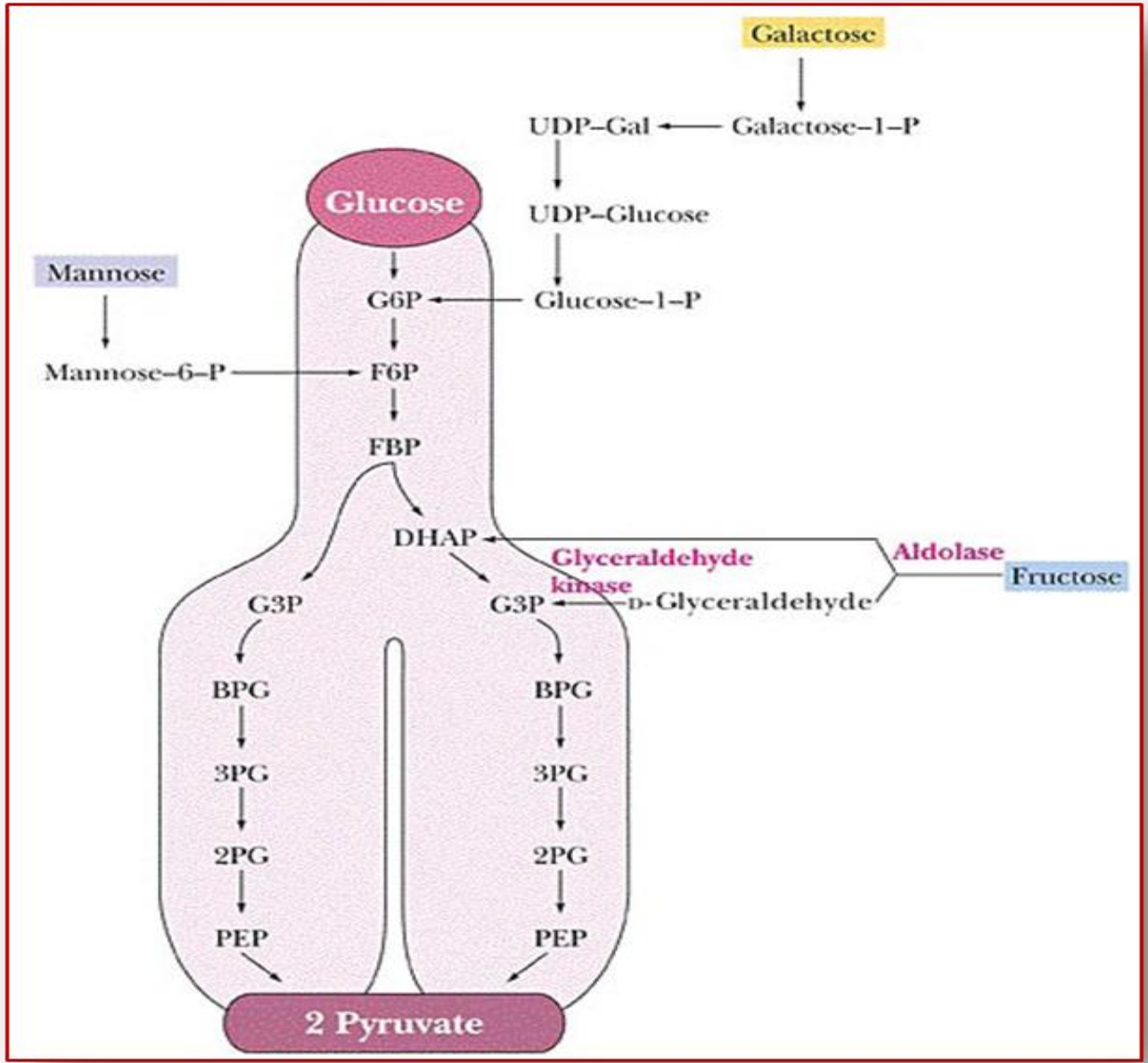
Fructose and Galactose Metabolism

Glucose is the most common monosaccharide consumed by humans.

Two other monosaccharaides—fructose and galactose—occur in significant amounts in the diet, and make important contributions to energy metabolism.

The metabolism of fructose and galactose are part of the essential pathways of energy metabolism in the body.


Galactose
UDP–Gal
Galactose–1–P
Glucose
UDP–Glucose
Mannose
G6P
Glucose–1–P
Mannose–6–P
F6P
FBP
DHAP
Aldolase
Fructose
Glyceraldehyde kinase
G3P
D-Glyceraldehyde
G3P
BPG
BPG
3PG
3PG
2PG
2PG
PEP
PEP
2 Pyruvate

FRUCTOSE METABOLISM

The major source of fructose is the disaccharide sucrose, which, when cleaved in the intestine, releases equimolar amounts of fructose and glucose.

Fructose is also found as a free monosaccharide in many fruits, in honey, and in high-fructose corn syrup (55% fructose/45% glucose typically), which is used to sweeten soft drinks and many foods.

Entry of fructose into cells is not insulin dependent, and, in contrast to glucose, fructose does not promote the secretion of insulin.

Phosphorylation of fructose

For fructose to enter the pathways of intermediary metabolism, it must first be phosphorylated. This can be accomplished by either hexokinase or fructokinase.

Hexokinase phosphorylates glucose in most cells of the body.

Fructokinase provides the primary mechanism for fructose phosphorylation . It is found in the liver, kidney, and the small intestinal, has a high affinity for fructose than hexokinase giving fructose-1-phosphate.

Fructose metabolism- Liver

In liver, dietary fructose is converted to Fructose-1-P by **fructokinase** (also in kidney and intestine).

Then, by the action of Fructose-1-P **aldolase** (aldolase B), Fructose-1-P is converted to DHAP and glyceraldehyde.

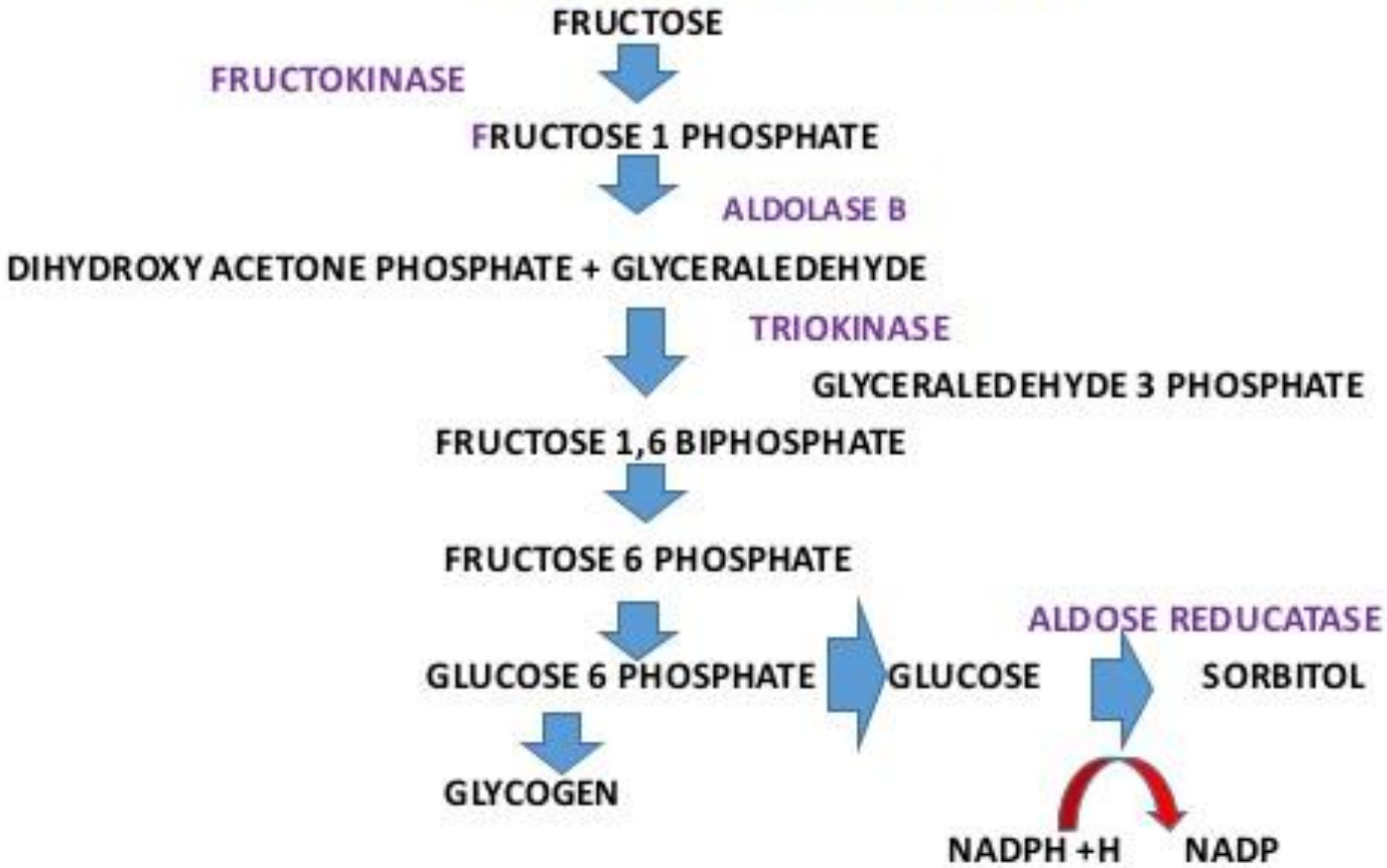
Glyceraldehyde is converted to glyceraldehyde-3-P by **triose kinase**

Fructose metabolism- Muscle

Muscle which contains only **hexokinase** can phosphorylate fructose to F6P which is a direct glycolytic intermediate

However, **hexokinase** has a very low affinity to fructose compared to glucose, So it is not a significant pathway for fructose metabolism. Unless it is present in very high concentration in blood.

FRUCTOSE METABOLISM



Galactose Metabolism

- This sugar is present in milk containing diets and it is slowly transformed into glucose in liver.
- It is synthesized from glucose in large quantities in actively lactating mammary gland and the blood and urine of lactating women may contain this sugar together with lactose.
- **Biochemical importance of galactose:**
- It enters in the formation of lactose.
- It enters in the formation of glycolipids.
- It enters in the formation of glycoproteins and proteoglycans

✓The major source of galactose is lactose (a disaccharide of glucose and galactose) obtained from milk and milk products.

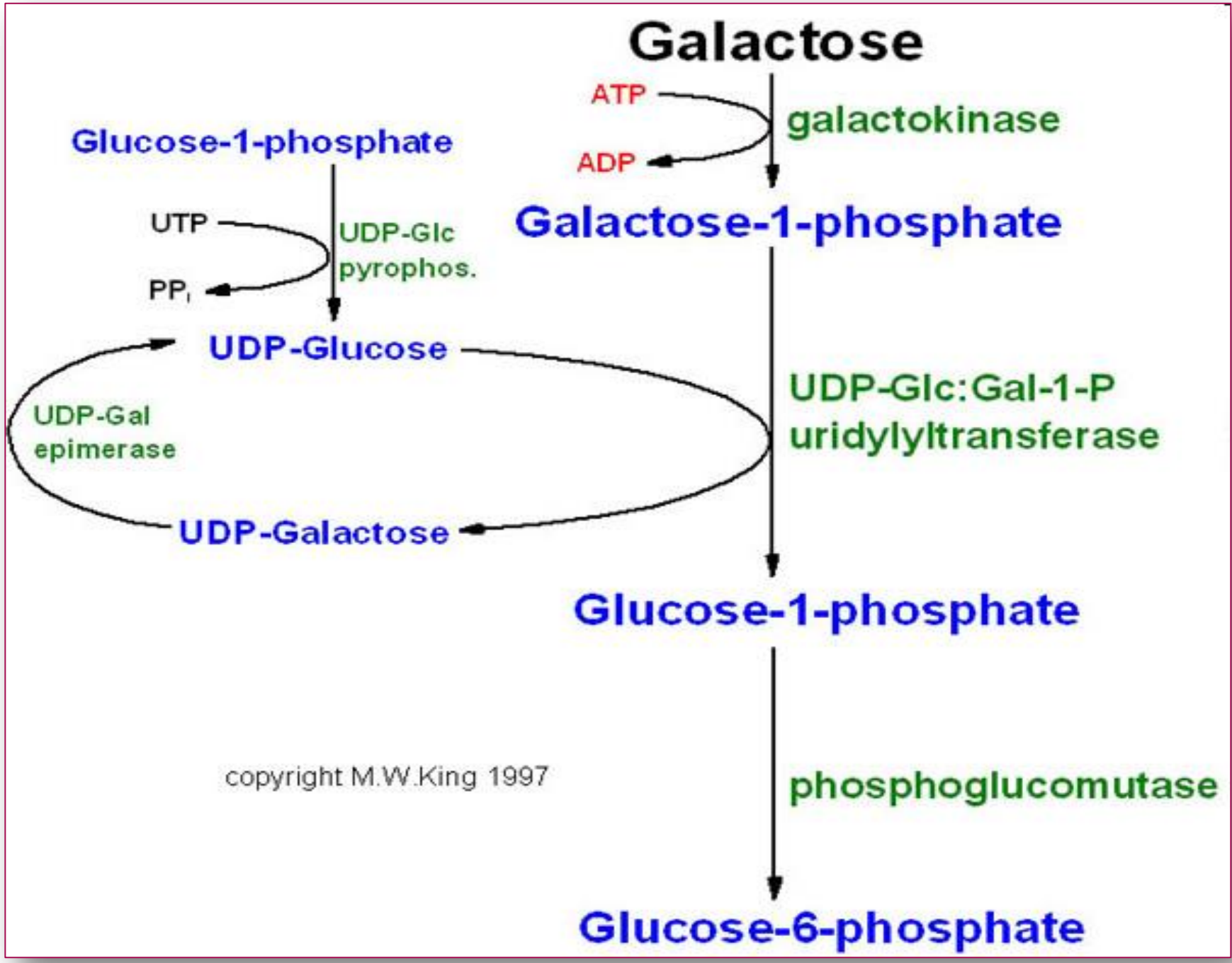
✓Galactose enters glycolysis by its conversion to glucose-1-phosphate (G1P). This occurs through a series of steps.

✓**Site:** liver

First the galactose is phosphorylated by **galactokinase** to yield galactose-1-p.

Epimerization of galactose-1-phosphate to G-1-P requires the transfer of UDP from uridine diphosphoglucose (UDP-glucose) catalyzed by galactose-1-phosphate uridyl transferase.

This generates UDP-galactose and G-1-P.


Galactose
ATP
ADP
galactokinase
Glucose-1-phosphate
Galactose-1-phosphate
UTP
PPi
UDP-Glc
pyrophos.
UDP-Glucose
UDP-Gal
epimerase
UDP-Glc:Gal-1-P
uridylyltransferase
UDP-Galactose
Glucose-1-phosphate
copyright M.W.King 1997
phosphoglucomutase
Glucose-6-phosphate

Answer true (T) and false (F) for the fowling:

1. Galactose is most common monosaccharide consumed by human.
2. TCA cycle occurs totally in mitochondria.
3. The major source of Galactose is lactose obtained from milk.
4. The metabolism of fructose and Galactose are part of the essential pathways of energy.

Disorders of Fructose Metabolism

Fructose is an important source of dietary carbohydrates.

The liver, kidney, and small intestine are the main sites of fructose metabolism, but adipose tissue also participates.

Fructose, given intravenously in high doses, is clearly toxic and causes hyperuricemia, hyperlactatemia, and ultrastructural alterations in liver and intestinal cells.

Essential fructosuria, an autosomal-recessive disorder, is a benign, asymptomatic metabolic anomaly caused by the absence of fructokinase.

Alimentary hyperfructosemia and fructosuria are the principal signs. Despite the interruption of the specific fructose pathway, up to nine tenths of the administered fructose is retained by fructokinase-deficient subjects.

Hereditary fructose intolerance, an autosomal-recessive disorder, is characterized by severe hypoglycemia and vomiting shortly after the intake of fructose.

Prolonged fructose ingestion in infants leads to poor feeding, vomiting, hepatomegaly, jaundice, hemorrhage, proximal renal tubular syndrome, and finally, hepatic failure and death. Patients develop a strong distaste for noxious food.

Patients remain healthy on a fructose- and sucrose-free diet. The severity of the disease phenotype appears to be independent of the nature of the aldolase B gene mutations so far identified.

Hereditary **fructose 1,6-bisphosphatase** deficiency, an autosomal-recessive disorder, is characterized by episodic spells of hyperventilation, apnea, hypoglycemia, ketosis, and lactic acidosis, with a precipitous and often lethal course in the newborn infant.

In conclusion

1. **Essential fructosuria**

Cause: due to deficiency of **fructokinase** enzyme
Effect: not serious condition. The excess accumulated fructose is lost in urine

2. **Fructose 1,6 biphosphatase deficiency**
   It leads to accumulation of fructose 1,6 biphosphate which inhibits phosphorylase enzyme (glycogenolysis) and fasting hypoglycemia

3. Hereditary fructose intolerance

Cause: due to deficiency of **aldolase B**. This leads to accumulation of fructose-1-P

Effect: the accumulation of fructose-1-P leads to :

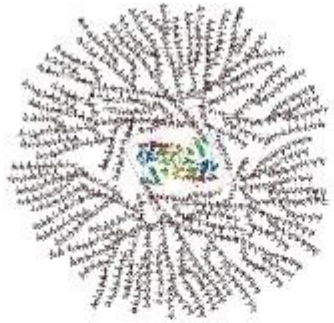
- ✓Damage of liver and kidney tissues.
- ✓Inhibition of glycogen phosphorylase leading to inhibition of
- ✓glycogenolysis and fasting hypoglycemia

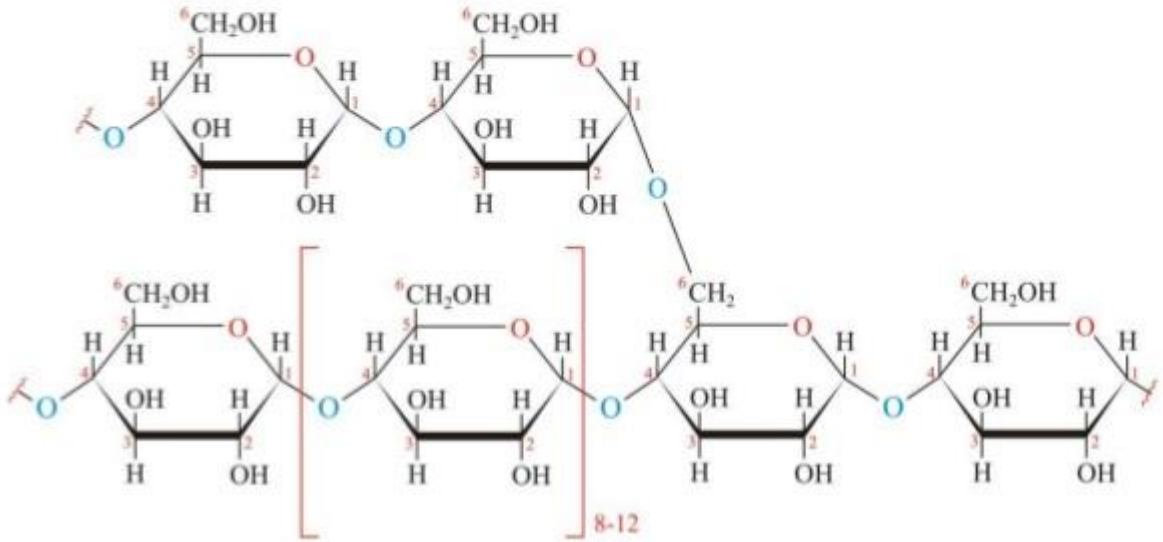
Glycogen Metabolism

Glycogen Metabolism

Glycogen is a readily mobilized storage form of glucose. It is a very large, branched polymer of glucose residues that can be broken down to yield glucose molecules when energy is needed.

Most of the glucose residues in glycogen are linked by α-1,4-glycosidic bonds. Branches at about every tenth residue are created by α22-1,6-glycosidic bonds.




8-12

Glycogen is an important fuel reserve for several reasons. The controlled breakdown of glycogen and release of glucose increase the amount of glucose that is available between meals. Hence, glycogen serves as a buffer to maintain blood-glucose levels.

Glycogen's role in maintaining blood-glucose levels is especially important because glucose is virtually the only fuel used by the brain, except during prolonged starvation. Moreover, the glucose from glycogen is readily mobilized and is therefore a good source of energy for sudden, strenuous activity.

Unlike fatty acids, the released glucose can provide energy in the absence of oxygen and can thus supply energy for anaerobic activity.

The two major sites of glycogen storage are the **liver** and **skeletal muscle.**

The concentration of glycogen is higher in the liver than in muscle (10% versus 2% by weight).

Glycogen is present in the cytosol in the form of granules ranging in diameter from 10 to 40 nm. In the liver, glycogen synthesis and degradation are regulated to maintain blood-glucose levels as required to meet the needs of the organism as a whole.

In contrast, in muscle, these processes are regulated to meet the energy needs of the muscle itself.

Glycogen Metabolism

Glycogen degradation and synthesis are relatively simple biochemical processes.
Glycogen degradation consists of three steps: (1) the release of glucose 1-phosphate from glycogen, (2) the remodeling of the glycogen substrate to permit further degradation, and (3) the conversion of glucose 1-phosphate into glucose 6-phosphate for further metabolism.

The glucose 6-phosphate derived from the breakdown of glycogen has three fates: (1) It is the initial substrate for glycolysis, (2) it can be processed by the pentose phosphate pathway to yield NADPH and ribose derivatives; and (3) it can be converted into free glucose for release into the bloodstream. This conversion takes place mainly in the liver and to a lesser extent in the intestines and kidneys.

Glycogen synthesis requires an activated form of glucose, uridine diphosphate glucose (UDP-glucose).
UDP-glucose is added to the nonreducing end of glycogen molecules.
As is the case for glycogen degradation, the glycogen molecule must be remodeled for continued synthesis.

- Initially glucose is phosphorylated to glucose 6-phosphate. This reaction is catalyzed by hexokinase (muscle) or glucokinase (liver).

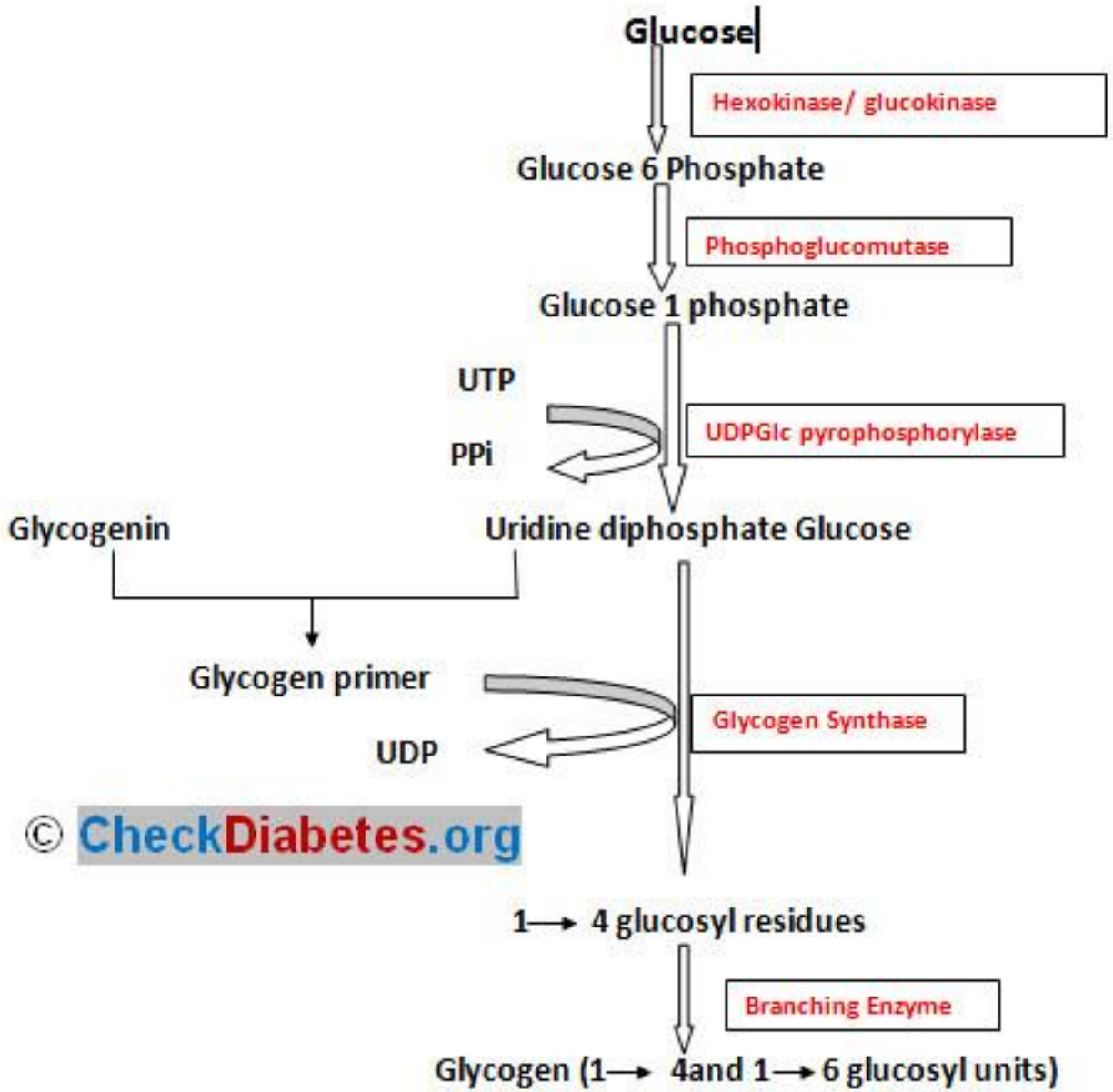
- Phosphoglucomutase catalyse the isomerisation of Glucose 6-phosphate to glucose 1-phosphate.

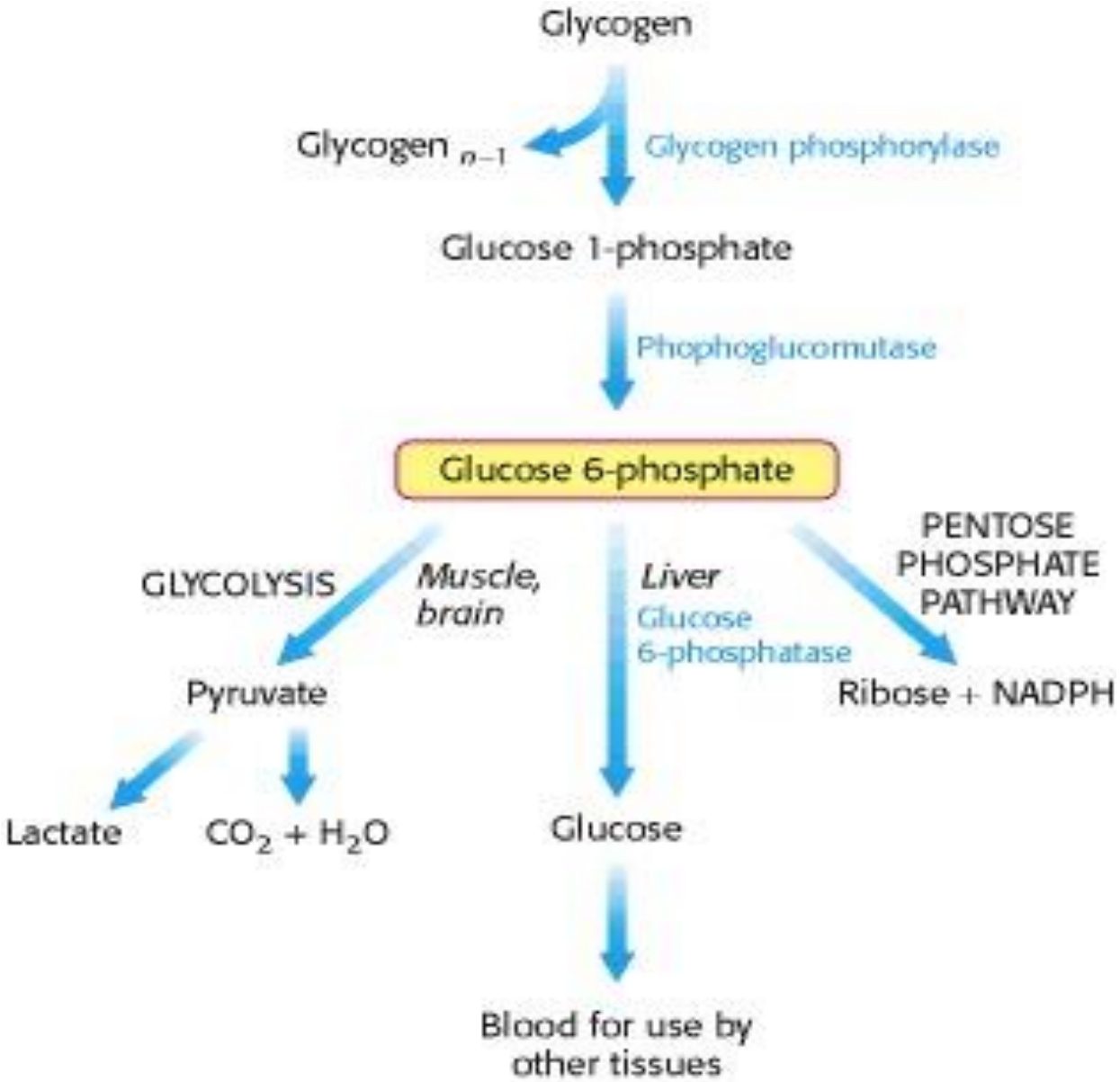
- Now UDP-glucose pyrophosphorylase catalyse the formation of UDP -glucose from UTP and glucose 1-phosphate.

Glycogen synthase transfers the glucosyl residue from UDP-glucose to the non reducing terminal residues of glycogen. It is transferred to hydroxyl terminal of C4 end of glycogen to form an α-1–4 glycosidic bond.

- Glycogen synthase catalyzes only α- 1–4 glycosidic bonds. It results in to the formation of α- amylose. Branching is catalysed by separate enzyme called Branching enzyme. It is also known as amylo-(1–4→1–6) transglycosylase.

Glycogenesis steps




Glycogen
Glycogen $_{n-1}$
Glycogen phosphorylase
Glucose 1-phosphate
Phophoglucomutase
Glucose 6-phosphate
GLYCOLYSIS
Muscle, brain
Liver
Glucose 6-phosphatase
PENTOSE PHOSPHATE PATHWAY
Pyruvate
Ribose + NADPH
Lactate
$CO_2 + H_2O$
Glucose
Blood for use by other tissues

The regulation of these processes is quite complex. Several enzymes taking part in glycogen metabolism allosterically respond to metabolites that signal the energy needs of the cell.

These allosteric responses allow the adjustment of enzyme activity to meet the needs of the cell in which the enzymes are expressed.

Glycogen metabolism is also regulated by hormonally stimulated cascades that lead to the reversible phosphorylation of enzymes, which alters their kinetic properties.

Regulation by hormones allows glycogen metabolism to adjust to the needs of the entire organism. By both these mechanisms, glycogen degradation is integrated with glycogen synthesis.

Mechanism of regulation

- Covalent modification of Glycogen synthase
- Allosteric control of Glycogen synthase
- Hormonal control: Inhibition of glycogen synthesis by adrenaline and glucagon
- Hormonal control : stimulation of glycogen synthesis by insulin

Glycogen synthase enzyme exists in two forms. They are **Glycogen synthase a** and **Glycogen synthase b**. G **Covalent modification of Glycogen synthase**

 Glycogen synthase a is an active form of an enzyme while Glycogen synthase b is normally inactive form of an enzyme. **Glycogen synthase b** is converted in to **Glycogen synthase a** by the process of dephosphorylation. It is catalysed by **Protein phosphatase**.

 Active Glycogen synthase, i.e. dephosphorylated glycogen synthase, is converted back in to inactive phosphorylated glycogen synthase by the process of phosphorylation. It is catalyzed by enzyme **Protein kinase A**.

Allosteric control of Glycogen synthase

 High concentration of Glucose 6-phosphate activates glycogen synthase b. Glucose-6-phosphate concentration is low during muscle contraction. Therefore activity of glycogen synthase b is inhibited. During muscular contraction phosphorylase b is more active (refer glycogen breakdown). Therefore during muscular exercise glycogen degradation promoted while glycogen synthesis is inhibited. This is important for preventing futile cycle.

 ATP and glucose 6-phosphate concentration is high during resting stage. This condition inhibits activity of phosphorylase b (refer glycogen breakdown) whereas glycogen synthase is activated to restore the glycogen.

 Glucose-6-phosphate does not affect Glycogen synthase a. Therefore Glycogen synthase a form is active and does not affected by the concentration of glucose 6-phosphate.

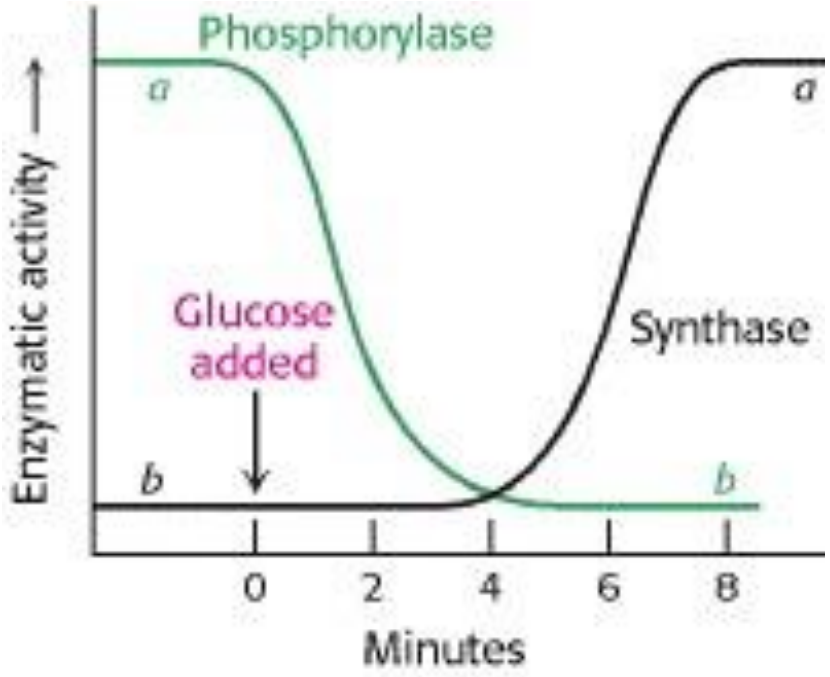
Hormonal control: Adrenalin inhibits the glycogen synthesis

 Glycogenesis and glycogenolysis is regulated by hormones. When level of blood glucose fall, α cells of pancreases secretes the glucagon. Glucagon stimulates glycogenolysis inside the liver. Glycogenolysis releases glucose into the bloodstream to improve blood glucose levels again. ‘Flight or fight’ response stimulates the adrenal medulla to releases adrenaline (epinephrine).

 Adrenaline binds to the β-adrenergic receptor on the plasma membrane of the target cell. It causes a conformational change in the protein. It activates a G-protein, which in turn activates the adenylate cyclase enzyme. Activated adenylate cyclase converts ATP to 3’5’ cyclic AMP (cAMP).

Cyclic AMP acts as a second messenger. The cAMP binds to cAMP-dependent protein kinase (PKA).The active protein kinase A phosphorylates phosphorylase kinase. Phosphorylated phosphorylase kinase is active form of phosphorylase kinase. It phosphorylates serine residue in phosphorylase b, which converts it into phosphorylase a, that is a more active form. This promotes the glycogenolysis

 Active Glycogen synthase, i.e. dephosphorylated glycogen synthase, is converted back in to inactive phosphorylated glycogen synthase by the process of phosphorylation. It is catalyzed by enzyme **Protein kinase A**.



Blood Glucose Regulates Liver Glycogen Metabolism

The infusion of glucose into the bloodstream leads to the inactivation of **phosphorylase**, followed by the activation of glycogen synthase, in the liver

TABLE 21.1 Glycogen-storage diseases

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe disease	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori disease	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen disease	Branching enzyme (α-1,4 ⟶ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle disease	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers disease	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.

NUCLEOTIDE METABOLISM

Prof Dr. Radhi Al-Rashidi
Kut University College

NUCLEOTIDE METABOLISM

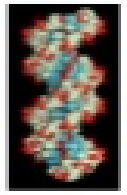
Disorder of Purines and Pyrimidines Metabolism

Uric acid synthesis & Hyperuricemia

Purines (adenine and guanine) and pyrimidines (cytosine, thymine, uracil) serve fundamental roles in the replication of genetic material, gene transcription, protein synthesis, and cellular metabolism.

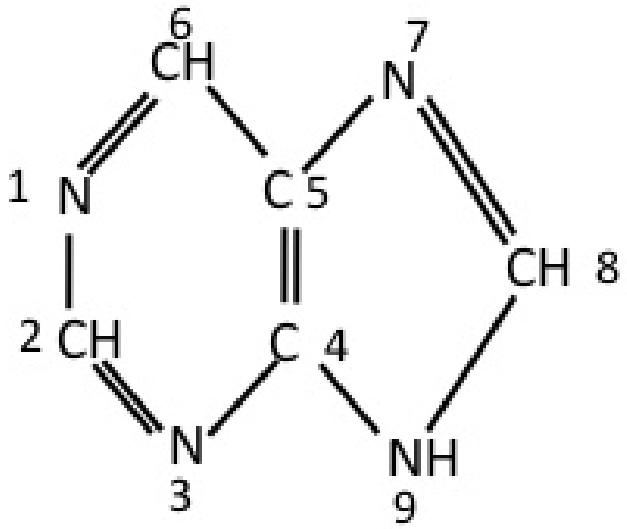
Disorders that involve abnormalities of nucleotide metabolism range from relatively common diseases such as hyperuricemia and gout, in which there is increased production or impaired excretion of a metabolic end product of purine metabolism (uric acid), to rare enzyme deficiencies that affect purine and pyrimidine synthesis or degradation.

Understanding these biochemical pathways has led, in some instances, to the development of specific forms of treatment, such as the use of allopurinol, to reduce uric acid production.

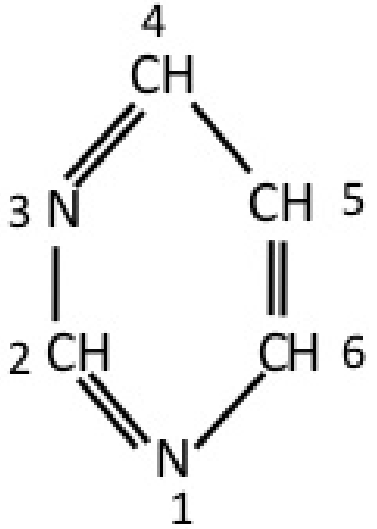


Bases present in nucleic acids

- Nitrogen-containing heterocyclic compounds
- Purines and pyrimidines

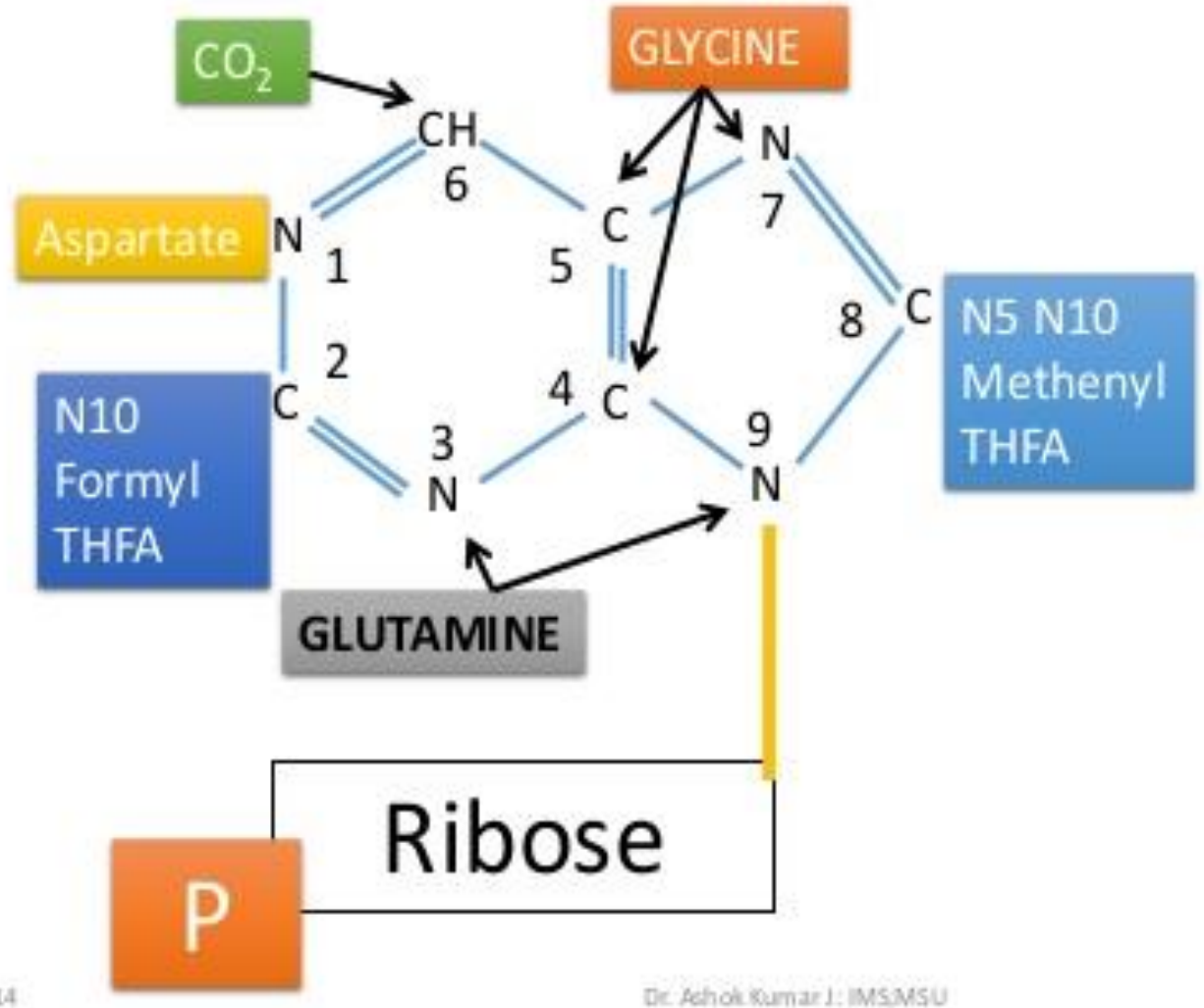


Purine

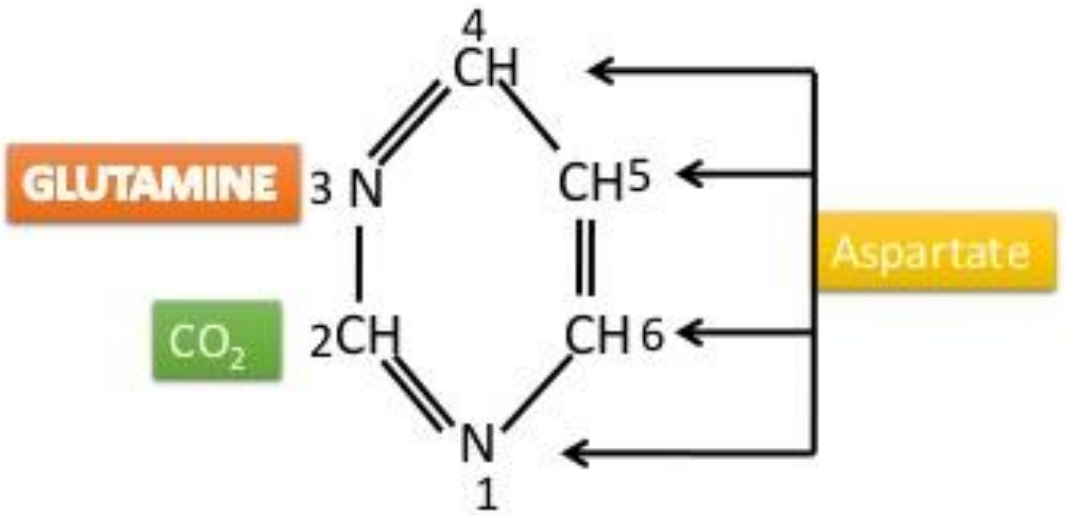


Pyrimidine

Synthesis of Purine nucleotide



Pyrimidine Biosynthesis



Pyrimidine

Purine Metabolism

Purine nucleotides are essential cellular constituents which intervene in **energy transfer**, **metabolic regulation**, and **synthesis of DNA and RNA**. Purine metabolism can be divided into three pathways:

1. The biosynthetic pathway, often termed *de novo*, starts with the formation of phosphoribosyl pyrophosphate (PRPP).
2. The catabolic pathway produces uric acid, a poorly soluble compound, which tends to crystallize once its plasma concentration surpasses 6.5–7 mg/dl (0.38–0.47 mmol/l).

3. Phosphorylation of purine

Uric acid is the final breakdown product of purine degradation in humans. It is a weak acid with. Urates, the ionized forms of uric acid, predominate in plasma extracellular fluid, with ˜98% existing as monosodium urate at pH 7.4.

Plasma is saturated with monosodium urate at a concentration of 405 μmol/L (6.8 mg/dL) at 37°C. At higher concentrations, plasma is therefore supersaturated, creating the potential for urate crystal precipitation. However, plasma urate concentrations can reach 4800 μmol/L (80 mg/dL).

The pH of urine greatly influences the solubility of uric acid. At pH 5.0, urine is saturated with uric acid at concentrations ranging from 360 to 900 µmol/L (6–15 mg/dL). At pH 7, saturation is reached at concentrations between 9480 and 12,000 µmol/L (158 and 200 mg/dL). Ionized forms of uric acid in urine include mono- and disodium, potassium, ammonium, and calcium urates.

Purine nucleotides are synthesized and degraded in all tissues, urate is produced only in tissues that contain xanthine oxidase, primarily the liver and small intestine.

Urate production varies with the purine content of the diet and the rates of purine biosynthesis, degradation, and salvage.

Normally, two-thirds to three-fourths of urate is excreted by the kidneys, and most of the remainder is eliminated through the intestines.

The total-body urate pool is the net result between urate production and excretion

Urate production is influenced by dietary intake of purines and the rates of de novo biosynthesis of purines from nonpurine precursors.

The formed urate is normally excreted by urinary and intestinal routes. Hyperuricemia can result from increased production, decreased excretion, or a combination of both mechanisms. When hyperuricemia exists, urate can precipitate and deposit in tissues as tophi.

Hyperuricemia

Hyperuricemia is a part of metabolic syndrome and a common health problem. Two third patients of hyperuricemia remain a symptomatic. It clinically presents in two forms. First uric acid crystal deposition in the form of Gout, and second in raised serum uric acid levels which present in associations with hypertension, insulin resistance, chronic kidney disease, cardiovascular disease and obesity.

Hypertension share a major health burden all other the world. Though exact cause of hypertension is not known but is considered as multifactorial and raised serum uric acid concentration is considered as an independent risk factor for that.

A number of mechanism have been considered leading to development of hypertension in hyperuricemic individuals. One of these mechanism includes uric acid induced vascular injury of pre renal vessels through stimulation of rennin angiotensin system.

Uric acid synthesis

- Uric acid is formed from the breakdown of nucleic acids and is an end product of purine metabolism.
- Uric acid is transported by the plasma from the liver to the kidney, where it is filtered and where about 70% is excreted in Urine.
- The remainder of uric acid is excreted into the GI tract.

Clinical Significance

- Disease states with increased plasma uric acid
  - Gout
  - Increased catabolism of nucleic acids
  - And renal disease

- In Gout increased serum levels of uric acid lead to formation of *monosodium urate crystals* around the joints.

- Uric acid test is useful to assess for gout and to monitor patients with renal failure

Specimen

Serum or plasma may be used
Stability in serum / plasma:

- 6 months at -20°C
- 7 days at 4-8°C
- 3 days at 20-25°C

ANALYTIC METHODS—URIC ACID

- Chemical Method (old) :
  - Phosphotungstic Acid, read the absorbance(Ab) at 700nm (UV). blue Colored product
- Enzymatic Method: is More specific
  - By using Couple reaction of uricase and Peroxidase. Pink solution (Ab at 500nm spectrophotometric) Pink color solution.

Enzymatic Colorimetric

Principle

Uricase oxidizes uric acid to allantoin and hydrogen peroxide. The hydrogen peroxide formed further reacts with a phenolic compound and 4 aminoantipyrine by the catalytic action of peroxidase to form a Pink colored quinoneimine dye complex. Intensity of the color formed is directly proportional to the amount of uric acid present in the sample.

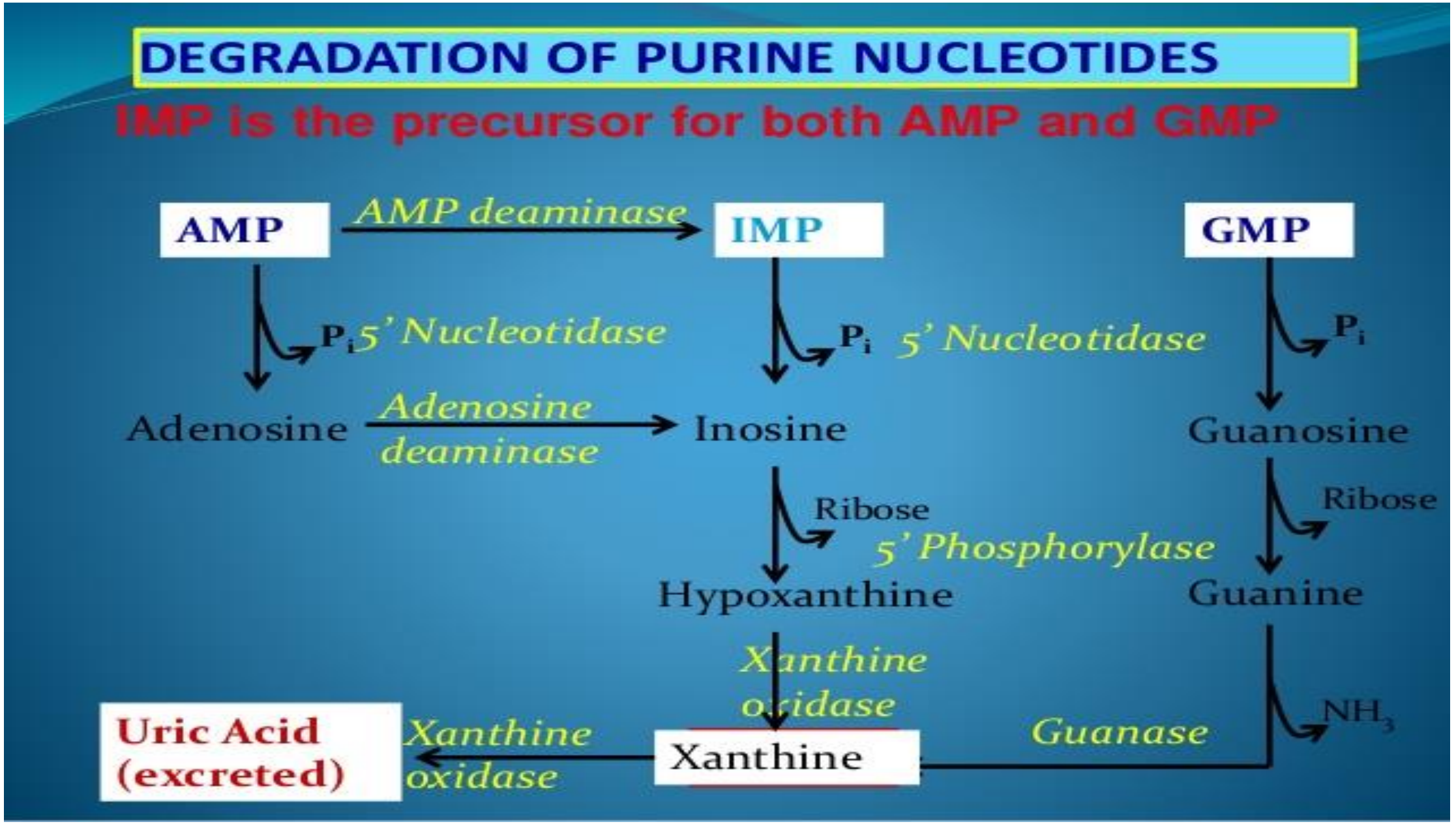
Normal Range

Female: 2.6 - 6.0 mg/dL
Male: 3.5-7.2 mg/dL

Functions of Nucleotides

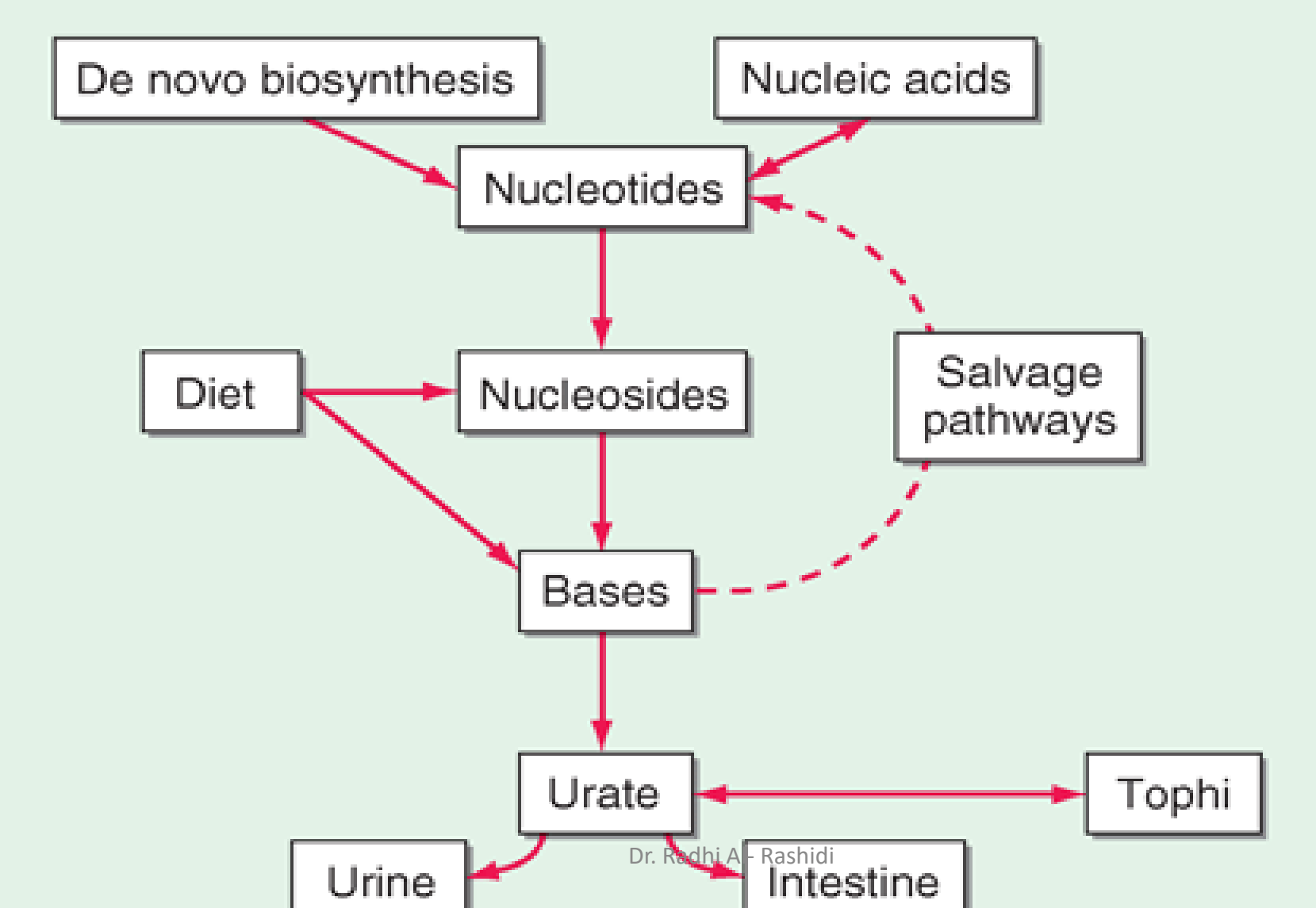
- Polymerize to made DNA and RNA
- Energy currency of the cell e.g. ATP
- Act as carriers of active intermediate in various metabolic pathways e.g. glycogen syntheses
- Component of coenzymes e.g. FAD, NADH and NADPH
- Act as 2^{nd} messengers e.g. cAMP and cGMP
- Allosteric regulation of various metabolic pathways

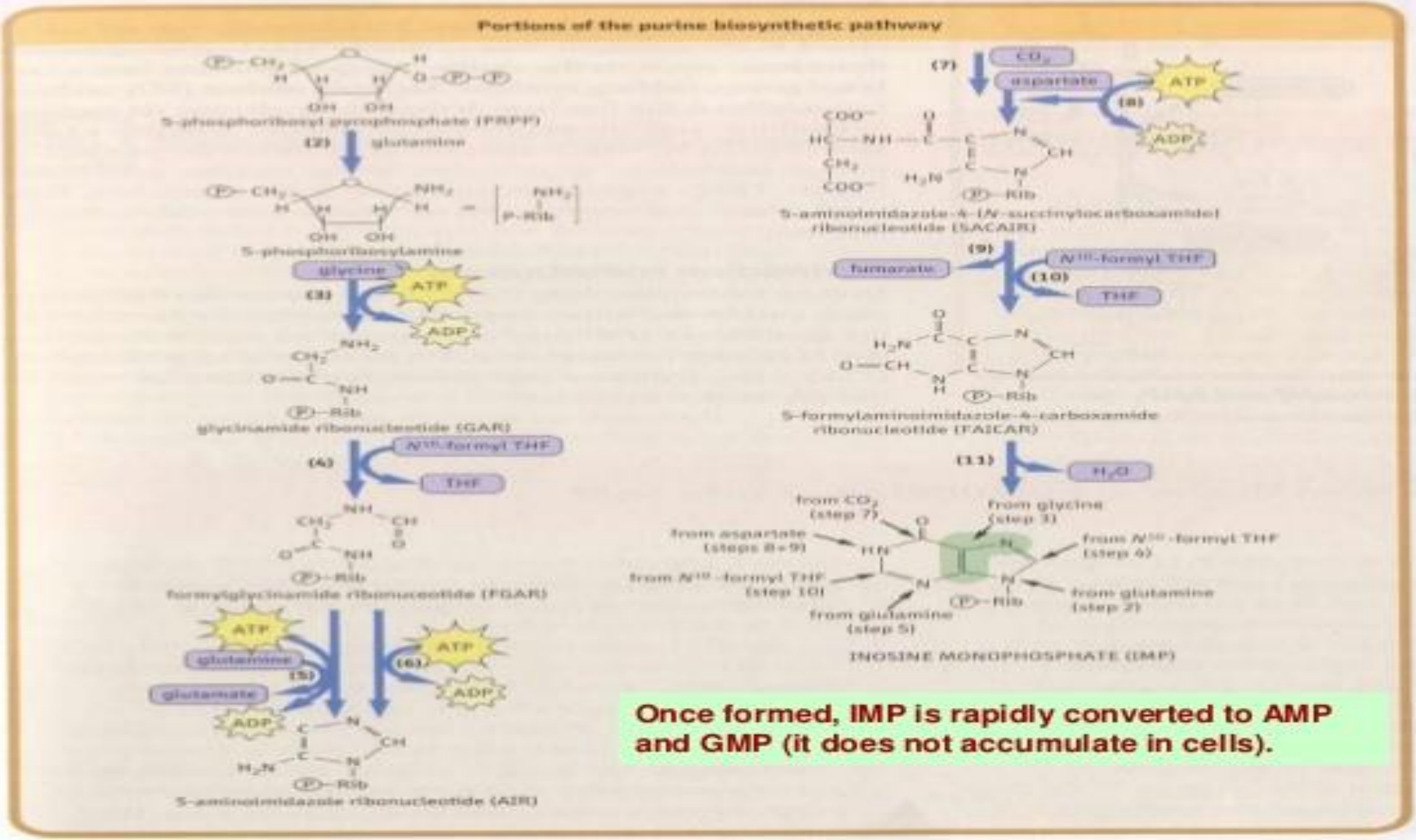
DEGRADATION OF PURINE NUCLEOTIDES



There are two pathways leading to nucleotides

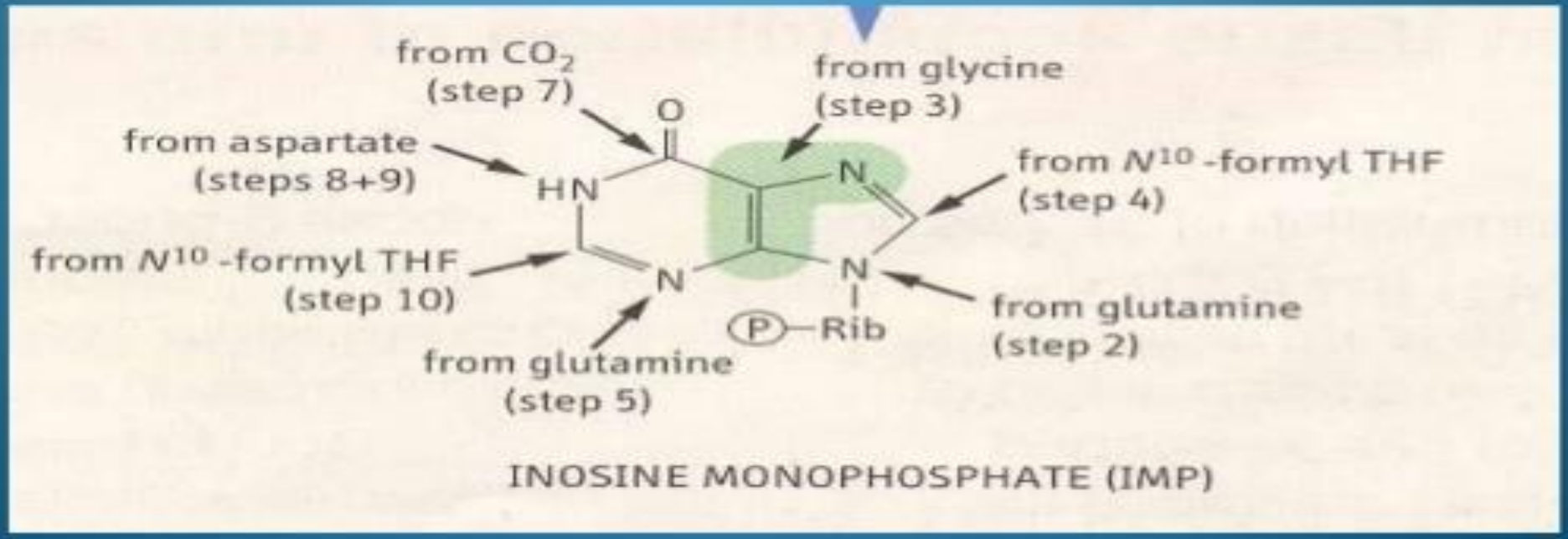
- **De novo synthesis**: The synthesis of nucleotides begins with their metabolic precursors: ***amino acids, ribose-5-phosphate, CO_2, and one-carbon units***.
- **Salvage pathways**: The synthesis of nucleotide by recycle the free bases or nucleosides released from nucleic acid breakdown.


De novo biosynthesis
Nucleic acids
Nucleotides
Diet
Nucleosides
Salvage pathways
Bases
Urate
Tophi
Urine
Intestine


Portions of the purine biosynthetic pathway
5-phosphoribosyl pyrophosphate (PRPP)
(2) glutamine
5-phosphoribosylamine
glycine
ATP
(3)
ADP
glycinamide ribonucleotide (GAR)
N^{10}-formyl THF
(4)
THF
formylglycinamide ribonucleotide (FGAR)
ATP
glutamine
(5)
glutamate
ADP
ATP
(6)
ADP
5-aminoimidazole ribonucleotide (AIR)
(7)
CO_2
aspartate
ATP
(8)
ADP
5-aminoimidazole-4-(N-succinylocarboxamide) ribonucleotide (SACAIR)
(9)
fumarate
N^{10}-formyl THF
(10)
THF
5-formylaminoimidazole-4-carboxamide ribonucleotide (FAICAR)
(11)
H_2O
from CO_2 (step 7)
from aspartate (steps 8+9)
from N^{10}-formyl THF (step 10)
from glutamine (step 5)
from glycine (step 3)
from N^{10}-formyl THF (step 6)
from glutamine (step 2)
INOSINE MONOPHOSPHATE (IMP)
Once formed, IMP is rapidly converted to AMP and GMP (it does not accumulate in cells).

IMP Synthesis - Significance

- IMP = serves as a precursor for synthesis of all other purine nucleotides such as adenine and guanosine monophosphate (AMP & GMP)and ATP.



INOSINE MONOPHOSPHATE (IMP)

DISEASES ASSOCIATED WITH DEFECTS IN PURINE METABOLISM

- HYPERURICEMIA
- GOUT
- LESCH-NYHAN SYNDROME
- KIDNEY STONES
- SEVERE COMBINED IMMUNODEFECIENCY (SCID)

HYPERURICEMIA

Characterized by plasma urate (uric acid) level greater than 7.0 mg/dL

Normal plasma levels

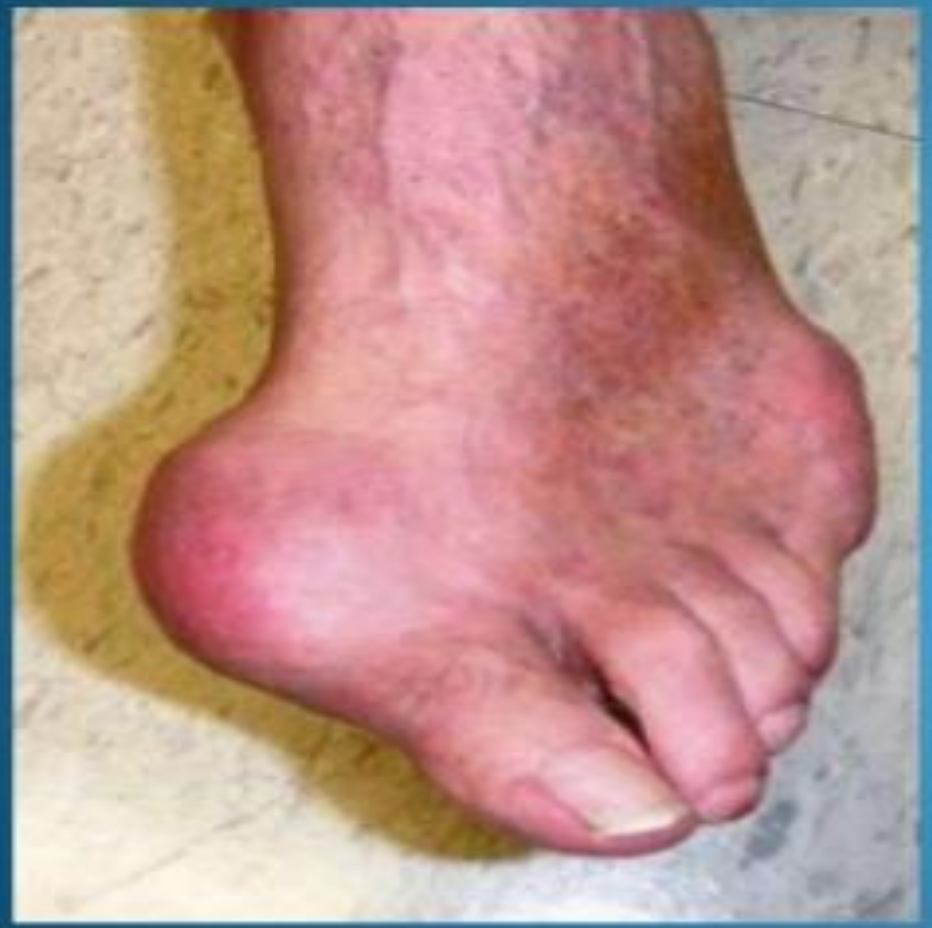
Females	=	2.4 - 6 mg/dL
Males	=	3.4 - 7 mg/dL

HYPERURICEMIA

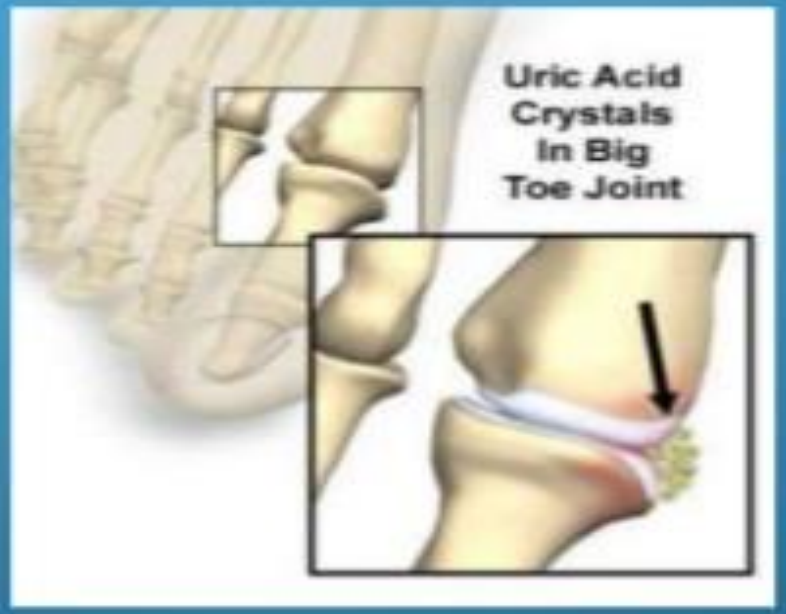
- **Primary Hyperuricemia**: an innate defect in purine metabolism and/or uric acid excretion

- **Secondary Hyperuricemia**: increased availability of purines due to medications/ medical conditions or through diet.

GOUT



Gout is caused by precipitation of sodium urate crystals in the joints resulting in inflammation and pain.



Progression of Hyperuricemia to Gout

Stage 1: Asymptomatic hyperuricemia. At a serum urate concentration greater than 6.8 mg/dL, urate crystals may start to deposit in the joints. No evidence that treatment is required.

Stages 2 : Acute gout. If sufficient urate deposits develop around joints, and if the local environment or some trauma triggers the release of crystals into the joint space, an inflammatory response occurs. These flares can be self-resolving but are likely to recur.

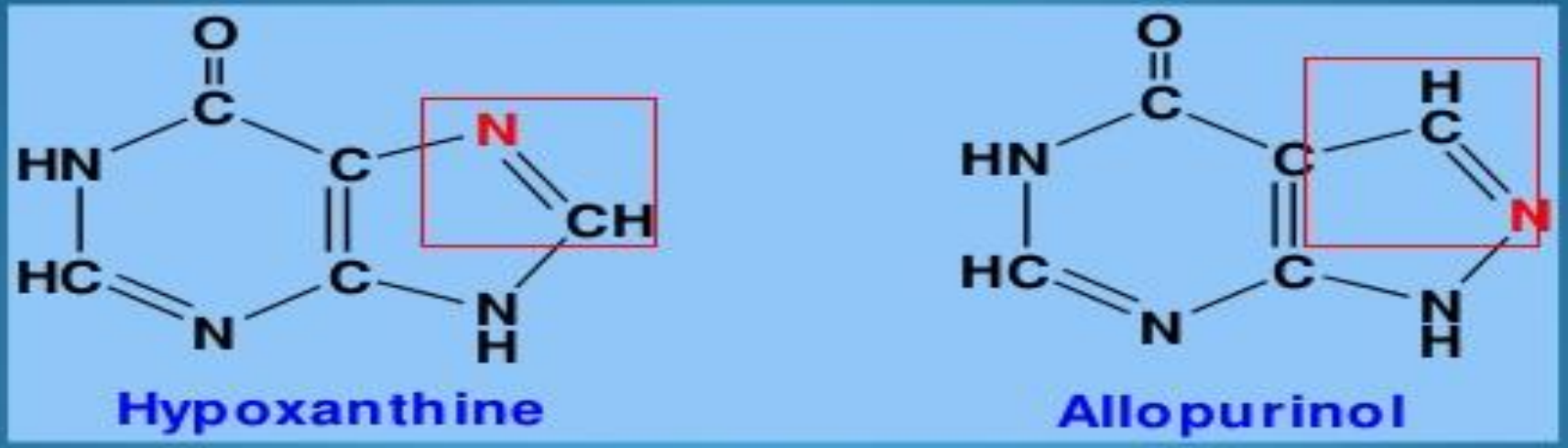
Stage 3: Intercritical periods. These are the intervals between attacks. During these periods, crystals may still be present at a low level in the synovial tissue and fluid, resulting in future attacks.

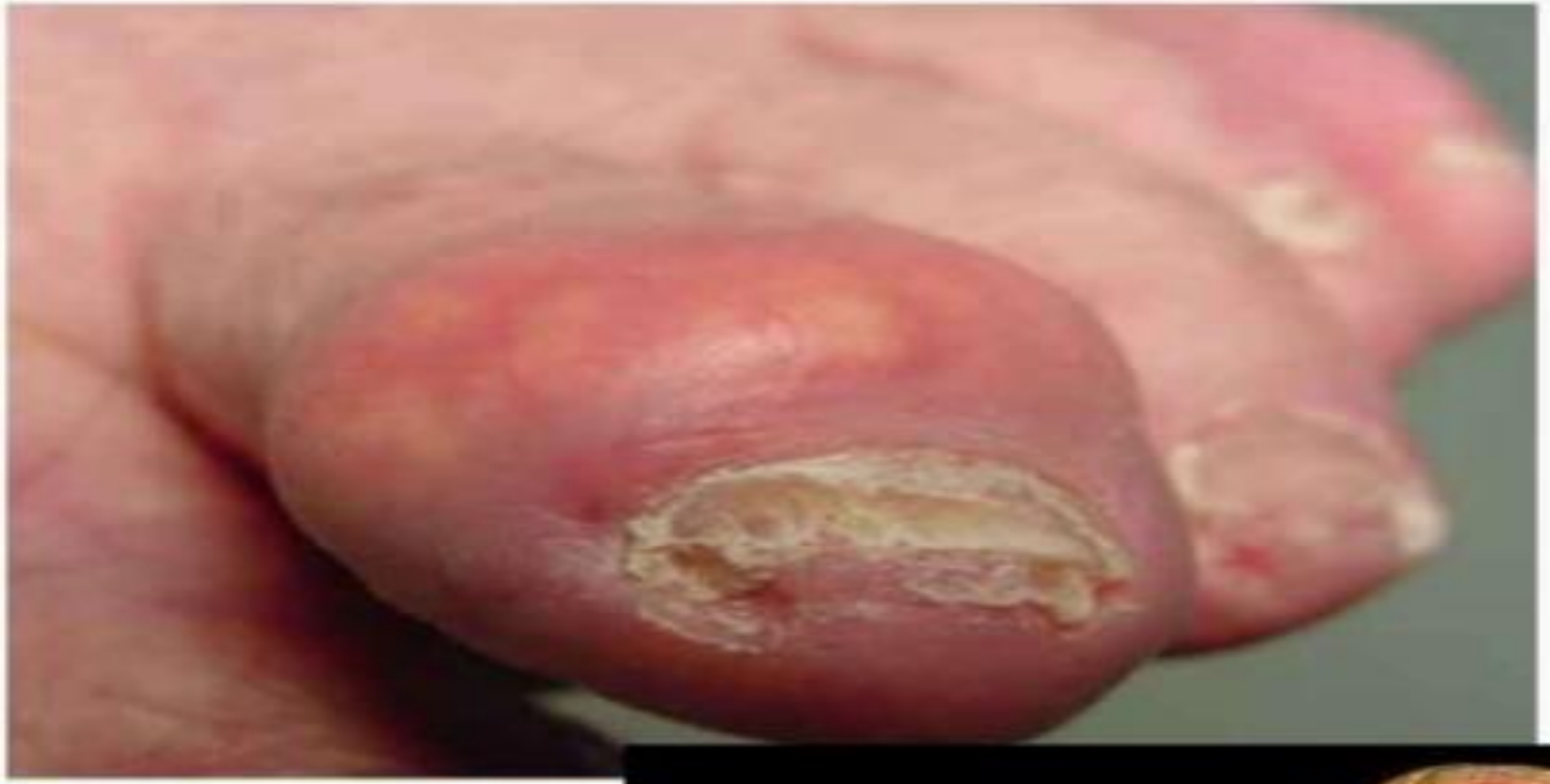
Stage 4: Advanced gout. If crystal deposits continue to accumulate, patients may develop chronically stiff, swollen joints and tophi. This advanced stage of gout is relatively uncommon generally avoidable with therapy.

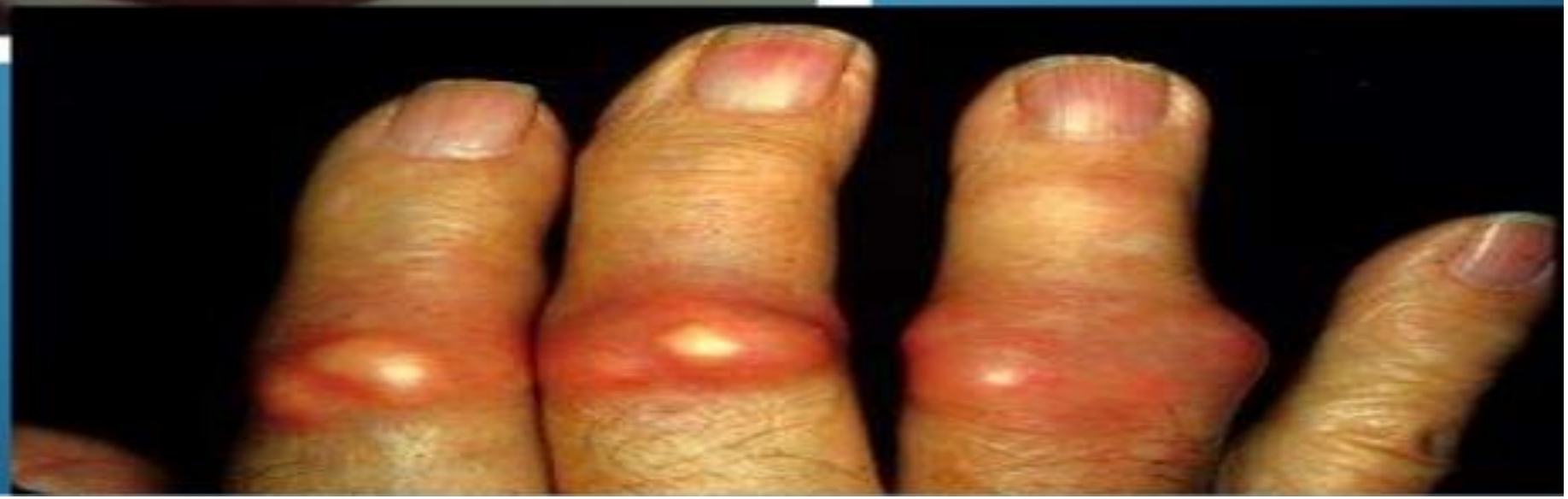
GOUT - Treatment

- **Colchicine** –reduces inflammation
- **Allopurinol** – inhibits uric acid synthesis
- **Low purine diet - Foods that are high in purine include:**
  - Red meat and organ meats (eg. liver)
  - Yeasts and yeast extracts (eg. beer and alcoholic beverages)
  - Asparagus, spinach, beans, peas, lentils, oatmeal, cauliflower and mushrooms
- **Avoid caffeine and alcohol**
- **Keep hydrated**

Allopurinol – a suicide inhibitor used to treat Gout

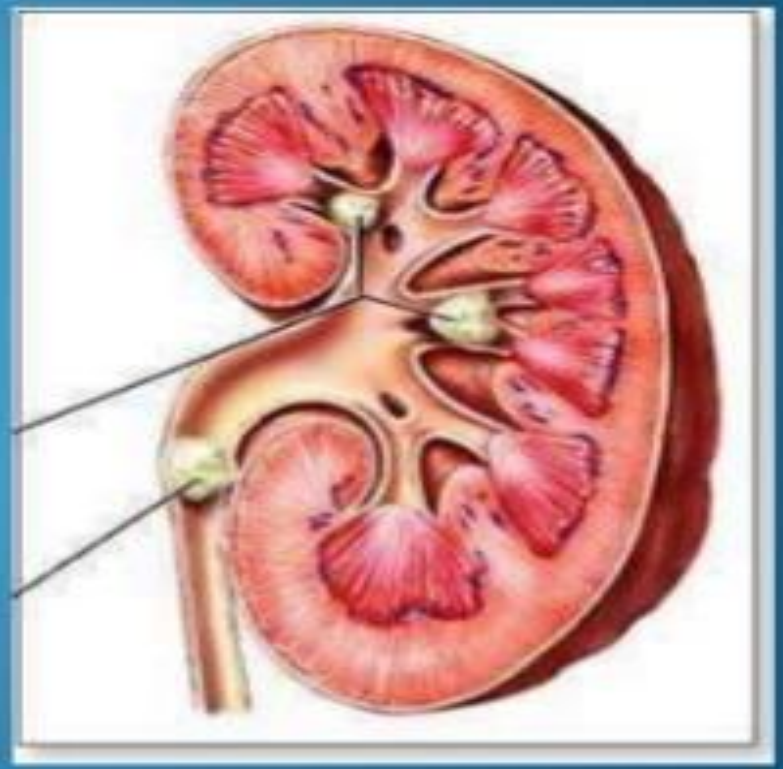


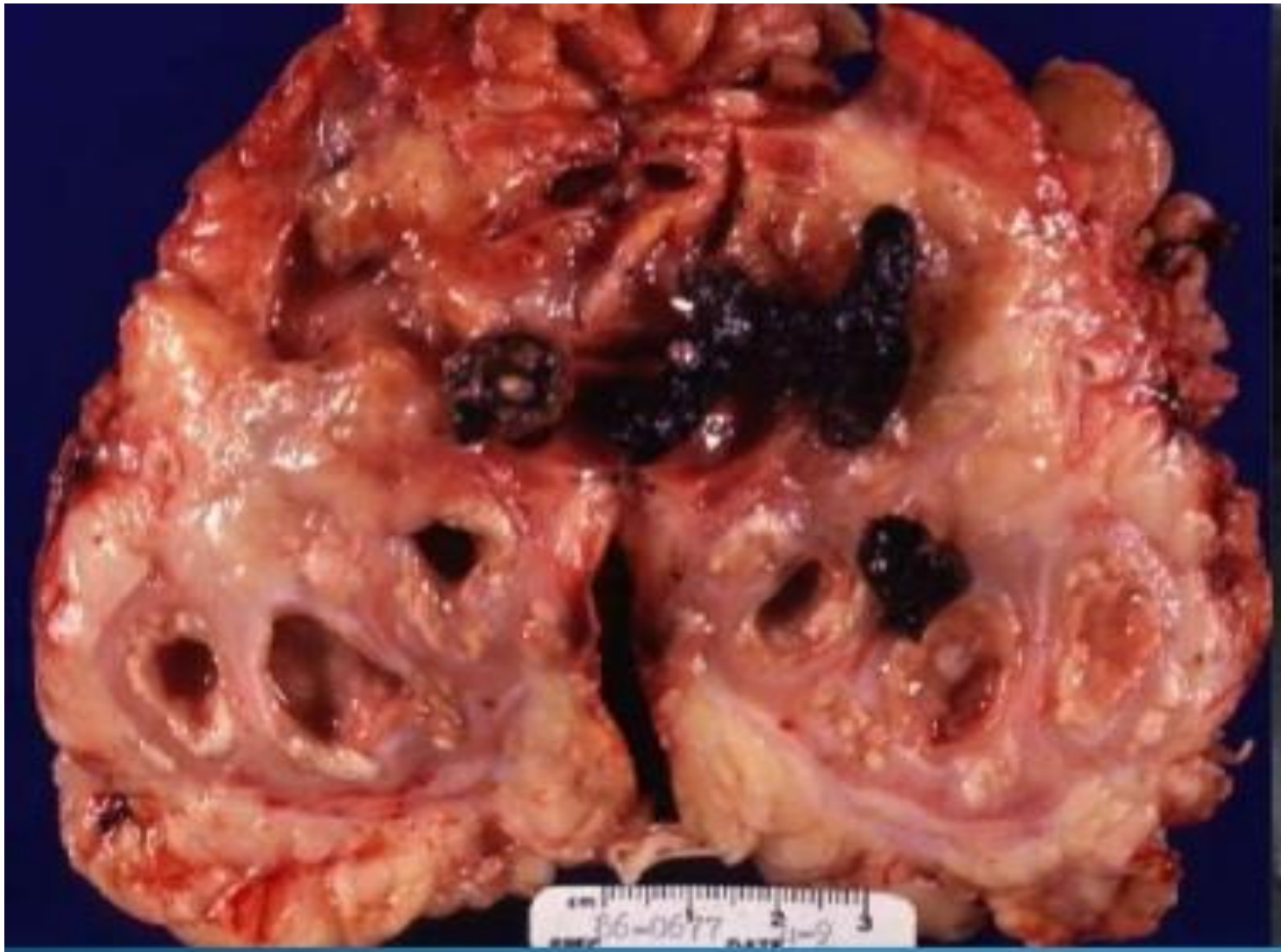


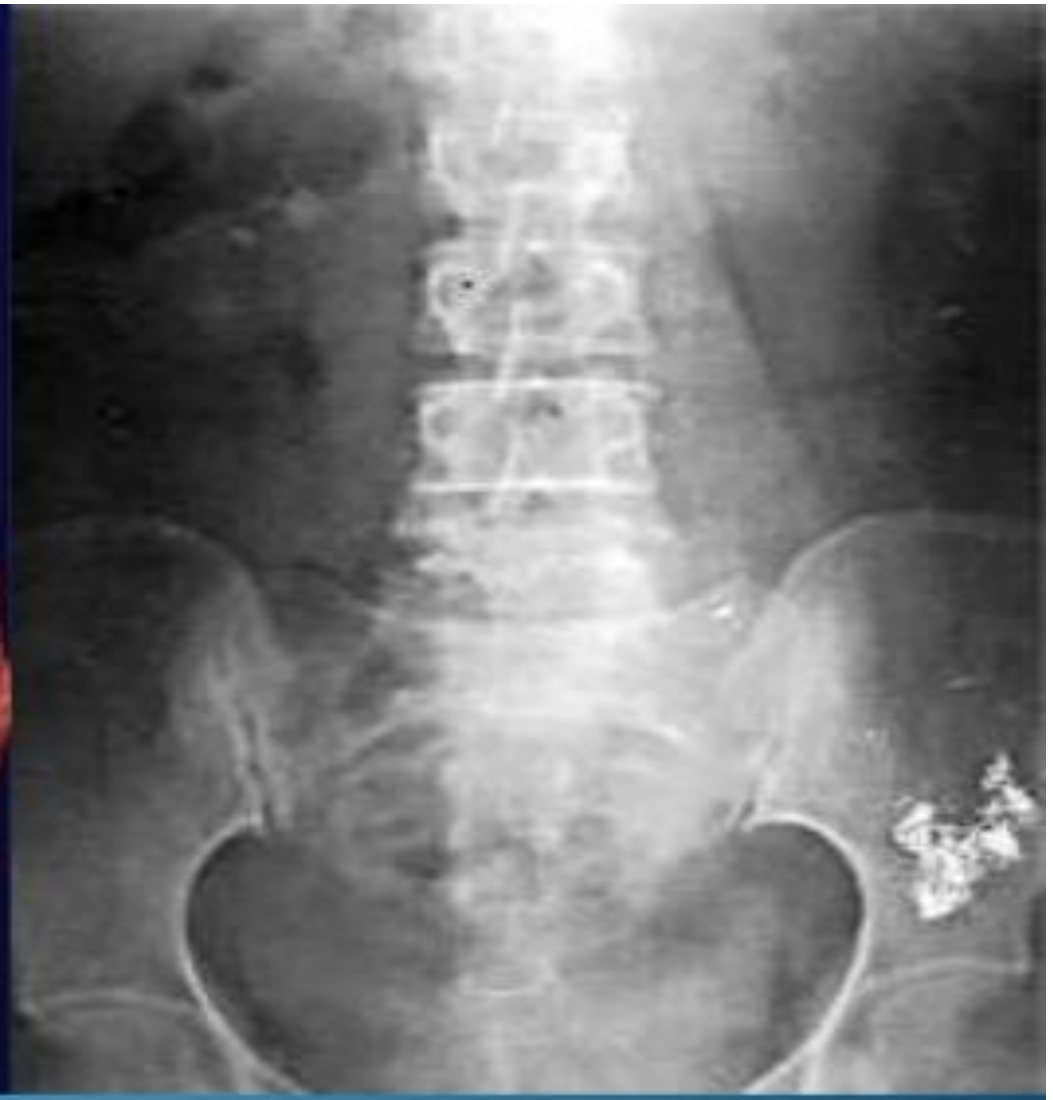


KIDNEY STONES

When uric acid is present in high concentrations in the blood, it may precipitate as a salt in the kidneys. The salt can form stones, which can in turn cause pain, infection, and kidney damage.







Gout: kidney stones

Lesch-Nyhan Syndrom: is a inherited disorder caused by a deficiency of the enzyme **hypoxanthine-guanine phosphoribosyltransferase.** LNS is present at birth in baby boys.

Hypoxanthine and guanine are not used in the salvage pathway of purine nucleotides synthesis.

Hypoxanthine and guanine are not utilizied repeatedly but converted into uric acid.

Symptoms:

- severe gout

-severe mental and physical problems

- self-mutilating behaviors

Degradation of Pyrimidines

- CMP and UMP degraded to bases similarly to purines by
  - Dephosphorylation
  - Deamination
  - Glycosidic bond cleavage
- Uracil reduced in liver, forming β-alanine
  - Converted to malonyl-CoA → fatty acid synthesis for energy metabolism

OROTACIDURIA

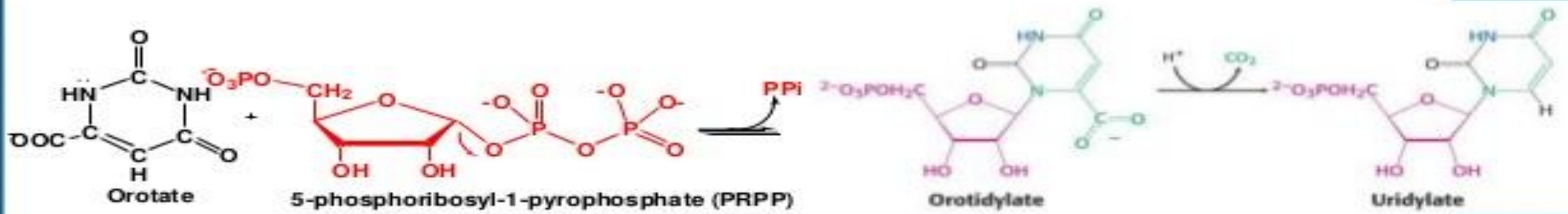
inherited disorder of pyrimidine synthesis caused by a deficiency of the enzyme of *orotate-phosphoribosyltransferase* and *decarboxylase*.

Symptoms:

–excess of orotic acid and its excretion with urine (1.0-1.5 g)

-mental and physical retardation

-megaloblastic anemia



– **Treatment: patients are fed uridine**

U → UMP → UDP → UTP

UTP inhibits carbamoyl phosphate synthase II, preventing the biosynthesis and accumulation of orotic acid

HEMOGLOBIN

Prof Dr. Radhi Al-Rashidi
Kut University College

Introduction

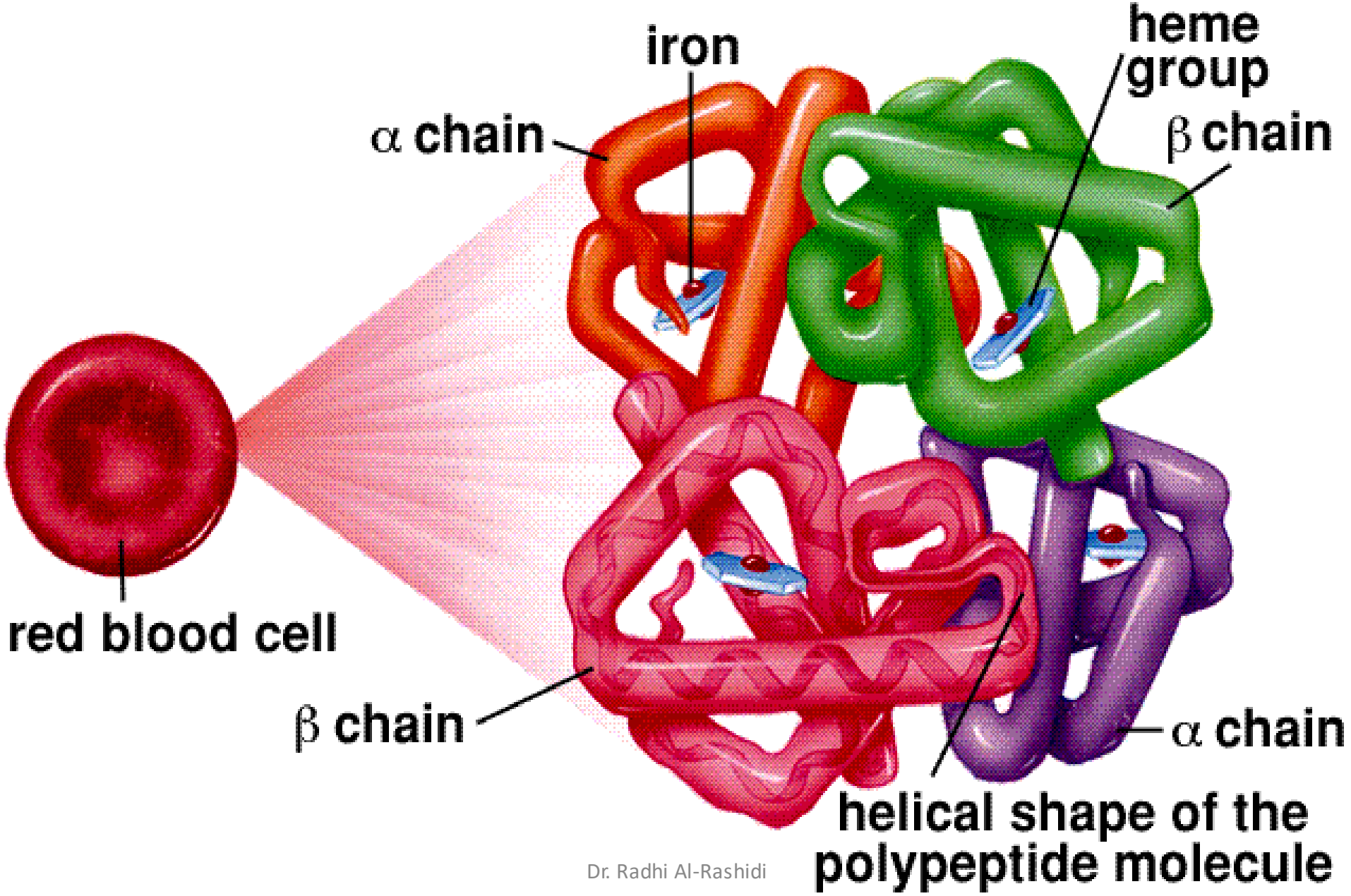
- The main function of red blood cell
  - Transfer of O_2 from lungs to tissue
  - Transfer of CO_2 from tissue to lungs
- To accomplish this function red cells has hemoglobin (Hb)
- Each red cell has 640 million molecules of Hb

- Hemoglobin (Hb), protein constituting 1/3 of the red blood cells

- Synthesis begins in proerythroblast
    - 65% at erythroblast stage
    - 35% at reticulocyte stage

- Two parts
    - Heme
    - Globin

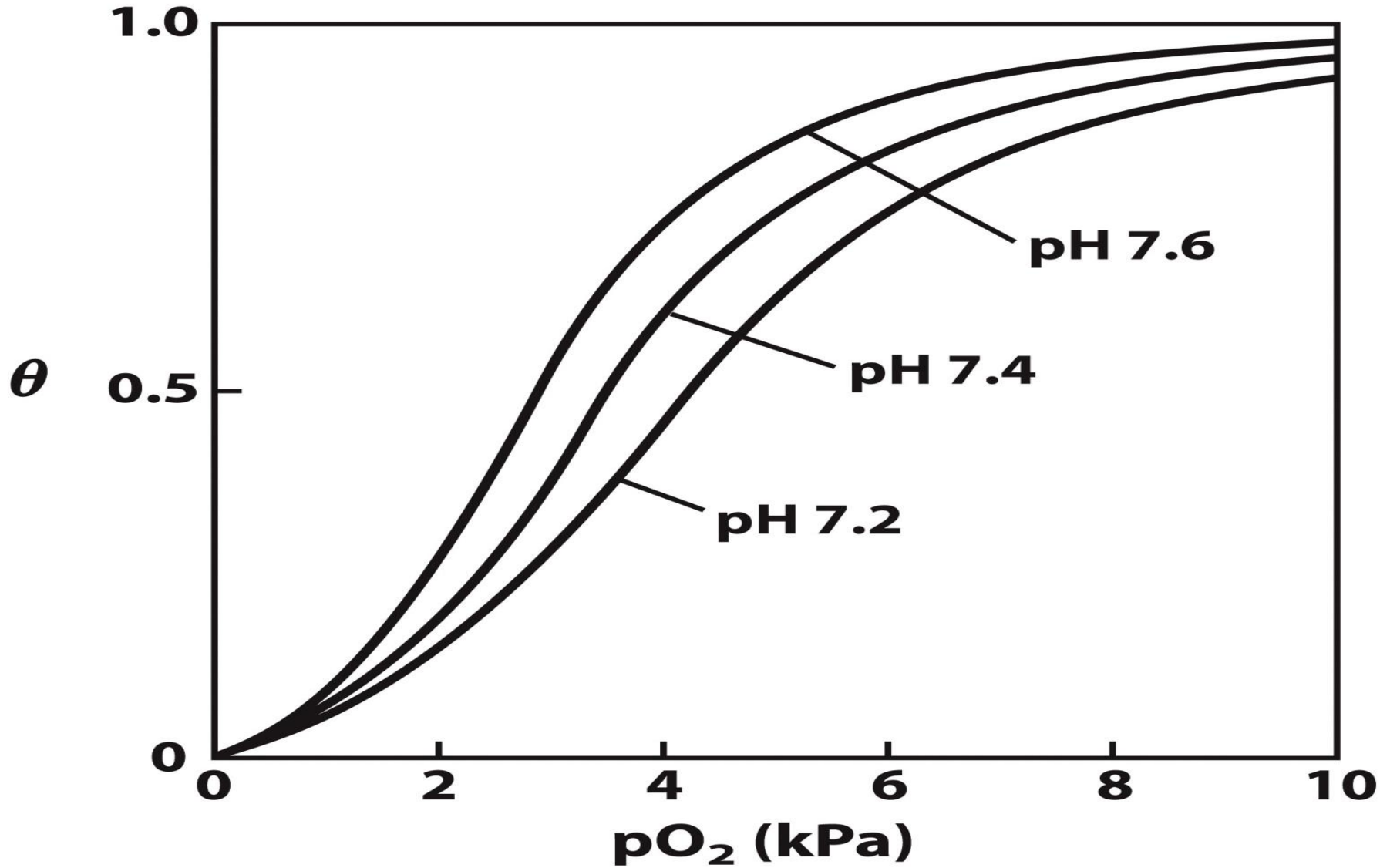
Hemoglobin Molecule



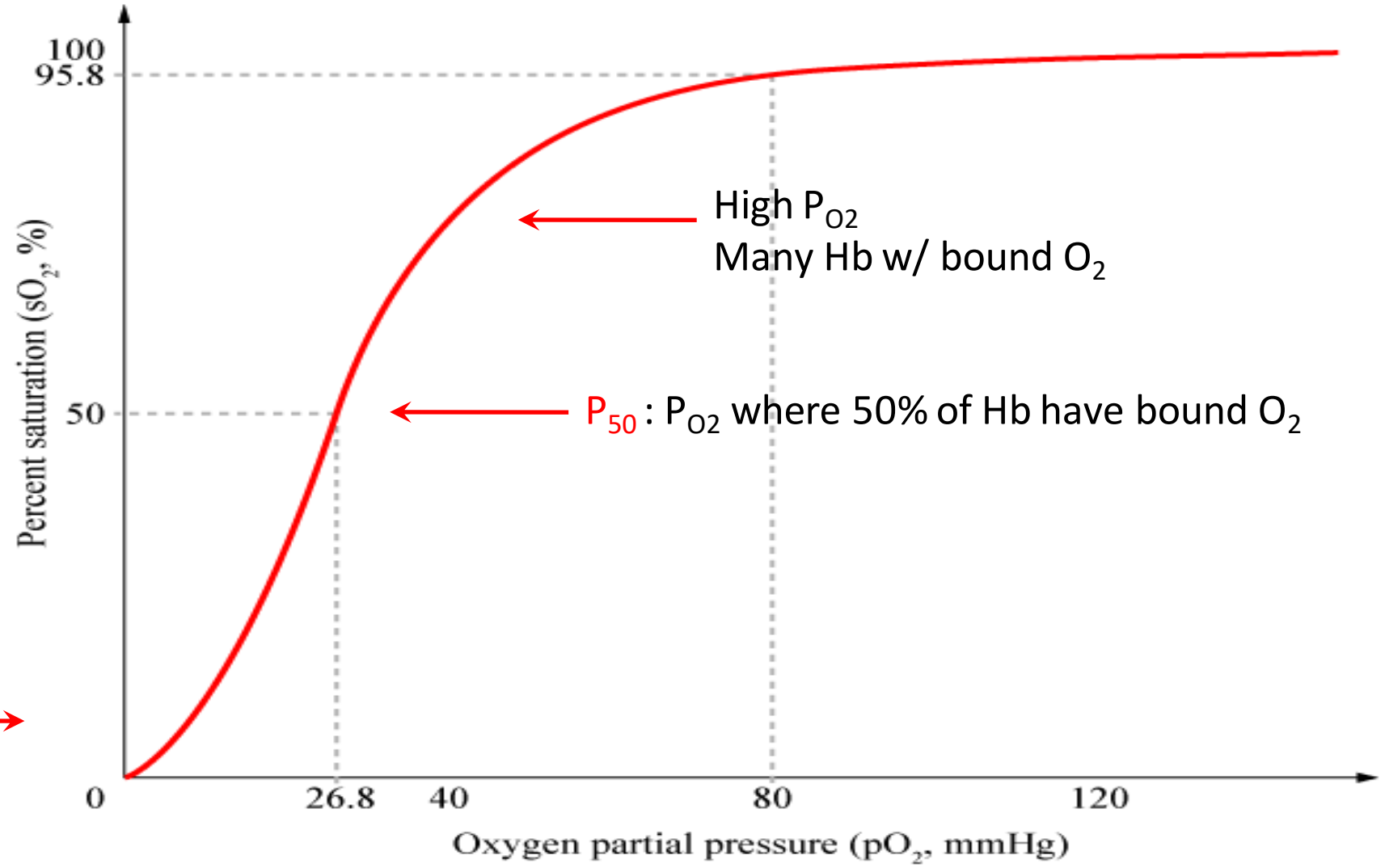
Transport of H^+ and CO_2 by Hb

Hb binds to and transports about 40% of the total H^+ and 15% to 20% of the CO_2 formed in peripheral tissues to the lungs and kidneys. The remainder of the H^+ is absorbed by the plasma's bicarbonate buffer system. The remainder of the CO_2 is transported as dissolved HCO_3^- and CO_2. [Note that the solubility of CO_2 in the blood is increased by the carbonic anhydrase reaction ($CO_2 + H_2O \leftrightarrows H^+ + HCO_3^-$) which occurs in erythrocytes.]

The binding of H^+ and CO_2 to Hb decreases the affinity ofHb for O_2, favoring the release of O_2 to the tissues where the concentrations of these components are relatively high. Conversely, in the capillaries of the lung, as CO_2 is excreted and the blood pH consequently rises, the affinity of Hb for O_2 increases and the protein binds more O_2 for transport to the peripheral tissues. The effect of pH and CO_2 concentration on the binding and release of O_2 by Hb is known as the Bohr effect. The effect of pH on Hb O_2 binding curves is shown in Fig. below:


1.0
θ
0.5
0
0
2
4
6
8
10
pO2 (kPa)
pH 7.6
pH 7.4
pH 7.2

Hemoglobin-O_2 dissociation curves



The shape of the curve is *sigmoidal*; this is due to *cooperative* binding of oxygen to hemoglobin.

Hemoglobin is a protein in your red blood cells that carries oxygen to your body's organs and tissues and transports carbon dioxide from your organs and tissues back to your lungs. If a **hemoglobin** test reveals that your **hemoglobin** level is lower than normal, it means you have a low red blood cell count (anemia).

Low hemoglobin levels usually indicate that a person has **anemia**. There are several kinds of **anemia**: Iron-deficiency **anemia** is the most common type. This form of **anemia** occurs when a person **does** not have enough iron in their body, and it cannot make the **hemoglobin** it needs.

Synthesis

Hemoglobin (Hb) is synthesized in a complex series of steps. The heme part is synthesized in a series of steps in the mitochondria and the cytosol of immature red blood cells, while the globin protein parts are synthesized by ribosomes in the cytosol.

Production of Hb continues in the cell throughout its early development from the proerythroblast to the reticulocyte in the bone marrow.

Oxygen saturation[
]
In general, hemoglobin can be saturated with oxygen molecules (oxyhemoglobin), or desaturated with oxygen molecules (deoxyhemoglobin).]

Oxyhemoglobin
Oxyhemoglobin is formed during physiological respiration when oxygen binds to the heme component of the protein hemoglobin in red blood cells. This process occurs in the pulmonary capillaries adjacent to the alveoli of the lungs. The oxygen then travels through the blood stream to be dropped off at cells where it is utilized as a terminal electron acceptor in the production of ATP by the process of oxidative phosphorylation. It does not, however, help to counteract a decrease in blood pH. Ventilation, or breathing, may reverse this condition by removal of carbon dioxide, thus causing a shift up in pH

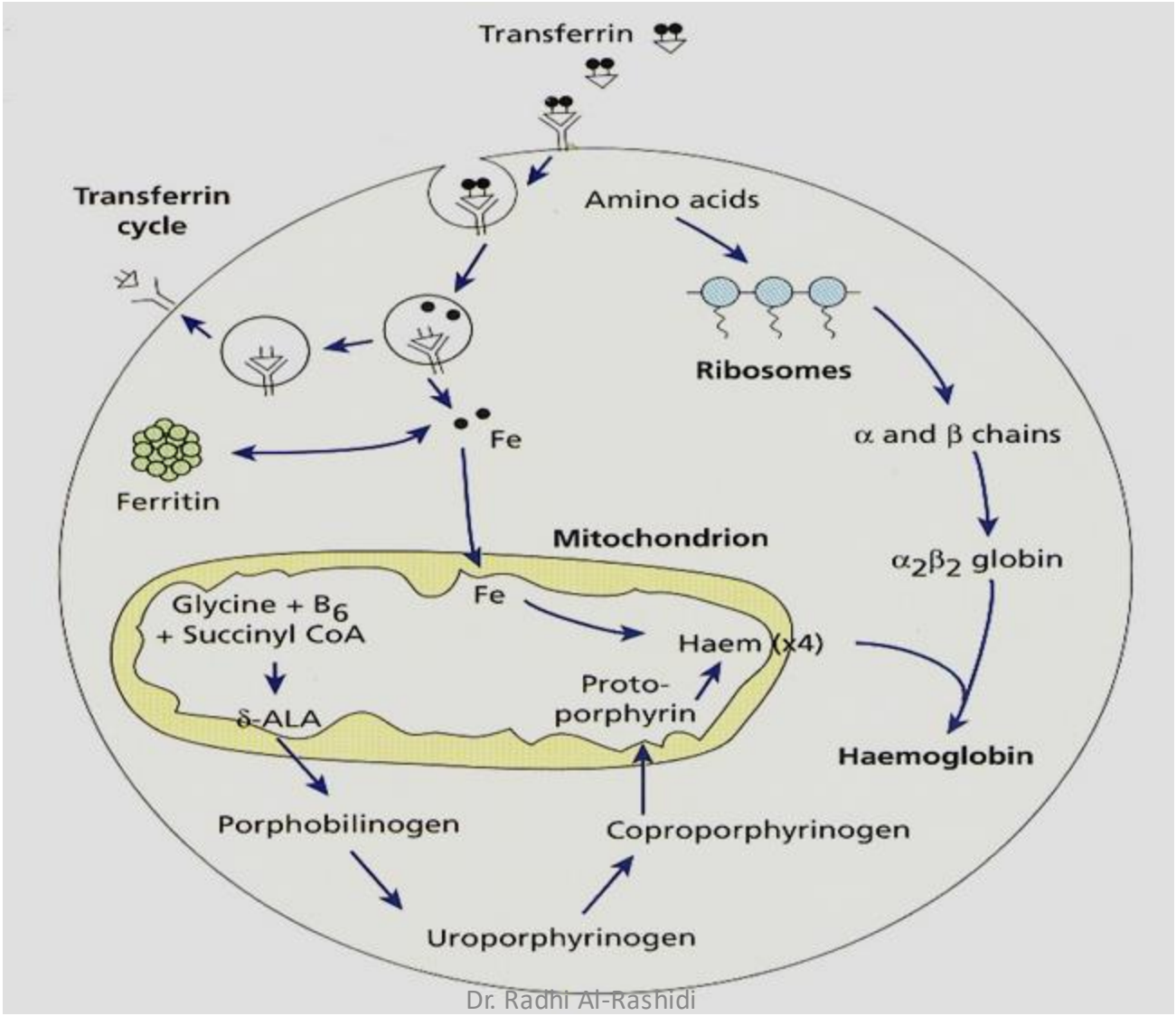
Deoxygenated

Deoxygenated hemoglobin is the form of hemoglobin without the bound oxygen.
The absorption spectra of oxyhemoglobin and deoxyhemoglobin differ. The oxyhemoglobin has significantly lower absorption of the 660 nm wavelength than deoxyhemoglobin, while at 940 nm its absorption is slightly higher. This difference is used for the measurement of the amount of oxygen in a patient's blood by an instrument called a pulse oximeter. This difference also accounts for the presentation of cyanosis, the blue to purplish color that tissues develop during hypoxia
Deoxygenated hemoglobin is paramagnetic; it is weakly attracted to magnetic fields. In contrast, oxygenated hemoglobin exhibits diamagnetism, a weak repulsion from a magnetic field

Synthesis of Hemoglobin (Hb)

- Heme & globin produced at two different sites in the cells
    - Heme in mitochondria
    - Globin in polyribosomes
- Well synchronized

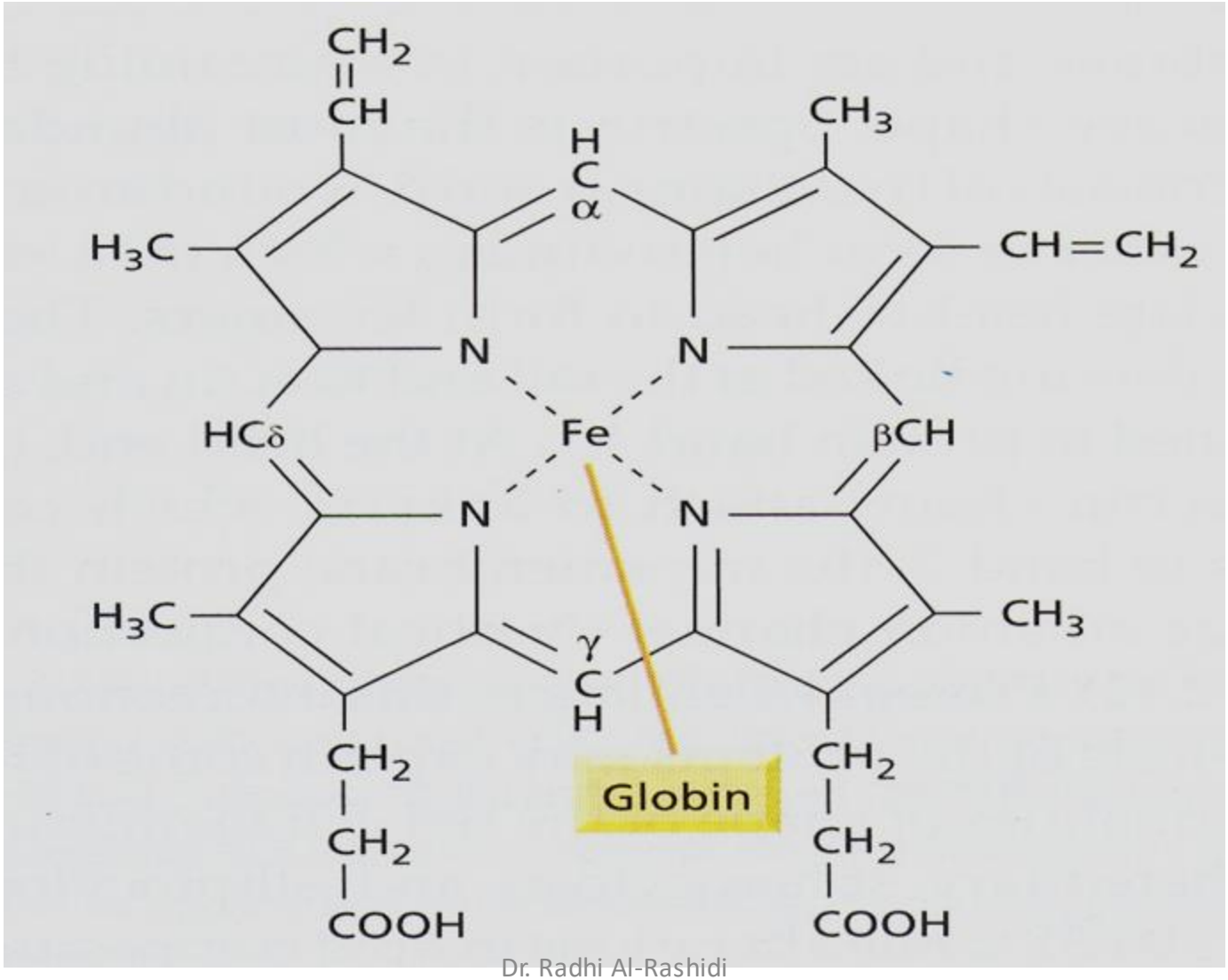
Synthesis of Hemoglobin



Synthesis of Heme

- Protoporphyrin ring with an iron atom in centre
- The main site is mitochondria
- Mature red cell does not contain mitochondria

Structure of Heme



HEME-CONTAINING PROTEINS

- Hemoglobin
- Myoglobin
- Cytochromes
- Catalase
- Some peroxidases

Types of hemoglobin

Fetal hemoglobin (HbF):

- Major hemoglobin found in the fetus and newborn
- Tetramer with two a and two g chains
- Higher affinity for O_2 than HbA
- Transfers O_2 from maternal to fetal circulation across placenta

Types of hemoglobin

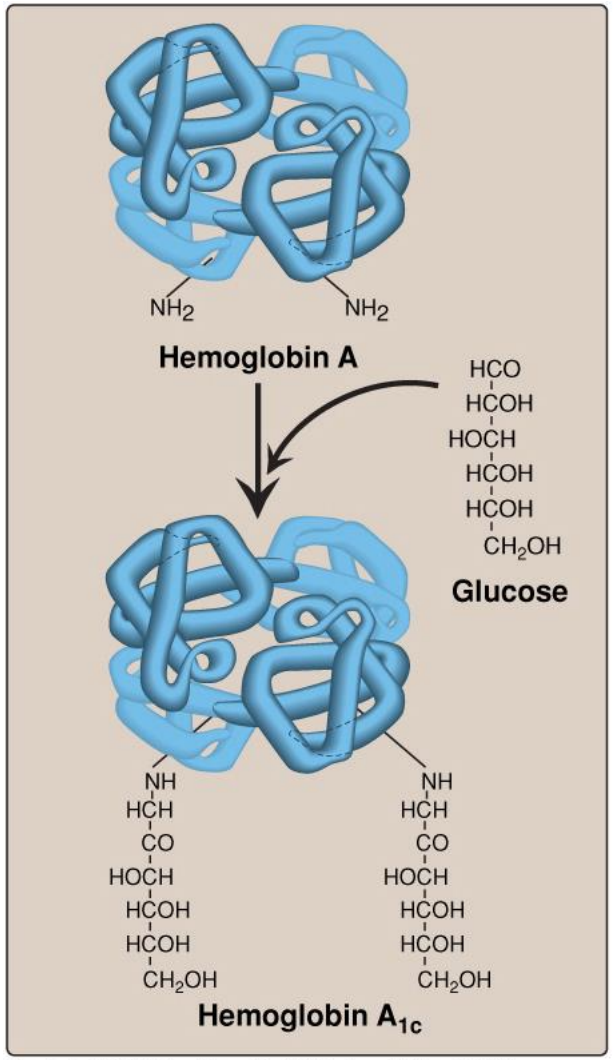
HbA_2:

- Appears ~12 weeks after birth
- Constitutes ~2% of total Hb
- Composed of two α and two δ globin chains

Types of hemoglobin

HbA_{1c}:

- HbA undergoes non-enzymatic glycosylation
- Glycosylation depends on plasma glucose levels
- HbA1c levels are high in patients with diabetes mellitus



Abnormal Hbs

Unable to transport O_2 due to abnormal structure:

- Carboxy-Hb: CO replaces O_2 and binds 200X tighter than O_2 (in smokers)
- Met-Hb: Contains oxidized Fe^{3+} (~2%) that cannot carry O_2
- Sulf-HB: Forms due to high sulfur levels in blood (irreversible reaction)

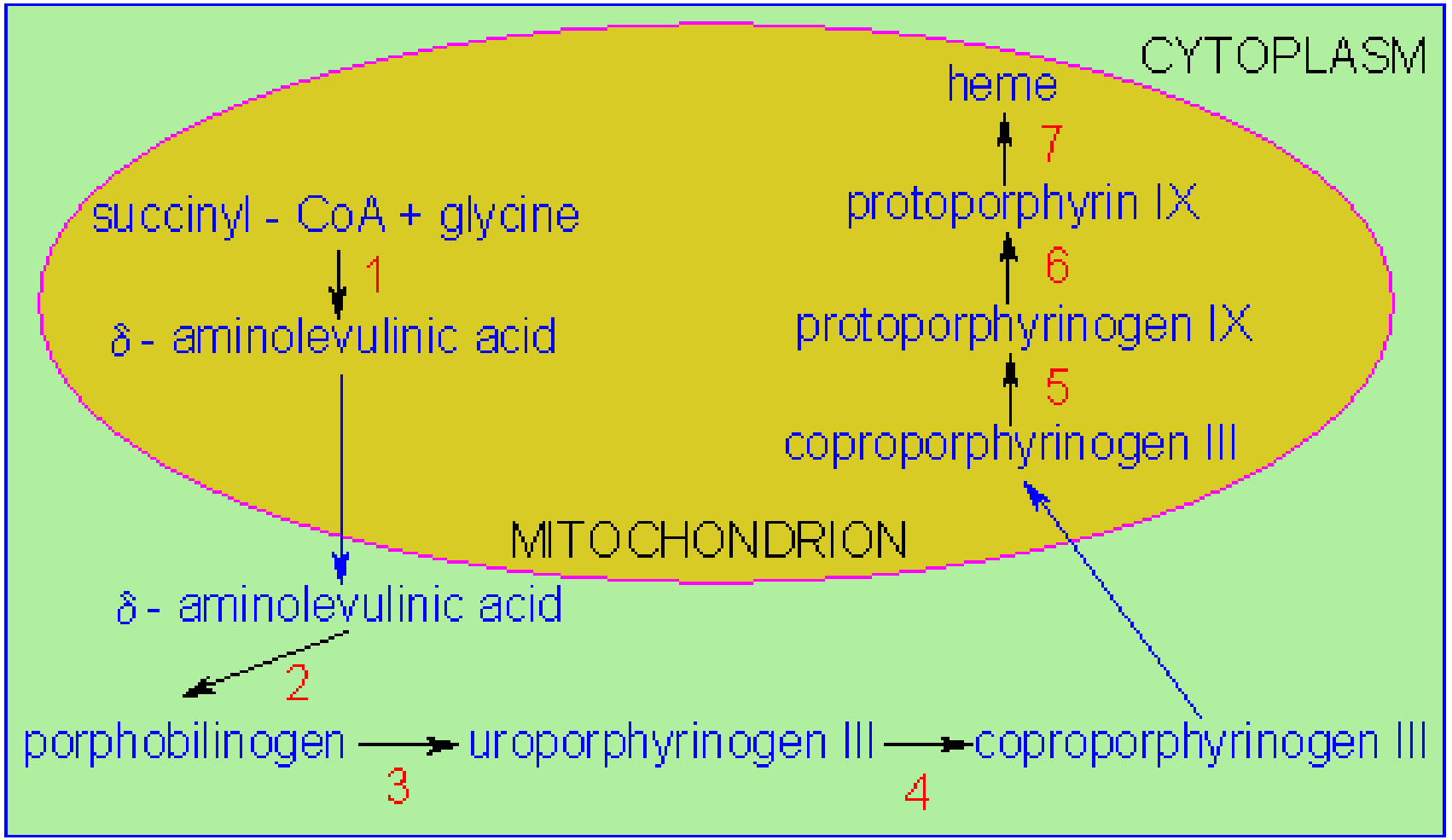
Introduction

- The hemoglobin are red globular proteins which have a molecular weight of about 64,500 and comprise almost one third of the weight of a red cell. Their primary function is the carriage of oxygen from the lungs to the tissues.
- Over 500 different haemoglobin variants have been described but all share the same basic structure of four globin polypeptide chains each with haem group. Functional haemoglobin composed of two pairs of dissimilar globins.

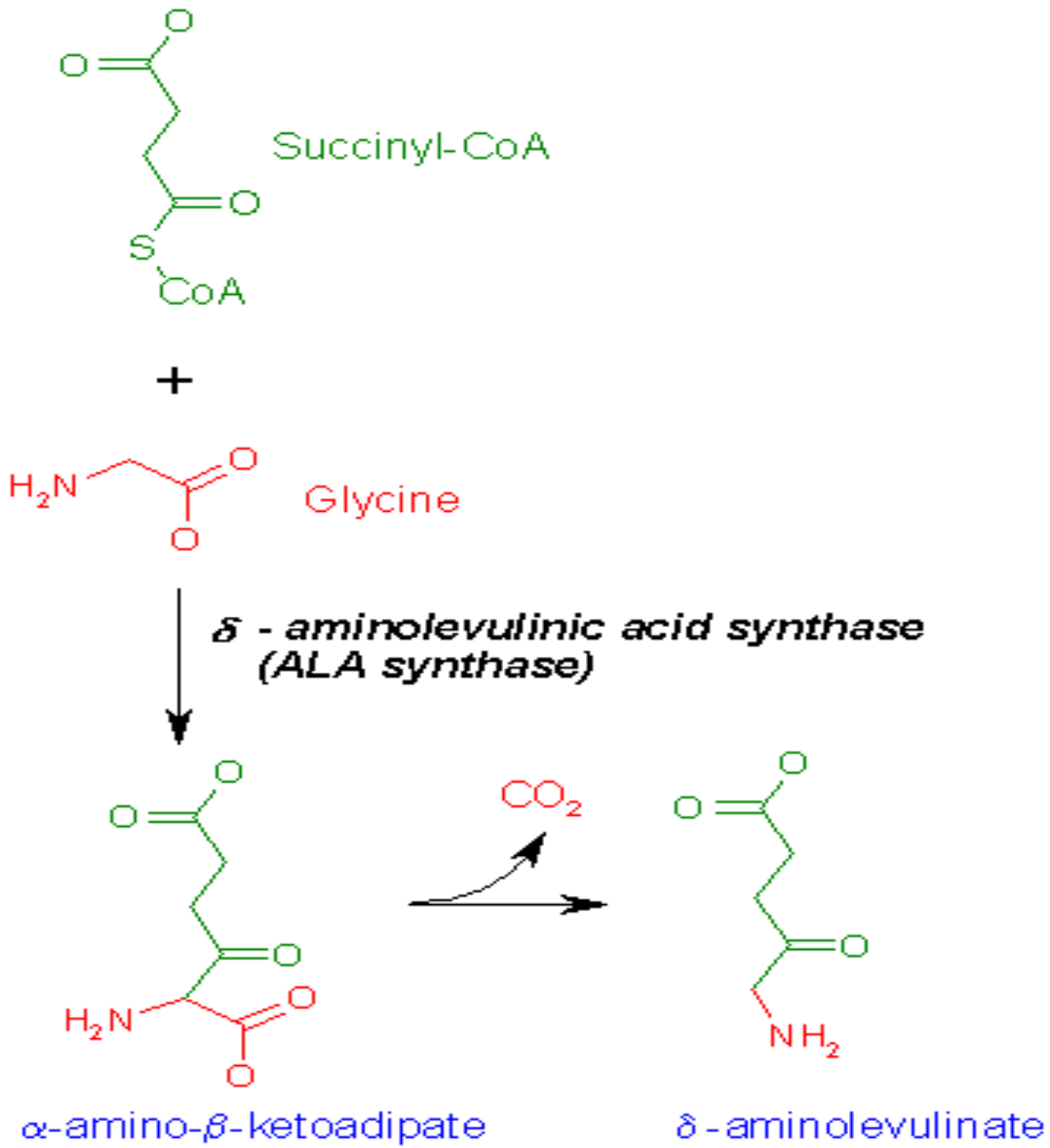
Haemoglobin synthesis

Although haem & globin synthesis separately within developing red cell precursors their rate of synthesis are carefully coordinated to ensure optimal efficiency of haemoglobin assembly.

1st : Haem synthesis

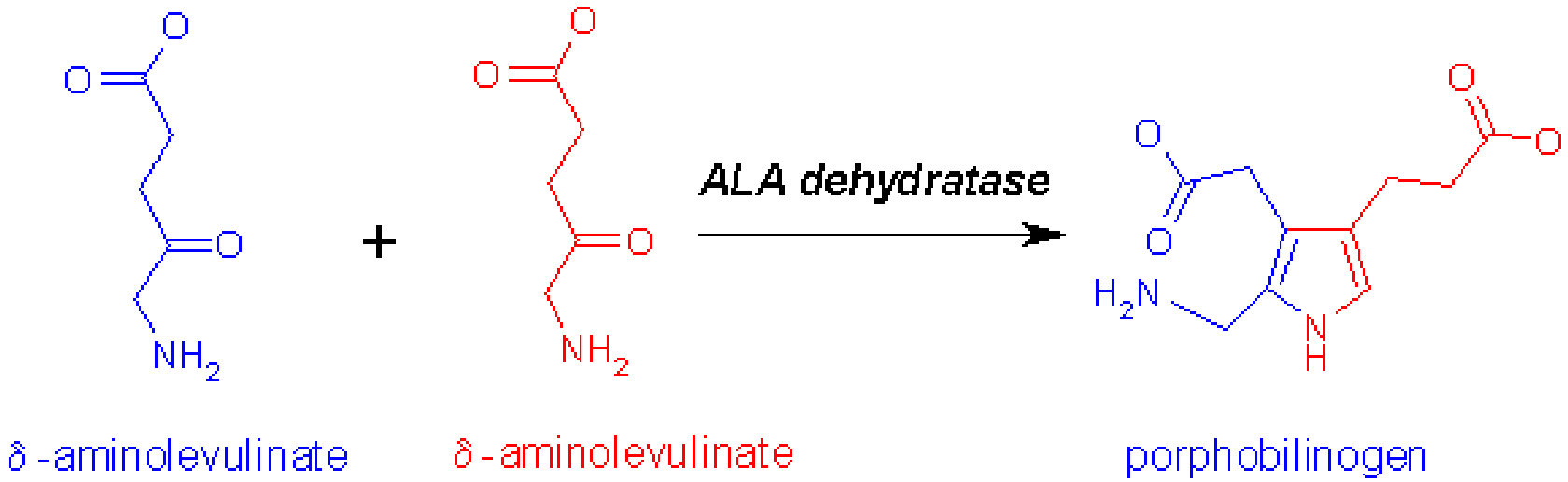


The first step in haem synthesis is the combination of succinyl CoA and glycin to produce δ aminolaevulinic acid (δ ALA). This reaction is energy dependent and so occurs in the mitochondria.



Haem synthesis

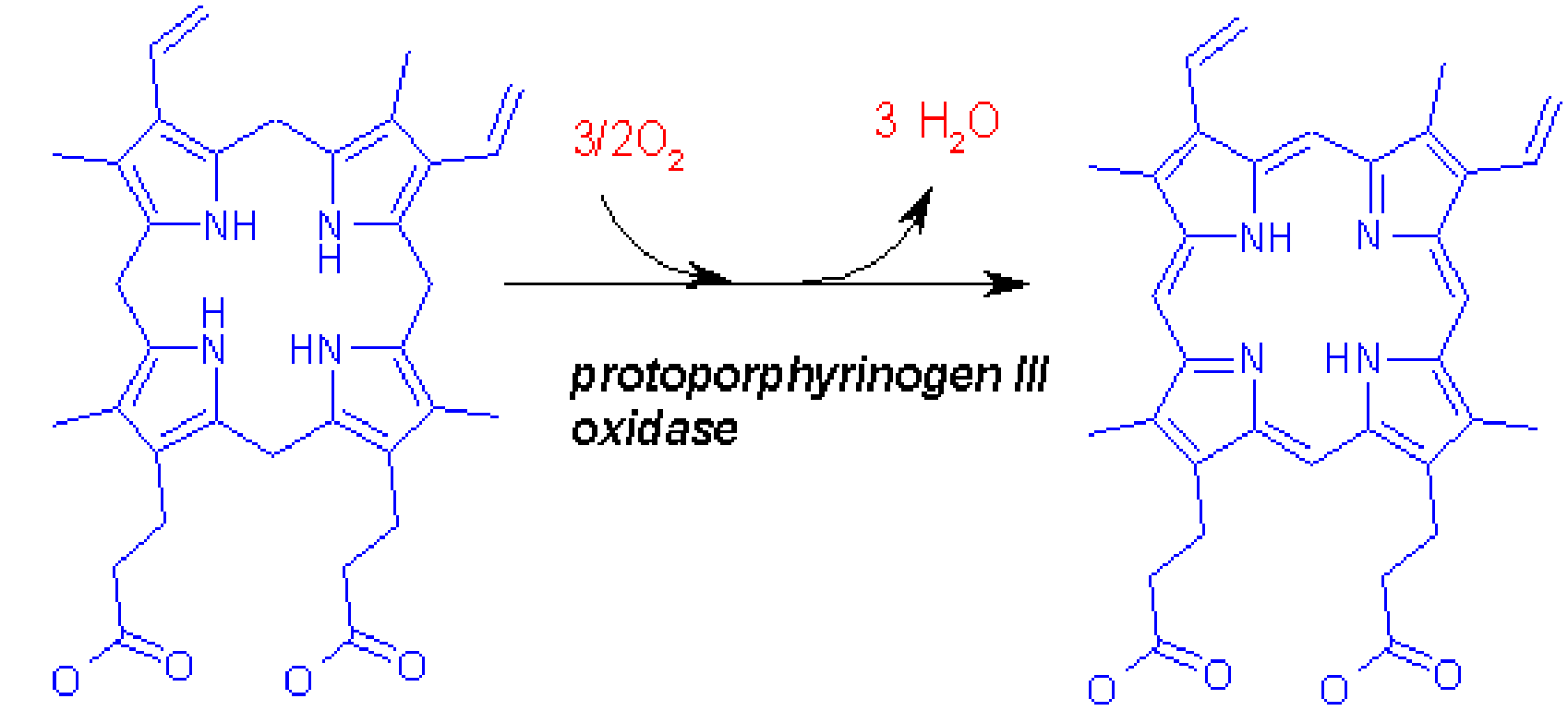
- It’s catalyzed by the enzyme δ ALA synthetase.
- This step is a first-limiting step for the whole process of haem synthesis.
- It is stimulated by the presence of globin chains and inhibited by the presence of free haem groups.
- This represents an important control mechanism of the rate of haem synthesis and it’s coordination with globin synthesis.
- Several factors are required for this step, including vitamin B6, free ferrous and copper ions.
- Synthesis of the enzyme δ ALA synthetase is inhibited by the presence of free haem.
- This represents a further feedback mechanism for haem synthesis.



Mitochondrial δ -aminolevulinic acid (ALA) is transported to the cytoplasm, where ***ALA dehydratase*** (also called ***porphobilinogen synthase***) dimerizes 2 molecules of ALA to produce the pyrrole ring compound **porphobilinogen (PBG)**.

Haem synthesis

- The next step requires the synthesis of porphyrin ring.
- The reactions involved are extremely complex but can be summarized as the condensation of four PBG molecules to form the asymmetric cyclic uroporphyrinogen III (UPGIII).
- Synthesis of UPGIII requires the presence of two enzymes (uroporphyrinogen I synthetase and uroporphyrinogen III cosynthetase) and involves the formation of several short-lived intermediates.



PPG IX is further converted within the mitochondria to protoporphrin IX.

2^{nd} : Globin synthesis

- Humans normally carry 8 functional globin genes, arranged in two duplicate gene clusters:
- The β-like cluster on the short arm of chromosome 11.
- The α-like cluster on the short arm of chromosome 16.
- These genes code for 6 different types of globin chains: α,β,γ,δ,ε,ζ, globin.

Methemoglobinemia

- In order to bind oxygen reversibly, the iron in the heme moiety of hemoglobin must be maintained in the **reduced** (ferrous) state despite exposure to a variety of endogenous and exogenous oxidizing agents.

- The red cell maintains several metabolic pathways to prevent the action of these oxidizing agents and to reduce the hemoglobin iron if it becomes oxidized. Under certain circumstances, these mechanisms fail and hemoglobin becomes nonfunctional.

Methemoglobinemia

- At times, hemolytic anemia supervenes as well. These abnormalities are particularly likely to occur

(1) if the red cell is exposed to certain oxidant drugs or toxins
(2) if the intrinsic protective mechanisms of the cell are defective or
(3) if there are genetic abnormalities of the hemoglobin molecule affecting globin stability or the heme crevice.

- **Hemoglobin levels are measured by the amount of hemoglobin in grams (gm) per deciliter (dl) of blood. The normal ranges for hemoglobin values are dependent on the age and sex. Normal ranges are:**
-
- Newborns: 17-22 gm/dl
-
- One (1) week of age: 15-20 gm/dl
-
- One (1) month of age: 11-15 gm/dl
-
- Children: 11-13 gm/dl
-
- Adult women: 12-16 gm/dl
-
- Adult males: 14-18 gm/dl
-
- Women after middle age: 11.7-13.8 gm/dl
-
- Men after middle age: 12.4-14.9 gm/dl
-

Diseases related to hemoglobin

Hemoglobin deficiency can be caused either by a decreased amount of hemoglobin molecules, as in anemia, or by decreased ability of each molecule to bind oxygen at the same partial pressure of oxygen. Hemoglobinopathies (genetic defects resulting in abnormal structure of the hemoglobin molecule) may cause both. In any case, hemoglobin deficiency decreases blood oxygen-carrying capacity. Hemoglobin deficiency is, in general, strictly distinguished from hypoxemia, defined as decreased partial pressure of oxygen in blood, although both are causes of hypoxia (insufficient oxygen supply to tissues).

Other common causes of low hemoglobin include loss of blood, nutritional deficiency, bone marrow problems, chemotherapy, kidney failure, or abnormal hemoglobin (such as that of sickle-cell disease).

Decrease of hemoglobin, with or without an absolute decrease of red blood cells, leads to symptoms of anemia. Anemia has many different causes, although iron deficiency and its resultant iron deficiency anemia are the most common causes in the Western world. As absence of iron decreases heme synthesis, red blood cells in iron deficiency anemia are *hypochromic* (lacking the red hemoglobin pigment) and *microcytic* (smaller than normal). Other anemias are rarer.
In hemolysis (accelerated breakdown of red blood cells), associated jaundice is caused by the hemoglobin metabolite bilirubin, and the circulating hemoglobin can cause kidney failure.
Some mutations in the globin chain are associated with the hemoglobinopathies, such as sickle-cell disease and thalassemia. Other mutations, as discussed at the beginning of the article, are benign and are referred to merely as hemoglobin variants.

Diagnostic

Hemoglobin concentration measurement is among the most commonly performed blood tests, usually as part of a complete blood count. For example, it is typically tested before or after blood donation. Results are reported in g/L, g/dL or mol/L. 1 g/dL equals about 0.6206 mmol/L, although the latter units are not used as often due to uncertainty regarding the polymeric state of the molecule.[92] This conversion factor, using the single globin unit molecular weight of 16,000 Da, is more common for hemoglobin concentration in blood. For MCHC (mean corpuscular hemoglobin concentration) the conversion factor 0.155, which uses the tetramer weight of 64,500 Da, is more common.uses

Normal levels are:

- Men: 13.8 to 18.0 g/dL (138 to 180 g/L, or 8.56 to 11.17 mmol/L)
- Women: 12.1 to 15.1 g/dL (121 to 151 g/L, or 7.51 to 9.37 mmol/L)
- Children: 11 to 16 g/dL (110 to 160 g/L, or 6.83 to 9.93 mmol/L)
- Pregnant women: 11 to 14 g/dL (110 to 140 g/L, or 6.83 to 8.69 mmol/L)
- (9.5 to 15 usual value during pregnancy)[1]

Blood glucose and its regulation

Blood glucose regulation involves maintaining blood glucose levels at constant levels in the face of dynamic glucose intake and energy use by the body. Glucose is key in the energy intake of humans.

On average this target range is 60-100 mg/dL for an adult although people can be asymptomatic at much more varied levels. In order to maintain this range there are two main hormones that control blood glucose levels: insulin and glucagon. Insulin is released when there are high amounts of glucose in the blood stream.

Glucagon is released when there are low levels of glucose in the blood stream. There are other hormones that effect glucose regulation and are mainly controlled by the sympathetic nervous system. Blood glucose regulation is very important to the maintenance of the human body. The brain doesn’t have any energy storage of its own and as a result needs a constant flow of glucose, using about 120 grams of glucose daily or about 60% of total glucose used by the body at resting state. With out proper blood glucose regulation the brain and other organs could starve leading to death.

A key regulatory pathway to control blood glucose levels is the hormone insulin. Insulin is released from the beta cells in the islets of Langerhans found in the pancreas. Insulin is released when there is a high concentration of glucose in the blood stream.

Glucose enters the cell and ATP is produce in the mitochondria through the Krebs cycle and electron transport chain.

The process by which insulin is degraded and metabolized is poorly understood. However it is known that the liver is responsible for the majority of insulin break down. Since the liver is so important to proper insulin levels when the liver is damaged perhaps by alcohol the regulatory system can be interfered with.

The kidney is also key in the break down of insulin. Peripheral tissue is thought to hold on to insulin perhaps reversibly binding to membrane receptors. These means it is possible for insulin to be removed from the blood stream with out being broken down. Insulin clearance rates are shown to decrease in those who are obese or have diabetes. This may create insensitivity to insulin.

Blood contains glucose which is an important source of energy for the body, including the brain and nervous system.

The glucose in blood must be kept within a normal range for the body to work properly.

If it rises or falls significantly, the body can usually bring it back to normal. This process is called homeostasis.

Regulation of glucose by hormones

Hormones are chemical messengers produced in one part of the body and carried in the blood to cause some action in another part of the body. Different hormones have different actions.

The level of glucose is regulated by the hormones, insulin and glucagon, both released by the pancreas.

The amount of glucose in blood increases after a meal. This is called hyperglycaemia.

Insulin is released from the pancreas and causes the cells in the body, the liver, muscle and fat tissues in particular, to take up glucose from the bloodstream.

This reduces the amount of glucose in blood and the pancreas stops producing insulin. The blood glucose level then falls back to normal.

As the body takes up the glucose in blood for energy, its level falls. The pancreas releases glucagon, which has the opposite effect from insulin. It increases the level of glucose in the blood by stimulating the liver to release glucose.

Other hormones are also produced when the blood glucose level falls too low, e.g. adrenaline and cortisol. These help to bring the level of glucose in the blood back to normal.

Diabetes Mellitus

Diabetes Mellitus, commonly referred to as diabetes, is a condition where chronic hyperglycaemia occurs since the body is unable to control the amount of glucose in blood. The glucose rises above the normal range.

People with diabetes do not produce enough insulin or the insulin they produce is not effective.

Health problems caused by diabetes

Diabetes cannot be cured and is a common, serious, chronic disease which affects health and life expectance.

Symptoms of diabetes include thirst, large amounts of urine, tiredness, blurred vision, dry skin and the loss of weight in some cases.

In the long-term, uncontrolled diabetes can lead to damage to the eyes, nerves, kidneys and blood vessels. Coma and death may also result.

There are two main types of diabetes:

Type 1 diabetes
Also known as Insulin dependent diabetes mellitus. This accounts for 5% to 15% of all cases of diabetes.

Type 2 diabetes
Also known as Non-insulin dependent diabetes mellitus. This accounts for 85% to 95% of all cases of diabetes.

Type 1 diabetes

The pancreatic cells which normally produce insulin in people with Type 1 diabetes are missing or damaged. The body does not produce insulin so blood glucose levels remain high.

This must be treated by daily injections of insulin which helps control the blood glucose level. Type 1 diabetes usually begins before the age of 40, often in early childhood.

Type 2 diabetes

This is also called adult-onset diabetes. People with Type 2 diabetes produce insulin in their pancreas, but it is insufficient to control blood glucose effectively. This is often because the body tissues are resistant to the action of insulin.

Type 2 diabetes can be controlled or improved by diet. If someone with Type 2 diabetes is overweight, then weight loss will usually improve the symptoms. Some people with Type 2 diabetes need to take medicines to reduce the level of glucose in blood.

Risk factors for diabetes

Type 1 diabetes:

- family history/genetics;
- viral infection.

Type 2 diabetes:

- family history/genetics;
- overweight or obesity, especially central obesity;
- adults aged over 40;
- people of Asian or African-Caribbean origin;
- lower socio-economic status;
- low birth weight;
- previous gestational diabetes (during pregnancy).

Diet and diabetes

Having a healthy, balanced diet is important for controlling the symptoms of both types of diabetes.

People with diabetes should try to keep their blood glucose levels within the normal range. To do this, it is important to eat regular meals, with lots of fruit and vegetables and plenty of wholegrain starchy foods.

Carbohydrate

Foods that provide carbohydrate (starch and sugar) raise blood glucose levels significantly.

It is recommended that 50% of total energy intake should come from carbohydrate.

Most of this should be from starchy foods, such as bread, rice, potatoes and pasta as these raise blood levels fairly slowly. It is important to have these foods distributed evenly throughout the day.

Foods that are high in sugar should only be eaten in small amounts. Sweeteners, such as saccharin and aspartame, may be useful sugar replacements.

Fibre

There are two types of fibre: soluble and insoluble.

Foods providing soluble fibre, such as fruits, vegetables, beans and pulses, have shown to slow the absorption of carbohydrate in the gut.

Wholegrain cereals, wholemeal bread and brown rice are high in insoluble fibre, have beneficial effects on the digestive system and have been shown to regulate the level of blood glucose in blood.

Fat

It is particularly important for people with diabetes to cut down on their fat intake. Having diabetes and high fat intakes can increase the risk of coronary heart disease.

People with diabetes are recommended to reduce fat intake to 30-35% of energy. Of this, 10% of energy should be from saturated fat.

Alcohol

Advice on alcoholic drinks is the same as the general population. Alcohol can be included in the diets of people with diabetes in moderation: 2 to 3 units per day for women and 3 to 4 units per day for men.

Intakes should be carefully planned into the diet, e.g. alcohol should never be taken on an empty stomach.

Diabetic Foods

Special diabetic cakes, biscuits or pastries are of no particular benefit and may contain a lot of fat.

Special diabetic foods are available for people with diabetes, but people with diabetes can eat a diet using popular foods, as long as it is well-balanced.

Energy balance

Physical inactivity, overweight and obesity have been strongly linked to an increased risk of Type 2 diabetes, as well as other diseases, such as hypertension, heart disease, stroke and cancer.

It is important to balance the energy from food with the energy used through activity and keep a healthy weight to maintain health.

Hypoglycemia

Hypoglycemia is a condition caused by a very low level of blood sugar (glucose), your body's main energy source.

Hypoglycemia is often related to the treatment of diabetes. However, a variety of conditions can cause low blood sugar in people without diabetes. Like fever, hypoglycemia isn't a disease itself — it's an indicator of a health problem.

Immediate treatment of hypoglycemia is necessary when blood sugar levels are at 70 milligrams per deciliter (mg/dL) or 3.9 millimoles per liter (mmol/L) or below.

Treatment involves quick steps to get your blood sugar level back into a normal range either with high-sugar foods or drinks or with medications. Long-term treatment requires identifying and treating the underlying cause of hypoglycemia.

Symptoms

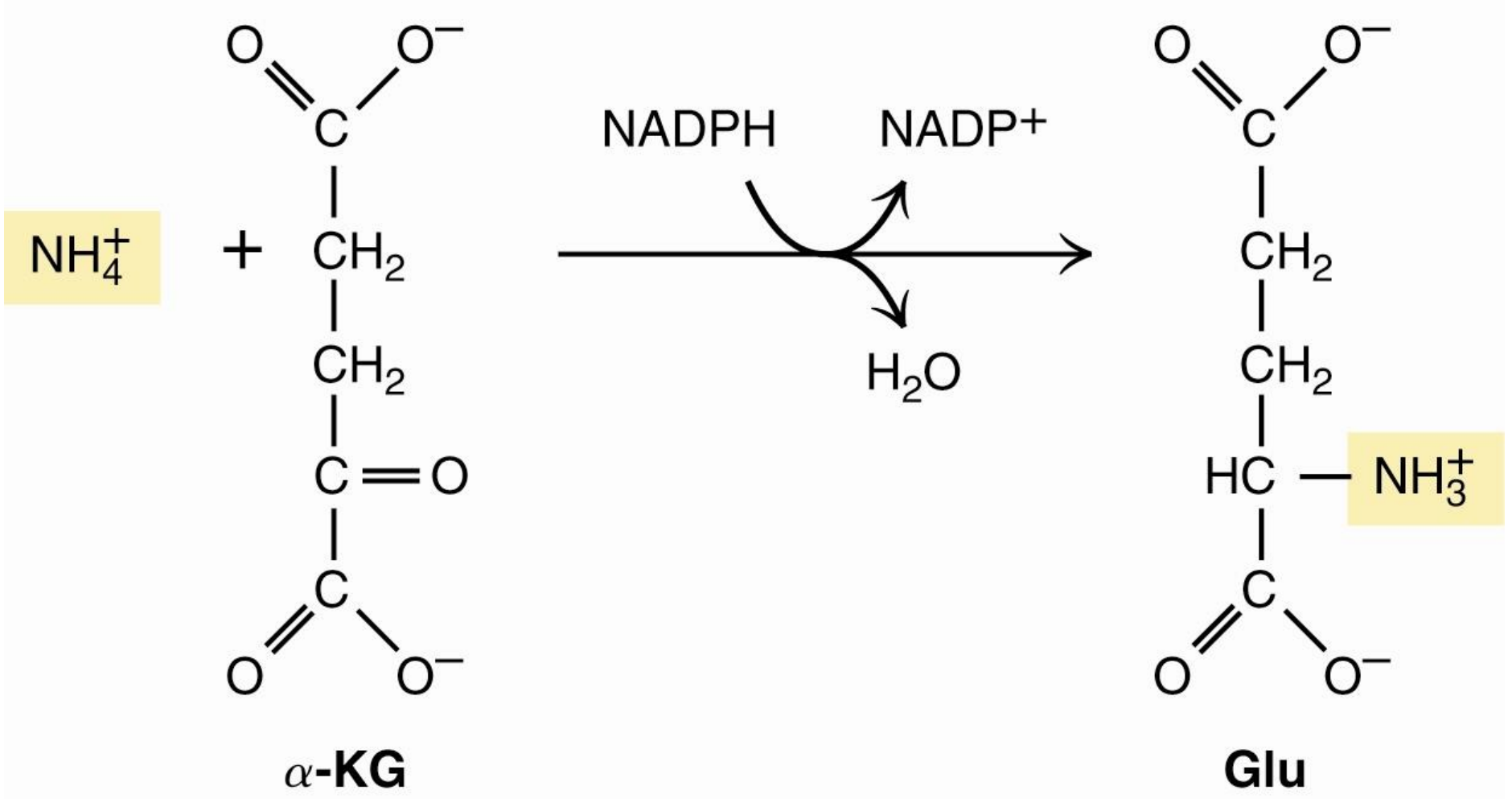
If blood sugar levels become too low, signs and symptoms may include:
•An irregular heart rhythm
•Fatigue
•Pale skin
•Shakiness
•Anxiety
•Sweating
•Hunger
•Irritability
•Tingling sensation around the mouth
•Crying out during sleep

As hypoglycemia worsens, signs and symptoms may include:
•Confusion, abnormal behavior or both, such as the inability to complete routine tasks
•Visual disturbances, such as blurred vision
•Seizures
•Loss of consciousness

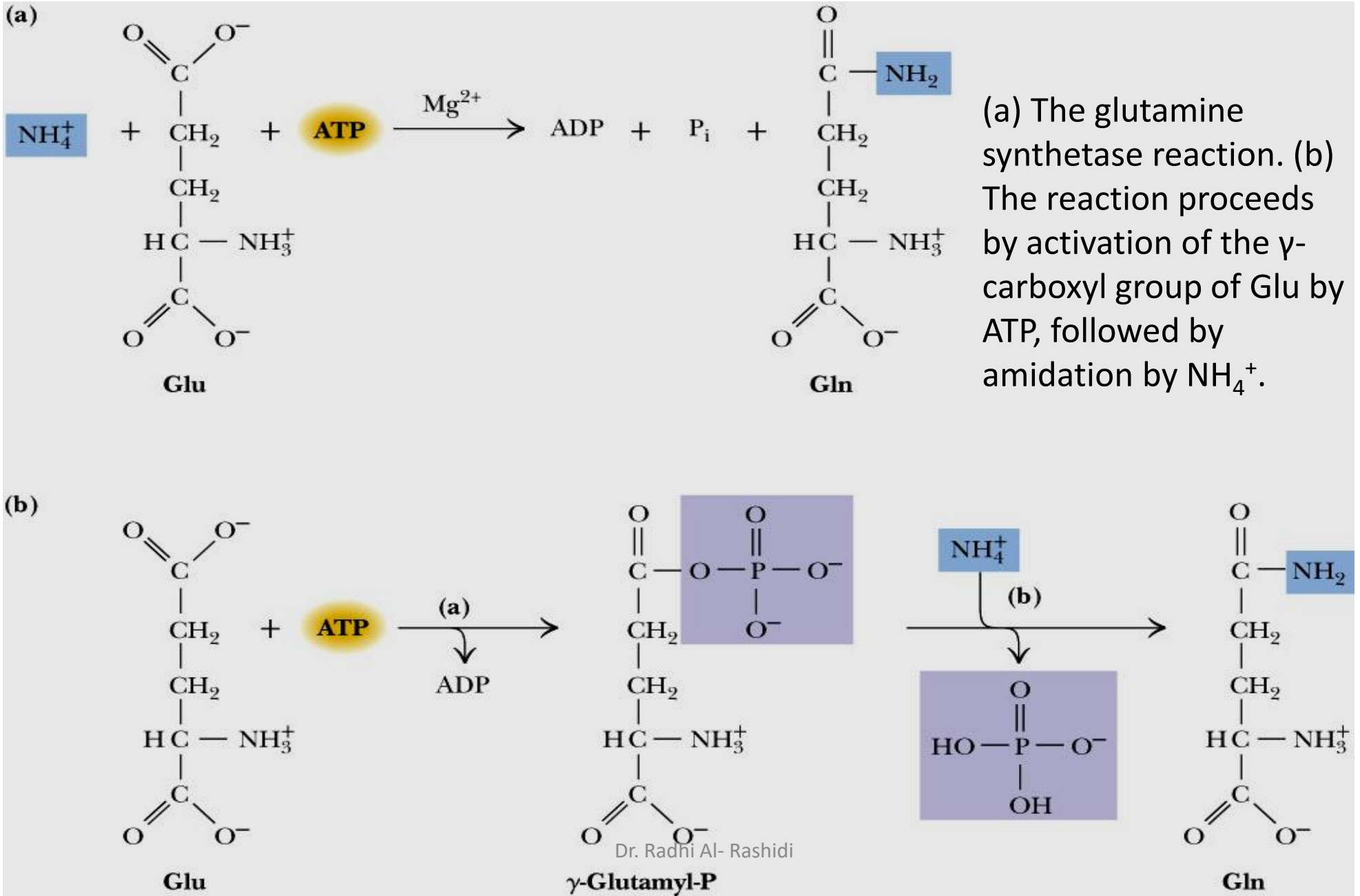
Fate of Ammonium Ions

- Only three major reactions introduce NH_4 into cells:
  - Glutamate dehydrogenase
  - Glutamine synthetase
  - Carbamoyl-phosphate synthetase I (mitochondrial enzyme of urea cycle)

Glutamate Dehydrogenase



Glutamine Synthetase



(a) The glutamine synthetase reaction. (b) The reaction proceeds by activation of the γ-carboxyl group of Glu by ATP, followed by amidation by NH_4^+.

Carbamoyl-Phosphate Synthetase

- **Reaction is:**

- **This reaction is an early step in the urea cycle**
- **Note the name "synthetase", which is reserved for synthetic enzymes that use ATP**
- **Enzymes that synthesize but do not use ATP are termed "synthases"**

Formation of Ammonia

1. In liver amino acids undergo deamination
2. In liver and kidney glutamate undergo deamination
3. In kidney glutamine is deaminated
4. From intestinal bacteria flora
5. From degradation of purine and pyrimidine nitrogenous bases

Fate of Ammonia

1. Amination of keto acids by transaminase enzyme
2. Amination of ketoglutarate to glutamate
3. Amination of glutamate to glutamine
4. Detoxification of ammonia to urea in liver

Urea

Urea is the principal nitrogenous waste product of metabolism and is generated from protein breakdown.
It is eliminated from the body almost exclusively by the kidneys in urine, and measurement of its concentration, first in urine and later in blood, has had clinical application in the assessment of kidney (renal) function.

Measurement of plasma/serum urea – a note on nomenclature and units

Around the world, essentially the same method of urea analyses is used, but the result is expressed in two quite different ways.

In the US and a few other countries, plasma or serum urea concentration is expressed as the amount of urea nitrogen.

Although plasma or serum is used for the analysis, commonly referred to as blood urea nitrogen (BUN), and the unit of BUN concentration is mg/dL.

In all other parts of the world, urea is expressed as the whole molecule (not just the nitrogen part of the molecule) in SI units (mmol/L).

Since BUN reflects only the nitrogen content of urea (MW 28) and urea measurement reflects the whole of the molecule (MW 60), urea is approximately twice (60/28 = 2.14) that of BUN.

Thus BUN 10 mg/dL is equivalent to urea 21.4 mg/dL.

To convert BUN (mg/dL) to urea (mmol/L):

multiply by 10 to convert from /dL to /L and divide by 28 to convert from mg BUN to mmol urea, i.e. 10/28 = 0.357

So the conversion factor is 0.357
BUN mg/dL multiplied by 0.357 = urea (mmol/L)
Urea (mmol/L) divided by 0.357 = BUN (mg/dL)

Approximate reference (normal) range:
Serum/plasma urea 2.5-7.8 mmol/L
Serum/plasma BUN 7.0-22 mg/dL

It is widely accepted that there is an age-related increase in plasma/serum urea concentration, but this is not well defined and there is uncertainty as to whether it simply reflects an age-related decline in renal function as some studies suggest, or occurs despite normal renal function as others seem to suggest. The results of suggest that healthy elderly individuals (without any apparent loss of renal function), may have BUN levels as high as 40-50mg/dL (14.3-17.8 mmol/L).

Uremia

Uremia occurs when your kidneys become damaged. The toxins, or bodily waste, that your kidneys normally send out in your urine end up in your bloodstream instead. These toxins are known as creatinine and urea.

Uremia is a serious condition and, if untreated, can be life-threatening. Uremia is a major symptom of renal failure. Uremia is also a sign of the last stages of chronic kidney disease.

Symptoms of uremia

At the beginning of chronic kidney disease, you may not notice any symptoms. However, by the time uremia has started, your kidneys are very damaged. Uremia may cause you to have some of the following symptoms:

- extreme tiredness or fatigue
- cramping in your legs
- little or no appetite
- headache
- nausea
- vomiting
- trouble concentrating

Causes of uremia

Uremia is caused by extreme and usually irreversible damage to your kidneys. This is usually from chronic kidney disease. The kidneys are no longer able to filter the waste from your body and send it out through your urine. Instead, that waste gets into your bloodstream, causing a potentially life-threatening condition.

Treatment options

By the time you have developed uremia, your kidneys are extremely damaged. Dialysis is the main treatment option for uremia. Dialysis is when the removal of wastes, extra fluids, and toxins from your bloodstream is handled artificially instead of by your kidneys.

Amino acids act as buffer

Amino acids are important in a number of ways. Not only are they essential for the synthesis of proteins but they are also responsible for your enzymes, hormones, neurotransmitters, metabolic pathways, mental stabilization, and just about every function that takes place within the human body.

This is because protein too plays a crucial role in almost all biological processes (not just getting bigger muscles) and amino acids are the building blocks of it all.

An amino acid can act as a buffer due to the fact it can react with acids **and** bases to keep the pH constant.

A good example of this would be the protein hemoglobin. It can bind to small amounts of acid in the blood, helping to remove that acid before it changes the blood's pH thus making it an excellent buffer.

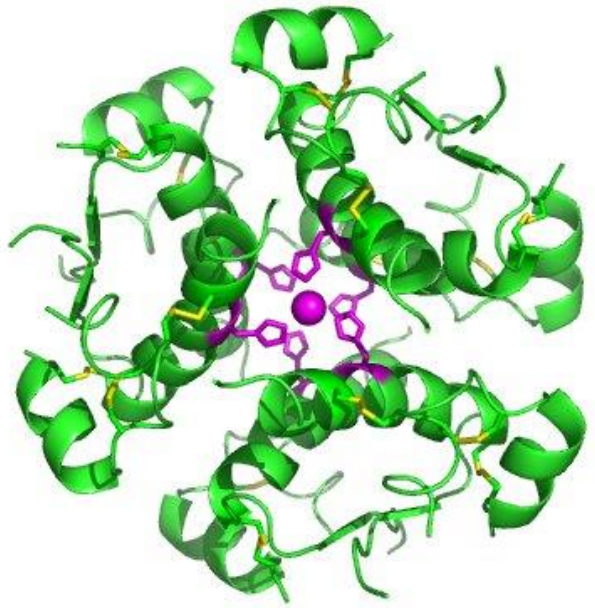
Serum Protein Components

Serum proteins (also blood or plasma proteins) are proteins present in blood that serve many different functions, including transport of lipids, hormones, vitamins and minerals in the circulatory system and the regulation of acellular activity and functioning of the immune system.
Other blood proteins act as enzymes, complement components, protease inhibitors. Although serum proteins have very high concentration, they exhibit an uneven distribution in terms of composition. That is, only about 22 proteins account for 99% of all the serum proteins. These include serum albumin, globulins and fibrinogen. The remainder 1% of blood proteins is composed of low abundance circulatory proteins as well as proteins secreted by live, apoptotic and necrotic cells. Most of blood proteins are secreted by the liver and intestines except for the gamma globulins, synthesized by the immune system.

Insulin Structure

Insulin is a peptide hormone composed of 51 amino acids and has a molecular weight of 5808 Da.

Insulin is produced and stored in the body as a hexamer , while the active form is the monomer.



- Hexamer is more stable then the monomer, which is better for practical reasons.
- Monomer is a much faster-reacting drug, it means that insulin injections do not have to precede mealtimes by hours.

- Insulin is produced by beta cells in the islets of Langerhans, which release insuln in two phases: The first phase release is triggered in response to rising or increased blood glucose levels. The second phase is a sustained, slow release of newly formed vesicles triggered independently of sugar.
- Beta cells in the islets of Langerhans take up as much as 60%-80% of all the cells.

LIPID METABOLISM

Prof Dr. Radhi Al-Rashidi

Kut University College

LIPID METABOLISM

Fatty acid oxidation
Ketone bodies
Cholestrol metabolism
Lipoprotein metabolism

Definition of Lipids

- Substances in dairy foods
- Known as fats and oils
- Hydrophobic and soluble in ethanol like alcohol, petroleum and chloroform
- Classified into 2 general types
  Fats and waxes (can be hydrolyzed with ester linkages)
  cholesterol and steroids (cannot be hydrolyzed

Type of Lipids

- Saturated fat
  Animal oil like meat, milk, butter
  Vegetable oil like coconut and palm kernel oil
- Polyunsaturated fat
  Plant source like safflower, corn, cottonseed, sunflower oil and soybean oil
- Monounsaturated fat
  Plant and animal product like olive oil, canola oil, avocado and peanut oil

Lipids Functions

- Excellent energy reserves
- Structure of cell membranes
- Organ padding
- Body thermal insulation
- Essential fatty acids (EFA)
- Hormone synthesis
- Fat soluble vitamin absorption

Type of Lipids

- Saturated fat
  Animal oil like meat, milk, butter
  Vegetable oil like coconut and palm kernel oil
- Polyunsaturated fat
  Plant source like safflower, corn, cottonseed, sunflower oil and soybean oil
- Monounsaturated fat
  Plant and animal product like olive oil, canola oil, avocado and peanut oil

Lipids Disorder

- Lipids deficiency (Shortage in Lipids intake)
- Lipids exceeding (Overtaking in Lipids intake)

Lipids Deficiency

- Fat should comprise of 3% of total calories to prevent fatty acid deficiency
- Fatty acid deficiency syndromes
  Dry scaly skin, dermatitis (Linoleic acid deficiency)
  Hand tremors (Prostaglandin deficiency)
  Inability to control blood pressure

Body Mass Index

- **Current best single gauge for body fat**
- **BMI =(Weight in Kg)/((Height in cm)(Height in cm)) X 10,000**

BMI	Weight Status
Below 18.5	Underweight
18.5 – 24.9	Healthy Weight
25.0 – 29.9	Overweight
30.0 and Above	Obese

Health Problems

- Energy Intake > Energy needed = Lipids overtaking
- Develop medical problem
  - Cancer
  - Heart disease
  - Diabetes
  - Obesity
  - High blood pressure
  - High blood cholesterol

Cholesterol

- Plant and animal food contain sterols but only animal food contain cholesterol
- Why? Cholesterol is made in the liver and plants do no have a liver
- Cholesterol is needed to make bile, sex hormones, steroids and vitamin D.
- It is the constituent of cell membrane structure
- Dietary recommendation - <300 mg/d
- Sources – egg yolks, liver, shellfish, organ foods

Lipoproteins

- Low Density Lipoproteins (LDL) – is made by the liver and is comprised of cholesterol that is delivered to the cells in the body.
  High levels of LDL is strongly correlated with heart disease
- High Density Lipoproteins (HDL) - made by the liver and picks up cholesterol from the cells from recycling or excretion.
  High levels of HDL is inversely correlated with heart disease
  It is protective

Blood levels for Lipids

Total Cholesterol:

- <200 mg/dl = desirable
- 200-239 mg/dl = borderline hyperlipidemia
- >240 mg/dl = hyperlipidemia

LDL < 130 mg/dl is favorable

HDL > 35 mg/dl is favorable

Prevention of Lipid Disorder

- Reduce fat
  Cut down on high fat foods E.g. butter, margarine, oil, mayonnaise
- Consume small amounts of unsaturated fats
  Do not eliminate fat completely since it is high in calories
- Limit added sugar and alcohol
  Added sugar and alcohol are ‘empty calories’
- Watch portions of all food
  fat free’ ≠ ‘calorie-free’
- Drink at least 8 glasses of water everyday
  Water is calorie-free, refreshing, and filling

- Increase intake of vegetables, fruits, and whole grains
  Loaded with fiber
  Contain high amounts of vitamins, minerals, and phytonutrients
- Include low-fat protein-rich food with every meal
  E.g. tofu, beans, eggs, and fish
- Slow down when eating

Too fast eating will exceed calorie needs before realizing we are full

Chapter 17: Oxidation of Fatty Acids

keystone concepts

- The insolubility of triglycerides in dietary lipids and adipose tissue must be accommodated
- Fatty acids are oxidized in the mitochondria
- Fatty acids must be transported across the inner mitochondrial membrane
- Oxidation of fatty acids in the mitochondria has three stages
- Oxidation of unsaturated and odd chain fatty acids requires additional reactions
- In mammals, an alternative pathway for acetyl-CoA produces ketone bodies

1

ES OF FATTY ACID
DATION

cids can be oxidized by-

n oxidation- Major mechanism, occurs in the ondria matrix. 2-C units are released as CoA per cycle.

na oxidation- Predominantly takes place in nd liver, one carbon is lost in the form of er cycle.

ega oxidation- Minor mechanism, but es important in conditions of impaired beta on

oxisomal oxidation- Mainly for the trimming long chain fatty acids.

BETA-OXIDATION

- Fatty acids (FA) from the diet or from the degradation of triglycerides stored in adipose cells are broken down further to smaller molecules to completely metabolize them and therefore release energy.
- This process of catabolism of FA includes three major parts:
  - Activation of FA and its transport into mitochondria
  - Beta-oxidation
  - Electron Transport Chain

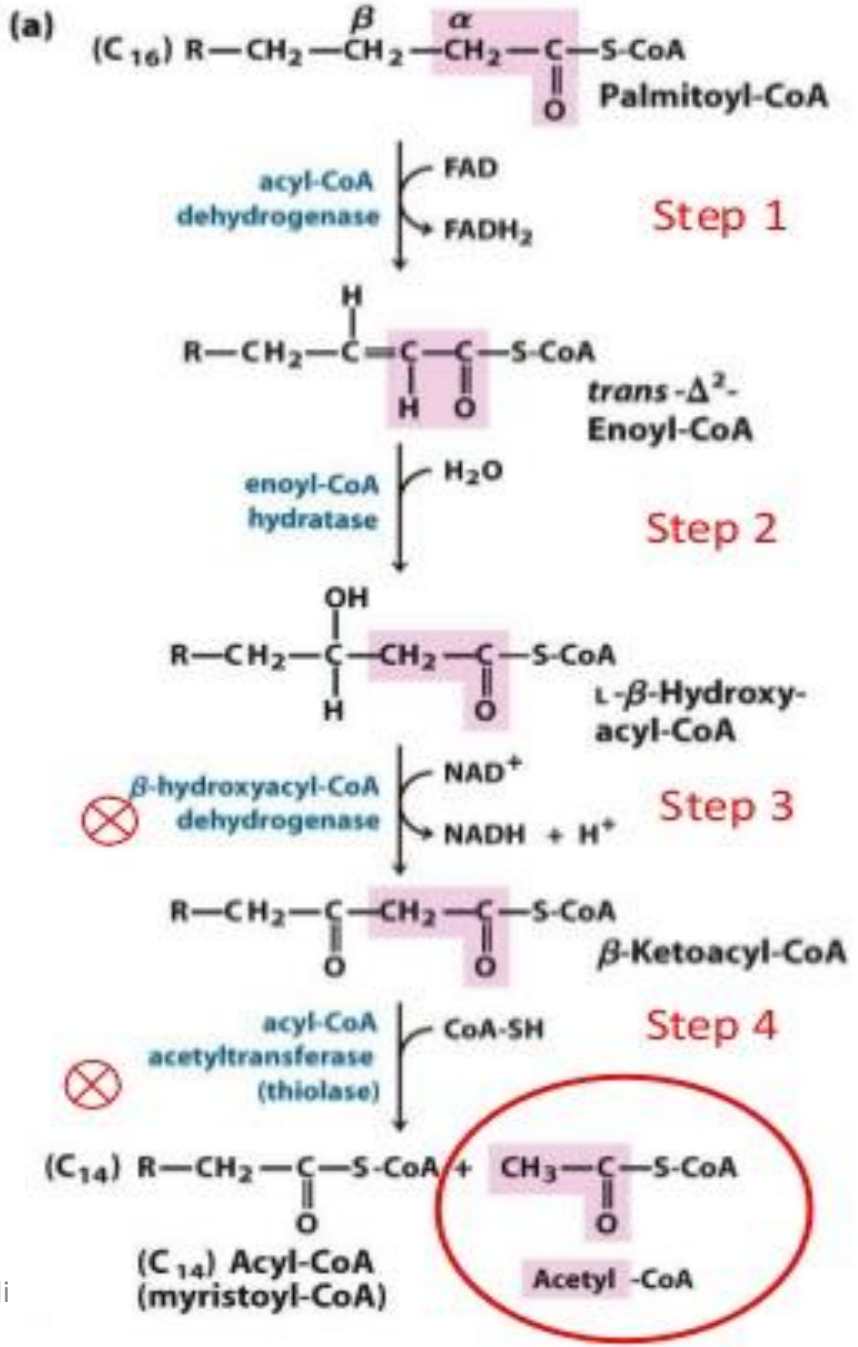
4 Steps of β-oxidation

1. Dehydrogenation of the fatty acyl-CoA to make a trans double bond between α and β carbon.
   - Short, medium, and long chain acyl-CoAdehydrogenases
   - e^- removed transferred to FAD
2. Hydration of the double bond

1. Dehydrogenation of the β-hydroxyl group to a ketone

   - e^- removed transferred to NAD^+

1. Acylation – addition of CoA and production of acetyl-CoA



Alpha-oxidation of phytanic acid is believed to take place entirely within peroxisomes.

1. Phytanic acid is first attached to CoA to form phytanoyl-CoA.

2. Phytanoyl-CoA is oxidized by phytanoyl-CoA dioxygenase, in a process using Fe^{2+} and O_2, to yield 2-hydroxyphytanoyl-CoA.

3. 2-hydroxyphytanoyl-CoA is cleaved by 2-hydroxyphytanoyl-CoA lyase in a TPP-dependent reaction to form pristanal and formyl-CoA (in turn later broken down into formate and eventually CO_2).

4. Pristanal is oxidized by aldehyde dehydrogenase to form pristanic acid (which can then undergo beta-oxidation).
(Propionyl-CoA is released as a result of beta oxidation when the beta carbon is substituted)

Deficiency

Enzymatic deficiency in alpha-oxidation (most frequently in phytanoyl-CoA dioxygenase) leads to Refsum's disease, in which the accumulation of phytanic acid and its derivatives leads to neurological damage. Other disorders of peroxisome biogenesis also prevent alpha-oxidation from occurring.

Fatty Acids and Energy

- Fatty acids in triglycerides are the principal storage form of energy for most organisms.
  - Hydrocarbon chains are a highly reduced form of carbon.
  - The energy yield per gram of fatty acid oxidized is greater than that per gram of carbohydrate oxidized.

	Energy ($kcal \cdot mol^{-1}$)	Energy ($kcal \cdot g^{-1}$)
$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O$ **Glucose**	686	3.8
$CH_3(CH_2)_{14}COOH + 23O_2 \longrightarrow 16CO_2 + 16H_2O$ **Palmitic acid**	2,340	9.3

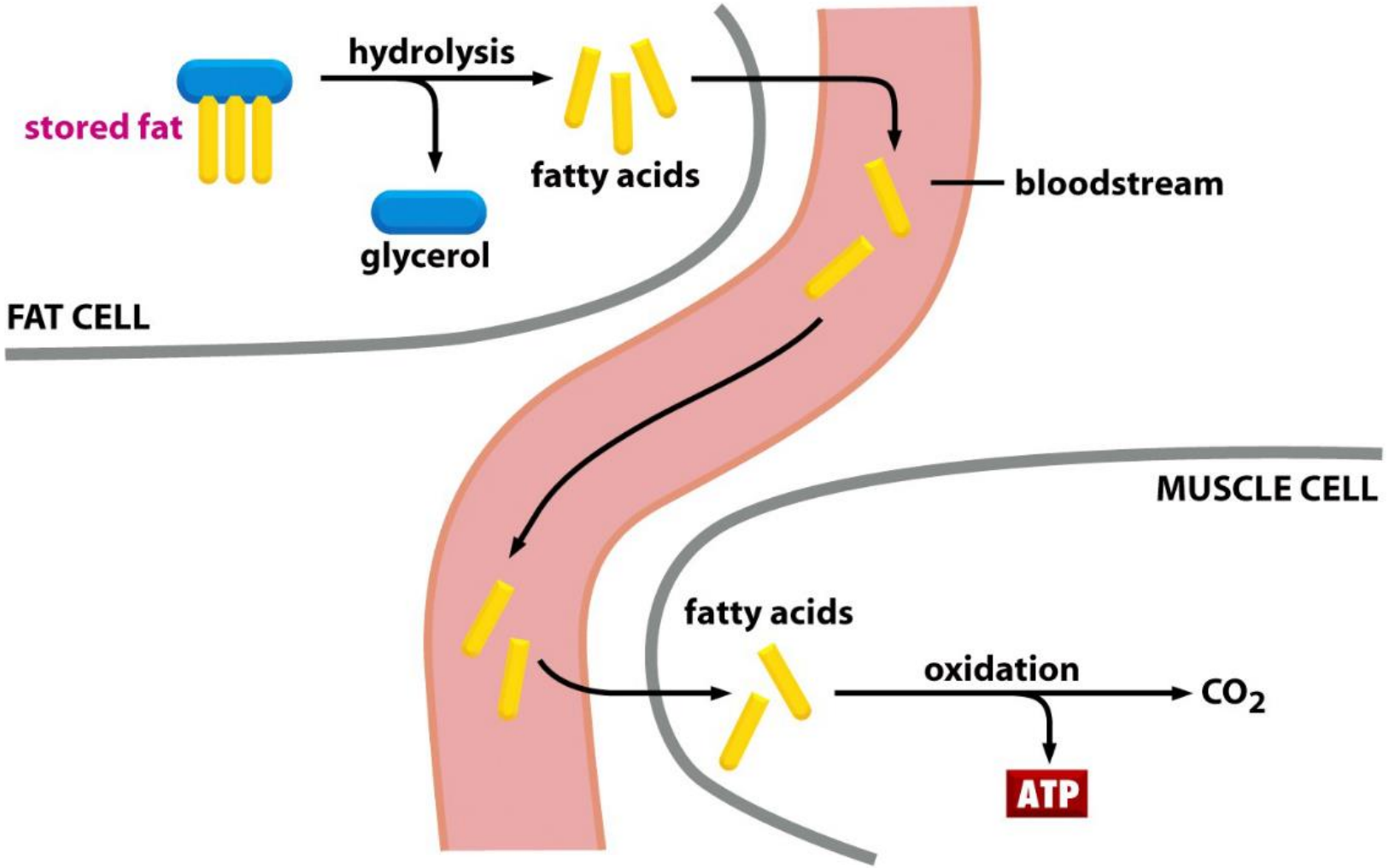


Figure 2-78 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Ketone Bodies

- **Ketone bodies**: acetone, β-hydroxybutyrate, and acetoacetate;
  - are formed principally in liver mitochondria.
  - can be used as a fuel in most tissues and organs.
- Formation occurs when the amount of acetyl CoA produced is excessive compared to the amount of oxaloacetate available to react with it and take it into the TCA; for example:
  - intake is high in lipids and low in carbohydrates.
  - diabetes is not suitably controlled.
  - starvation.

Ketone bodies

Fasting

Diabetes

high level of ketone bodies in the blood

KETOSIS

Formation in the liver exceeds the use in the periphery.

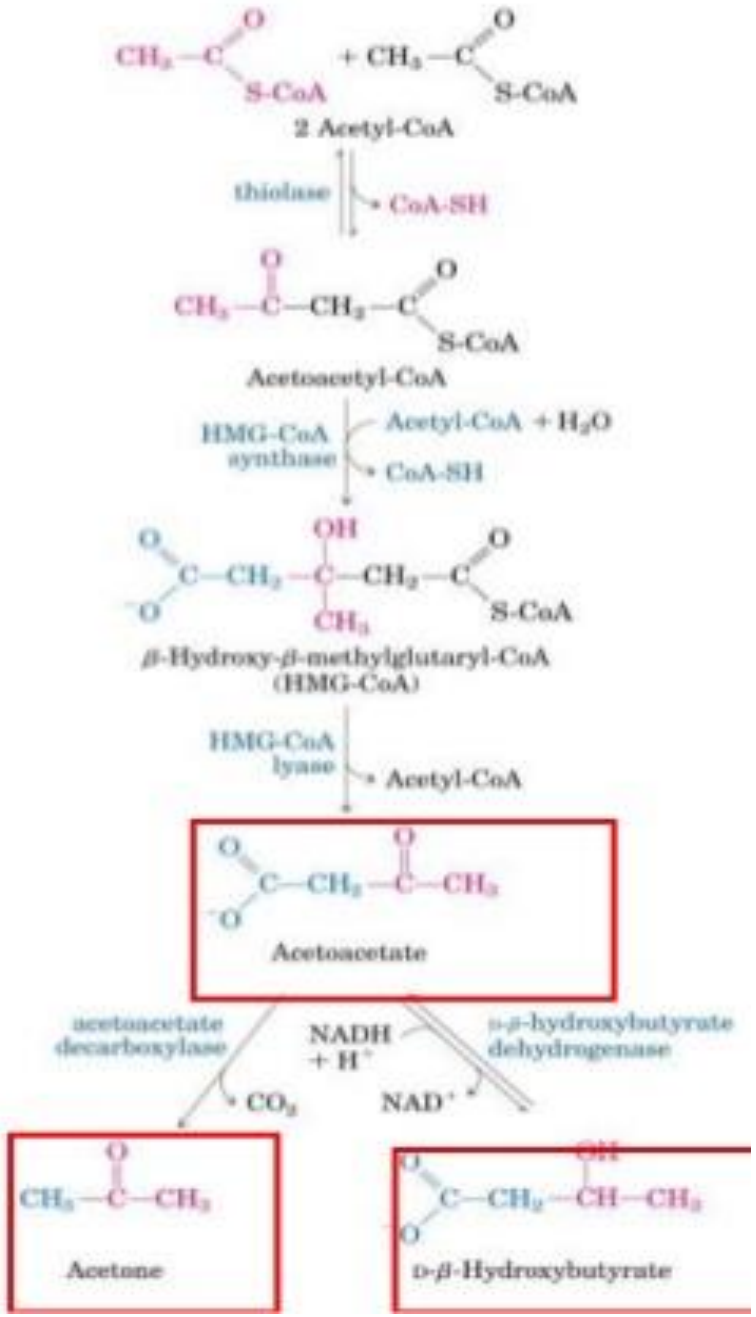
Level of ketone bodies after an overnight fast: ~0.05 mM

2 days starvation: 2 mM (40-fold increase!)

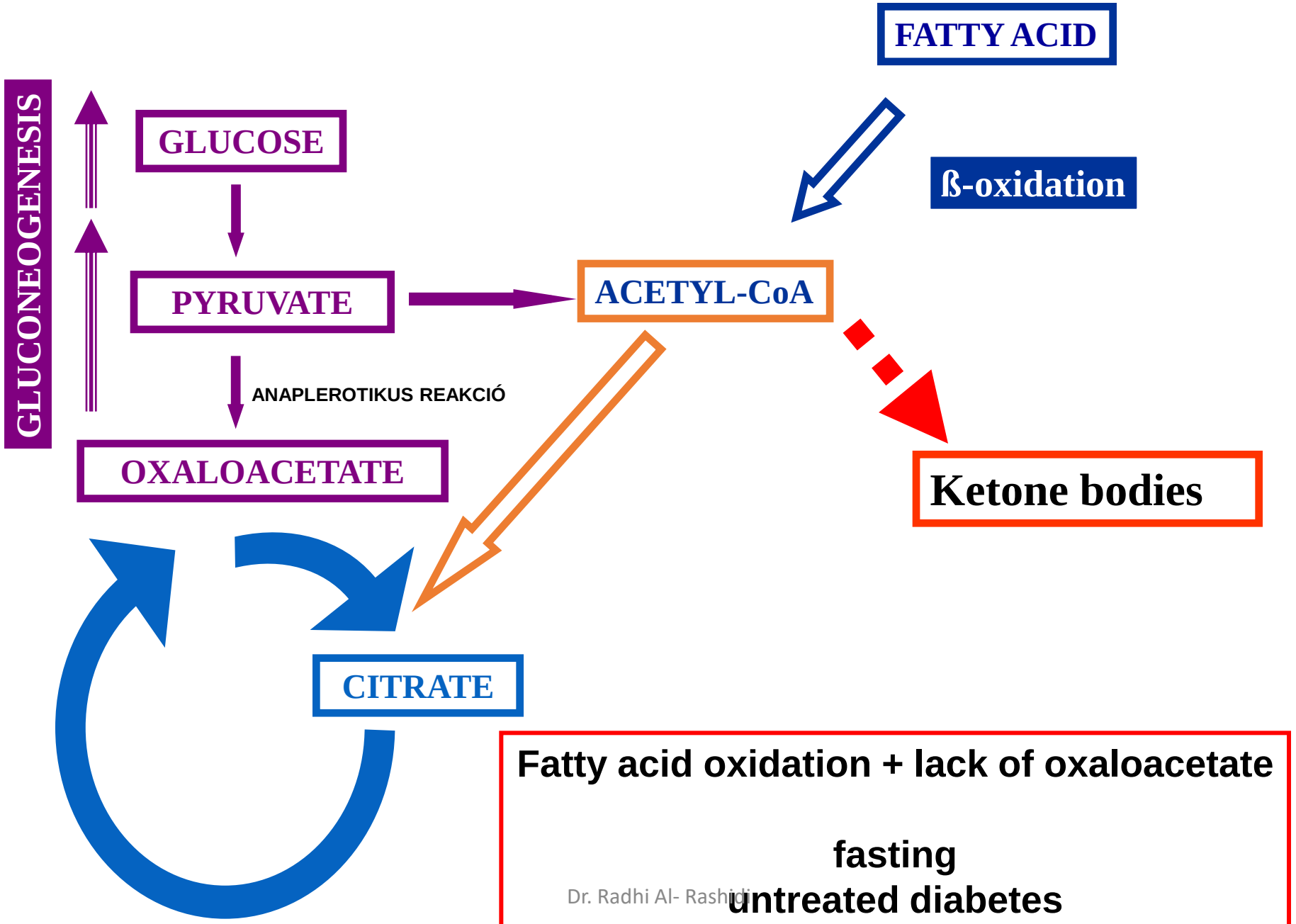
40 days: 7 mM

ketone bodies:
another fate for acetyl-CoA

- Formed in the liver
- Exported
- Oxidized in citric acid cycle
- Step 1: thiolasereversed – joins 2 acetyl-CoA
- Step 2: acetyl-CoA condensation
- Step 3: cleavage of acetyl-CoA
- Step 4: reduction or decarboxylation



FORMATION OF KETONE BODIES



Fatty acid oxidation + lack of oxaloacetate

fasting
untreated diabetes

Cholesterol metabolism

INTRODUCTION

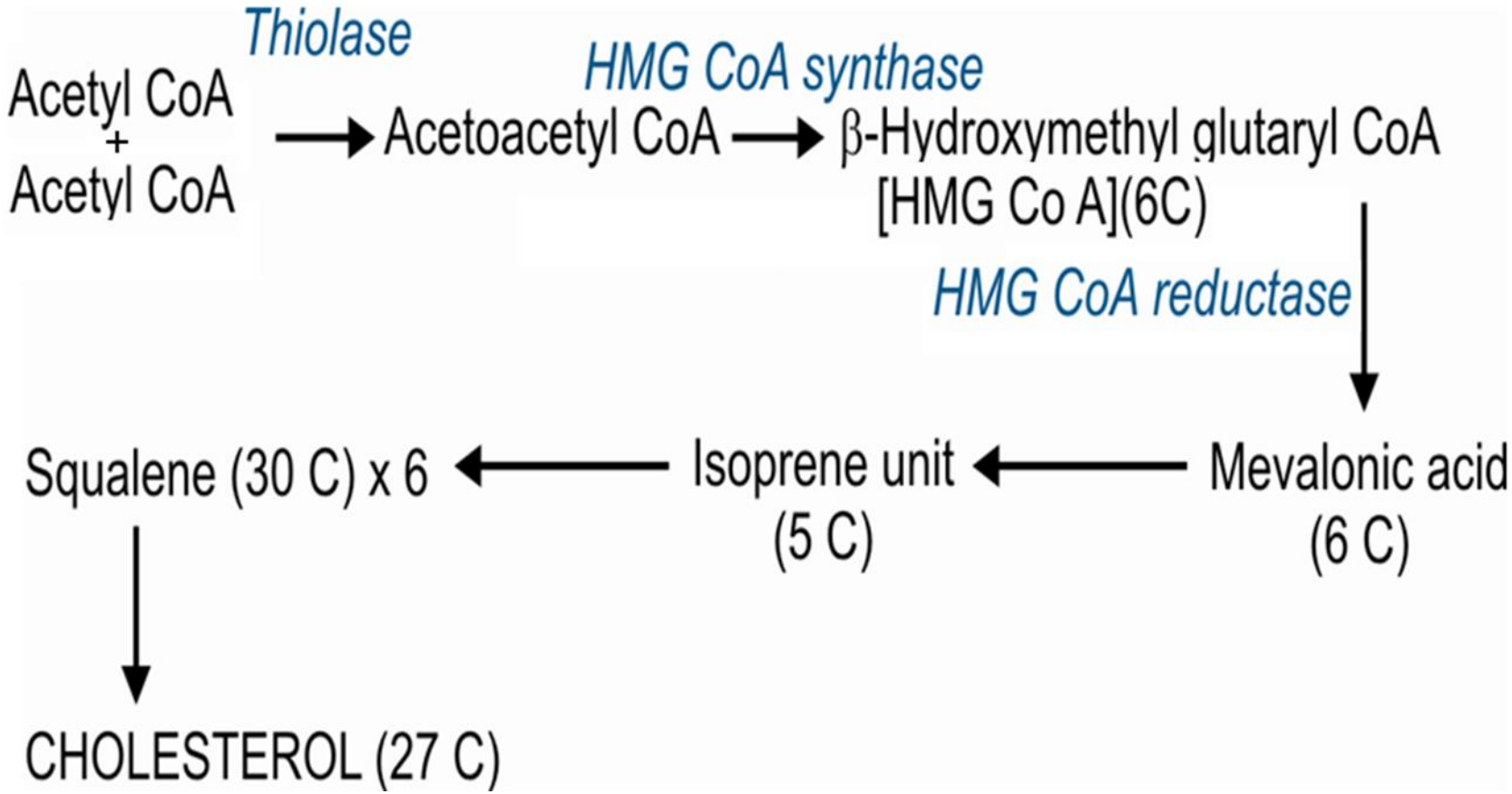
- Cholesterol is a sterol, present in cell membrane, brain and lipoprotein
- It is a precursor for all steroids
- About 1 g of cholesterol is synthesized per day in humans
- It is an amphipathic lipid
- Lipoproteins transports the free cholesterol in the circulation
- Cholesterol ester is a storage form of cholesterol found in most tissues

- 80% of the liver cholesterol converted to bile acids
- Vitamin D3 formed from 7-dehydrocholesterol.
- All the steroids have cyclopentanoperhy drophenanthrene ring.Made up of three cyclohexane rings, A,B and C and a cyclopentane ring D
- Normal Blood level is 150-200 mg%

- Hypercholesterolemia seen in nephrosis, diabetes mellitus, hypothyroidism and obstructive jaundice
- Increased cholesterol level leads to atherosclerosis
- The OH group in the 3rd position can get esterified to fatty acids to form cholesterol esters. This esterification occurs in the body by transfer of PUFA moiety by Lecithin cholesterol acyl transferase. This step is important in the regulation of cholesterol level.
- It is a poor conductor of electricity

SYNTHESIS

- Site: Extra Mitochondrial. The enzymes involved are found in cytosol and microsomal fractions of the cell.
- Synthesis takes place in liver, skin and intestine and also in adrenal cortex & testis.
- All the 27 carbon atoms are derived from acetyl CoA
- 18 acetyl Co A are required
- Acetyl CoA formed in glycolysis and □-Oxidation of fatty acid are the precursors for the cholesterol synthesis


Thiolase
HMG CoA synthase
Acetyl CoA
+
Acetyl CoA
Acetoacetyl CoA
β-Hydroxymethyl glutaryl CoA
[HMG Co A](6C)
HMG CoA reductase
Mevalonic acid
(6 C)
Isoprene unit
(5 C)
Squalene (30 C) x 6
CHOLESTEROL (27 C)

Regulation of Cholesterol synthesis

Cholesterol biosynthesis is controlled by the rate limiting enzyme HMG-CO A reductase

- Feedback control: The end product cholesterol controls its own synthesis of the enzyme by a feedback mechanism. Increase in the cellular concentration of cholesterol reduces the synthesis of the enzyme by decreasing the transcription of the gene responsible for the production of HMG CoA reductase.

- Hormonal regulation: The HMG CoA reductase exists in two interconvertible forms. Insulin and thyroid hormones Increase HMG CoA reductase activity. The dephosphorylated form of the enzyme is more active, phosphorylated is less active.

- Glucagon and glucocorticoids decrease HMG-CoA reductase activity
- Inhibition by drugs: The drugs Compactin and lovastatin, mevastatin, simvastin are competitive inhibitors used to decrease the cholesterol.
- HMG CoA reductase is inhibited by bile acids.
- LDL transports cholesterol from the liver to peripheral tissues.
- HDL transports cholesterol from tissues to liver

METABOLIC FATE OF CHOLESTEROL

Cholesterol is converted into following compounds as shown below.
Cholesterol is mainly excreted in the form of bile salts in stool.

Acetyl CoA >Cholesterol > Steroid hormone (Testosterone, estrogens progesterone ,glucocorticoids mineralocorticoids)
Vitamin D3 Bile acids [salts]

Increased plasma cholesterol results in the accumulation of cholesterol under the tunica intima of the arteries causing atherosclerosis. The progression of the disease process leads to narrowing of the blood vessels. Dietary intake of polyunsaturated fatty acid (PUFA) helps in transport and metabolism of cholesterol and prevents atherosclerosis

Role of LCAT:

- High density lipoprotein (HDL) and the enzyme lecithin-cholesterol acyl transferase (LCAT) are responsible for the transport and elimination of cholesterol from the body.
- LCAT is a plasma enzyme, synthesized by the liver.
- LCAT catalyses the transfer of fatty acid from the second position of phosphatidyl choline (lecithin) to the OH group of cholesterol.
- HDL cholesterol is the real substrate for LCAT and this reaction is freely reversible.

Lipoprotein

Cholesterol and triglycerides are insoluble in water and therefore these lipids must be transported in association with proteins. Lipoproteins are complex particles with a central core containing cholesterol esters and triglycerides surrounded by free cholesterol, phospholipids, and apolipoproteins, which facilitate lipoprotein formation and function. Plasma lipoproteins can be divided into seven classes based on size, lipid composition, and apolipoproteins (chylomicrons, chylomicron remnants, VLDL, IDL, LDL, HDL, and Lp (a)).

The exogenous lipoprotein pathway starts with the incorporation of dietary lipids into chylomicrons in the intestine. In the circulation, the triglycerides carried in chylomicrons are metabolized in muscle and adipose tissue by lipoprotein lipase releasing free fatty acids, which are subsequently metabolized by muscle and adipose tissue, and chylomicron remnants are formed. Chylomicron remnants are then taken up by the liver. The endogenous lipoprotein pathway begins in the liver with the formation of VLDL. The triglycerides carried in VLDL are metabolized in muscle and adipose tissue by lipoprotein lipase releasing free fatty acids and IDL are formed. The IDL are further metabolized to LDL, which are taken up by via the LDL receptor in numerous tissues including the liver, the predominant site of uptake. Reverse cholesterol transport begins with the formation of nascent HDL by the liver and intestine.

Lipoprotein particle metabolism can occur via the exogenous or endogenous pathway, depending whether the source of origin is dietary or hepatic. Both the exogenous and endogenous metabolic pathways of lipoproteins are outlined below.

Exogenous Metabolism

The vast majority of dietary lipids are triglycerides (>95%), and the remaining are phospholipids, free fatty acids, cholesterol and fat-soluble vitamins.

Triglycerides from the diet are digested in the gastrointestinal tract to form monoglycerides and free fatty acids through various processes, including gastric lipase, bile emulsification and pancreatic lipase. Similarly, cholesterol esters from the diet undergo a process of de-esterification to form free cholesterol.

Monoglycerides, free fatty acids and cholesterol are soluble in the bile acid micelles and can be absorbed from the chymus into the enterocytes due to their smaller size.

Inside the enterocytes, they are reassembled into triglycerides and combined with cholesterol to form large chylomicron lipoproteins. Apolipoprotein B-48 regulates the secretion of these particles into the lacteals, and the chylomicrons then circulate through the lymphatic vessels and into the bloodstream.

Chylomicrons are responsible for the transport of dietary triglycerides and cholesterol from the enterocytes and into the circulation system. In the adipose and muscle tissue the majority of the triglycerides in the chylomicron can be converted to fatty acids and glycerol to provide a source of energy. Depleted of energy, the chylomicron remnants rich in cholesterol travel back to the liver to be cleared from the body, through a process mediated by apoprotein E.

Endogenous Metabolism

Lipoproteins can be synthesized in the liver with endogenous triglycerides and cholesterol in the hepatocytes, such as those from chylomicron remnants.

Apolipoprotein B-100 is important in the synthesis of very low-density lipoproteins (VLDL) particles in the liver. When the VLDL particles are released into the bloodstream, they encounter high-density lipoprotein (HDL) particles that donate apolipoprotein C-II and apolipoprotein E to the VLDL particles.

HDL particles are lipoproteins that are initially free of cholesterol and are synthesized in the enterocytes and the liver. The complex metabolism of HDL involved the acquisition of cholesterol from peripheral tissues and other lipoproteins, such that it can be transported to where it is needed.

The VLDL then circulates in the bloodstream and travel to the peripheral adipose and muscle tissues in the body. By way of a hydrolysis reaction, the triglycerides can be broken down to supply fatty acids and glycerol to the cells as a source of energy.

The energy-depleted VLDL remnants, also known as intermediate density lipoproteins (IDLs), have a higher proportion of cholesterol, as the triglycerides have been consumed. They continue to circulate in the bloodstream until they are absorbed by the liver with the involvement of apolipoproetein E. Alternatively, the remnants can be further hydrolyzed by hepatic lipase, releasing more glycerol and fatty acids, to form low-density lipoproteins (LDL) that are the type of lipoproteins that are richest in cholesterol.

The LDL circulates in the bloodstream and can be absorbed by cells in the liver or peripheral tissues. The particles can bind to the target tissue with the LDL receptor with the involvement of apolipoprotein B-100. The LDL can then be absorbed by endocytosis, and the particles hydrolyzed to release lipids such as cholesterol.

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease. Atherosclerosis begins with fatty streak which is a accumulation of lipid laden foam cells in the intimal layer of the artery .
Lipid retention is the first step in the pathogenesis of atherosclerosis which is followed by chronic inflammation at susceptible sites in the walls of the major arteries lead to fatty streaks, which then progress to fibroatheromas which are fibrous in nature.

Atherosclerosis is a continuous progressive development. Fatty streak develop at 11-12 years and fibrous plaques at 15-30 years and they develop at the same anatomic sites as the fatty streaks making it more evident that fibrous plaques arise from fatty streak.

Pathologic intimal thickening leads to fatty streak, leads to fibrous cap atheromas, lead to plaques, finally leading to sudden cardiac death.

Risk factors

Age, Family history, Male sex, smoking, Diabetes mellitus, hypertension, alcohol, Chlamydia infection, Hyper homocysteinemia, Obesity, Sedentary lifestyle