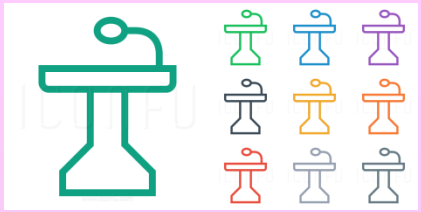
Biological Chemistry Department

Biological Chemistry

General Amino Acid Pathways. Hemoproteins and Nucleoproteins Metabolism in Healthy State and under Pathology.

Speciality: Pharmacy for foreign students (Language of instructions – English)

Lecturer: ass. prof. Kravchenko G.B.



Lecture Plan

1. *Hemoprotein metabolism in healthy state and under pathology.*

1.1. Iron and hemoprotein digestion and absorption.

1.2. Heme biosynthesis. Porphyrias.

1.3. Heme degradation. Types of Jaundice.

2. Nucleoprotein Metabolism in Healthy State and under Pathology.

2.1. Nucleoprotein digestion and absorption.

2.2. Nucleotide biosynthesis.

2.3. Nucleotide catabolism. Gout and its treatment.

<u>Individual work</u>

1. *Lesch-Nyhan syndrome.*
2. *Acute intermittent porphyria.*
3. *Eriythropoietic porphyria.*
4. *Hereditary coproporphyria.*

Information Resources

1. Biological Chemistry: Textbook / A.L. Zagayko, L.M. Voronina, G.B. Kravchenko, K.V. Strel`chenko. – Kharkiv: NUPh; Original, 2011. – 140-153 p.

2. Training Journal for Licensed Exam "KROK-1": Study Material in Biological Chemistry. – Kharkiv: NUPh, 2017. – 92-100 p.

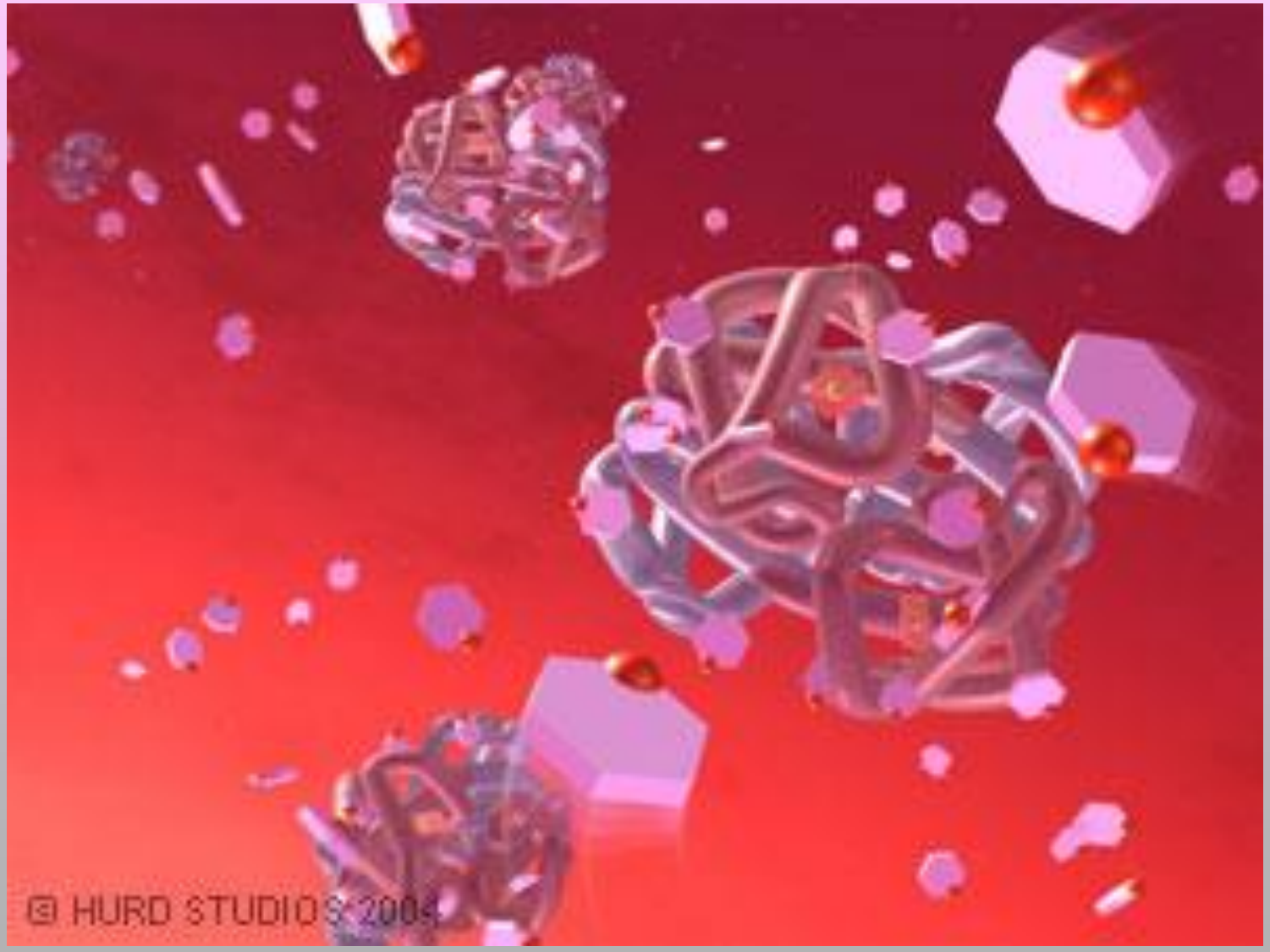
3. Laboratory Manual on Biochemistry. Kharkiv: NUPh, 2017. - 59-64 p.

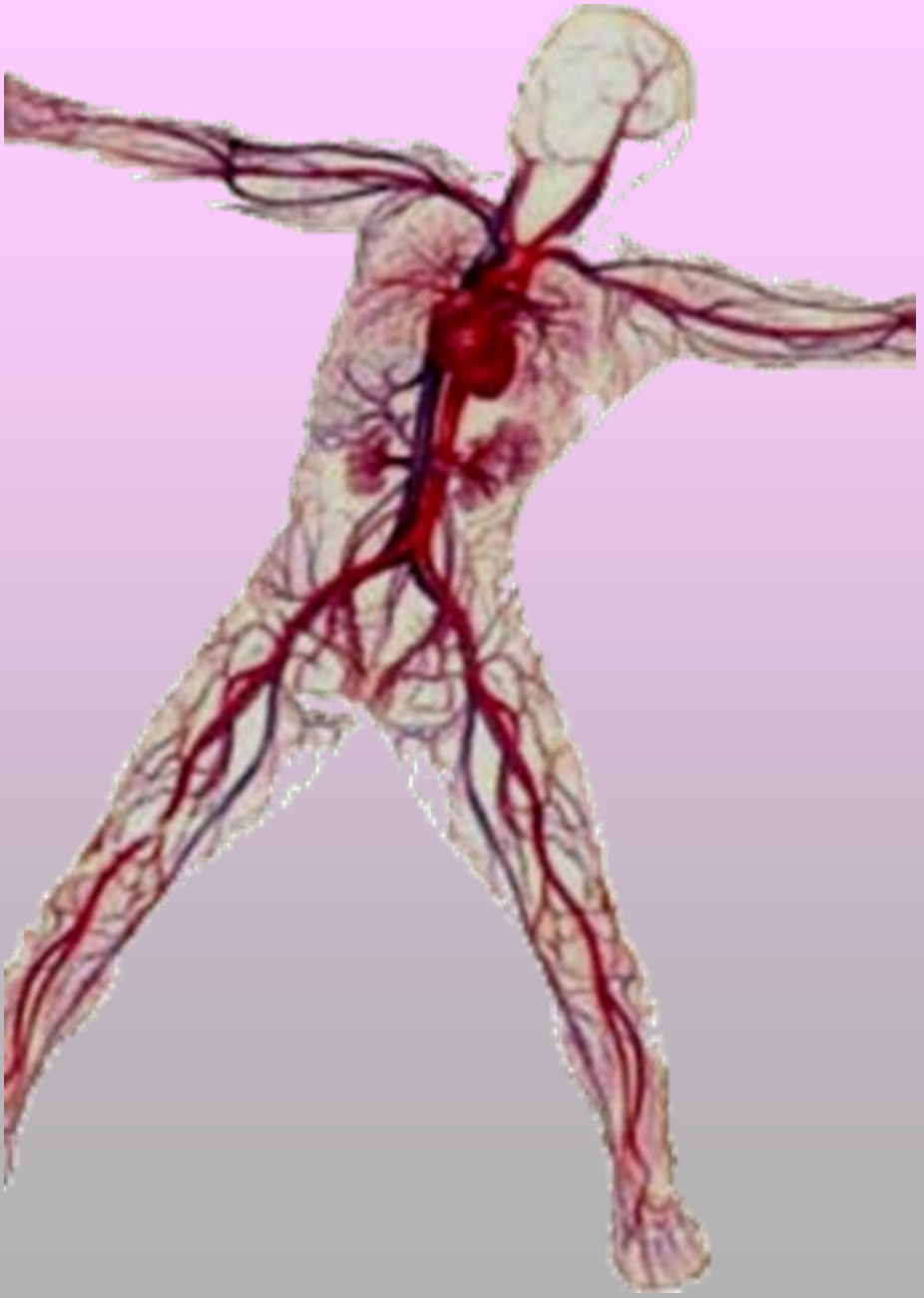
4. Nucleotide Metabolism: The Medical Biochemistry Page. Available on: **https://themedicalbiochemistrypage.org/nucleotide-metabolism.php.**

5. Iron and and Copper Homeostasis: The Medical Biochemistry Page. Available on: **https://themedicalbiochemistrypage.org/iron-copper.php.**

6. Porphyrin and Heme Metabolism: The Medical Biochemistry Page. Available on: **https://themedicalbiochemistrypage.org/heme-porphyrin.php.**

Hemoprotein Metabolism in Healthy State and under Pathology.





There are almost 5 grams of iron in the human body:

60-70% - hemoglobin;

20% - ferritin;

3-5% - myoglobin

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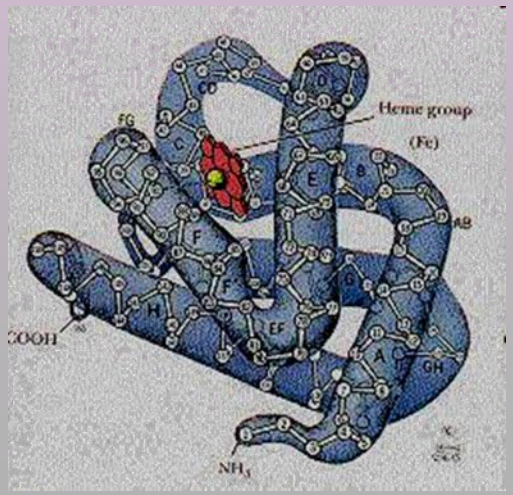
The only Fe2+ is absorbed in intestine!

But in GIT epithelial cells it oxidized to Fe3+,
and transferred with protein transferrin,
store with ferritin and hemosiderin



The food heme is immediately oxidized into hematin, which is not absorbed, but is excreted with feces

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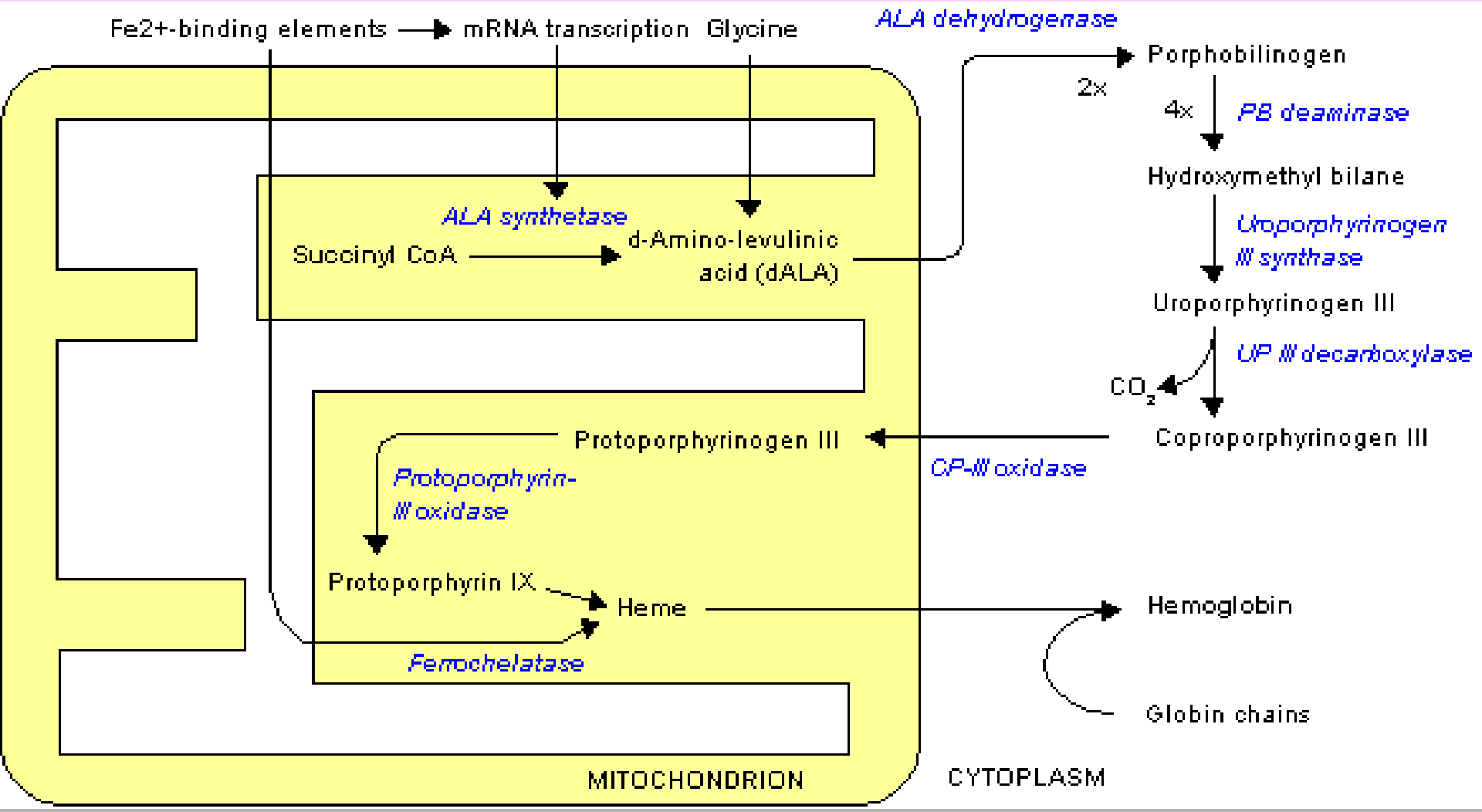
Synthesis of Porphobilinogen and Heme



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Porphyria

(Genetic defect in heme metabolism)

Disease state	Genetics
Acute intermittent porphyria	Dominant
Hereditary coproporphyria	Dominant
Variegate porphyria	Dominant
Porphyria cutanea tarda	Dominant
Hereditary protoporphyria	Dominant
Erythropoietic porphyria	Recessive
Lead poisoning	None

Symptoms

Teeth turn fluorescent reddish brown

Red urine

Neurological dysfunction

Skin is light sensitive

Increased hair growth

Treatment

Glucose infusion and exclusion of drugs causing ALA synthase elevation

Administration of intravenous hematin to inhibit ALA synthase synthesis and activity

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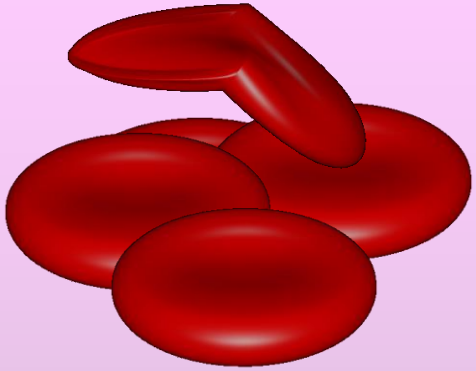
ecgrhRHD4HGaThw=s114

*They are broadly classified as **hepatic porphyrias** or **erythropoietic porphyrias**, based on the site of the overproduction and mainly accumulation of the porphyrins (or their chemical precursors).*

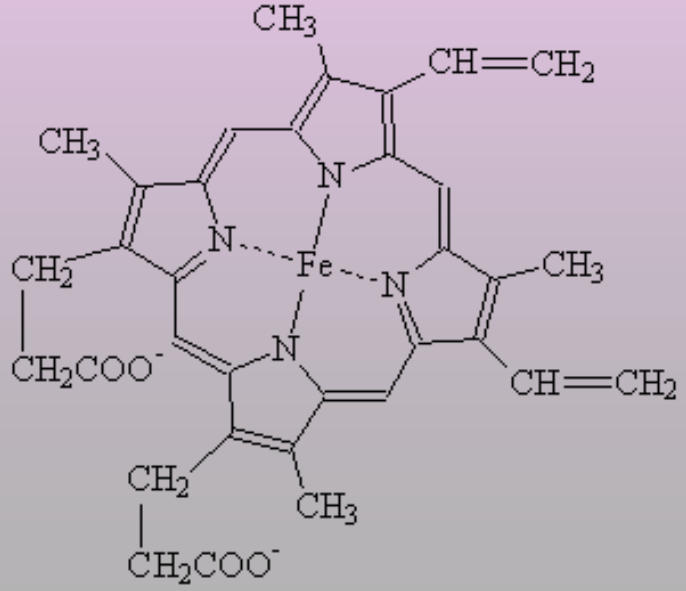
*The **hepatic porphyrias** primarily affect the nervous system, resulting in abdominal pain, vomiting, acute neuropathy, seizures, and mental disturbances, including hallucinations, depression, anxiety, and paranoia. Cardiac arrhythmias and tachycardia may develop as the autonomic nervous system is affected.*

*The **erythropoietic porphyrias** primarily affect the skin, causing photosensitivity, blisters, necrosis of the skin and gums, itching, and swelling, and increased hair growth on areas such as the forehead.*
In some forms of porphyria, accumulated heme precursors excreted in the urine may cause various changes in color, after exposure to sunlight, to a dark reddish or dark brown color. Heme precursors may also accumulate in the teeth and fingernails, giving them a reddish appearance.

Degradation of Heme Yields Bile Pigments



Erythrocytes are continuously undergoing a hemolysis process. The average of their life-time is 120 days. As the erytrocytes disintegrate, the hemoglobin is degraded or broken into globin, the protein part, iron , and heme.



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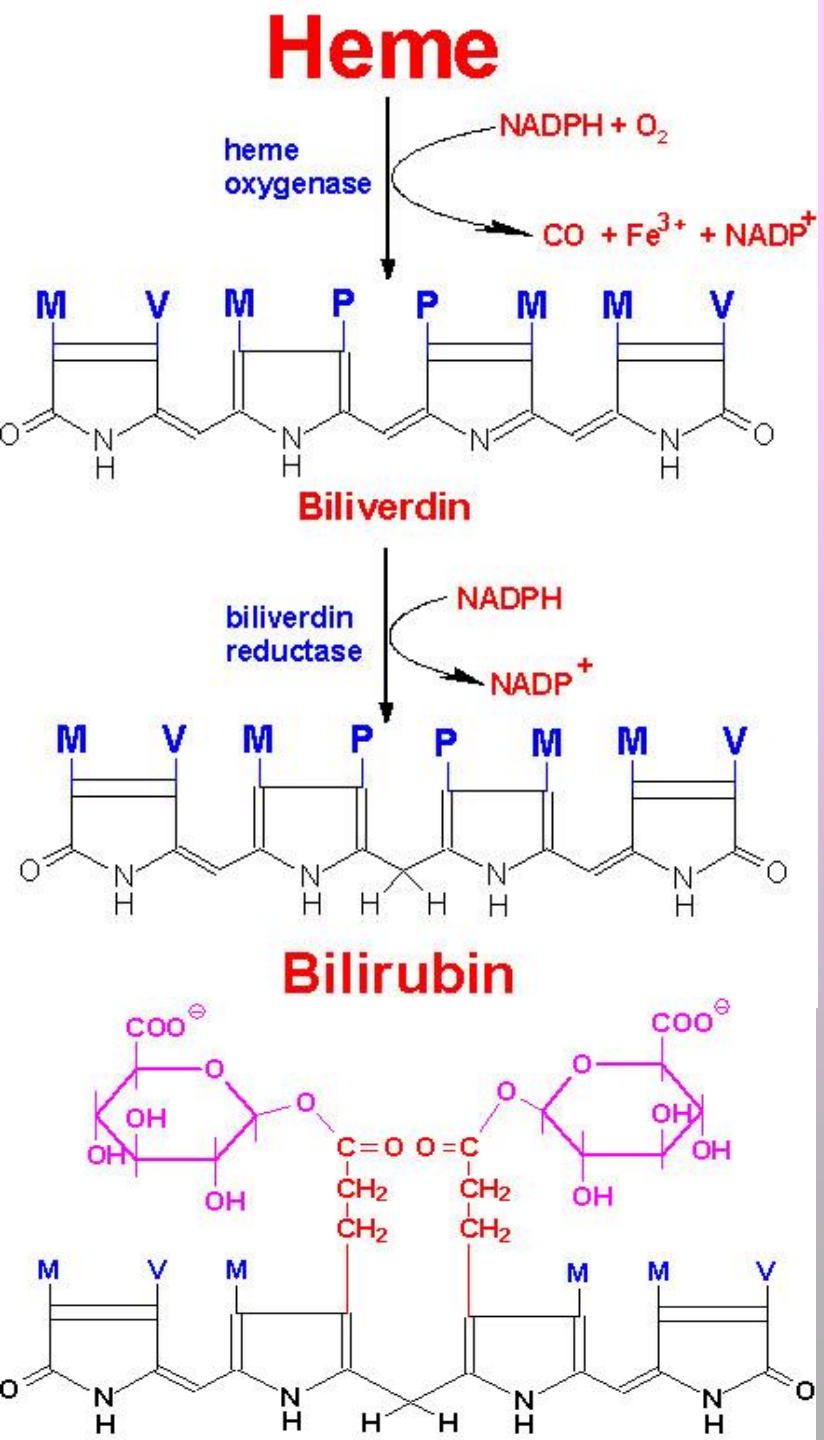
Protoporphyrin IX



Pathway for the degradation of heme to bilirubin

These processes all occur in the reticuloendothelial cells of the liver, spleen, and bone marrow.

The heme initially breaks apart into biliverdin, a green pigment which is rapidly reduced to bilirubin, an orange-yellow pigment.

The bilirubin is then transported to the liver where it reacts with a glucuronic acid. This more soluble form of bilirubin (conjugated) is excreted into the bile.

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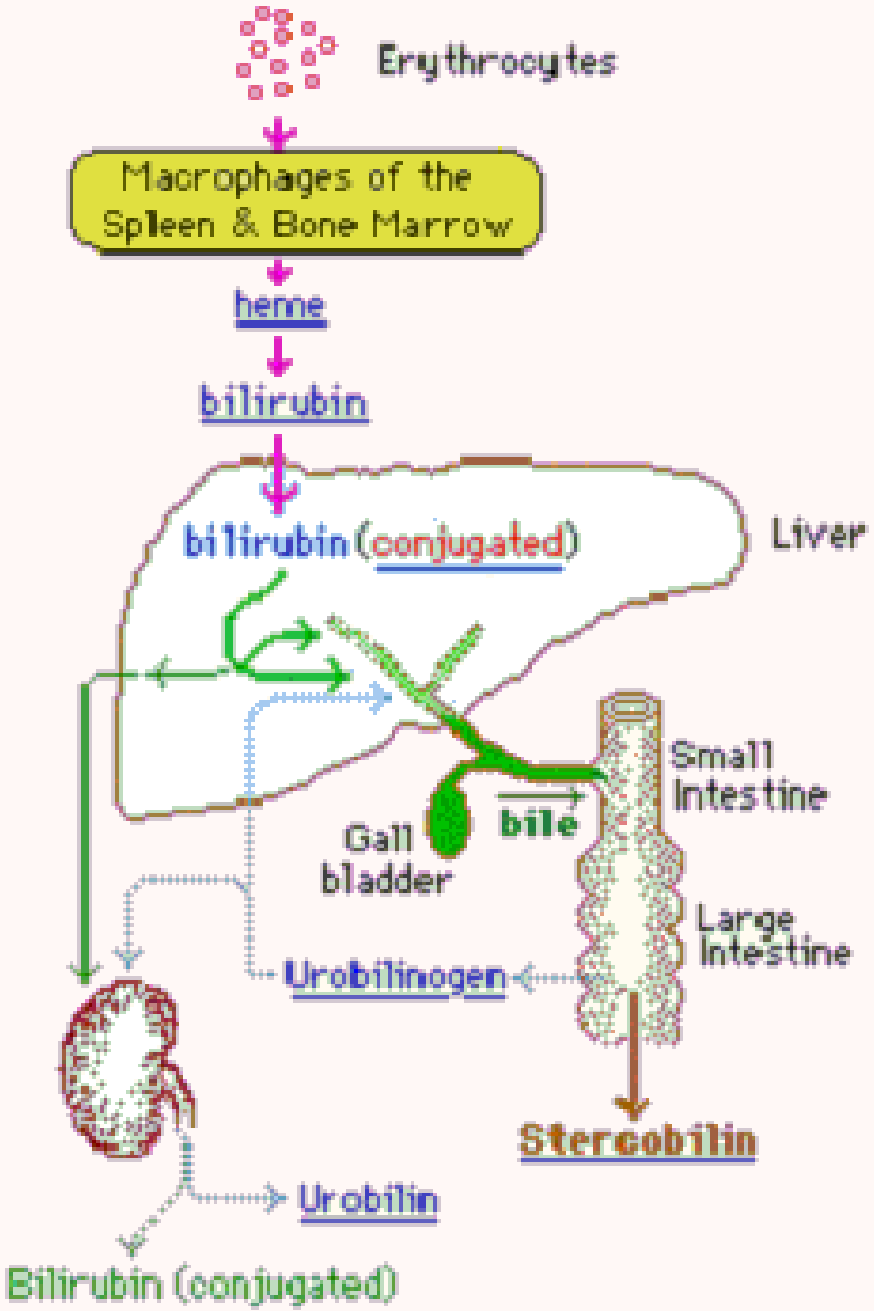
Bilirubin diglucuronide

The bile goes through the gall bladder into the intestines where the bilirubin is changed into a variety of pigments. The most important ones are stercobilin, which is excreted in the feces, and urobilinogen, which is reabsorbed back into the blood.

The blood transports the urobilinogen back to the liver where it is either re-excreted into the bile or into the blood for transport to the kidneys. Urobilinogen is finally excreted as a normal component of the urine.



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The clinical determination of plasma bilirubin distinguishes between conjugated (direct) and unconjugated (indirect) bilirubin.

The reaction, called the van den Bergh reaction, is a coupling of bilirubin with a diazonium salt to form a colored complex. Only conjugated bilirubin is water soluble and reacts directly. This is called the direct bilirubin.

To measure the unconjugated bilirubin bound to albumin, alcohol or caffeine reactive is added to release it into solution, where it can now react. This is called the indirect bilirubin.

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Reference value:

Total bilirubin: 0.3 ~ 1.2 mg/dl

Direct bilirubin: 0.0 ~ 0.3 mg/dl

***Direct type bilirubin actually does not exist in the serum**, however, a small portion of indirect reacting bilirubin may presents direct reaction, thus the result of direct bilirubin may show the maximum value of 0.3 mg/dl, but never above. It is about 20 ~ 30 % of the total bilirubin concentration.*

In some liver diseases, the total bilirubin will be within 1.2 mg/dl, but when the direct bilirubin concentration is above 0.3 mg/dl, the existence of liver disease should be considered.

***Starvation, pregnancy, pill intake, post-operation, hemolysis, alcohol intake, and steroid administation** will show the increase in bilirubin level.*

*Administration of **sulfa drug, and phenobarbital** will decrease the level of serum bilirubin concentration.*

Various conditions of jaundice result from the accumulation of bilirubin in the blood. A jaundice condition is characterized by yellow colored skin due to the presence of bilirubin.

Bilirubin is potentially toxic waste product. Persons with extremeelevation in unconjugated bilirubin are susceptible to bilirubin encephalopathy, also referred to as kernicterus.

Jaundice is not itself a disease, but it is a sign of several disorders that affect the liver, the blood, the gallbladder, or bile.

Types of Jaundice:

1. **Hemolytic Jaundice**
2. **Hepatic Jaundice**
3. **Biliary Obstruction**
4. **Physiologic jaundice of the newborn**

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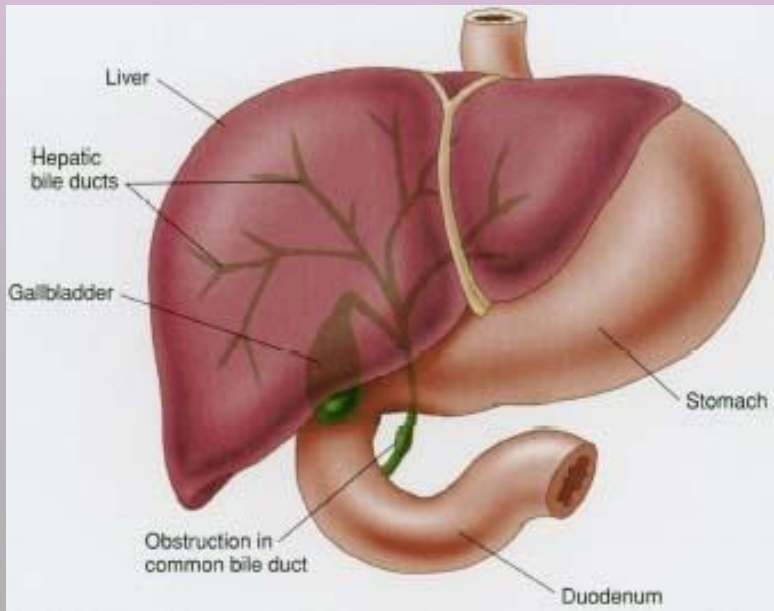
Hemolytic Jaundice: *Excessive hemolysis or breakdown of erythrocytes causes the formation of higher than normal amounts of bilirubin. The liver works normally, but could eventually be damaged from overwork. Usually the liver can handle the excess and the bilirubin is excreted via intestines and does not usually spill over into the kidneys. Urobilinogen levels are likely to be elevated in the blood and urine.*

Hepatic Jaundice: *Hepatic jaundice is caused by damage or disease in the liver. Heme enters the liver but it does not take out as much bilirubin as is normal.*

Bilirubin builds up in the blood and spills over into the kidneys which filter it out into the urine. The amount of urobilinogen in the urine will be either normal or low if not enough bilirubin is being removed by the liver into bile and the intestines.



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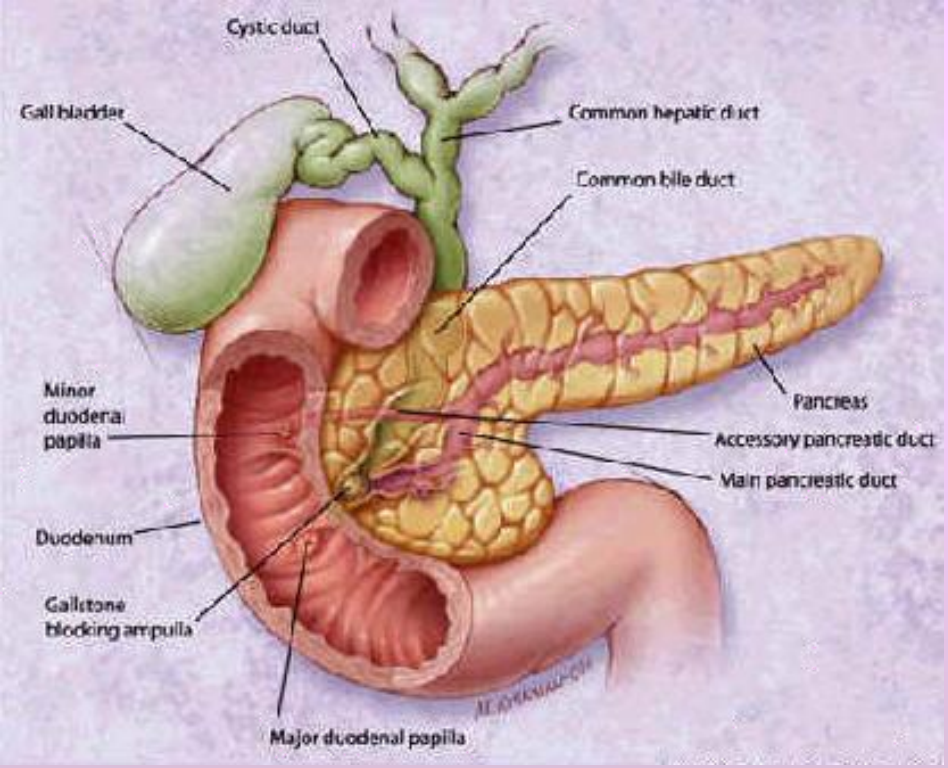

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Biliary Obstruction: *If bilirubin cannot reach the intestinal area because of a blockage in the bile duct, than bilirubin builds up in the blood because it cannot get out of the liver. Bilirubin is then removed by the kidneys into the urine. Little if any, urobilinogen will be found in the urine since little or no bilirubin is reaching the intestines.*

Physiologic Jaundice of the Newborn: *sometimes occurs when newborn babies have too much bilirubin in the blood. This form of jaundice usually disappears within a few days as the infant's liver matures in its ability to handle bilirubin.*

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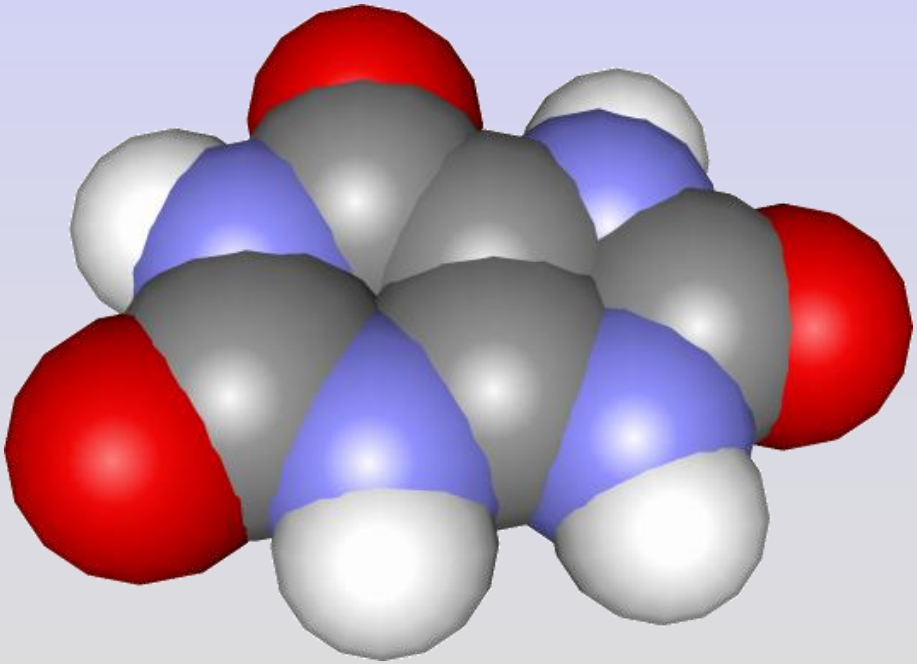
NUCLEOTIDE METABOLISM



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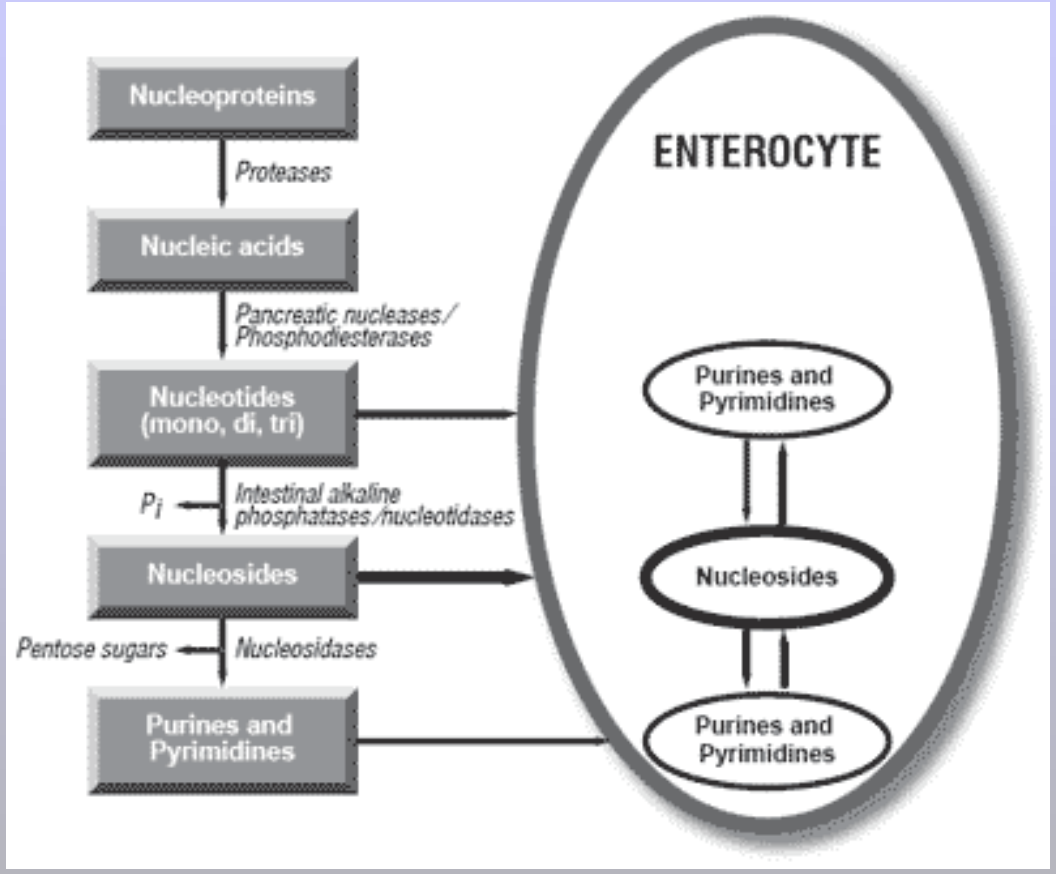
Nucleoprotein Digestion

Stomach: under the action of HCl, nucleic acids dissociate from proteins;

Proteins are hydrolyzed by pepsine;

Duodenum: pancreatic DNAase, RNAase hydrolyzed molecules to oligonucleotides and some mononucleotides;

Phosphatases (acidic and basic) hydrolyzed fragments to mononucleotides, which are absorbed

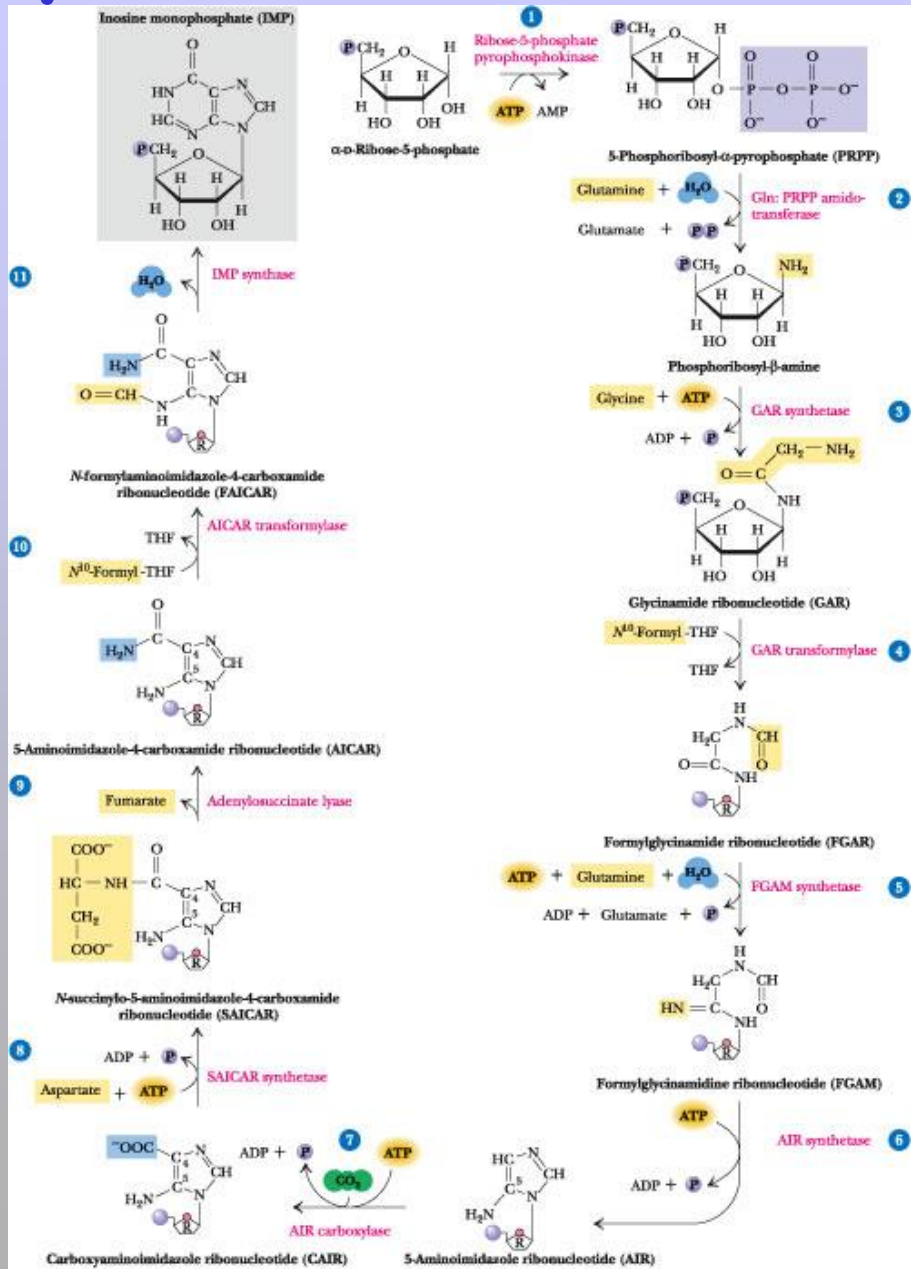


FOOD NUCLEOTIDES PRACTICALLY NOT INCLUDED IN NUCLEIC ACIDS

https://en.engormix.com/pig-industry/articles/digestion-absorbtion-of-dietary-nucleoprotein-t33582.htm

Nucleotide Biosynthesis

Nearly all organisms can make the purine and pyrimidine nucleotides via de novo biosynthetic pathways. Many organisms also have salvage pathways to recover purine and pyrimidine compounds obtained in the diet or released during nucleic acid turnover and degradation. Many antibiotics and anticancer drugs are inhibitors of purine or pyrimidine nucleotide biosynthesis.



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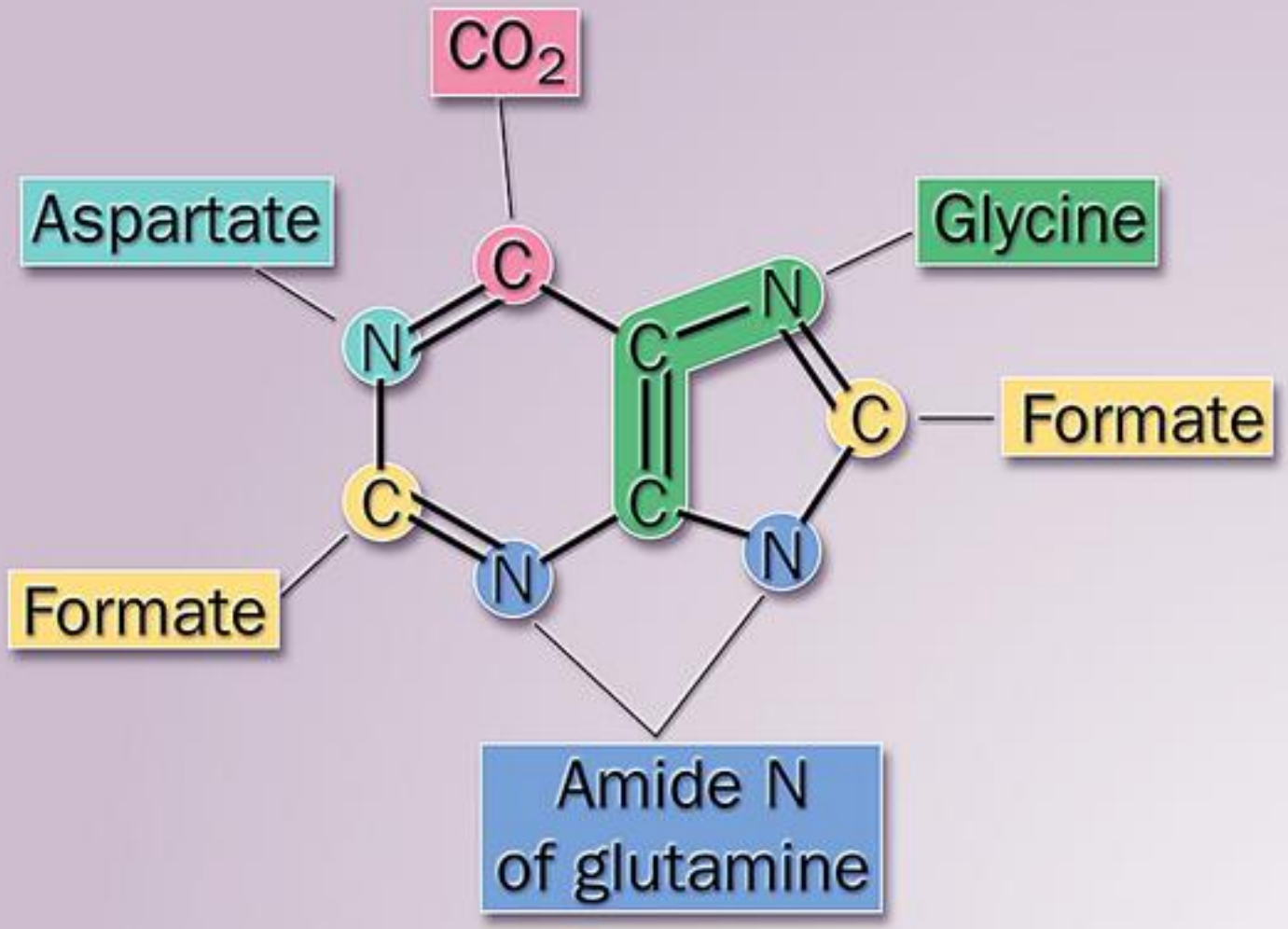
Origin of purine ring atoms



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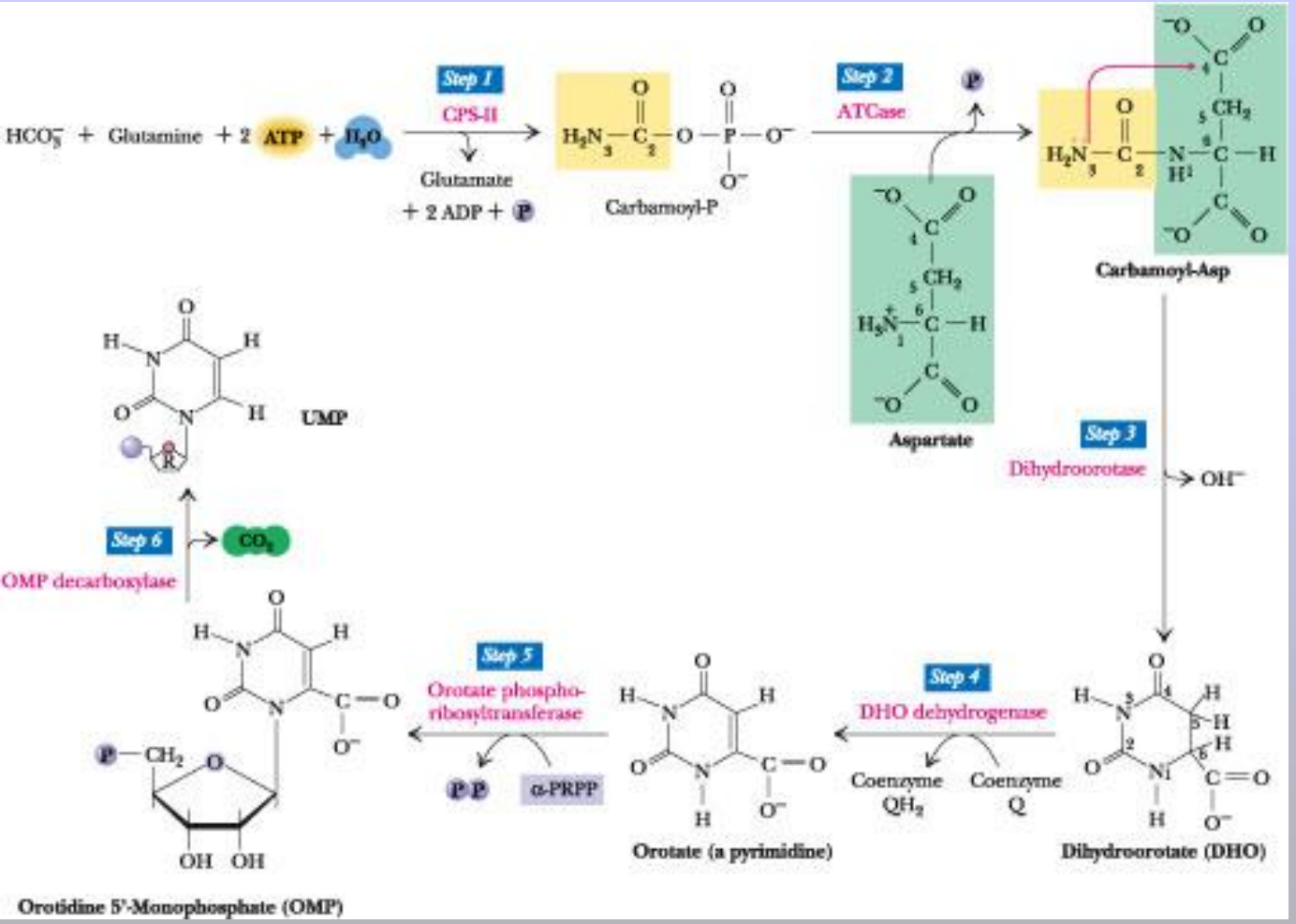
The Biosynthesis of Pyrimidines



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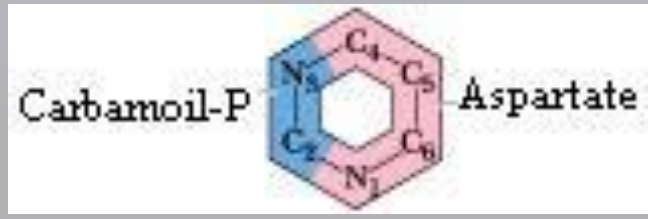
The metabolic origin of the six atoms of the pyrimidine ring.



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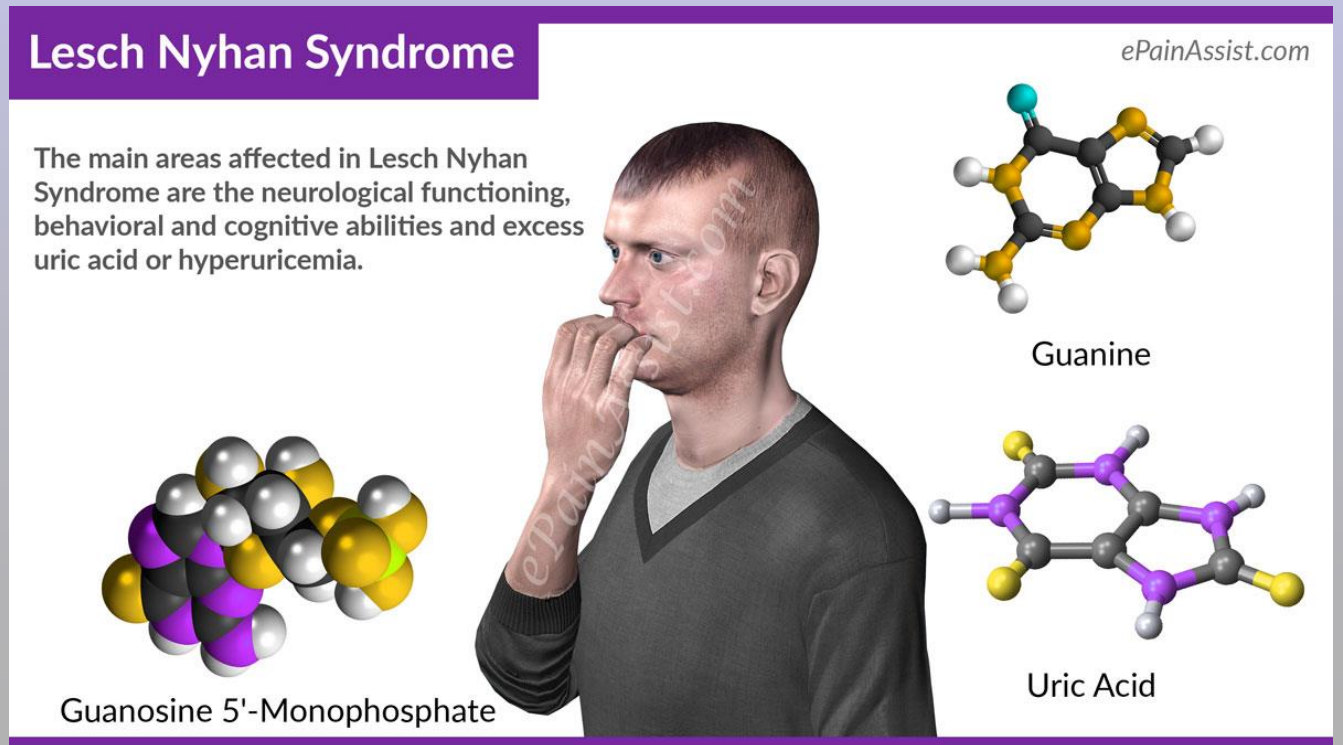
Lesch-Nyhan syndrome

The genetic lack of hypoxanthine-guanine phosphoribosyltransferase activity, seen almost exclusively in male children, results in a bizarre set of symptoms, called Lesch-Nyhan syndrome. Children with this genetic disorder, which becomes manifest by the age of 2 years, are mentally retarded and badly coordinated. In addition, they are extremely hostile and show compulsive self destructive tendencies: they mutilate themselves by biting off their fingers, toes, and lips.

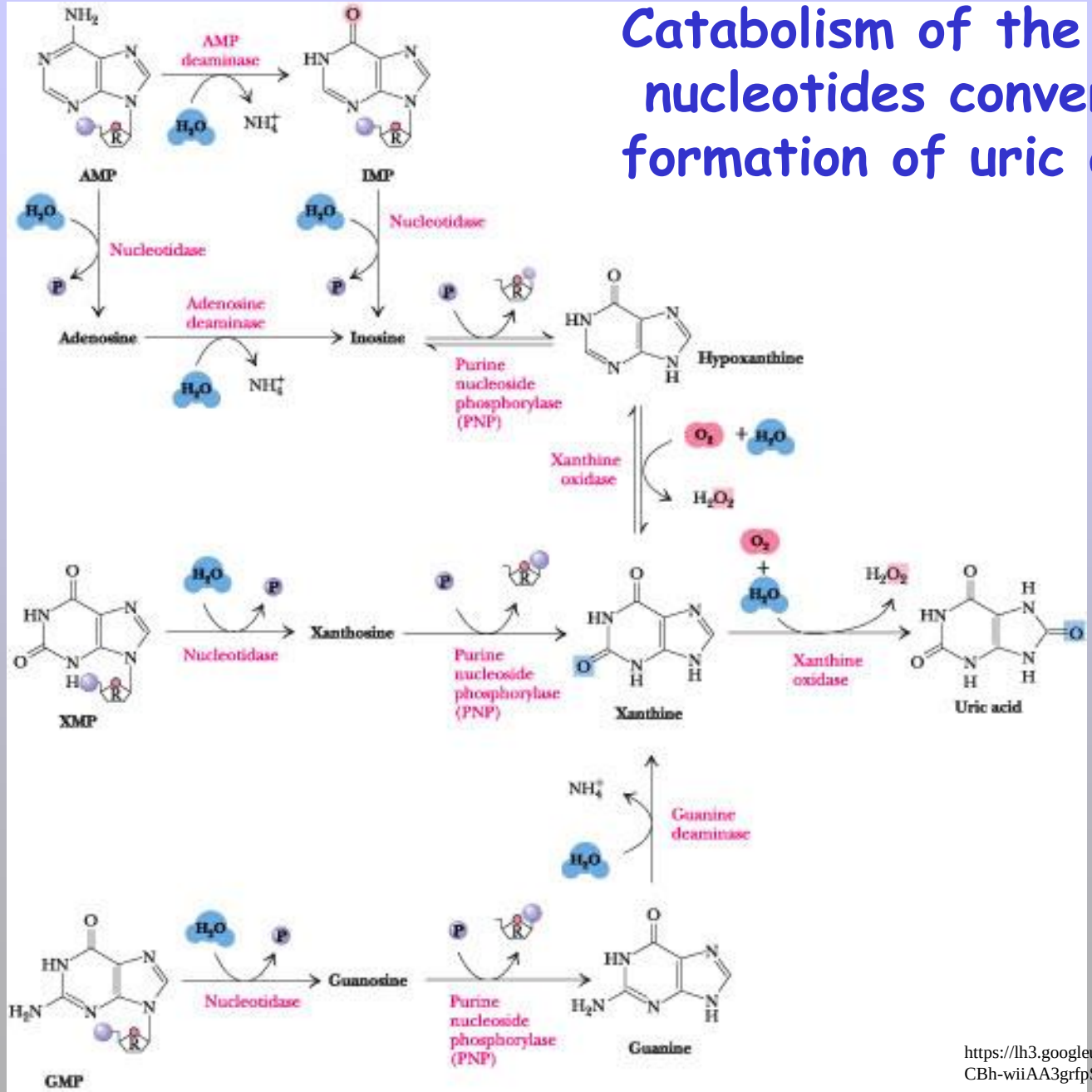
Lesch-Nyhan syndrome illustrates the importance of the salvage pathways. The brain is especially dependent on the salvage pathways, and this may account for the central nervous system damage that occurs in children with LeschNyhan syndrome.



https://www.epainassist.com/metabolic-disorders/lesch-nyhan-syndrome

The major pathways for purine catabolism in animals.

Catabolism of the different purine nucleotides converges in the formation of uric acid.



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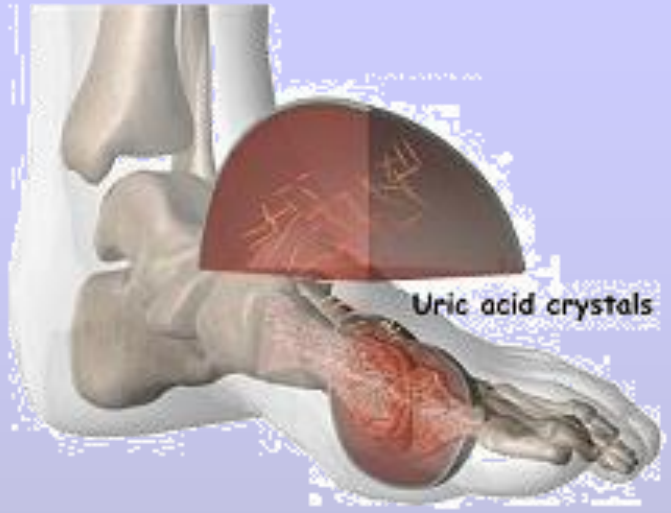
GOUT

Uric acid and urate salts are rather insoluble in water and tend to precipitate from solution if produced in excess. The most common symptom of gout is arthritic pain in the joints as a result of urate deposition in cartilaginous tissue. Urate crystals may also appear as kidney stones and lead to painful obstruction of the urinary tract.



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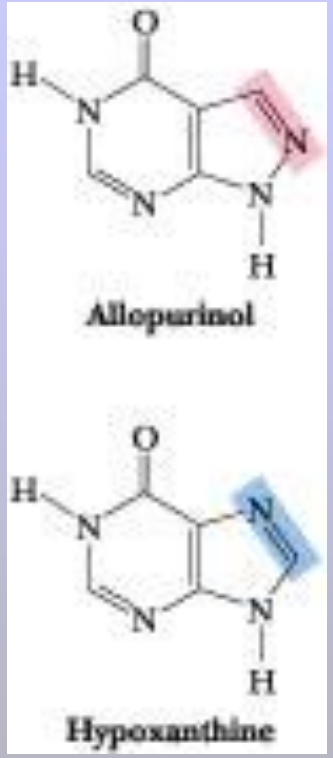
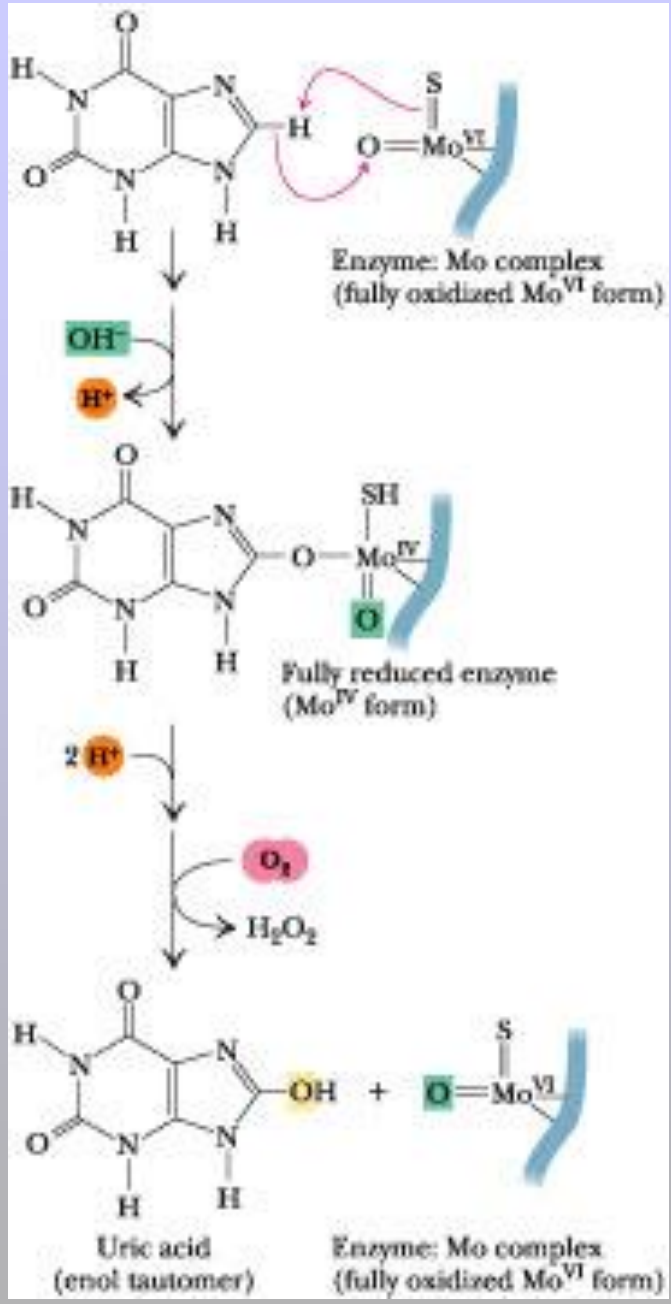
Hyperuricemia, chronic elevation of blood uric acid levels, occurs in about 3% of the population as a consequence of impaired excretion of uric acid or overproduction of purines. Purine-rich foods (such as caviar—fish eggs rich in nucleic acids) may exacerbate the condition.

The joint of the big toe is particularly susceptible.

A common treatment is allopurinol. This hypoxanthine analog binds tightly to xanthine oxidase, thereby inhibiting its activity and preventing uric acid formation. Hypoxanthine and xanthine do not accumulate to harmful concentrations because they are more soluble and thus more easily excreted.





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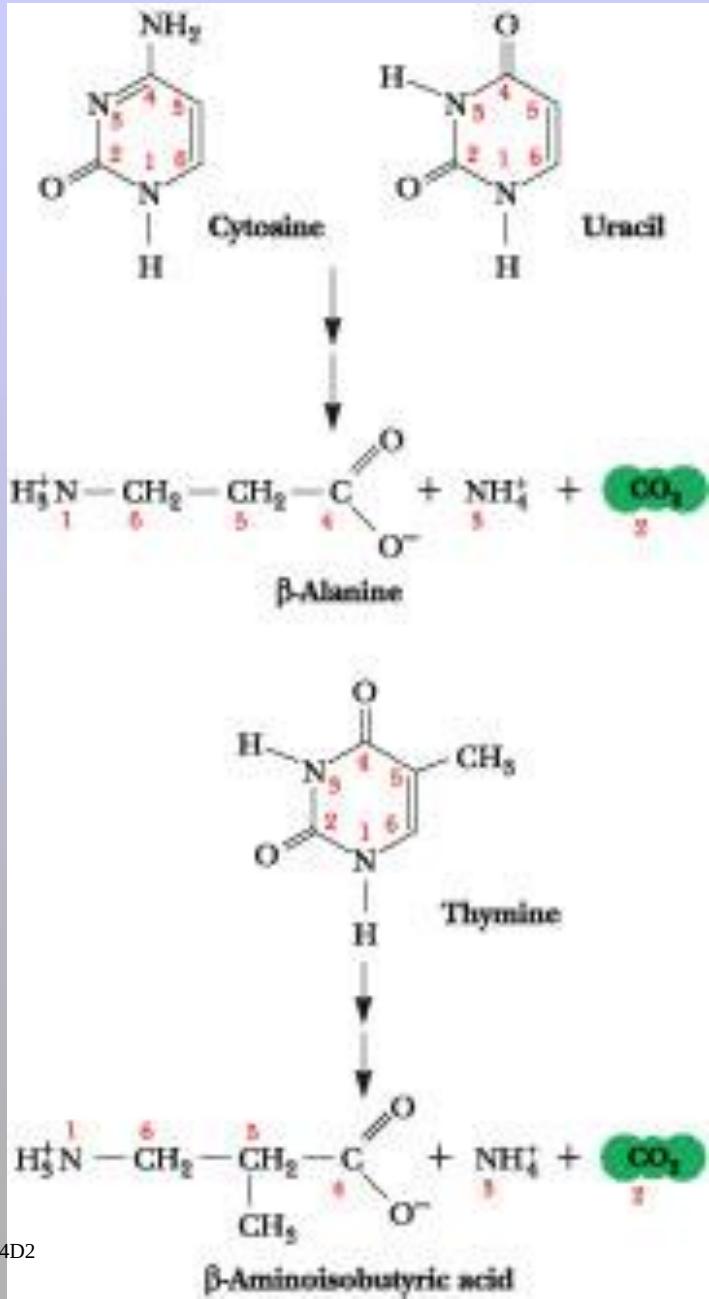
Pyrimidine Degradation

Pyrimidine catabolism results in degradation of the pyrimidine ring to products reminiscent of the original substrates, aspartate, CO_2, and ammonia. β - Alanine can be recycled into the synthesis of coenzyme A. Catabolism of the pyrimidine base, thymine (5-methyluracil) yields β - amino-isobutyric acid instead of β - alanine.



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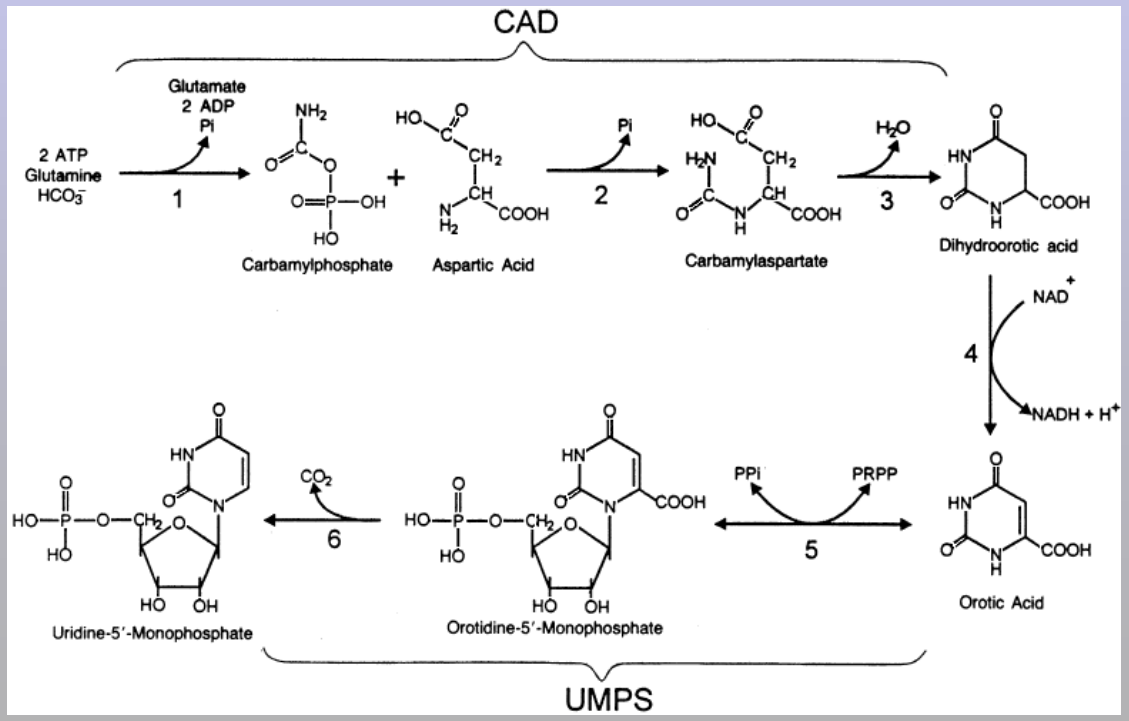
Pyrimidine Metabolism Disorders

Because the products of pyrimidine catabolism are soluble, few disorders result from excess levels of their synthesis or catabolism. Two inherited disorders affecting pyrimidine biosynthesis are the result of deficiencies in the bifunctional enzyme catalyzing the last two steps of UMP synthesis, orotate phosphoribosyl transferase and OMP decarboxylase. These deficiencies result in orotic aciduria that causes retarded growth, and severe anemia caused by hypochromic erythrocytes and megaloblastic bone marrow. Leukopenia is also common in orotic acidurias.

The disorders can be treated with uridine and/or cytidine, which leads to increased UMP production via the action of nucleoside kinases. The UMP then inhibits CPS-II, thus attenuating orotic acid production.

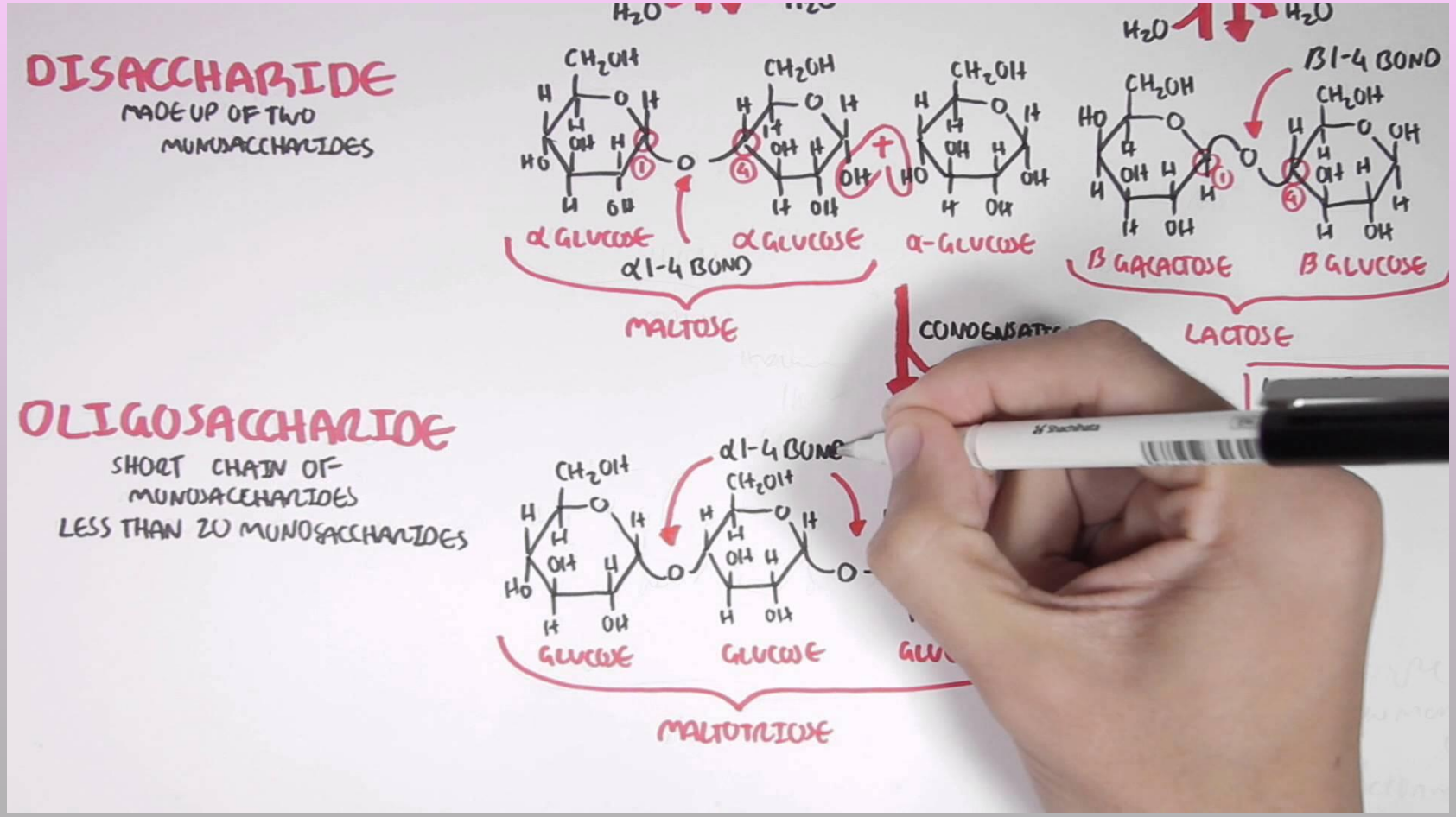


Conclusions

1. Iron serves numerous important functions in the body.
2. Heme is synthesized from glycine and succinyl-CoA. The heme biosynthetic pathway is especially prominent in the liver and bone marrow.
3. Bilirubin is the end product of heme metabolism.
4. Jaundice is clinically described as yellow color seen in hyperbilirubinemia and is due to deposits of bilirubin in the skin and conjunctiva.
5. Dietary nucleoproteins are degradated by pancreatic enzymes and tissue nucleoprotein by lysosomal enzymes.

Do you have any questions?

Thank you for your attention!



https://www.youtube.com/watch?v=JxK5rZxbyQY