STUDY MATERIAL

VIVEKANANDA COLLEGE THAKURPUKUR

NAAC ACCREDITED GRADE—'A'

Subject: Nucleotide Metabolism
Topic: Nucleotide degradation

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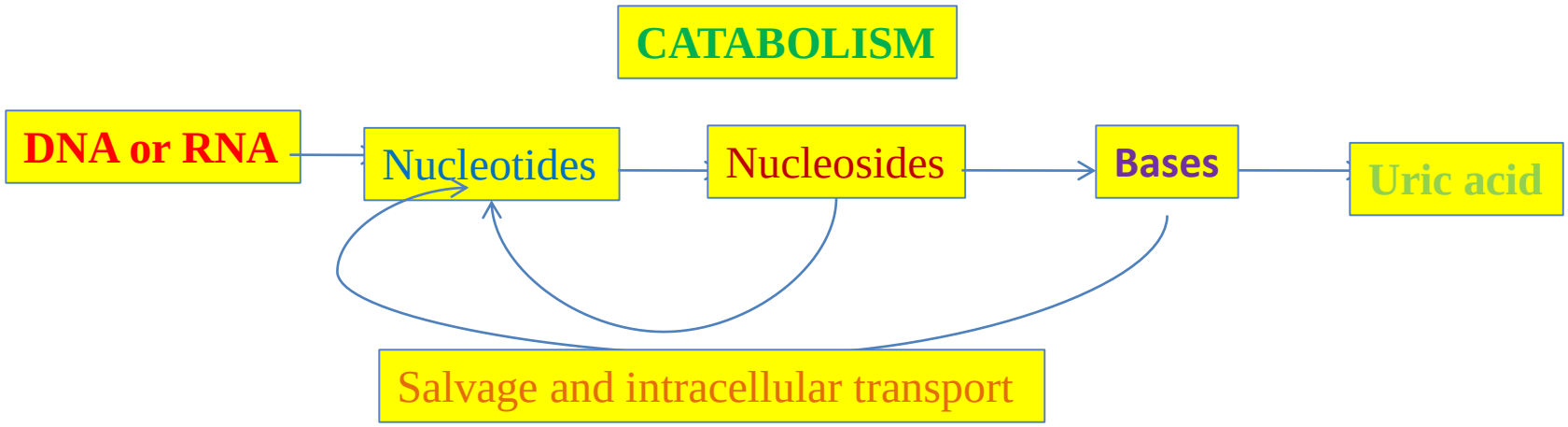
NUCLEOTIDE DEGRADATION ?

- **The breakdown or cleavage of DNA and RNA or more appropriately their nucleotides through several catabolic ways.**
- **Purine and pyrimidine nucleosides can either be degraded to waste products and excreted or salvaged to form NUCLEOTIDE COMPONENTS.**
- **Mammalians and most of the lower vertebrates can produce purine and pyrimidine components and are said to be PROTOTROPHIC.**
- **Nucleotide degradation or catabolism of nucleotides is thus one of the basic metabolic pathways.**
- **It can survive in the acidic medium of stomach and are degraded in duodenum.**
- **PANCREATIC NUCLEASES and INTESTINAL PHOSPHODIESTERASES assist in the degradation of nucleotides.**
- **Nucleotides are first converted to nucleosides then these nucleosides may be directly absorbed by intestinal mucosa or undergo further degradation to free bases or ribose or ribose-1-phosphate.**



Nucleotide degradation involves;

i. Catabolism of Purines

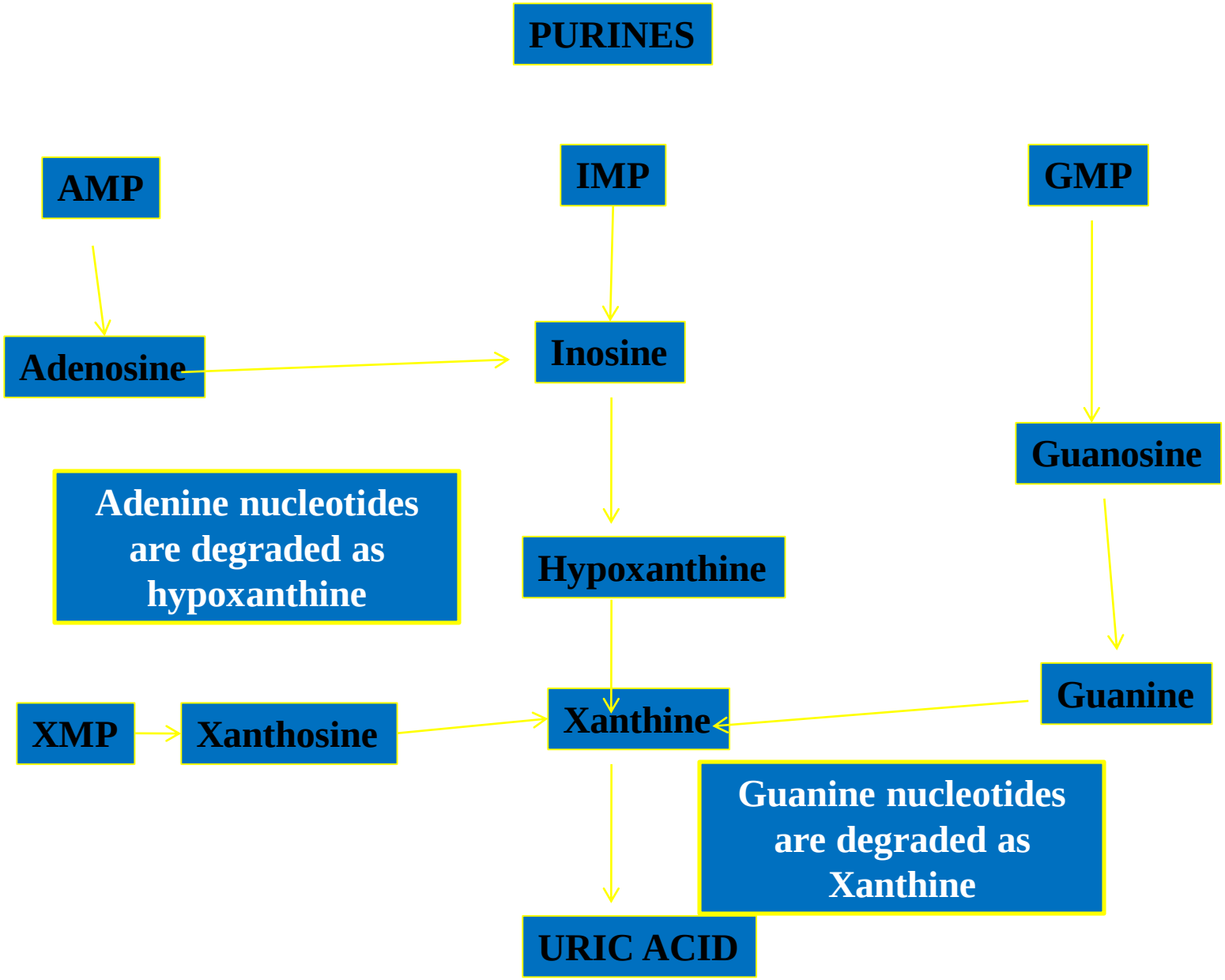
ii. Catabolism of Pyrimidines

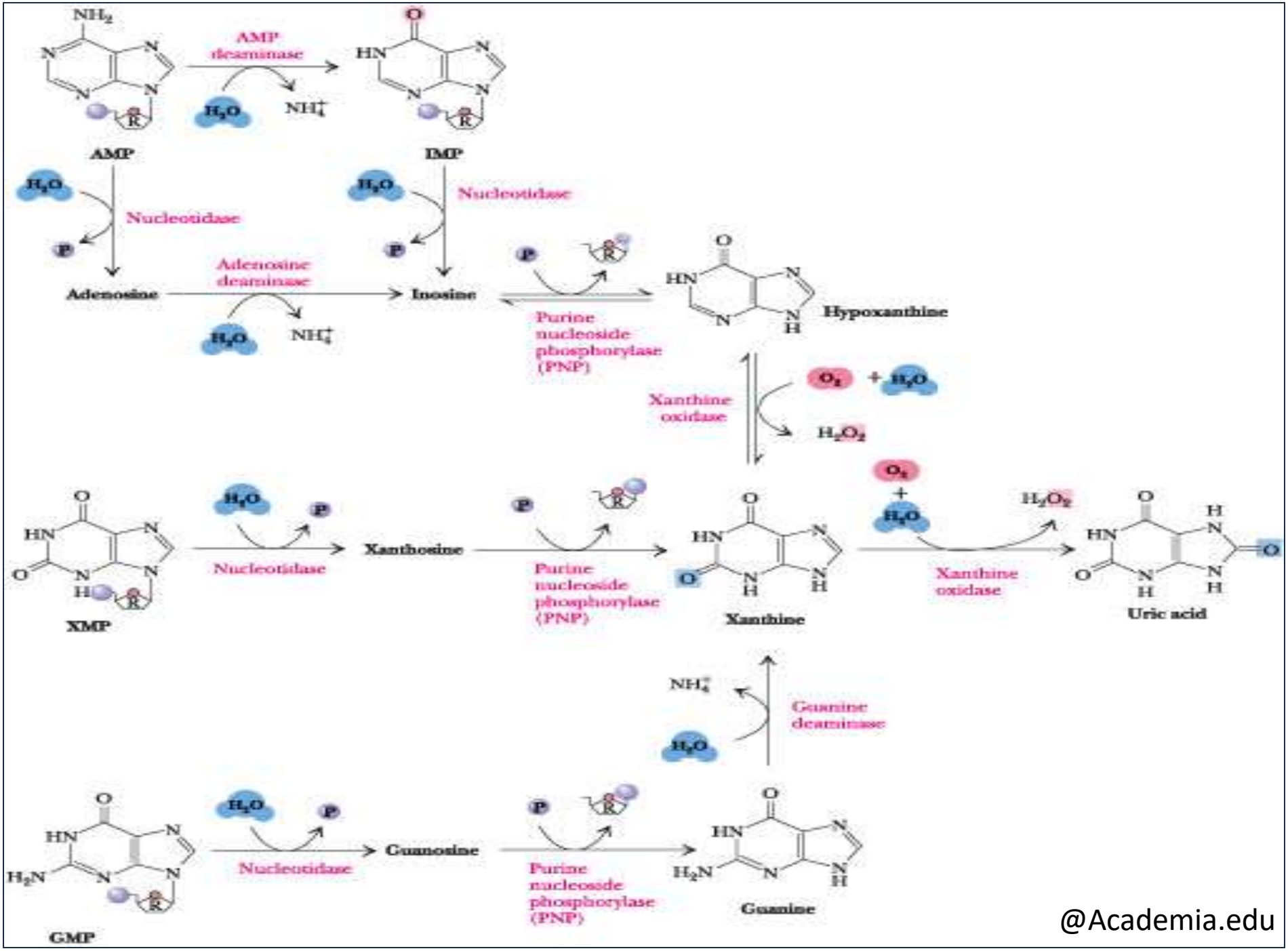
PURINE CATABOLISM

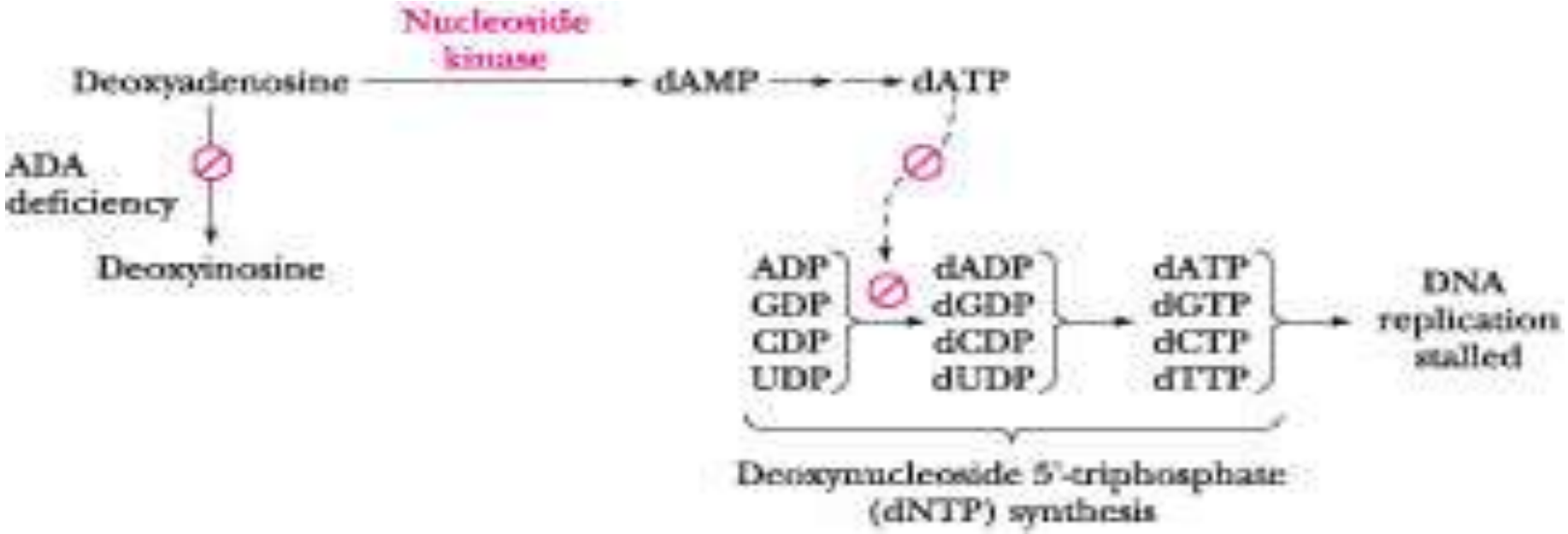
- The major pathways of purine nucleotide catabolism in animals and other organisms may differ but all of these pathways lead to URIC ACID.
- **CATABOLISM OF ADENINE NUCLEOTIDE**:
- An enzyme *purine-5`-nucleotidase* hydrolyzes adenylate as a result adenosine is produced.
- *Adenosine deaminase* removes ammonia from adenosine and forms inosine.
- *Purine nucleoside phosphorylase* phosphorolyses inosine to ribose-1-phosphate and hypoxanthine.
- *Xanthine oxidase* then converts hypoxanthine to xanthine and then to uric acid.

CATABOLISM OF GUANINE NUCLEOTIDE

- GMP is hydrolyzed by *purine-5'-nucleotidase* into guanosine.
- *Purine nucleoside phosphorylase* phosphorolyses guanosine into ribose-1-phosphate and guanine.
- *Guanine deaminase* deaminates guanine to xanthine and produces ammonia.
- Oxidation of xanthine to uric acid is brought about by *Xanthine oxidase.*


PURINES
AMP
IMP
GMP
Adenosine
Inosine
Guanosine
Adenine nucleotides are degraded as hypoxanthine
Hypoxanthine
Guanine
XMP
Xanthosine
Xanthine
Guanine nucleotides are degraded as Xanthine
URIC ACID





The effect of elevated levels of deoxyadenosine on purine metabolism. If ADA is deficient or absent, deoxyadenosine is not converted into deoxyinosine as normal. Instead, it is salvaged by a nucleoside kinase, which converts it to dAMP, leading to accumulation of dATP and inhibition of deoxynucleotide synthesis . Thus, DNA replication is stalled.

In the absence of ADA, deoxyadenosine is not degraded but instead is converted into dAMP and then into dATP. dATP is a potent feedback inhibitor of deoxynucleotide biosynthesis. Without deoxyribonucleotides, DNA cannot be replicated and cells cannot divide. Rapidly proliferating cell types such as lymphocytes are particularly susceptible if DNA synthesis is impaired.

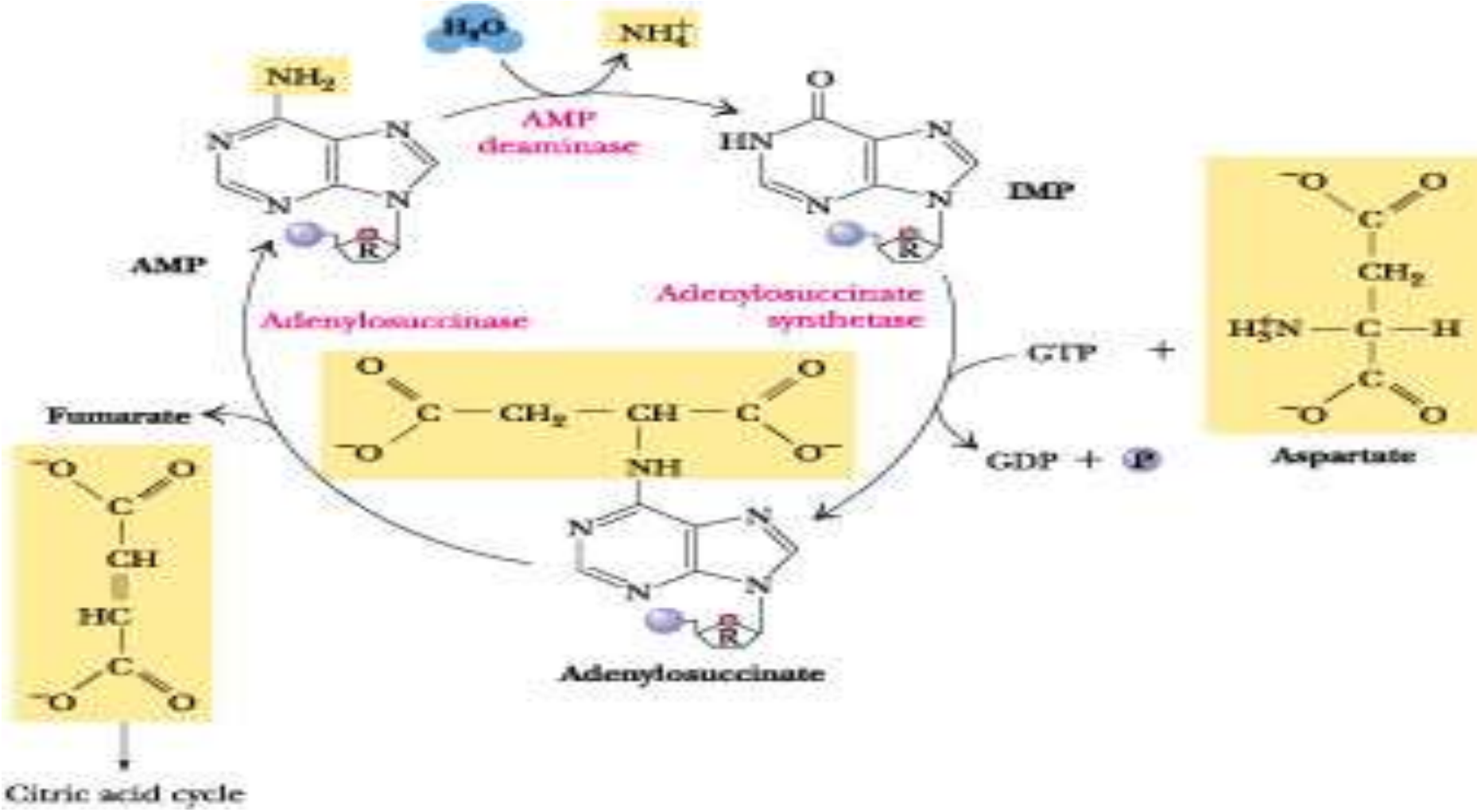


Fig: The purine nucleoside cycle for anaplerotic replenishment of citric acid cycle intermediates in skeletal muscle.

Deamination of AMP to IMP by **AMP deaminase** followed by resynthesis of AMP from IMP by the *de novo* purine pathway enzymes, *adenylosuccinate synthetase* and *adenylosuccinate lyase*, constitutes a purine nucleoside cycle. This cycle has the net effect of converting aspartate to fumarate plus NH_4^+. Although this cycle might seem like senseless energy consumption, it plays an important role in energy metabolism in skeletal muscle: the fumarate that it generates replenishes the levels of citric acid cycle intermediates lost in amphibolic side reactions. Skeletal muscle lacks the usual complement of anaplerotic enzymes and relies on enhanced levels of AMP deaminase, adenylosuccinate synthetase, and adenylosuccinate lyase to compensate.

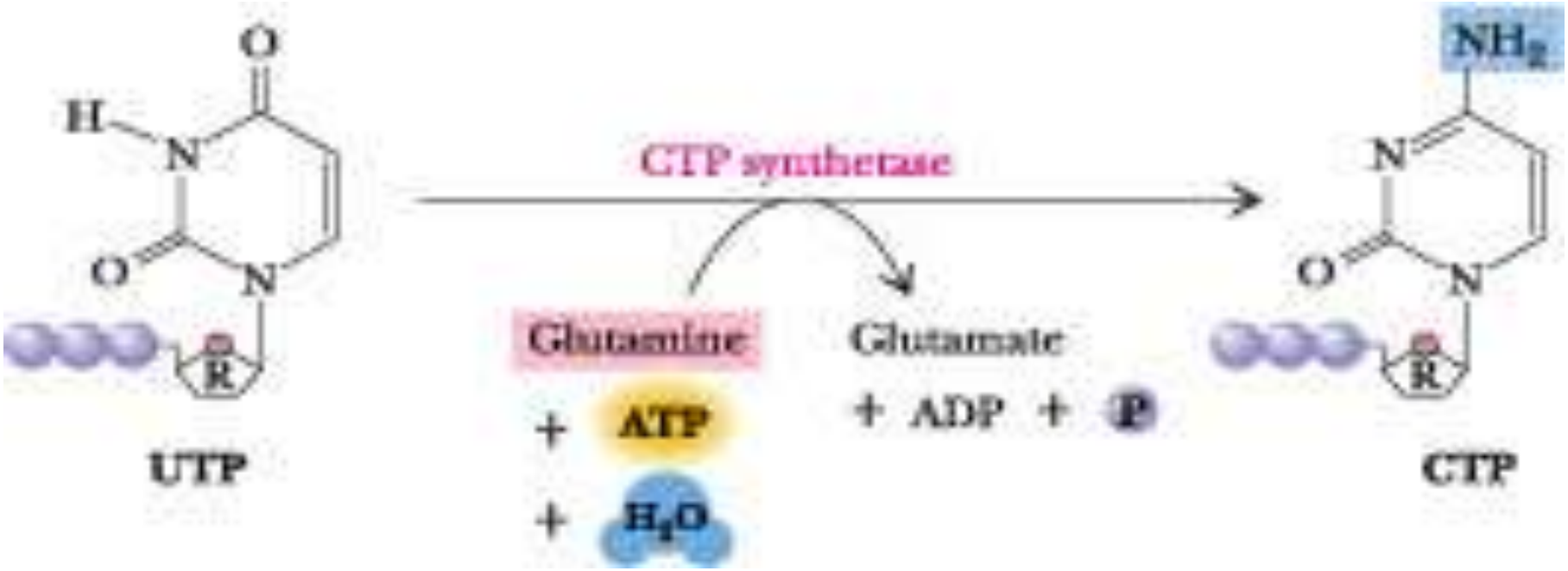


Fig: CTP synthesis from UTP. CTP synthetase catalyzes amination of the 4-position of the UTP pyrimidine ring, yielding CTP. In eukaryotes, this NH_2 comes from the amide-N of glutamine; in bacteria, NH_4^+ serves this role.

Amination of UTP at the 6-position gives CTP. The enzyme, **CTP synthetase,** is a glutamine amidotransferase. ATP hydrolysis provides the energy to drive the reaction.

PYRIMIDINE CATABOLISM

- Animal cells degrade pyrimidine nucleotides to their component bases. These reactions like those of purine nucleotides occur through dephosphorylation, deamination and glycosidic bond cleavages.
- The resulting uracil and thymine are then broken down in liver through reduction rather than oxidation as in purine catabolism.
- β-alanine and β-aminoisobutyrate are the end products of pyrimidine catabolism.
- Then these are converted to malonyl-CoA and methylmalonyl-CoA for further utilization.
- *5`-nucleotidases* dephosphorylates pyrimidines to respective nucleosides.
- Nucleosides are then phosphorolysed into free pyrimidines and ribose-1-phosphate by Pi and *nucleoside phosphorylasese*.
- *Dihydrouracil dehydrogenase* uses NADPH to reduce uracil to 5,6-dihydrouracil.
- *Hydropyrimidine hydrase* hydrolyzes 5,6-dihydrouracil into β-ureidopropionic acid.

β-*ureidopropiomase* hydrolyzes β-ureidopropionic acid into carbon dioxide, ammonia and β-alanine. β-alanine can be used to produce anserine or CoA or can be oxidized to acetate, ammonia and carbon dioxide.

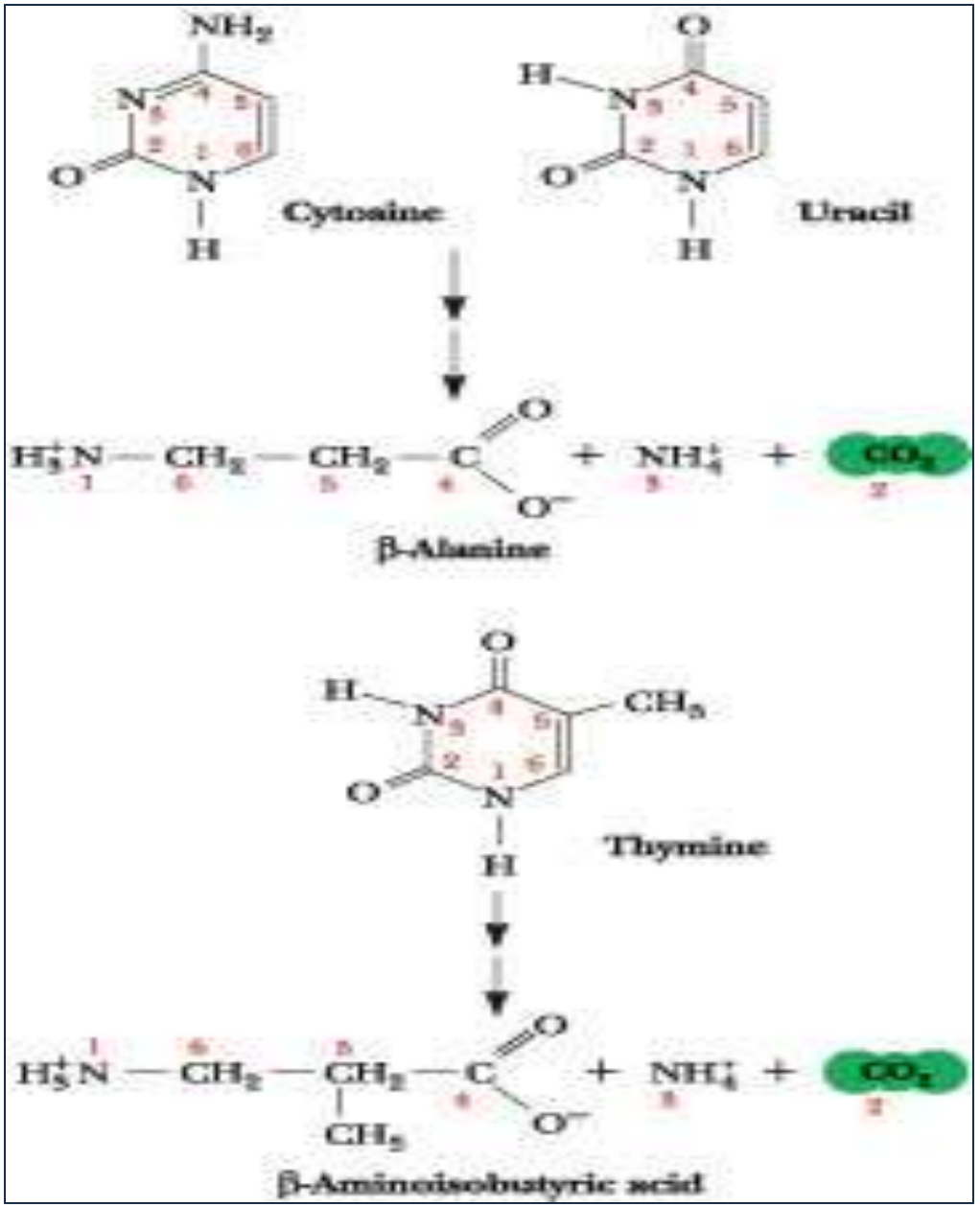
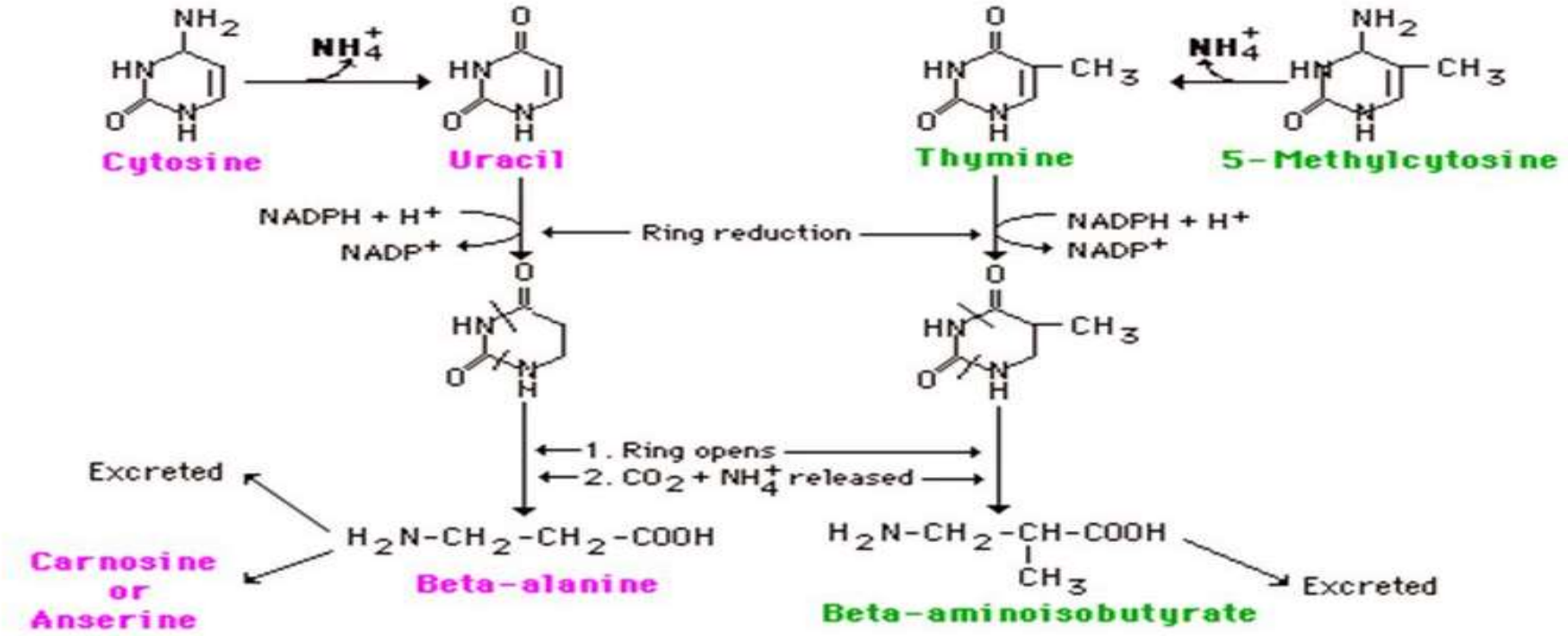


Fig: Pyrimidine degradation. Carbons 4, 5, and 6 plus N-1 are released as b-alanine, N-3 as NH_4^+, and C-2 as CO_2. (The pyrimidine thymine yields b-aminoisobutyric acid.) Recall that aspartate was the source of N-1 and C-4, -5, and -6, while C-2 came from CO_2 and N-3 from NH_4^+ via glutamine.

CATABOLISM OF THYMINE

- Thymine *dehydrogenase* with the help of NADH reduces 5`-methylcytosine to dihydrothymine.
- *Hydrase* causes the hydrolysis of dihydrothymine to give β-ureidoisobutyric acid.
- β-*ureidoisobutyrase* hydrolyzes β-ureidoisobutyric acid into carbon dioxide, ammonia and β-amino isobutyrate.

Catabolism of pyrimidine



SIGNIFICANCE OF NUCLEOTIDE DEGRADATION

- Nucleotide degradation has importance in cellular processes due to involvement of certain enzymes that carry out several important reactions.

❖ So the deficiency or malfunctioning of these enzymes exhibits serious effects.

1- Genetic defects in *Adenosine deaminase* result in SCID.

2- *Xanthine oxidase* is a mini-electron-transport protein.

3- Deficiency of *AMP deaminase* causes fatigue and cramps.

4- *HGPRT* deficiency causes accumulation of *PRPP* and leads to severe form of Gout.