SHEET NO.

Nucleic Acids

METABOLISM

DOCTOR 2019 | MEDICINE | JU

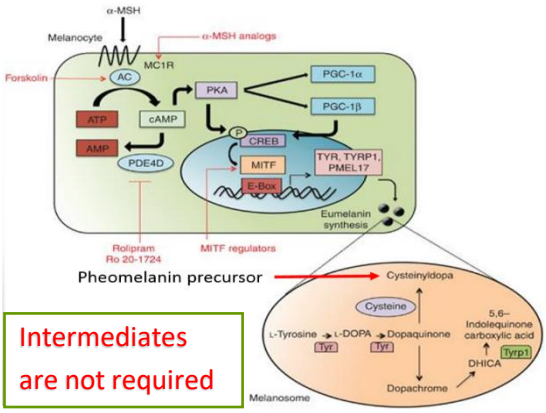
DONE BY : Doctor 2018

SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

DOCTOR :

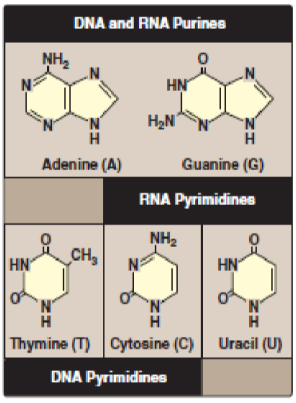
- **Eumelanin** (Brown and black).
- **Pheomelanin** (responsible for the color of **red hair**).
- A defect in melanin production results in albinism (the most common form is due to defects in copper-containing tyrosinase).



Nucleotide metabolism

♠ Purine and pyrimidine structures and roles:

- Essential for RNA and DNA synthesis.
- They serve as carriers of activated intermediates in the synthesis of some carbohydrates, lipids, and conjugated proteins, such as, UDP-glucose and CDP-choline
- They are structural components of several essential coenzymes, such as coenzyme A, FAD, NAD+, and NADP+.
- They serve as second messengers in signal transduction pathways, such as cAMP and cGMP
- They are "energy currency" in the cell, nucleotides are needed for energy transfer. Nucleoside triphosphates (ATP and GTP) provide energy for reactions that would otherwise be extremely unfavorable in the cell.
- They act as regulatory compounds for many metabolic pathways by inhibiting or activating key enzymes.
- Nucleotides are composed of a nitrogenous base, pentose sugar and one, two, or three phosphate group.
- Purines are larger than pyrimidines because they have a two-ring structure (six and five membered rings) while pyrimidines only have a single ring (six membered ring).
- If you can't distinguish between purines and pyrimidines, please refer to Bashar's post.

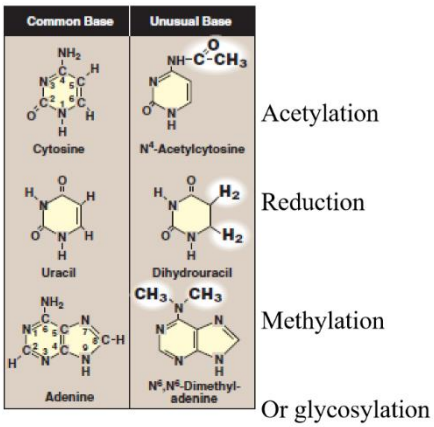


♠ Purine and pyrimidine synthesis:

- The purine and pyrimidine bases can be synthesized de novo (from scratch).
- Or can be obtained through salvage pathways (reuse of the preformed bases resulting from normal cell turnover).
- In many cells the capacity for de novo synthesis to supply purines and pyrimidines is insufficient, and salvage pathway is essential for adequate nucleotide synthesis.
- Little of the purines and pyrimidines supplied by diet are utilized, and are degraded instead

♠ Base modifications:

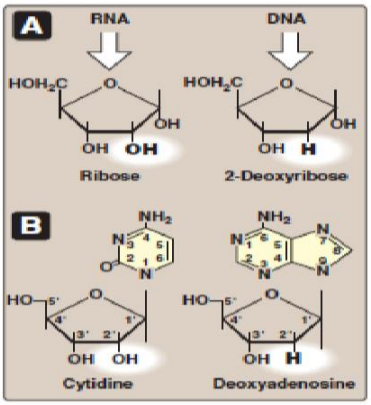
- Base modifications include methylation, glycosylation, acetylation and reduction.
- DNA methylation is associated with gene silencing and inactivation of chromosome X, while acetylation is associated with gene activation.
- Epigenetic changes (base modification) play an important role in the aging process and are responsible for some human diseases.



- The presence of an unusual base in a nucleotide sequence may aid in its recognition by specific enzymes, or protect it from being degraded by nucleases.

♠ Nucleosides:

Nucleoside= Pentose sugar + Base
Ribose + base = Ribonucleoside

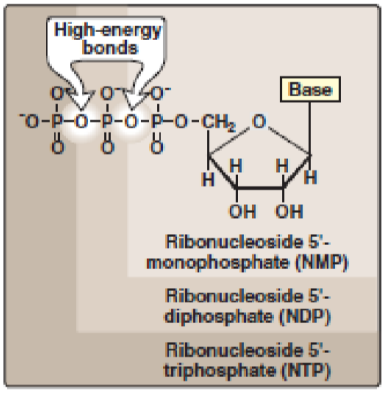


- The ribonucleosides of A, G, C, and U are named adenosine, guanosine, cytidine, and uridine, respectively.
- 2-deoxyribose + base = deoxyribonucleoside.
- The deoxyribonucleosides of A, G, C, and T are named deoxyadenosine, deoxyguanosine, deoxycytidine, and deoxythymidine, respectively.

- Numbering is separate and different (prime and on prime)

♠ **Nucleotides:**

- Nucleoside + one or more phosphate groups= Nucleotide
- The first P group is attached by an ester linkage to the 5'-OH of the pentose forming a nucleoside 5'-phosphate or a 5'-nucleotide.
- The type of pentose is denoted by the prefix in the names “5'-ribonucleotide” and “5'-deoxyribonucleotide.”



- The second and third phosphates are each connected to the nucleotide by a “high-energy” bond.
- The phosphate groups are negatively charged causing DNA and RNA to be nucleic acids.

GOOD LUCK

In the previous lecture we started talking about nucleotides, and in this one we'll talk about how they're synthesized from scratch !

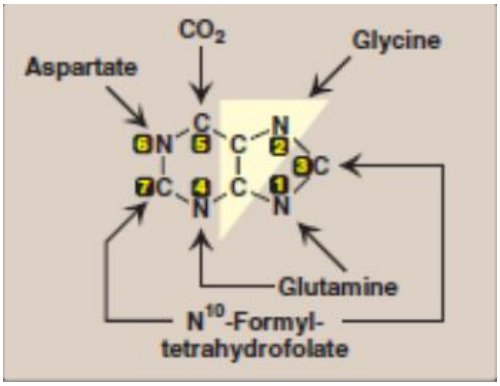
I. Purine synthesis:

Purines are bigger, they're made of <u>two connected rings</u>, which indicates that they require a longer pathway to be synthesized than pyrimidines

- The contributing compounds:

i. **3 kinds of Amino acids** (aspartic acid, glycine and glutamine)
ii. **CO_2** (from the surrounding decarboxylation reactions)
iii. **N^{10}–formyltetrahydrofolate**

you're not required to know where each atom came from



⇒ The purine ring is **constructed primarily in the liver.**

There are actually **two ways** to synthesize a nucleotide,
<u>either</u> **de novo** where it's made from scratch and each atom is added to the ring separately *de novo is the major source of DNA synthesis purines*
<u>or</u> **Salvaged**, where big pieces (like the nitrogenous ring) are priorly synthesized and we just put them together.

- The steps of synthesis (de novo):

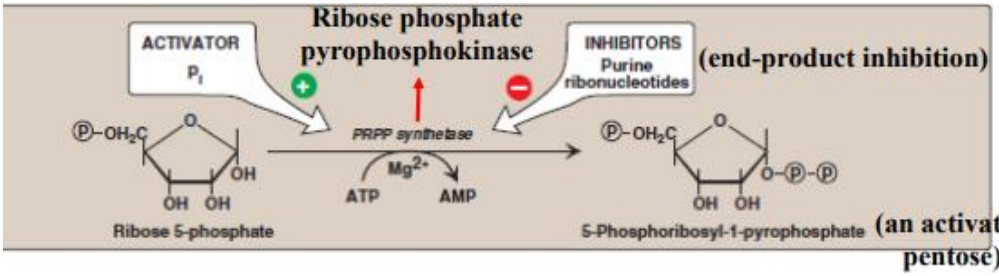
We start with the preformed molecule **Ribose-5-phosphate, and the build up is accomplished by the serial addition of donated nitrogens and carbons.**

⇒ **Ribose 5-phosphate** is synthesized by the **pentose phosphate pathway**

* You're only required to know the names of the main ones like PRPP, IMP. you're not required to know the order of the steps *

Just don't forget that the pentagon ring was formed first.

Step 1: activation of synthesis by the addition of pyrophosphate to R-5-P



- Activation of of R-5-P occurs by the **addition of a pyrophosphate** from an ATP molecule by the following equation **ATP= PP_i + AMP.**

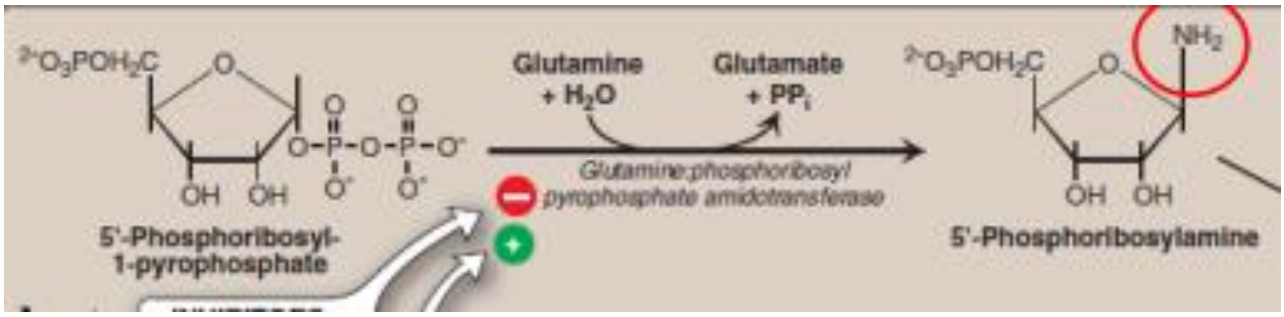
  Enzyme: PRPP synthetase (ribose phosphate pyrophosphokinase)
- The **pyrophosphate is added to carbon number one** since it's the eventual attachment site of the nitrogenous base.
  The resulting compound is 5-phosphoribosyl-1-pyrophosphate (PRPP)

- The sugar moiety of PRPP is ribose, therefore, ribonucleotides are the end products of de novo purine synthesis. When deoxy ribonucleotides are required for DNA synthesis, the ribose sugar moiety is reduced.

The pyrophosphate is then removed because the addition of it was just for activation not for building and in its place the building atoms are added starting with NH_2

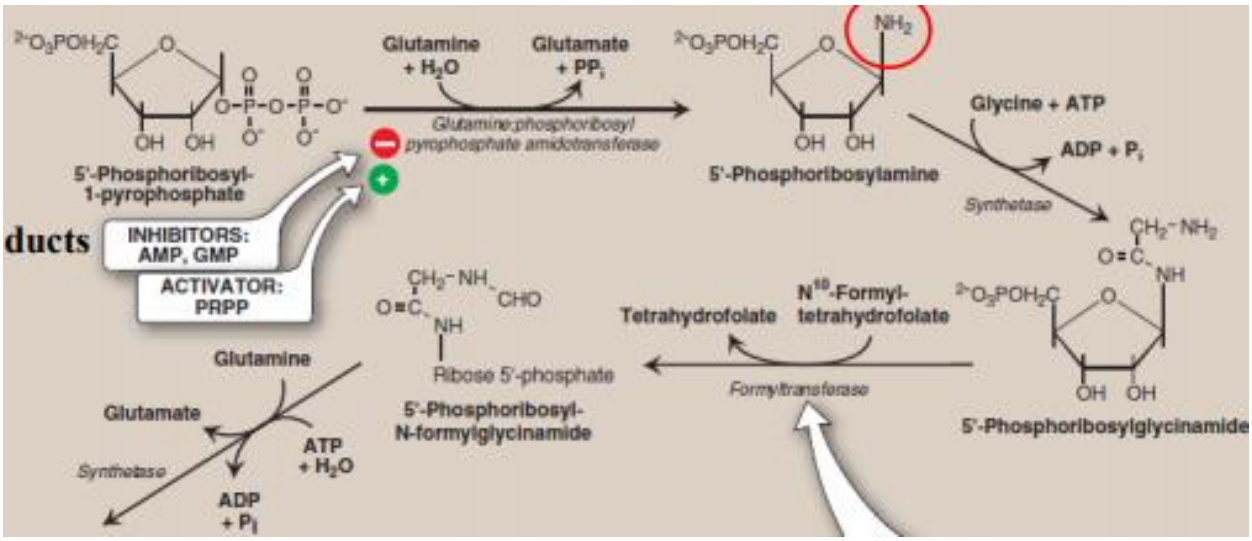
Step 2: Synthesis of 5'-phosphoribosylamine (first step to IMP)

the committed step in purine nucleotide biosynthesis



This step is accomplished by the entry of Glutamine which **gives its NH2 group** and leaves as glutamate. By the enzyme amidotransferase

Step 3: Synthesis of inosine monophosphate



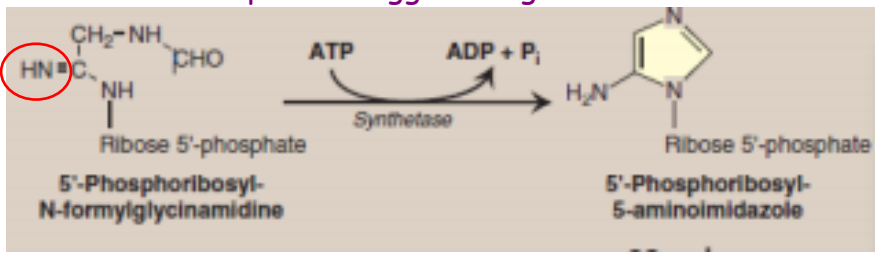
This is accomplished by multistep modification that starts with **addition of glycine (all of it) on the NH_2** added previously, with the **use of ATP;** hence the enzyme is called synthetase.

When glycine is added, **4 atoms of the pentagon ring of purine will be present** (three atoms from Gly + N from glutamine), we need to add a fifth one in order to have all the atoms necessary to close the ring.

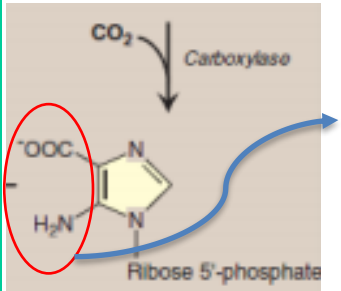
The fifth atom comes from **N^{10}- Formyl-tetrahydrofolate** in the form of **-CHO** (H-C=O).

glutamine enters and gives **NH which will bind in the form of =NH**, catalyzed by synthetase**.**

This is the step that triggers ring closure

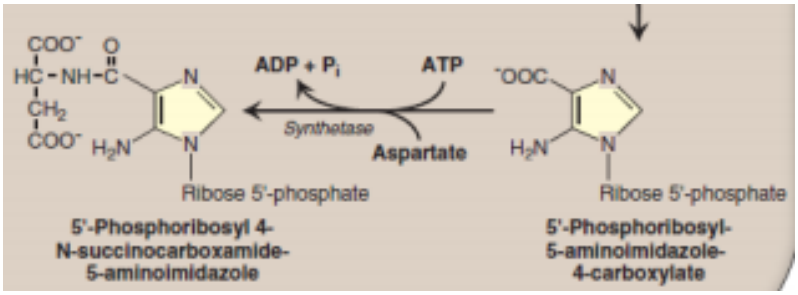


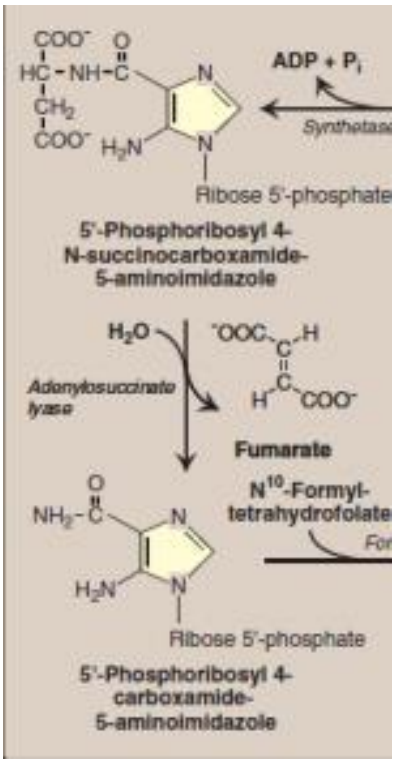
After that a CO2 molecule is added by a carboxylase



Thus, four atoms of the hexagon ring are present. Two shared with the other ring and two added.

Then aspartate is added entirely enters by a synthetase enzyme.

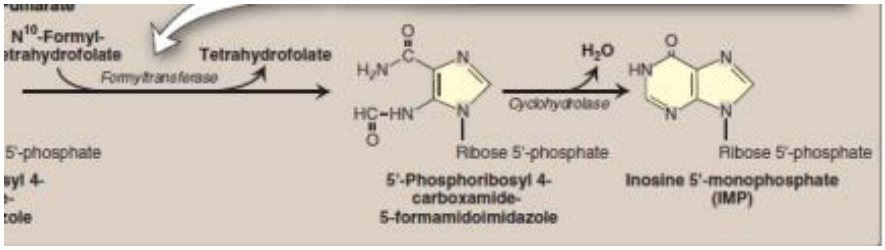




- Then we cut part of this aspartate in the form of **fumarate** and **only NH2 of it remains**.

  * 5 out of 6 ring atoms are present*

- An **N^{10}- formyl-tetraydropholate molecule** comes and donates a **carbon atom in the form of -CHO**

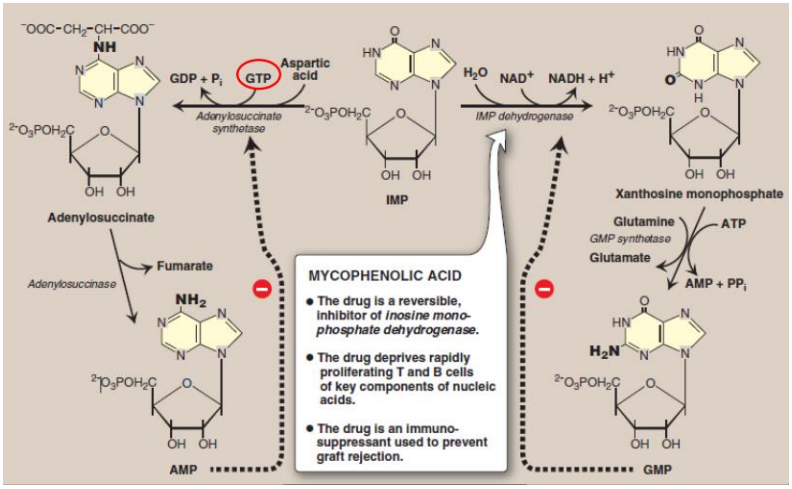


(6 out of 6 atoms are present and the second ring is closed)

marking the birth of the first nucleotide compound:

Inosine- 5'-monophosphate (IMP) the parent purine nucleotide.

- Inosine monophosphate acts as a branching point:
  GMP and AMP are formed from IMP



⇒ AMP production

Adenylosuccinate synthetase adds aspartate (look on the left) by the N atom in place of O on the hexagon ring (GTP used) and **adenylosuccinate** is formed, then most of the structure of succinate is removed in the form of fumarate , only NH2 is left and AMP is produced (adenosine monophosphate)

⇒ GMP production

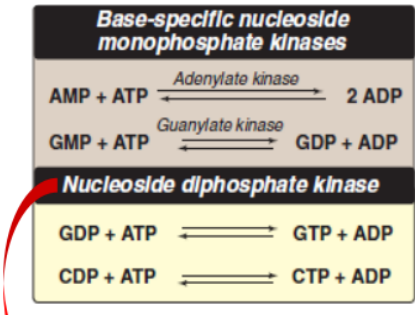
An amine group is added as well but on a different position. First an oxidation-reduction reaction occurs by IMP dehydrogenase (NAD+ reduced to NADH) and we from **xanthosine monophosphate**.

Glutamine donates an amine group, with ATP used as a source of energy, on a different site forming GMP

How do we regulate this pathway?

- **on the first step**, purines inhibit **PRPP synthetase**, while Pi (high concentration of inorganic phosphate) activates this pathway.
- **First step of IMP production**, final products AMP and GMP if in high concentrations **inhibit the pathway** at this step. The first substrate PRPP activates it.
- **Final products** affect the diversion of the pathway. AMP works on adenylosuccinate synthetase and inhibits it and GMP inhibits IMP dehydrogenase.
- In the final step we have specific inhibition by the needs of the cells.

- Further modification: phosphorylation by kinases to form nucleoside di and tri phosphates



They're phosphorylated in two steps: first, to nucleosides diphosphate by **base specific kinases**:

Adenylate kinase works on AMP and Guanylate kinase works on GMP.

Then, they're phosphorylated to nucleosides triphosphate by a nonbase-specific enzyme:

Nucleoside diphosphate kinase works on both (on ALL actually)

ATP is the general source of the phosphate, since it is present in higher concentrations than the other nucleoside triphosphates.

Adenylate kinase (AK) is particularly active in liver and muscle. AK maintains an equilibrium among AMP, ADP, and ATP (since they use a lot of energy)

⇒ one of the most important functions of nucleotides is **using them in DNA synthesis or DNA replication in cell division**.

We can inhibit purine synthesis and thus stop cell division by some synthetic agents which in turn can be used as treatment for cancer.

Some drugs were produced to affect this pathway like **methotrexate.**

It's a chemotherapeutic agent that **takes the place of tetrahydrofolate** and blocks the procedure of synthesis.

They also used this finding to **inhibit the purine synthesis of microorganisms** like in sulfonamide antibiotics.

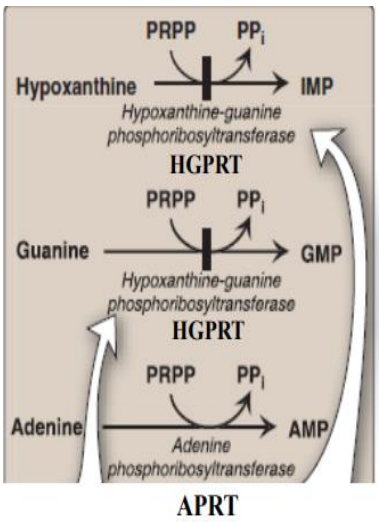
FOLIC ACID ANALOGS

- **Methotrexate and related compounds inhibit the reduction of dihydrofolate to tetrahydrofolate, catalyzed by *dihydrofolate reductase* (see p. 374).**
- **These drugs limit the amount of tetrahydrofolate available for use in purine synthesis and, thus, slow down DNA replication in mammalian cells. These compounds are, therefore, useful in treating rapidly growing cancers, but are also toxic to all dividing cells.**

PABA ANALOGS

- **Sulfonamides are structural analogs of para-aminobenzoic acid that competitively inhibit bacterial synthesis of folic acid (see p. 371). Because purine synthesis requires tetrahydrofolate as a coenzyme, the sulfa drugs slow down this pathway in bacteria.**
- **Humans cannot synthesize folic acid, and must rely on external sources of this vitamin. Therefore, sulfa drugs do not interfere with human purine synthesis.**

- Salvage pathway for purines (recycling pathway)



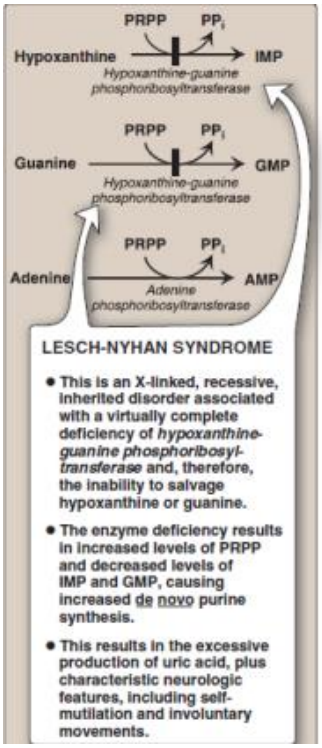
We get the nitrogenous base from wherever and just add PRPP to it, then pyrophosphate is removed, and N-base is placed instead of it and nucleotides are produced.

Adenine by the enzyme APRT is recycled to→ AMP
Guanine by the enzyme HGPRT is recycled to→ GMP
HGPRT works on two substrates, it can add PRPP to guanine and produce GMP or add PRPP to hypoxanthine and produce IMP which can proceed to form AMP and GMP.

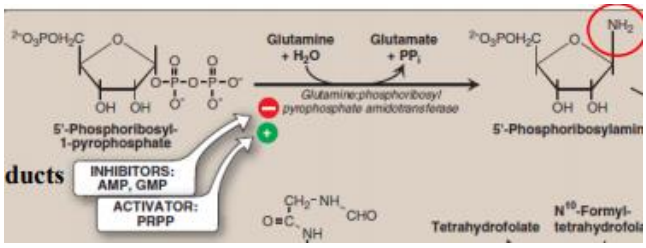
⇒ Adenosine is the only **nucleoside** we can salvage.

Salvage pathway for purines-Lesch-Nyhan syndrome

A rare, X-linked, recessive disorder associated with HGPRT deficiency.



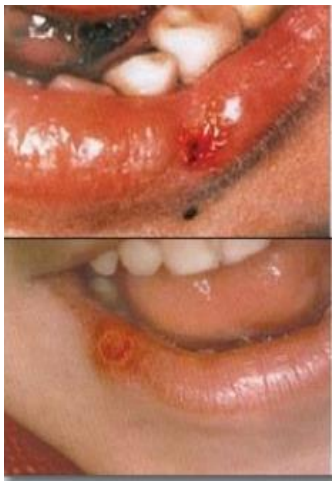
- **Inability to salvage hypoxanthine** or **guanine** resulting in **high amounts of uric acid** (the end product of purine degradation)



- **Because of Increased PRPP** levels and **decreased** IMP and GMP levels,

  The committed step in purine synthesis has **excess substrate** and **decreased inhibitors** available, and de novo purine synthesis is increased to make up for it.

  The **increased purine synthesis** due to de novo activation and **decreased purine reutilization** results in **increased degradation of purines** and the production of large amounts of uric acid **(hyperuricemia)**

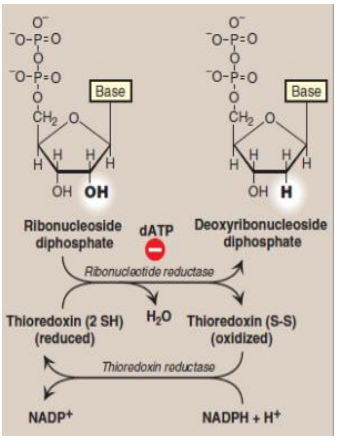


  Increased concentration of uric acid leads to:

  1. **Uric acid stones** in the kidneys (urolithiasis)
  2. **The deposition of urate crystals** in the joints (gouty arthritis) and soft tissues.

  The syndrome is characterized by:

- Motor dysfunction
- Cognitive deficits
- Behavioral disturbances that include self-mutilation (biting of lips and fingers)



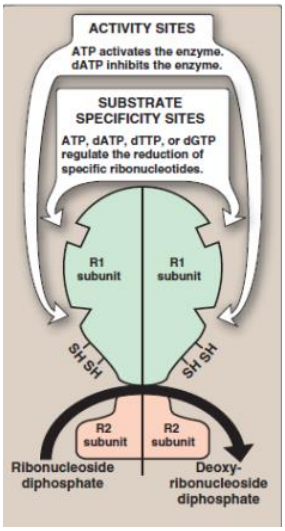
Synthesis of Deoxyribonucleotides: (to be used in DNA)

The enzyme doing the work is Ribonucleotide reductase (RR)

It replaces the oxygen with a hydrogen by a reduction reaction. It works on **nucleotide diphosphates (C, G, A and T)**

Thioredoxin— is the peptide coenzyme of RR. It gets oxidized and forms a **disulfide bridge**.

Thioredoxin gets reduced back (recycled) by the **oxidation of NADPH** to **NADP+**.
Through the enzyme thioredoxin reductase.



This enzyme doesn't distinguish between purines and pyrimidines or any of their subtypes and it needs to be **highly regulated**. It has four subunits (R1 R1, R2 R2).

It has different allosteric (regulatory) sites:

- **activity sites**, where activators and inhibitors bind and determine the activity of the enzyme
    - Example:
      dATP → decreases activity
      ATP→ increases activity of the enzyme on all types.
- **substrate specificity sites**, differs in that the binding of a certain nucleotide activates or inhibits the production of a certain nucleotide with a different nitrogenous base.
    - Example:
      dTTP binds the allosteric site and activates conversion of GDP to dGDP.

Hydroxyurea and ribonucleotide reductase:
This enzyme was targeted to specifically block the **synthesis of DNA**.
A drug made for such purpose is Hydroxyurea, which was used as an anti-cancerous agent for the treatment of cancers like **Chronic Myelogenous Leukemia (CML)**
The drug hydroxyurea destroys the free radical required for the activity of ribonucleotide reductase.

II. purine degradation

First, Digestion: Dietary nucleic acids degradation occurs in the small intestine by a family of pancreatic enzymes:

nucleases break DNA into fragments.
phosphodiesterases break fragments into free nucleotides.

Then, **In the intestinal mucosal cells**, purines are degraded as such:

Phosphates are removed from nucleotides to make them nucleosides by Nucleotidases
Sugars are separated from bases by Nucleosidases. Dietary purines are generally degraded in the intestinal mucosal cells.

Purine nucleotides from de novo synthesis are degraded in the liver primarily.

The free bases are sent out from liver and salvaged by peripheral tissues

* degradation of the base that occurs in all types of cells producing end products common between all purines as we'll see next*

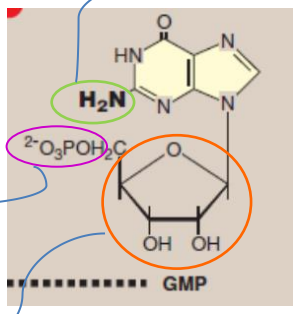
Main principle:

Phosphates are removed from nucleotides to make them nucleosides by Nucleotidases
Sugars are separated from bases by phosphorylase (phosphorylated sugar)

Then specific Nitrogenous base degradation follows:

GMP degradation:

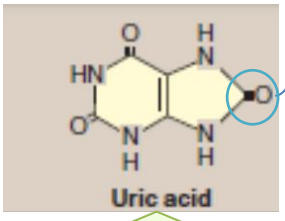
1-First phosphate is removed by nucleotidase, and guanosine is formed.



3-H_2O is added to guanine by guanase, removing NH_2 and making it **xanthine** (=O instead of NH_2)

2-Sugar is removed from guanosine in the form ribose-1-phosphate by the enzyme purine nucleoside phosphorylase turning it into guanine.

4-H_2O and O_2 are then added by xanthine oxidase adding an oxygen in this position making it uric acid (the final product)



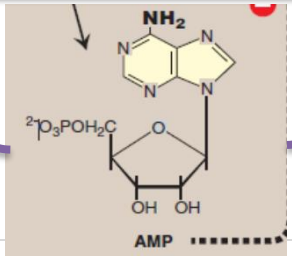
AMP degradation:

there are two possible ways:

2-Then, the sugar is **phosphorylytically removed** by phosphorylase. After that **hypoxanthine is formed**, an oxygen is then double bonded on a certain site making it **xanthine**. Finally, O_2 and H_2O enter by xanthine oxidase adding an oxygen and yielding **uric acid**

1A-phosphate is removed by nucleotidase, making it adenosine, then the amino group is removed by adenosine deaminase converting it into inosine

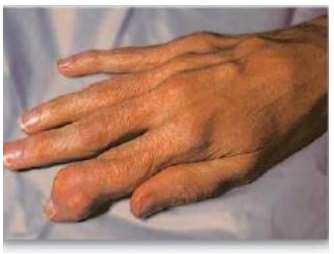
1B-The other choice is to do deamination first (by AMP deaminase) to IMP then remove the phosphate by nucleotidase forming inosine



⇒Intermediates of degradation have some resemblance to intermediates of synthesis, like IMP for example. So, we might actually start synthesizing a molecule then find that there's too much of it and decide to degrade it from that point on.

III. Diseases associated with purine degradation

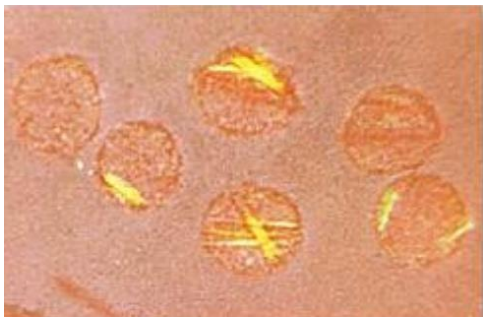
Gout



accumulation of uric acid due to over production or under excretion of uric acid.

Uric acid's concentration increases,

Leading to:



1. Formation of **monosodium urate crystals** that **deposit in the synovial fluid** of joints. These crystals will be recognized by the immune system inducing an **inflammatory reaction** causing acute then chronic gouty arthritis.
2. Nodular masses of monosodium urate crystals (tophi) may be deposited in the soft tissues, resulting in chronic tophaceous gout.
3. Formation of uric acid stones in the kidney (urolithiasis)

Underexcretion of uric acid: *Most gout patients have under excretion*

Underexcretion can be **primary** (due to unidentified inherent excretory defects) Or **secondary** to:

1. A known disease that affects the kidney function in handling urate, such as lactic acidosis (lactate and urate compete for the same renal transporter)
2. Environmental factors such as drugs (thiazide diuretics)
3. Exposure to lead (saturnine gout) Overproduction of uric acid: less common. Several identified mutations in the X-linked PRPP synthetase gene that increase PRPP production

   This disease called kings' disease because it's related to over ingestion of meat which increases the amount of uric acid.

Treatment depends on the cause, under excretion we give things to enhance excretion, over production we fix that.

Adenosine deaminase (ADA) deficiency: (autosomal recessive)

It's involved in **AMP degradation**.

ADA is expressed in many tissues, but lymphocytes have the highest activity in humans. A **deficiency of ADA** results in an **accumulation of adenosine**, which is **converted to its ribonucleotide or deoxyribonucleotide** forms by cellular kinases.

- **dATP levels rise** and ribonucleotide reductase is inhibited, **thus preventing deoxynucleotides production**, and **DNA synthesis for cell division stops.**
- The dATP and adenosine that accumulate lead to **developmental arrest** and **apoptosis of lymphocytes** (arrest of growth)

Treatment requires either **bone marrow transplantation** (BMT) or **enzyme replacement therapy** (ERT).

Without appropriate treatment, children usually die by the age of two

"Molecules, when broken, yield as much energy as was invested in them when they were made.. Everything in life works as such, you must invest today as much as you want to yield tomorrow."

This sheet will cover the first topic discussed in lecture 37: **pyrimidines**

I. Pyrimidines synthesis:

Pyrimidines are nitrogenous bases that are composed of a single hexagon ring.

- The main difference in their synthesis from purines is that the base is **built before it's added to the sugar** (NOT built ON the sugar).

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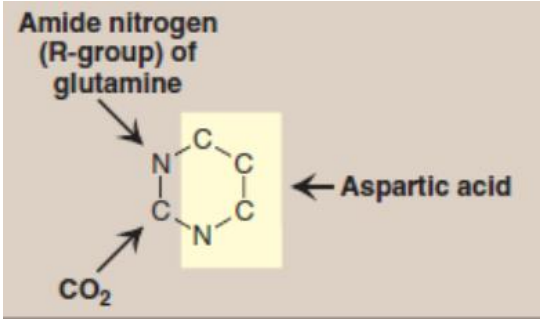
a. De novo synthesis:



- **Sources of atoms:** 2 amino acids (glutamine, aspartate) and CO_2. *In addition to PRPP later*

- **Pathway:**

  Step 1: gathering atoms

  Amino group of glutamine + a CO_2 molecule + 2 ATP molecules are used to form a **carbamoyl phosphate** by **carbamoyl phosphate synthetase II**

  this is the regulated step of pyrimidine synthesis

  CPS II is inhibited by UTP (the end product of this pathway) and is activated by PRPP

  Step 2: adding aspartate

  Aspartate enters and attaches to carbamoyl phosphate displacing the phosphate and producing **carbamoyl aspartate.**

  *now we have the *six* atoms of the ring ready, *one* from glutamine, *one* from CO2 and, *four* from aspartate*

Step 3: ring formation

By the enzyme **dihydroorotase**, the terminal atoms are bonded together to close the ring forming dihydroorotate and an H2O molecule is released.

* The first three enzymic activities in this pathway (**CPS II, aspartate transcarbamoylase, and dihydroorotase)** are three different catalytic domains of a single polypeptide chain (CAD)*

Step 4: oxidation on dihydroorotate

Dihydroorotate gets oxidized by **dihydroorotate dehydrogenase** to **orotate** with the reduction of FAD to FADH2.

* This enzyme is associated with the inner mitochondrial membrane, all the other enzymes of this pathway are **cytosolic***

- **See? As mentioned earlier, unlike purine nucleotides, pyrimidine rings are completely formed before they're converted to nucleotides by the addition of sugar monomers.**

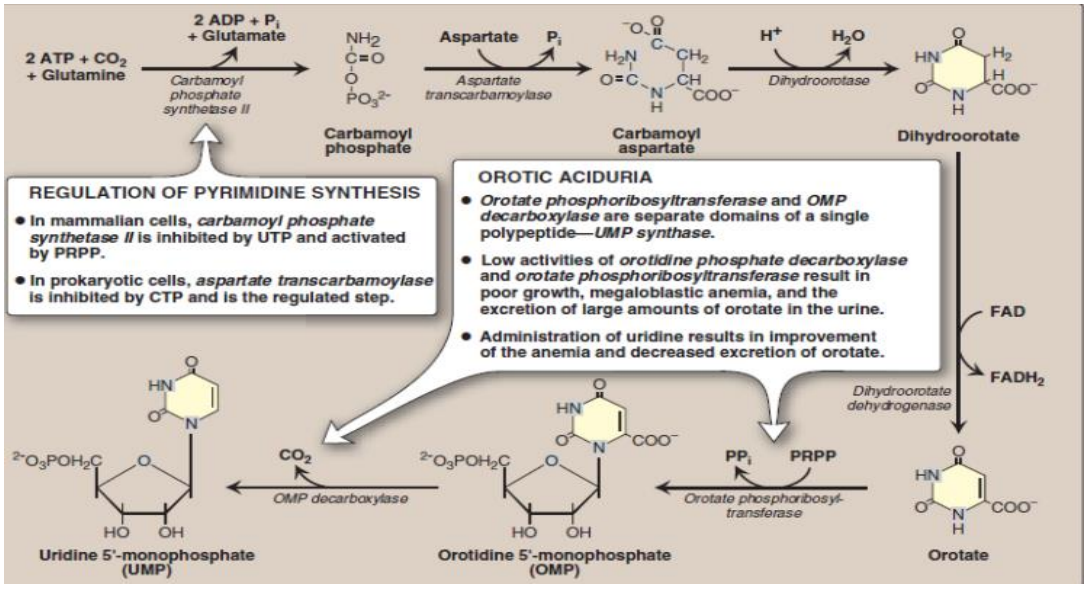
Step 5: sugar addition

PRPP enters and **donates a phosoribose** with the irreversible release of pyrophosphate by Orotate phosphoribosyl transferase , producing **orotidine monophosphate (OMP)**, the **parent pyrimidine mononucleotide.**

Step 6: Pyrimidine nucleotide synthesis (UMP, TMP, CMP)

- **OMP decarboxylase** removes a carboxyl group from the nitrogenous base (it was part of the aspartate when we added it) producing **Uridine monophosphate** (UMP).
- **Orotate phosphoribosyl transferase and orotidylate (OMP) decarboxylase** are catalytic domains of a single polypeptide chain called UMP synthase.

Orotic aciduria, a rare genetic defect, is caused by a deficiency of one or both activities of the bifunctional UMP synthase resulting in **orotic acid in the urine.**



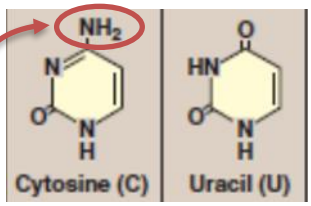
- UMP is a mono nucleotide that can be phosphorylated to di and tri nucleotides which are **used in the synthesis of RNA**. However, UMP is also modified someway to **synthesize TMP and CMP which are used in the synthesis of DNA.**

- **Cytosine and thymine formation:**
- For the synthesis of CTP and TTP, UMP needs to go under some changes.
- UMP is phosphorylated to UDP and then UTP.

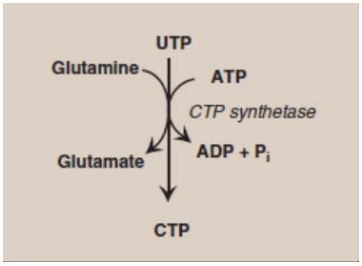
  UTP used in CTP synthesis
- UDP is a substrate for **ribonucleotide reductase**, which generates **dUDP.**
- **dUDP** can be phosphorylated to **dUTP**, which is rapidly hydrolyzed to **dUMP** by **UTP di-phosphatase (dUTPase)**. *dUMP used in dTMP synthesis*

*dUTPase reduces (decrease) the available dUTP for DNA synthesis, thus preventing incorporation of uracil into DNA.

➢ **Cytosine: (UTP → CTP)**

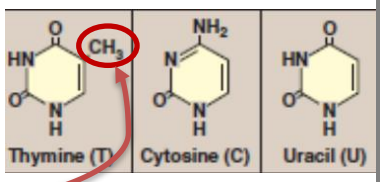


The difference between cytosine and uracil is this **amino group**; so, **glutamine** donates this amino group becoming glutamate with the help of **CTP syntheTASE** (ATP requiring enzyme).



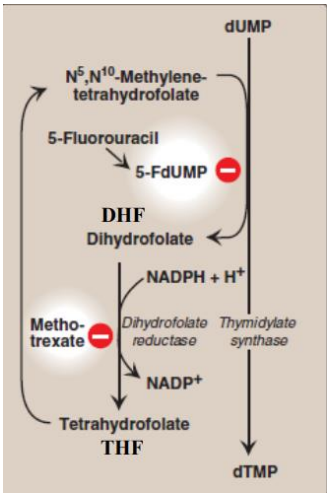
Some CTP is dephosphorylated to CDP (which is a substrate for **ribonucleotide reductase** - produces dCDP which can be phosphorylated to dCTP for DNA synthesis).

➢ **Thymine: (dUMP → dTMP)**



We start with **deoxy**-UMP to produce **deoxy**-TMP by the action of an enzyme called **thymidylate synthASE**.

The difference between uracil and thymine is this **methyl group.**



Thymidylate synthase **methylates** uracil to form thymine using **N^5, N_{10}-methylene-tetrahydropholate** as the source of the methyl group.

This results in the conversion of **N^5, N_{10}-methylene-tetrahydropholate** to **dihydrofolate.**

Therefore, we need to recycle it back to **tetrahydrofolate** in order to reuse it, and that's accomplished by **dihydrofolate reductase**, which adds two hydrogens reducing it back to **tetrahydrofolate** with oxidation of NADPH to $NADP^+$.

➢ Some anti cancerous agents target this process to inhibit the growth of tumor cells:

- **Thymidylate synthase inhibitors** include **thymine analogs** such as **5-Fluorouracil** (antitumor agents).

  5-Fluorouracil (suicide inhibitor) is converted to 5-Fd**UMP** that **permanently** binds and **inactivates thymidylate synthase.**

- **Methotrexate** inhibits dihydrofolate reductase.

  Methotrexate (folate analog) reduces the amount of THF, thus inhibits **purine** synthesis and **prevents methylation of dUMP to dTMP**, resulting in **DNA synthesis inhibition and cell growth slow down**.

How does the cell distinguish whether this carbamoyl phosphate is going into nucleotide synthesis or urea cycle? (CPS= carbamoyl phosphate synthetase)

- Mainly, depending on the **site** of the reaction.

(CPS I) is active in **hepatocytes** - specifically in the **mitochondria-**. The **pathway** it's involved in is **the urea cycle** and the added **amino group's source is ammonia**.

(CPS II) is active in the **cytosol** of **many different cells**, the source of the amino group it adds is **glutamine** and the pathway it's involved in is **pyrimidine synthesis**.

	CPS I	CPS II
Cellular location	Mitochondria	Cytosol
Pathway involved	Urea cycle	Pyrimidine synthesis
Source of nitrogen	Ammonia	γ-Amide group of glutamine
Regulators	Activator: N–acetyl-glutamate	Activator: PRPP Inhibitor: UTP

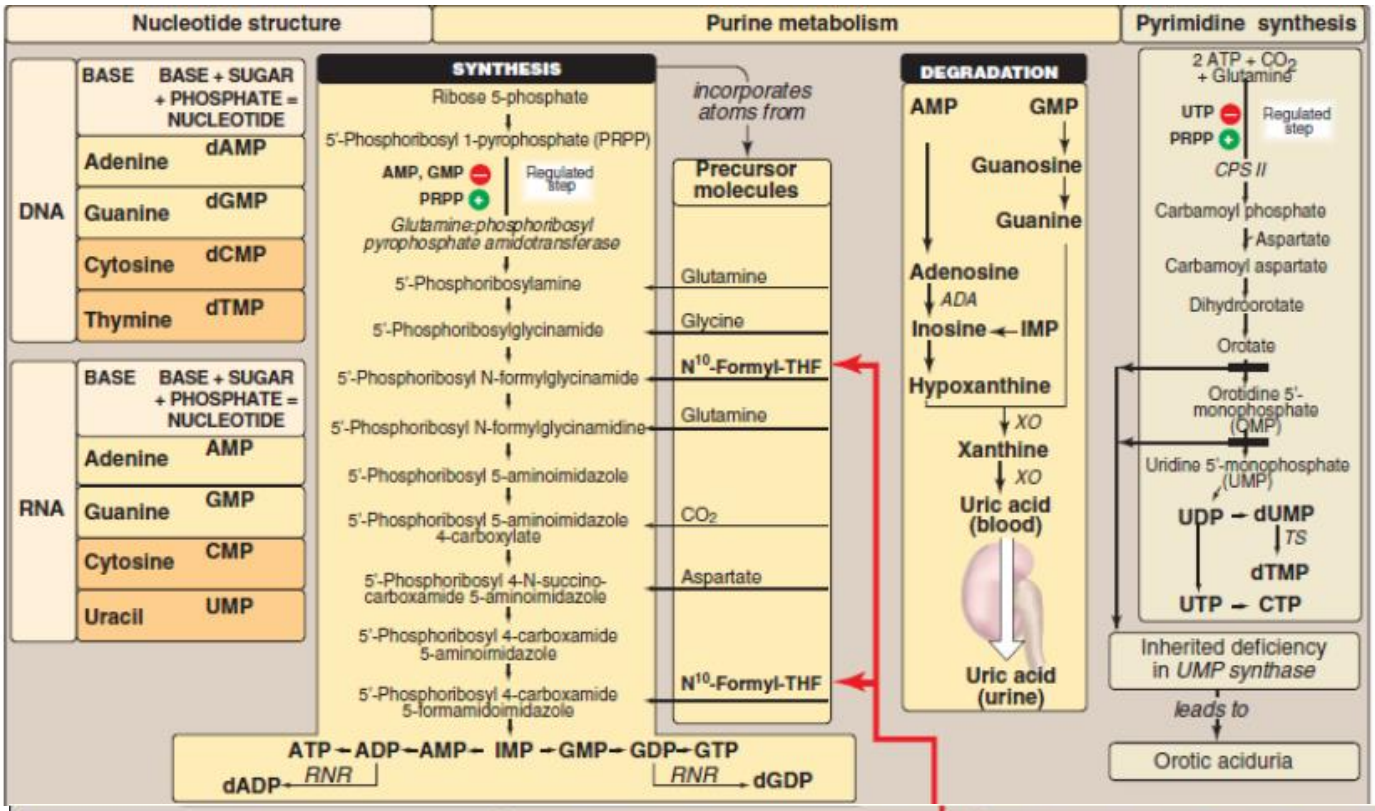
b. salvage synthesis:

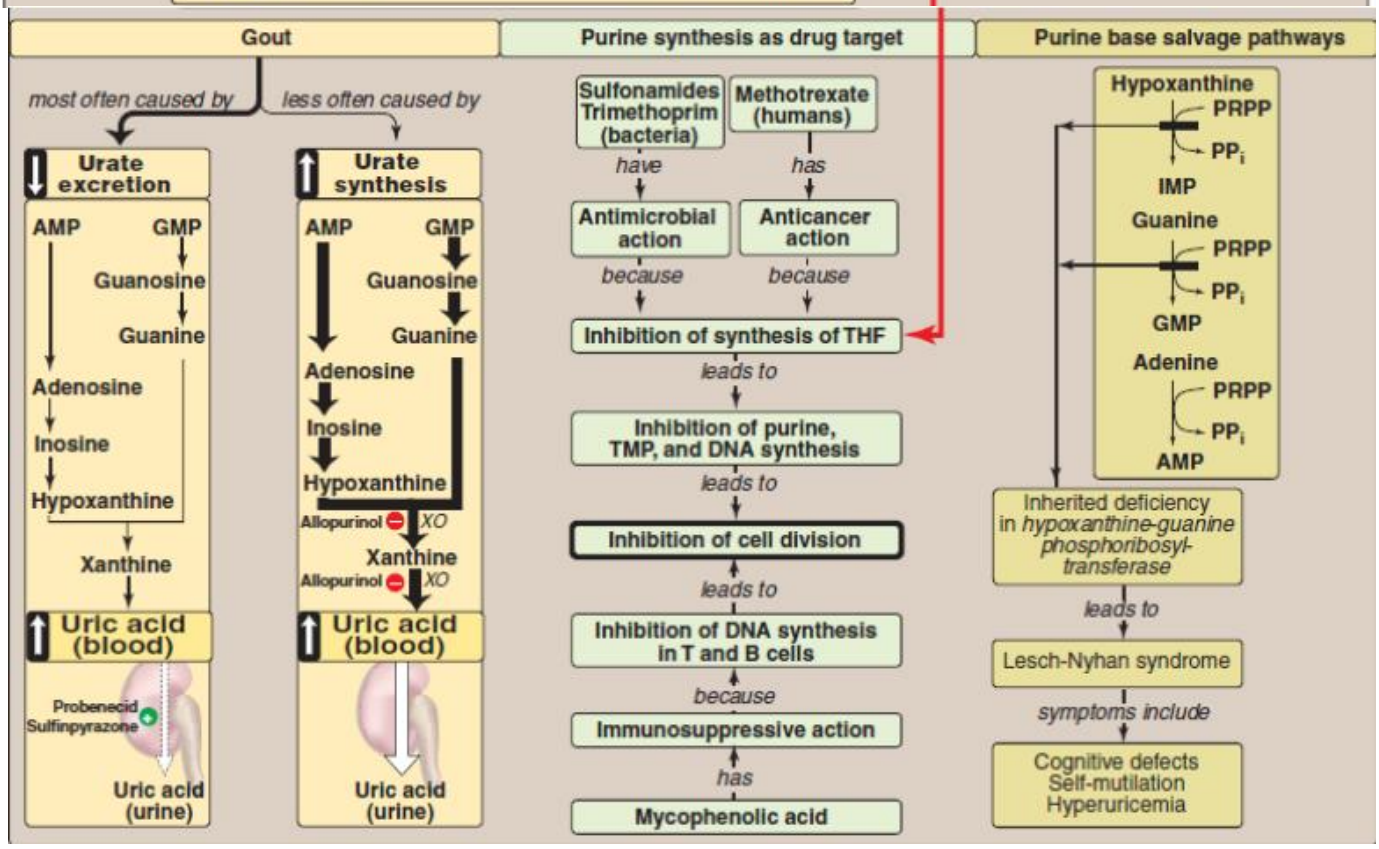
phosphorylation of nucleosides of pyrimidines (Nitrogenous base + sugar) by a kinase enzyme with the use of ATP gives us **salvage synthesized nucleotides**

II. Degradation

Simply, the pyrimidine ring is opened and degraded to highly soluble products: **β-alanine and β-aminoisobutyrate** with the production of NH_3 and CO_2.

Good luck :)


Nucleotide structure
Purine metabolism
Pyrimidine synthesis
DNA
BASE
BASE + SUGAR + PHOSPHATE = NUCLEOTIDE
Adenine
dAMP
Guanine
dGMP
Cytosine
dCMP
Thymine
dTMP
RNA
BASE
BASE + SUGAR + PHOSPHATE = NUCLEOTIDE
Adenine
AMP
Guanine
GMP
Cytosine
CMP
Uracil
UMP
SYNTHESIS
Ribose 5-phosphate
5'-Phosphoribosyl 1-pyrophosphate (PRPP)
AMP, GMP
PRPP
Regulated step
Glutamine:phosphoribosyl pyrophosphate amidotransferase
5'-Phosphoribosylamine
5'-Phosphoribosylglycinamide
5'-Phosphoribosyl N-formylglycinamide
5'-Phosphoribosyl N-formylglycinamidine
5'-Phosphoribosyl 5-aminoimidazole
5'-Phosphoribosyl 5-aminoimidazole 4-carboxylate
5'-Phosphoribosyl 4-N-succino-carboxamide 5-aminoimidazole
5'-Phosphoribosyl 4-carboxamide 5-aminoimidazole
5'-Phosphoribosyl 4-carboxamide 5-formamidoimidazole
incorporates atoms from
Precursor molecules
Glutamine
Glycine
N10-Formyl-THF
Glutamine
CO2
Aspartate
N10-Formyl-THF
ATP – ADP – AMP – IMP – GMP – GDP – GTP
dADP
RNR
RNR
dGDP
DEGRADATION
AMP
GMP
Guanosine
Guanine
Adenosine
ADA
Inosine
IMP
Hypoxanthine
XO
Xanthine
XO
Uric acid (blood)
Uric acid (urine)
2 ATP + CO2 + Glutamine
UTP
PRPP
Regulated step
CPS II
Carbamoyl phosphate
Aspartate
Carbamoyl aspartate
Dihydroorotate
Orotate
Orotidine 5'-monophosphate (OMP)
Uridine 5'-monophosphate (UMP)
UDP – dUMP
TS
dTMP
UTP – CTP
Inherited deficiency in UMP synthase
leads to
Orotic aciduria


Gout
most often caused by
less often caused by
Urate excretion
AMP
GMP
Guanosine
Guanine
Adenosine
Inosine
Hypoxanthine
Xanthine
Uric acid (blood)
Probenecid
Sulfinpyrazone
Uric acid (urine)
Urate synthesis
AMP
GMP
Guanosine
Guanine
Adenosine
Inosine
Hypoxanthine
Allopurinol
XO
Xanthine
Allopurinol
XO
Uric acid (blood)
Uric acid (urine)
Purine synthesis as drug target
Sulfonamides Trimethoprim (bacteria)
Methotrexate (humans)
have
has
Antimicrobial action
Anticancer action
because
because
Inhibition of synthesis of THF
leads to
Inhibition of purine, TMP, and DNA synthesis
leads to
Inhibition of cell division
leads to
Inhibition of DNA synthesis in T and B cells
because
Immunosuppressive action
has
Mycophenolic acid
Purine base salvage pathways
Hypoxanthine
PRPP
PPi
IMP
Guanine
PRPP
PPi
GMP
Adenine
PRPP
PPi
AMP
Inherited deficiency in hypoxanthine-guanine phosphoribosyl-transferase
leads to
Lesch-Nyhan syndrome
symptoms include
Cognitive defects
Self-mutilation
Hyperuricemia