# ) UNIVERSITY IYAMHO

## Faculty of Basic Medical Sciences

## Department of Biochemistry



**BCH 314: AMINO ACID, PROTEIN AND NUCLEIC ACID METABOLISM (3 CREDITS) (2 Credits)**

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Office hours: Mondays, Wednesdays and Thursdays, 11.00-3.00pm

**Co-Lecturer------ Dr. A. Ugbenyen**

**General overview of lecture:**
Detailed treatment of metabolism of amino acids degradation and biosynthesis.Inborn errors of metabolism.
The urea cycle; metabolism of inorganic nitrogen.
Disorders of amino acid metabolism. Oxidative and Non-oxidative deamination, Transamination and decarboxylation, Transamidation, Transport and toxicity of ammonia, Creatine metabolism. Polyamines.
Nucleoside, nucleotide and nucleic acid synthesis/degradation.
Disorders of nucleotide metabolism. Hyperuricemia & other inborn errors. One carbon metabolism,Transmethylation. Protoporphyrin synthesis in animals and plants.
Hormone and regulatory role in intermediary metabolism.

**Learning outcomes:** At the completion of this course, students are expected to:

1. Have vast and detail knowledge of the Formation of Purine/Pyrimidine Nucleotides.
2. Understand disorders of Purine/Pyrimidine Nucleotide metabolism
3. Expatiate on the Biosynthesis of Porphyrin
4. Knowledge on the genetic diseases known as porphyrias.

**Assignments:** We expect to have 3 homework assignments throughout the course in addition to a Mid-Term Test and a Final Exam. Term papers are to be given and submission made on the due date. Home works in the form of individual assignments, and group assignments are to be organized and structured as preparation for the midterm and final exam, and are meant to be a studying material for both exams.

**Grading:** We will assign 10% of this class grade to home works, 10% for the student presentation, 10% for the mid-term test and 70% for the final exam. The Final exam is comprehensive.

**Textbook**: The recommended textbook for this class are as stated:
*(i) Biochemistry by LubertStryer*
*(ii) Biochemistry by Voet and V*oet
*(iii) Lehninger, A. L. Principles of Biochemistry*
*(iv) Harper, H.A. Review of Physiological Chemistry*
*(v) Karlson P. Introduction to Modern Biochemistry.*

**Courseware: - BCH 314 – Amino Acid, Protein and Nucleic Acid Metabolism (3 Credits)**

The following documents outline the courseware for the course **BCH 314 – Amino Acid, Protein and Nucleic Acid Metabolism**. Much of this material is taken from recommended text books.

1. Formation of purine/pyrimidine nucleotides
2. Purine nucleotide biosynthesis
3. Salvage pathway of purine nucleotide production
4. Disorders of purine nucleotide metabolism
5. Pyrimidine nucleotide biosynthesis
6. Degradation of purine and pyrimidine nucleotides
7. Disorders of pyrimidine nucleotide metabolism.
8. Biosynthesis of porphyrins
9. Structure and functions of various heme proteins

**MAIN LECTURE**

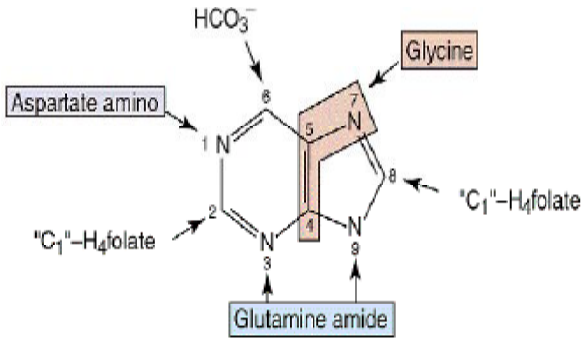
# FORMATION OF PURINE/PYRIMIDINE NUCLEOTIDES

ÅAre produced from N-bases (these come from the diet and from partly degraded nucleotides)

ÅAre produced by de novo pathways.

**DE NOVO BIOSYNTHESIS OF NUCLEOTIDES.**

**Origin of atoms in purinerings**

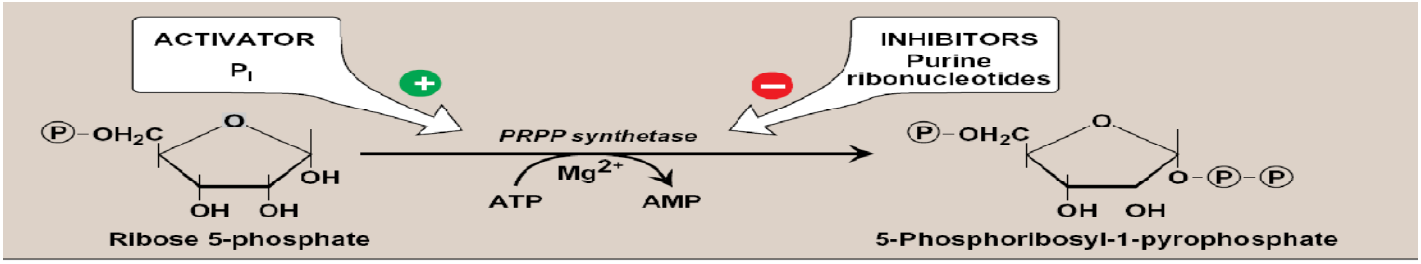



**PURINE NUCLEOTIDE BIOSYNTHESIS.**

The **purine skeleton** is synthesized from **glycine, aspartate, glutamine, CO2, and two one-carbonfragments** provided by tetrahydrofolate derivatives.

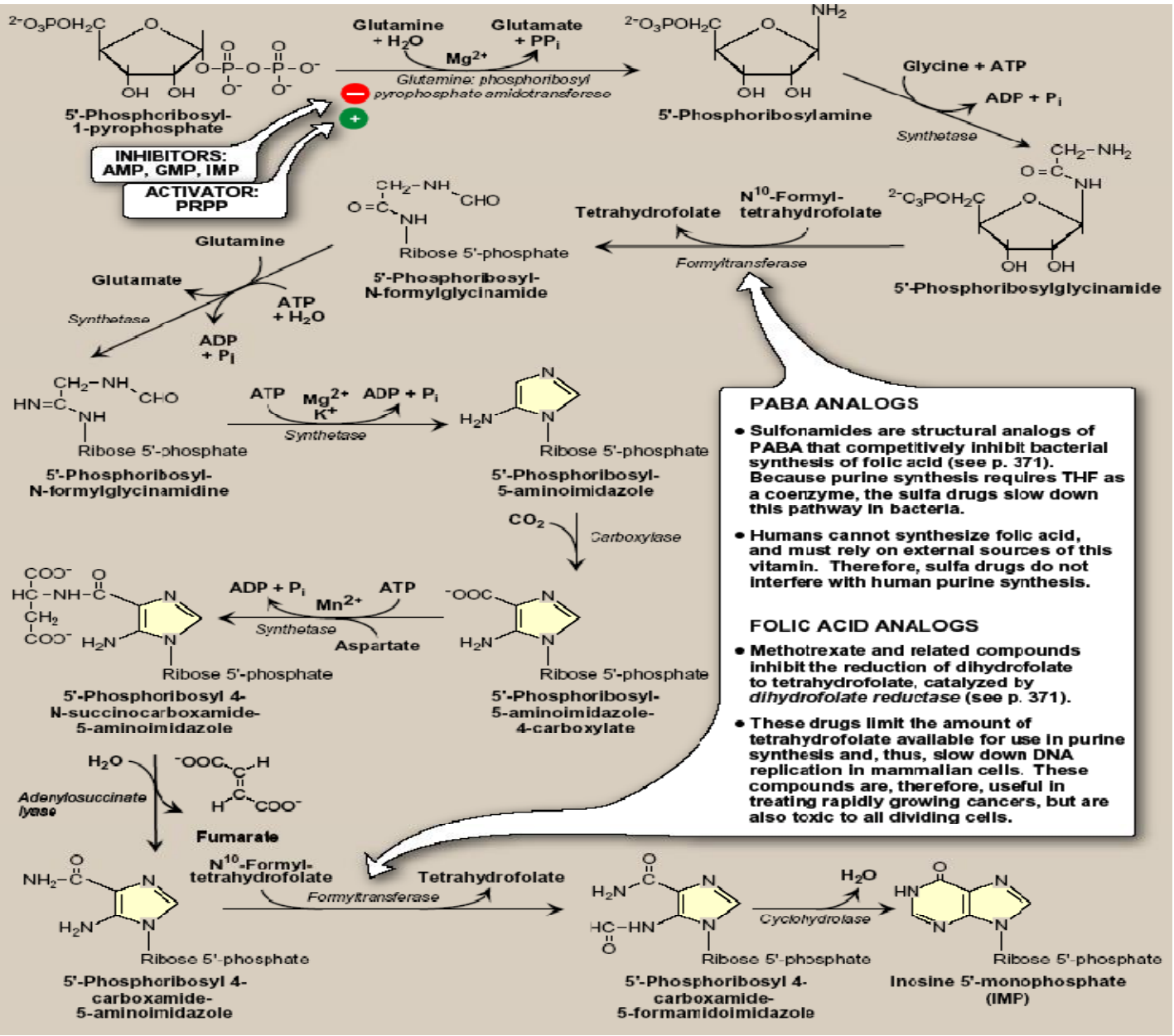
Ribose 5-phosphate from pentose phosphate pathway is used as the first substrate in the synthesis. ATP and GTP are required as sources of energy.

The first step in purine biosynthesis is thephosphorylation of ribose 5-phosphate to**5-phosphoribosyl-1-pyrophosphate (PRPP).**

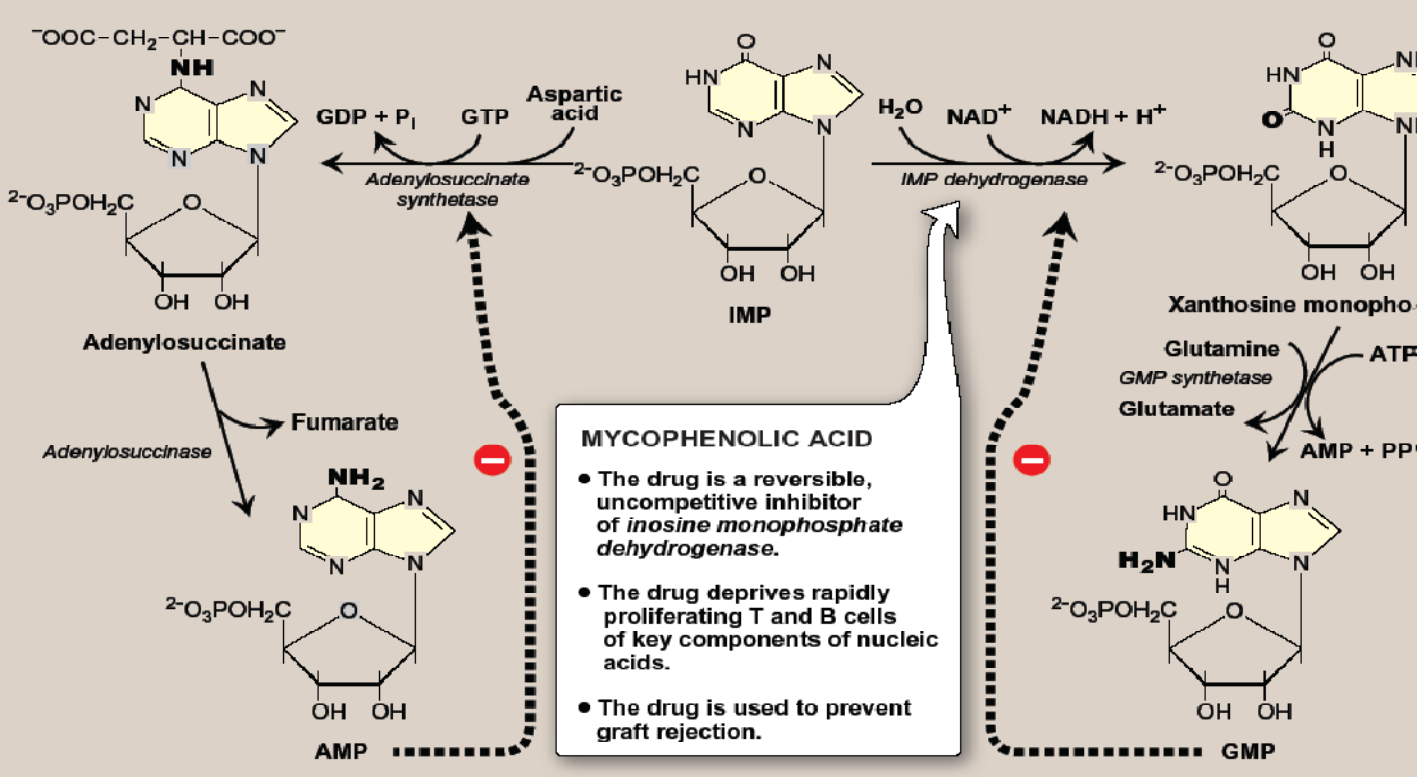



**Synthesis of 5-phosphoribosyl-1-pyrophosphate (PRPP)**

The next step, the formation of 5-phosphoribosyl-1-amine, is the **committed step** in purine biosynthesis. The enzyme **amidotransferase** is feedback-inhibited by the end products of the pathway, ATP and GTP. (AMP and GMP also inhibit.) In a series of nine further reactions the purine nucleotide **inosine monophosphate (IMP)** is formed.




**Synthesis of purine nucleotides**




**Synthesis of AMP and GMP from IMP showing feedback inhibition.**

IMP is the substrate for two short pathways that yields AMP and GMP. In AMP synthesis, an amino group from aspartate is transferred to the purine. In GMP synthesis, glutamate is the source of the amino group. Kinases then catalyzes phosphoryl-group transfer reactions to convert the nucleoside monophosphates to diphosphates and then triphosphates (ATP and GMP).

Inosine monophosphate is converted to **guanosine monophosphate (GMP)** via xanthosinemonophosphate, and to **adenosine monophosphate (AMP)** via adenylosuccinate. The initialstep in each reaction is inhibited by its end product (GMP or AMP, respectively), and activated bythe triphosphate of the other reactionôs product. This cross-regulation ensures the balancedsynthesis of adenine and guanine nucleotides.

GTP Participates in AMP synthesis and ATP participates in GMP synthesis. High concentration of ATP therefore promote GMP production and high concentration of GTP promote AMP production. This reciprocal relationship is one mechanism for balancing the production of adenine and guanine nucleotides (because most nucleotides are destined for DNA or RNA synthesis, they are required in roughly equal amounts).

**PURINENUCLEOTIDE SYNTHESIS FROM N-BASES**
**SALVAGE PATHWAY OF PURINENUCLEOTIDE PRODUCTION**

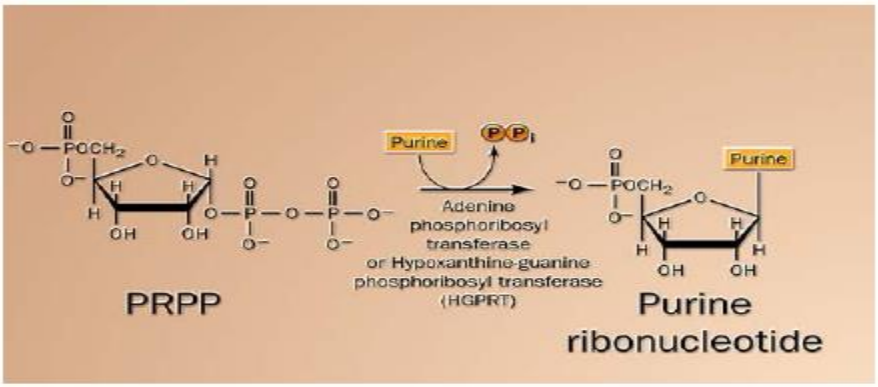
- Saves purinebases from degradation
- Saves energy
- Prevents over-production of uric acid
- The pathway is important in brain and in RBC

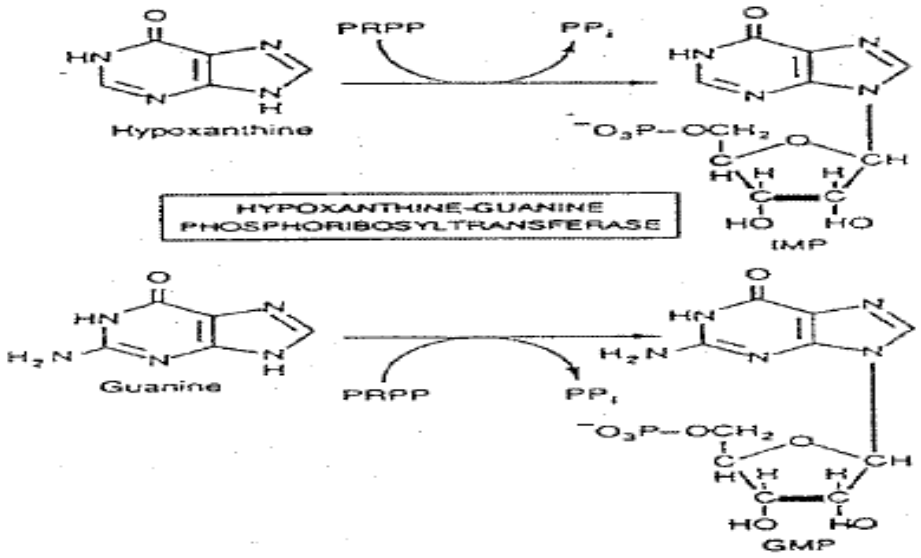
A salvage pathway is a pathway in which nucleotides (purine and pyrimidine) are synthesized from intermediates in the degradativepathway for nucleotides.

Salvage pathways are used to recover bases and nucleosides that are formed during degradation of RNA and DNA. This is important insome organs because some tissues cannot undergo de novosynthesis.

The salvaged bases and nucleosides can then be converted back into nucleotides.

Salvage pathway of purine nucleotide synthesis



## DISORDERS OF PURINENUCLEOTIDE METABOLISM

Uric acid is rather poorly soluble in water. Normal adult humans synthesize between 600 and 700mg of uric acid per day, and dietary purines contribute another 300 to 600 mg (total miscible pool: 1200 mg). This amount of uric acid must be excreted daily through the kidney (66%) and thegastrointestinal tract (33%). Serum levels below 7 mg/100 ml of uric acid are considerednormal. Hyperuricemia (>7 mg/100 ml) may lead to gout. Causes of hyperuricemia: impaired excretion of uric acid in kidney, wrong dietary habits, disturbances in purine synthesis regulation. Severe hyperuricemia is acharacteristic for neurologic Lesh-Nyhan syndrome.

## GOUT

GOUT is characterized by elevated uric acid concentrations in blood and urine due to a variety of metabolic abnormalities that lead to overproduction of purine nucleotides via the de novo pathway.

Gout (*Metabolicarthritis)* is a disease caused by a disorder of purine metabolismresulting in hyperuricemia.Sodium urate crystals are deposited on the articularcartilage of joints and in the particular tissue liketendons and clinically manifesting as recurrent acutearthritis progressing to chronic deforming arthritis,formation of tophi and development of systemiccomplications like renal failure.Normally, the human bloodstream only carries smallamounts of uric acid.However, if the blood has an elevated concentration ofuric acid, uric acid crystals are deposited in thecartilage and tissue surrounding joints.

Renalexcretion of uric acid proceeds as follows.Uric acid is filtered freely in the glomerulus but is subsequently reabsorbed to at least98% in the proximal tubules. Activesecretion of uric acid in the distal tubulesaccounts for most of the urate that finallyappears in the urine**.**

There are different approaches to the treatment of gout that include colchicine, antihyperuricemic drugs and allopurinol. Allopurinol and its metabolite, alloxanthine are effective inhibitors of xanthine oxidase and will cause a decrease in uric acid levels.

## LESCH-NYHAN SYNDROME

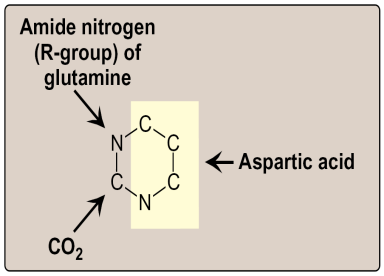
Lessch-Nyhan syndrome is a disease caused by a severe deficiency in HPRTase activity. The role of HPRTase is to catalyze reactions in which hypoxanthine and guanine are converted to nucleotides. In the absence of HPRTase, hypoxanthine and guanine are not converted to IMP and GMP, respectively, in the salvage reactions. The disease is characterized by the accumulation of excessive amounts of uric acid, a product of nucleotide degradation which causes neurological abnormalities and destructive behavior including self-mutilation.

In **Lesch-Nyhan disease** the enzyme **hypoxanthine-guanine-phosphoribosyl transferase(HPRTase)** is defective. Patients with this disease have elevated levels of uric acid and show anincreased rate of de novo synthesis of purines. The gene for HPRTase is on the Y-chromosome, hence the deficiency is virtually limited to males and, since patients with this disease usually do not reach sexualmaturity. In addition to **hyperuricemia**, thepatients show neurological disorders such as severe self-mutilation and mental retardation.

Leschï Nyhan syndrome (LNS)also known as Juvenile gout, is a rare inherited disorder caused by adeficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase(HGPRT), produced by mutations in the HPRT gene.The disorder was first recognized and clinically characterized by medicalstudent Michael Lesch and his mentor, pediatrician Bill Nyhan, who publishedtheir findings in 1964.The HGPRT deficiency causes a build-up of uric acid in all body fluids. Thisresults in both hyperuricemia and hyperuricosuria, associateed with severegout and kidney problems. Neurological signs include poor muscle controland moderate mental retardation.The symptoms caused by the buildup of uric acid (gout and renal symptoms)respond well to treatment with drugs such as allopurinol that reduce the levels of uric acid in the blood.

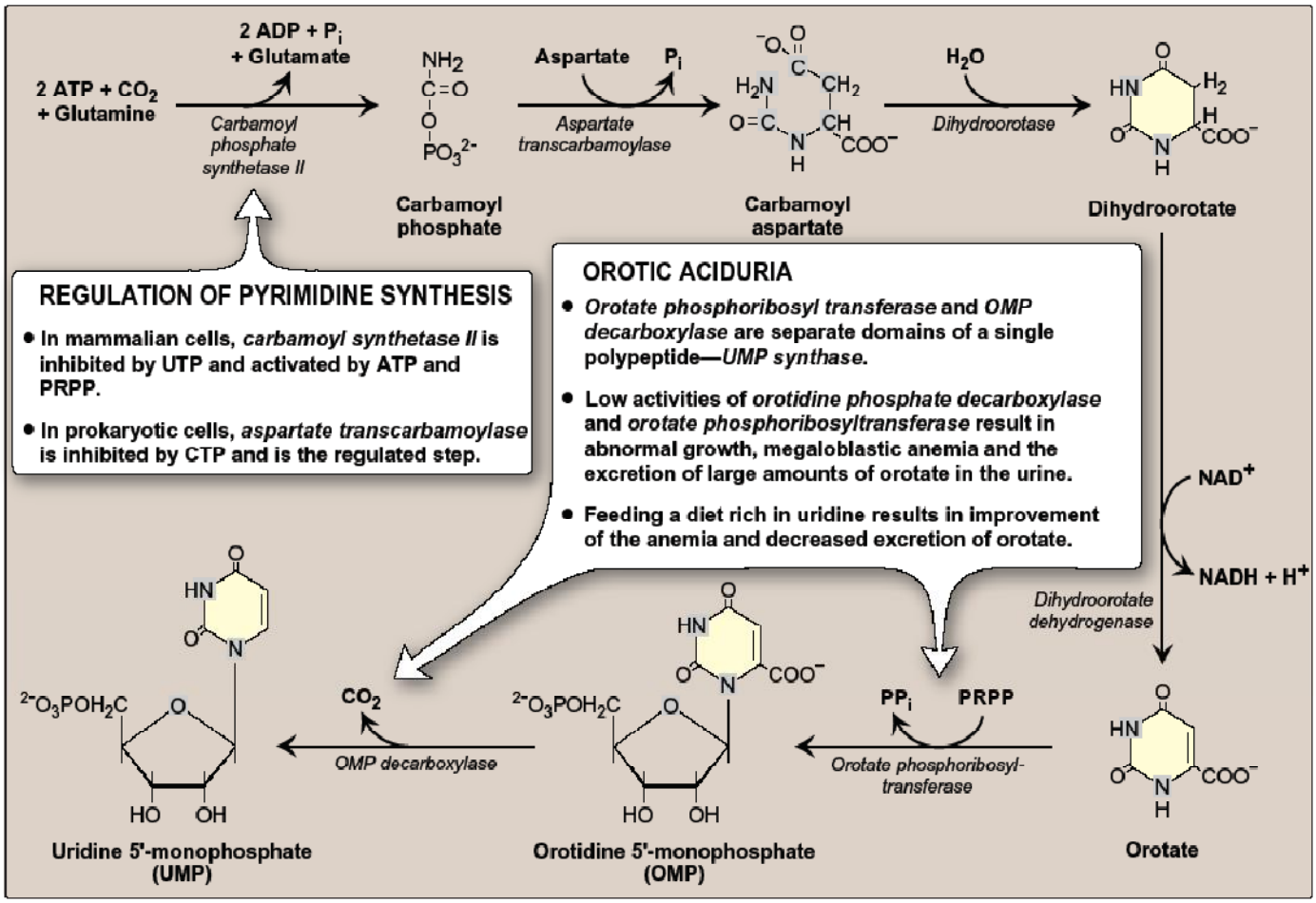
# PYRIMIDINE NUCLEOTIDE BIOSYNTHESIS.

The **pyrimidine skeleton** is synthesizedfrom **carbamoyl phosphate and aspartate**. The synthesis of carbamoylphosphate from **glutamine, $CO_2$, and twoATP's** occurs in the cytoplasm of the cell and is inhibited by UTP. (Compare this reaction with the synthesis of urea in themitochondrion, where ammonium ion is used instead of glutamine.)




**Sources of atoms in the pyrimidine ring.**

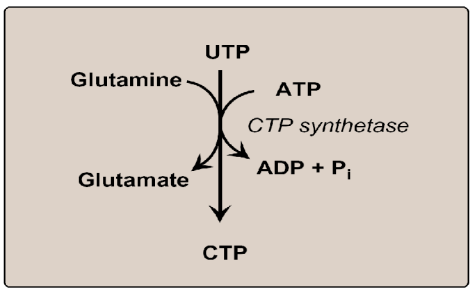
The **committed step** in pyrimidine biosynthesis is the formation of **N-carbamoyl aspartate**. The enzyme **aspartate transcarbamoylase** is allosterically inhibited by CTP andactivated by ATP. The binding of ATP and CTP to the regulatory site of the enzyme iscompetitive. This mechanism seems to balance the synthesis of purines and pyrimidines.




**De novo synthesis of pyrimidines.**

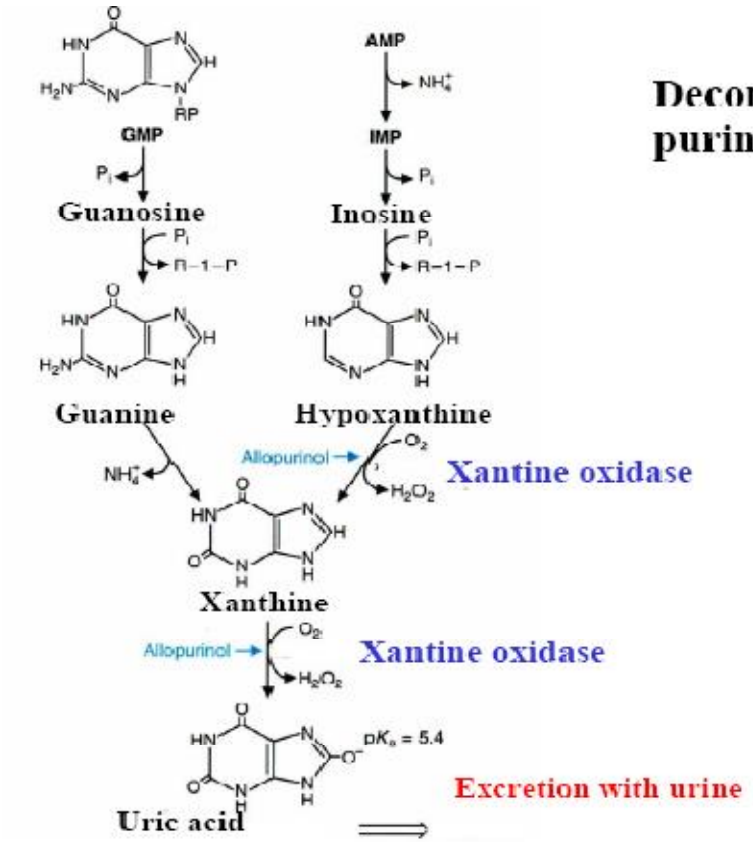
Carbamoyl aspartate cyclizes to **dihydroorotate**, which is then dehydrogenated to **orotate** by $NAD^+$. Orotate is converted to **uridine monophosphate (UMP)** by condensation withphosphoribosyl pyrophosphate, followed by **decarboxylation.**

**Cytosine nucleotides** are synthesized by amination of UTP. Glutamine is the amino donor, and one ATP is hydrolyzed in the reaction.




**Synthesis of CTP from UTP**

# DEGRADATION OF PURINE AND PYRIMIDINE NUCLEOTIDES

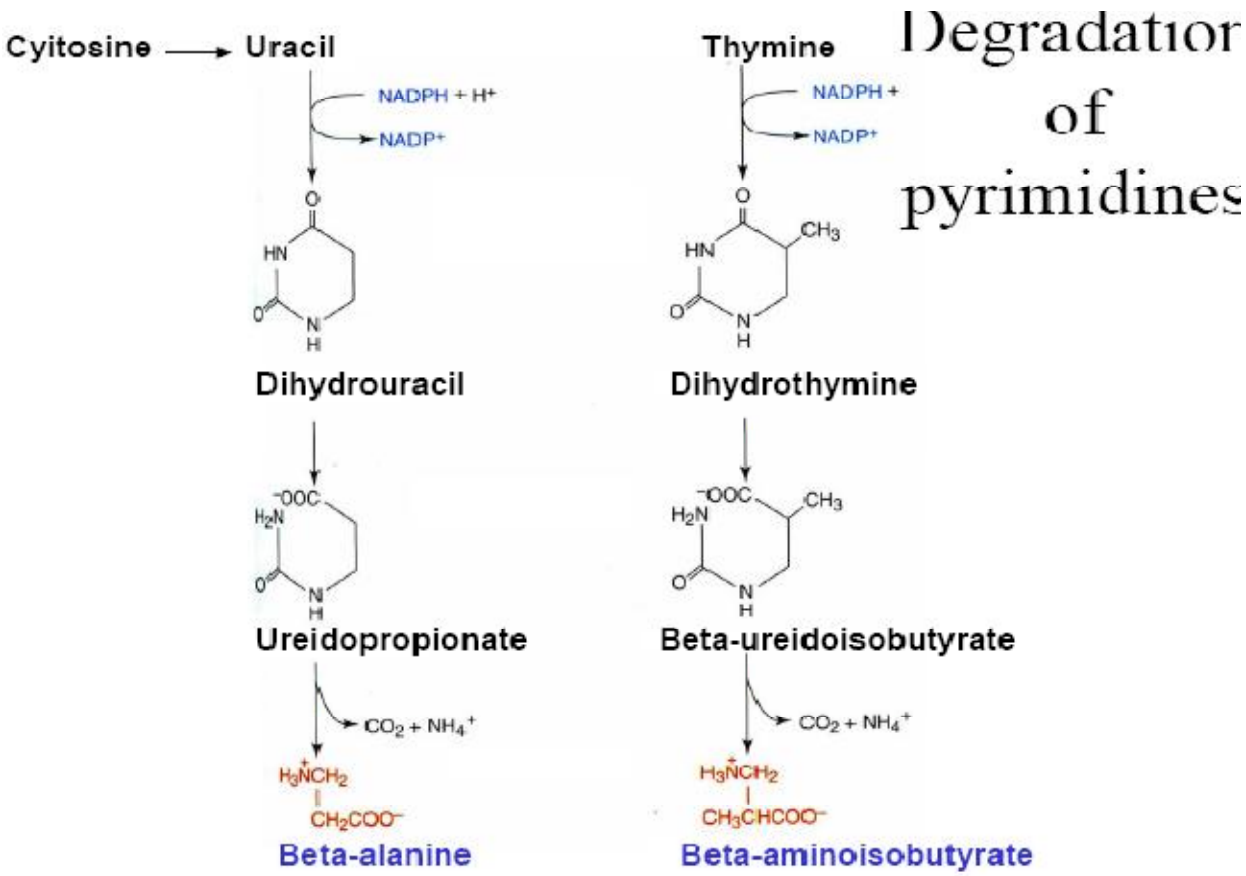



**Uric acid**, the final product of purine catabolism in humans, is formed by successive oxidations of hypoxanthine and xanthine both catalyzed by the molybdenum-containing enzyme **xanthineoxidase**.

The end product of purine catabolism is uric acid which must be excreted. Excretion occurs via the kidney and the gastrointestinal tract.

Since uric acid is not very soluble in aqueous medium, there are clinical conditios in which elevated levels of uric acid results in deposition of sodium urate crystals primarily in joints.

Hyperuricemia is a clinical condition characterized by excess levels of uric acid in the blood and generally increased levels of uric acid excretion in the urine (hyperuricuria).




Uracil and cytosine are converted to ɓ-alanine, thymine to ɓ-aminoisobutyrate. Both amino acids can be oxidized further to $CO_2$ and $NH_3$, but ɓ-aminoisobutyrate is metabolized only slowly and is often found excreted directly with urine. (ɓ-Aminoisobutyrate can be converted to methylmalonate, whichis then rearranged, as a CoA derivative, to succinyl CoA in a vitamin-$B_{12}$-dependent reaction.).

$NH_3$ is detoxicatedin the liver. $CO_3$ is exhaled or used for biosynthetic purposesas bicarbonate.

**DISORDERS OF PYRIMIDINE NUCLEOTIDE METABOLISM.**

**Orotic aciduria**, a very rare hereditary disorder, is a pyrimidine auxotrophism in humans. Orotic Aciduria is characterized by severe anemia, growth retardation and high levels of orotic acid excretion. The biochemical basis for orotic aciduria is a defect in one or both of the activities of orotate phosphoribosylytransferase or orotidine decarboxylase associated with UMP synthase, the bifunctional protein.

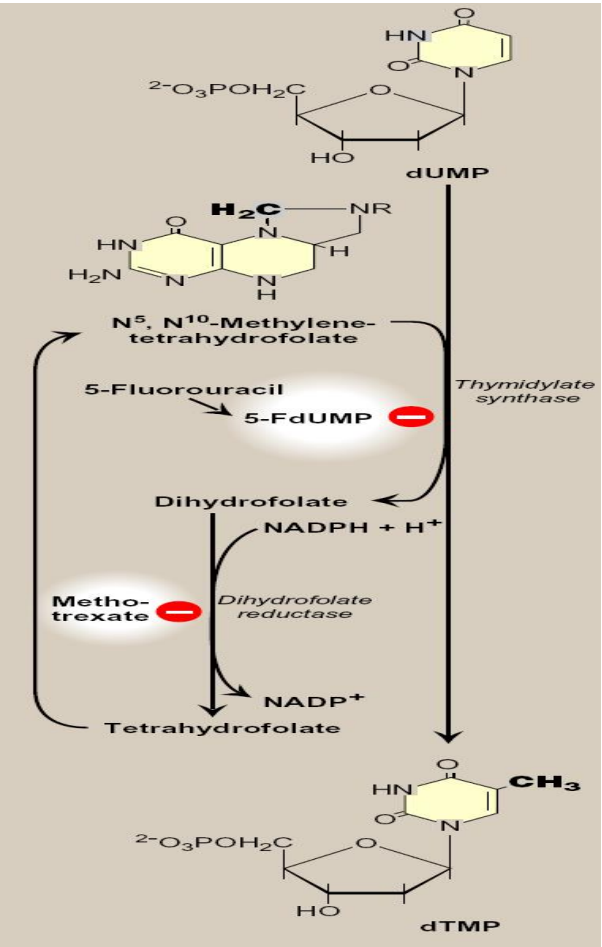
Replacement therapy with uridine is possible. To treat this disorder, patients are fed uridine which leads not only to reversals of the problem but also to decreased formation of orotic acid. Uridine is taken up by cells and converted by uridine phosphotransferase to UMP that is sequentially converted to UDP and then to UTP. UTP formed exogenous uridine in turn inhibits carbamoyl phosphate synthase II, the major regulated step in the de novo pathway.

**ANTICANCER DRUGS THAT INTERFERE WITH NUCLEOTIDE BIOSYNTHESIS.**

Cancer cells divide more rapidly than most normal cells. Thus,by interfering with nucleotide synthesis one can oftenpreferentially starve cancer cells of vital precursors for their DNA synthesis. Rapidly dividing normal cells, such as in bone marrowand intestinal epithelium are also affected by these drugs thuslimiting their use. One of the most successful anticancer drugs is**amethopterin,** a folic acid analog that inhibits the enzyme**dihydrofolate reductase**.

**5-Fluorouracil** is another often used anticancer drug.In the cell, it is converted into its deoxyribonucleotide monophosphate, 5-fluorodeoxyuridine monophosphate, which directly inhibits **thymidylate synthetase**.

6-Mercaptopurine,when converted to its ribonucleoside 5'-phosphate inhibitsseveral enzymes in purine biosynthesis. It is used in thetreatment of leukemia.

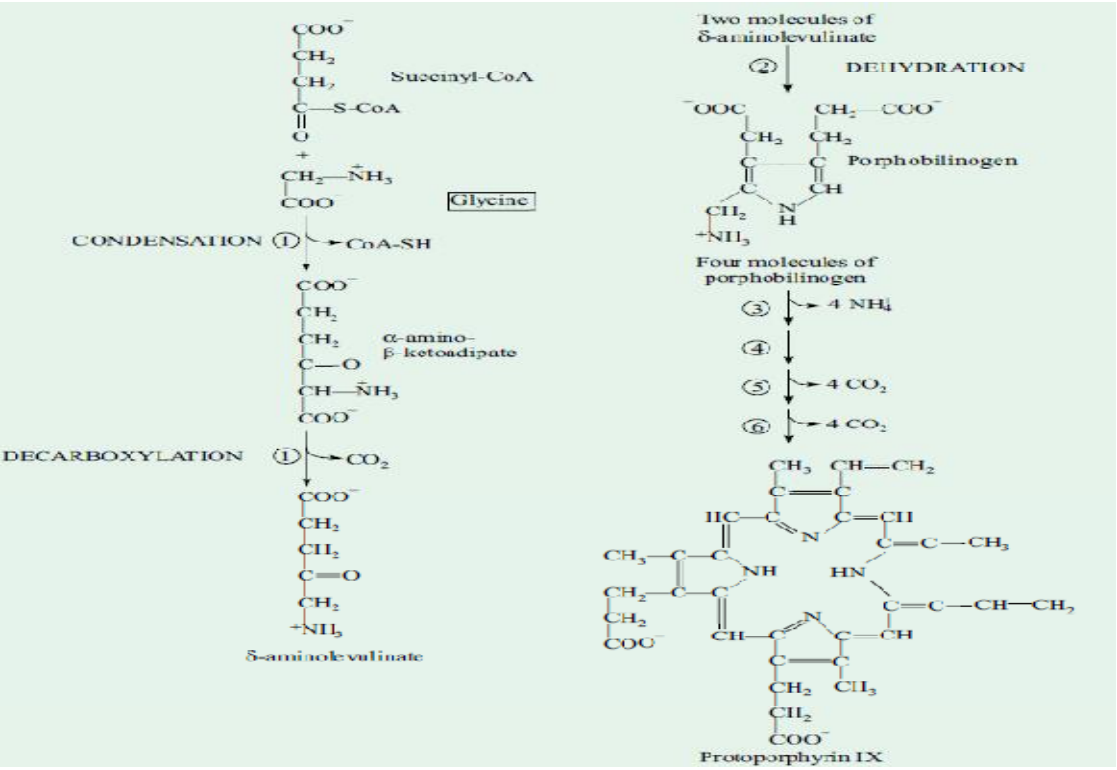


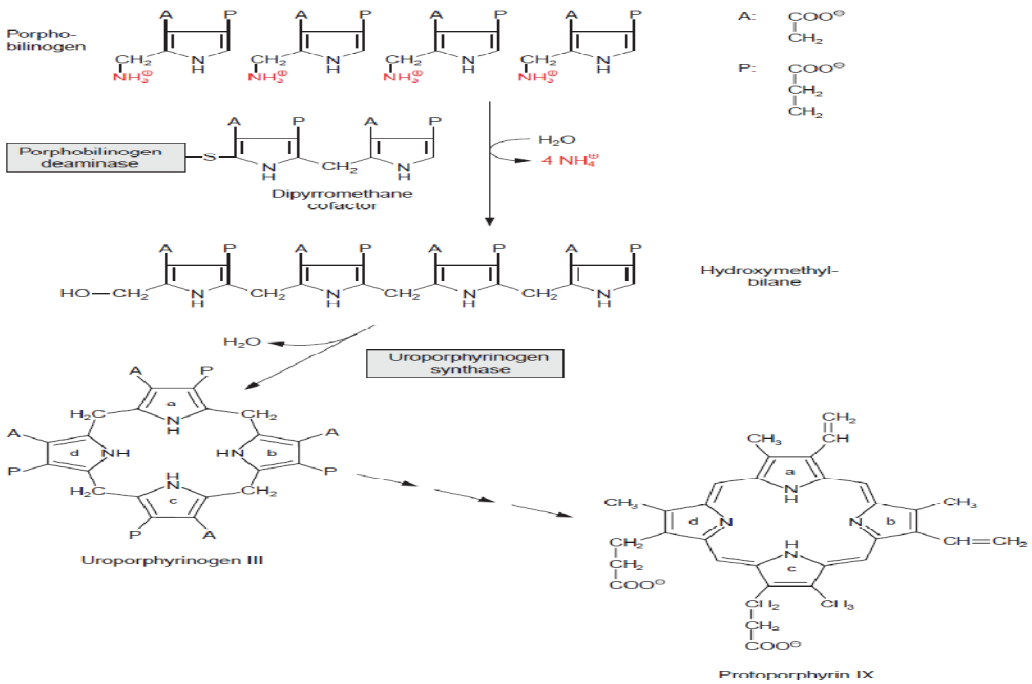

Because cancer cells undergo rapid cell division, the enzymes of nucleotide synthesis, including thymidylate synthase and dihydrofolate reductase are highly active. Compounds that inhibit either of these reaction can therefore act as anticancer agents. For example the dUMP analog 5-fluorodeoxyuridylate inactivates thymidylate sythase. Antifolates such as methotrexate are competitive inhibitors of dihydrofolate reductase because they compete with dihydrofolate for binding to the enzyme. In the presence of methotrexate, a cencer cell cannot regenerate the tetrahydrofolate required for dTMP production and the cell dies. Most non cancer cells which grow much more slowly are not as sensitive to the effect of the drug.

# PORPHYRIN

## BIOSYNTHESIS OF PORPHYRINS

- Porphyrins are highly coloured cyclic tetrapyrrolic pigments formed by the linkage of four pyrrole rings through methene (ï HC=) bridges.
- Porphyrins mediate critical functions in a variety of biological systems ranging from electron transfer, oxygen transport, photosynthetic energy transduction and conversion of carbon dioxide into fuel.
- Common examples of important porphyrins include heme and cytochrome (with chelated iron), chlorophyll (with chelated magnesium), coenzyme $B_{12}$ (with chelated nickel).
- Porphyrins occur in green leaves and other green parts of plants, in bread, fish, Beer and milk.
- Relatively high is their content in potatoes and in spinach.
- In the animal the young cells of the erythrocyte series, and the bone marrow possess porphyrins.
- The spotted egg shells, and the feathers of certain species of birds owe their color to free porphyrins, or to their metal complex salts.
- Naturally occurring porphyrins and porphyrin derivatives are of the types I, or III.
- In human hemoglobin the ratio of type III to type I is greatly in favor of type III, about 10,000:1.
- The "natural" protoporphyrin IX (type III), into which iron is introduced in the synthesis of the prosthetic group of hemoglobin, is present in human blood (8 to 15 micrograms per 100 ml.).
- Glycine acts as a major precursor of porphyrins, which are constituents of hemoglobin, the cytochromes, and chlorophyll.
- All the porphyrins are derived from a common monopyrrolic precursor, ŭ**-amino-levulinic acid (ALA)**.



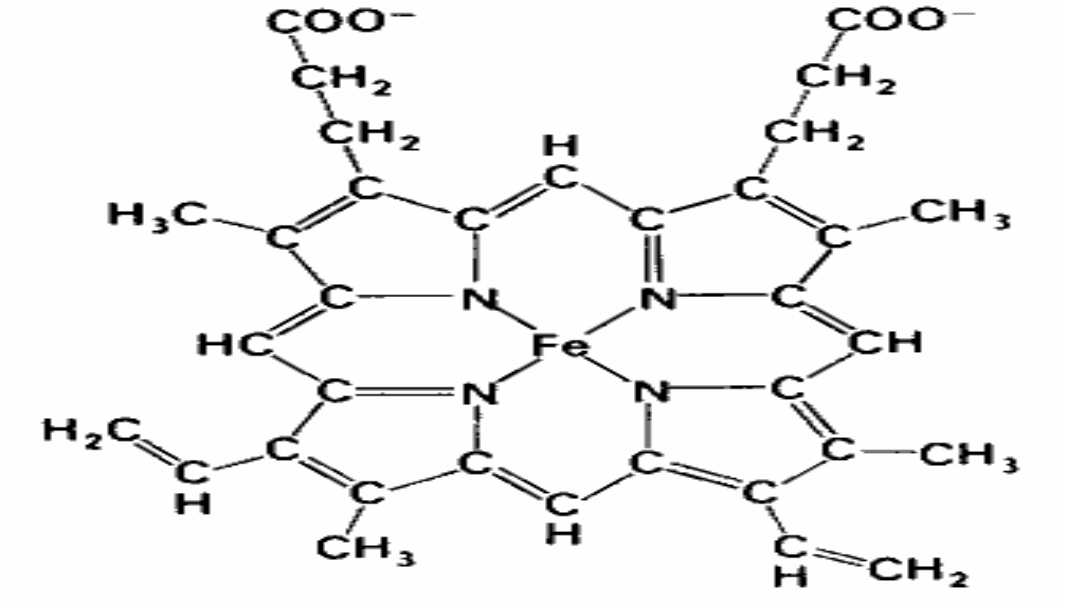



- The first step in biosynthesis of porphyrins is condensation of glycine and succinyl coenzyme A to form ŭ-amino-levulinate (ALA) catalyzed by ŭ-amino-levulinate synthase, a pyridoxal phosphate-requiring enzyme present in mitochondria and is the rate-limiting step.
- ALA is transported out of mitochondria and inside the cytoplasm two molecules of ŭ- amino-levulinate condense to form porphobilinogen (PBA), the next intermediate.
- The reaction is catalyzed by ŭ-amino-levulinate dehydratase / dehydrogenase
- Four molecules of porphobilinogen then condense head to tail to form a linear tetrapyrrole (hydroxymethyl bilane) in a reaction catalyzed by porphobilinogen deaminase (PBG deaminase).
- This enzyme-bound linear tetrapyrrole then cyclizes to form uroporphyrinogen III, which has an asymmetric arrangement of side chains. This reaction requires uroporphyrinogen cosynthase.
- However, in the presence of synthase alone, uroporphyrinogen I, the nonphysiologic symmetric isomer, is produced.
- The desaturation of the porphyrin ring and the conversion of two of the propionate side chains into vinyl groups yield protoporphyrin IX.
- The reaction is catalyzed by coproporphyrinogen oxidase and protoporphyrinogen oxidase, with the intermediate formation of protoporphyrin III
- Protoporphrin IX is the only isomeric form of protoporphyrin that exists in nature.
- It serves as precursor for the biosynthesis of haemoglobin, myoglobin (Mb), most of the cytochromes (cyt), catalase and peroxidase.
- The biosynthesis of various porphyrins, such as chlorophyll, vitamin $B_{12}$, heme etc., branches from the two intermediates, uroporphyrinogen III and protoporphrin IX by insertion of either magnesium or iron into the central cavity and further modifications occur.
- In humans, genetic defects of certain enzymes of this pathway lead to the accumulation of specific porphyrin precursors in body fluids and in the liver.
- These genetic diseases are known as porphyrias

- In **congenital erythropoietic porphyria**, which affects mainly erythrocytes, there is an accumulation of uroporphyrinogen I.
- It stains the urine red and causes the teeth to fluoresce strongly in UV light and the skin to be abnormally sensitive to light.
- Patients with this disease are anemic, shy away from sunlight and have a propensity to drink blood.
- This condition may have given rise to the vampire myths in medieval folk legend.
- Acute intermittent porphyria is the most prevalent of the porphyrias affecting the liver.
- This porphyria is characterized by the overproduction of porphobilinogen and ŭ-aminolevulinate, which results in severe intermitent abdominal pain, neurological dysfunction, vomitting, constipation, paralysis and psychological symptoms.
- The urine of the afflicted may have a port wine colour from photooxidation of the porphobilinogen excreted, together with ŭ-aminolevulinate, in large amounts.

**Metalloporphyrins occurring in nature**

- Porphyrins containing the metal atom are called metalloproteins.
- The porphyrins have characteristic property of formation of complexes with metal ions bound to the nitrogen atom of the pyrrole rings.
- Various examples of metalloproteins occurring in nature are:
- Iron containing porphyrins: Heme proteins (hemoglobin, myoglobin, cytochrome, enzymes catalase and peroxidase)
- Magnesium containing porphyrin: Chlorophyll
- Cobalt containing porphyrins: Vitamin $B_{12}$
- ***Heme proteins***
- Incorporation of an iron atom into protoporphyrin IX by a **ferro-chelatase** results in the formation of heme.
- By assembling the heme with apoproteins,chloroplasts are able to synthesize their own cytochromes.
- Also, mitochondriapossess the enzymes for the biosynthesis of their cytochromes from protoporphyrinIX.
- Heme is an essential molecule for all living organisms; it is the prosthetic group of several apoproteins, including hemoglobin, cytochromes, which are involved in the electron transport chains of photosynthesis and respiration, peroxidases, catalases, nitrite reductase and nitric oxide synthase.
- Heme is responsible for the characteristic red colour and is the site at which each globin monomer binds one molecule of $O_2$.
- In all Heme proteins, the function of the heme is either to bind and release a ligand to its central iron atom, or for the iron atom to undergo a change in oxidation state, releasing or accepting an electron for participation in a redox reaction.




**Structure of heme (Fe-protoporphyrin IX**

**STRUCTURE AND FUNCTIONS OF VARIOUS HEME PROTEINS**

**Haemoglobin (Hb)**

- Hb is a member of the family of pigments called tetrapyrroles.
- It is a oxygen Binding allosteric heme protein and the heme group is responsible for the deep red-brown colour of Hb.
- Although many invertebrate species have haemoglobin-based oxygen transport systems, others produce one of two alternative types of $O_2$-binding proteins:

(i) Haemocyanin, a copper containing protein that is
blue in complex with oxygen and colorless otherwise;
(ii) Haemerythrin, a non-heme Fe-containing protein that is burgundy coloured in complex with oxygen and colorless otherwise

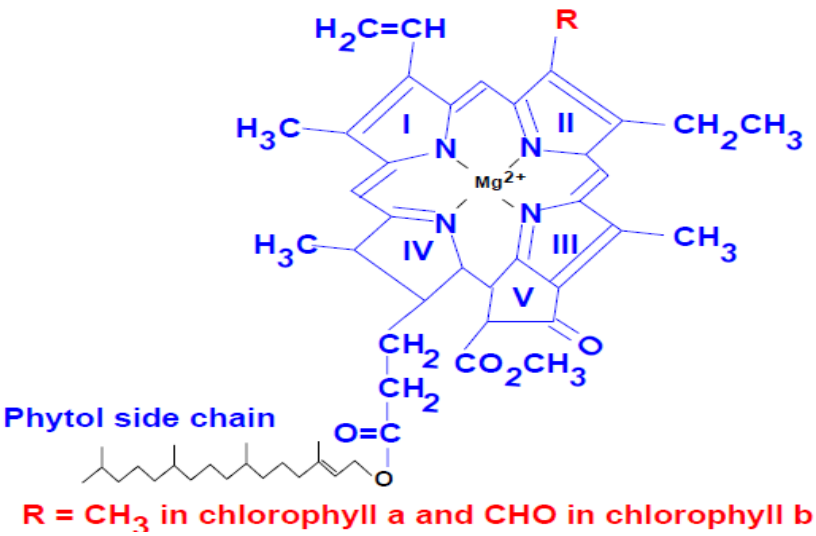
**Cytochromes (Cyt)**

- They are intracellular, electron-transferring hemoproteins containing iron-porphyrin groups.
- These are found only in aerobic cells. Some are located in the inner mitochondrial membrane, where they act sequentially to carry electrons originating from various dehydrogenase systems toward molecular oxygen.
- Cytochrome P450 is found in endoplasmic reticulum, where it plays a role in specialized hydroxylation reactions.
- All cytochromes undergo reversible Fe (II)-Fe (III) valence changes during their catalytic cycles.

***Chlorophyll***

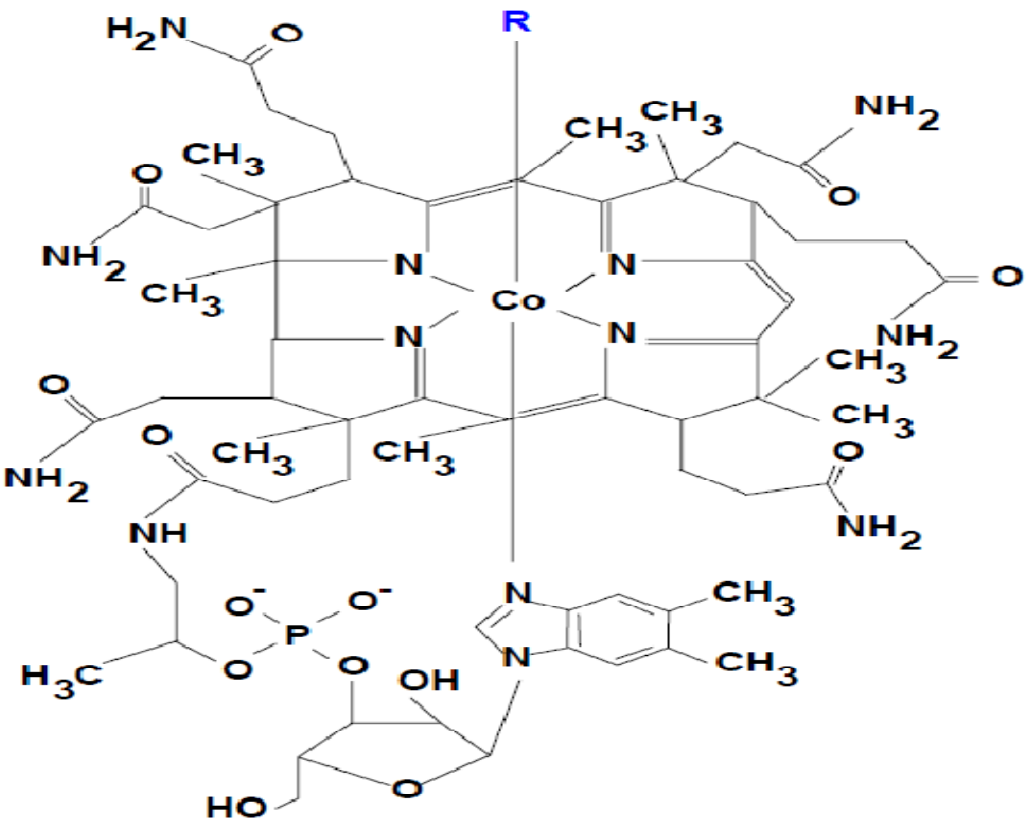
- Chlorophylls are the essential components for photosynthesis and occur in chloroplasts as green pigments in all photosynthetic plant tissues. These are important in the energy producing mechanisms of photosynthesis.

- Like Hb, it is a member of the family of pigments called tetrapyrroles. Chemically, each chlorophyll molecule contains a porphyrin (tetrapyrrole) nucleus with a chelated magnesium atom at the center and a long chain hydrocarbon (phytyl) side chain attached through a carboxylic acid group.
- There are at least five types of chlorophylls in plants. Chlorophyll ‘a’ and ‘b’ occur in higher plants, ferns and mosses. Chlorophyll ‘c’, ‘d’ and ‘e’ are only found in algae and in certain bacteria




***Vitamin $B_{12}$***

- Vitamin $B_{12}$ is also called cyanocobalamin or anti-pernicious anemia factor. It has been found only in animals, liver, milk, eggs, fish, oysters.
- Animals and plants are unable to synthesize this vitamin. Cyanocobalamin is unique in that it appears to be synthesized only by microorganisms, especially anaerobic bacteria.
- The structure comprises of a centrally situated cobalt atom, surrounded by a macrocyclic structure of four reduced pyrrole rings (A, B, C and D) collectively called corrin.
- The six coordinate valencies of cobalt atom ($Co^{2+}$) are satisfied by the four nitrogens of the reduced tetrapyrrole, one nitrogen atom of 5,6-dimethylbenzimidazole and one cyanide ion.
- ***Vitamin $B_{12}$*** is deep red crystalline substance soluble in water, alcohol and acetone but not in chloroform.
- It is stable to heat in neutral solutions but is destroyed by heat in acidic or alkaline solutions.
- Vitamin $B_{12}$ is converted to coenzyme $B_{12}$ by microorganisms in presence of ATP.
- Coenzyme $B_{12}$ is also called 5ô-deoxyadenosyl cobalamin. Its structure is similar to that of cyanocobalamin except that the cyanide group is replaced by adenosine and the linking with cobalt atom takes place at 5ô carbon atom of the ribose of adenosine.
- Another example of coenzyme $B_{12}$ is methyl cobalamin, where methyl group occupies the sixth coordination position. Coenzyme $B_{12}$ is the only known example of a carbon-metal bond in a biomolecule




**INTERACTION AND QUESTIONS**

(1). Using Inosine 5`-monophosphate (IMP) as the starting material, describe the synthesis of Adenosine 5`-monophosphate (AMP) and Guanosine 5`-monophosphate (GMP)?

(2). Using biochemical pathway/structures, show the degradation of the following: (i) GMP (ii) AMP (iii) Cytosine (iv) Thymine.

(3). Using biochemical structures, describe the synthesis of Uridine 5`-monophosphate?

(4) Write briefly on the following: (i) Lesch-Nyhan syndrome (ii) Gout (iii) Orotic aciduria

(5) Write briefly on the genetic diseases known as porphyrias.

(6). Using Glycine and SuccinylCoA as starting materials, Discuss the Biosynthesis of Porphyrin.

(7). Write briefly on following: (a) Heme proteins (b) Chlorophyl © *Vitamin $B_{12}$*