DIABETES MELLITUS

Dr Falih Jabor

Review of Anatomy and Physiology

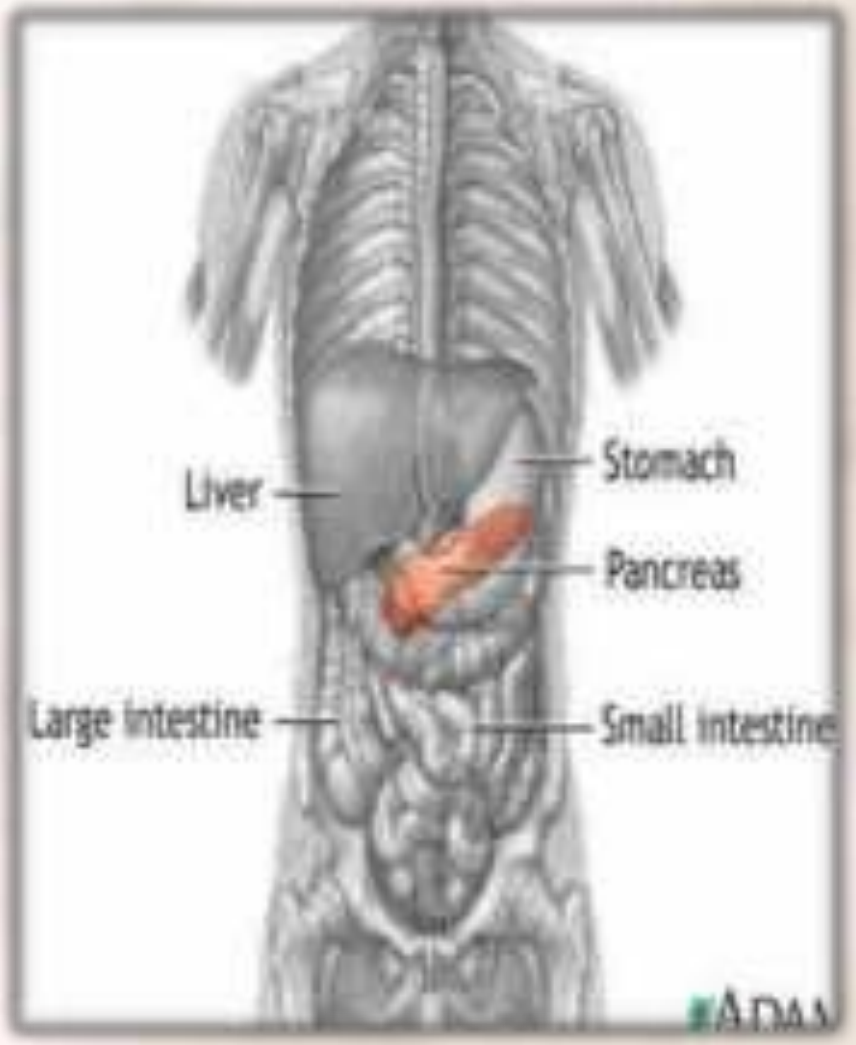
PANCREAS

HORMONES:

BY BETA CELLS INSULIN •

BY ALPHA CELLS GLUCAGON •

- **Pancreas** secretes 40 -50 units of insulin daily in two steps:
  - Secreted at low levels during fasting **(basal insulin secretion)**
  - Increased levels after eating – **(prandial)**
  - An early burst of insulin occur 10 minutes of eating –
  - Then proceeds with increasing release as long as hyperglycemia is present –



Insulin

- Insulin allows glucose to move into cells to make energy
- Inhibits glucagon activity

DIABETES MELLITUS

is a chronic disorder of carbohydrate, protein, and fat - metabolism resulting from **insulin deficiency** or abnormality in the use of insulin

✓Type 1

✓formerly known as **Insulin – Dependent Diabetes Mellitus (IDDM)**

Autoimmune (Islet cell antibodies)✓

Intake of medicine during pregnancy•

Indoor smoking of family members•

destruction of beta cells of the pancreas ✓

little or no insulin production

requires daily insulin admin.✓

Type II .2

formerly known as **Non Insulin- Dependent Diabetes Mellitus (NIDDM)** ✓

probably caused by: ✓

disturbance in insulin reception in the ▪ cells

number of insulin receptors ▪

loss of beta cell responsiveness to glucose leading to ▪ slow or insulin release by the pancreas n

common in overweight or obese ✓

w/ some circulating insulin present, often do not ✓ require insulin

Plasma glucose test	Normal	Prediabetes
Random	Below 11.1 mmol/l Below 200 mg/dl	N/A
Fasting	Below 5.5 mmol/l Below 100 mg/dl	5.5 to 6.9 mmol/l 100 to 125 mg/dl
2 hour post-prandial	Below 7.8 mmol/l Below 140 mg/dl	7.8 to 11.0 mmol/l 140 to 199 mg/dl

Who are at risk?

Risk Factors

- Obesity
- History of CVD
- Physical inactivity
- Familial history
- Gestational Diabetes

Clinical Manifestations (Signs and Symptoms)

Polyuria -
Polydipsia -
Polyphagia -
weight loss -
nausea / vomiting -
(severe hyperglycemia) -
(sleepiness, drowsiness → coma)
recurrent infection, prolonged wound healing -
altered immune and inflammatory response, -
weakness -
fatigue -
blood sugar / glucose level -
(+) glucose in urine (glycosuria) -

Diagnostics

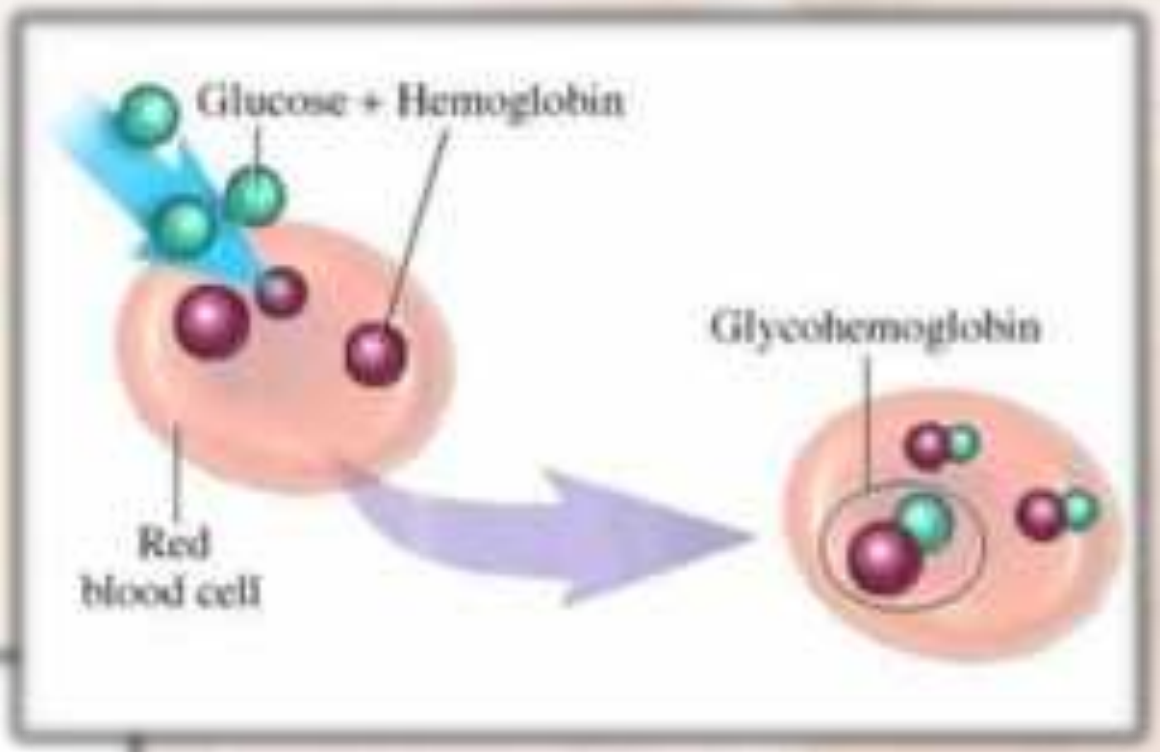
Fasting Plasma Glucose

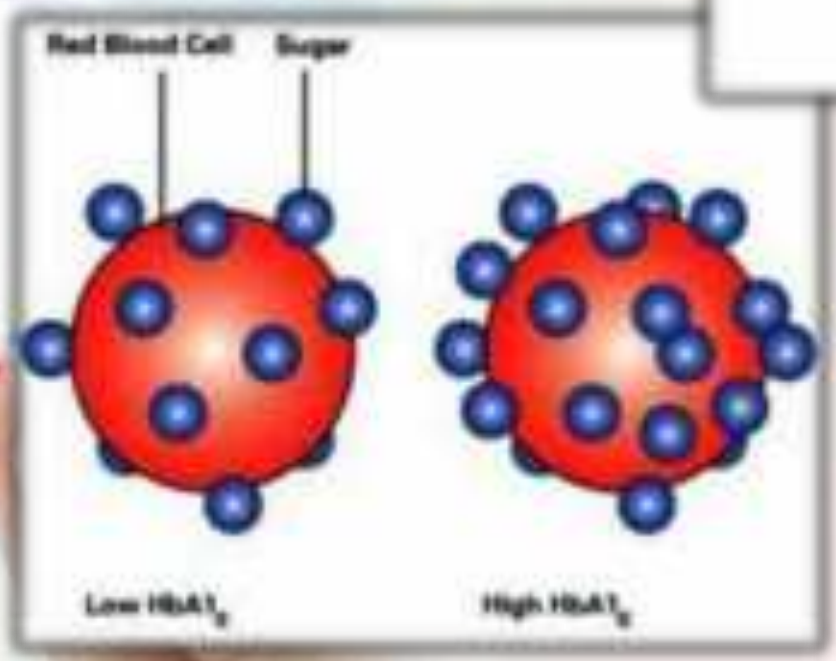
Oral Glucose Tolerance Test (OGTT)

Glycoselated Hemoglobin (HbA1c)

- HbA1c is a test that measures the amount of glycated hemoglobin in your blood. Glycated hemoglobin is a substance in red blood cells that is formed when blood sugar (glucose) attaches to hemoglobin.

(HbA1c)


Glucose + Hemoglobin
Glycohemoglobin
Red
blood cell


Red Blood Cell
Sugar
Low HbA1c
High HbA1c

Urinalysis

- Glycosuria
- Ketone bodies

Diagnostic Criteria

- **Classic signs of HYPERGLYSEMIA with RBG ≥200mg/dL**
- OGTT ≥200mg/dL
- FBG ≥126 mg/dL
- HbA1C ≥ 6.5%

ons of diabetes develop gradually. The longer you have dia
lood sugar — the higher the risk of complications. Possible

ease. Diabetes dramatically increases the risk of various ca
oronary artery disease with chest pain (angina), heart attac
(atherosclerosis). If you have diabetes, you're more likely t

ropathy). Excess sugar can injure the walls of the tiny bloo
ish your nerves, especially in your legs. This can cause tin
sually begins at the tips of the toes or fingers and gradually
ould lose all sense of feeling in the affected limbs.
phropathy). The kidneys contain millions of tiny blood vess
blood. Diabetes can damage this delicate filtering system.
lure or irreversible end-stage kidney disease, which may re

opathy). Diabetes can damage the blood vessels of the ret
), potentially leading to blindness.
e damage in the feet or poor blood flow to the feet increase
lications. Left untreated, cuts and blisters can develop seri
en heal poorly. These infections may ultimately require toe

t. Hearing problems are more common in people with diab
e. Type 2 diabetes may increase the risk of Alzheimer's dis
ugar control, the greater the risk appears to be.
ssion symptoms are common in people with type 1 and typ

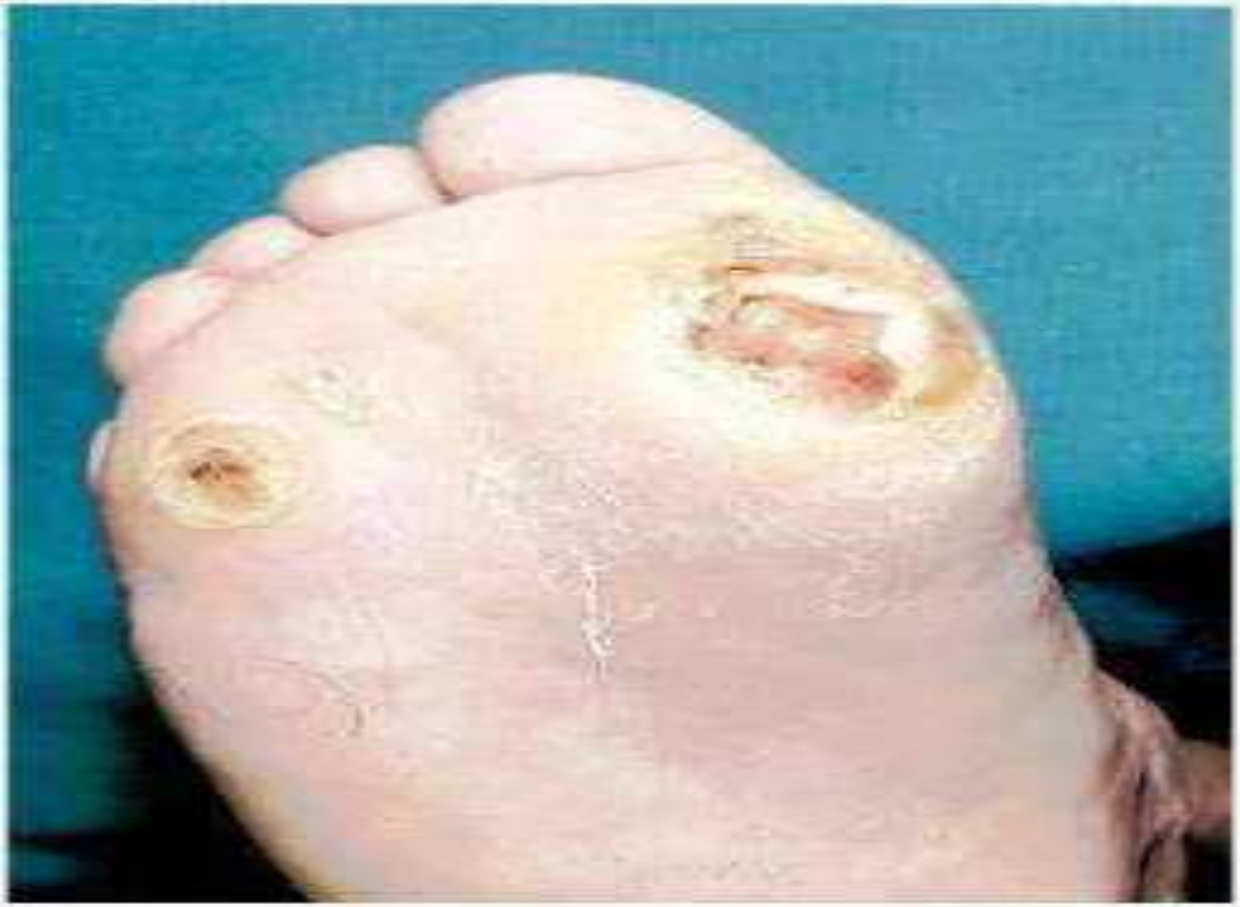


Figure 41-10 Neuropathic ulcers occur on pressure points in areas with diminished sensation in diabetic polyneuropathy. Pain is absent (and therefore the ulcer may go unnoticed).

Copyright © 2004 Lippincott Williams & Wilkins.

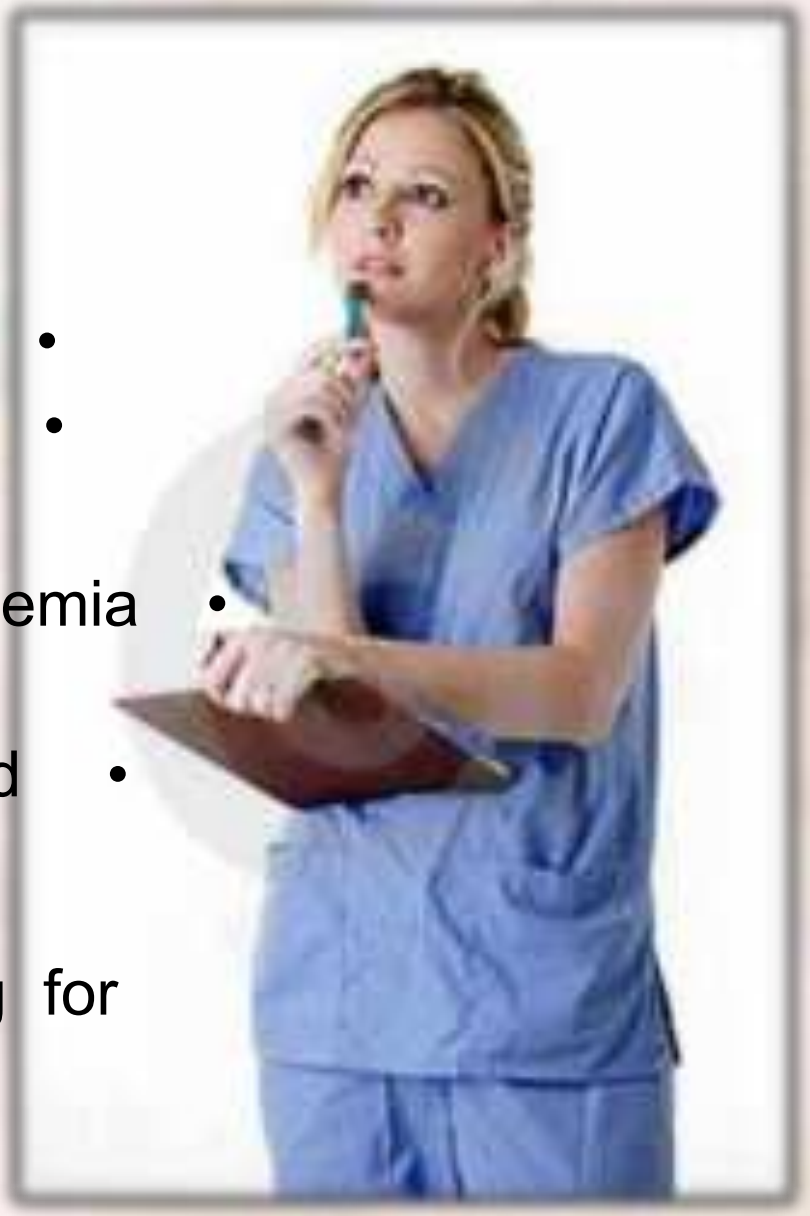
Hypoglycemia

- low blood glucose (usually below 60mg/dl)
  - results from too much insulin, not enough food, and/or excessive physical activity
- may occur 1-3 hrs after regular insulin injection

S/Sx:

- Sweating, tremor, pallor, tachycardia, and nervousness .1
- caused by release of epinephrine from the CNS when blood glucose falls rapidly
- Headache, light-headedness, confusion, numbness of lips and tongue, slurred speech, drowsiness, convulsions and .2

Diabetes Mellitus Summary



- Treatable, but not curable.
- Preventable in obesity, adult client.
- Controllable- DIET and EXERCISE
- Diagnostic Tests
- Signs and symptoms of hypoglycemia and hyperglycemia.
- Treatment of hypoglycemia and hyperglycemia – diet and oral hypoglycemics.

monitoring, teaching and assessing for complications.

Of course too much is bad for youll


Thank You

Dr Falih Jabor

Lipid Metabolism

Fatty Acid Synthesis
Origin of Acetyl-CoA for Fat Synthesis
Regulation of Fatty Acid Synthesis
Elongation and Desaturation of Fatty Acids
Triacylglyceride Synthesis
Fatty Acid Oxidation
Cholesterol and Bile Acid Synthesis
Lipids and Lipoproteins

Triacylglycerols (The body fuel reserve)

Lipids constitute about 15- 20 % of the body weight in humans. TG are the most abundant lipids comprising 85-90 % of body lipids. Most TG are stored in the adipose tissue and serve as energy reserve of the body. This is in contrast to carbohydrates and proteins which cannot be stored to a significant extent for energy purposes.

Why should fat be the fuel reserve of the body ?

1. TG are highly concentrated form of energy yielding 9 cal/g in contrast to carbohydrate and proteins that produce only 4 cal/g.
2. TG are hydrophobic in nature, hence stored in pure form without any association with water . Whereas, glycogen and protein are polar. One gram of glycogen combines with 2 g of water for storage.

- For healthy adult (weighing 70 Kg) about 10-11 kg of fat is stored in adipose tissue which corresponds to a fuel reserve of 100,000 cals. If this much of energy were to be stored as glycogen (instead of fat) then the weight of the person would increase significantly.
- Long chain fatty acids are the ideal storage fuel reserves of the body. Fats can support the body energy needs for long periods of food deprivation. Humans can fast and survive for 60-90 days and the obese persons can survive even longer 6 months without food.

Lipids

Are biomolecules which are soluble in organic solvents lipids. Fats and lipids are insoluble in water .

Lipid Function :

1. **Fats and lipids are important because they serve as energy source as well as a storage for energy in the form of fat cells.**
2. **Lipids have a major cellular function as structural components in cell membranes.**
3. **Hormones steroids and prostaglandin are chemical messengers between body tissues.**
4. **Vitamins A, D , E and K are lipid soluble.**
5. **Lipids act as a shock absorber to protect vital organs and insulate the body from temperature extremes.**

Digestion and Transport of Dietary Lipids :

Triacylglycerols are the major fat in human diet , consisting of three fatty acids esterified to a glycerol backbone . In the intestine , the fats are emulsified by bile salts that are released from the gallbladder. This increases the available surface area of the lipids for pancreatic lipase . Degradation products are free fatty acids and 2- monoacylglycerol .

In addition to triacylglycerols , phospholipids , cholesterol and cholesterol esters (cholesterol esterified to fatty acids) are present in the foods . Phospholipids are hydrolyzed in the intestinal lumen by phospholipase A2 and cholesterol esters are hydrolyzed by cholesterol esterase. Both of these enzymes are secreted from the pancreas.

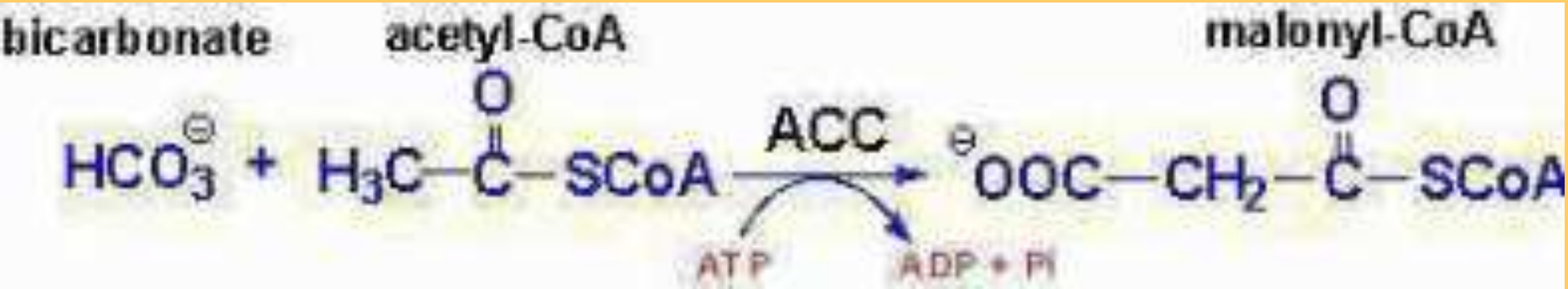
Control of lipid digestion

- Panceatic secretion of enzymes that degrade dietary lipids in the small intestine is hormonally controlled. Cells in the mucosa of lower duodenum produce cholecystokinin in response to the presence of lipids and partially digested proteins entering these regions CKK acts on the gallbladder (causing them to release bile) , and on pancreas to release digestive enzymes. It also decrease gastric motility , resulting in a slower release of gastric contents into the small intestine. Other intestinal cells produce another hormone , secretin in response to the low pH of the chyme entering into the small intestine. Secretin causes the pancreas and the liver to release a watery solution rich in bicarbonate that helps to neutralize the pH of the intestinal contents , bringing them to the appropriate pH for enzymes digestive activity by pancreatic enzymes.

Fatty Acid Synthesis

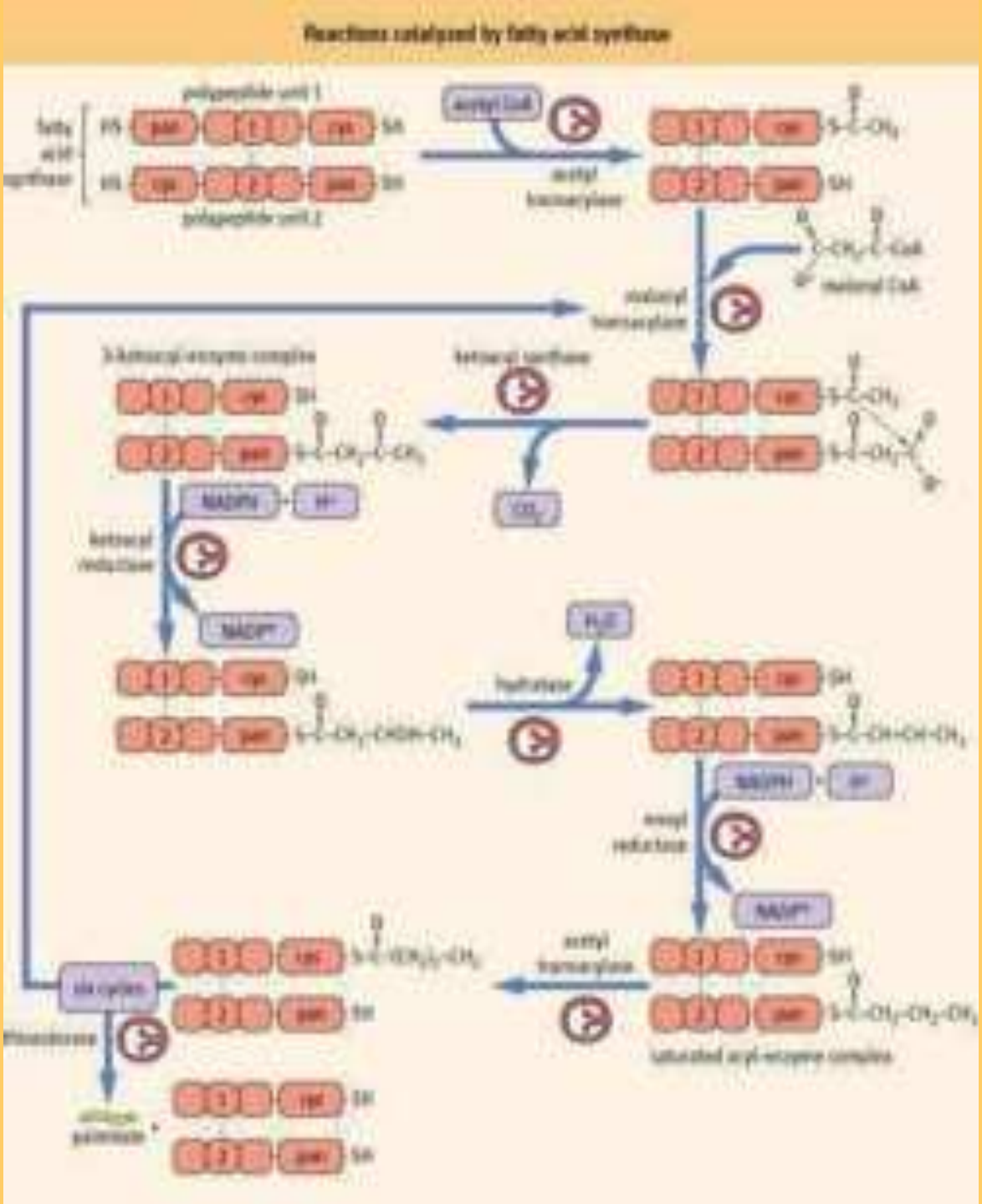
The pathway for fatty acid synthesis occurs in the cytoplasm, whereas, oxidation occurs in the mitochondria. The other major difference is the use of nucleotide co-factors. Oxidation of fats involves the reduction of FAD+ and NAD+. Synthesis of fats involves the oxidation of NADPH.

– The synthesis of malonyl-CoA is the first committed step of fatty acid synthesis and the enzyme that catalyzes this reaction, acetyl-CoA carboxylase (ACC), is the major site of regulation of fatty acid synthesis.



The synthesis of fatty acids from acetyl-CoA and malonyl-CoA is carried out by fatty acid synthase, FAS.

- All of the reactions of fatty acid synthesis are carried out by the multiple enzymatic activities of FAS. The two reduction reactions require NADPH oxidation to NADP+.
- The primary fatty acid synthesized by FAS is palmitate. Palmitate is then released from the enzyme and can then undergo separate elongation and/or unsaturation to yield other fatty acid molecules.


Reactions catalysed by fatty acid synthase
polypeptide unit 1
polypeptide unit 2
acetyl CoA
acetyl transacylase
malonyl CoA
malonyl transacylase
3-ketoacyl-enzyme complex
ketoacyl synthase
NADPH + H+
ketoacyl reductase
NADP+
H2O
hydratase
enoyl reductase
acyl transferase
palmitate
saturated acyl-enzyme complex

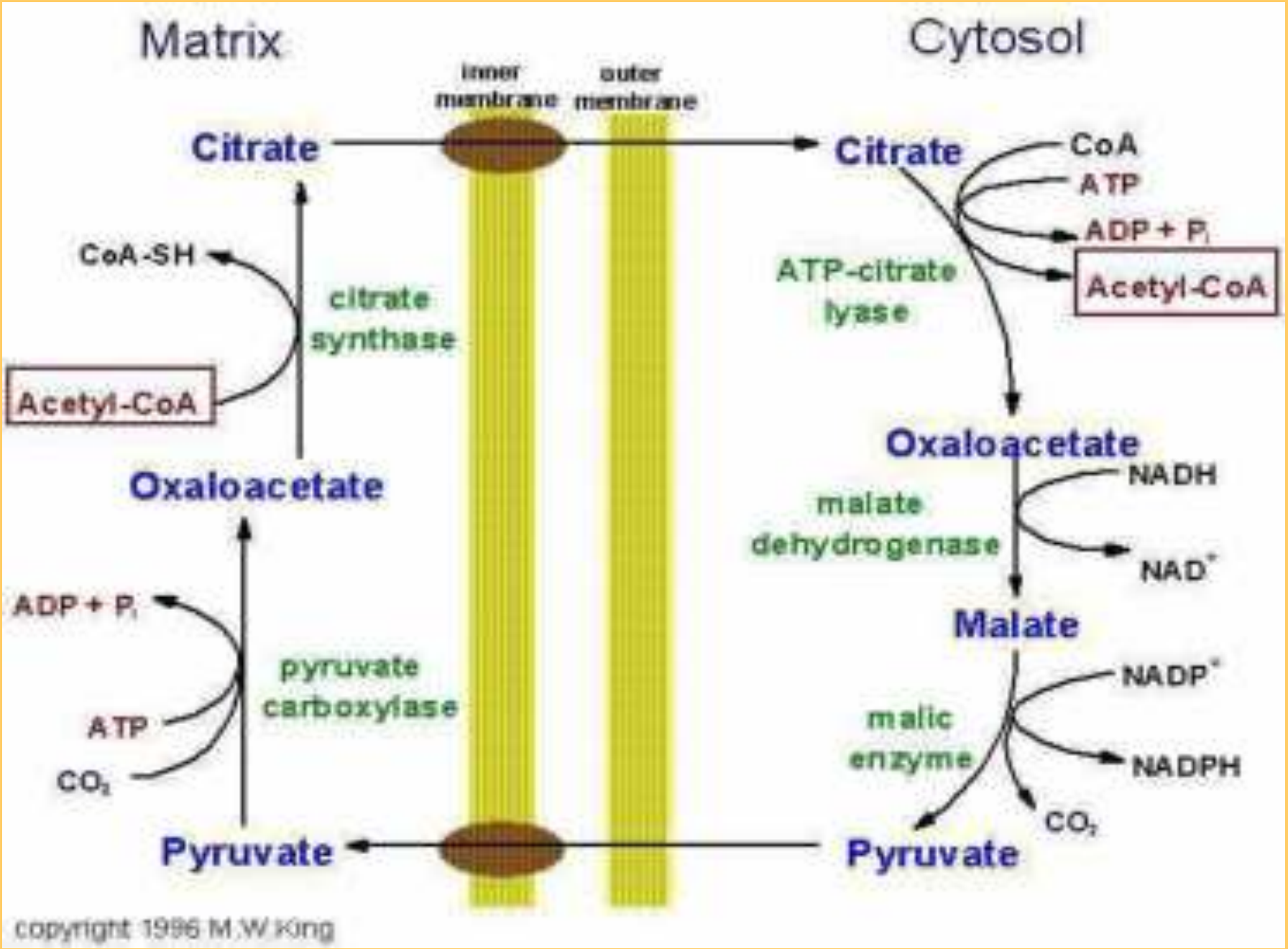
Physiologically Relevant Fatty Acids

Numerical Symbol	Common Name	Structure	Comments
14:0	Myristic acid	$CH_3(CH_2)_{12}COOH$	Often found attached to the N-term. of plasma membrane-associated cytoplasmic proteins
16:0	Palmitic acid	$CH_3(CH_2)_{14}COOH$	End product of mammalian fatty acid synthesis
$16:1^{\Delta 9}$	Palmitoleic acid	$CH_3(CH_2)_5C{=}C(CH_2)_7COOH$	
18:0	Stearic acid	$CH_3(CH_2)_{16}COOH$	
$18:1^{\Delta 9}$	Oleic acid	$CH_3(CH_2)_7C{=}C(CH_2)_7COOH$	
$18:2^{\Delta 9,12}$	Linoleic acid	$CH_3(CH_2)_4C{=}CCH_2C{=}C(CH_2)_7COOH$	Essential fatty acid
$18:3^{\Delta 9,12,15}$	Linolenic acid	$CH_3CH_2C{=}CCH_2C{=}CCH_2C{=}C(CH_2)_7COOH$	Essential fatty acid
$20:4^{\Delta 5,8,11,14}$	Arachidonic acid	$CH_3(CH_2)_3(CH_2C{=}C)_4(CH_2)_3COOH$	Precursor for eicosanoid synthesis

Origin of Cytoplasmic Acetyl-CoA

Acetyl-CoA is generated in the mitochondria primarily from two sources :

- the pyruvate dehydrogenase (PDH) reaction
- fatty acid oxidation.
- In order for these acetyl units to be utilized for fatty acid synthesis they must be present in the cytoplasm.
  - Acetyl-CoA enters the cytoplasm in the form of citrate via the tricarboxylate transport system. In the cytoplasm, citrate is converted to oxaloacetate and acetyl-CoA by the ATP driven ATP-citrate lyase reaction. The resultant oxaloacetate is converted to malate by malate dehydrogenase (MDH).


Matrix
Cytosol
inner membrane
outer membrane
Citrate
Citrate
CoA
ATP
ADP + Pi
Acetyl-CoA
ATP-citrate lyase
CoA-SH
citrate synthase
Acetyl-CoA
Oxaloacetate
Oxaloacetate
NADH
malate dehydrogenase
NAD+
Malate
ADP + Pi
pyruvate carboxylase
NADP+
ATP
malic enzyme
NADPH
CO2
CO2
Pyruvate
Pyruvate
copyright 1996 M.W.King

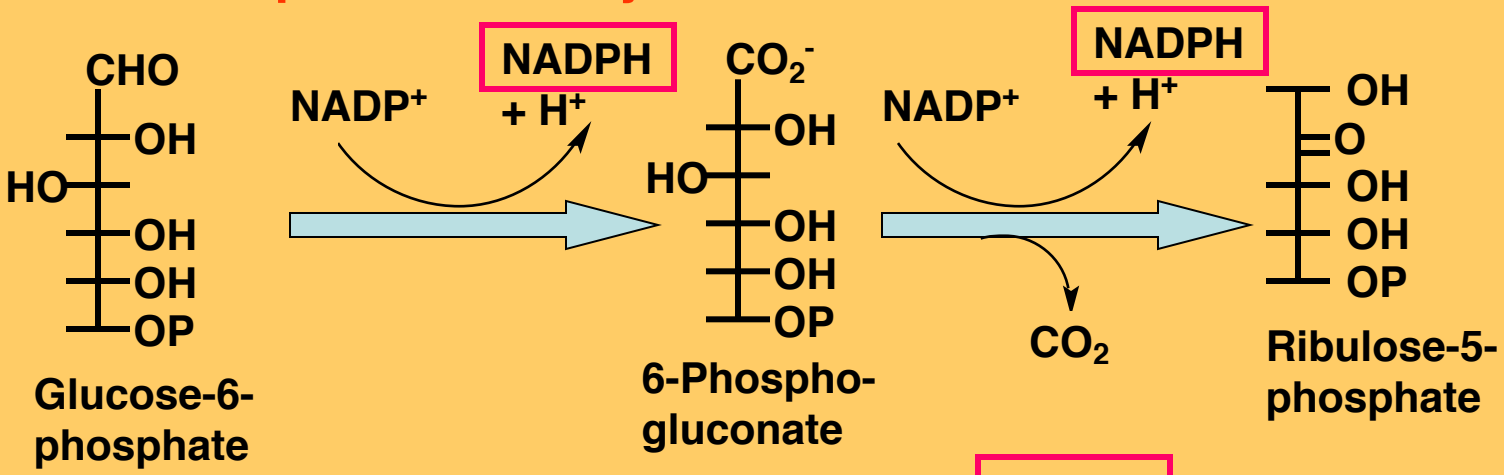
Major sources of the NADPH required for fatty acid synthesis

1. **Pentose phosphate pathway : this pathway is the major supplier of NADPH for fatty acid synthesis. Two NADPH are produced for each molecule of glucose that enters this pathway.**

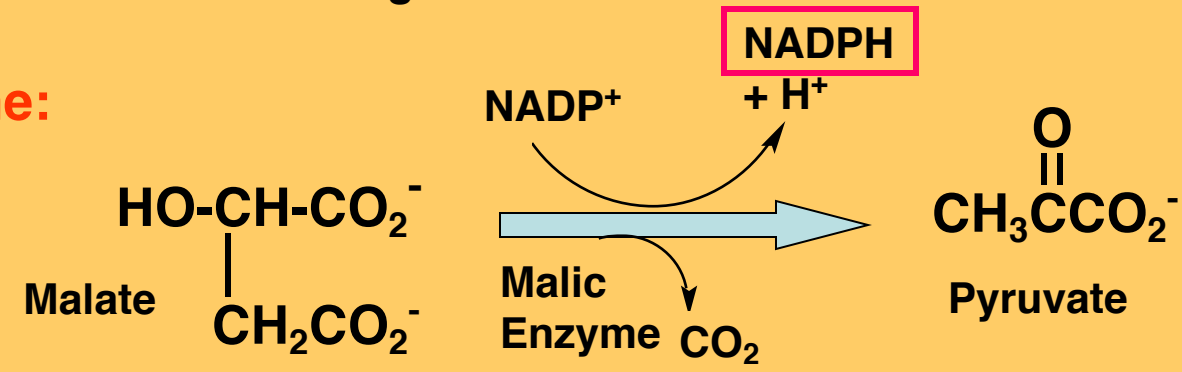
2. **Cytoplasmic conversion of malate to pyruvate : Malate is oxidized and decarboxylated by malate dehydrogenase enzyme to form pyruvate.**

Fatty Acid Biosynthesis: Sources of NADPH

Pentose Phosphate Pathway:



Malic Enzyme:



Elongation and Desaturation

- **The fatty acid product released from FAS is palmitate which is a 16:0 fatty acid, i.e. 16 carbons and no sites of unsaturation.**

- **Elongation and unsaturation of fatty acids occurs in both the mitochondria and endoplasmic reticulum.**

- **The predominant site of these processes is in the ER membranes. Elongation involves condensation of acyl-CoA groups with malonyl-CoA. The resultant product is two carbons longer yielding a saturated fatty acid. Mitochondrial elongation involves acetyl-CoA units.**

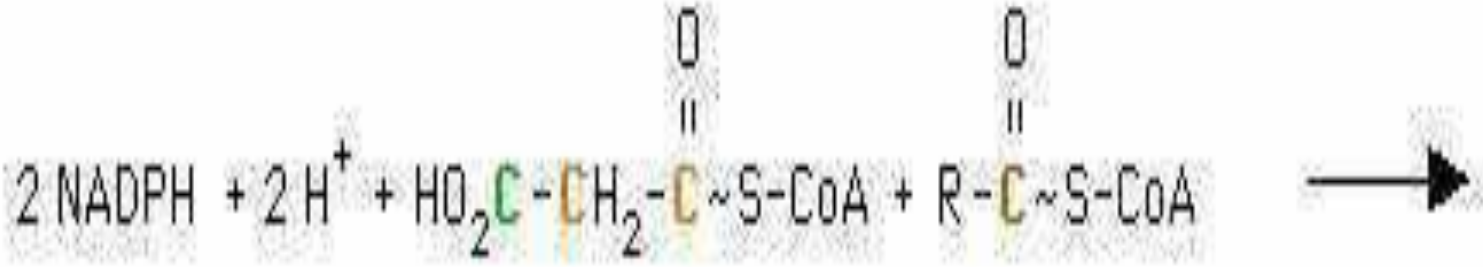
Desaturation occurs in the ER membranes in mammalian cells involves 4 broad specificity fatty acyl-CoA desaturases. These enzymes introduce unsaturation at C4, C5, C6 or C9.

Since these enzymes cannot introduce sites of unsaturation beyond C9 they cannot synthesize either linoleate (18:2D9, 12) or linolenate (18:3D9, 12, 15).

These fatty acids must be acquired from the diet and are, therefore, referred to as essential fatty acids.

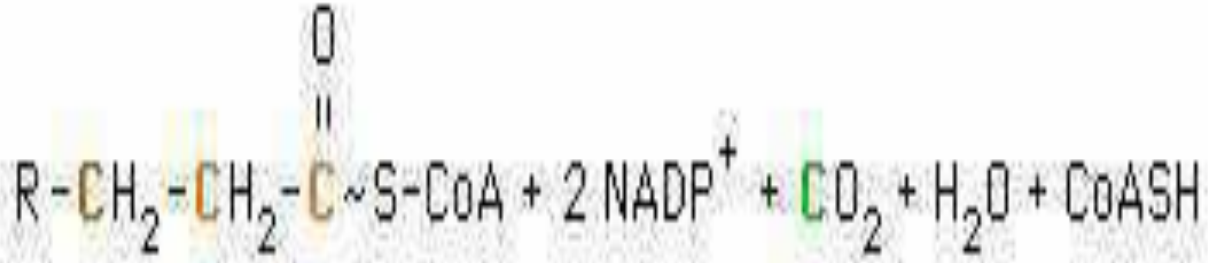
Linoleic is especially important for the synthesis of arachidonic acid.

Arachindonate is a precursor for the eicosanoids (prostaglandins and thromboxanes).It is this role of fatty acids in eicosanoid synthesis that leads to poor growth, wound healing and dermatitis in persons on fat free diets. Also, linoleic acid is a constituent of epidermal cell sphingolipids that function as the skins water permeability barrier.



malonyl CoA

long chain fatty acyl CoA

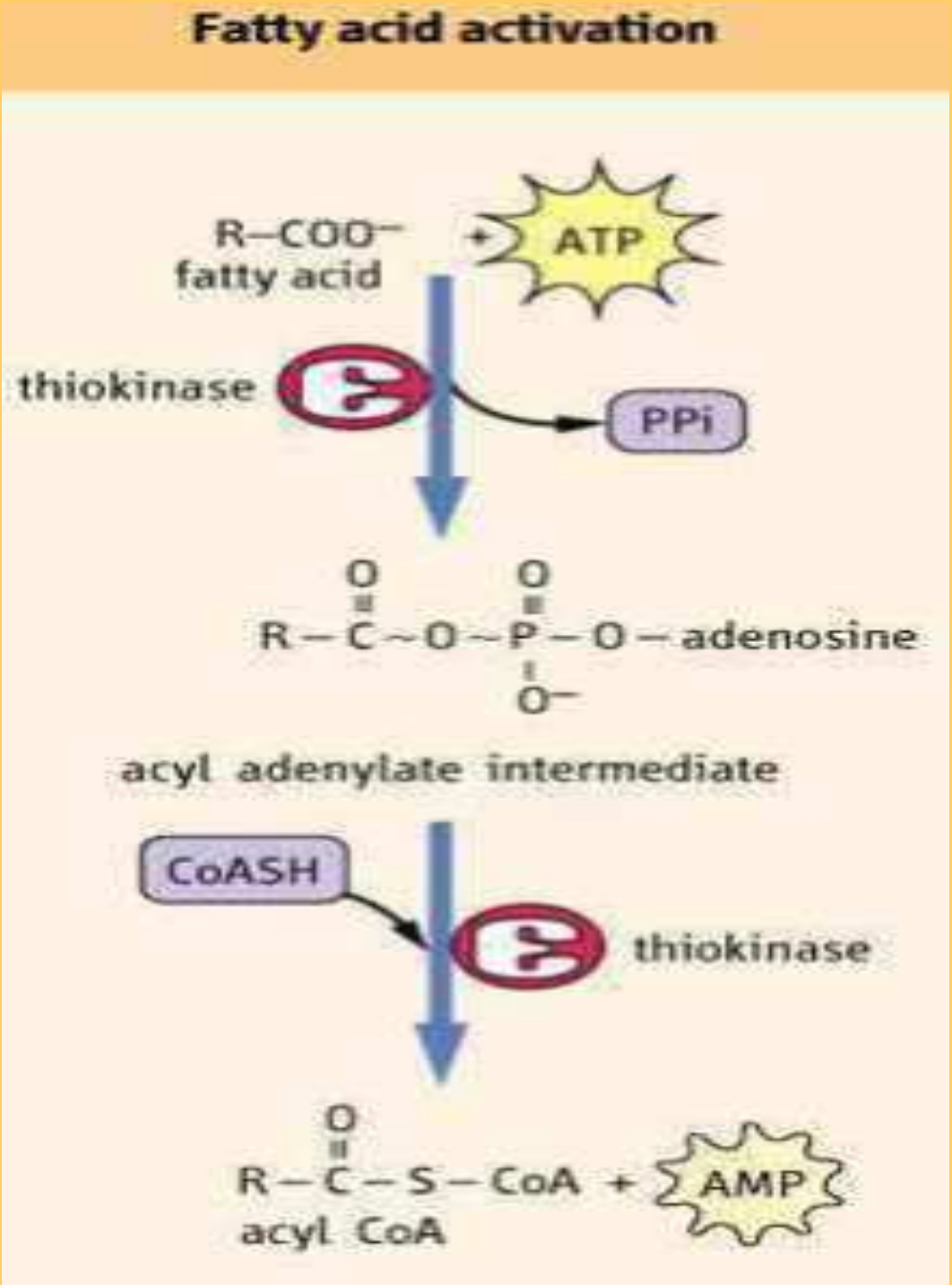


fatty acyl CoA lengthened by two carbons

Activation of fatty acids and their transport to the mitochondria

- **Fatty acids do not exist in free form in the body .In blood fatty acids are bound to albumin which is present at a concentration 35mg/ml in plasma. Each molecule of albumin can bind six to eight fatty acid molecules. As the priming step for their catabolism, the fatty acids are activated to their CoA derivative using ATP as the energy source.**

Fatty acid activation

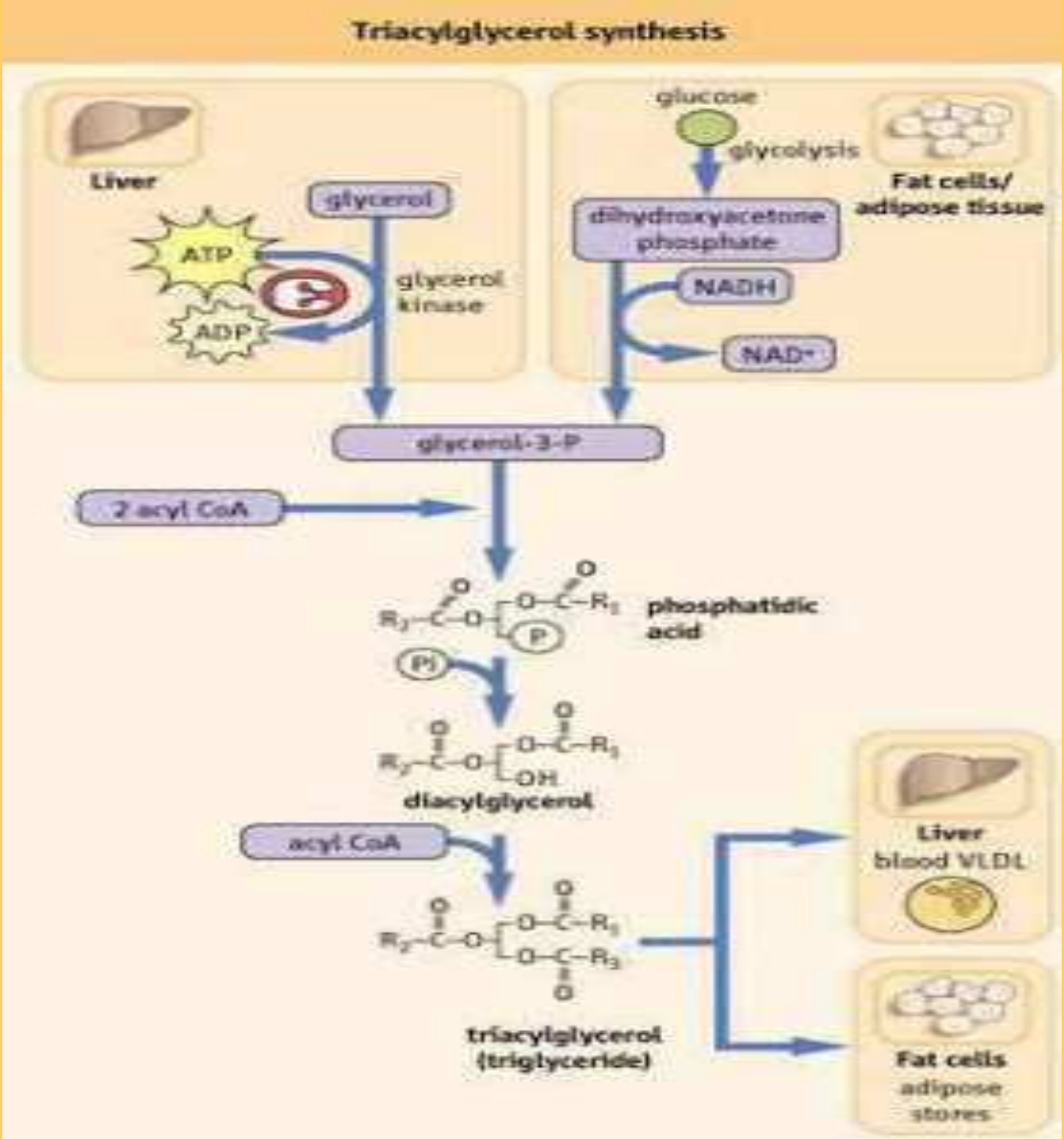


Synthesis of Triglycerides

Fatty acids are stored for future use as tri acylglycerol in all cells, but primarily in adipose tissue. Tri acylglycerol constitute molecules of glycerol to which three fatty acids have been esterified.

The fatty acids present in tri acylglycerol are predominantly saturated.

The major building block for the synthesis of tri acylglycerols, in tissues other than adipose tissue, is glycerol. Adipocytes lack *glycerol kinase*, therefore, dihydroxyacetone phosphate (DHAP), produced during glycolysis, is the precursor for tri acylglycerol synthesis in adipose tissue. This means that adipoctes must have glucose to oxidize in order to store fatty acids in the form of tri acylglycerol.


Triacylglycerol synthesis
Liver
glycerol
ATP
ADP
glycerol kinase
glucose
glycolysis
Fat cells/ adipose tissue
dihydroxyacetone phosphate
NADH
NAD+
glycerol-3-P
2 acyl CoA
phosphatidic acid
Pi
diacylglycerol
acyl CoA
triacylglycerol (triglyceride)
Liver
blood VLDL
Fat cells
adipose stores

The length of the fatty acid dictates where it is activated to CoA

- **Short and medium chain fatty acids can cross the mitochondrial membrane by passive diffusion and are activated to their CoA derivative within the mitochondria.**
- **Very long chain fatty acids are shortened to long chain fatty acids in peroxisomes. Peroxisomes are part of the process of cell metabolism, which keeps cells running smoothly to ensure that they have enough energy to perform their functions. People can develop disorders related to a buildup of lipids and other toxins in their bodies. This can manifest in the form of a variety of conditions, including the neurological disorder known as Zellweger Syndrome.**
- **Long chain fatty acids 16 ±4 carbons are the major components of storage triglycerides and dietary fats. They are activated to their CoA derivative in the cytoplasm and are transported into the mitochondria via the carnitine shuttle.**

The carnitine shuttle

- **For the transport of long chain fatty acids, the fatty acid is first transferred to the small molecule, carnitine by carnitine palmitoyl transferase 1 located in the outer mitochondrial membrane.**

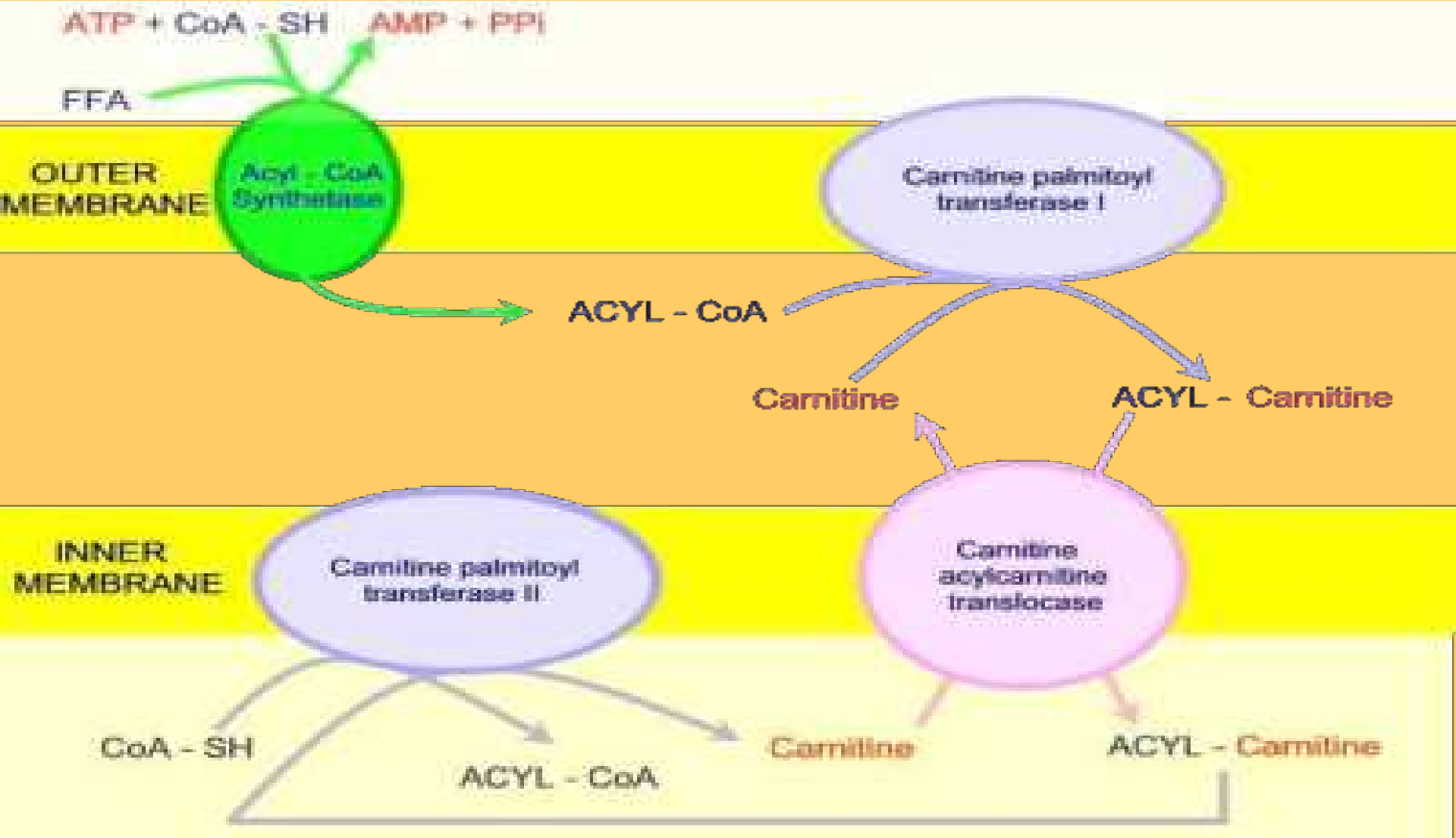
- **An acyl carnitine transporter or translocase in the inner mitochondrial membrane then facilates transfer of the fatty acid into the mitochondria , where CPT-11 regenerates the acyl CoA releasing free carnitine.**

- **The carntine shuttle operates by an antiport mechanism in which free carnitine and acyl carnitine derivative move in opposite direction across the inner mitochondrial membrane.**

- **The carnitine shuttle is inhibited by malonyl CoA after the ingestion of carbohydrate rich meals preventing the catabolism of newly synthesized fatty acids and favoring their export from the liver for storage in adipose tissue.**

- Carnitine is a nutrient that helps the body turn fat into energy. It is produced by the body in the liver and kidneys and stored in the skeletal muscles, heart, brain, and sperm.
- Usually, the body can make all the carnitine it needs. Some people, however, may be deficient in carnitine because their bodies cannot make enough carnitine or transport it into tissues so it can be used.
- Biosynthesized from the amino acids lysine and methionine.

Carnitine shuttle



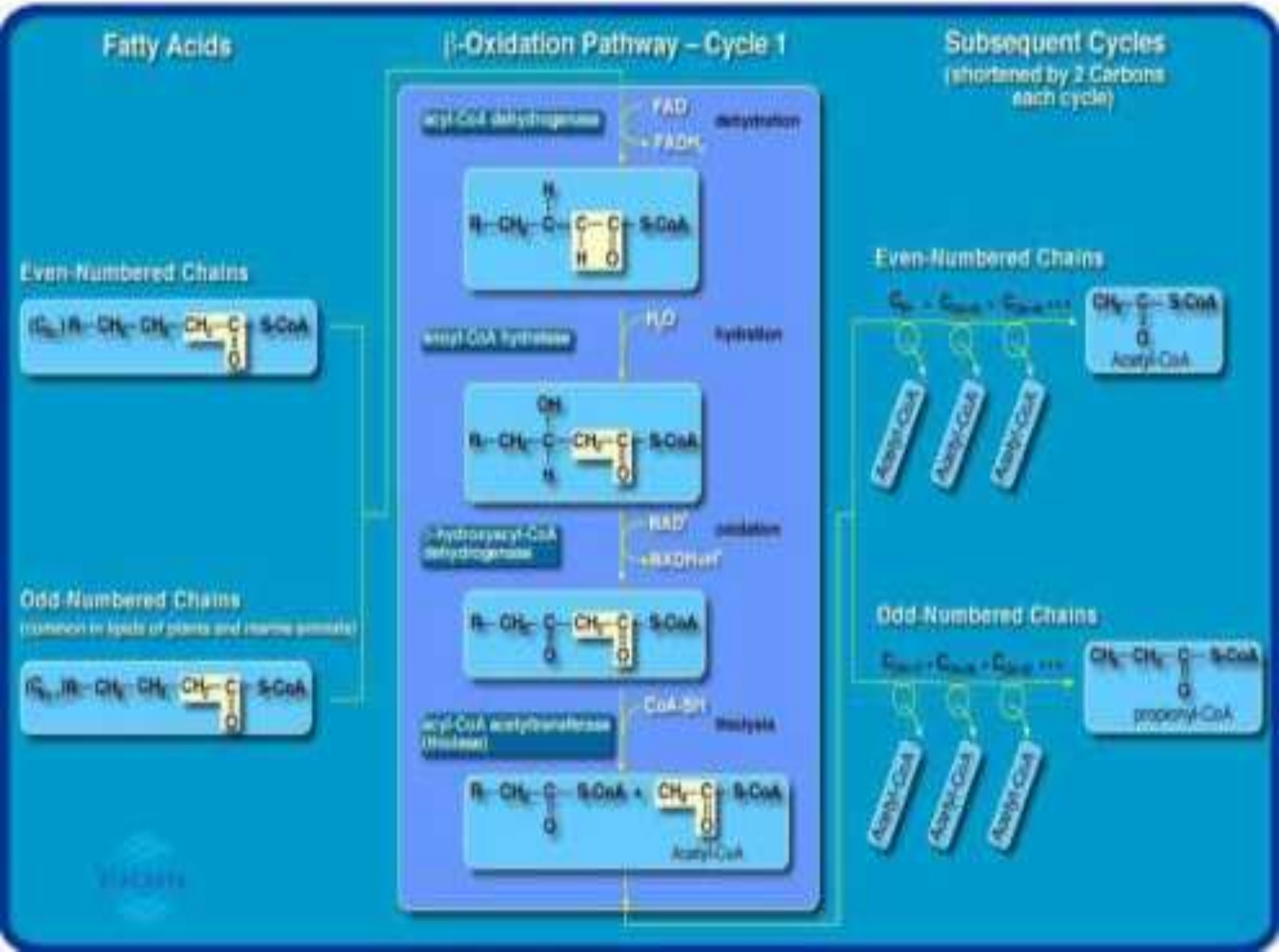
Oxidation of fatty acids.

- **Fatty acyl CoAs are oxidized in a cycle of reactions involving oxidation of the β carbon. The oxidation is followed by cleavage between the α and β carbons by thiolase reaction.**

- **One mole each of acetyl CoA , FADH2 and NADH+H+ is formed during each cycle along with fatty acyl CoA two fewer carbon atoms.**

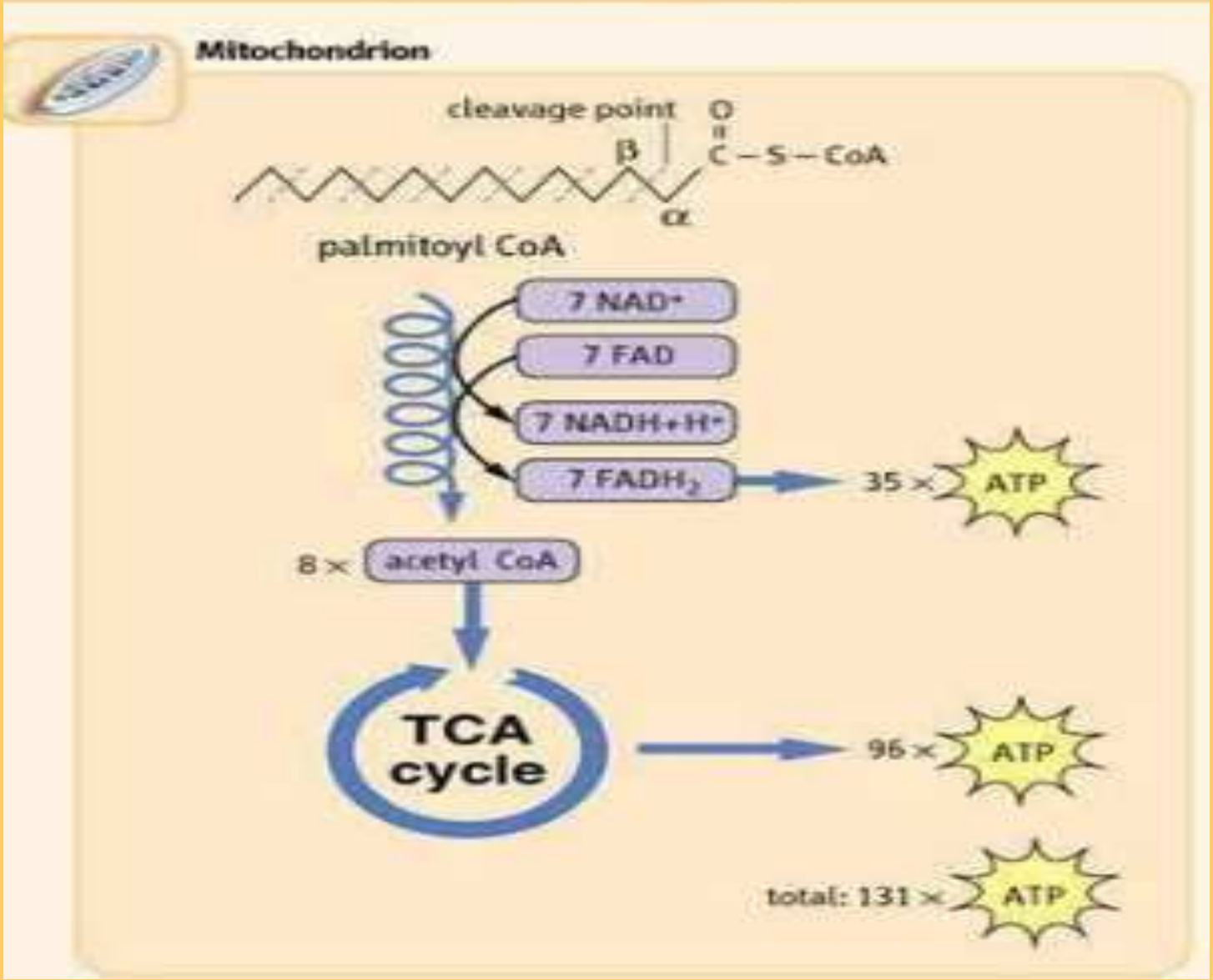
For 16 carbon fatty acid such as palmitate , the cycle is repeated seven times, yielding eight moles of acetyl CoA plus seven moles of FADH2 and seven moles of NADH+H+.

- **This process occurs in the mitochondria and the reduced nucleotides are used directly for synthesis of ATP by oxidative phosphorylation.**


Fatty Acids
β-Oxidation Pathway – Cycle 1
Subsequent Cycles
(shortened by 2 Carbons each cycle)
Even-Numbered Chains
Odd-Numbered Chains
(common in lipids of plants and marine animals)
acyl-CoA dehydrogenase
FAD
FADH2
dehydration
enoyl-CoA hydratase
H2O
hydration
β-hydroxyacyl-CoA dehydrogenase
NAD+
NADH+H+
oxidation
acyl-CoA acetyltransferase (thiolase)
CoA-SH
thiolysis
Acetyl-CoA
propionyl-CoA

- SIDS : A disorder due to blockade in Beta- Oxidation :
- SIDS is unexpected death of healthy infants usually overnight. The real cause of SIDS is not known. But at least 10% is due to deficiency of medium chain acyl CoA dehydrogenase. The occurrence of SIDS is explained that the glucose is the principal source of energy soon after eating or feeding babies. After a few hours, the glucose level decreases and the rate of fatty acid oxidation must increase to meet the energy needs. The sudden death in infants is due to a blockade in beta- oxidation caused by a deficiency in medium chain acyl CoA dehydrogenase (MCAD).
- Zellweger syndrome : This is rare disorder characterized by the absence of peroxisomes in almost all the tissue. AS a result , the long chain fatty acids are not oxidized . They accumulate in tissues, particularly in brain, liver and kidney.

β-oxidation of palmitate

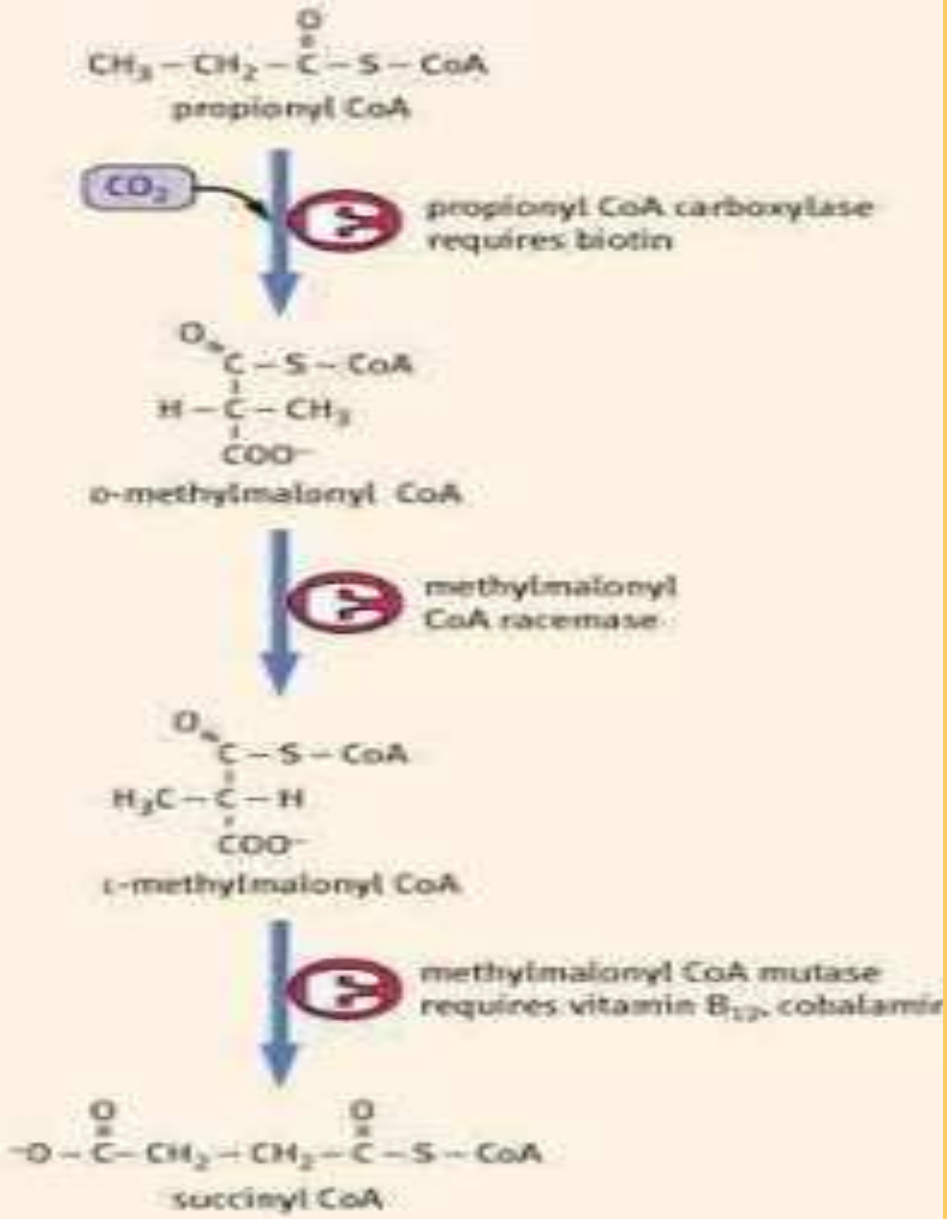


Alternative pathways of oxidation of fatty acids.

- **Unsaturated fatty acids yield less FADH2 when they are oxidized.**

- **Unsaturated fatty acids are partially oxidized so less FADH2 is produced by their oxidation. The double bonds in polyunsaturated fatty acids occurs at three carbon intervals, whereas the intermediates in β oxidation proceed in two carbon steps.**

Propionyl CoA metabolism of odd-chain fatty acids



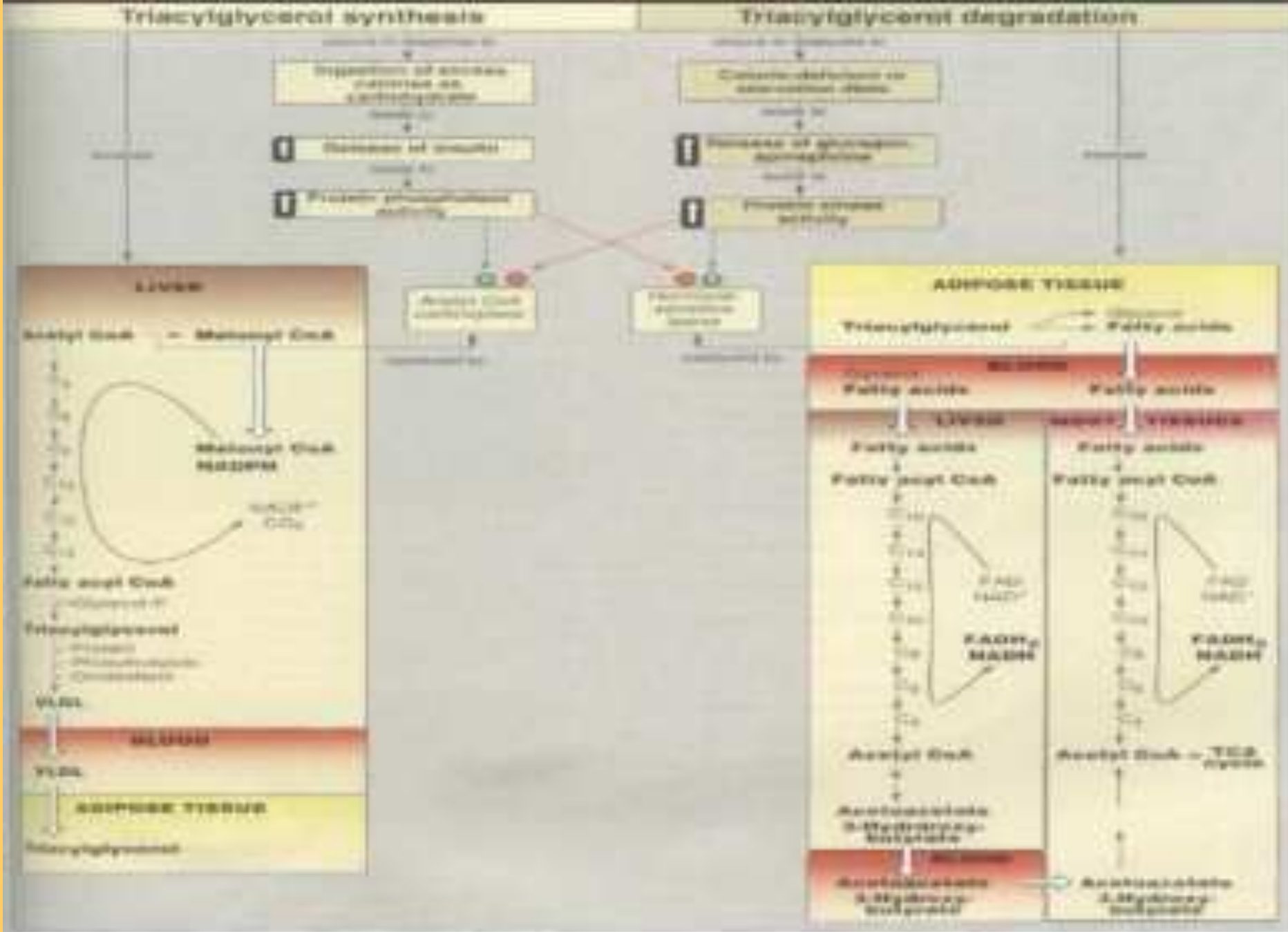
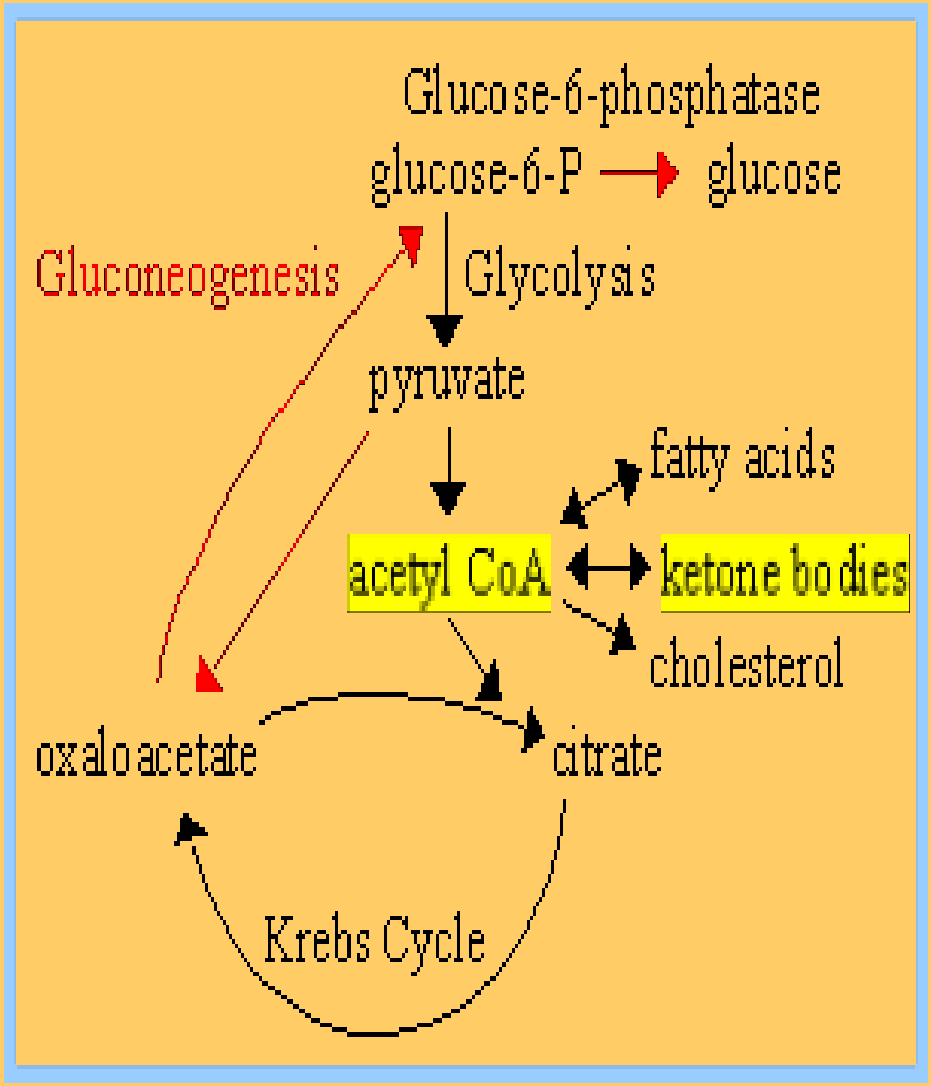
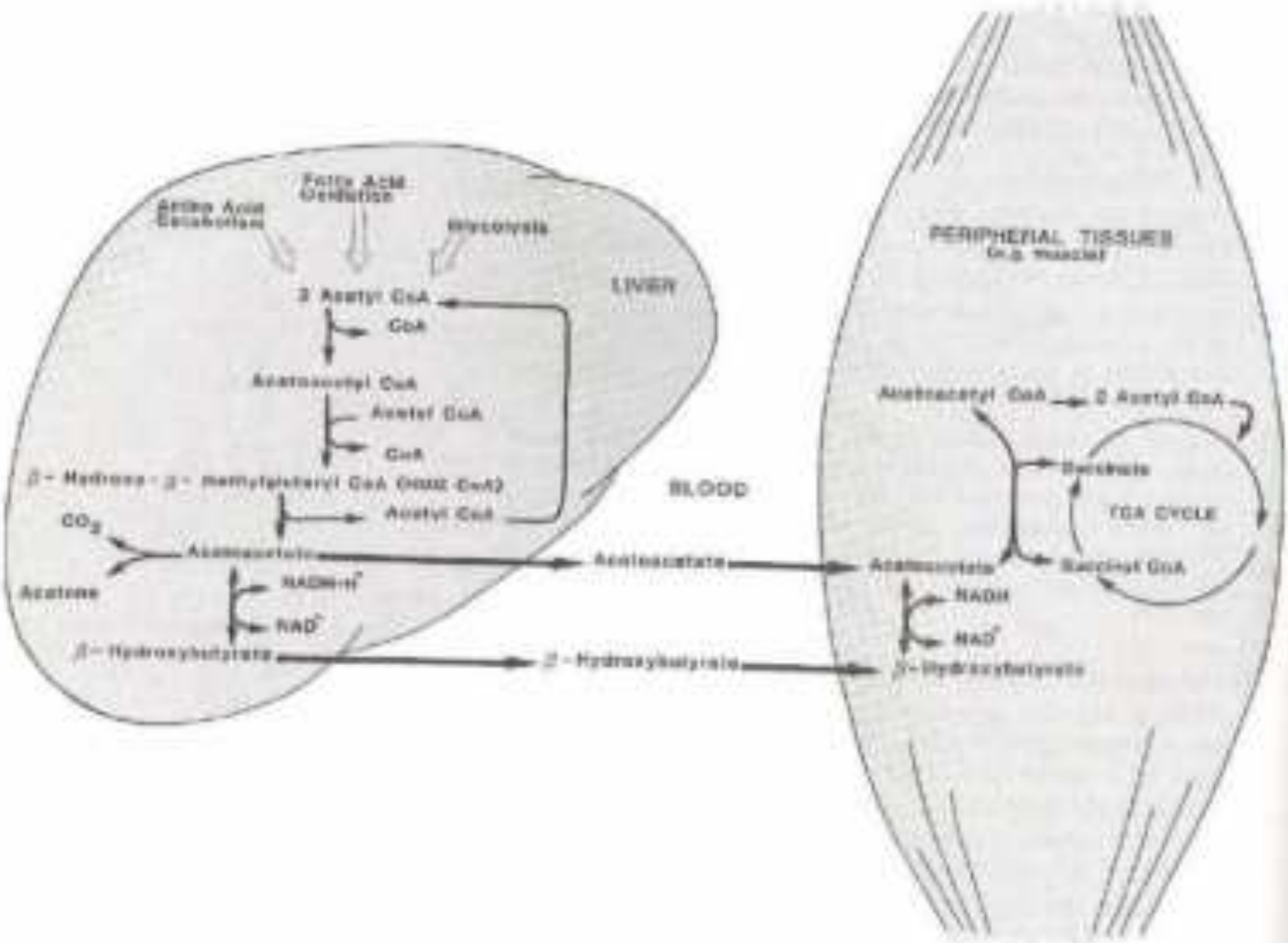


Figure 10.25
Key concept map for fatty acid and triacylglycerol metabolism.

Ketone bodies

Ketone bodies: During fasting or carbohydrate starvation, oxaloacetate is depleted in liver because it is used for gluconeogenesis. This impedes entry of acetyl-CoA into Krebs cycle. Acetyl-CoA then is converted in liver mitochondria to ketone bodies, acetoacetate and Beta-hydroxybutyrate.

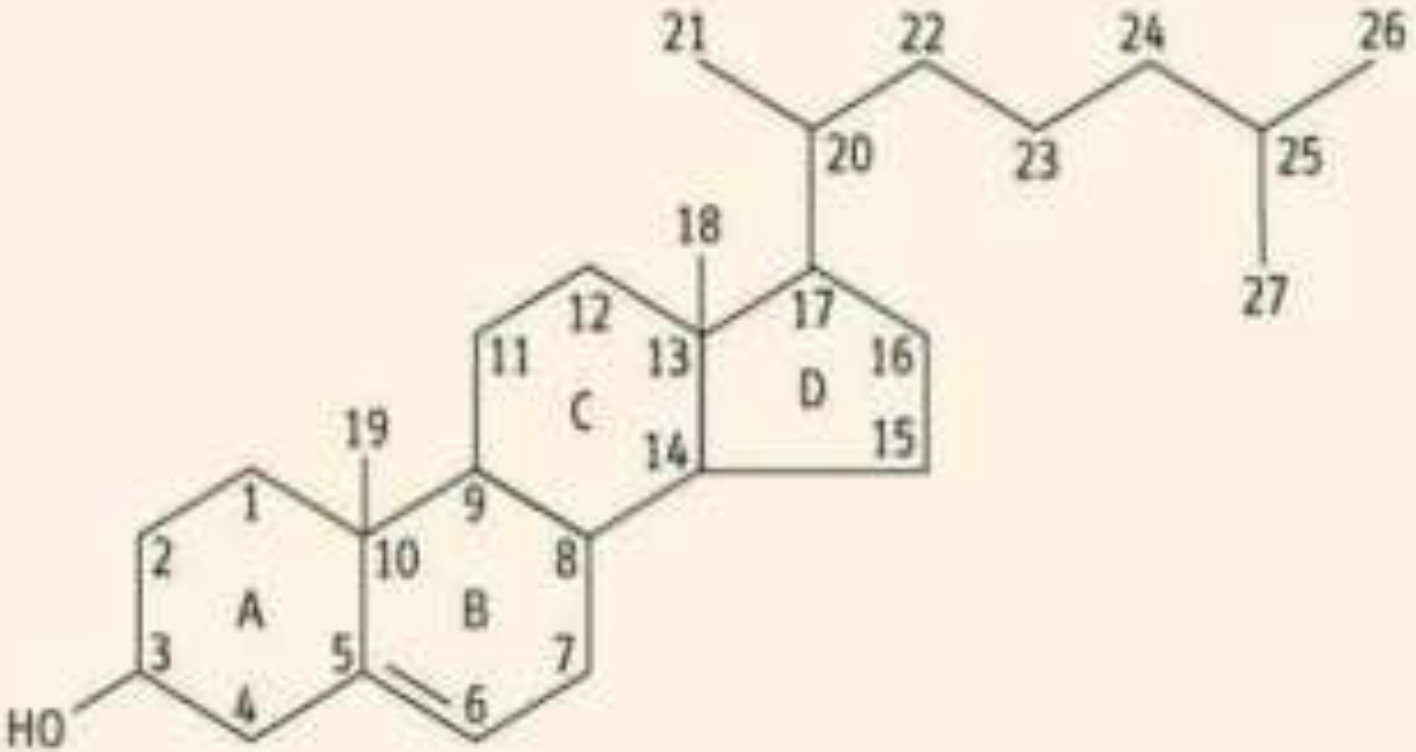



Amino Acid Catabolism
Fatty Acid Oxidation
Glycolysis
LIVER
2 Acetyl CoA
CoA
Acetoacetyl CoA
Acetyl CoA
CoA
β - Hydroxy - β - methylglutaryl CoA (HMG-CoA)
Acetyl CoA
CO_2
Acetoacetate
Acetone
NADH+H$^+$
NAD$^+$
β - Hydroxybutyrate
BLOOD
Acetoacetate
β - Hydroxybutyrate
PERIPHERAL TISSUES
(e.g. muscle)
Acetoacetyl CoA
2 Acetyl CoA
Succinate
TCA CYCLE
Acetoacetate
Succinyl CoA
NADH
NAD$^+$
β - Hydroxybutyrate

Biosynthesis of cholesterol in liver

- **Cholesterol is one of the most well recognized molecules in human biology, in part because of the direct relationship between its concentrations in blood and tissues and the development of atherosclerotic vascular disease. Cholesterol which is transported in the blood in lipoproteins because of its absolute insolubility in water, serves as a stabilizing component of cell membranes and as a precursor of the bile salts and steroids hormones. Cholesterol is precursor of cholecalciferol the active form of vitamin D in skin.**
- **Cholesterol can appear in its free , unesterified form in the outer shell of these macromolecules and as cholesterol esters in the lipoprotein core.**

Structure of cholesterol



Structure of cholesterol

It contains 27 carbon atoms ,of which 17 are incorporated into four fused rings (the perhydrocyclopentano-phenanthrene nucleus. This structure gives cholesterol a low solubility in water (about 5µmol/L). Only about 30% of circulating cholesterol occurs in the free form , the majority is esterified through the hydroxyl group to a wide range of long chain fatty acids including oleic and linoleic acids.

Cholesterol esters are less soluble in water than free cholesterol and the conc in plasma 5 mmole/L (200mg/dl).The lipoproteins which bind with cholesterol solubilize it. Within these lipoproteins the hydrophobic cholesterol esters are located in the core of the molecule, with free cholesterol in the outside layer.

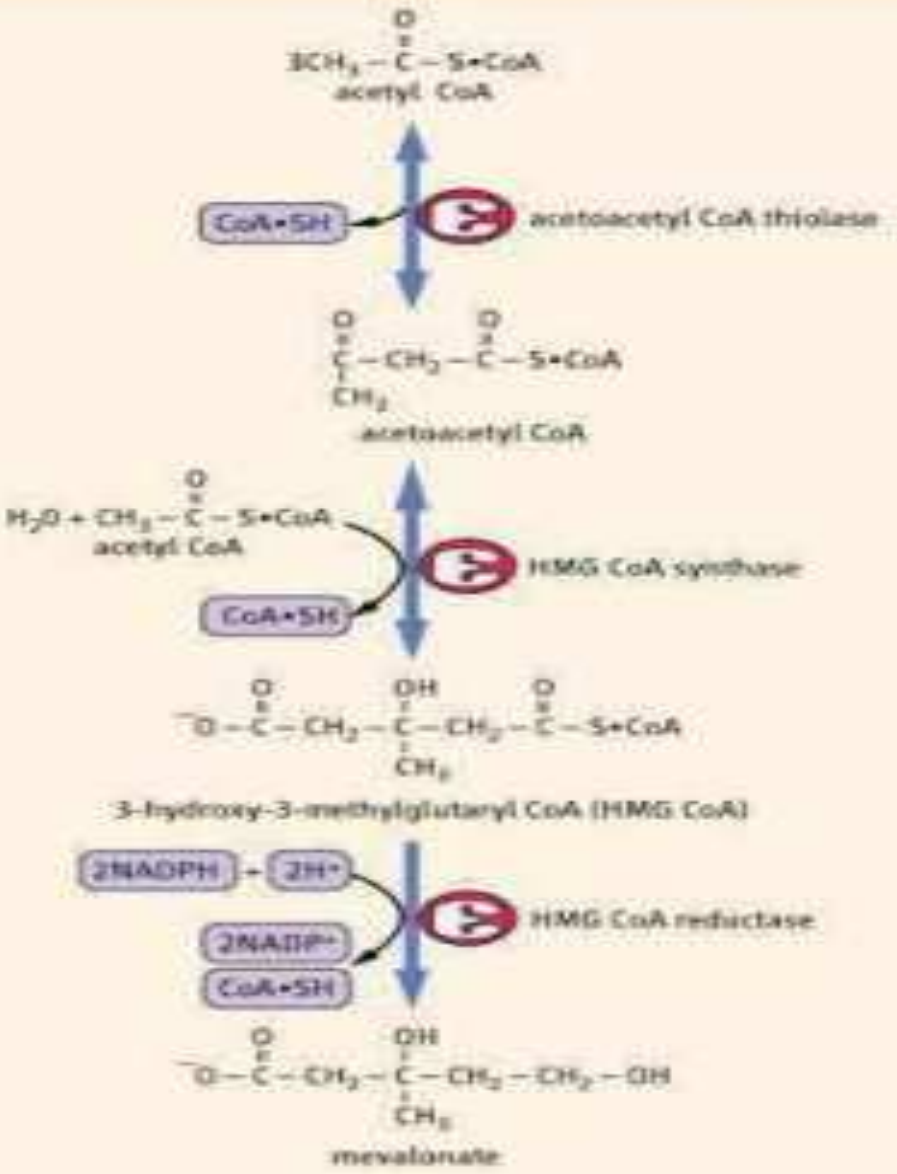
Biosynthesis of cholesterol

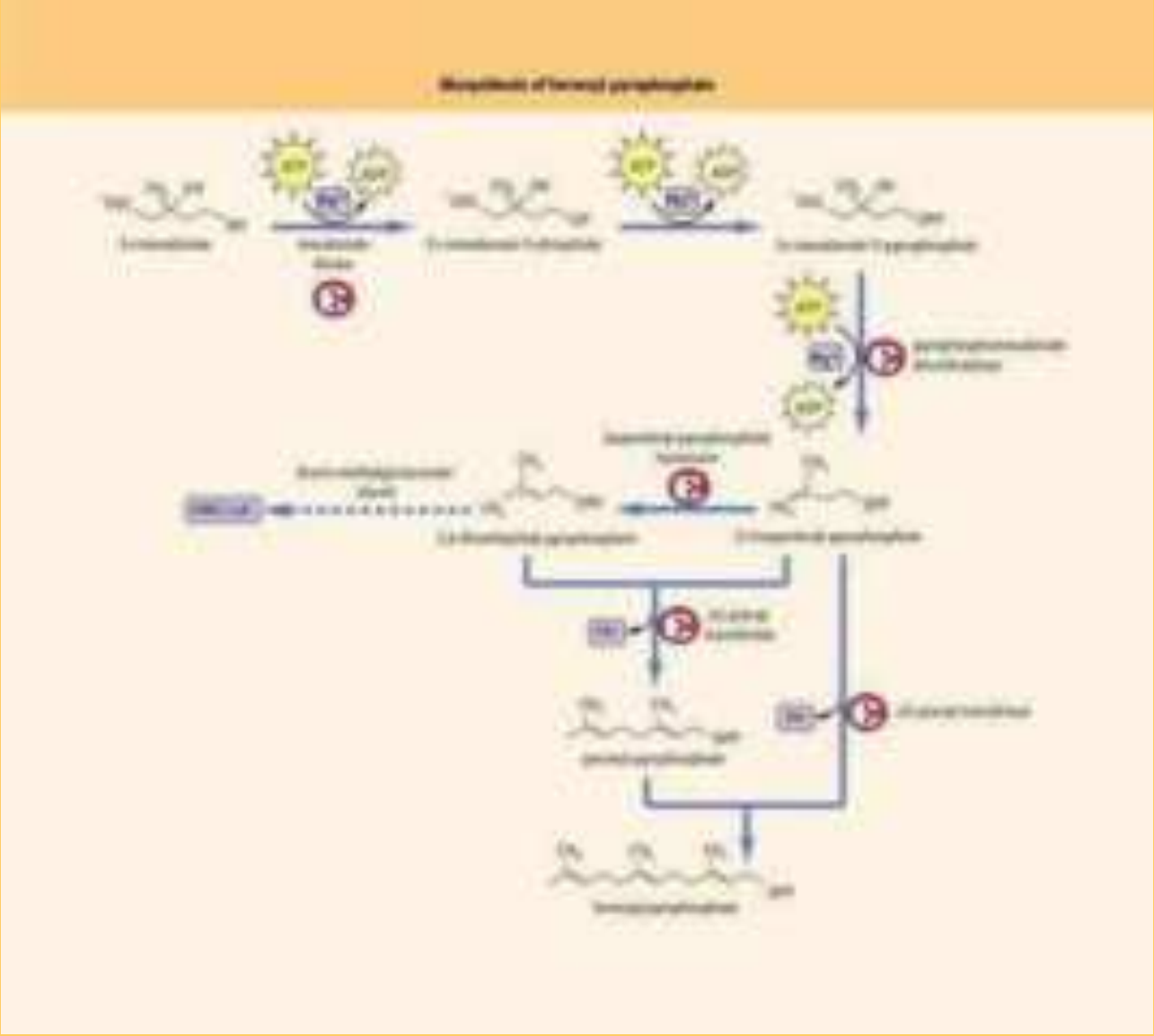
Acetyl CoA is the starting point in the biosynthesis of cholesterol . All human cells have the capacity to make cholesterol , however the liver is the major site of cholesterol synthesis with the intestine , adrenal cortex and gonads. The production of 1 mole of cholesterol requires 18 moles of acetyl CoA , 36 moles of ATP and 16 moles of NADPH. All the biosynthetic reactions occur within the cytoplasm.

Mevalonic acid is the first compound :

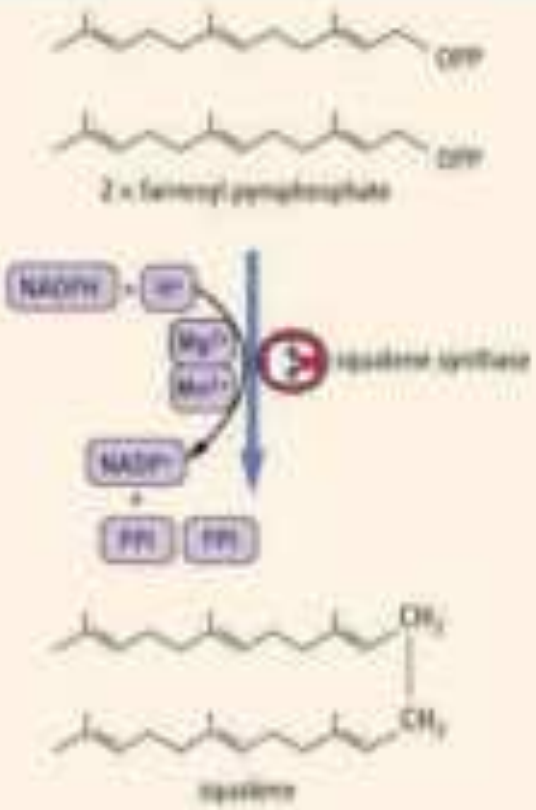
Three molecules of acetyl CoA are converted into the six carbon atom mevalonic acid. The first two steps are condensation reactions leading to the formation of HMG CoA .These reactions are common to the formation of KB although the latter process occurs within mitochondria rather than the cytosol. However the key reaction in the early stages of cholesterol biosynthesis is catalyzed by microsomal enzyme HMG CoA reductase which leads to the irreversible formation of mevalonic acid.

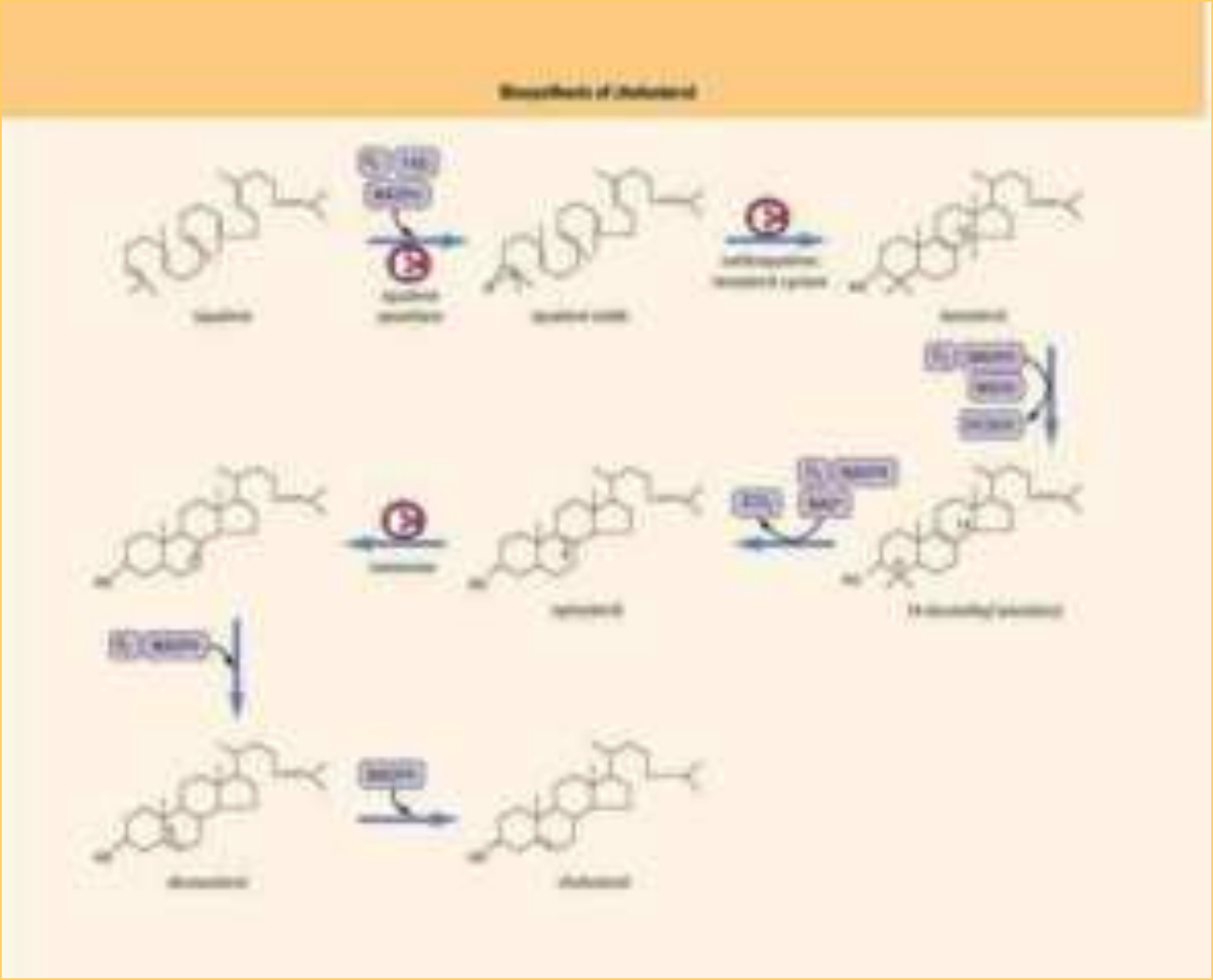
Biosynthesis of mevalonic acid





Biosynthesis of squalene





Bile acids

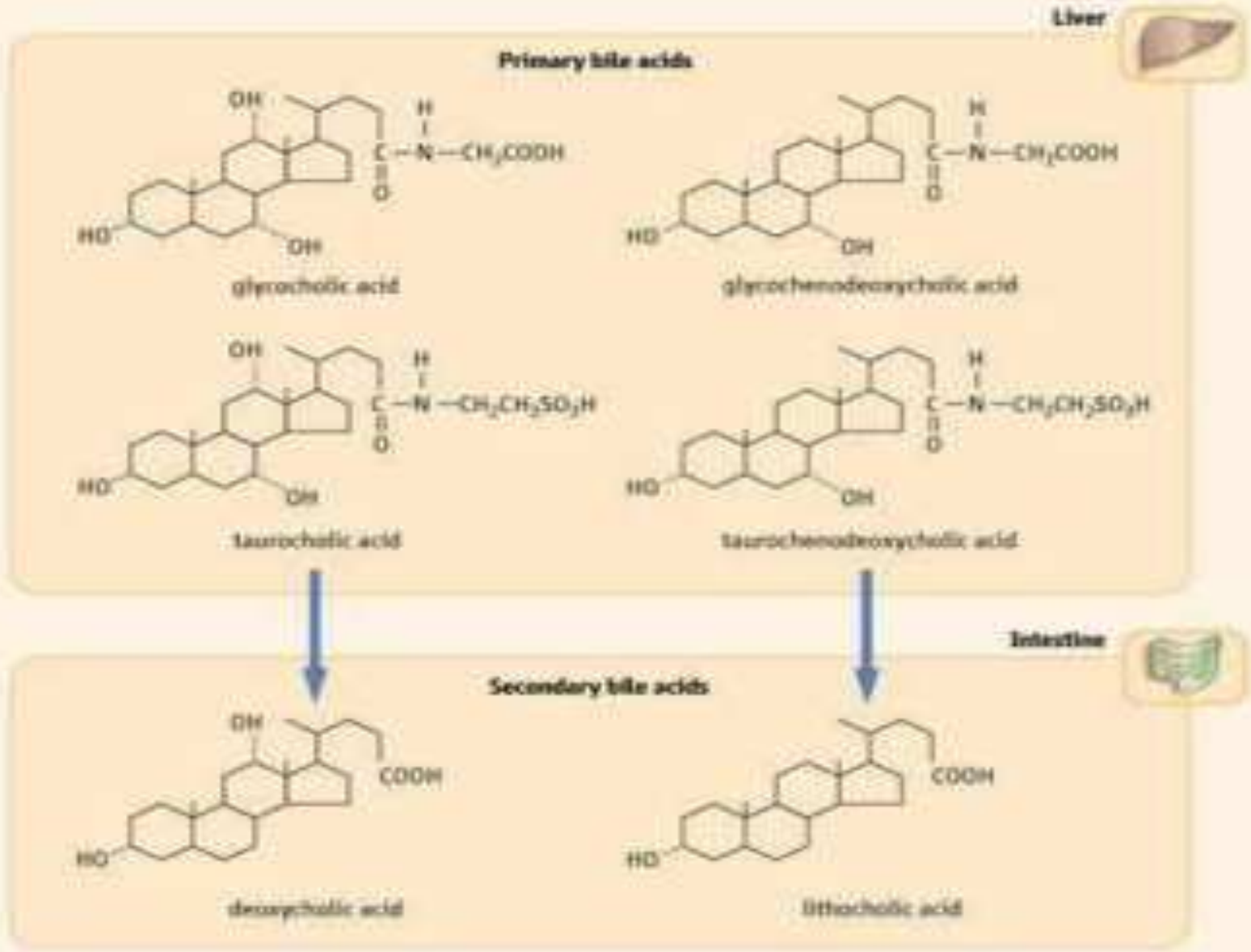
Quantitatively the most important metabolic products of cholesterol are the bile acids. In man there are four main bile acids .These bile acids all have 24 carbon atoms.

Biosynthesis occurs within the liver cells to produce cholic and chenodeoxycholic acids. The rate limiting step in the biosynthesis is the microsomal 7- hydroxylase enzyme. Prior to secretion these primary bile acids are conjugated with either glycine or taurine.The secreted products are thus principally glycoholic , glycochenodeoxycholic , taurocholic and taurochenodeoxycholic acids.

These compounds are secreted from the liver via bile ducts either directly into the duodenum or for storage in the gall bladder. They are an important component of bile , together with water , phospholipids , cholesterol , salts and excretory products such as bilirubin.

Deoxycholic and lithocholic acids are secondary bile acids formed within the intestine through the action of bacterial enzymes on the primary bile acids.

Structure of bile acids



- **Cholelithiasis :**
- **Bile salts and phospholipids are responsible for keeping the cholesterol in bile in a soluble state. Due to their deficiency in bile , cholesterol crystals precipitate in the gall bladder often resulting in cholelithiasis – cholesterol gall stone disease.**
- **Cholelithiasis may be due to defective absorption of bile salts from the intestine, impairment in liver function, obstruction of biliary tract.**

Steroid hormones

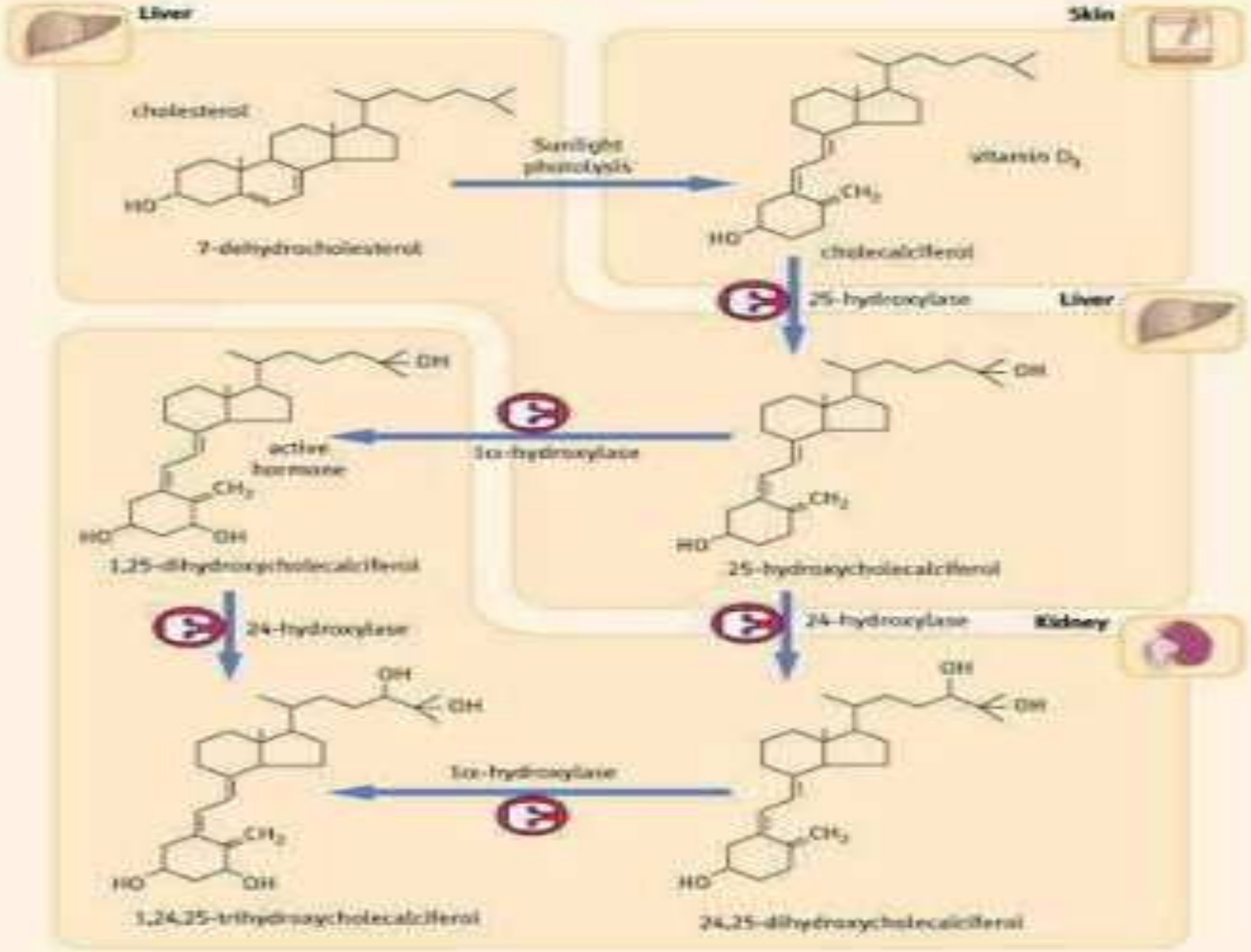
Cholesterol is the precursor of all the steroid hormones. The biosynthesis of the steroid hormones occurs within the adrenal cortex , the testis in man and the ovary in woman.

Vitamin D3

Vitamin D3 is known as cholecalciferol , it is derived from cholesterol .The majority of cholecalciferol is made in malpighian layer of the epidermis of the skin.

Cholesterol is converted to 7-dehydrocholesterol which acts as the substrate for non enzymatic photolysis reaction in which UV rays from sunlight mediate the opening of the B-ring of cholesterol , so destroying the steroid nucleus. This reaction is inversely related to the amount of pigment in the skin and directly related to the amount of sunlight exposure.

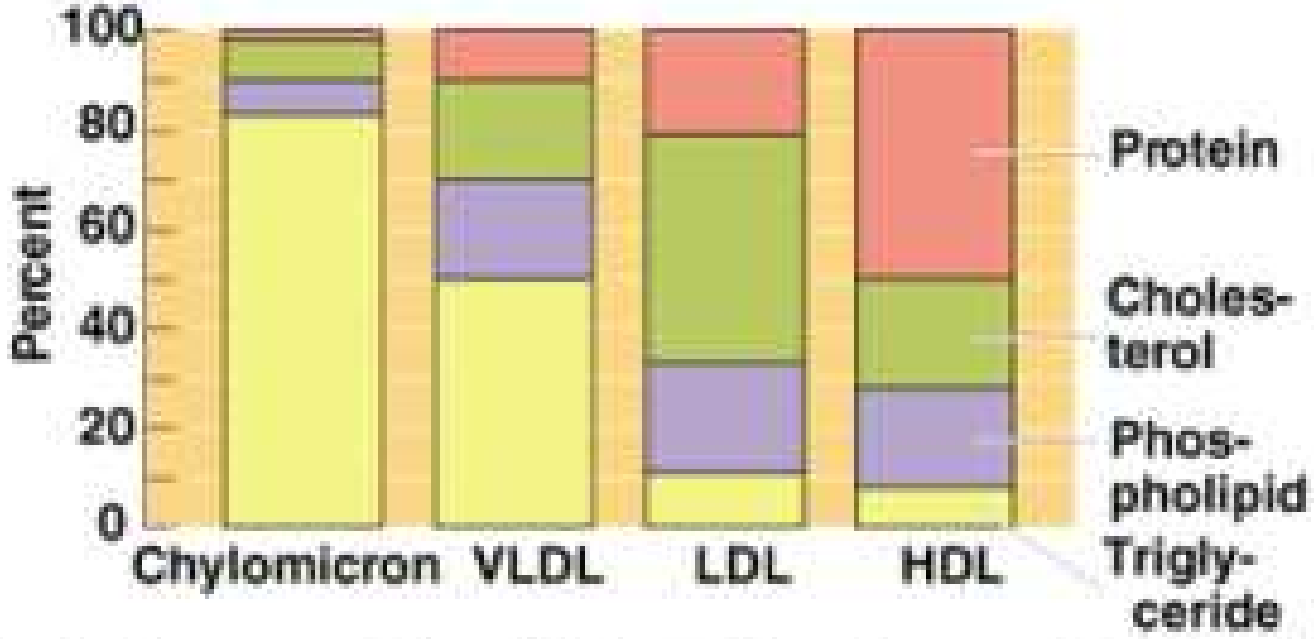
Formation and hydroxylation of vitamin D



Lipids and lipoproteins

Lipoproteins :

Lipoproteins are important because the provide means for fat transport between different organs and tissues. Their clinical importance is the role they play in the development of atherosclerosis; a phenomenon that underlies a range of disease of the cardiovascular system such as coronary heart disease and stroke.



Chylomicons contain so little protein and so much triglyceride that they are the lowest in density

Very-low-density lipoproteins (VLDL) are half triglycerides, accounting for their low density

Low-density lipoproteins (LDL) are half cholesterol for their implication in heart disease.

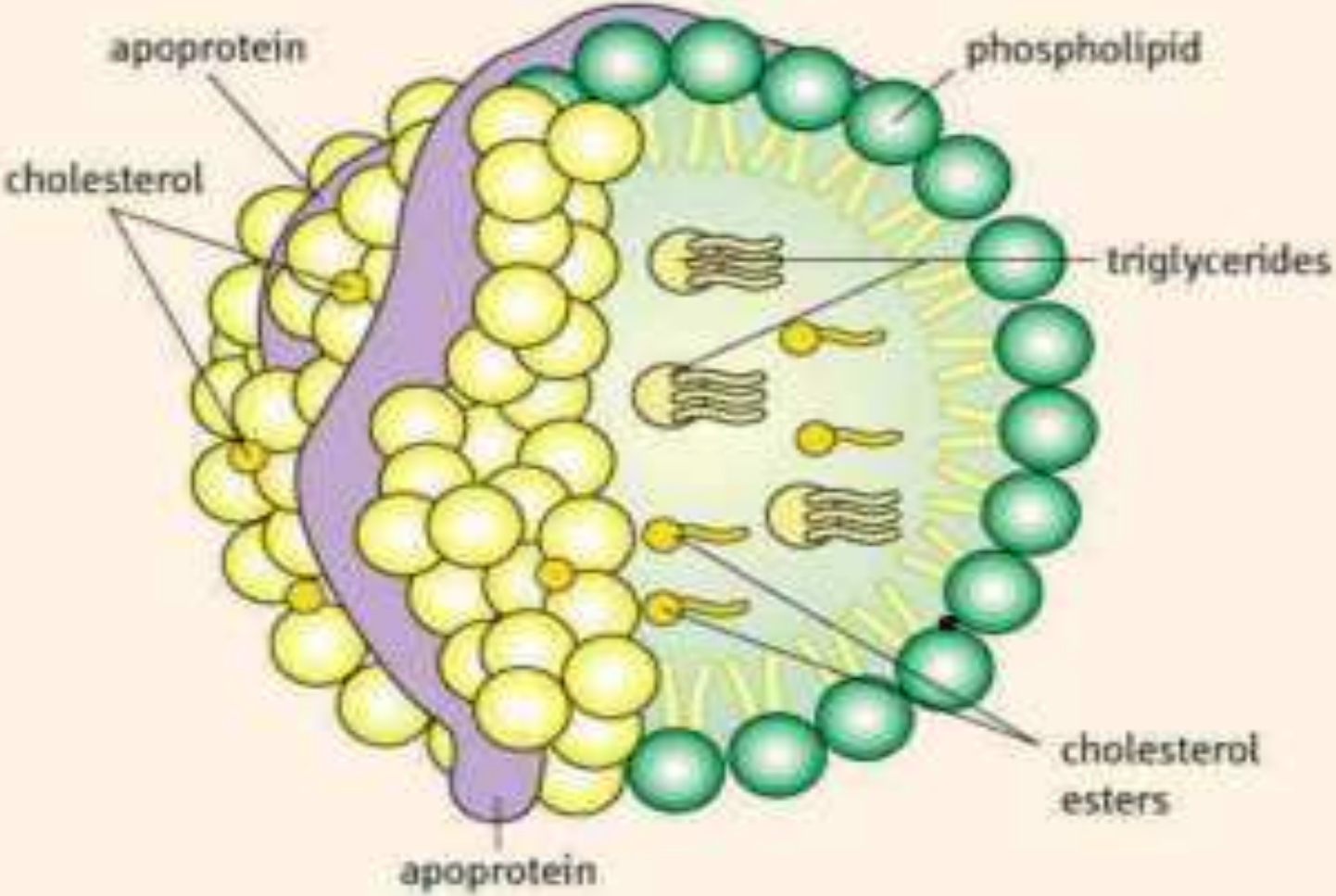
High-density lipoproteins (HDL) are half protein, accounting for their high density

© 1999 Wadsworth Publishing Company/ITP

The lipoprotein classes

Particle	Density (kg/L)	Main component	Apoproteins	Diameter (μm)
chylomicrons	<0.95	TG	B48 (A, C, E)	75–1200
VLDL	0.95–1.006	TG	B100 (A, C, E)	30–80
IDL	1.006–1.019	TG & cholesterol	B100, E	25–35
LDL	1.019–1.063	Cholesterol	B100	18–25
HDL	1.063–1.210	Protein	AI, AII (C, E)	5–12

Lipoprotein structure




Artery
Cholesterol particles (lipoproteins)
Cholesterol deposited in lining of artery
Buildup begins
Plaque forms (atherosclerosis)


THANK
YOU

Dr Falih Jabor

Nucleotide Metabolism

Ribonucleosides and deoxyribonucleoside phosphates (nucleotides) are essential for all cells. Without them, neither DNA nor RNA can be produced and, therefore, proteins cannot be synthesized or cells proliferate.

1. Nucleotides serve as carriers of activated intermediates in the synthesis of some carbohydrates, lipids, and proteins.

2. They are structural components of several essential coenzymes, for example, coenzyme A,FAD.

3. Nucleotides, such as cyclic AMP (cAMP) and cyclic GMP (cGMP), serve as second messengers in signal transduction pathways.

4. Nucleotides play an important role as "energy currency" in the cell.

- The metabolic requirements for the nucleotides and their bases can be met by both dietary intake or synthesis de novo from low molecular weight precursors. The salvage pathways are a major source of nucleotides for synthesis of DNA, RNA and enzyme co-factors.

The activated sugar used is 5-phospho--D-ribosyl-1-pyrophosphate, PRPP: PRPP is generated by the action of PRPP synthetase and requires energy in the form of ATP as shown:

ribose-5-phosphate + ATP -------> PRPP + AMP

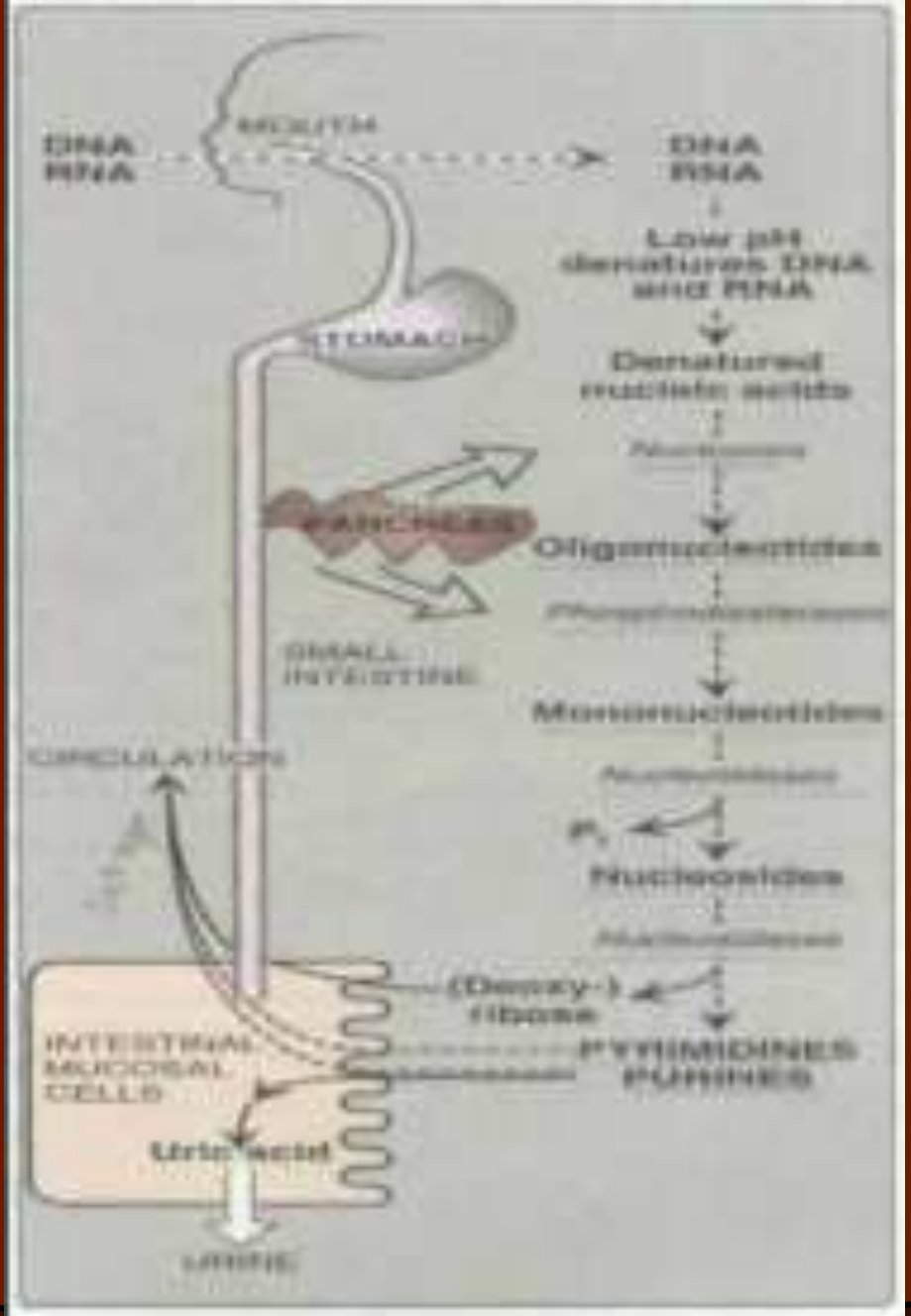


Figure 22.14
Digestion of dietary nucleic acids

Purine Nucleotide Biosynthesis

The major site of purine synthesis is in the liver. Synthesis of the purine nucleotides begins with PRPP and leads to the first fully formed nucleotide, inosine 5'-monophosphate (IMP).

Inosine monophosphate, IMP begins with 5-phospho-a-ribosyl-1-pyrophosphate, PRPP. Through a series of reactions utilizing ATP, tetrahydrofolate (THF) derivatives, glutamine, glycine and aspartate this pathway yields IMP. The two indicated enzymes (A and B) are those catalyzing the rate limiting step and the reaction necessary for the purine nucleotide cycle, respectively.

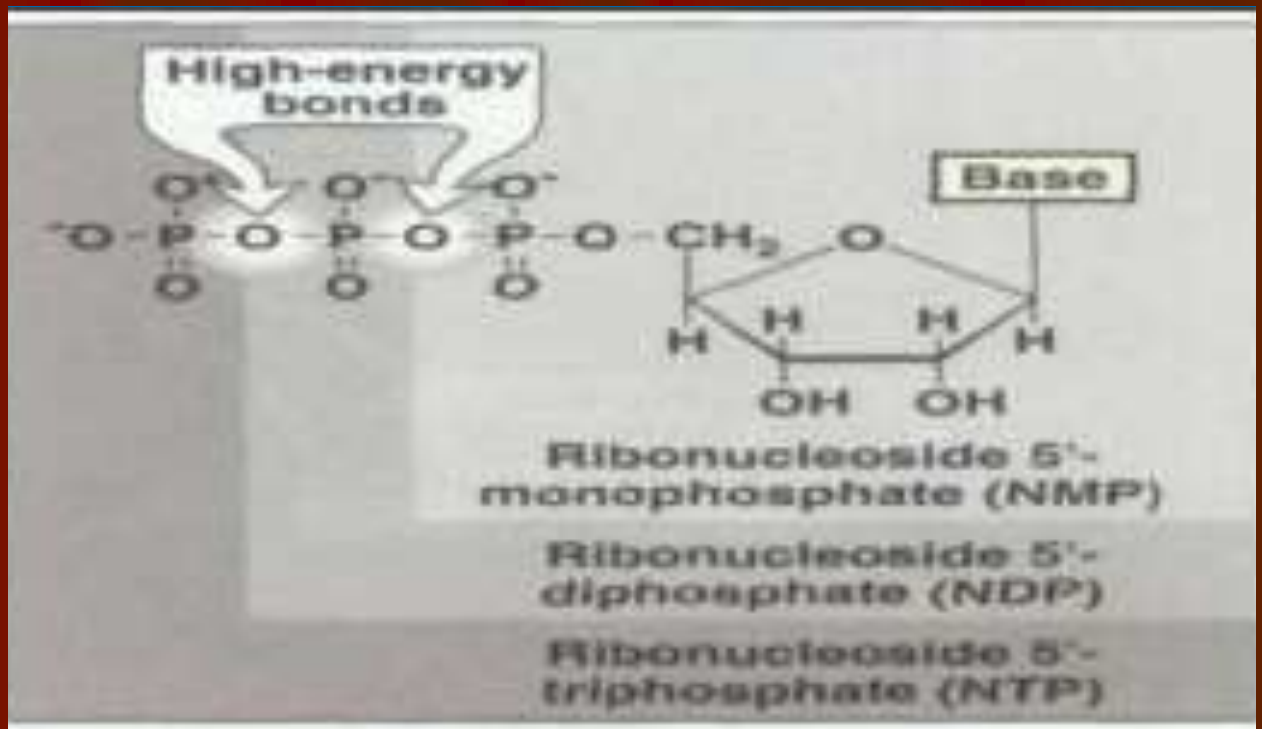
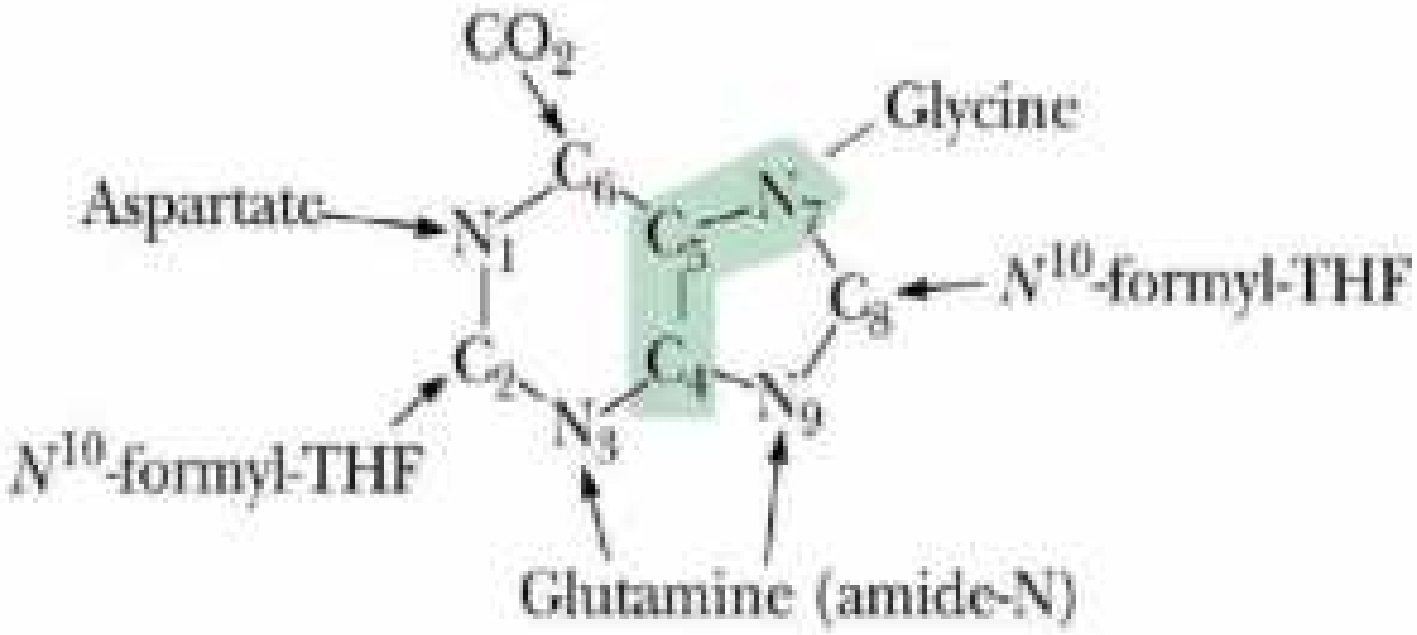


Figure 22.4
Ribonucleoside monophosphate, diphosphate, and triphosphate.


CO_2
Glycine
Aspartate
N^{10}-formyl-THF
N^{10}-formyl-THF
Glutamine (amide-N)

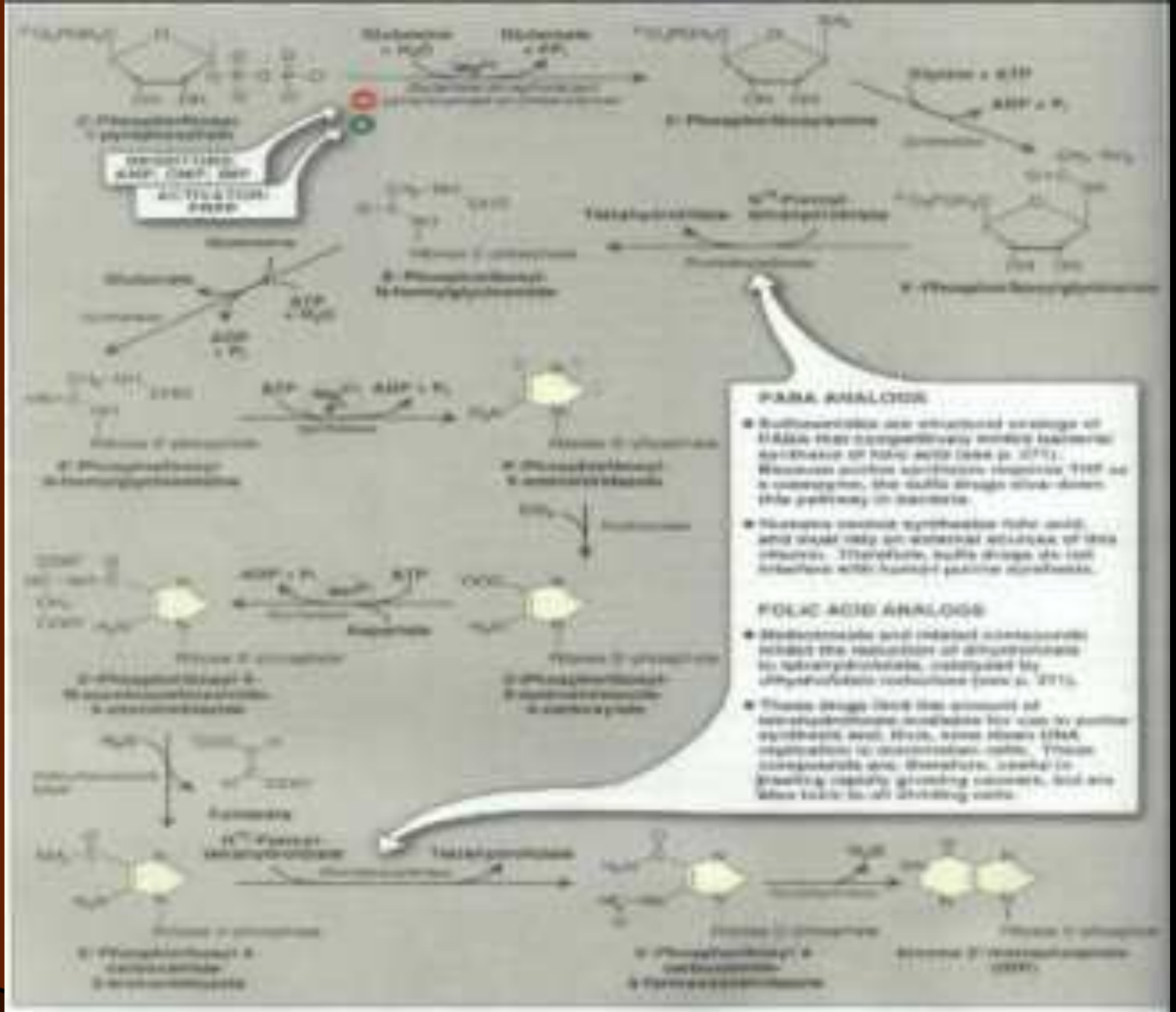


Figure 22.7
Synthesis of purine nucleotides, showing the inhibitory effect of some structural analogs.

IMP represents a branch point for purine biosynthesis, because it can be converted into either AMP or GMP through two distinct reaction pathways. The pathway leading to AMP requires energy in the form of GTP; that leading to GMP requires energy in the form of ATP. The utilization of GTP in the pathway to AMP synthesis allows the cell to control the proportions of AMP and GMP to near equivalence. The accumulation of excess GTP will lead to accelerated AMP synthesis from IMP instead, at the expense of GMP synthesis. Conversely, since the conversion of IMP to GMP requires ATP, the accumulation of excess ATP leads to accelerated synthesis of GMP over that of AMP.

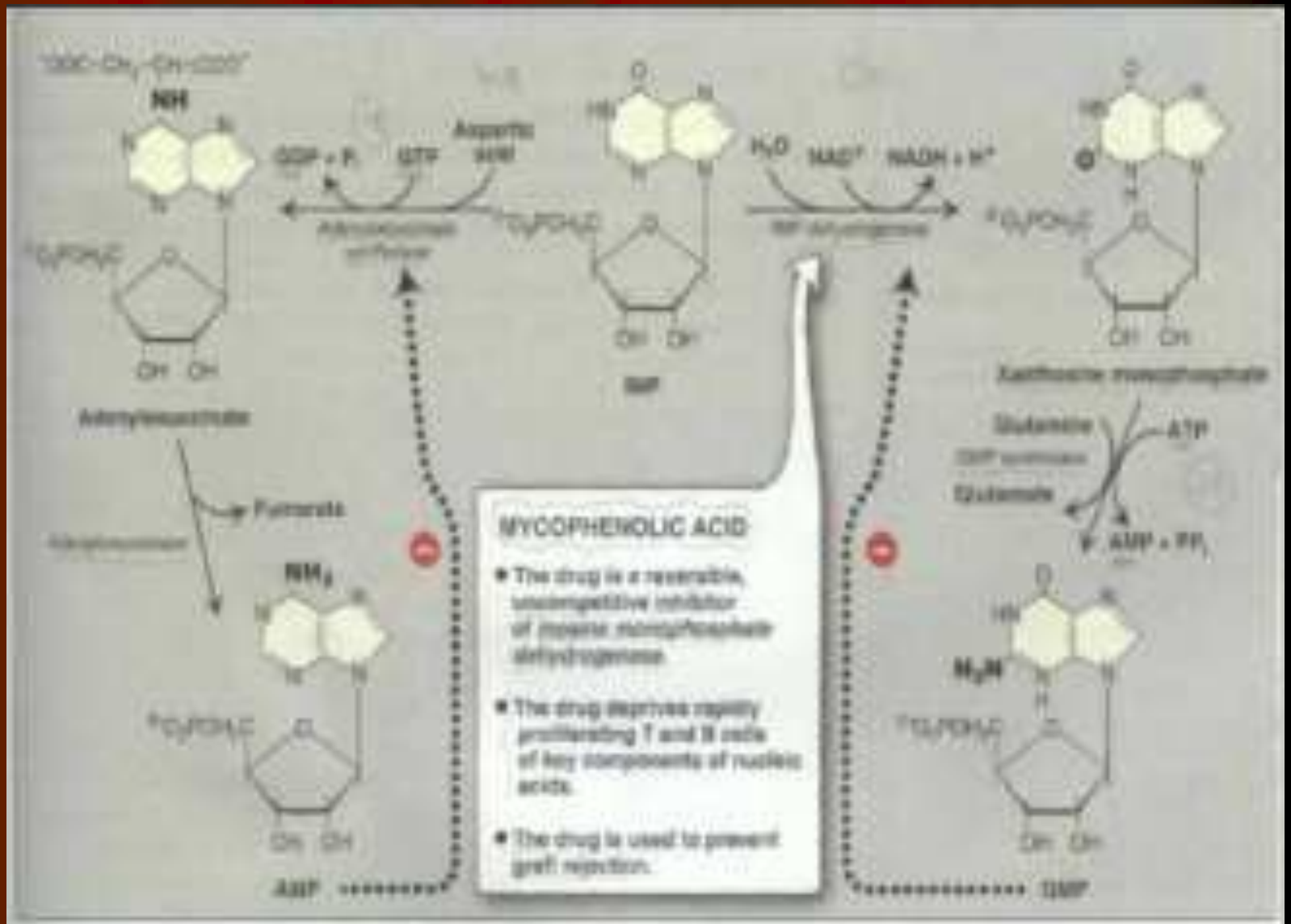


Figure 22.8
Conversion of IMP to AMP and GMP showing feedback inhibition.

See Chapters 24 and 49, in Lippincott's Illustrated Reviews: Pharmacology (3rd Ed.) and Chapters 29 and 33 (2nd Ed.) for a discussion of sulfonamides, trimethoprim, and methotrexate.

Catabolism and Salvage of Purine Nucleotides

Catabolism of the purine nucleotides leads ultimately to the production of uric acid which is insoluble and is excreted in the urine as sodium urate crystals.

Salvage pathways :

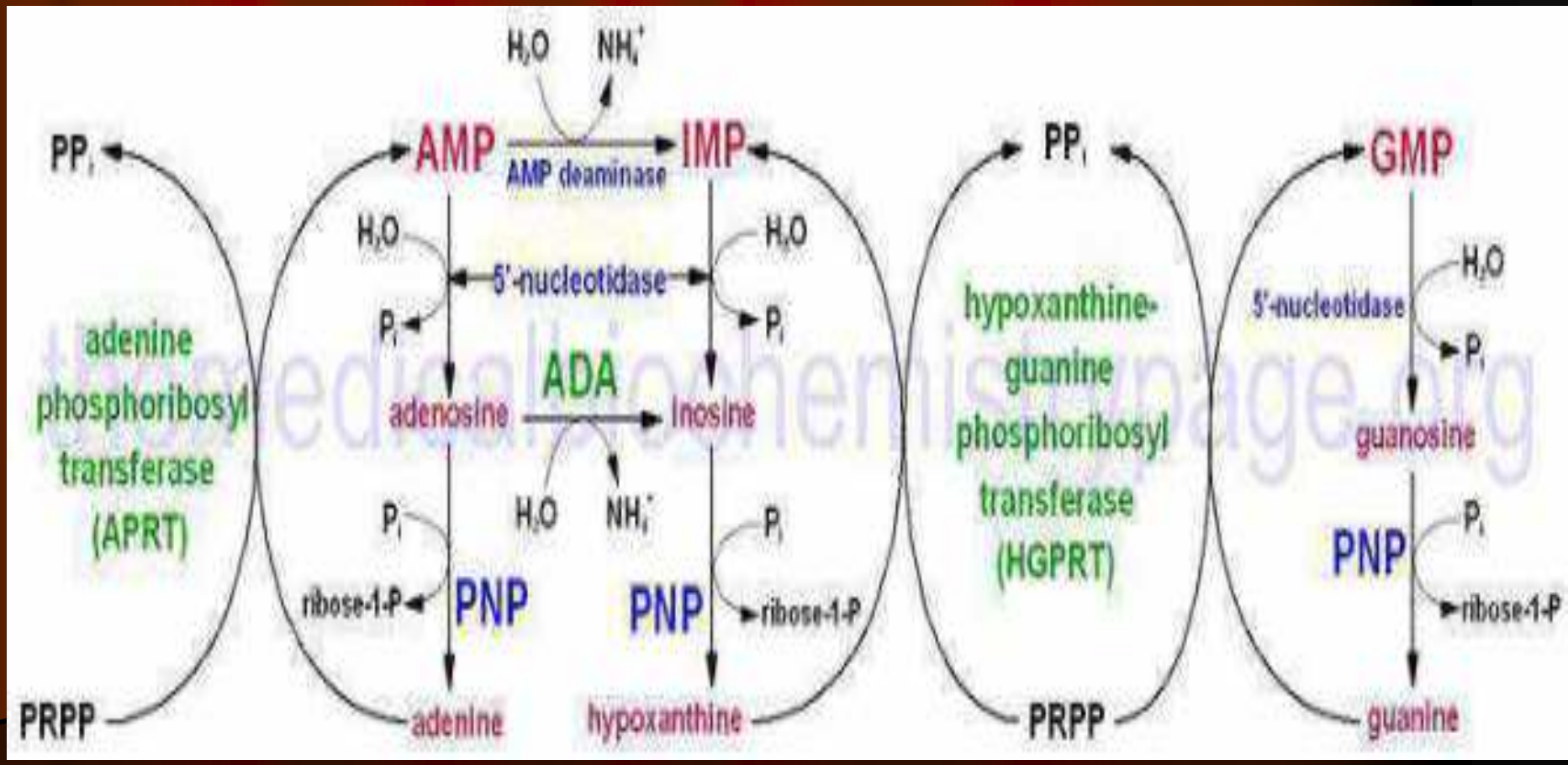
The synthesis of nucleotides from the purine bases and purine nucleosides takes place in a series of steps known as the salvage pathways. The free purine bases---adenine, guanine, and hypoxanthine---can be reconverted to their corresponding nucleotides by phosphoribosylation. Two key transferase enzymes are involved in the salvage of purines: adenosine phosphoribosyltransferase (APRT), which catalyzes the following reaction:

adenine + PRPP <-----> AMP + PPi

and hypoxanthine-guanine phosphoribosyltransferase (HGPRT), which catalyzes the following reactions:

hypoxanthine + PRPP <------> IMP + PPi

guanine + PRPP <--------> GMP + PPi


H2O
NH4+
AMP
AMP deaminase
IMP
PPi
H2O
5'-nucleotidase
Pi
H2O
Pi
adenine phosphoribosyl transferase (APRT)
ADA
adenosine
Inosine
H2O
NH4+
Pi
ribose-1-P
PNP
PNP
Pi
ribose-1-P
PRPP
adenine
hypoxanthine
PPi
hypoxanthine-guanine phosphoribosyl transferase (HGPRT)
GMP
H2O
5'-nucleotidase
Pi
guanosine
Pi
PNP
ribose-1-P
PRPP
guanine

Clinical Significances of Purine Metabolism

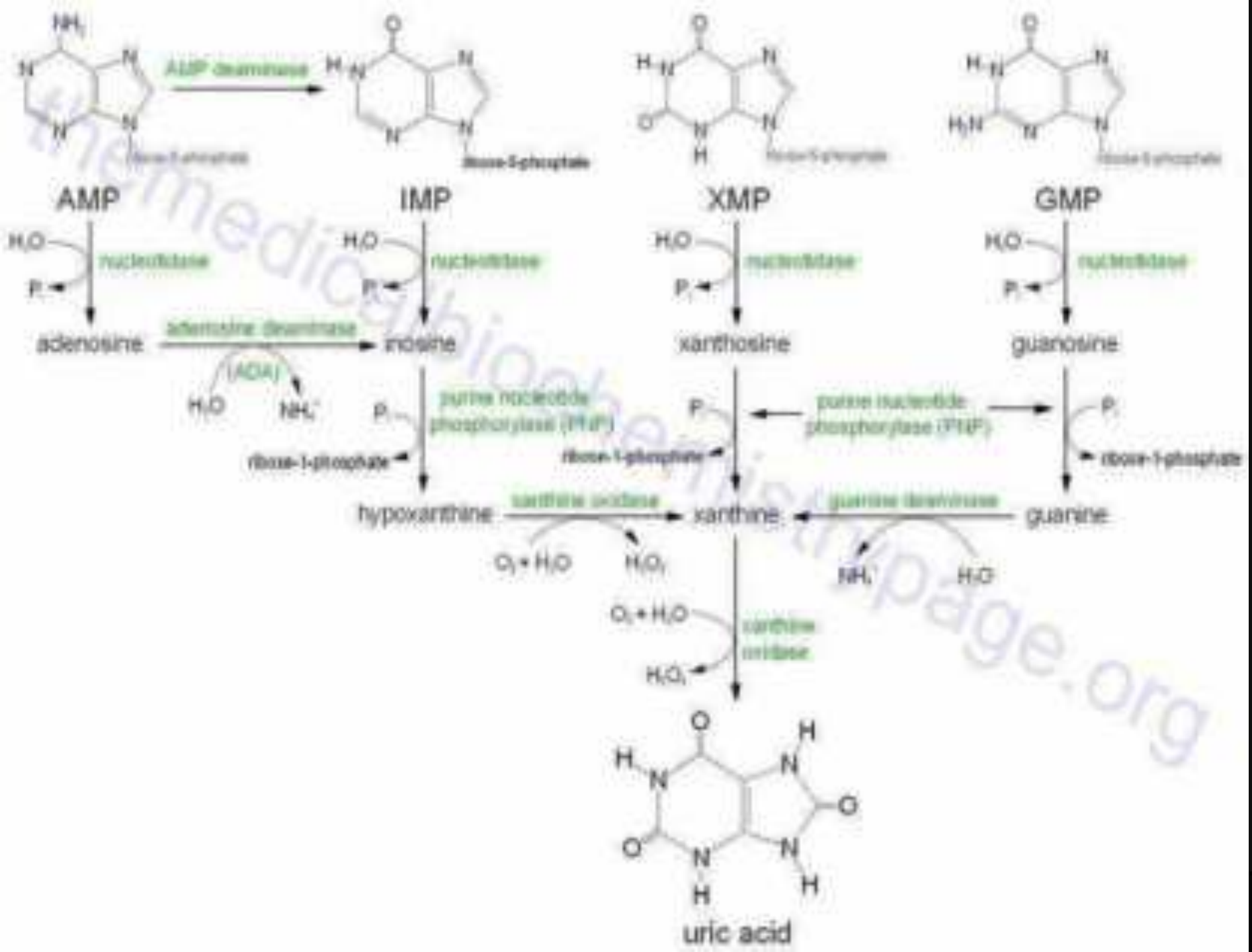
Clinical manifestations of abnormal purine catabolism arise from the insolubility of the degradation byproduct, uric acid. Excess accumulation of uric acid leads to hyperuricemia, more commonly known as gout. This condition results from the precipitation of sodium urate crystals in the synovial fluid of the joints, leading to severe inflammation and arthritis. Sodium urate and uric acid may also precipitate in kidneys and urethras that results in renal damage and stone formation. Historically , gout was found to be often associated with high living overeating .

Primary gout : It is an inborn error of metabolism due to overproduction of uric acid. This is mostly related to increased synthesis of purine nucleotides.

2. Secondary gout : Secondary hyperuricemia is due to various disease causing increased synthesis or decreased excretion of uric acid . Increased degradation of nucleic acid (More uric acid formation) is observed in different cancers (leukemia, lymphomas, polycythemia etc) psoriasis and increased tissue breakdown (trauma, starvation etc).

Most forms of gout are the result of excess purine or of a partial deficiency in the salvage enzyme, HGPRT.

- Two severe disorders,are associated with defects in purine metabolism: Lesch-Nyhan syndrome and severe combined immunodeficiency disease (SCID).

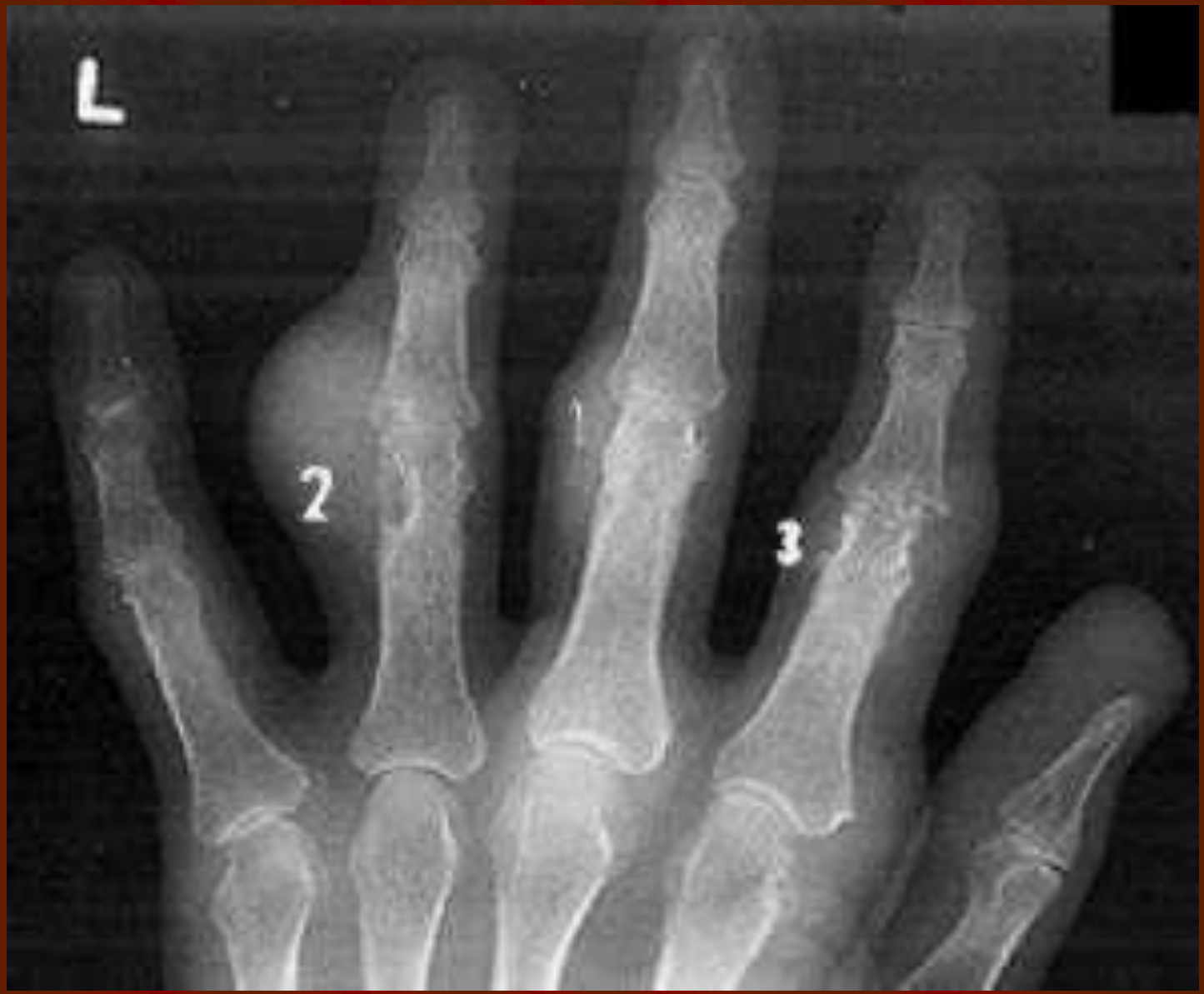


themedicalbiochemistrypage.org

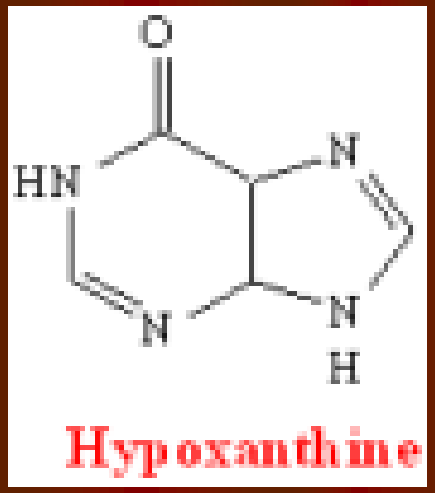
Non-pharmacological approaches

Avoid purine rich foods:

- red meat and organ meat (liver, kidneys)
- shellfish, anchovies, mackerel, herring
- meat extracts and gravies
- peas and beans, asparagus, lentils
- Weight loss


L
2
3

ALLOPURINOL IS A XANTHINE OXIDASE INHIBITOR
A SUBSTRATE ANALOG IS CONVERTED TO AN INHIBITOR, IN THIS CASE "SUICIDE-INHIBITOR



The drug of choice for the treatment of primary gout is allopurinol. This is a structural analog of hypoxanthine that inhibits the enzyme xanthine oxidase. Allopurinol is oxidized to alloxanthine by xanthine oxidase. Alloxanthine , in turn is a more effective inhibitor of xanthine oxidase This type of inhibition is referred to as suicide inhibition. This inhibition leads to accumulation of hypoxanthine and xanthine. These two compounds are more soluble than uric acid , hence easily excreted. Consumption of plenty of water will also be useful.

Lesch-Nyhan syndrome

- This disorder is due to the deficiency of hypoxanthine- guanine phosphoribosyl transferase (HGPRT) , an enzyme of purine salvage pathway.

  It affects only the males and is characterized by excessive uric acid production (often gouty arthritis) and neurological abnormalities such as mental retardation , aggressive behavior , learning disability etc. The patients of this disorder have an irresistible urge to bite their fingers and lips, often causing self mutilation. HGPRT deficiency results in the accumulation of PRPP and increase GMP and IMP , ultimately leading to increased synthesis and degradation of purines . Neurological symptoms may be related to the dependence of brain on the salvage pathway for de novo synthesis of purine nucleotides. Uric acid is not toxic to the brain. Allopurinol treatment that helps to decrease uric acid production , has no affect on the neurological manifestations in these patients. Death usually occurs before patients reach their 20th year.

Severe combined immuno deficiency disease :

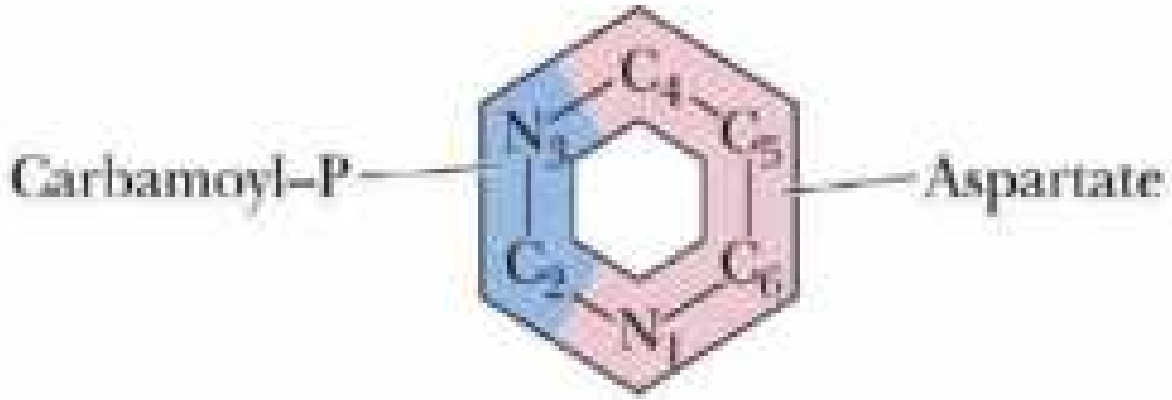
- SCID is caused by a deficiency in the enzyme adenosine deaminase (ADA). This is the compound responsible for converting adenosine to inosine in the catabolism of the purines. This deficiency selectively leads to a destruction of B and T lymphocytes, the cells that mount immune responses. In the absence of ADA, deoxyadenosine is phosphorylated to yield levels of dATP that are 50-fold higher than normal. The levels are especially high in lymphocytes, which have abundant amounts of the salvage enzymes, including nucleoside kinases. High concentrations of dATP inhibit ribonucleotide reductase thereby preventing other dNTPs from being produced. The net effect is to inhibit DNA synthesis. Since lymphocytes must be able to proliferate dramatically in response to antigenic challenge, the inability to synthesize DNA seriously impairs the immune responses, and the disease is usually fatal in infancy unless special protective measures are taken.

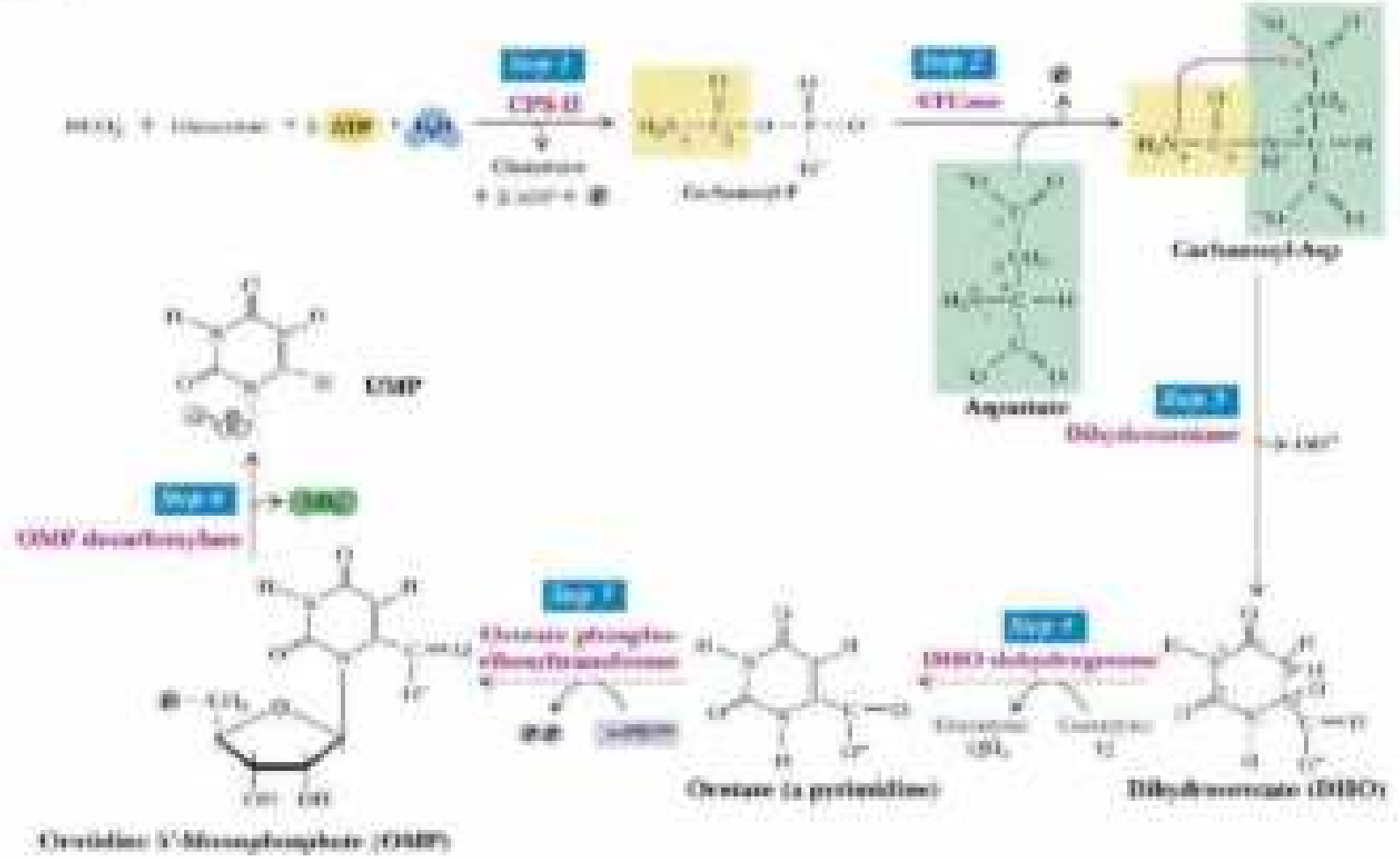
Pyrimidine Nucleotide Biosynthesis

The carbamoyl phosphate used for pyrimidine nucleotide synthesis is derived from glutamine and bicarbonate, within the cytosol, as opposed to the urea cycle carbamoyl phosphate derived from ammonia and bicarbonate in the mitochondrion. The urea cycle reaction is catalyzed by carbamoyl phosphate synthetase I (CPS-I) whereas the pyrimidine nucleotide precursor is synthesized by CPS-II. Carbamoyl phosphate is then condensed with aspartate in a reaction catalyzed by the rate limiting enzyme of pyrimidine nucleotide biosynthesis, aspartate transcarbamoylase (ATCase).

The synthesis of pyrimidines differs in two significant ways from that of purines. First, the ring structure is assembled as a free base, not built upon PRPP. PRPP is added to the first fully formed pyrimidine base (orotic acid), forming orotate monophosphate (OMP), which is subsequently decarboxylated to UMP. Second, there is no branch in the pyrimidine synthesis pathway.

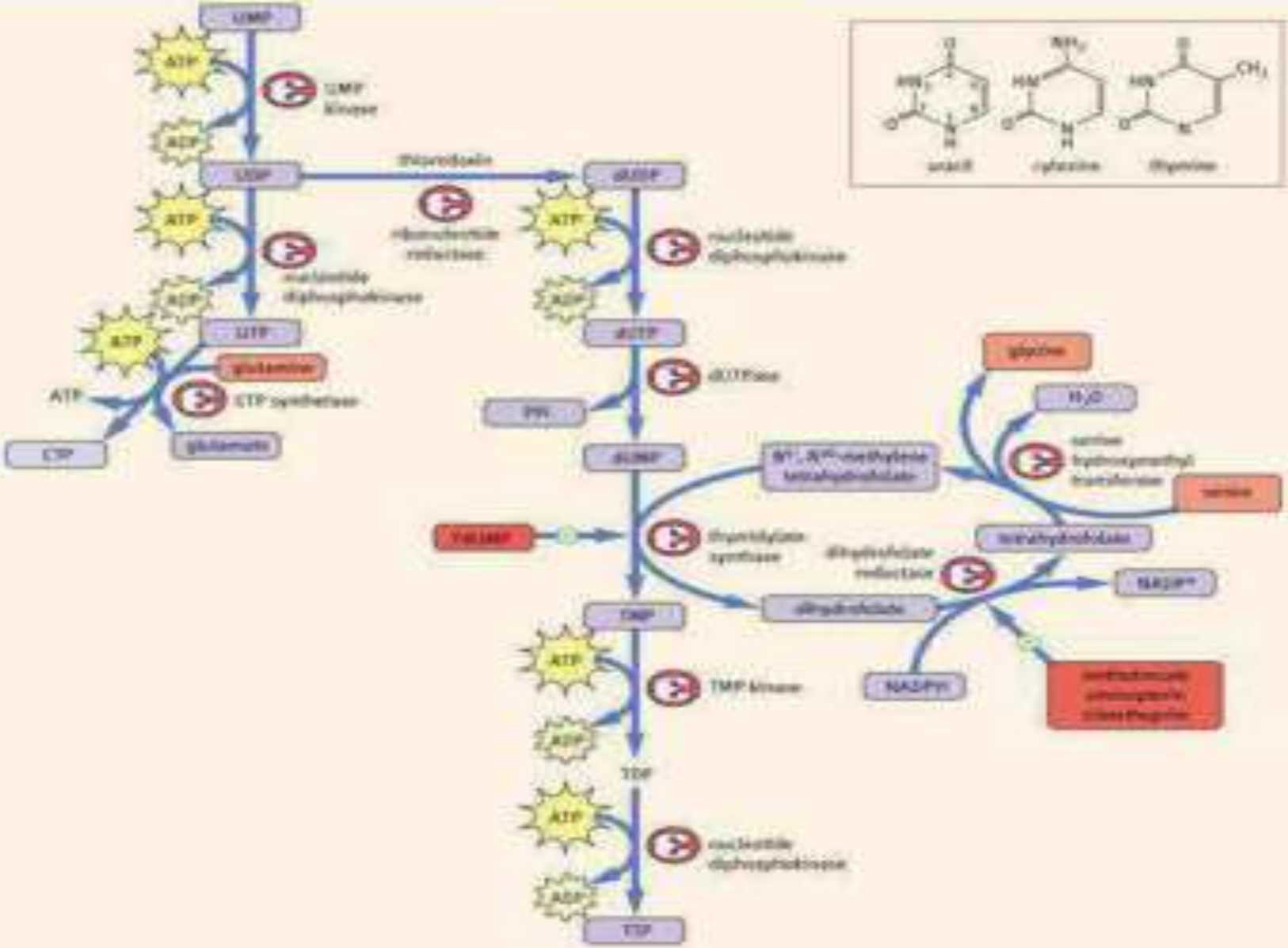
Origin of atoms in pyrimidine ring





1. Carbamoyl synthetase 11
2. Aspartate transcarbamylase
3. Dihydrorotase
4. Dihydroorotate dehydrogenase
5. Orotate phosphoribosyl transferase
6. Orotidine -5”-phosphate decarboxylase

Biosynthesis of CTP and TTP



Some chemotherapeutic agents block pyrimidine biosynthesis

When DNA synthesis is blocked, cells can not divide. Because of this, several important anticancer drugs that block the synthesis of TMP are widely used as chemotheraputic agents. These include pyrimidine analogs such as methotrexate.

FdUMP is a specific suicide inhibitor of thymidylate synthase. Flurouridine is used against gastric and uterine cancer. Methotrexate is folic acid analog that bind 1000 fold more tightly to DHFR than does dihydrofolate. Thus , the effectively block the synthesis of THF which in turn limit the formation of methylene THF . In this manner block the synthesis of dTMP and inhibit the synthesis of purine nucleotide.

Folate analogs are non specific chemotherapeutic agents. They poison rapidly dividing cells, including those in hair follicles and gut endothelia, causing the loss of hair and GIT side effects of chemotherapy.

Clinical Significances of Pyrimidine Metabolism

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 . 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 .


The end