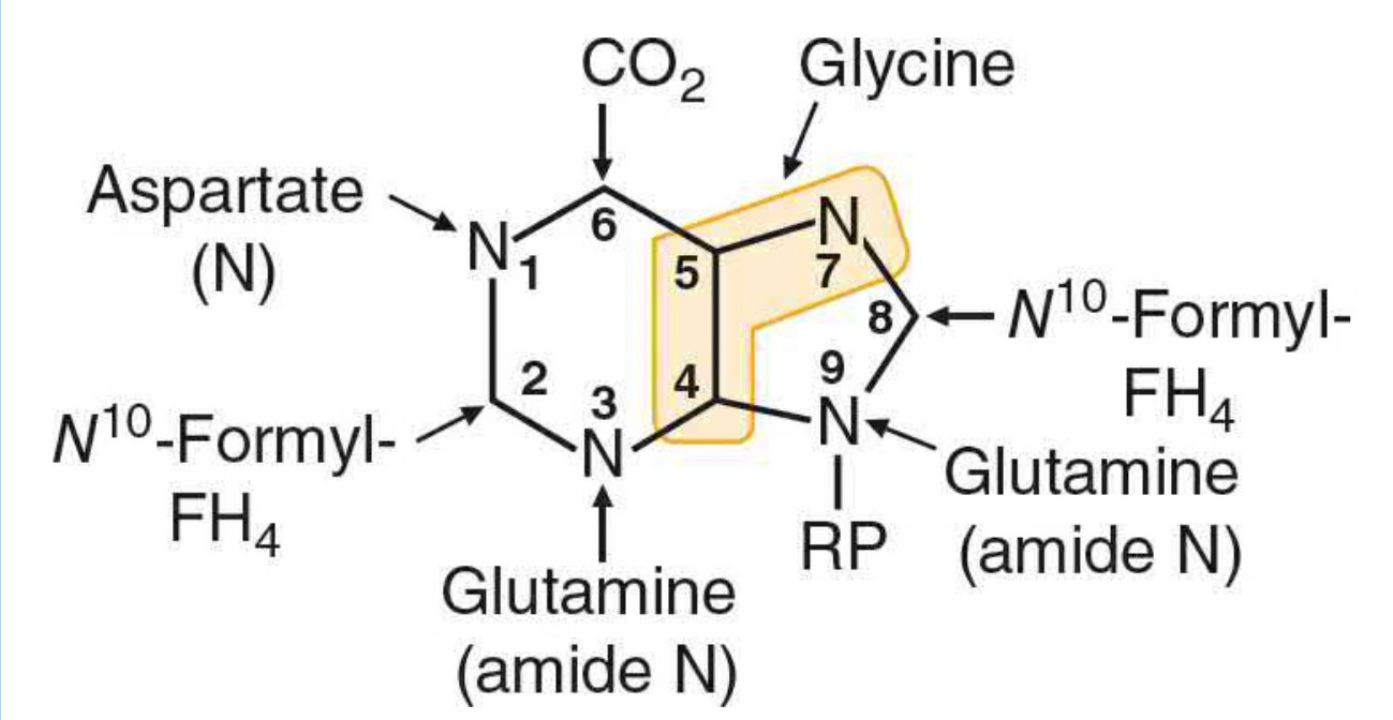
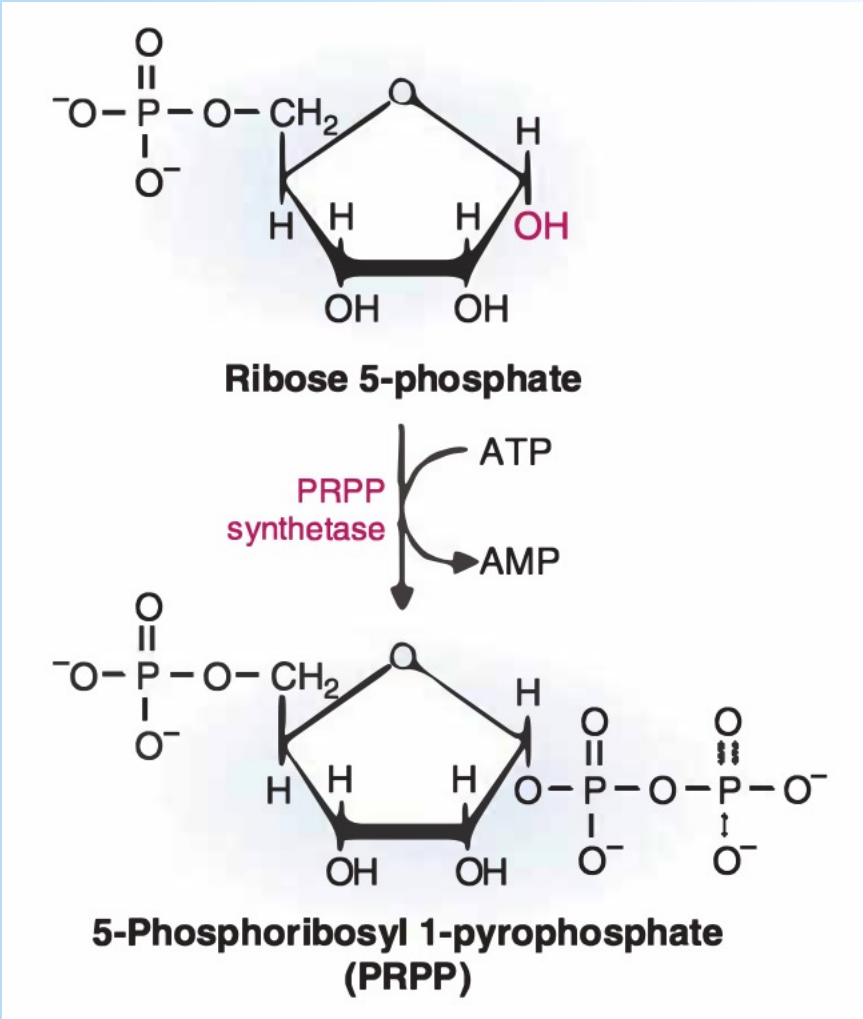
Sources of Atoms in Purine Rings



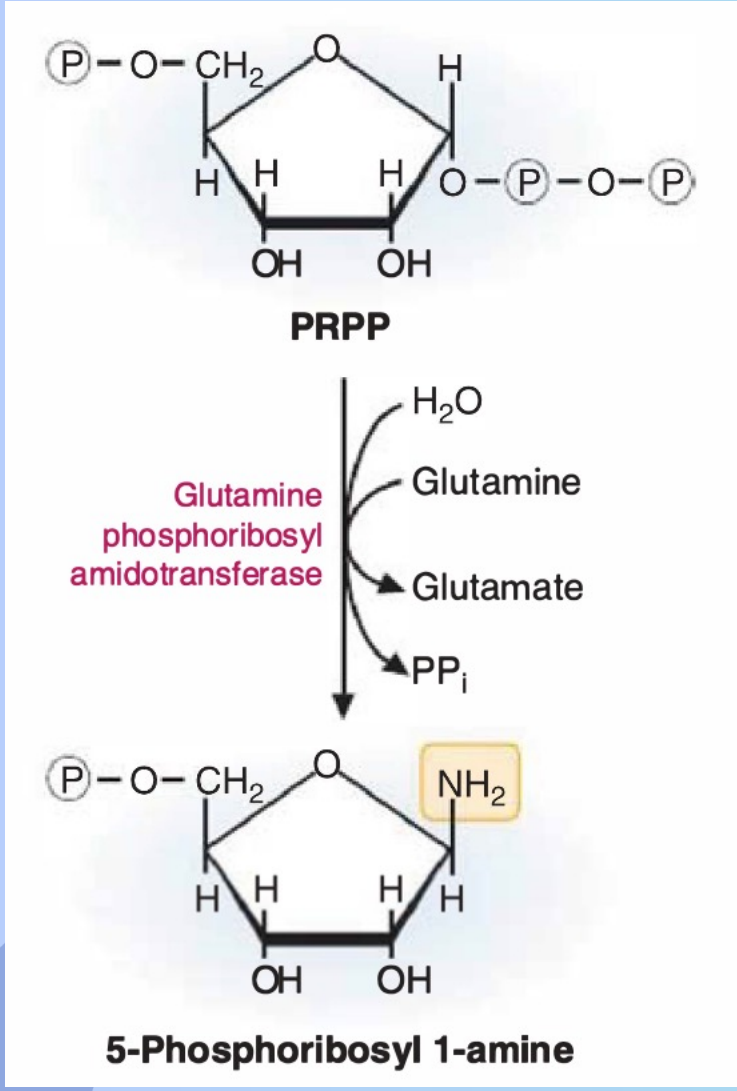
- Amino acids necessary for **pur**ine synthesis (cats **purr** until they **GAG**):
  - **G**lycine
  - **A**spartate
  - **G**lutamine

Step 1: Creating PRPP

- 5-Phosphoribosyl-1-pyrophosphate (PRPP) is an activated form of ribose used to initiate purine biosynthesis
- Synthesized from **ribose 5-phosphate** (produced from glucose via the pentose phosphate pathway) and **ATP** by the enzyme **PRPP synthetase**
- PRPP is used in **both** purine and pyrimidine biosynthesis !



Step 2: Rate Limiting Step !



- **PRPP** reacts with **glutamine** to form **5'-phosphoribosyl-1'-amine**
- Catalyzed by **glutamine phosphoribosylamidotransferase (GPAT)**
  - This enzyme is highly regulated, making this step the **committed/rate limiting step** of purine biosynthesis

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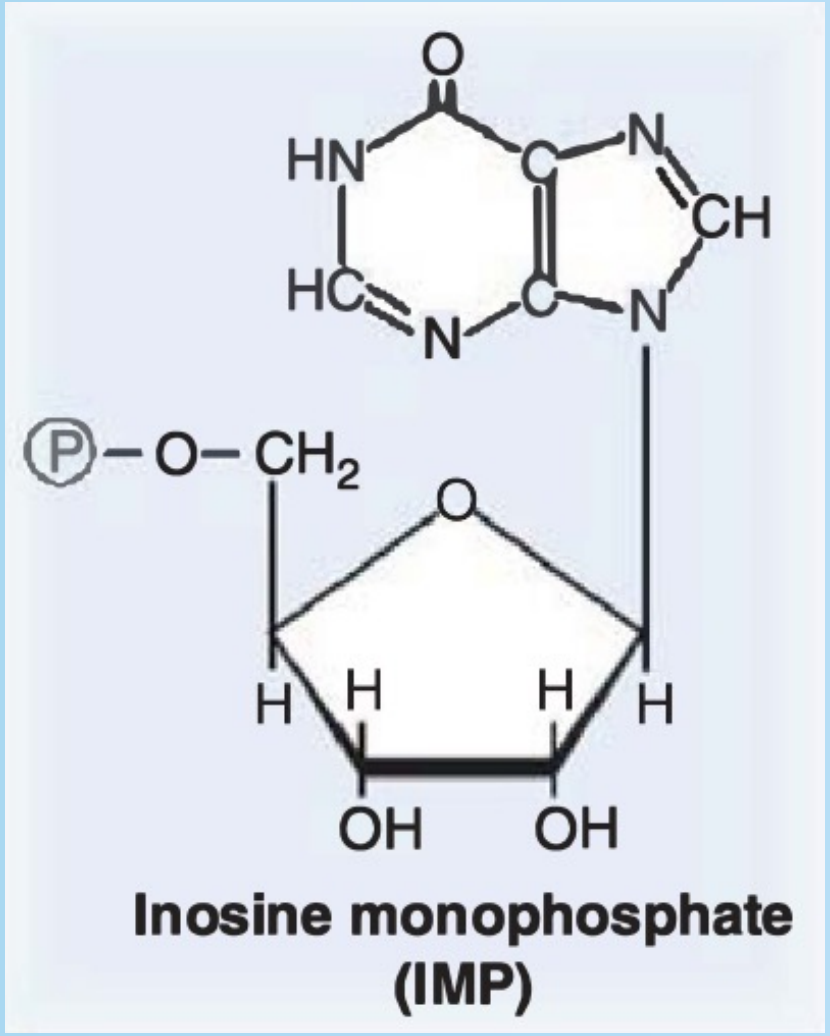
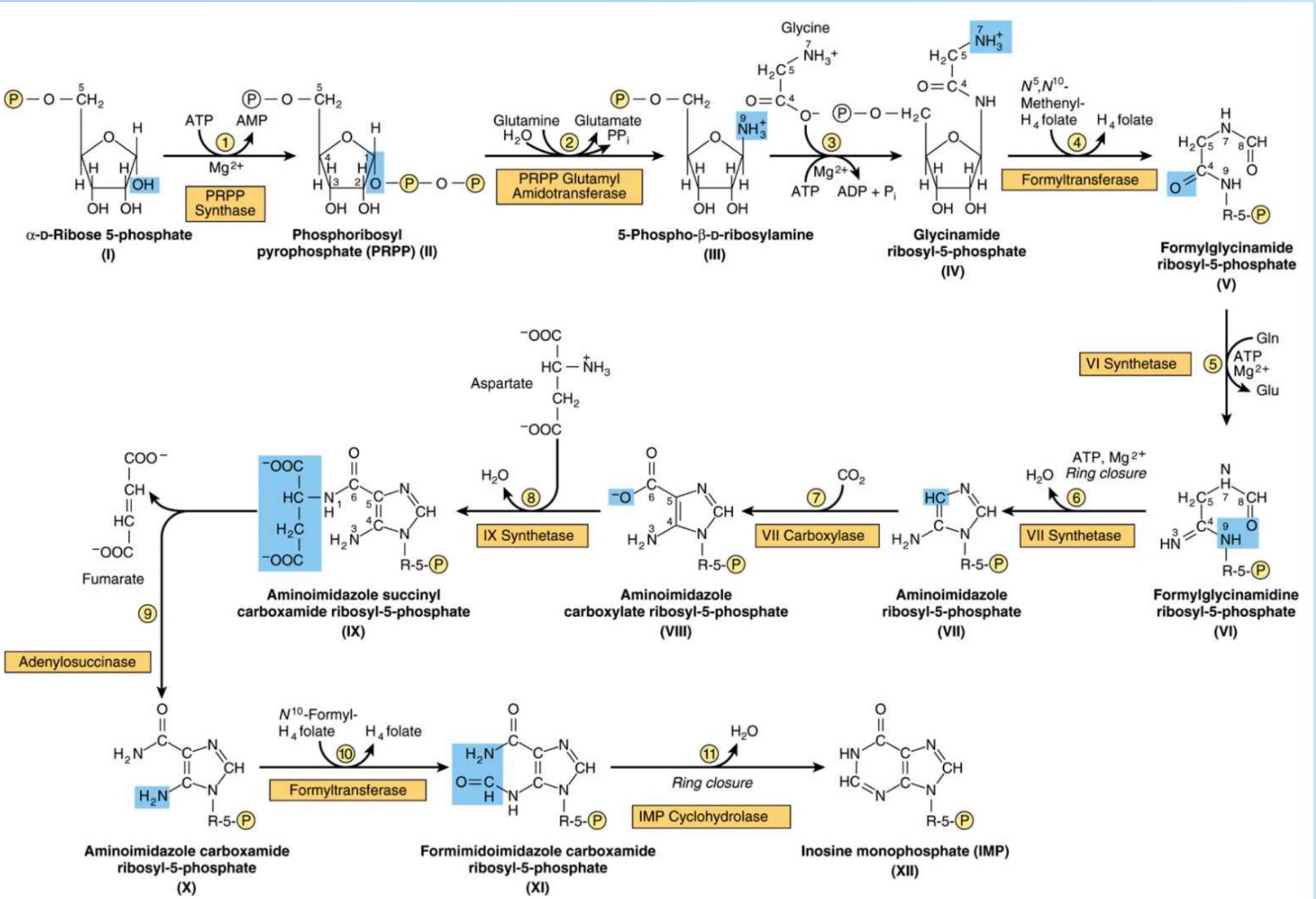
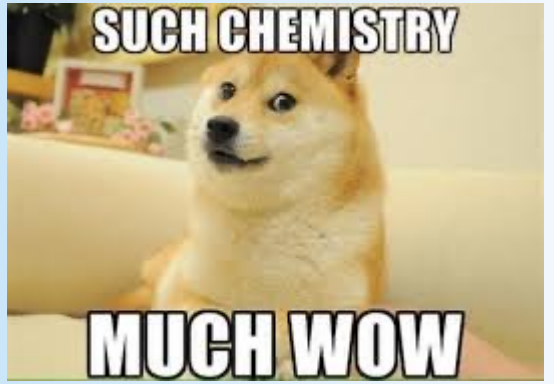
9 more steps to get to IMP!



Inosine monophosphate (IMP)


α-D-Ribose 5-phosphate
(I)
ATP
AMP
Mg2+
PRPP Synthase
Phosphoribosyl pyrophosphate (PRPP) (II)
Glutamine
Glutamate
PRPP Glutamyl Amidotransferase
Glycine
5-Phospho-β-D-ribosylamine
(III)
ATP
ADP + Pi
Glycinamide ribosyl-5-phosphate
(IV)
N5,N10-Methenyl-H4 folate
H4 folate
Formyltransferase
Formylglycinamide ribosyl-5-phosphate
(V)
VI Synthetase
Gln
ATP
Mg2+
Glu
Formylglycinamidine ribosyl-5-phosphate
(VI)
ATP, Mg2+
Ring closure
VII Synthetase
Aminoimidazole ribosyl-5-phosphate
(VII)
CO2
VII Carboxylase
Aminoimidazole carboxylate ribosyl-5-phosphate
(VIII)
Aspartate
IX Synthetase
Aminoimidazole succinyl carboxamide ribosyl-5-phosphate
(IX)
Fumarate
Adenylosuccinase
N10-Formyl-H4 folate
H4 folate
Formyltransferase
Aminoimidazole carboxamide ribosyl-5-phosphate
(X)
Ring closure
IMP Cyclohydrolase
Formimidoimidazole carboxamide ribosyl-5-phosphate
(XI)
Inosine monophosphate (IMP)
(XII)


SUCH CHEMISTRY
MUCH WOW

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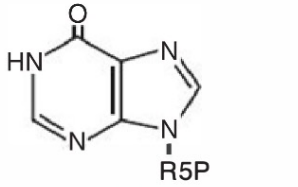


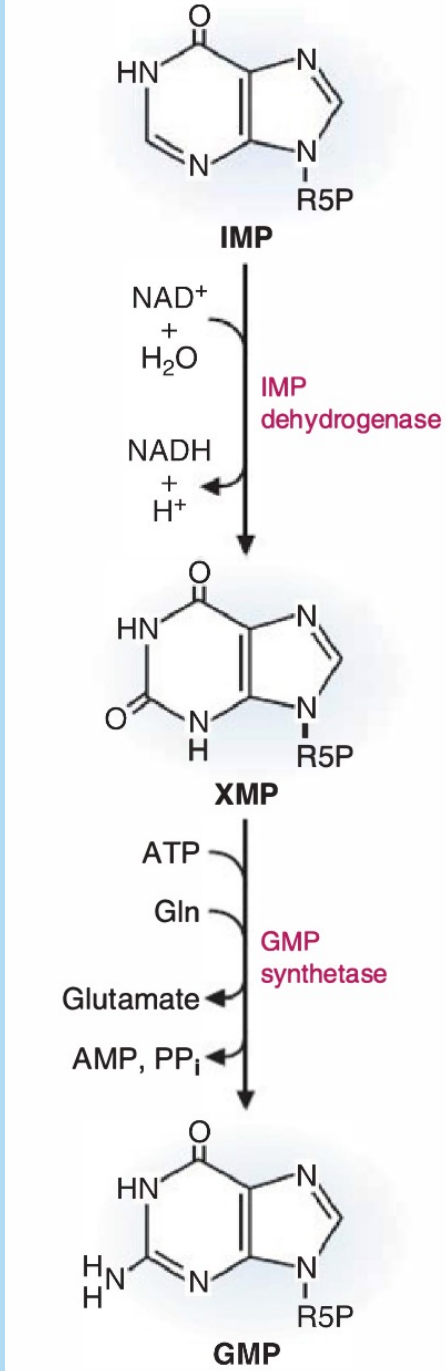
IMP to AMP

Formation of Adenylosuccinate

- **Aspartate** is added to IMP
- Enzyme: **Adenylosuccinate synthetase**
- Requires **GTP** as the energy source

Formation of AMP

- **Fumarate** is released from adenylosuccinate
- Enzyme: **Adenylosuccinate lyase**



IMP to GMP

Formation of XMP

- The **hypoxanthine base** of IMP is oxidized to **xanthine**
- Enzyme: **IMP dehydrogenase**

Conversion of XMP to GMP

- **Glutamine** donates an **amide nitrogen** to XMP
- Enzyme: **GMP synthetase**
- Requires **ATP** for energy

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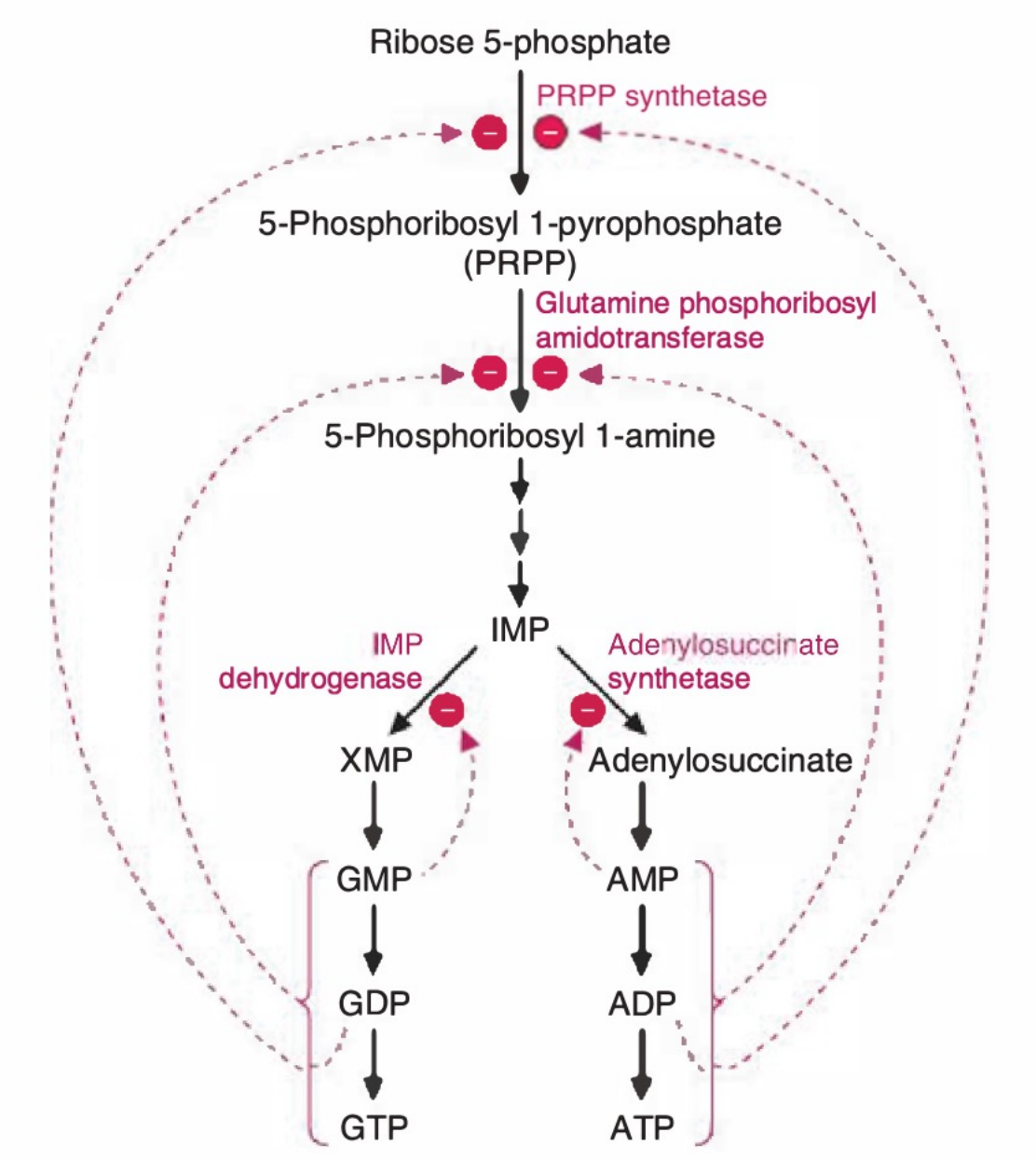

Purine Synthesis Regulation

Regulation of PRPP synthetase

- Inhibitors: GDP (oxypurine), ADP (aminopurine)

Regulation of GPAT

- Inhibitors: GMP, AMP
- Activators: PRPP, glutamine

Regulation of IMP dehydrogenase

- Inhibited by GMP
- Activated by high ATP

Regulation of Adenylosuccinate synthetase

- Inhibited by AMP
- Activated by high GTP

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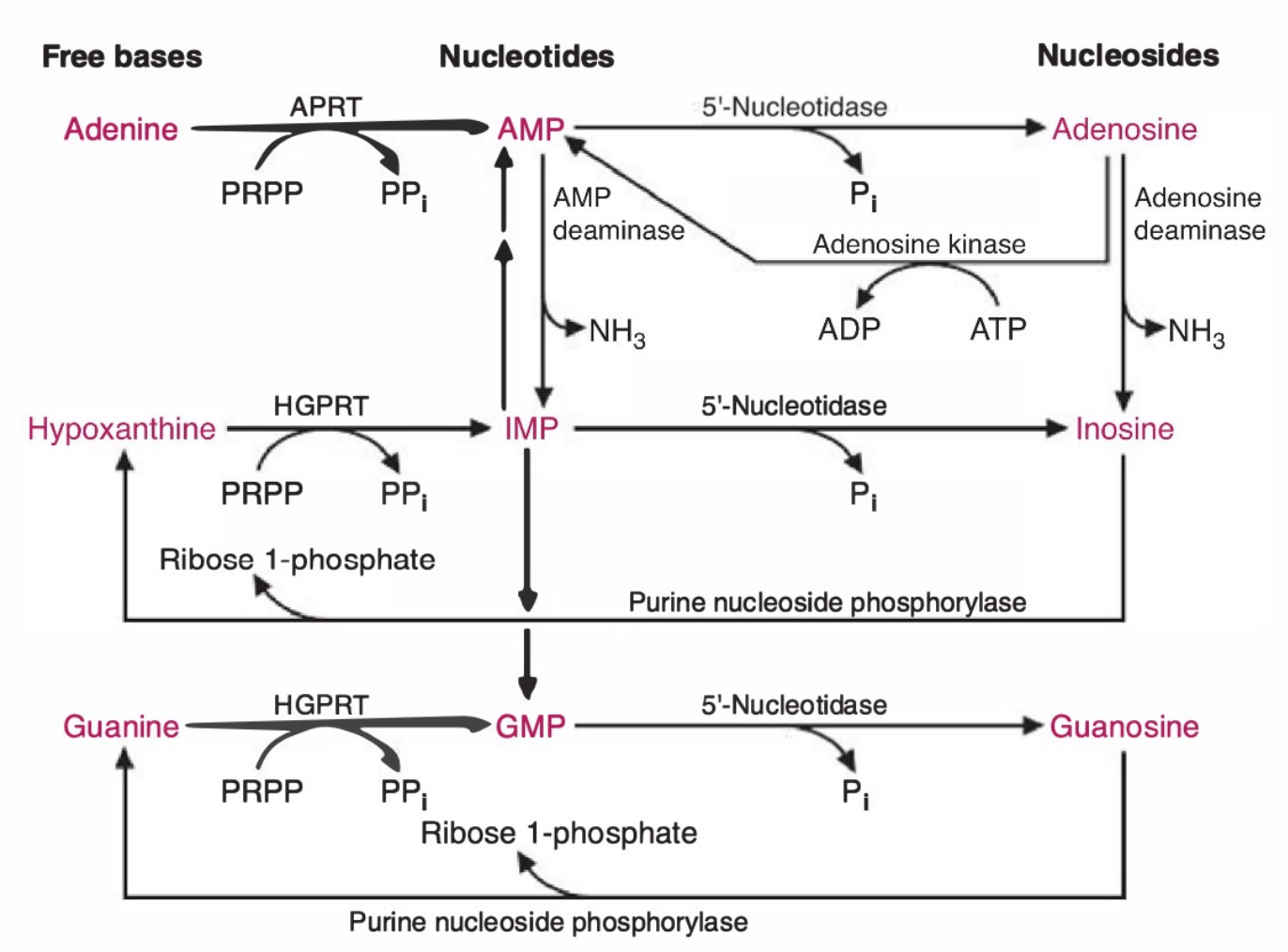
Purine Salvage Pathways



- Allows free bases, nucleosides, and nucleotides to be easily interconverted
- Requires significantly **less** energy compared to de novo synthesis
- Major form of nucleotide generation for specific cell types like **lymphocytes**
- Key enzymes
  - APRT
  - HGPRT
  - Adenosine deaminase (ADA)
  - Purine nucleoside phosphorylase (PNP)

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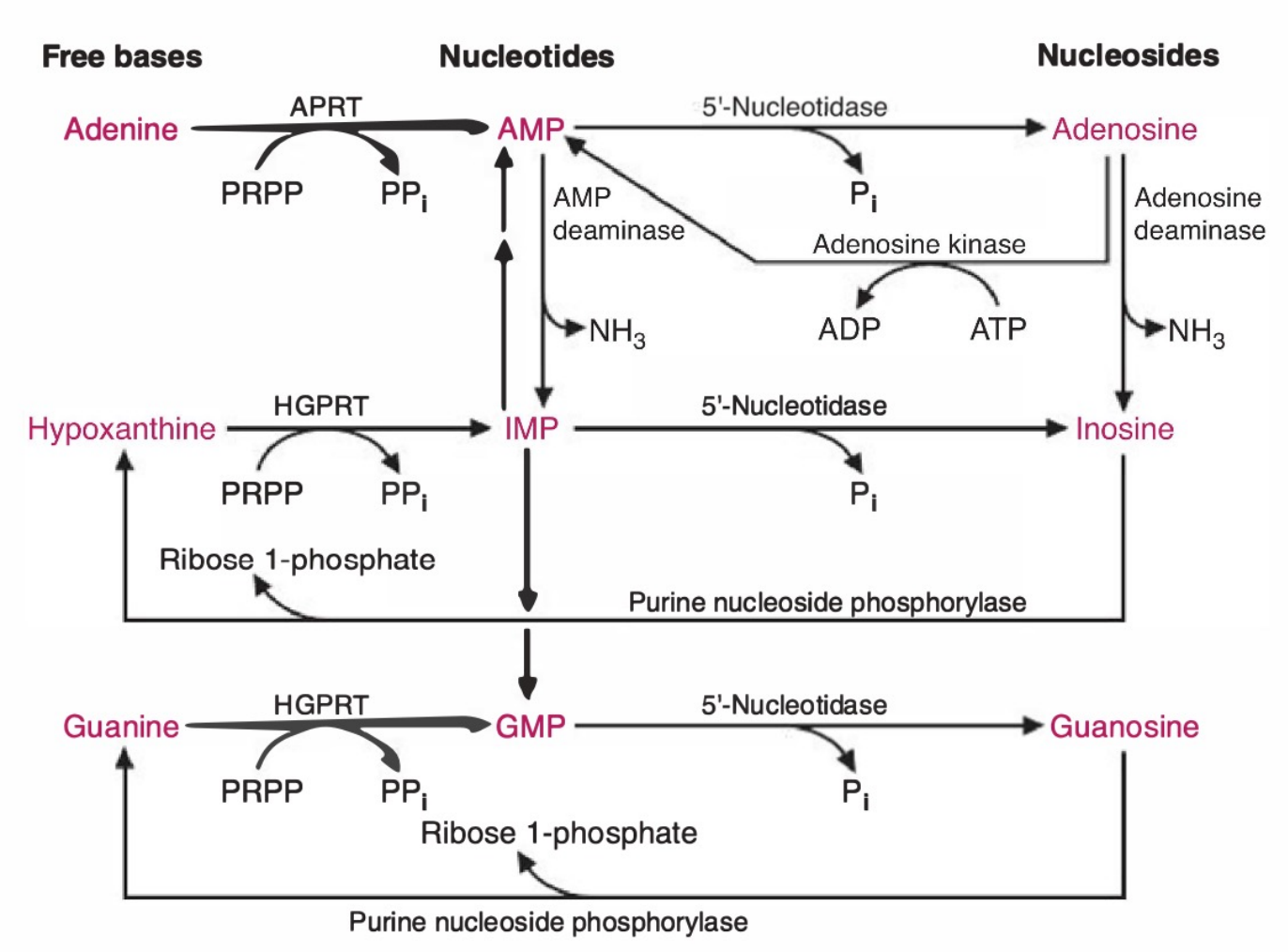
Lesch-Nyhan Syndrome



- Defective purine salvage
- HGPRT deficiency
- **Decreased** GMP and IMP formation
- Compensatory **increase** in purine synthesis (increased GPAT) leads to **excess uric acid** production!

HGPRT:

- **H**yperuricemia
- **G**out
- **P**issed off (aggression, self-mutilation)
- **R**ed/orange crystals in urine
- **T**ense muscles (dystonia)

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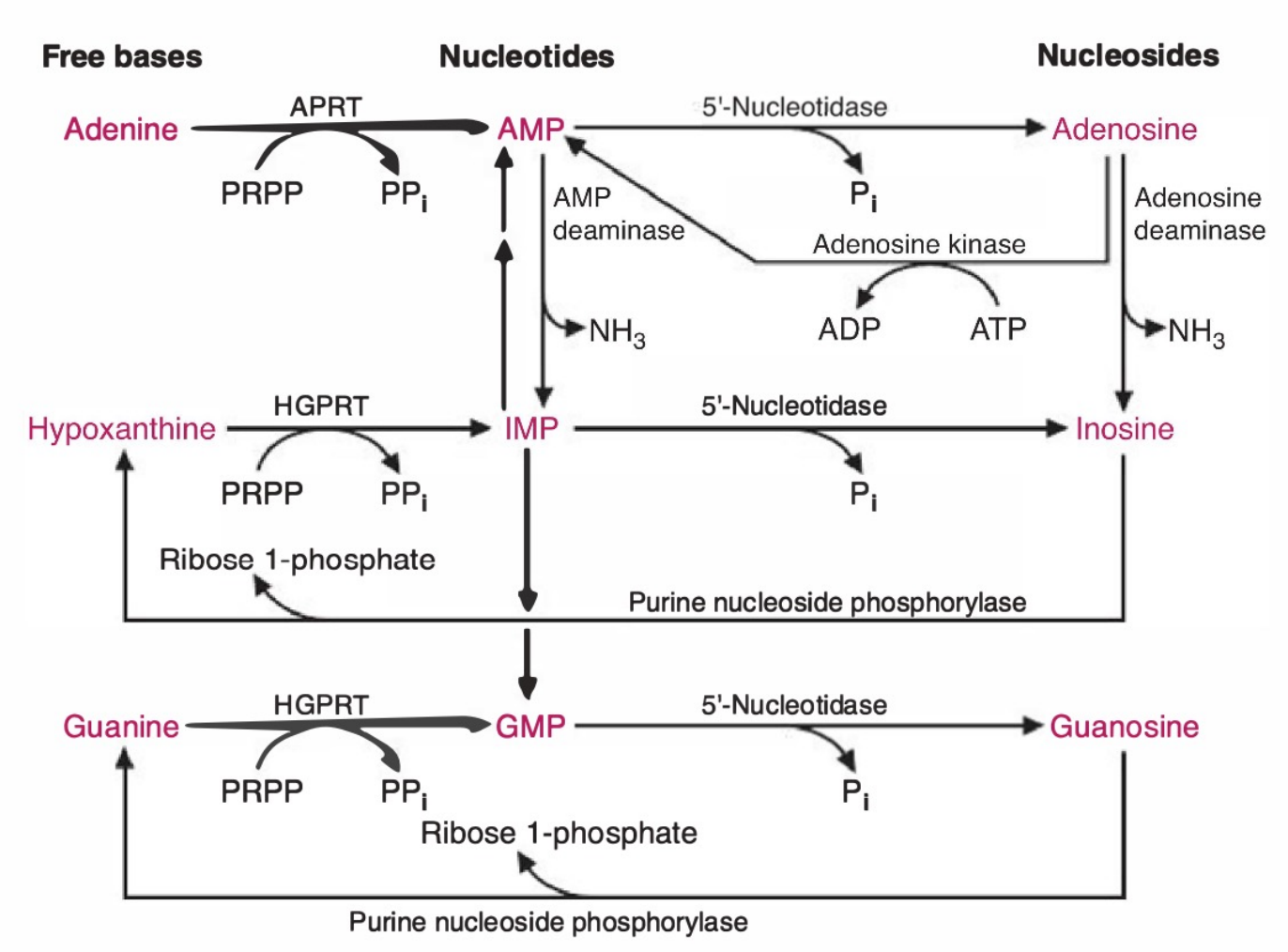
Adenosine Deaminase (ADA) Deficiency



- **Deoxyadenosine (dA)** and its toxic derivatives accumulate in blood and immune cells
- Elevated **dATP** levels inhibit **ribonucleotide reductase**, impairing DNA synthesis
- Severe dysfunction of both **T cells** and **B cells**
- Causes **Severe Combined Immunodeficiency** (SCID):
  - Increased susceptibility to infections
  - Failure to thrive and developmental delays

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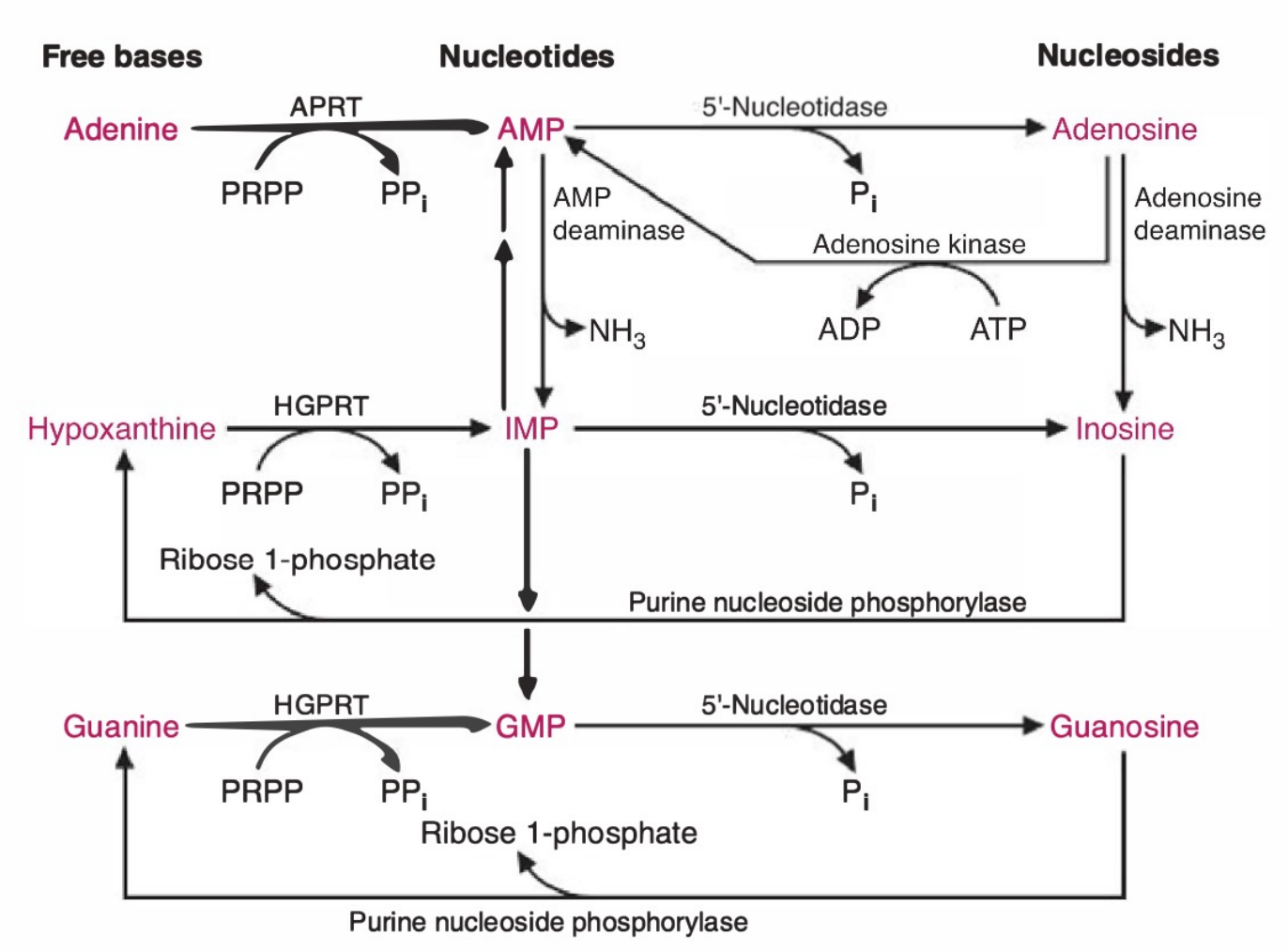
PNP Deficiency



- **Inosine** and **guanosine** accumulation
- Toxic effects of accumulated nucleosides selectively impair **T-cell function**, while **B-cell function remains near normal**
- Increased susceptibility to infections due to loss of **T-cell function**

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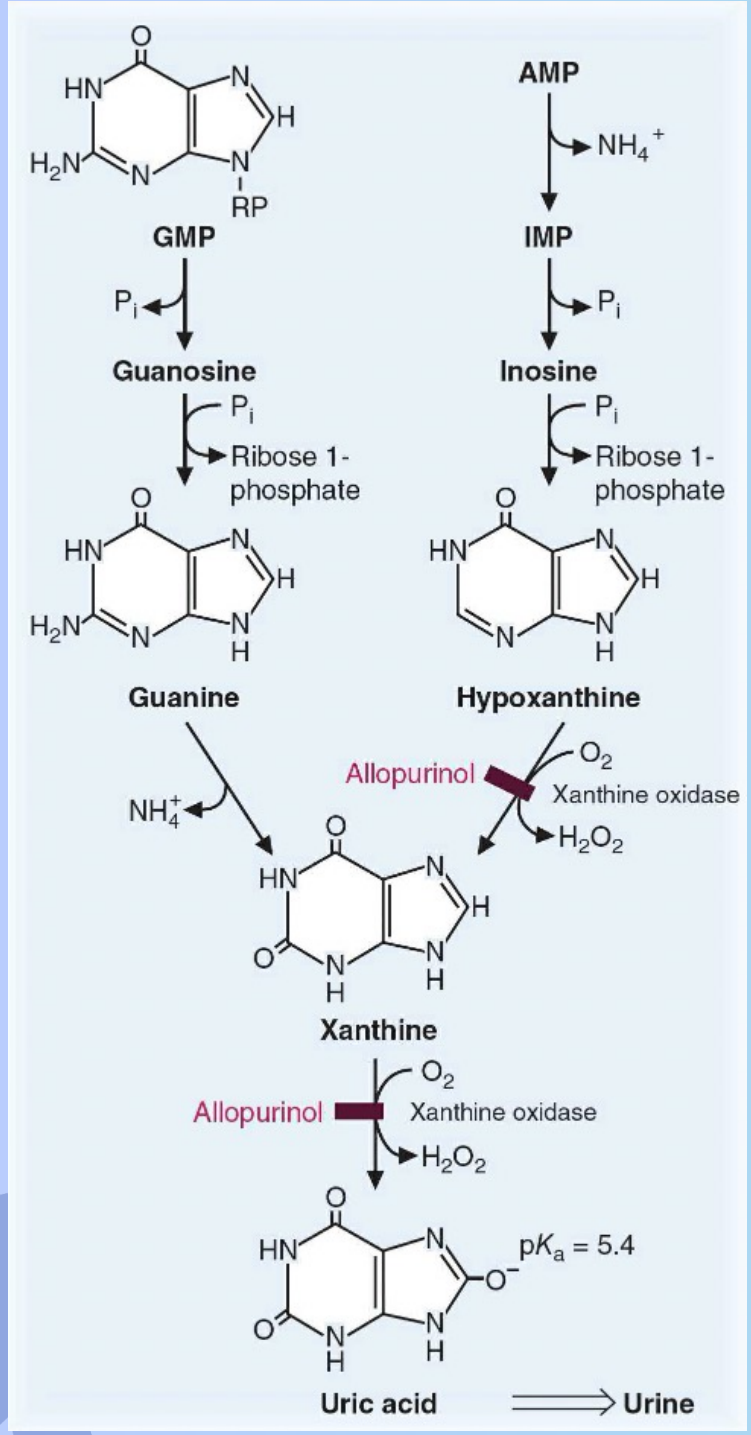

Purine Degradation

Degradation pathways:

- AMP → IMP → inosine → uric acid
- GMP → guanine → xanthine → uric acid

most of **uric acid** is excreted in urine !

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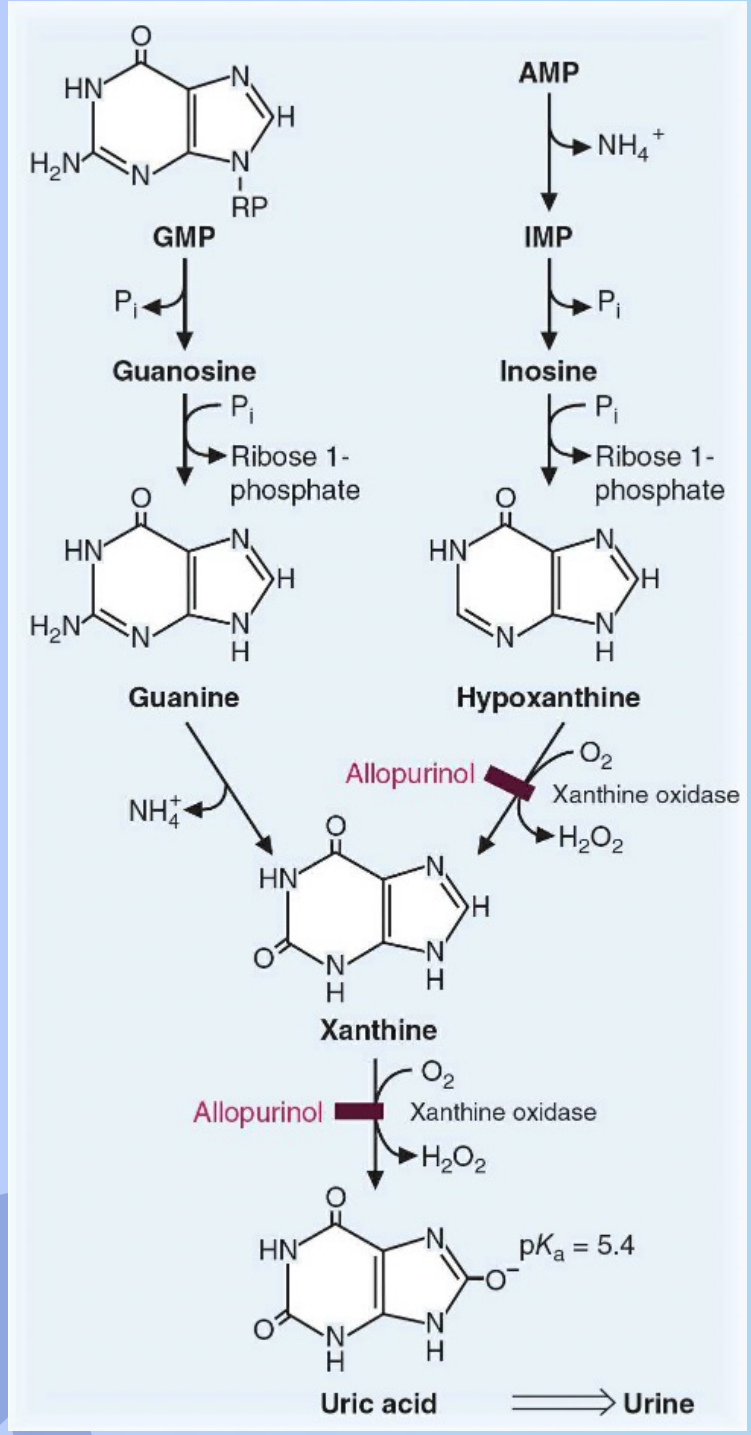
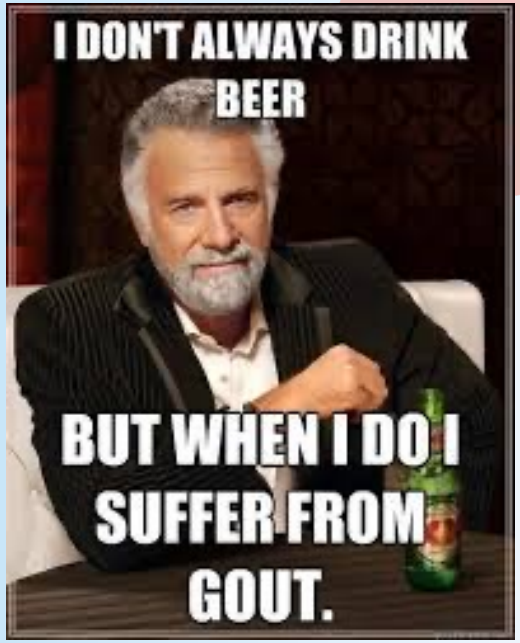


Gout



- Increased levels of **uric acid** in blood (hyperuricemia)
- Due to overproduction (10%) or **underexcretion (90%)** of uric acid
- Deposits of **monosodium urate (MSU) crystals** in joints causing an inflammatory response
- Treated with **Allopurinol** (hypoxanthine analogue), which inhibits Xanthine oxidase → decreased uric acid production

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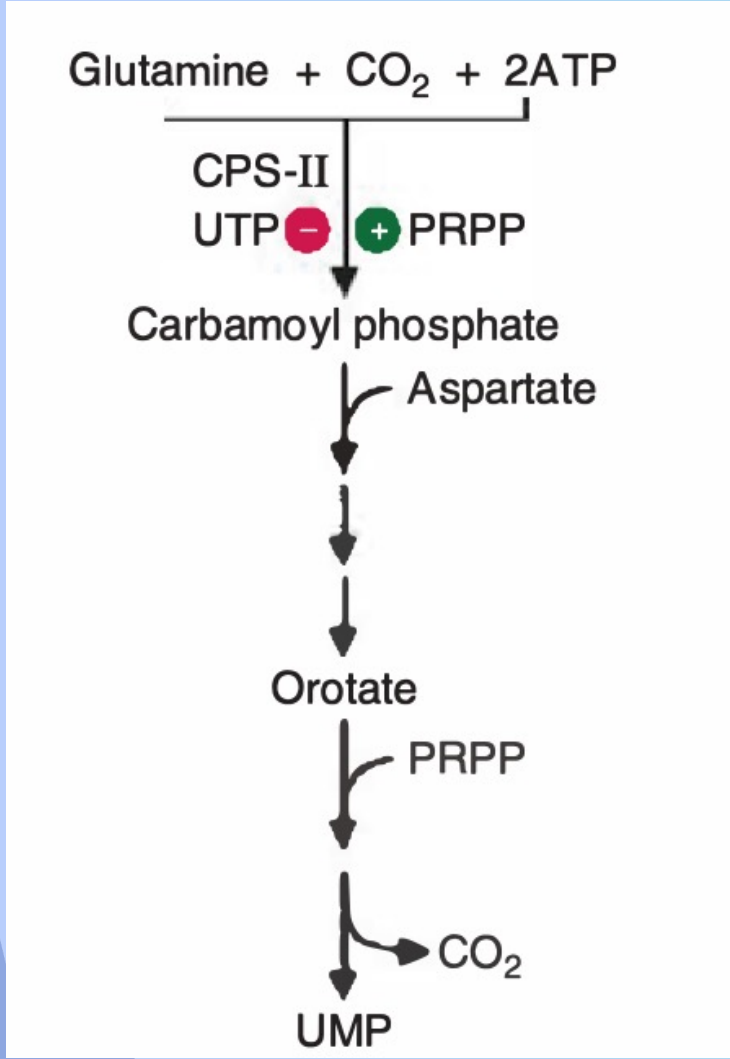
De Novo Pyrimidine Biosynthesis



- Pyrimidine bases are synthesized **first** and then attached to **ribose-5-phosphate** from PRPP
- Entire pathway occurs in the **cytosol**
- **CPSII** is the key regulatory enzyme
- Synthesis of any pyrimidine nucleotide begins with the formation of **uridine monophosphate (UMP)**

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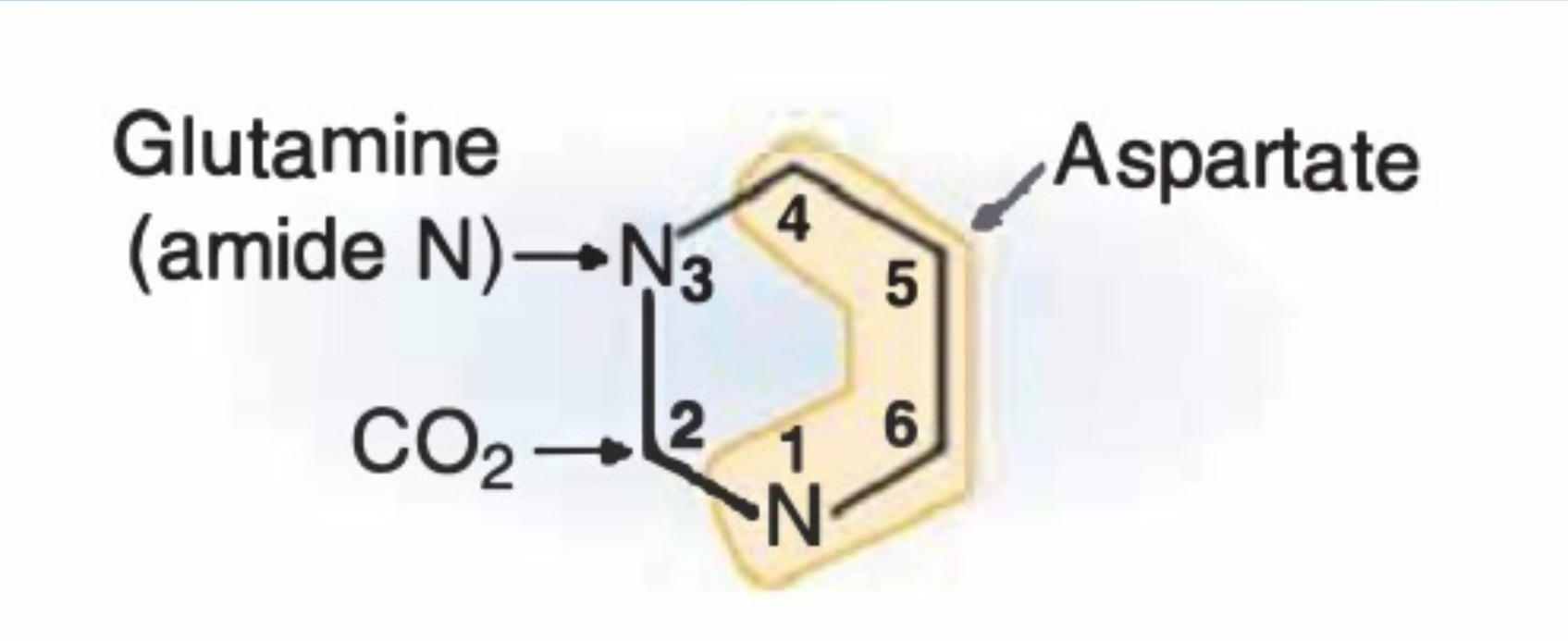
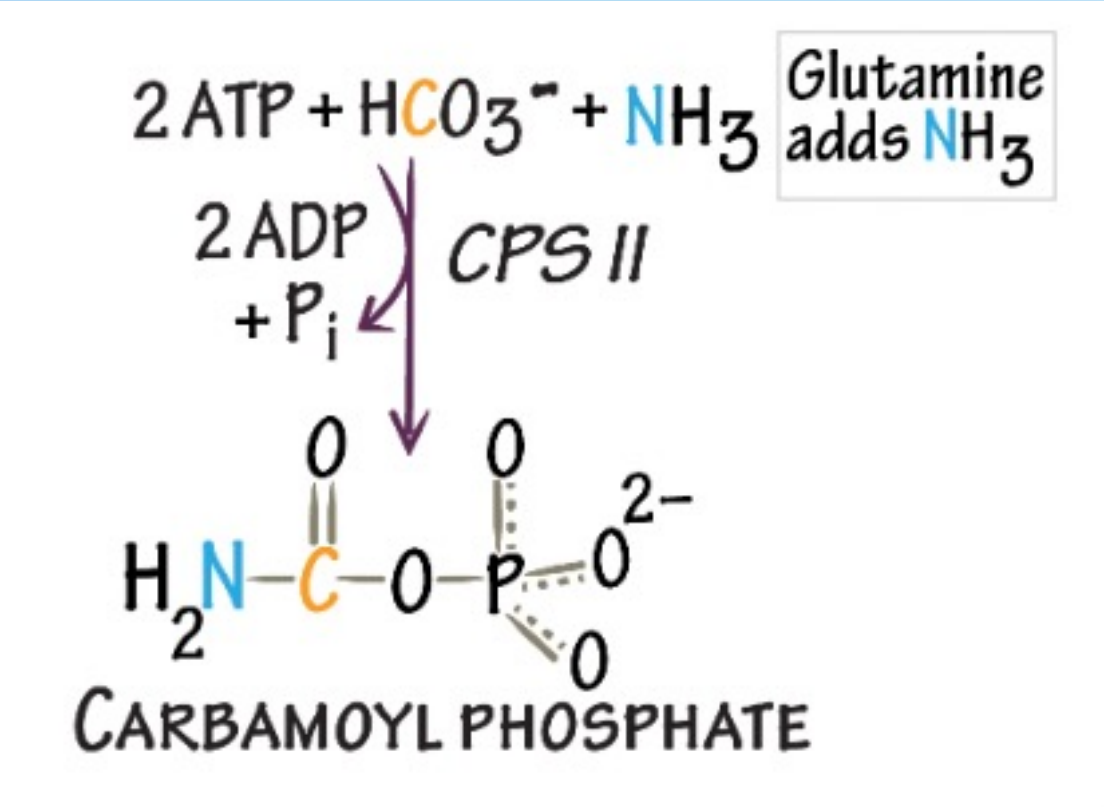
Sources of Atoms in a Pyrimidine Ring



Step 1: Formation of Carbamoyl Phosphate



- **Glutamine** + **Bicarbonate** + **ATP** → **Carbamoyl Phosphate**
- Enzyme: **Carbamoyl Phosphate Synthetase II (CPSII)**
- Occurs in the **cytosol** (unlike CPSI in the mitochondria)

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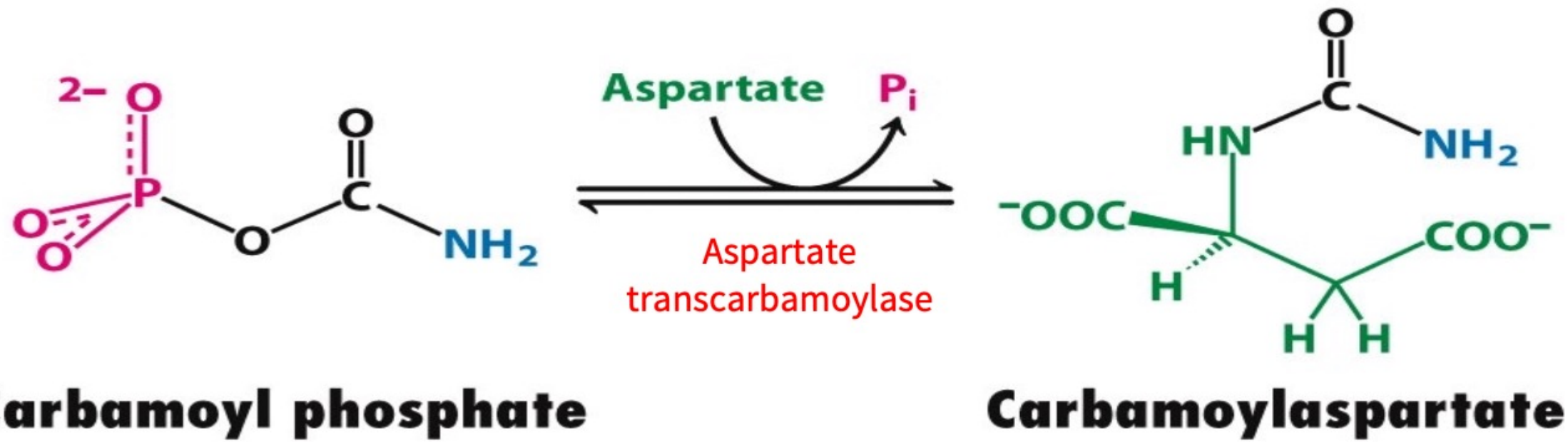
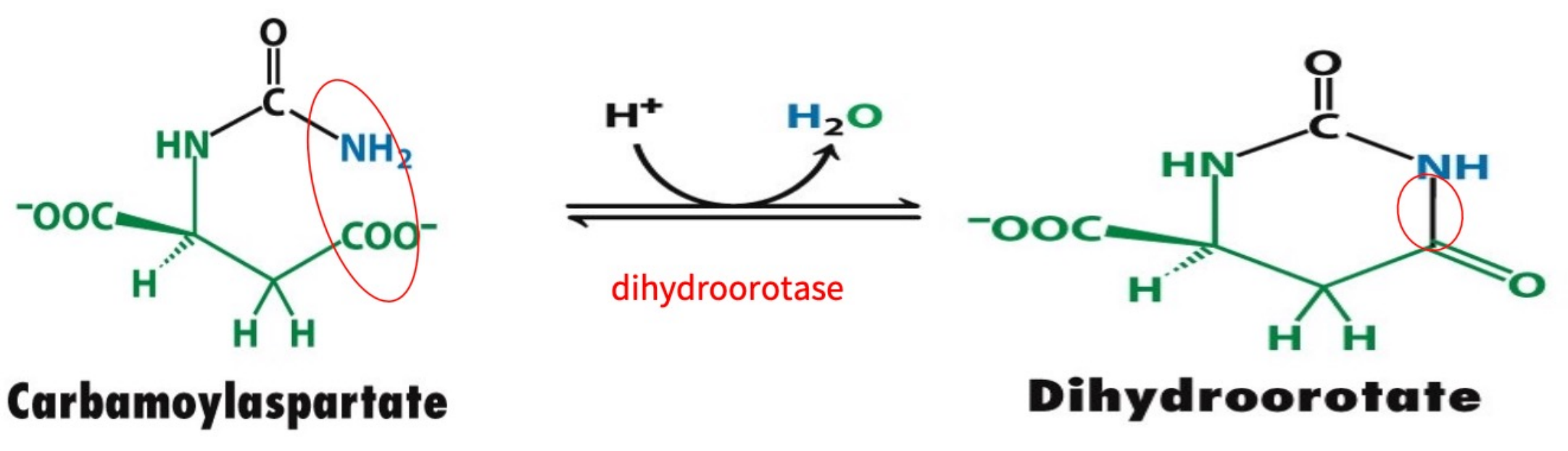
Step 2: Addition of Aspartate



Step 3: Ring Closure



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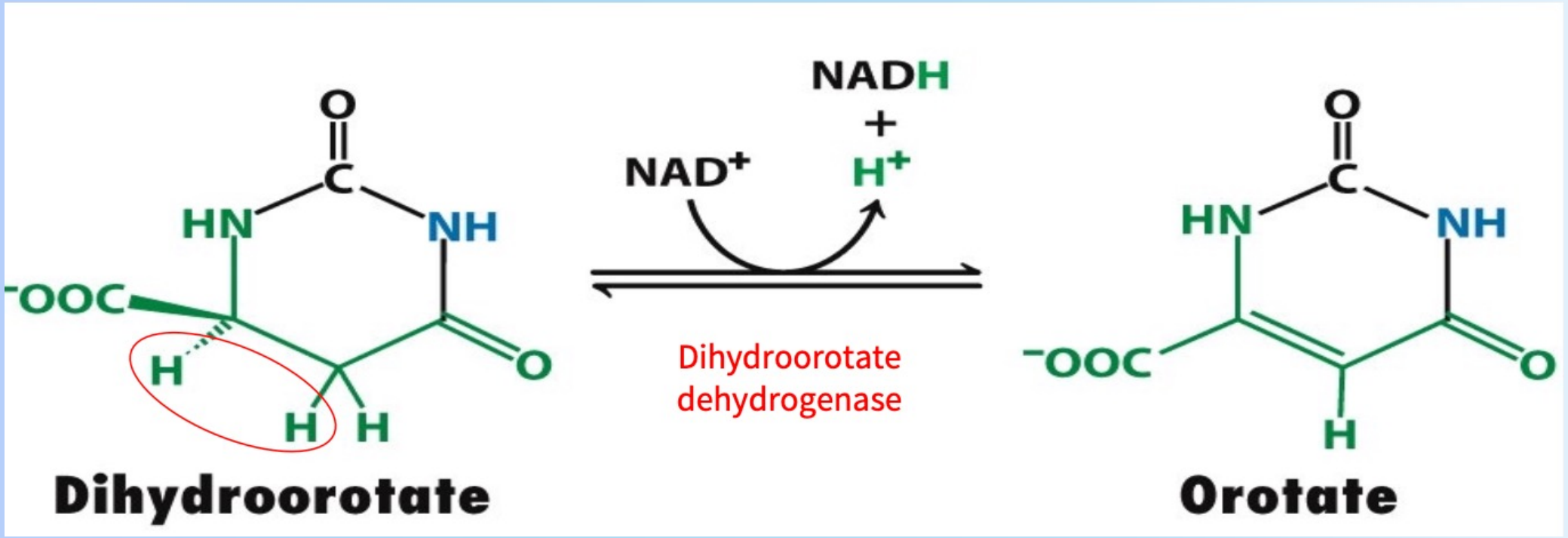
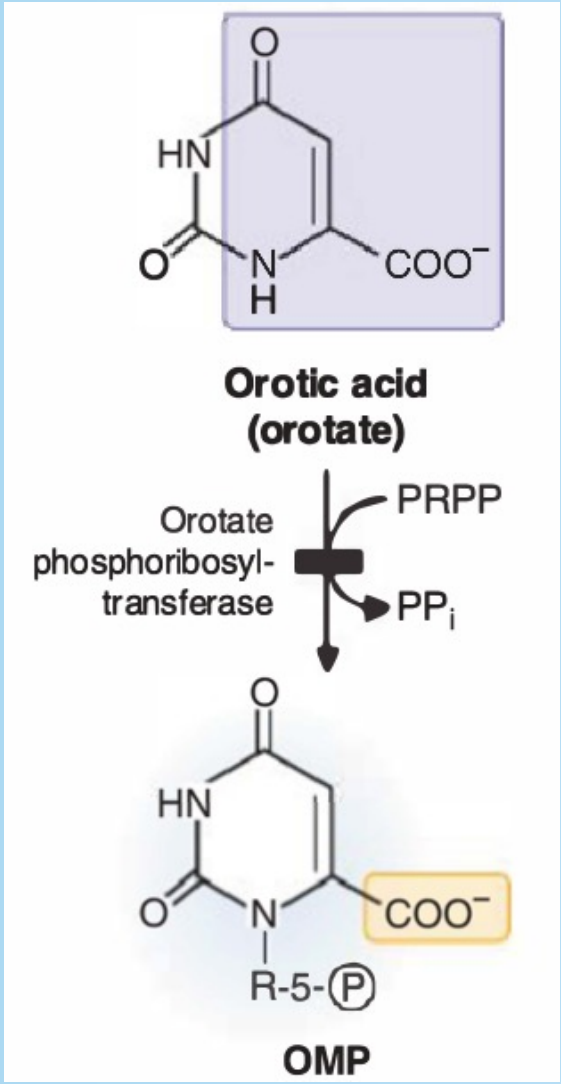
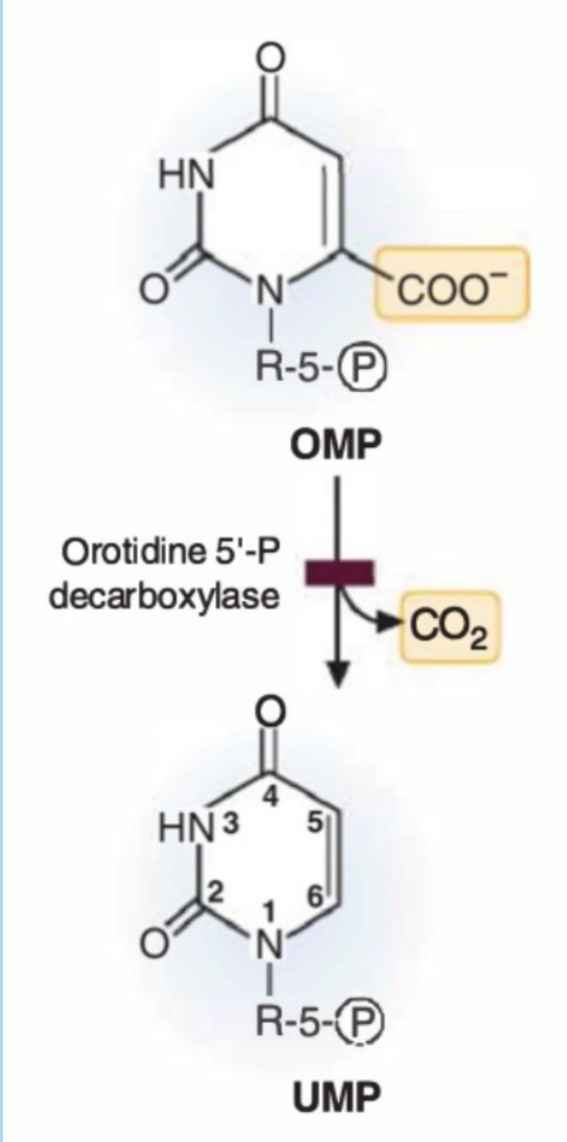
Step 4: Oxidation to Orotic Acid



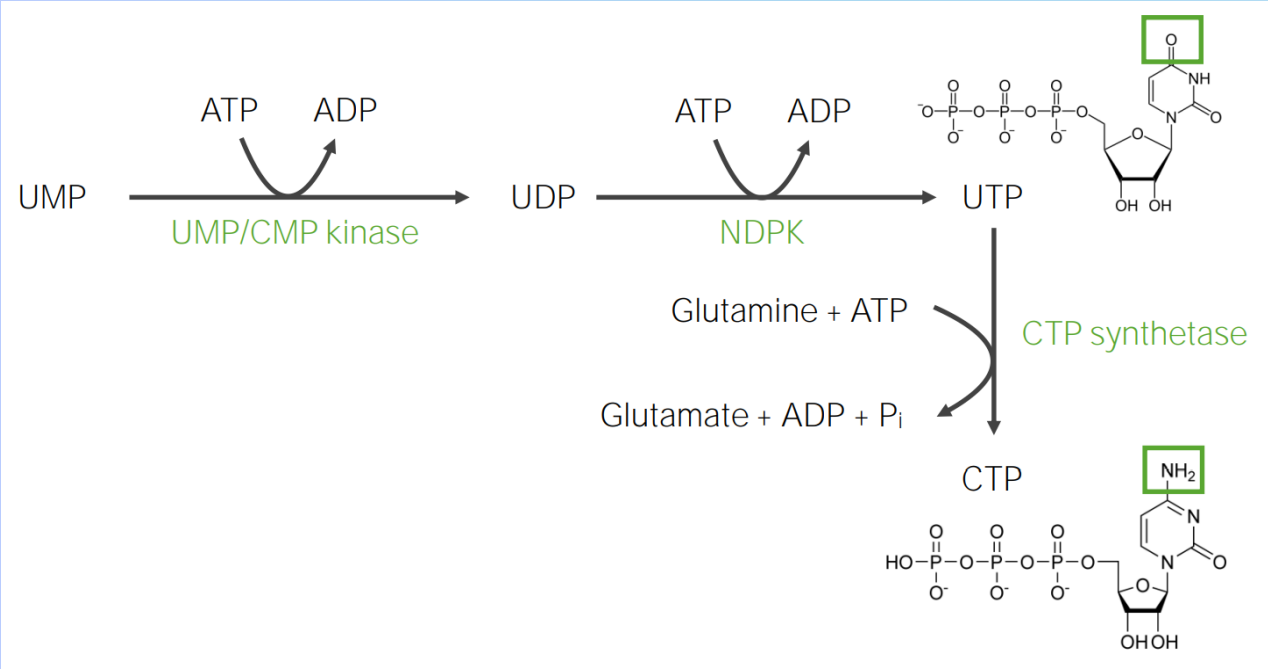
Step 5: Addition of PRPP



Step 6: Formation of UMP !



Conversion of UMP to CTP



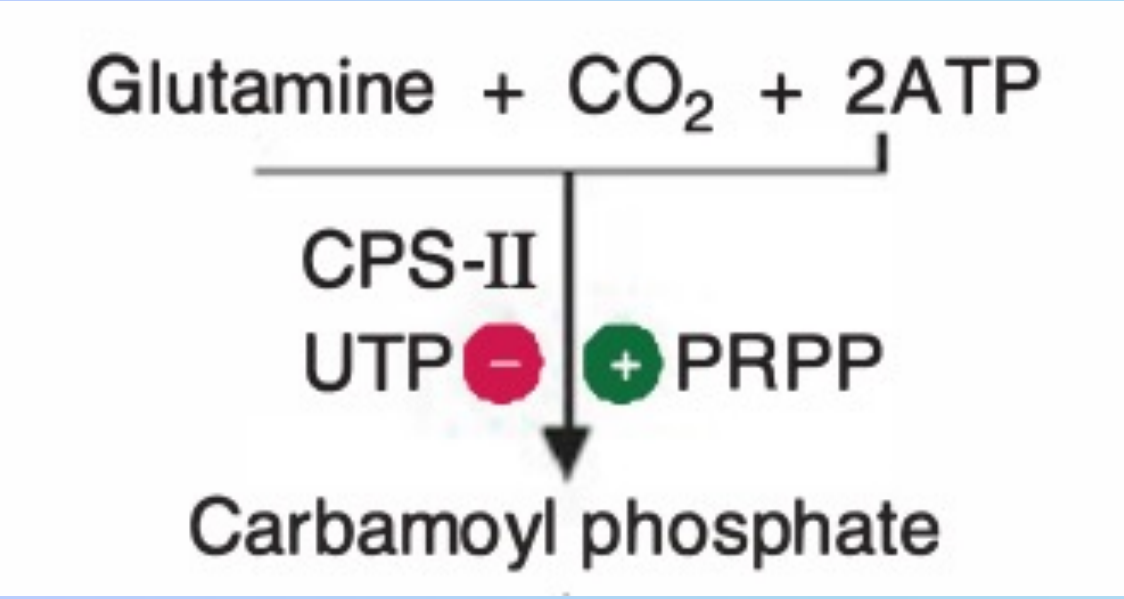
Phosphorylation of UMP to UTP

- UMP (uridine monophosphate) is phosphorylated to UTP (uridine triphosphate) through **nucleotide kinases**

Synthesis of CTP

- An **amine group** from **glutamine** is added to UTP forming CTP (cytidine triphosphate)
- Enzyme: **CTP synthetase**

Pyrimidine Synthesis Regulation



Regulated Step

- CPSII is the key regulatory enzyme in pyrimidine synthesis.

Allosteric Regulation

- Inhibited by **UTP** (high pyrimidine levels)
- Activated by **PRPP** (low pyrimidine levels)

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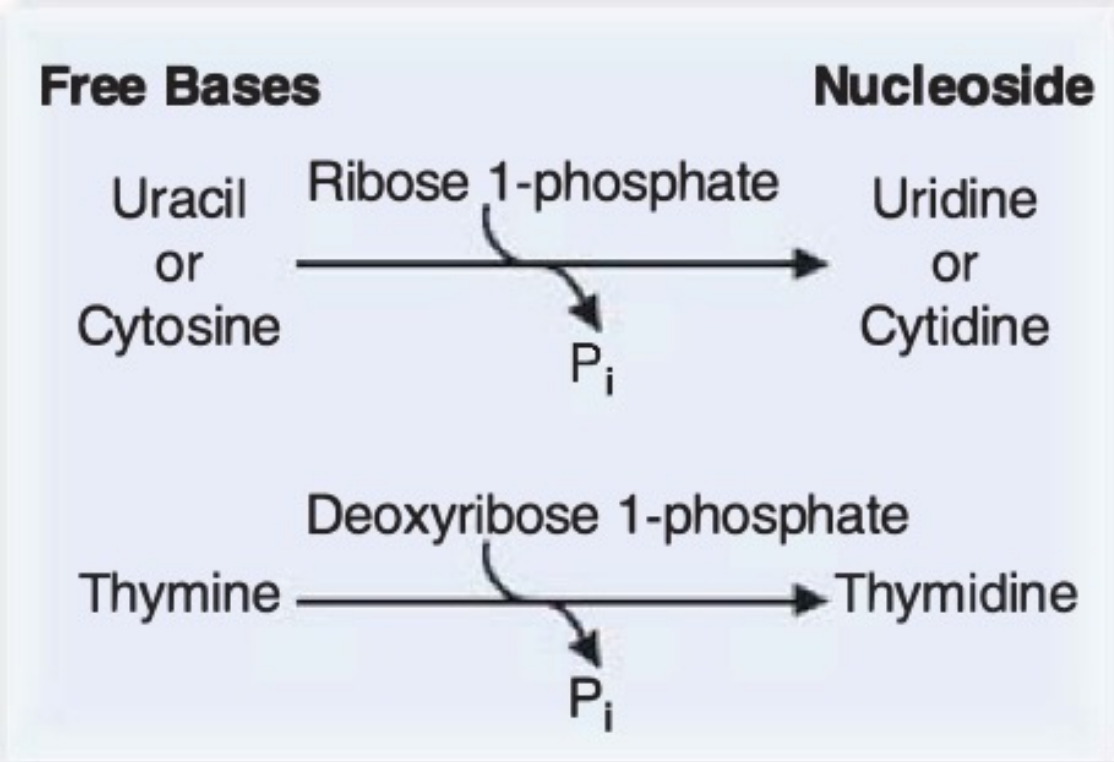
Pyrimidine Salvage Pathways



Pyrimidine Nucleoside Phosphorylase

- Converts pyrimidine **bases** to **nucleoside monophosphates**
- **Preference:**
  - **Uracil** is the preferred substrate, and this enzyme is sometimes called **uridine phosphorylase**
  - **Cytosine** is also utilized, though with lower efficiency
  - **Thymine** is poorly utilized, as the enzyme has very low affinity for it

Thymine Phosphorylase

- Converts **thymine** to a **deoxyribonucleoside** (adds a **deoxyribose** residue)
- Has a high affinity for thymine, facilitating its salvage into the nucleotide pool

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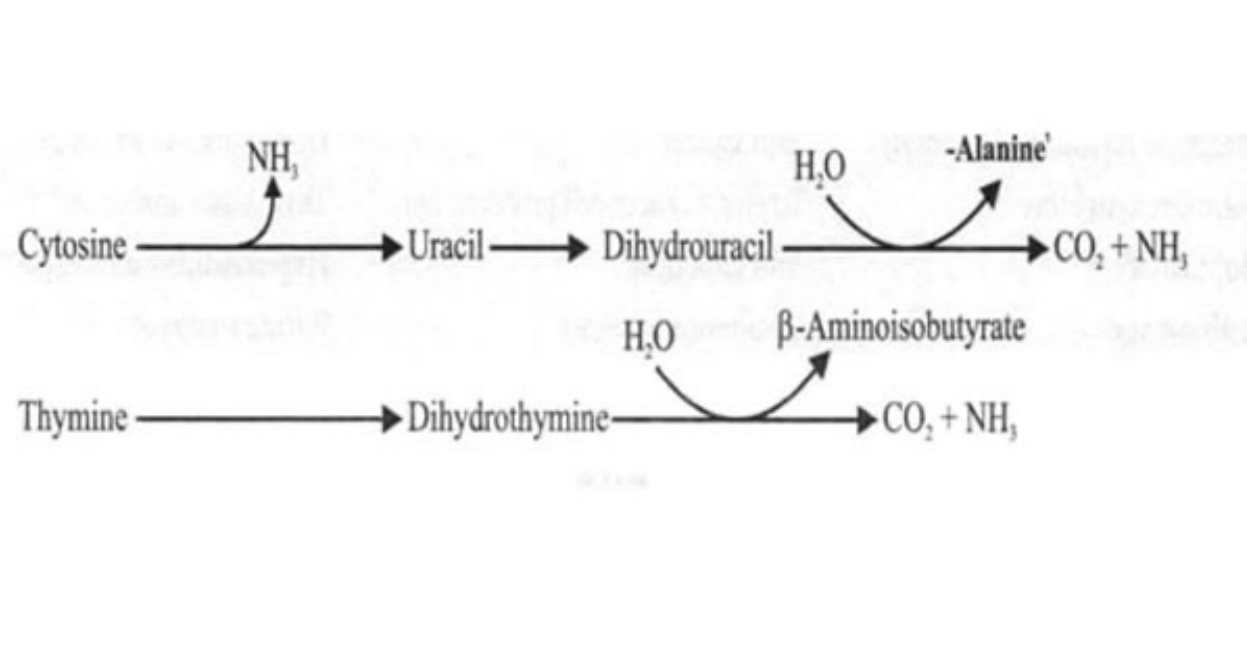
Pyrimidine Degradation



- Pyrimidines are broken down into soluble, non-problematic end products
- Degradation products, such as **β-alanine** and **β-aminoisobutyrate**, are safely excreted or metabolized
- Unlike purines, pyrimidine degradation **does not** pose health risks like gout

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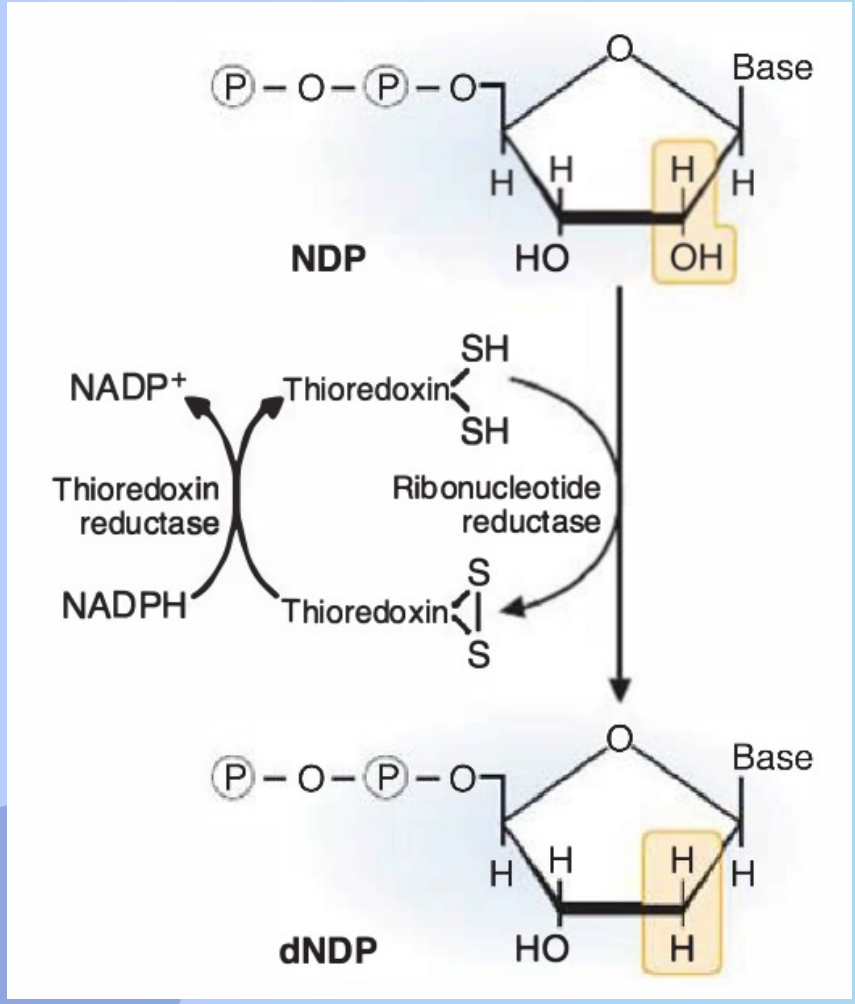
Production of Deoxyribonucleotides



- For DNA synthesis, ribose must be reduced to **deoxyribose** at the diphosphate level
- Enzyme: **Ribonucleotide reductase**
- Cofactor: **Thioredoxin**
- **Deoxyribonucleoside diphosphates** (dNDPs) are produced, which are further phosphorylated to triphosphates (dNTPs) for DNA synthesis
- **ATP** (+) and **dATP** (-) regulate activity

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WOOCLAP!


are u ok
no i forgot the nucleotide metabolism pathways again