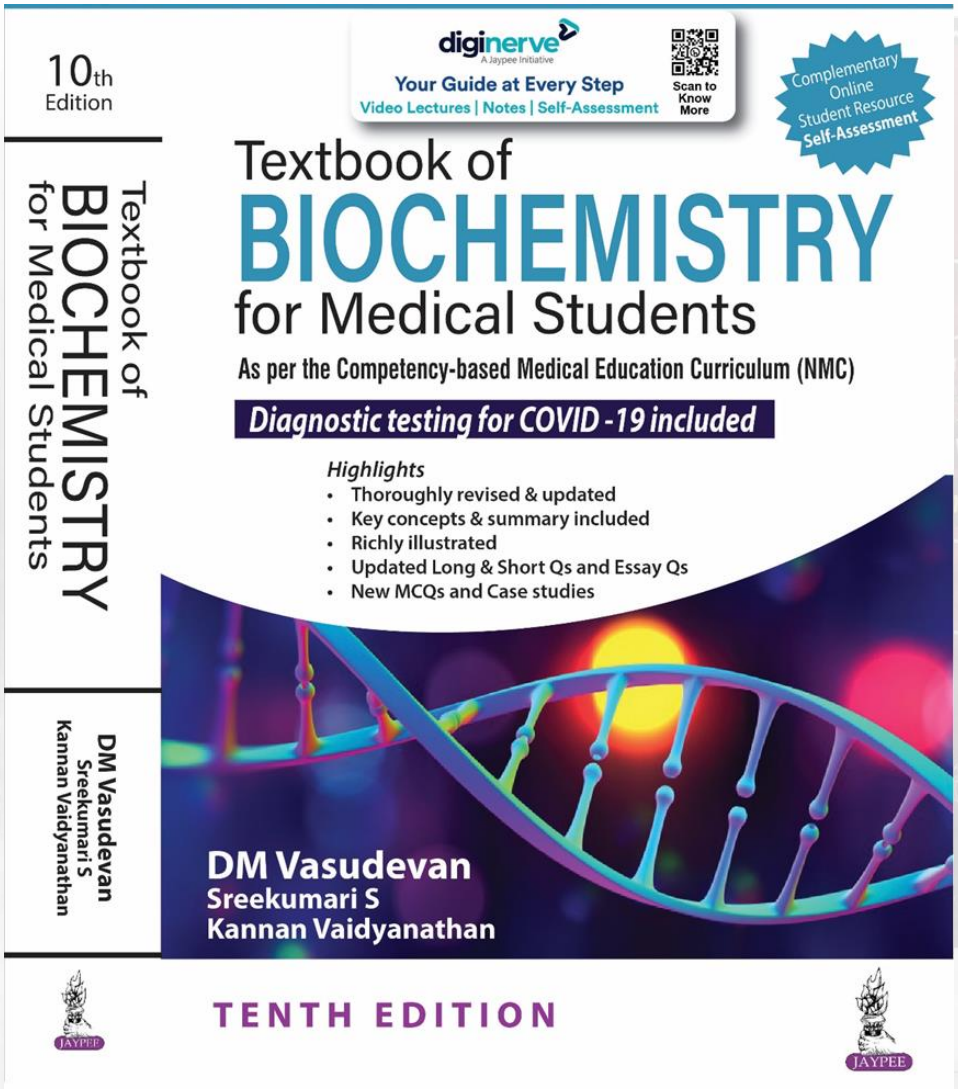
Chapter 28:

Fat Soluble Vitamins (Vitamin A, D, E, K)



Textbook of
BIOCHEMISTRY
for Medical Students

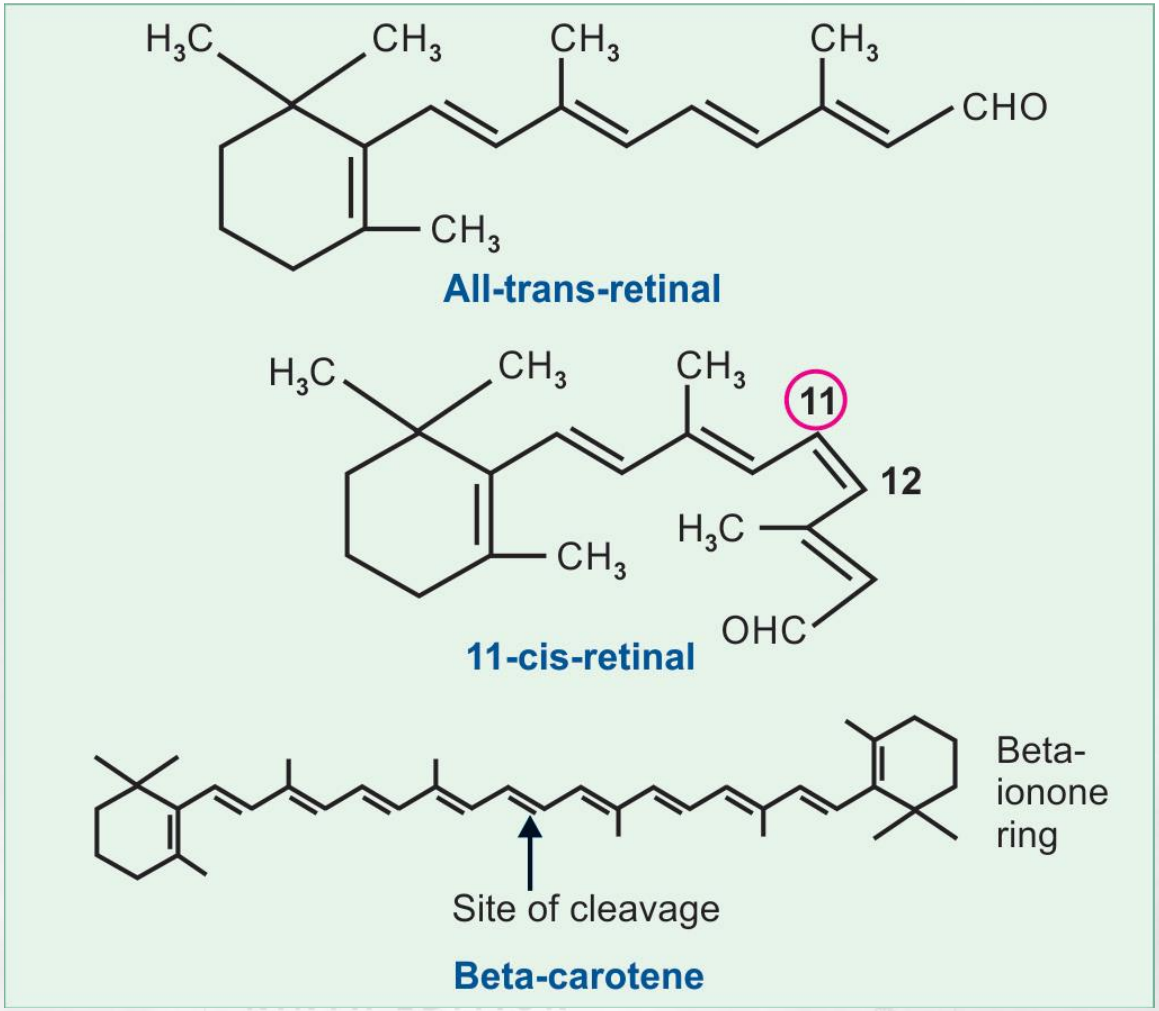
By DM Vasudevan, *et al.*

TENTH EDITION

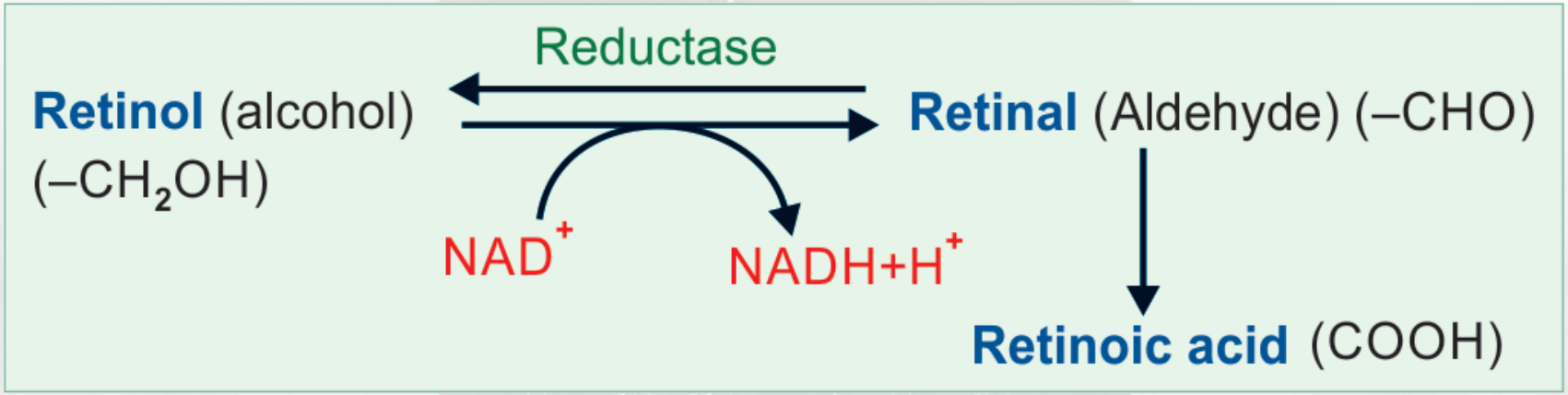
Comparison of two types of vitamins

	Fat soluble vitamins	Water soluble vitamins
Solubility in fat	Soluble	**Not soluble**
Water solubility	Not soluble	**Soluble**
Absorption	Along with lipids Requires bile salts	***Absorption simple**
Carrier proteins	Present	***No carrier proteins**
Storage	Stored in liver	***No storage**
Excretion	Not excreted	**Excreted**
Deficiency	Manifests only when stores are depleted	***Manifests rapidly as there is no storage**
Toxicity	Hypervitaminosis may result	**Unlikely, since excess is excreted**
Treatment of deficiency	Single large doses may prevent deficiency	**Regular dietary supply is required**
Major vitamins	A,D,E and K	**B and C**
***Vitamin B12 is an exception.**		

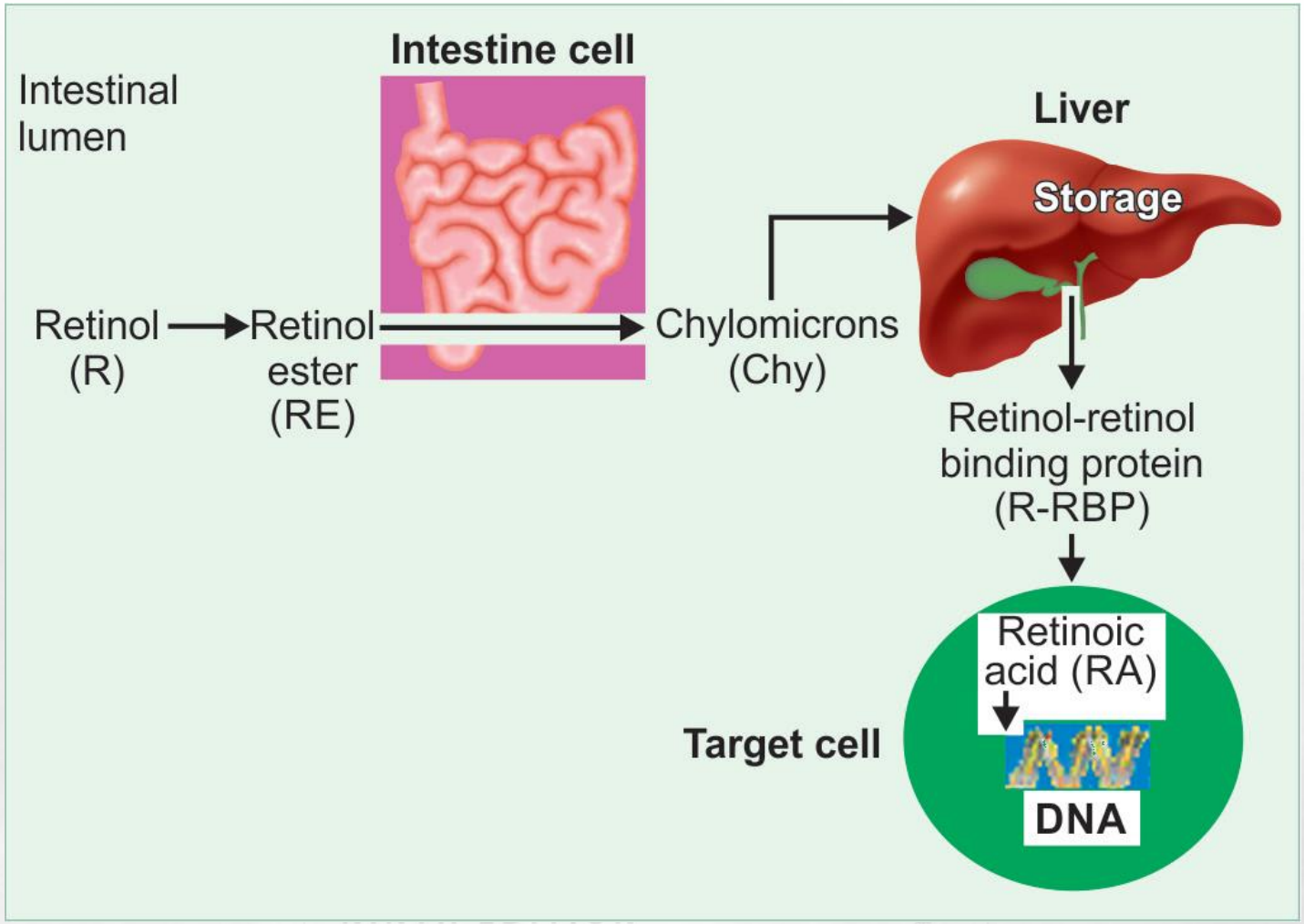
Vitamin A



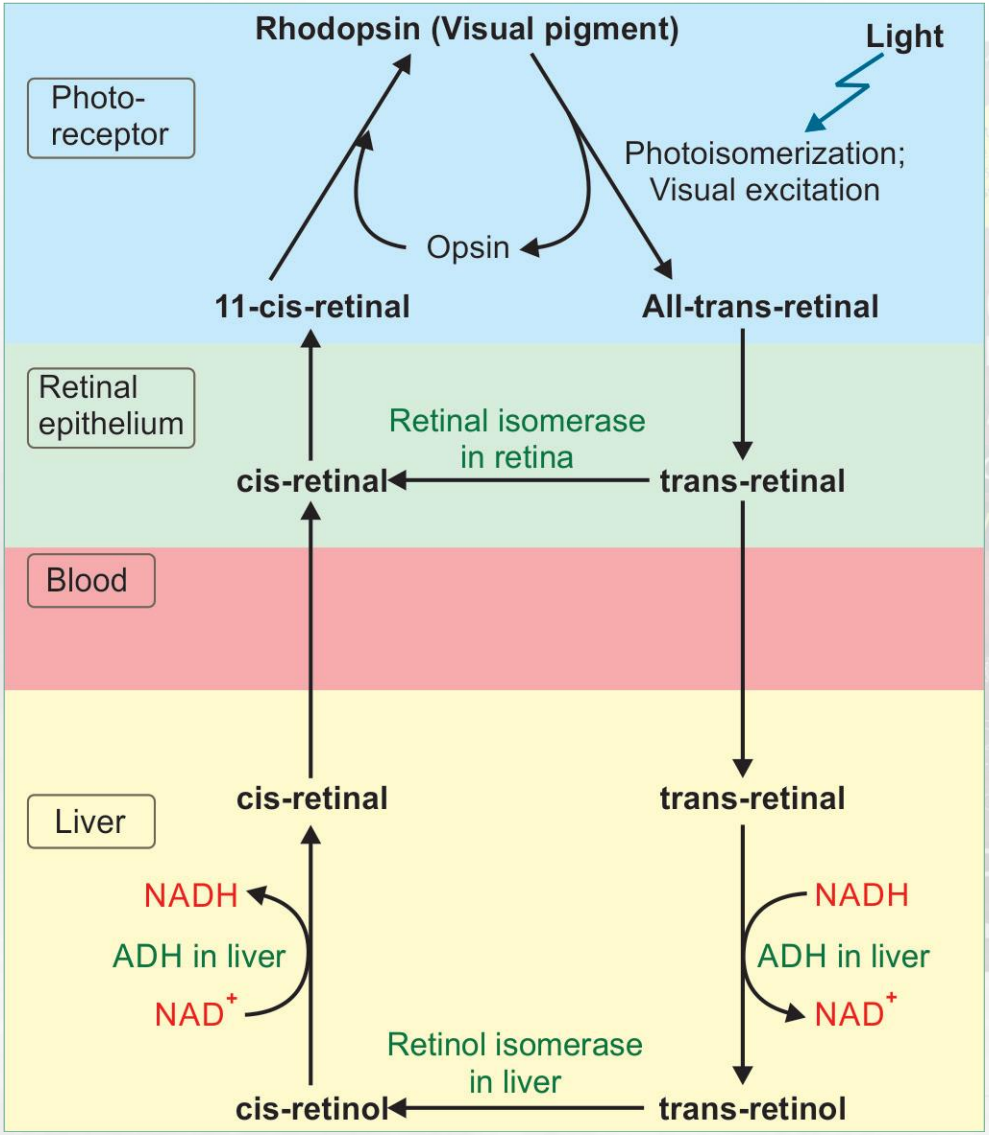
Structure of vitamin A.



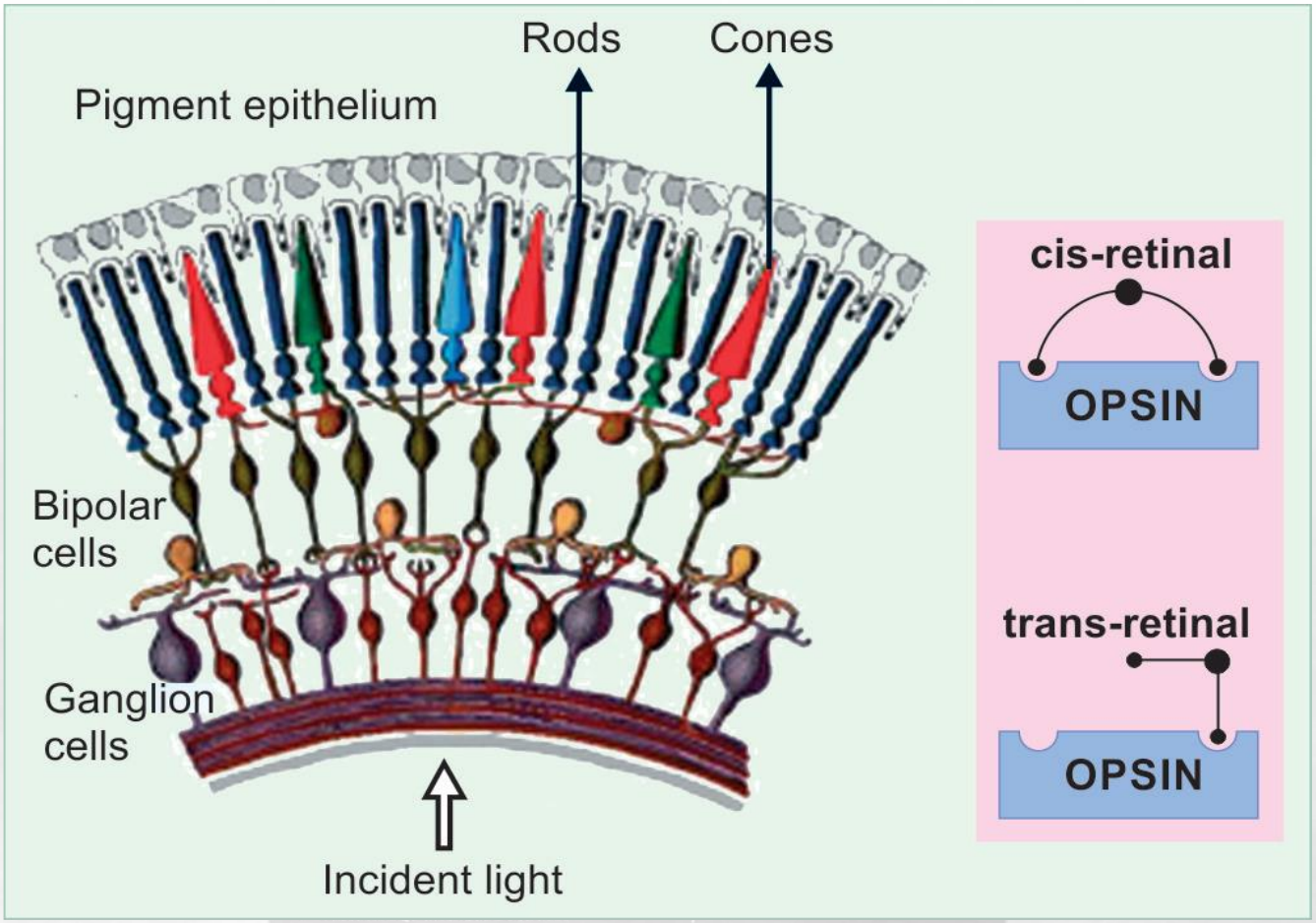
Interconversion of vitamin A molecules.



Vitamin A metabolism.



Wald's visual cycle. Blue background represents reactions in photoreceptor matrix. Green background represents reactions in retinal pigment epithelium. Rose background depicts blood. Yellow shows reactions taking place in the liver.



Structure of retina showing rods and cones. The inset on right side shows the structural alteration during photoisomerization.

Functions of Vitamin A

Vision

Visual cycle

Rods are for Vision in Dim Light

Cones are for Color Vision

Other Biochemical Functions

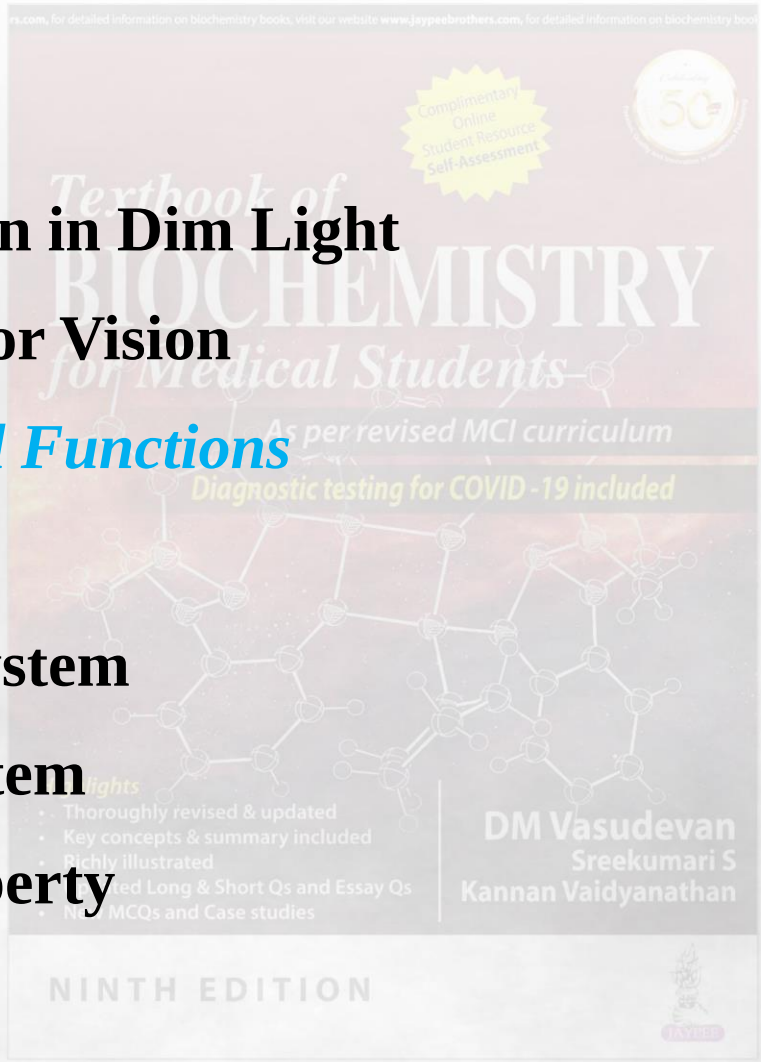
Gene Regulation

Immunological System

Reproductive System

Anti-oxidant Property

Effect on Skin



Deficiency Manifestations of Vitamin A

Night Blindness or Nyctalopia

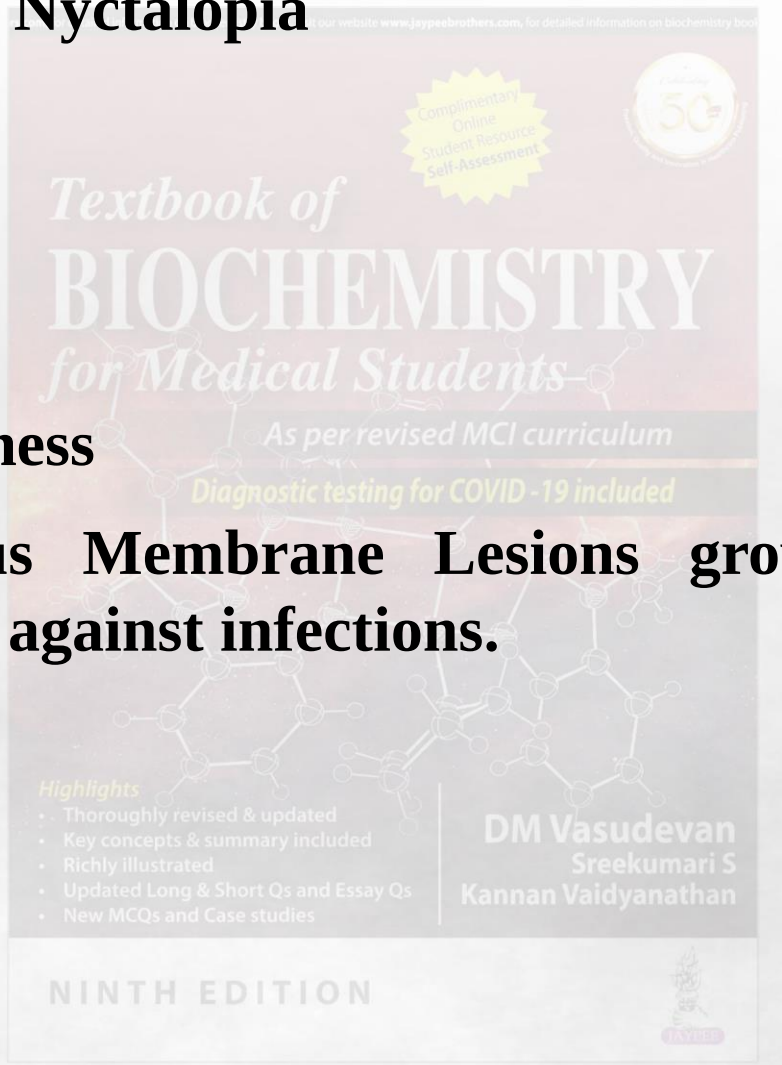
Bitot's Spots

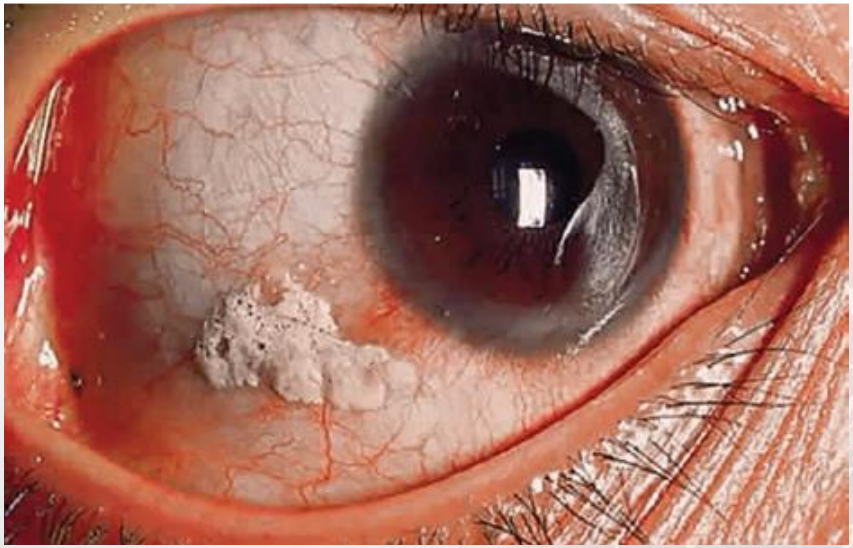
Xerophthalmia

Keratomalacia

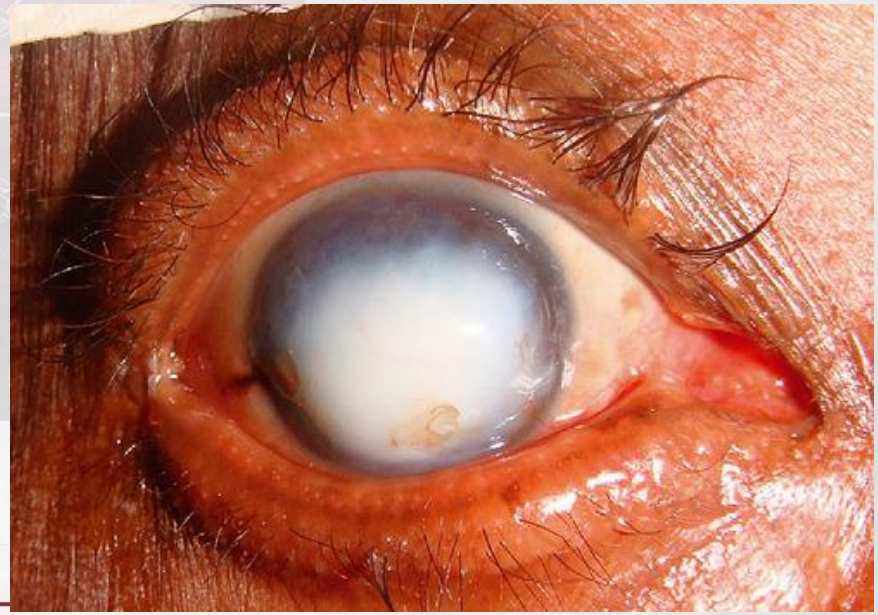
Preventable Blindness

Skin and Mucous Membrane Lesions growth retardation reduced immunity against infections.





Bitot spots



Keratomalacia.

Daily Requirement of Vitamin A

The recommended daily allowance (RDA) of Vitamin A for children = 400–650 μg/day,

for adult men = 1000 μg/day,

For adult women = 850 μg/day

pregnancy = 900 μg/day.

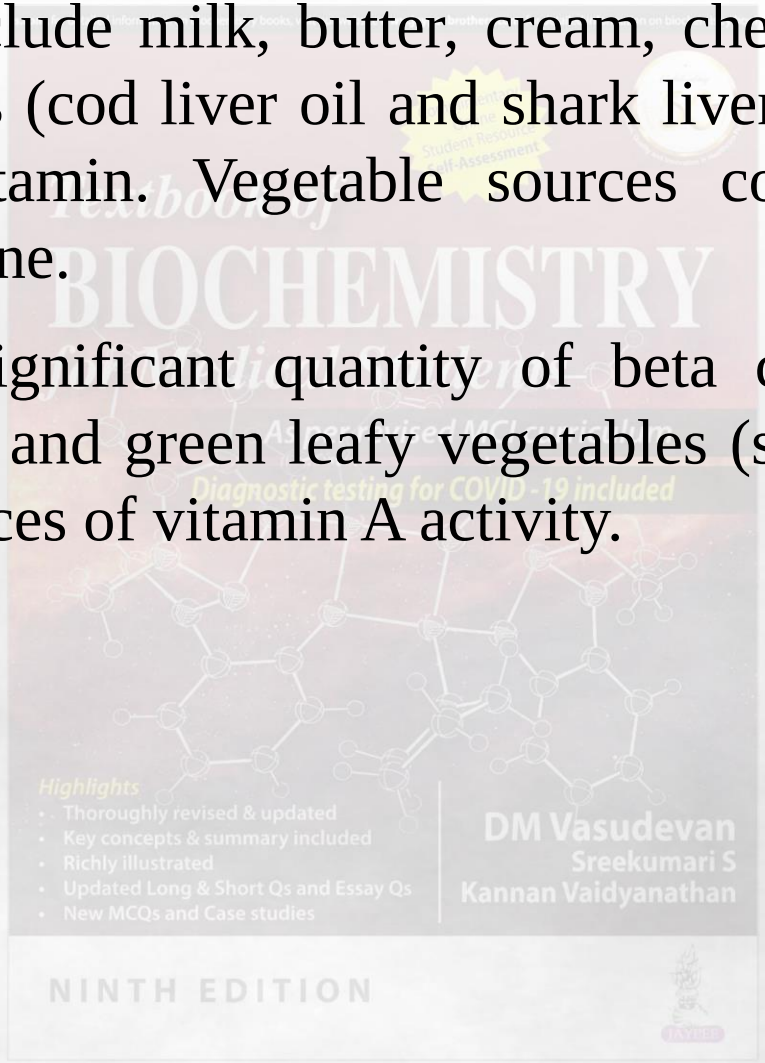
One international unit = 0.3 mg of retinol. One retinol equivalent = 1 μg of retinol or 6 μg of beta carotene.

One μg of retinol activity equivalent (RAE) corresponds to 1 μg retinol, or 2 μg of beta carotene

Dietary Sources of Vitamin A

Animal sources include milk, butter, cream, cheese, egg yolk and liver. Fish liver oils (cod liver oil and shark liver oil) are very rich sources of the vitamin. Vegetable sources contain the yellow pigment beta carotene.

Carrot contains significant quantity of beta carotene. **Papaya**, **mango**, **pumpkins** and green leafy vegetables (spinach, amaranth) are other good sources of vitamin A activity.

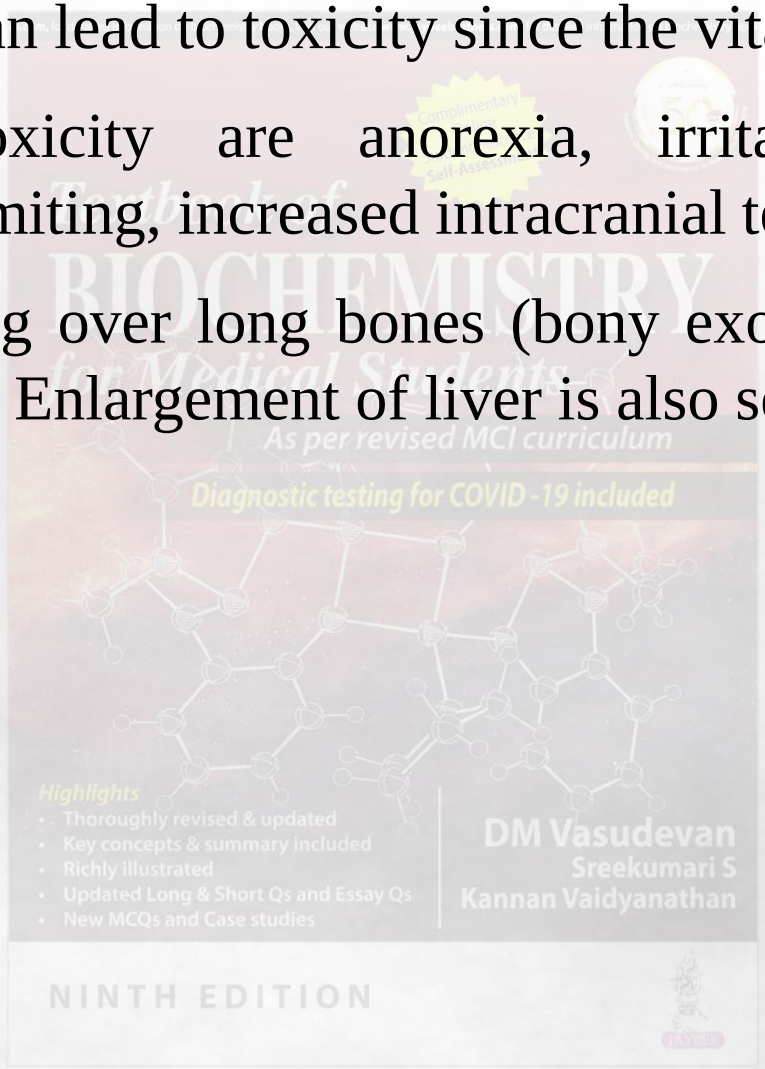


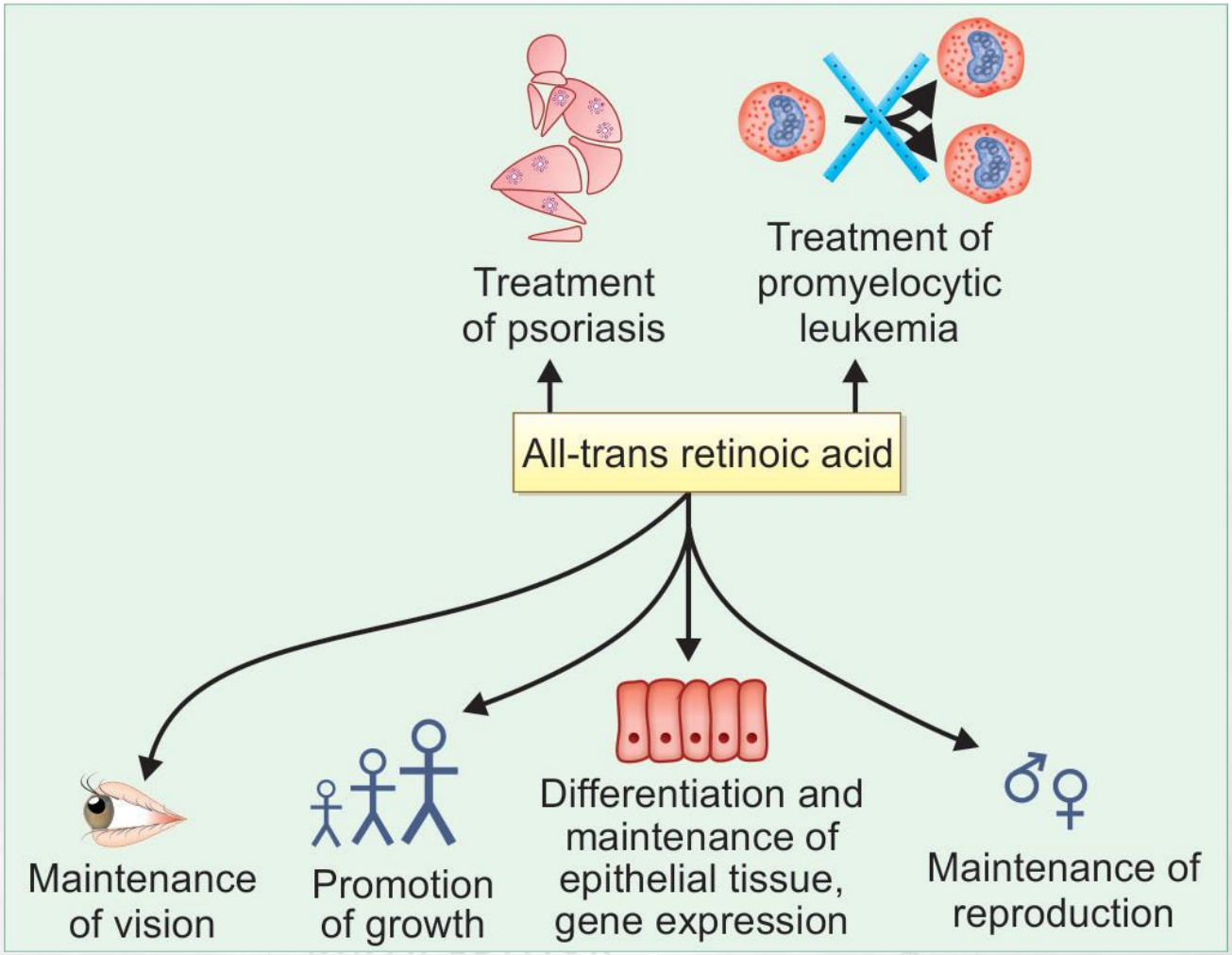
Hypervitaminosis A or Toxicity

Excessive intake can lead to toxicity since the vitamin is stored.

Symptoms of toxicity are anorexia, irritability, headache, drowsiness and vomiting, increased intracranial tension.

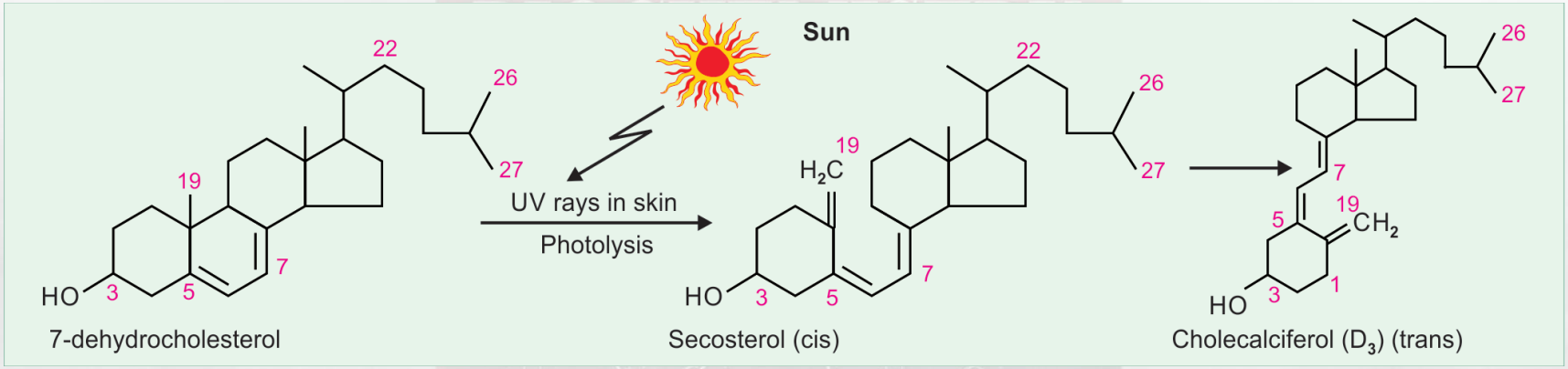
Sometimes swelling over long bones (bony exostosis) may occur with painful bones. Enlargement of liver is also seen in children.



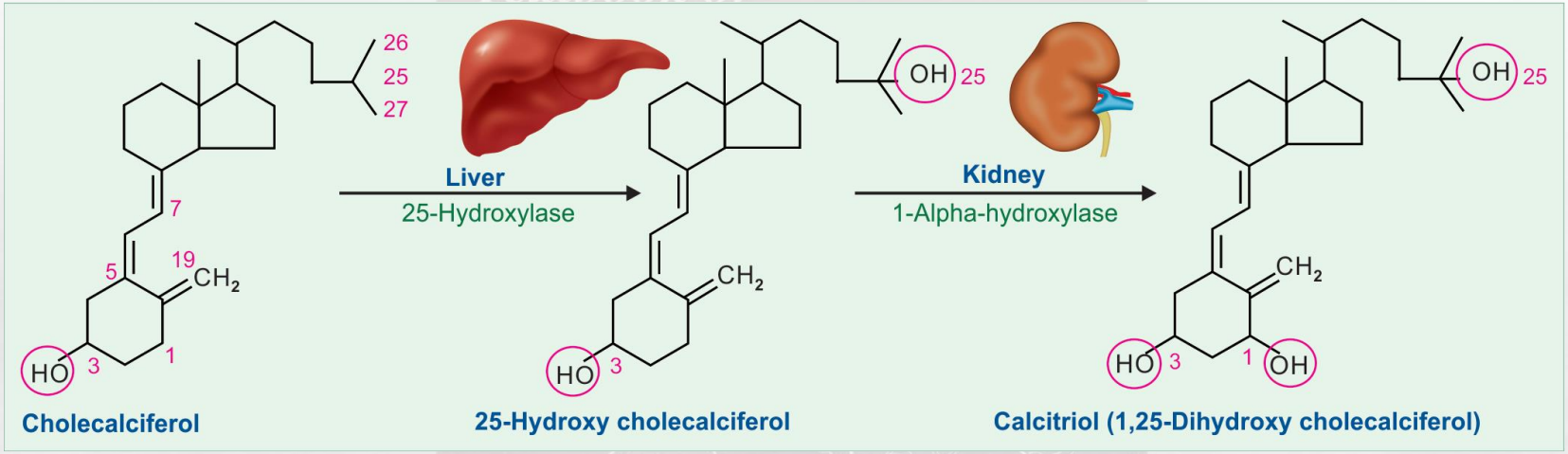


Summary of actions of vitamin A.

Vitamin D (Cholecalciferol)



Synthesis of cholecalciferol or vitamin D3.

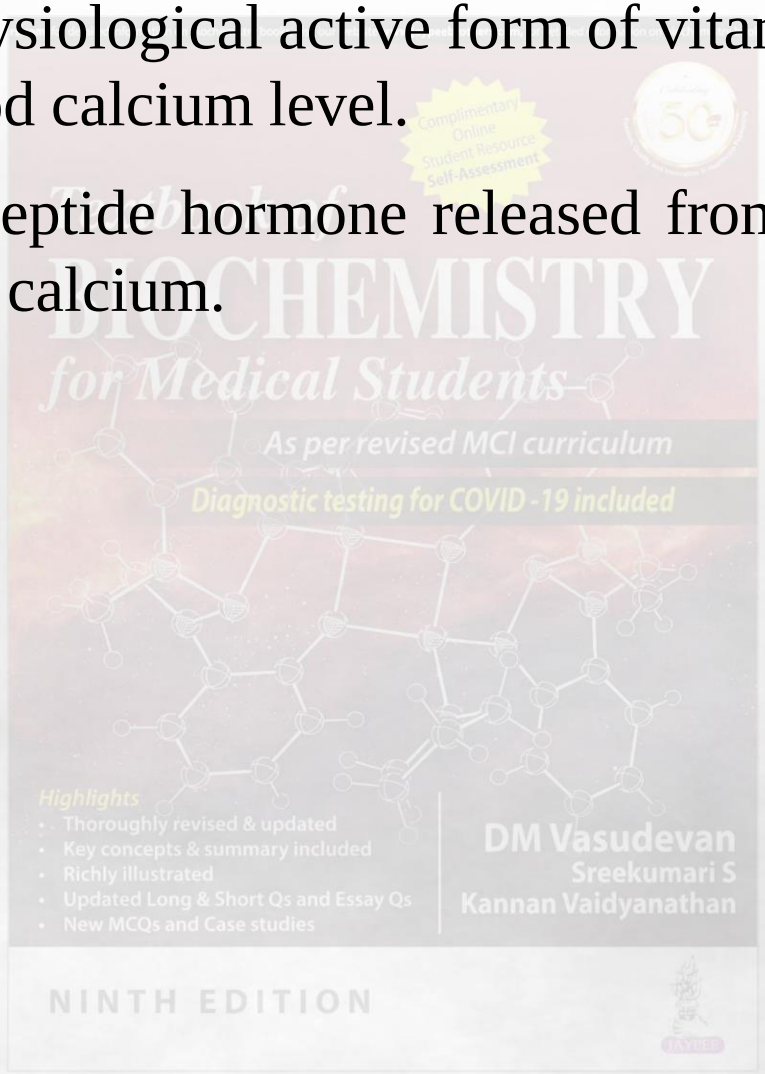


Generation of calcitriol.

Calcitriol and Calcitonin are Different

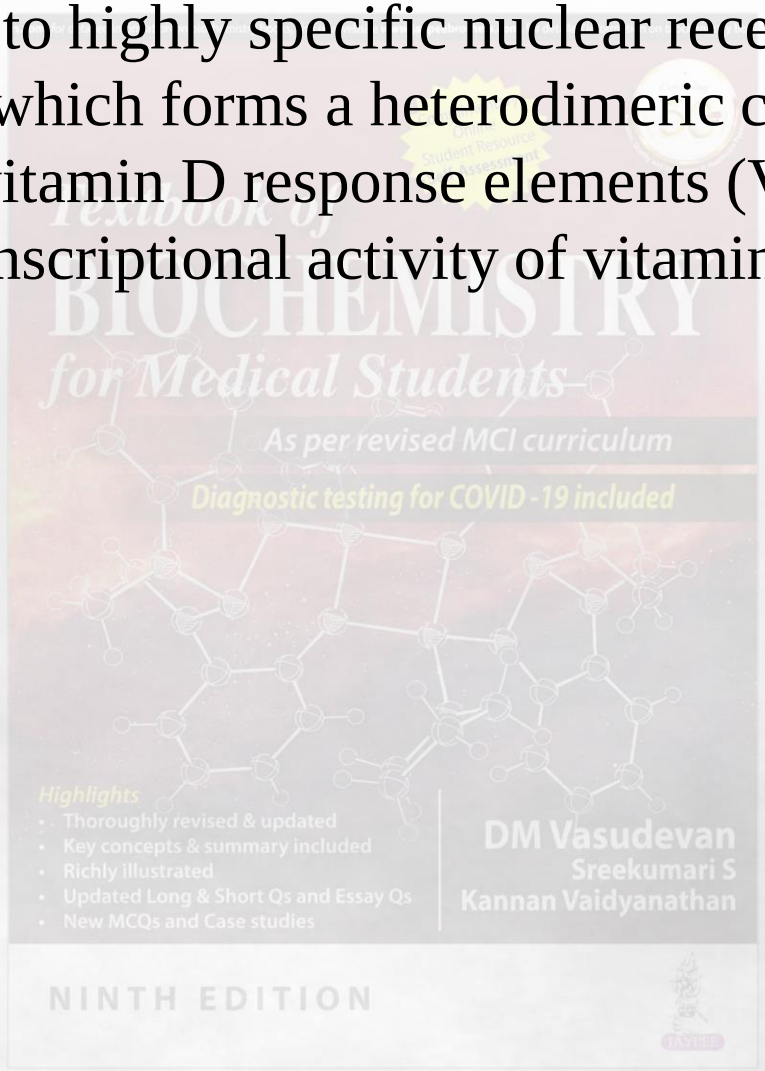
Calcitriol is the physiological active form of vitamin D.
It increases the blood calcium level.

Calcitonin is the peptide hormone released from thyroid gland. It decreases the blood calcium.



Vitamin D Receptor

The calcitriol binds to highly specific nuclear receptor vitamin D receptor (VDR), which forms a heterodimeric complex with RXR that binds to vitamin D response elements (VDRE) on DNA and odulates the transcriptional activity of vitamin D responsive enes.



Biochemical Effects of Vitamin D

The sites of action are:

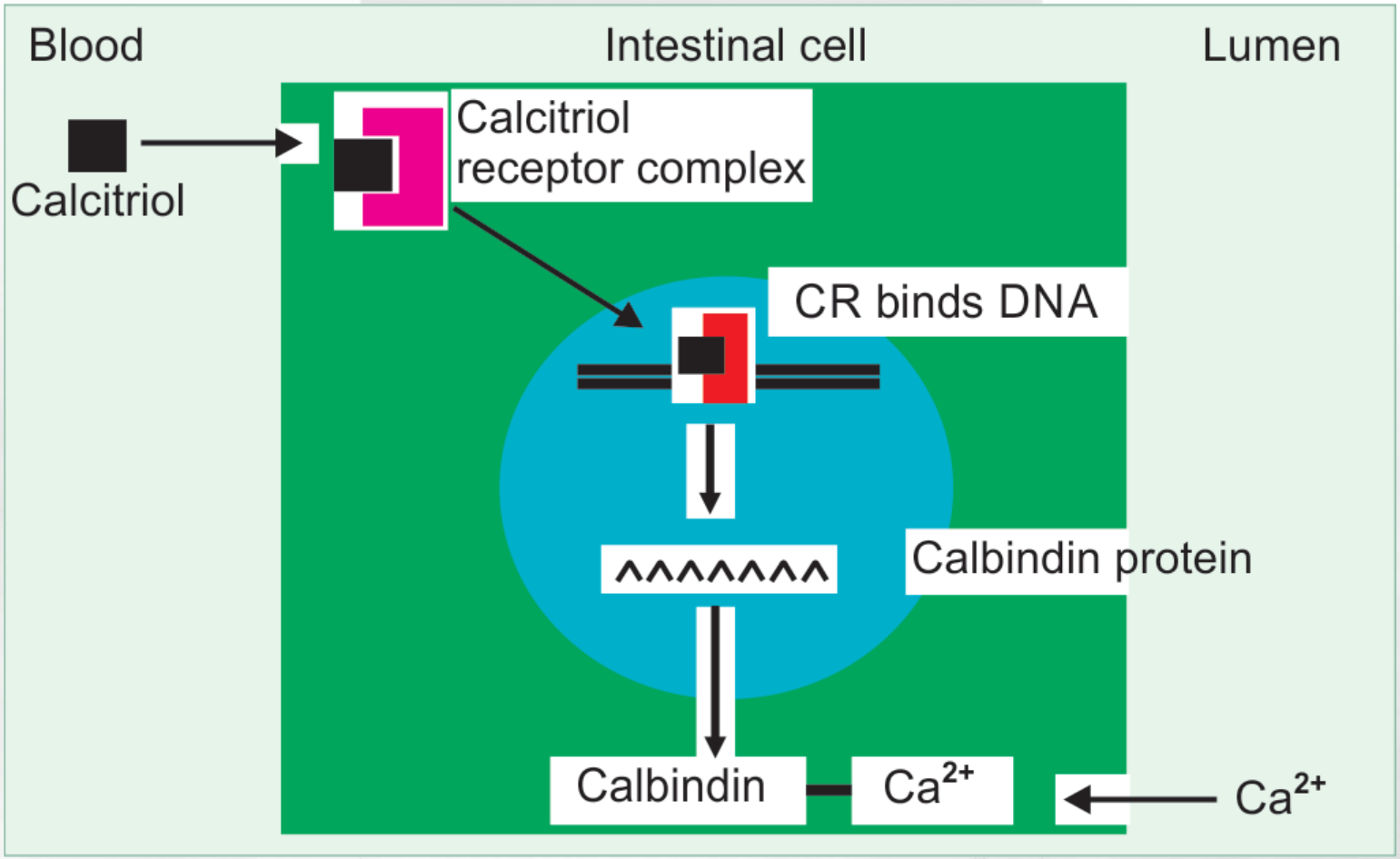
a. Intestinal villi cells

b. Bone osteoblasts

c. Kidney distal tubular cells.

Vitamin D and Absorption of Calcium

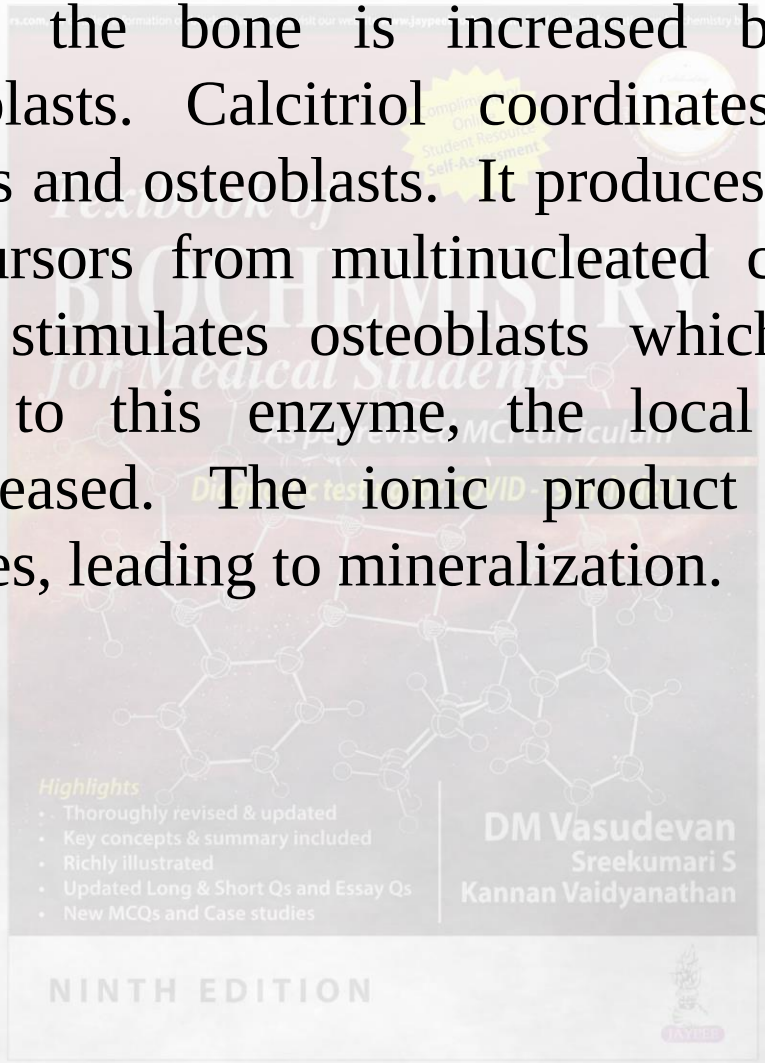
Calcitriol promotes the absorption of calcium and phosphorus from the intestine. **Calcitriol** acts like a steroid hormone. It enters the target cell and binds to a cytoplasmic receptor. The hormone-receptor complex interacts with DNA and causes derepression and consequent transcription of specific genes that code for **calbindin**. Due to the increased availability of calcium binding protein, the absorption of calcium is increased.



Calcitriol increases calcium absorption.

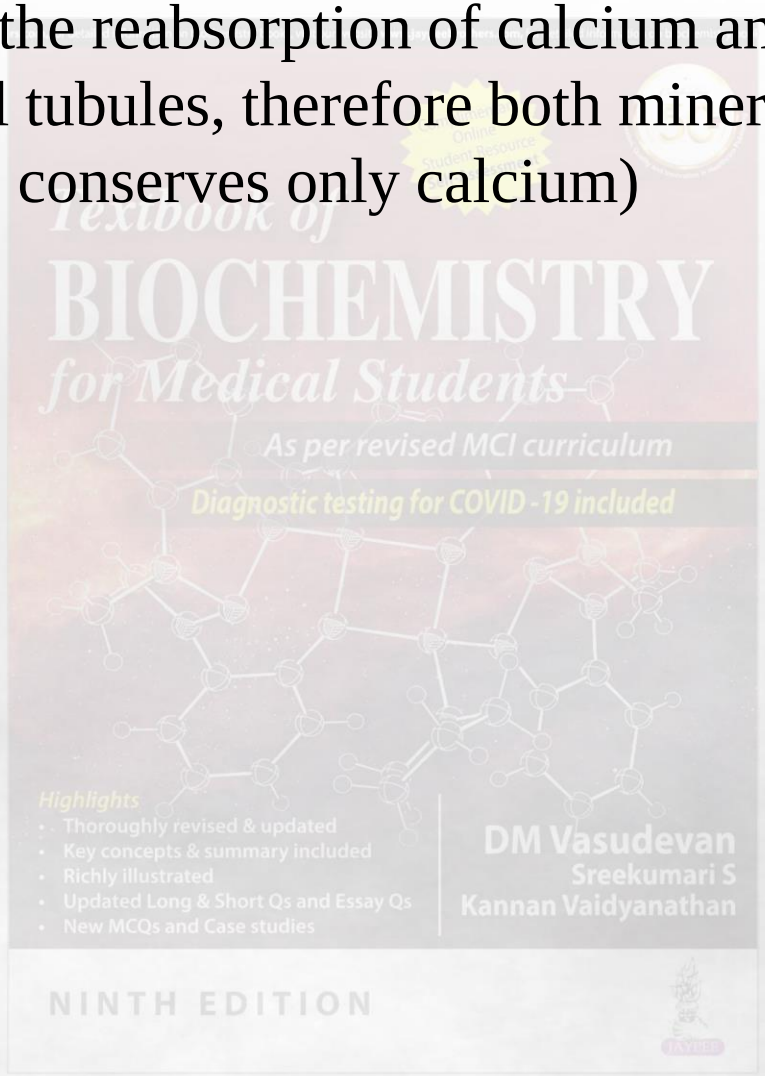
Effect of Vitamin D in Bone

Mineralization of the bone is increased by increasing the activity of osteoblasts. Calcitriol coordinates the remodeling action of osteoclasts and osteoblasts. It produces the differentiation of osteoclast precursors from multinucleated cells of osteoblast lineage. Calcitriol stimulates osteoblasts which secrete alkaline phosphatase. Due to this enzyme, the local concentration of phosphate is increased. The ionic product of calcium and phosphorus increases, leading to mineralization.



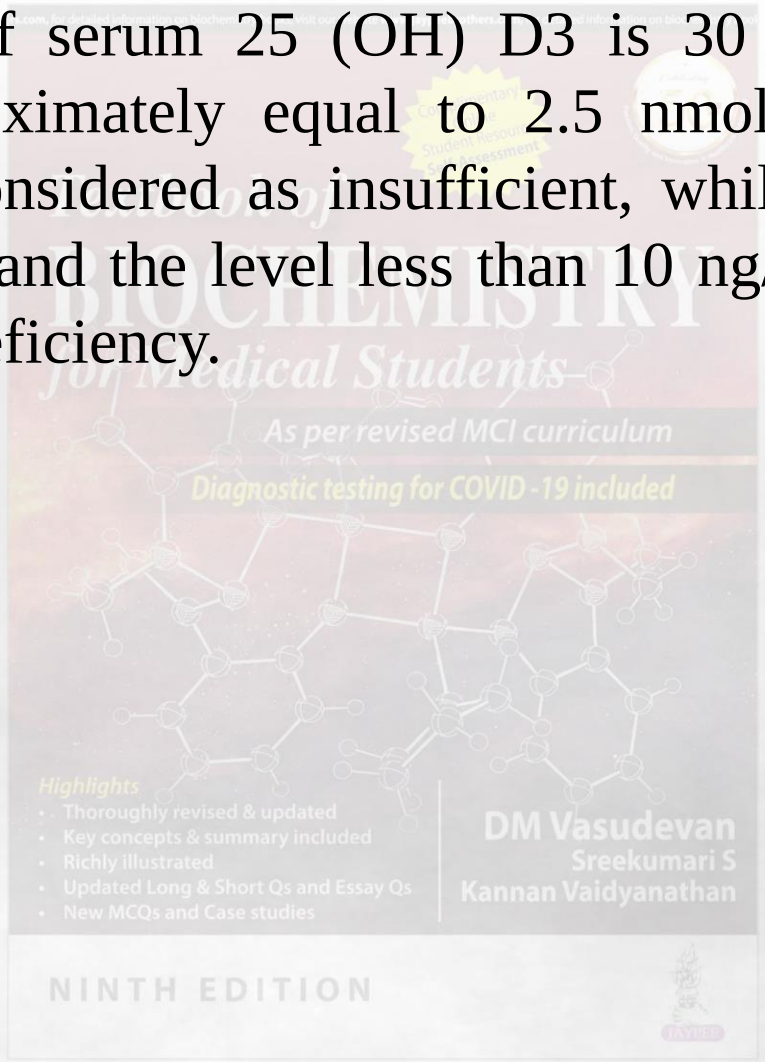
Effect of Vitamin D in Renal Tubules

Calcitriol increases the reabsorption of calcium and phosphorus by renal tubules, therefore both minerals are conserved (PTH conserves only calcium)



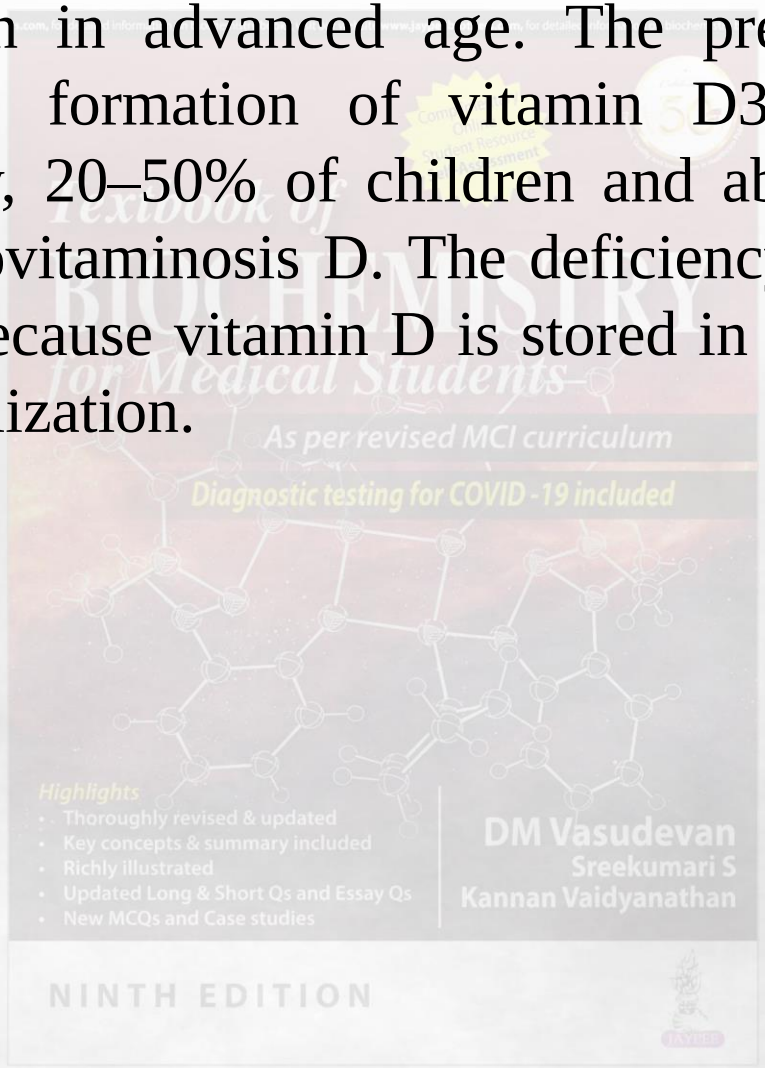
Serum Vitamin D3

Reference levels of serum 25 (OH) D3 is 30 ng/mL (75 nmol/L) (1 ng is approximately equal to 2.5 nmols). The levels of 20–29 ng/mL is considered as insufficient, while the level 11–20 ng/mL is deficient and the level less than 10 ng/ml is the mark of severe vitamin D deficiency.



Vitamin D Deficiency

Deficiency is seen in advanced age. The presence of melanin will decrease the formation of vitamin D3 on skin. About 50–80% of elderly, 20–50% of children and about 75% pregnant mothers have hypovitaminosis D. The deficiency is more common in obese people, because vitamin D is stored in adipose tissue, and not released for utilization.



Causes for Vitamin D Deficiency

a. Deficiency of vitamin D can occur in people who are not exposed to sunlight properly, e.g. inhabitants of northern latitudes, in winter months, in people who are bedridden for long periods, or those who cover the whole body *(purdah)*.

b. Nutritional deficiency of calcium or phosphate may also produce similar clinical picture.

c. Malabsorption of vitamin (obstructive jaundice and steatorrhea). High phytate content in diet may also reduce the absorption of vitamin.

d. Abnormality of vitamin D activation. Liver and renal diseases may retard hydroxylation reactions.

e. Deficient renal absorption of phosphates.

Clinical Features of Vitamin D Deficiency

The deficiency diseases are **rickets** in children and **osteomalacia** in adults. Hence vitamin D is known as antirachitic vitamin. Vitamin D deficiency causes reduced bone density (**osteoporosis**) and increase the tendency for bone fracture.

Rickets is seen in children. There is insufficient mineralization of bone. Bones become soft and pliable. The bone growth is markedly affected. Plasma calcium and phosphorus are low, with alkaline phosphatase being markedly elevated.

Bone deformities. Weight bearing bones are bent. X-ray of bone shows typical deformity, bow legs, knock knee, **rickety rosary**, bossing of frontal bones, and pigeon chest.

Different Types of Rickets

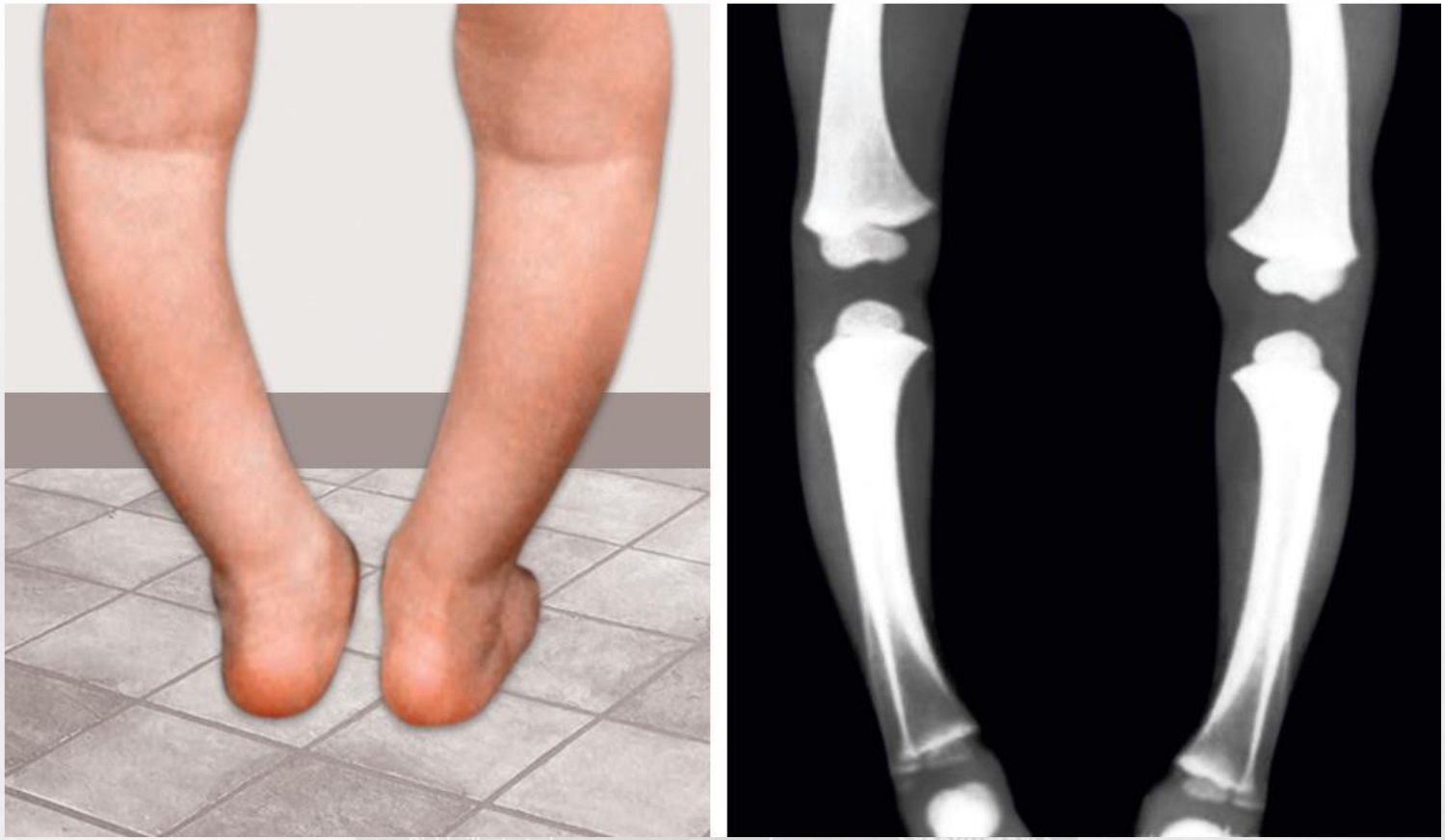
The classical vitamin D **deficiency** rickets.

The **hypophosphatemic** rickets mainly result from defective renal tubular reabsorption of phosphate.

Vitamin D resistant rickets is found to be associated with *Fanconi syndrome*.

Renal rickets: In kidney diseases, even if vitamin D is available, calcitriol is not synthesized. These cases will respond to administration of calcitriol.

End organ refractoriness to 1,25-DHCC will also lead to rickets. The bone disease has been found to respond to megadoses of calcitriol (35 mg/day).

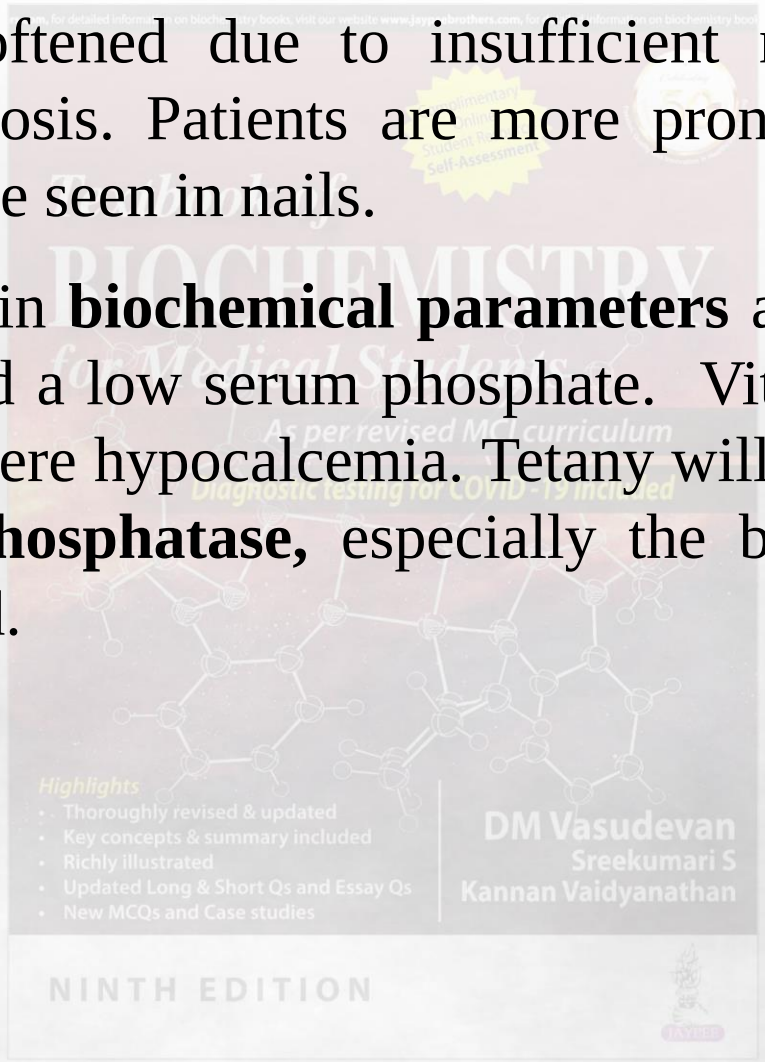


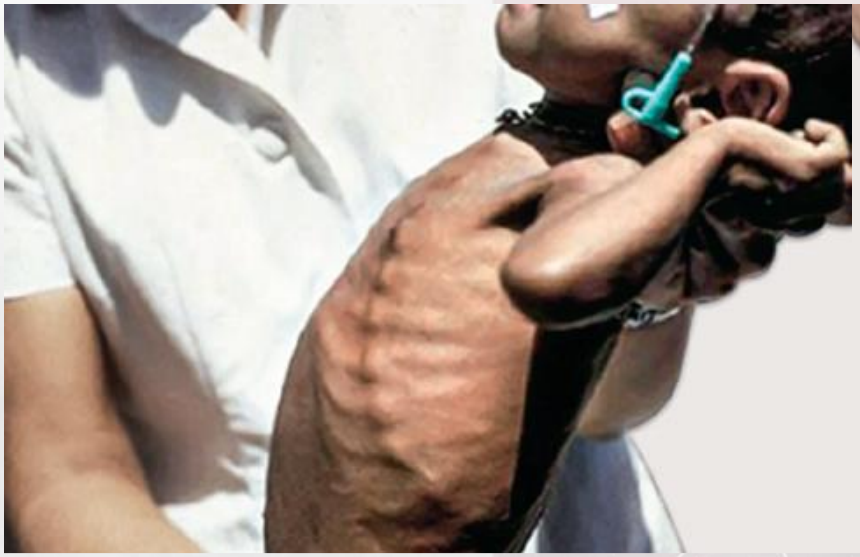
(A) Bone deformity in rickets; (B) Enlarged epiphysis is seen in X-ray findings in vitamin D deficiency.

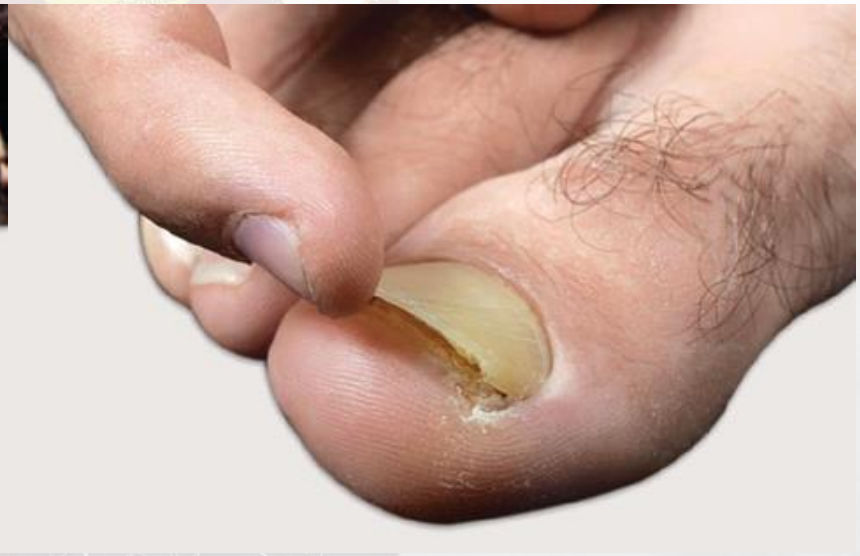
Clinical Features of Osteomalacia

The bones are softened due to insufficient mineralization and increased osteoporosis. Patients are more prone to get fractures. Onycholysis may be seen in nails.

The abnormalities in **biochemical parameters** are a slightly lower serum calcium, and a low serum phosphate. Vitamin D deficiency never produces severe hypocalcemia. Tetany will not be manifested. Serum **alkaline phosphatase,** especially the bone isoenzyme, is markedly increased.

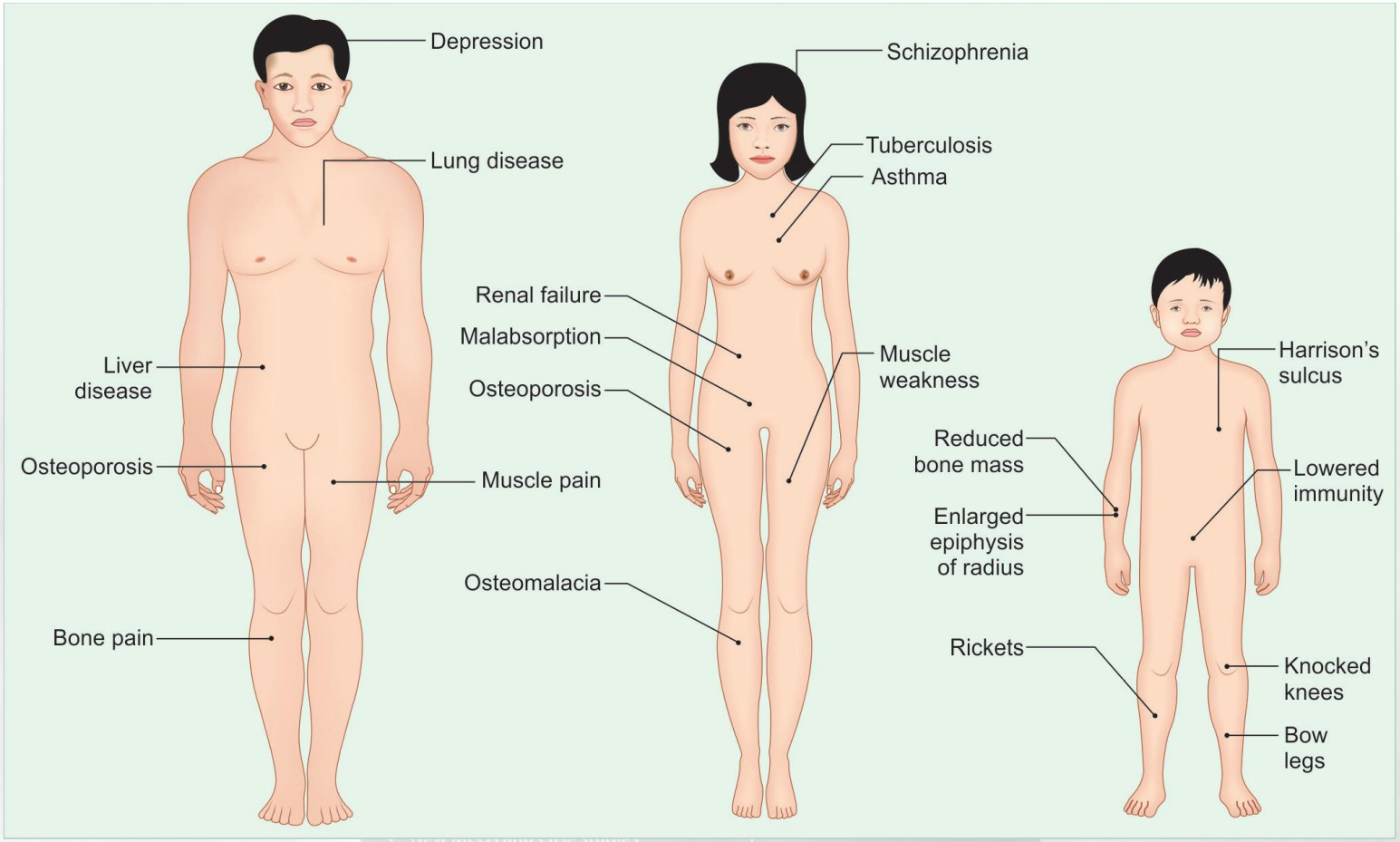






(A) Rickety rosary;

(B) Onycholysis in nails is a manifestation of vitamin D deficiency.

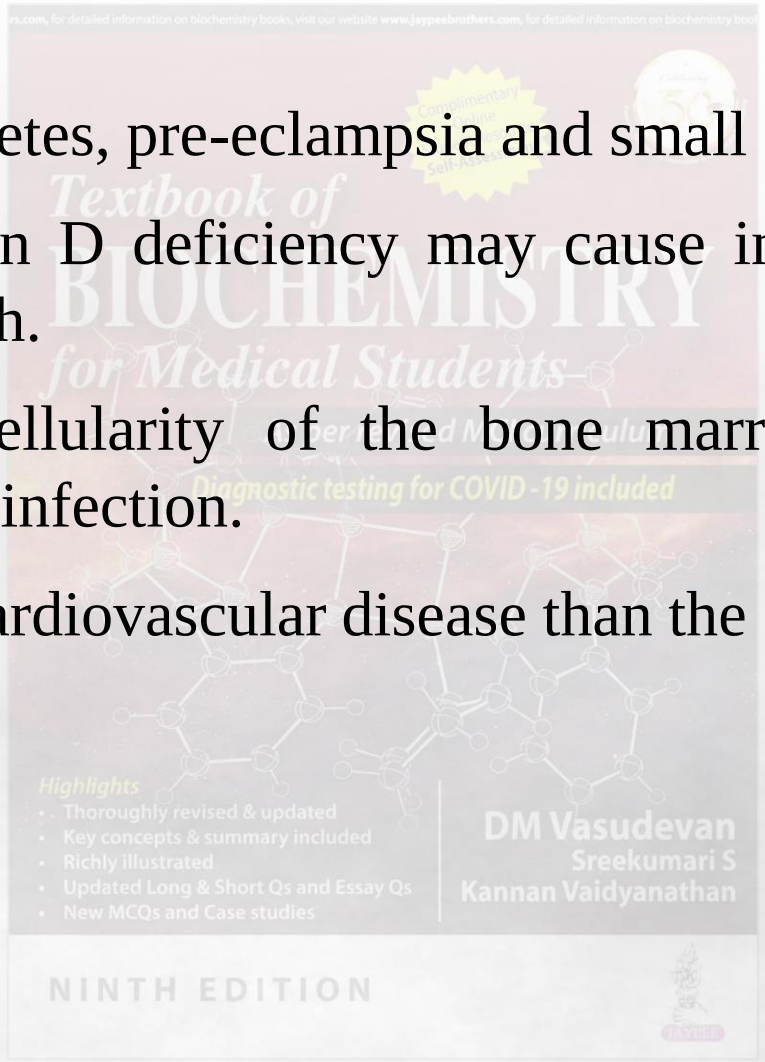


Clinical features of vitamin D deficiency.

Other Diseases Related with Vitamin D

Deficiency

- Gestational diabetes, pre-eclampsia and small size of infants.
- Maternal vitamin D deficiency may cause impairment of bone quality after birth.
- Anemia, hypocellularity of the bone marrow and increased susceptibility to infection.
- Higher risk of cardiovascular disease than the general population.



Requirement of Vitamin D

The recommended daily allowances for vitamin D are

a) for children, 600 IU/day;

b) for adults, (male and female) 600 IU/day;

c) for pregnancy, lactation, 600 IU/day;

d) for persons above the age of 60, 800 IU per day.

e) In obese children, supplementation with higher doses of vitamin D up to 800 IU/day

f) For treatment of osteoporosis, the dose of vitamin D is 1,000 units daily or 50,000 units weekly.

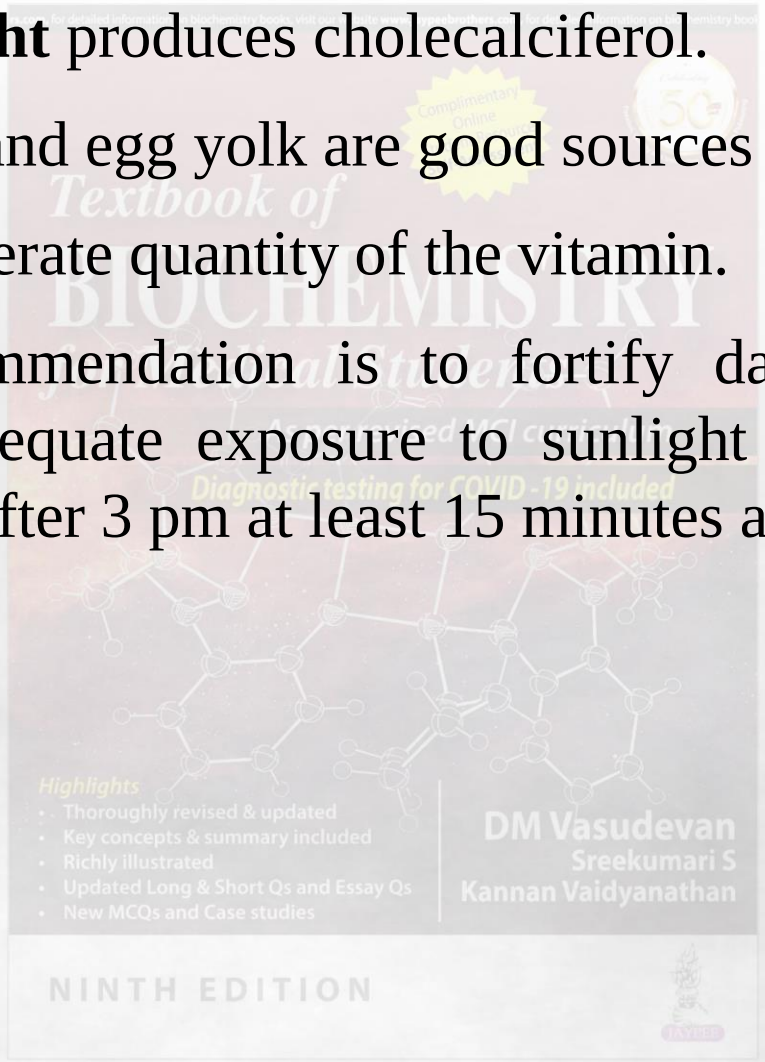
Sources of Vitamin D

Exposure to **sunlight** produces cholecalciferol.

Fish liver oil, fish and egg yolk are good sources of the vitamin.

Milk contains moderate quantity of the vitamin.

The current recommendation is to fortify dairy products with vitamin D and adequate exposure to sunlight without sunscreen before 10 am and after 3 pm at least 15 minutes a day (safe sun).



Hypervitaminosis D

Doses above 1500 units per day for very long periods may cause toxicity.

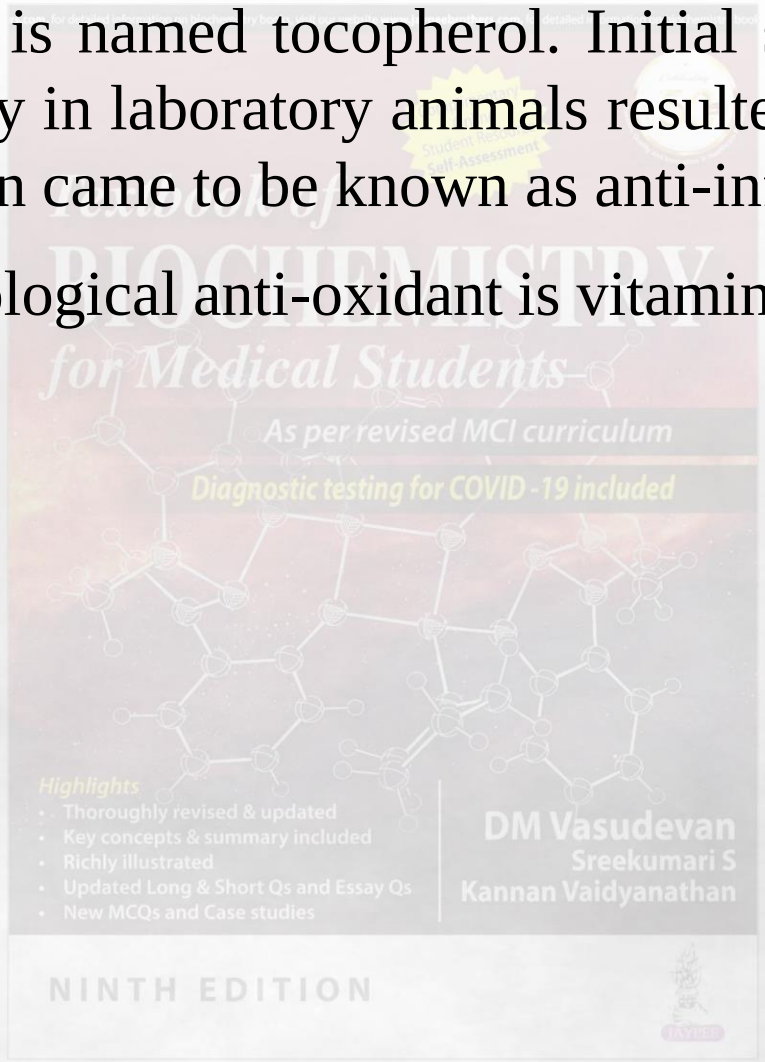
The symptoms include weakness, polyuria, intense thirst, difficulty in speaking, hypertension and weight loss. Hypercalcemia leads to calcification of soft tissues, (**metastatic calcification,** otherwise called **calcinosis**), especially in vascular and renal tissues.

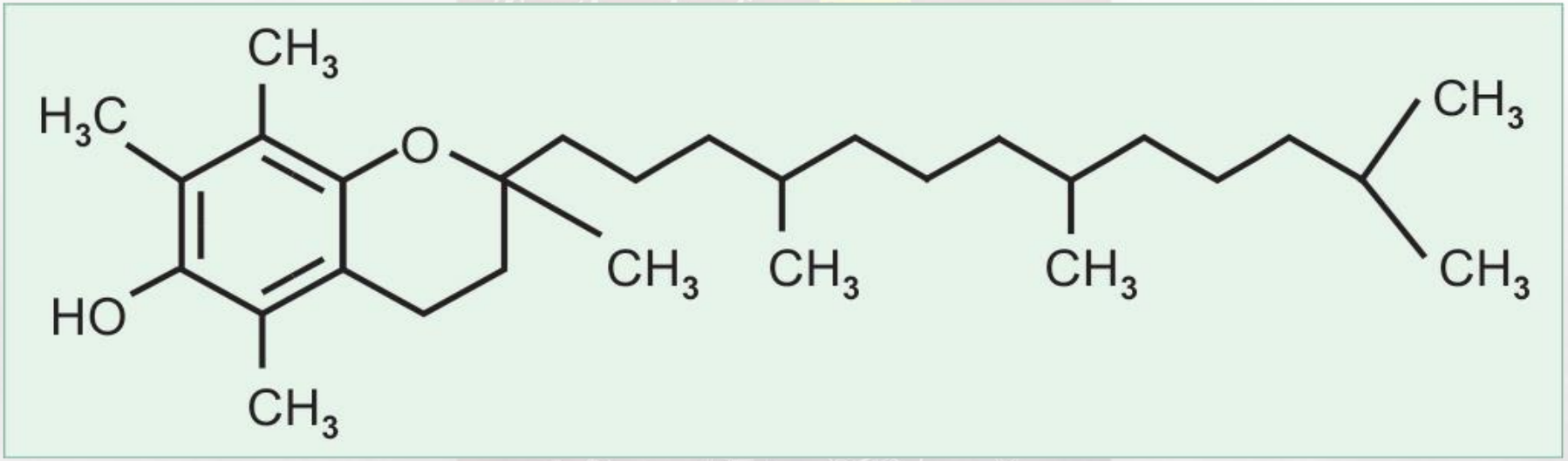
Although vitamin D is toxic in higher doses, excessive exposure to sunlight does not result in vitamin D toxicity, because excess D3 is destroyed by sunlight itself.

Vitamin E

The active vitamin is named tocopherol. Initial studies of induced vitamin E deficiency in laboratory animals resulted in infertility and therefore the vitamin came to be known as anti-infertility vitamin.

The most potent biological anti-oxidant is vitamin E.





Alpha-tocopherol.

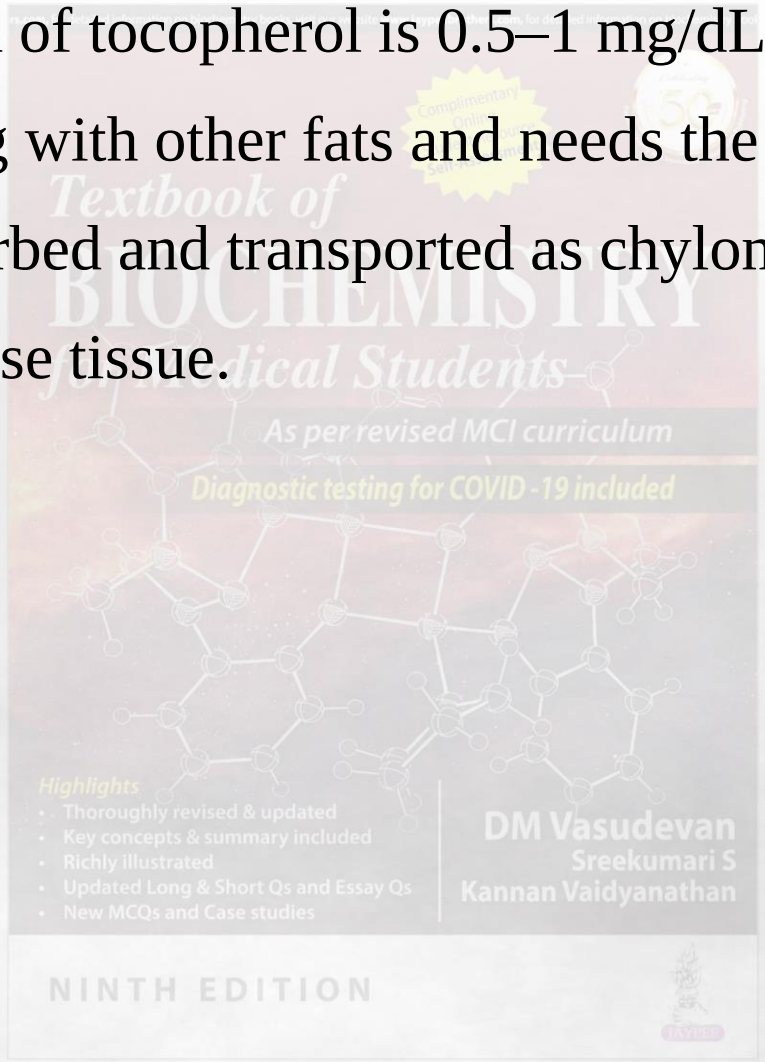
Metabolism of Vitamin E

Normal blood level of tocopherol is 0.5–1 mg/dL.

It is absorbed along with other fats and needs the help of bile salts.

Tocopherol is absorbed and transported as chylomicrons.

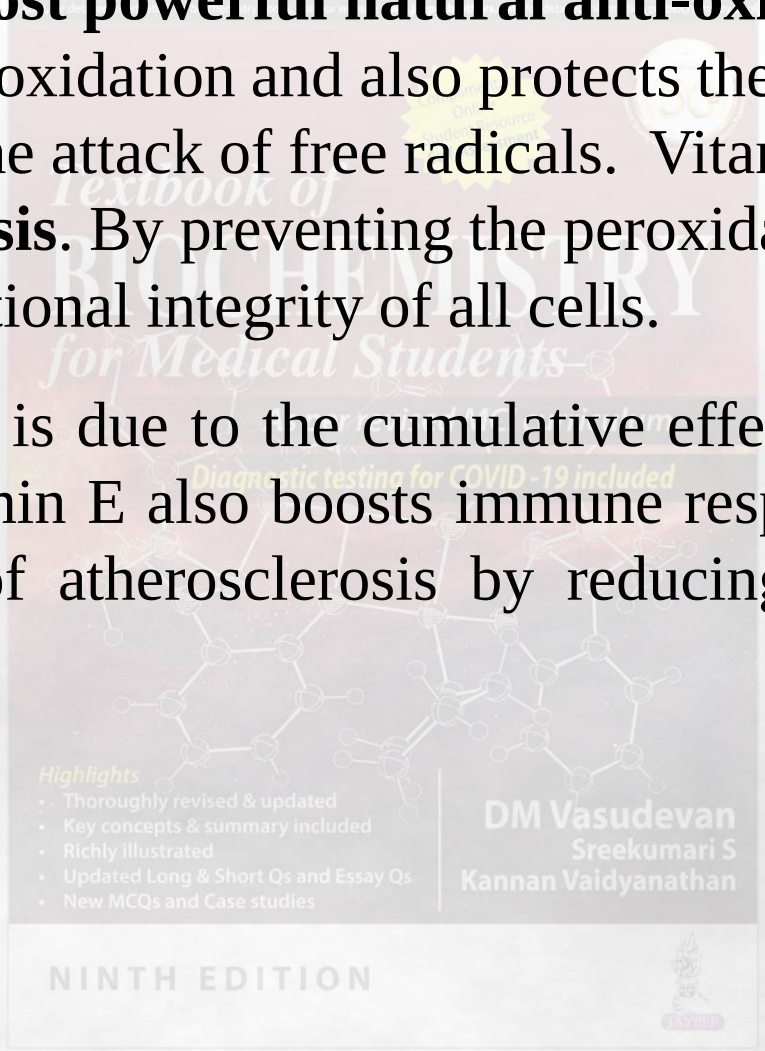
It is stored in adipose tissue.



Role of Vitamin E

Vitamin E is the **most powerful natural anti-oxidant**.
It protects lipid peroxidation and also protects the plasma membranes from the attack of free radicals. Vitamin E protects RBC from **hemolysis**. By preventing the peroxidation, it keeps the structural and functional integrity of all cells.

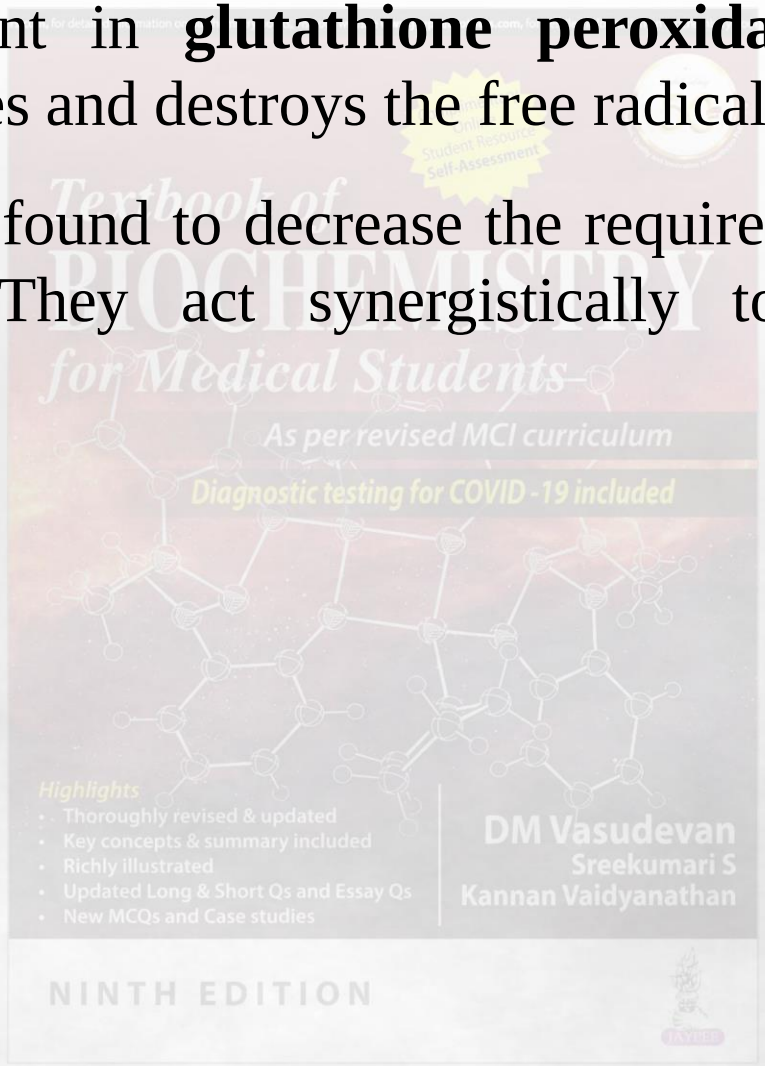
The **aging** process is due to the cumulative effects of attack of the free radicals. Vitamin E also boosts immune response. The vitamin reduces the risk of atherosclerosis by reducing the oxidation of LDL.



Inter-relationship with Selenium

Selenium is present in **glutathione peroxidase**; an important enzyme that oxidizes and destroys the free radicals.

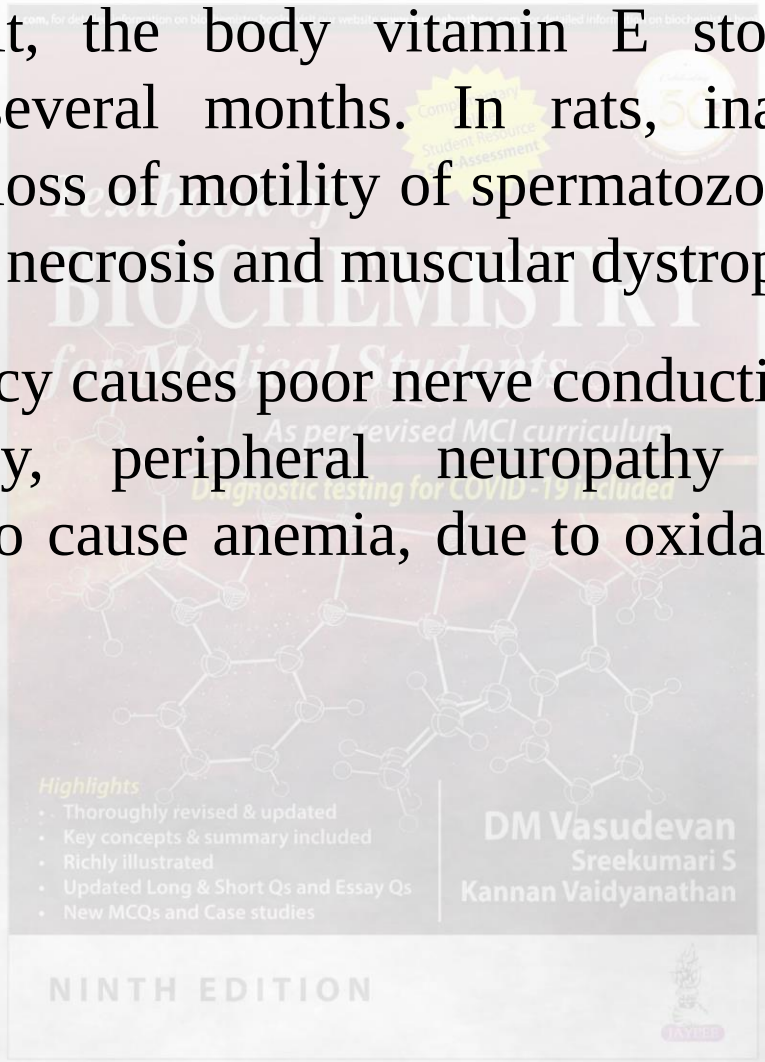
Selenium has been found to decrease the requirement of vitamin E and vice versa. They act synergistically to minimize lipid peroxidation.



Deficiency Manifestations of Vitamin E

In a normal adult, the body vitamin E stores can meet the requirement for several months. In rats, inability to produce healthy ovum and loss of motility of spermatozoa, hemolysis of red cells, acute hepatic necrosis and muscular dystrophy are observed.

Vitamin E deficiency causes poor nerve conduction, spinocerebellar ataxia, retinopathy, peripheral neuropathy and myopathies. Deficiency can also cause anemia, due to oxidative damage to red blood cells.



No major disease states have been found to be associated with vitamin E deficiency in human beings due to adequate levels in the average diet.

Vitamin E deficiency is seen in persons

a. Who cannot absorb dietary fat,

b. In premature infants (birthweight less than 1500 g),

c. In abetalipoproteinemia

d. In mutations in the gene for the tocopherol transfer protein.

Recommended Daily Allowance

for males is 10 mg per day,

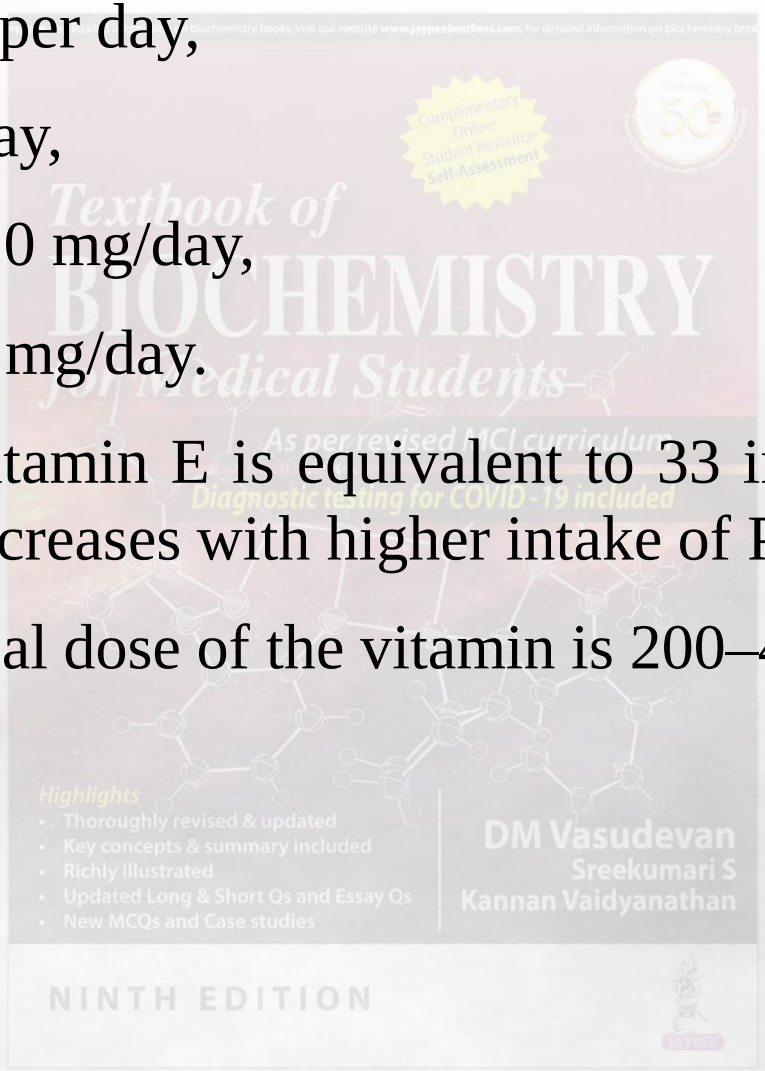
for females 8 mg/day,

during pregnancy 10 mg/day,

during lactation 12 mg/day.

About 15 mg of vitamin E is equivalent to 33 international units. The requirement increases with higher intake of PUFA.

The pharmacological dose of the vitamin is 200–400 IU per day.

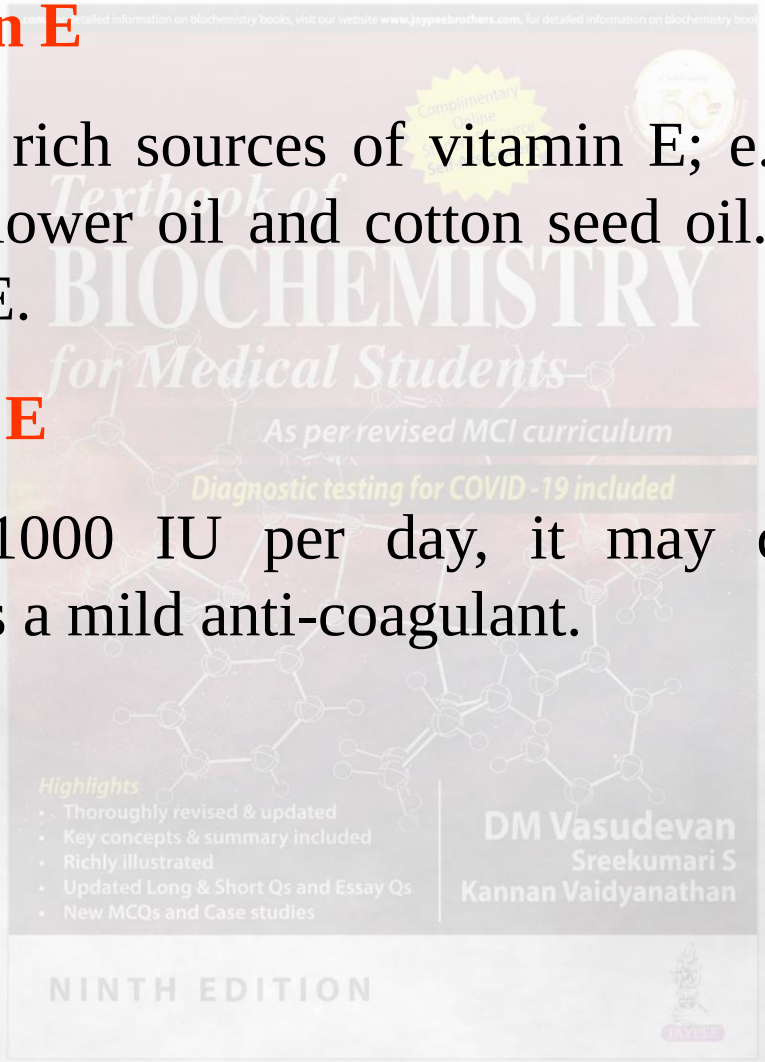


Sources of Vitamin E

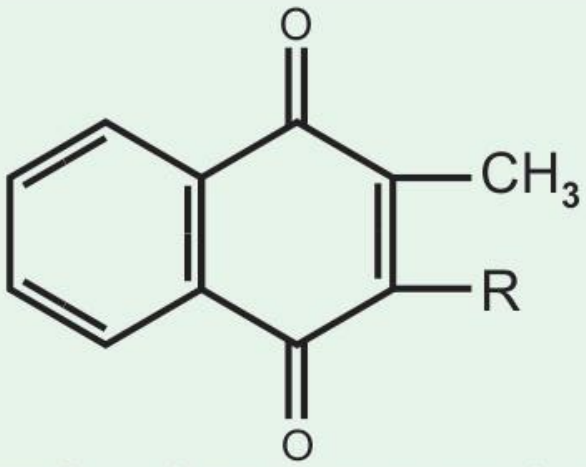
Vegetable oils are rich sources of vitamin E; e.g. wheat germ oil, sunflower oil, safflower oil and cotton seed oil. Fish liver oils are devoid of vitamin E.

Hypervitaminosis E

At doses above 1000 IU per day, it may cause tendency to hemorrhage, as it is a mild anti-coagulant.



Vitamin K



R = 20C in (Phylloquinone) in K_1

R = 30C in (Menaquinone) in K_2

R = H in Menadione

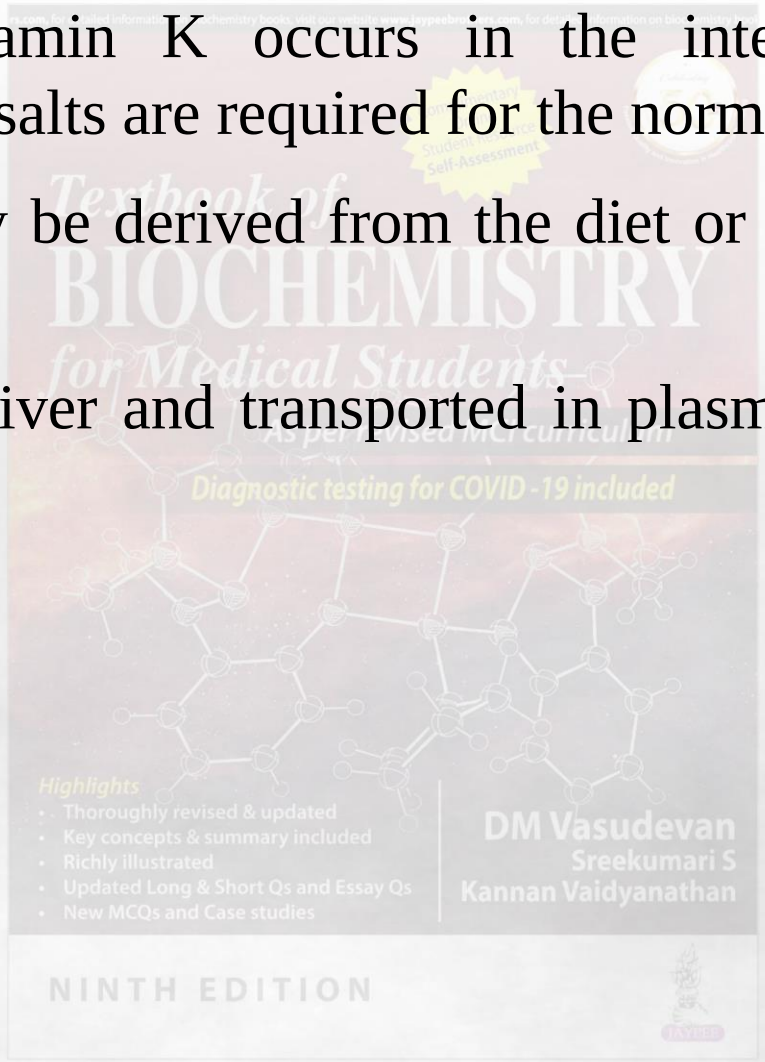
Structure of Vitamin K.

Absorption and Storage

Absorption of vitamin K occurs in the intestine along with chylomicrons. Bile salts are required for the normal absorption.

The vitamin K may be derived from the diet or intestinal bacterial synthesis.

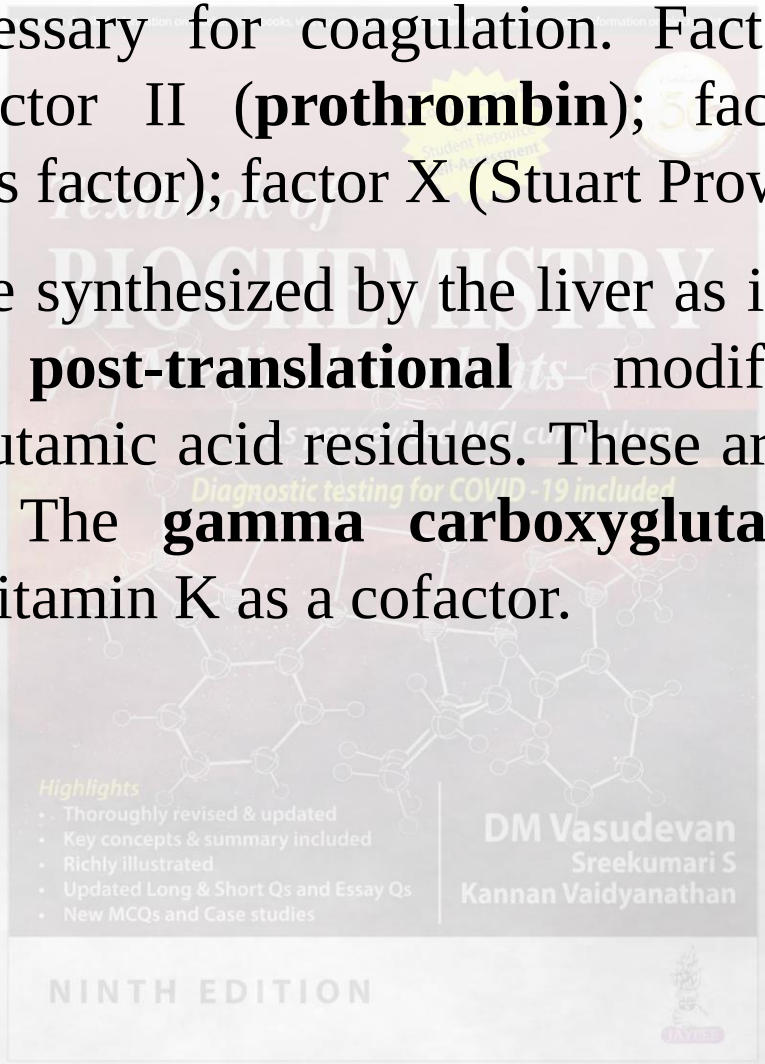
It is stored in the liver and transported in plasma along with beta lipoproteins.

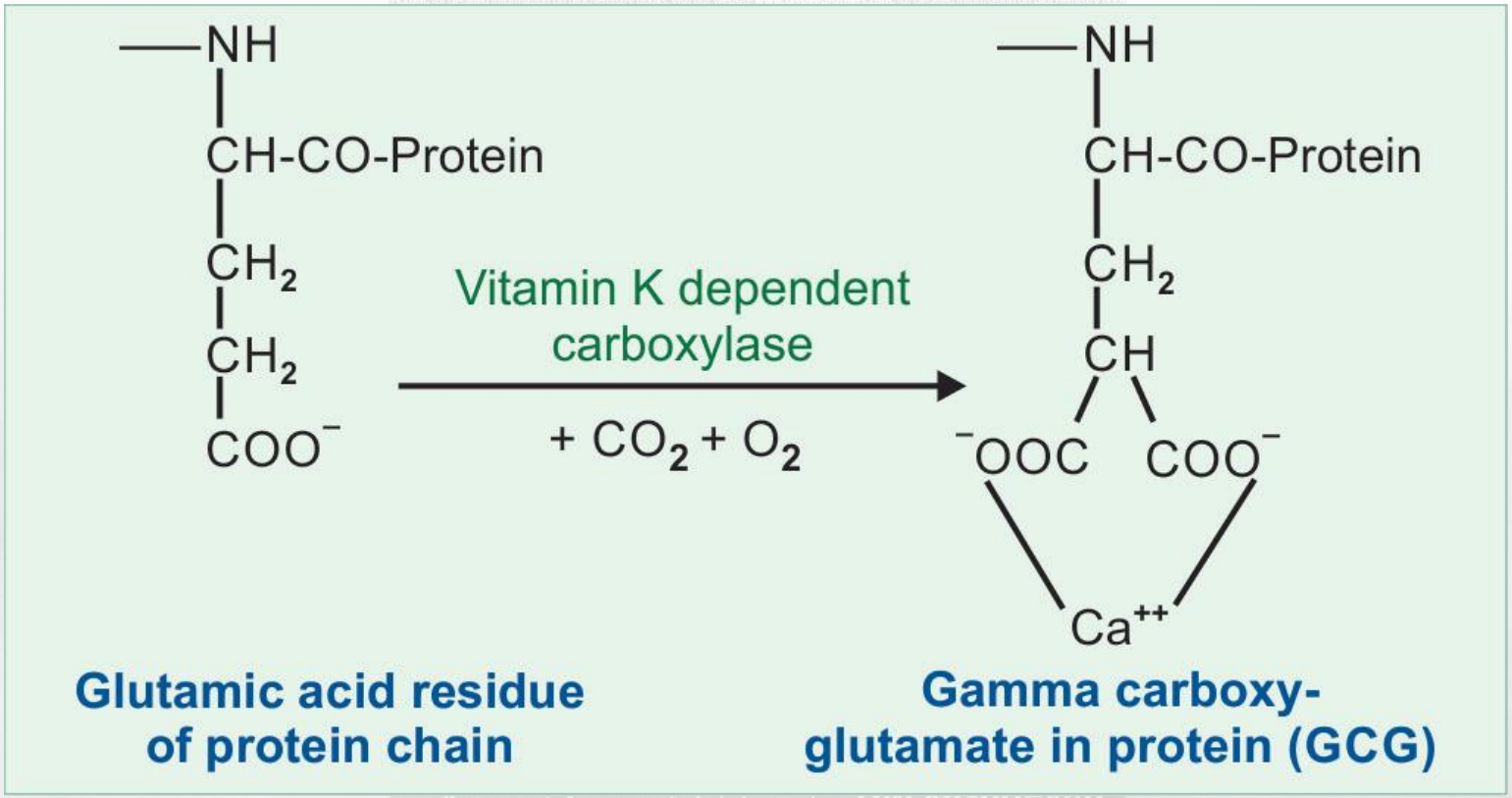


Biochemical Role of Vitamin K

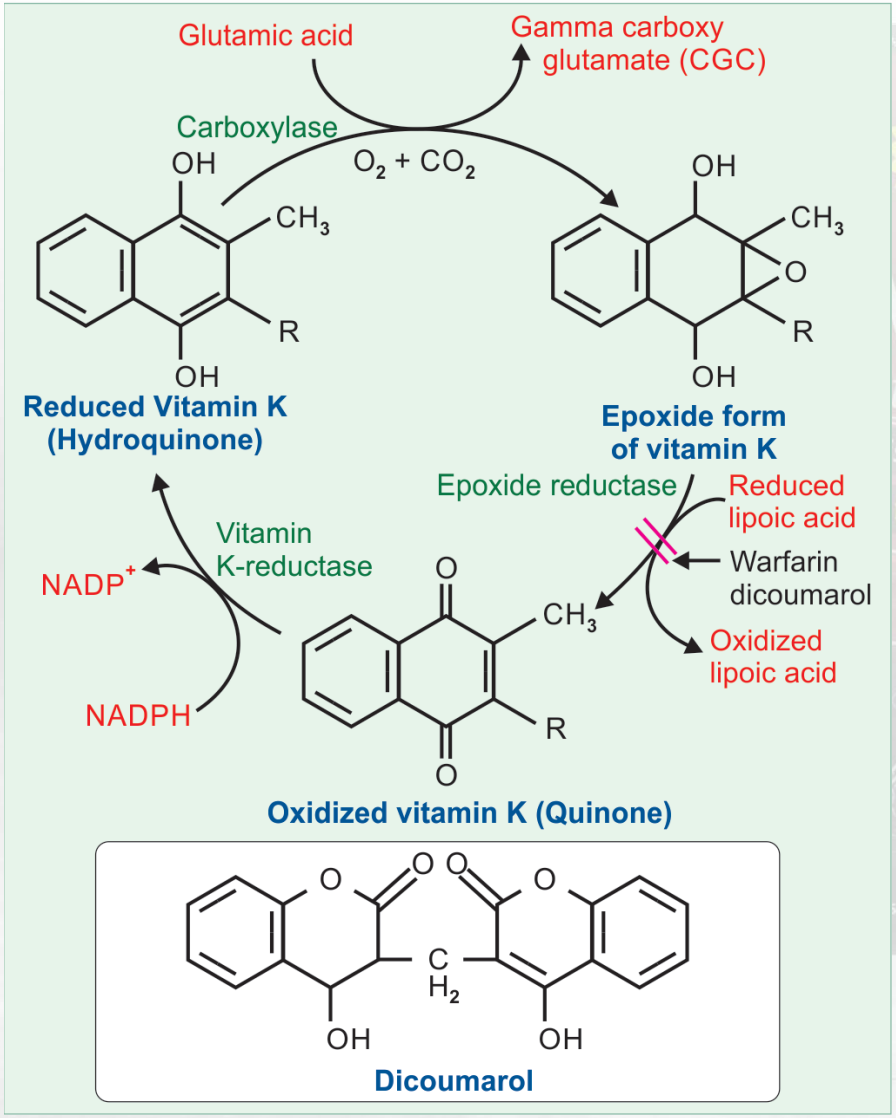
Vitamin K is necessary for coagulation. Factors dependent on vitamin K are factor II (**prothrombin**); factor VII (SPCA); factor IX (Christmas factor); factor X (Stuart Prower factor).

All these factors are synthesized by the liver as inactive zymogens. They undergo **post-translational** modification; gamma carboxylation of glutamic acid residues. These are the binding sites for calcium ions. The **gamma carboxyglutamic acid** (GCG) synthesis requires vitamin K as a cofactor.





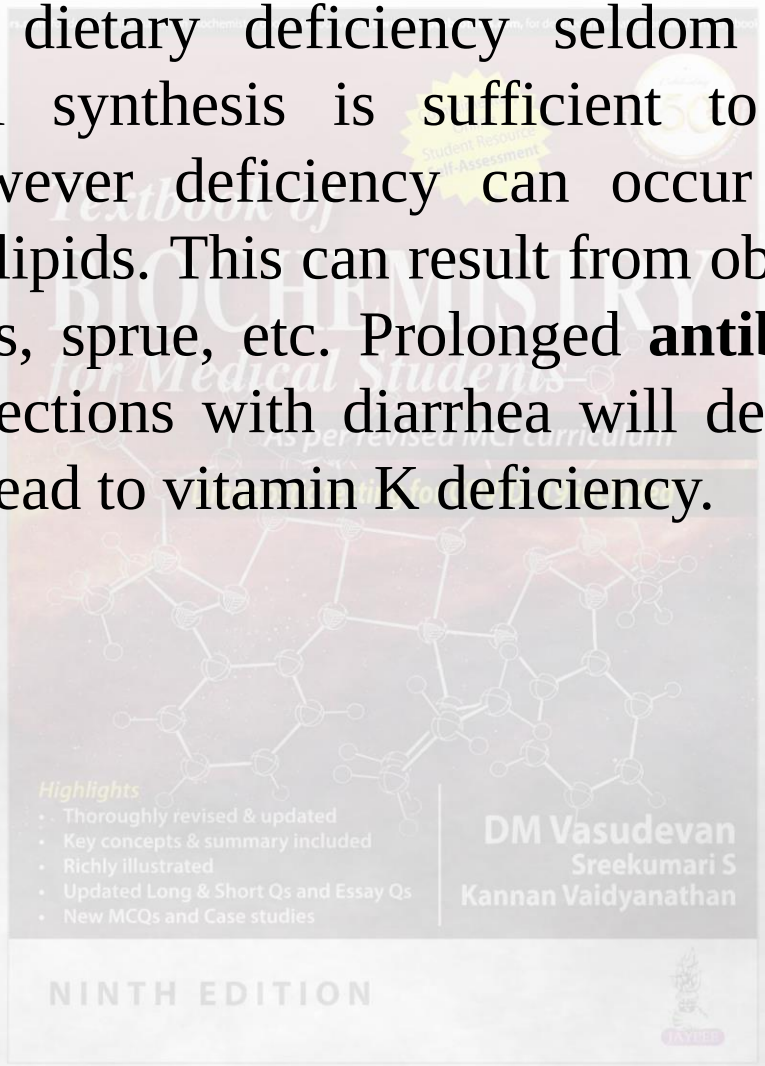
Vitamin K as cofactor in gamma carboxyglutamic acid (GCG) synthesis.



Vitamin K cycle. In the inset, the dicoumarol, a structural analogue is shown, which inhibits vitamin K reductase.

Causes for Deficiency of Vitamin K

In normal adults dietary deficiency seldom occurs since the intestinal bacterial synthesis is sufficient to meet the needs of the body. However deficiency can occur in conditions of **malabsorption** of lipids. This can result from obstructive jaundice, chronic pancreatitis, sprue, etc. Prolonged **antibiotic** therapy and gastrointestinal infections with diarrhea will destroy the bacterial flora and can also lead to vitamin K deficiency.



Clinical Manifestations of Vitamin K Deficiency

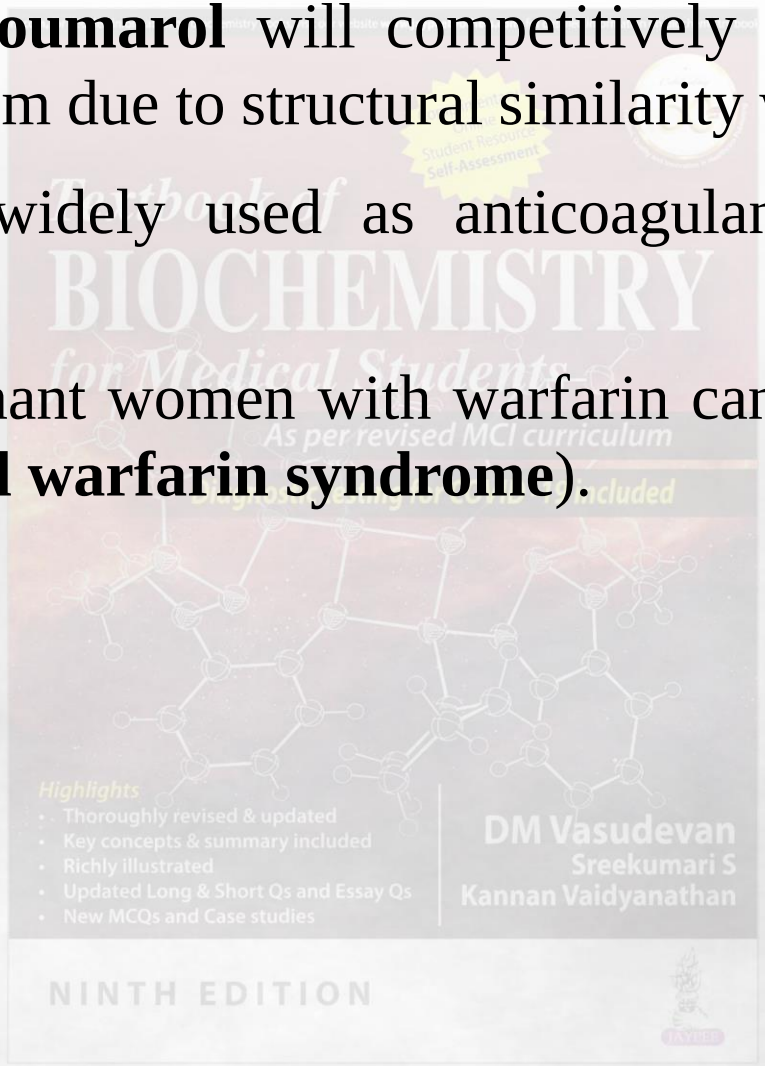
Hemorrhagic disease of the newborn is attributed to vitamin K deficiency. The newborns, especially the **premature infants** have relative vitamin K deficiency. It is advised that pre-term infants be given prophylactic doses of vitamin K (1 mg Menadione).

In children and adults, vitamin K deficiency may be manifested as bruising tendency, ecchymotic patches, mucous membrane hemorrhage, post-traumatic bleeding, **nasal bleeding** and internal bleeding. Prolongation of the prothrombin time (PT) and delayed clotting time are characteristic of vitamin K deficiency.

Warfarin and **dicoumarol** will competitively inhibit the gamma carboxylation system due to structural similarity with vitamin K.

Hence, they are widely used as anticoagulants for therapeutic purposes.

Treatment of pregnant women with warfarin can lead to fetal bone abnormalities (**fetal warfarin syndrome**).



Daily Requirement of Vitamin K

Recommended daily allowance is 55–65 μg/day. (roughly 1 mcg/kg body weight). This is usually available in a normal diet.

Sources of Vitamin K

Green leafy vegetables are good dietary sources. Intestinal bacterial synthesis will meet the daily requirements.

Hypervitaminosis K

Hemolysis, hyperbilirubinemia, kernicterus and brain damage are the manifestations of toxicity. Administration of large quantities of menadione may result in toxicity.

Summary of Fat Soluble Vitamins

Name	Active or Co-enzyme form	RDA	Functions	Deficiency disease	Dietary sources
Vitamin A	Retinol, retinal, retinoic acid	750 - 1000 mcg	Visual cycle; gene regulation; reproductive system; antioxidant; effect on skin.	Night blindness; Bitot spots; xerophthalmia, keratomalacia; skin lesions.	Milk, fish liver oil, fruits containing beta carotene.

Summary of Fat Soluble Vitamins

Name	Active or Co-enzyme form	RDA	Functions	Deficiency disease	Dietary sources
Vitamin D (chole-calciferol)	Calcitriol	15 mcg or 600 IU	Absorption of calcium, mineralization of bone (Intestine, bones and kidneys)	Rickets (different types) and osteomalacia. Hypo-vitaminosis D is common in general population	Sunlight

Summary of Fat Soluble Vitamins

Name	Active or Co-enzyme form	RDA	Functions	Defi-ciency disease	Dietary sources
Vitamin E (alpha-toco-pherol)		10 mg	Anti-oxidant; relation with selenium.	Sterility	Vegetable oils
Vitamin K		50 - 100 mg	Blood coagulation. Gamma carboxy-lation of glutamic acid	Hemor-rhage	Green leafy vege-tables