UNIT-I
ENZYMES

Definitionofenzyme

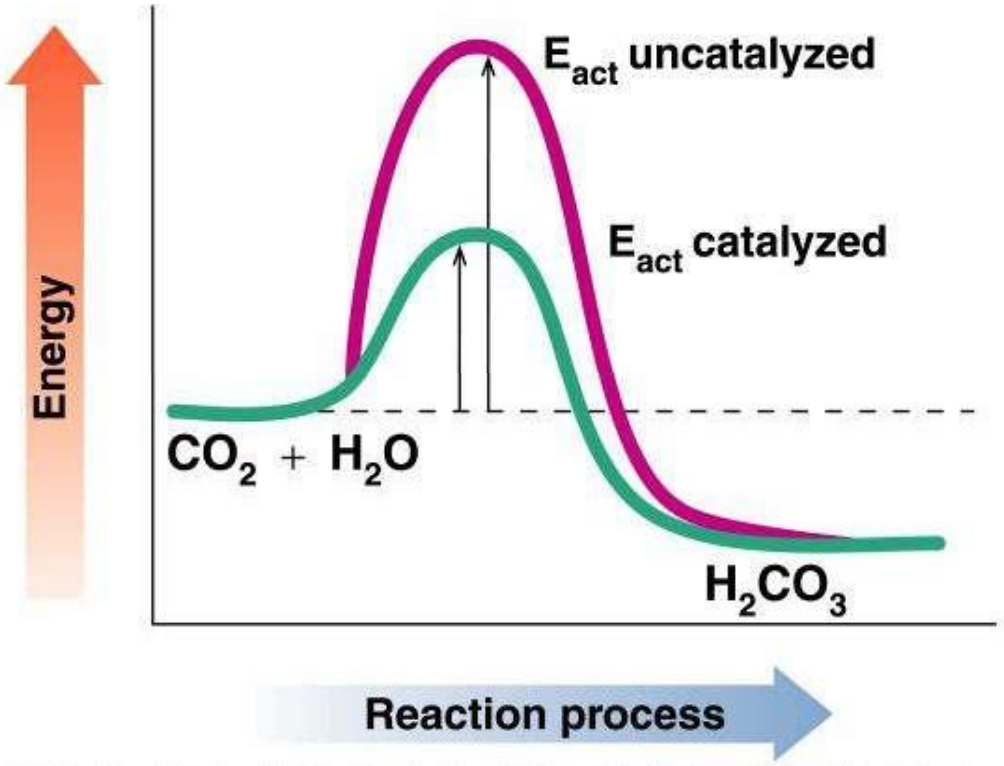
- Enzymesarebiologicalcatalysts.
- ACatalystisdefinedas"asubstancethatincreasestherate ofachemicalreactionwithoutbeingitselfchangedintheprocess."

EnzymesasBiologicalCatalysts

- **Enzymes**areproteinsth atincreasetherateofreact ionbyloweringtheenergy ofactivation

- Theycatalyzenearlyallth echemicalreactionstaki ngplaceinthecellsofthe body

- Enzymeshaveuniquet hree-dimensionalshapesth atfittheshapesofreact ants(**substrates**)



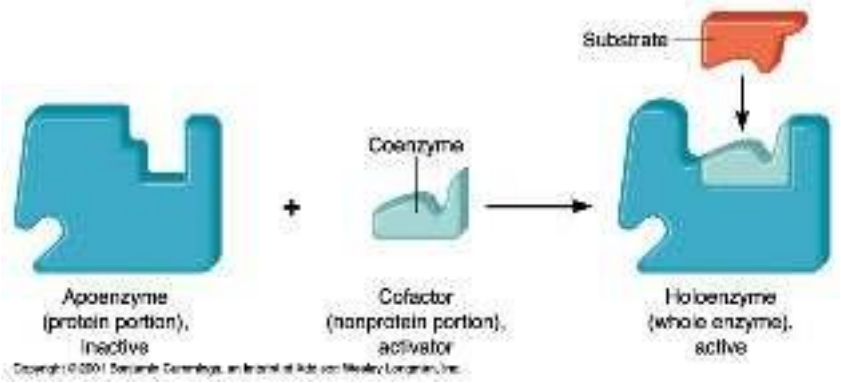
2. Propertiesofenzymes(important!)

- **Catalyticefficiency–highefficiency,10^3to10^{17}fasterthanthecorrespondinguncatalyzedreactions**
- **Specificity-highspecificity,interactingwithoneorafewspecificsubstratesandcatalyzingonlyonetypeofchemicalreaction.**
- **Mildreactionconditions-37℃,physiologicalpH,ambientatmosphericpressure**

3. Chemicalcompositionofenzymes

(1) Simpleprotein

(2) Conjugatedprotein

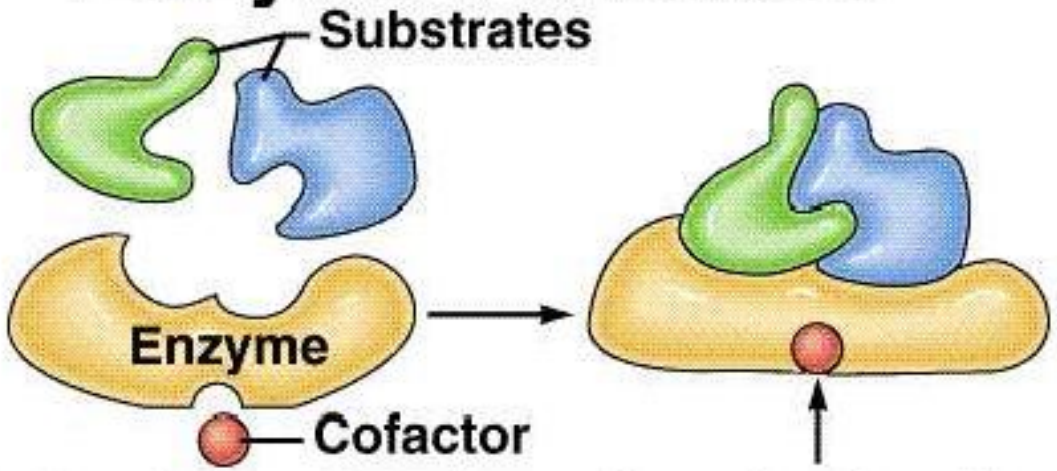


Holoenzyme=Apoenzyme+Cofactor

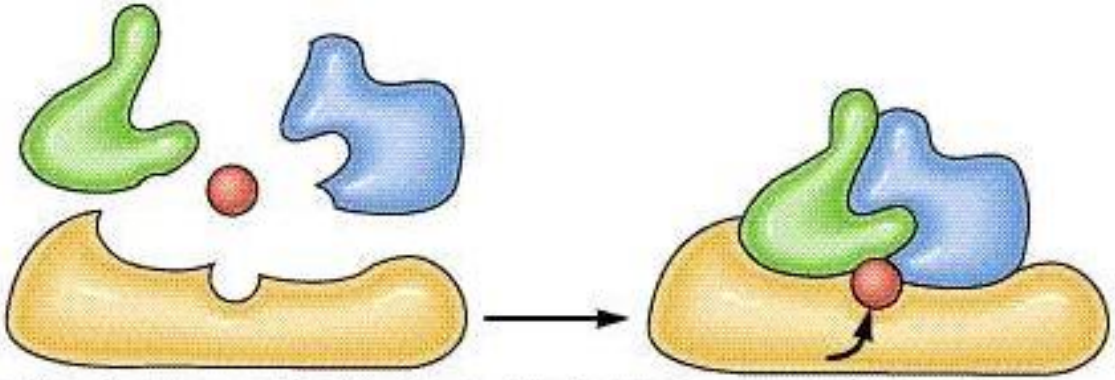
Cofactor

- Coenzyme:looselyboundtoenzyme(non-covalentlybound).
- Prostheticgroup:verytightlyorevencovalentlyboundtoenzyme(covalentlybound)

Roles of Cofactors in Enzyme Function



Cofactor changes conformation of active site.



Cofactor participates in temporary bonding between active site and substrates.

4. Classificationofenzymes

(1). Bytheircomposition

1). Monomericenzyme

2). Oligomericenzyme

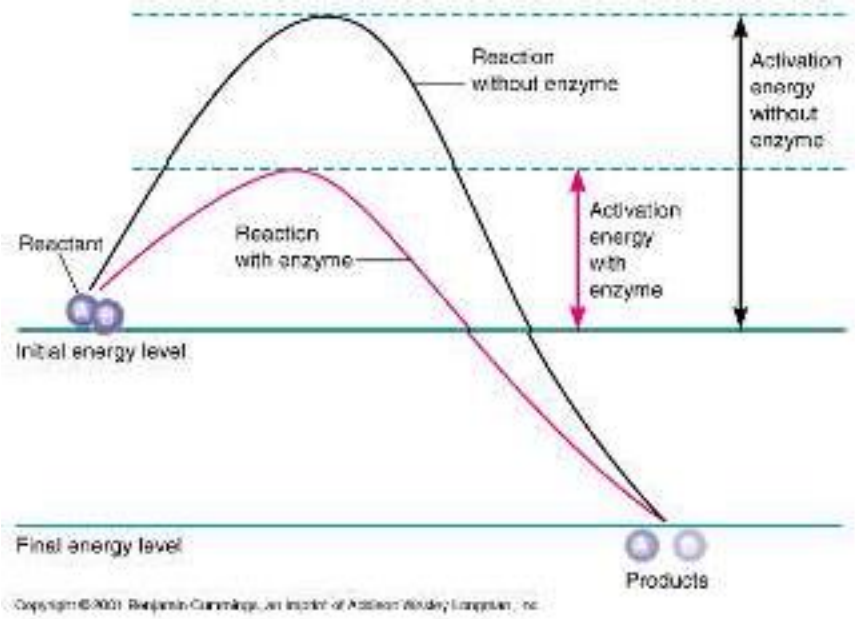
3). Multienzymecomplex:suchasFa ttyacidsynthase

(2)Nomenclature

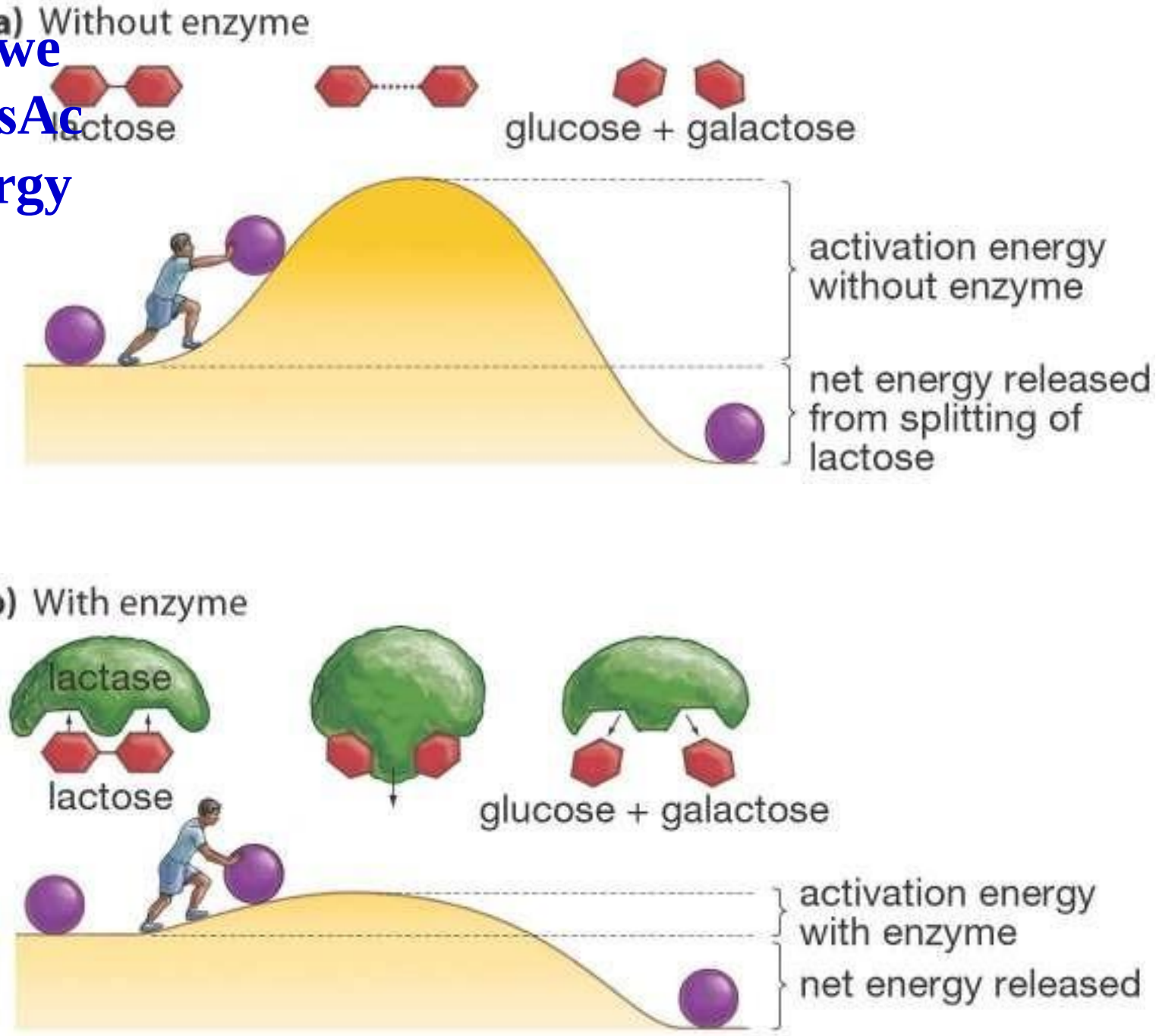
- Recommendedname
  - ·Enzymesareusuallynamedaccordingtothereactiontheycarryout.
    - ·Togeneratethenameofanenzyme,thesuffix *ase*isaddedtothenameofitssubstrate(*eg*,lactaseistheenzymethatcleaveslactose)orthetypeofreaction(*e.g.*,DNApolymeraseformsDNApolymers).
- ·Systematicname(Internationalclassification)
  - · Bythereactionstheycatalyze(Sixclasses)

5. Howenzymeswork(important!)

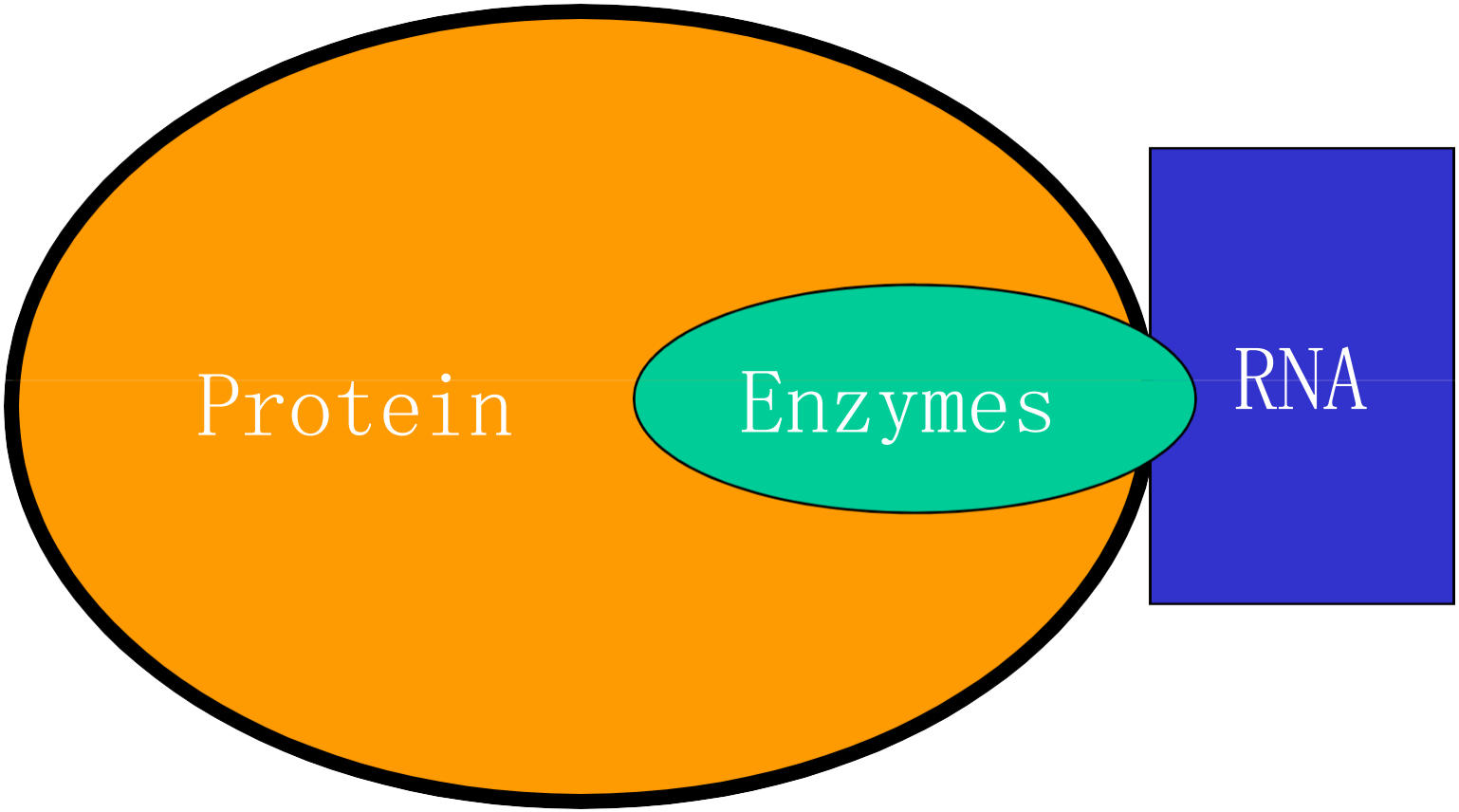
1) Enzymeslowerareaction'sactivationenergy
   - Allchemicalreactionshaveanenergybarrier,calledtheactivationenergy,separatingthereactantsandtheproducts.
   - activationenergy:amountofenergyneededtodisruptstablemoleculesothatreactioncantakeplace.



EnzymesLowe raReaction'sAc tivationEnergy



What is the difference between an enzyme and a protein?

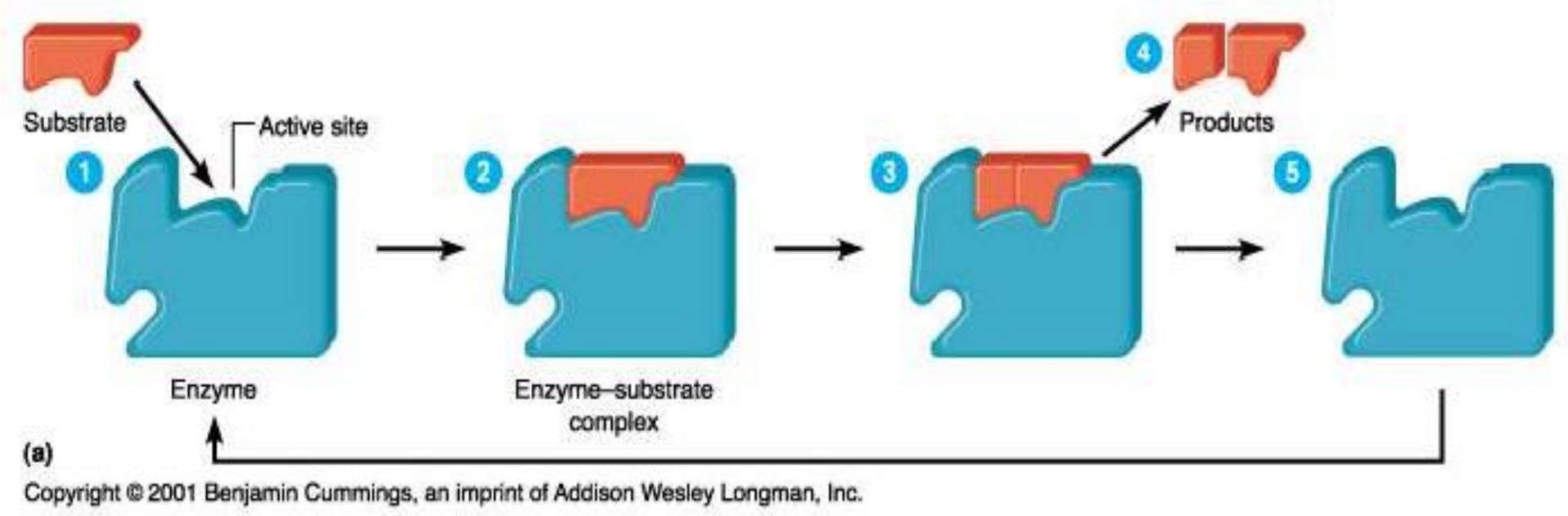


- **All enzymes are proteins except some RNAs**
- **not all proteins are enzymes**

2) Theactivesiteoftheenzyme

- Enzymesbindsubstratestotheiractivesiteandstabilizethetransitionstateofthereaction.
- Theactivesiteoftheenzymeistheplacewherethesubstratebindsandatwhichcatalysisoccurs.
- The active site binds the substrate, forming anenzyme-substrate(ES)complex.

Enzymaticreactionsteps



1. Substrateapproachesactivesite
2. Enzyme-substratecomplexforms
3. Substratetransformedintoproducts
4. Productsreleased
5. Enzymerecycled

6. Enzymeactivity

- Enzymesareneverexpressedintermsoftheirconcentration(asmgorμgetc.),butareexpressedonlyasactivities.
- Enzymeactivity=molesofsubstrateconvertedtoproductperunittime.
  - Therateofappearanceofproductortherateofdisappearanceofsubstrate
  - Testtheabsorbance:spectrophotometer

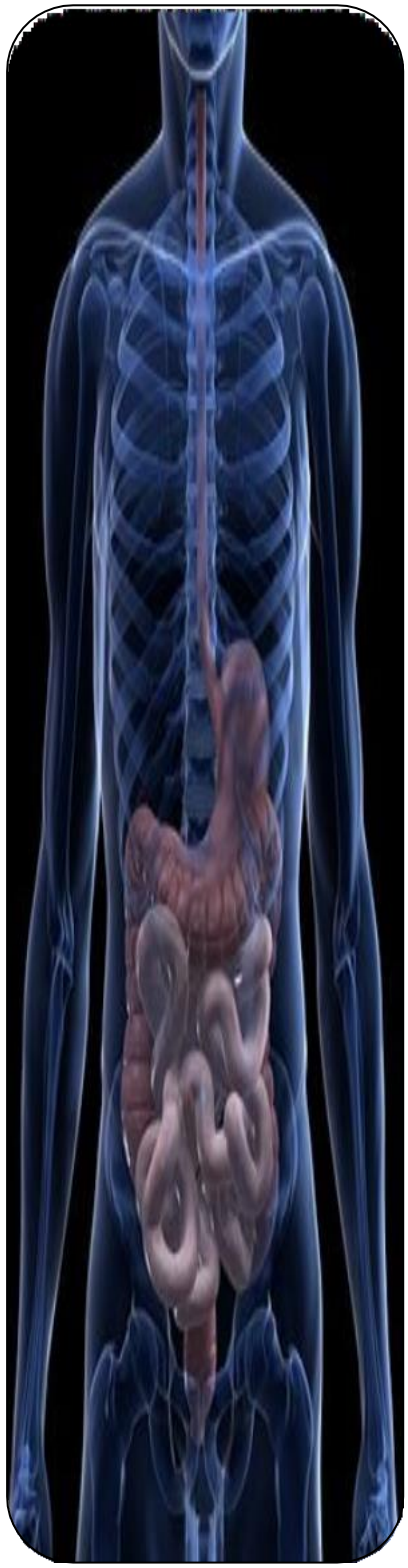
7. Factorsaffectingenzymeactivity

- Concentrationofsubstrate
- Concentrationofenzyme
- Temperature
- pH
- Activators
- Inhibitors

Enzymesinclinicaldiagnosis

- Anenzymetestisabloodtestorurinetestthatmeasureslevelsofcertainenzymestoassesshowwellthebody'ssystemsarefunctioningandwhetherthereehasbeenanytissuedamage.(why?)

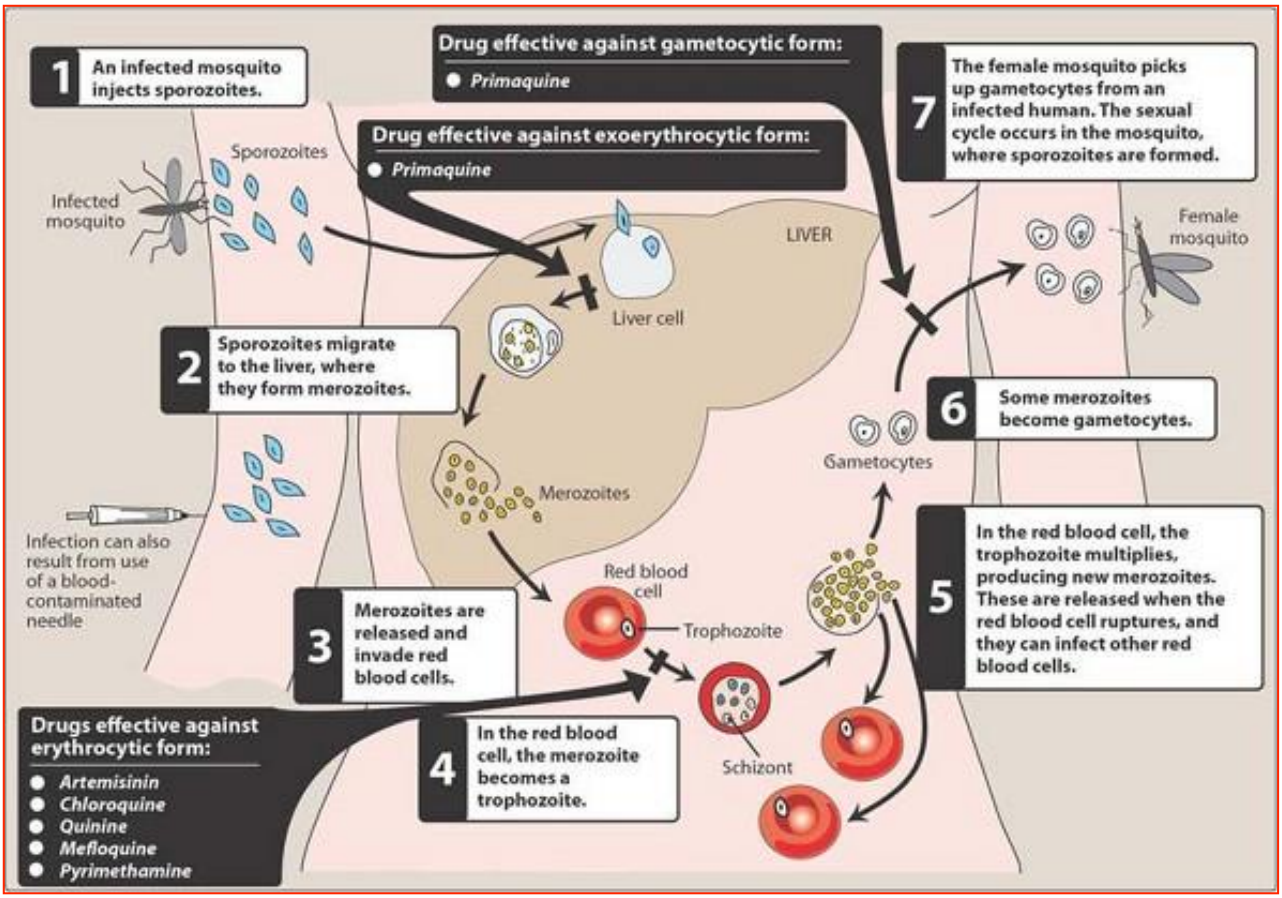
- Commonenzymesusedforclinicaldiagnosisin clude:
  - alanineaminotransferase(ALT,alsocalled glutamatepyruvatetransaminase,GPT)
  - alkalinephosphatase
  - amylase
  - aspartateaminotransferase
  - creatinekinase
  - lactatedehydrogenase



UNIT-II
ANTIMALARIAL DRUGS

Introduction

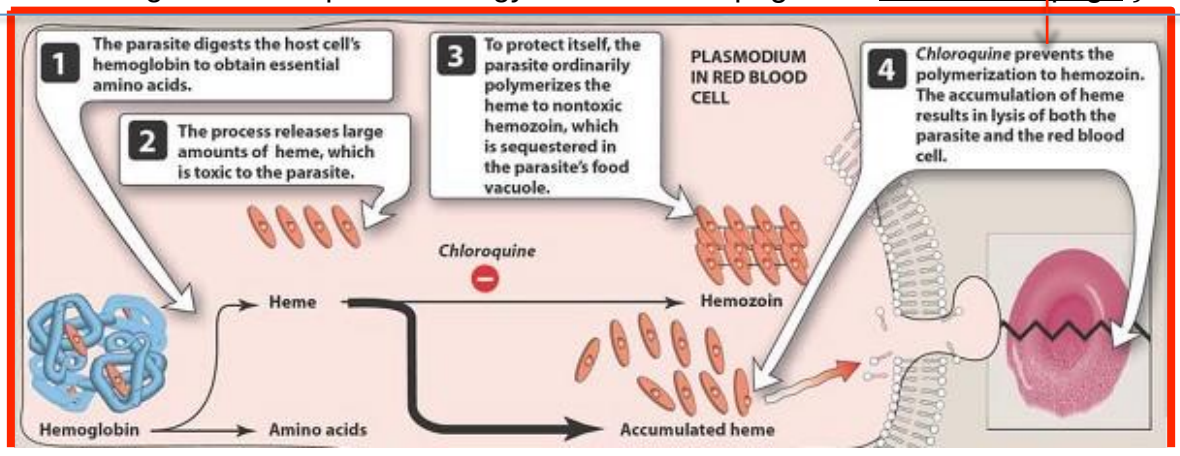
--- Malaria is an acute infectious disease caused by four species of the protozoal genus plasmodium.
--- **Plasmodium Falciparum**, Plasmodium malariae, Plasmodium Ovale, and **Plasmodium vivax**.
--- The parasite is transmitted to humans through the bite of female anopheles mosquito.
--- P. Falciparum is the most dangerous species, causing a severe disease. P. vivax causes a milder disease.
--- Resistance acquired by the mosquito to insecticides, and by the parasite to drugs, has led to new therapeutic challenges, particularly in the treatment to P. Falciparum.



Life cycle of malaria:

When an infected mosquito bites, it injects Plasmodium sporozoites into the bloodstream. The sporozoites migrate through the blood to the liver, where they form cyst-like structures containing thousands of merozoites. Upon release, each merozoite invades a red blood cell, becoming a trophozoite and **using hemoglobin as a nutrient**. The trophozoites multiply and become merozoites. Eventually, the infected cell ruptures, releasing heme and merozoites that can enter other erythrocytes. Alternatively, released merozoites can become **gametocytes, which are picked up by the mosquitoes from the blood they ingest**. The cycle thus begins again, with the gametocytes becoming sporozoites in the insect.

IMPORTANT*: Infections with **P.falciparum** and P.malariae **have no exoerythrocytic stage**
Infections with **P.vivax** and P.ovale **have exoerythrocytic stage**
(* the source: Rang and dale's pharmacology- sixth edition- page704 "see the last page")



Plasmodium uses hemoglobin as a nutrient:
It is in the food vacuole that parasite digest the host cell's hemoglobin to obtain essential amino acids. However, this process releases large amounts of heme, which is toxic to the parasite. To protect itself, the parasite ordinarily polymerizes the heme to hemozine, which is nontoxic, with the use of heme polymerase. Some drugs interfere with this process such as chloroquine.

Symptoms of malaria:
Fever, shivering, pain in the joints, headache, repeated vomiting, generalized convulsions, and coma.

Antimalarial drugs

Some drugs can be used prophylactically to prevent malaria, while others are directed towards treating acute attacks. In general, antimalarial drugs are classified in terms of the action against the different stages of the life cycle of the parasite

A) *Blood* schizonticidal agents:
Are used to treat the acute attack. They act on the erythrocytic forms of the plasmodium.
- **Atremisinin**
- **Chloroquine**
- **Quinine**

***B) Tissue* schizonticidal agents:**
Have a radical cure effect by acting on the parasites in the liver, these drugs also destroy gametocytes and thus reduce the spread of infection.
- **Primaquine**

Target of Therapy	Therapeutic Class	Drug Examples
To alleviate symptoms	**Blood schizontocidal drugs**	• **Artemisinin** • **Chloroquine (in vivax only)** • **Quinine (in pregnancy)**
To prevent Relapses	**Tissue schizontocidal drugs**	• **Primaquine**
To prevent Spread	**Gametocidal drugs**	• **Primaquine**

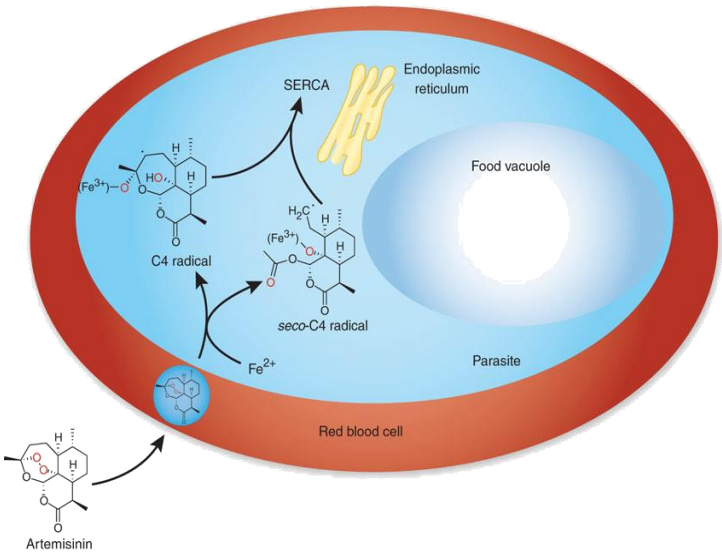
1- Atremisinin:

- Important drug because plasmodium have not developed resistance to it yet.
- Another preparations are available with better solubility: **Artensuate**, and **artemether**.

T1/2:

Artemisinin (4hrs)
Artesunate (45min)
Artemether (4-11hrs)

MOA: by production of **free radicals** within the plasmodium vacuole, following cleavage of the drug's endoperoxide bridge by heme iron in parasitized erythrocyte. These free radicals will attack the lipids, membranes and the structures of the organism, and inhibit its growth by inhibiting enzyme called sarco-endoplasmic reticulum Ca2+-ATPas (SERCA).



*Artemisinin **and its derivatives should not be used as monotherapy??** → Because it has got short half-life, so if we use alone recrudescent will happen "recurrence of the symptoms" and also to prevent resistance and delay its development to give better results.

ADRs:

- Transient heart block
- ↓ neutrophil count
- Brief episodes of fever
- Neuro, hepato and bone marrow toxicity

→ Overall, the drug is considered safe

Preparations:

1. Artesunate IV or IM preparations for severe complicated cases as cerebral malaria (24h) followed by complete course of **ACT.**

2. Artemisin-based combination therapies (ACTs):
   - Artemether + lumefantrine
   - Artemether + amodiaquine
   - Artemether + mefloquine
   - Artemether + sulfadoxine-pyrimethamine

- These combinations are used in mild to moderate malaria alone
- in case of severe malaria the treatment is initiated by artesunate for 24 hours then we continue the treatment with ACT.

2- Chloroquine:

--- Effective in the treatment of extraintestinal amebiasis (especially amebic liver abscess).
- It has anti-inflammatory action, therefore, can be used in rheumatoid arthritis and SLE.
--- Used in sensitive vivax malria ONLY
- Resistence to it has developed (especially chloroquine-resistant P.falciparum).

MOA:
As mentioned in the introduction, malaria parasite digest host cell's Hemoglobin RBC to obtain amino acids. Heme is released (which is Toxic to the parasite) So parasite detoxifies it by heme polymerase to Hemozin (which is non toxic to the parasite).
chloroquine prevents polymerization of heme to hemozoin ,leading to death of the parasite.

Pharmacokinetics:

Chloroquine concentrates 1000-fold in food vacuole of parasite. Why ?
1- Its protonation & ion trapping due to ▯ pH of vacuole (=because it is acidophilic and food vacuoles have low PH)
▯ -Its active uptake by a parasite transporter(s)
▯ -- Its binding to a specific receptor in the food vacuole

- Has high volume of distribution
- Concentrated in food vacuoles of parasites, in erythrocytes, in melanin containing tissues "pigments", and other tissues.
- Released slowly from tissues
- Initially t1/2=2-3days, terminal t1/2=1-2months

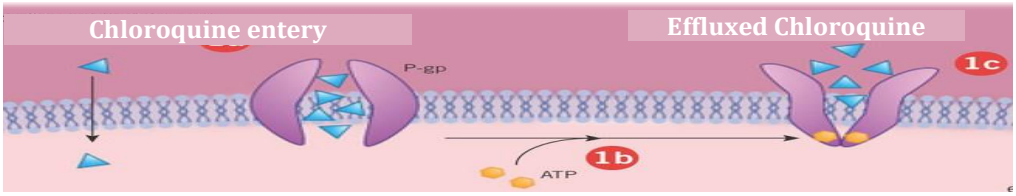
ADRs:
Because drug is concentrated in melanin containing tissues like retina and skin…

❖ **in Short-term use "as in malaria":**
1. Mild headache and visual disturbances.
2. Gastro-intestinal upsets; Nausea, vomiting .
3. Pruritus, urticaria "allergy".

❖ **Prolonged therapy "as in Rheumatoid arthritis":**
1. **Retinopathy**, characterized by loss of central visual acuity, macular pigmentation and retinal artery constriction. Progressive visual loss is halted by stopping the drug, but is not reversible.
2. Lichenoid skin eruption, bleaching of hair.
3. Weight loss
4. Hemolytic anemia in patients with G6PD deficiency (not mentioned in the slides nor during the lecture)

Bolus injection→ hypotension & dysrrhythmias

Chloroquine Resistance: (IMP!!)
Resistance against the drug develops as a result of enhanced efflux of parasite vesicle → because of increased expression of the human multi drug resistance transporter P-glycoprotein = MDR T P-GP
In another way, this means: once the drug enters the parasite cell, and before it starts its action, the parasite is able to identifies it as a drug that is toxic. As a defensive mechanism, the parasite will get rid of the drug and throw it out of the cell by the help of MDR T P-GP. When there is upregulation and increase expression of this protein, the parasite will develop resistance to the drug.



3-Quinine

MOA + Resistance mechanism: Same as chloroquine

Other Actions:

- Antiarrhythmic as well = quinidine like action.
- Mild oxytoxic effect on pregnant uterus
- Slight neuromuscular blocking action
- Weak antipyretic action

Oxytoxic effect: stimulate uterus contraction to deliver the fetus. In late pregnancy , it has a similar action to the natural the oxytocin hormone in the body.

Major ADRs:

❖ **In therapeutic does:**

- Bitter taste => poor compliance "patient may not take it regulatory or stop because of its tastes"

❖ **In Higher doses:**

- **Cinchonism (tinnitus, deafness, headaches, nausea & visual disturbances)** "it's called cinchonism reffering to its origin plant cinchona bark."
- Abdominal pain & diarrhea
- Rashes, fever, hypersensitivity reactions
- Hypotension & arrhythmias
- Blood dyscarasis; anaemia, thrombocytopenic purpura & hypoprothrombinaemia
- Blackwater fever, a fatal condition in which acute haemolytic anaemia is associated with renal failure.

Cinchonism: a syndrome causing nausea and vomiting, tinnitus, and vertigo

If given IV => neurotoxicity => tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration & coma.

Contraindications:

- Prolonged QT Interval.
- Glucose-6-Phosphate Dehydrogenase Deficiency.
- Myasthenia Gravis. "because of neuromuscular blocking action"
- Hypersensitivity.
- Optic Neuritis, auditory problems.
- Dose should be reduced in renal insufficiency.

Interactions

- Antacids: Antacids containing aluminum &/or magnesium may delay or decrease absorption of quinine.
- Erythromycin (CYP3A4 inhibitor)
- Cimetidine
- Mefloquine.
- Quinine can raise
- plasma levels of warfarin and digoxin.

Both Erythromycin and cimetidine are inhibitors of Quinine metabolism.

*** **Less resistance than chloroquine**

4- Primaquine:

MOA: Not well understood. Many theories. Believed to act as oxidant.

ADRs:

- **in regular doses:**
  - **Drug induced hemolytic anemia in patients with G6PD deficiency**
    how? Primaquine oxidizes the glutathione => no enough NADPH => RBCs lysis by oxidants.

- **In large doses:**
  - Epigastric distress & abdominal cramps.
  - Mild anemia, cyanosis & methemoglobinemia
  - Severe methemoglobinemia!rarely in patients with deficiency of NADH methemoglobin reductase.
  - Granulocytopenia & agranulocytosis => rare

Other drugs used in combination (=Other drugs that we can use to combine with the previous main drugs)

DRUG	MECHANISM	ADR
Lumefantrine	**heme polymerase**	
Amodiaquine	**heme polymerase**	
Mefloquine	**heme polymerase**	
Sulfadoxine-pyrimethamine	**Sequential block of dihydropteroate synthase & dihydrofolate reductase therefore DNA synthesis**	Allergy and Bone marrow suppression
Clindamycin	**inhibits parasite apicoplast (which is needed for survival & successful host invasion)**	Pseudomembranous colitis
Doxycycline	**Inhibit protein synthesis by binding to 30S subunit of ribosome**	Bone deformities and teeth discoloration

* Which one of the 4 main drugs that can be used in patients with G6PD deficiency??
Atremisinin

WHO treatment Guidelines:

P.vivax infection
If sensitive →
give Chloroquine for 3 days,
followed by **Primaquine** for 14 days.

If resistance →
Give ACT, followed by **Primaquine**

P.Falciparum infection → always show resistance to Chloroquine.
Uncomplicated "mild to moderate" → give ACT.

Complicated "severe" →
IV OR IM Artesunate for 24 hrs,
followed by
- ACT
- Or Artemether + [Clindamycin / doxycyline]
- Or Quinine + [Clindamycin / doxycyline]

in Pregnancy
Pregnancy; 1st trimester → Quinine + clindamycin

Pregnancy; 2nd & 3rd trimester
Lactating women
Infants & young children
→ ACT

- **Why quinine can be given in 1st trimester only?**
  Because of the oxytoxic effect.
- **Chloroquine is safe in pregnancy, but yet not given. Why?** Because if I give it and the pregnant lady has P.falciparum infection, she will die from the infection not the drug. So we must give another drug that is both safe and can attack all parasites whether sensitive or resistance.

Vitamins

Vitamins are organic compounds characterized by:

- Essential for normal health and growth.
- Essential for biological activity in the body.
- Present in food in very small concentration.
- Not enter in the tissue structure as carbohydrates, lipids and proteins.

- Act as catalysts and are not oxidized to give energy as carbohydrates, lipids and proteins.
- Deficiency of any vitamin in the body results in production of specific diseases.
- Many vitamin function as coenzymes.
- Not synthesized in the body by anabolic reaction, therefore should be taken in the diet.
- Some vitamin are present in food in the form of provitamins.

Provitamin

They are vitamin precursors.

Example:

- Carotenes are provitamin A.
- 7- dehydrocholesterol are provitamin D_3

Vitamer

When a vitamin is present in more than one chemical formula each is called a vitamers

Example:

- Vitamin A has Two vitamers A1 and A2.
- Vitamin D has two vitamers D2 and D3.
- Vitamin E has four vitamers alpha, beta, gama, delta.

Vitagen

These include both essential Amino acids and essential fatty acids.

Classification of vitamins

Vitamins can be classified according to their solubility and their function in metabolism into:

I- Fat soluble vitamins

II- Water soluble vitamins

I- Fat Soluble Vitamins

- **Vitamin A**
- **Vitamin D**
- **Vitamin E**
- **Vitamin K**

II-WATER SOLUBLE VITAMINS

I- B- complex

- **Thiamine (B_1)**
- **Riboflavin (B_2)**
- **Niacin (B_3)**
- **Folic acid**
- **Pyridoxine (B_6)**
- **Vitamin B_{12}**
- **Pantothenic Acid**
- **Biotin**

II- Non B- complex :

Vitamin C (ascorbic acid).

B- complex

a- Energy-releasing.

- **Thiamine (B_1)**
- **Riboflavin (B_2)**
- **Niacin (B_3)**
- **Biotin**
- **Pantothenic Acid**

b- Hematopoietic.

- **Folic acid**
- **Vitamin B_{12}**

c- Other.

- Pyridoxine (B6), pyridoxal, pyridoxamine

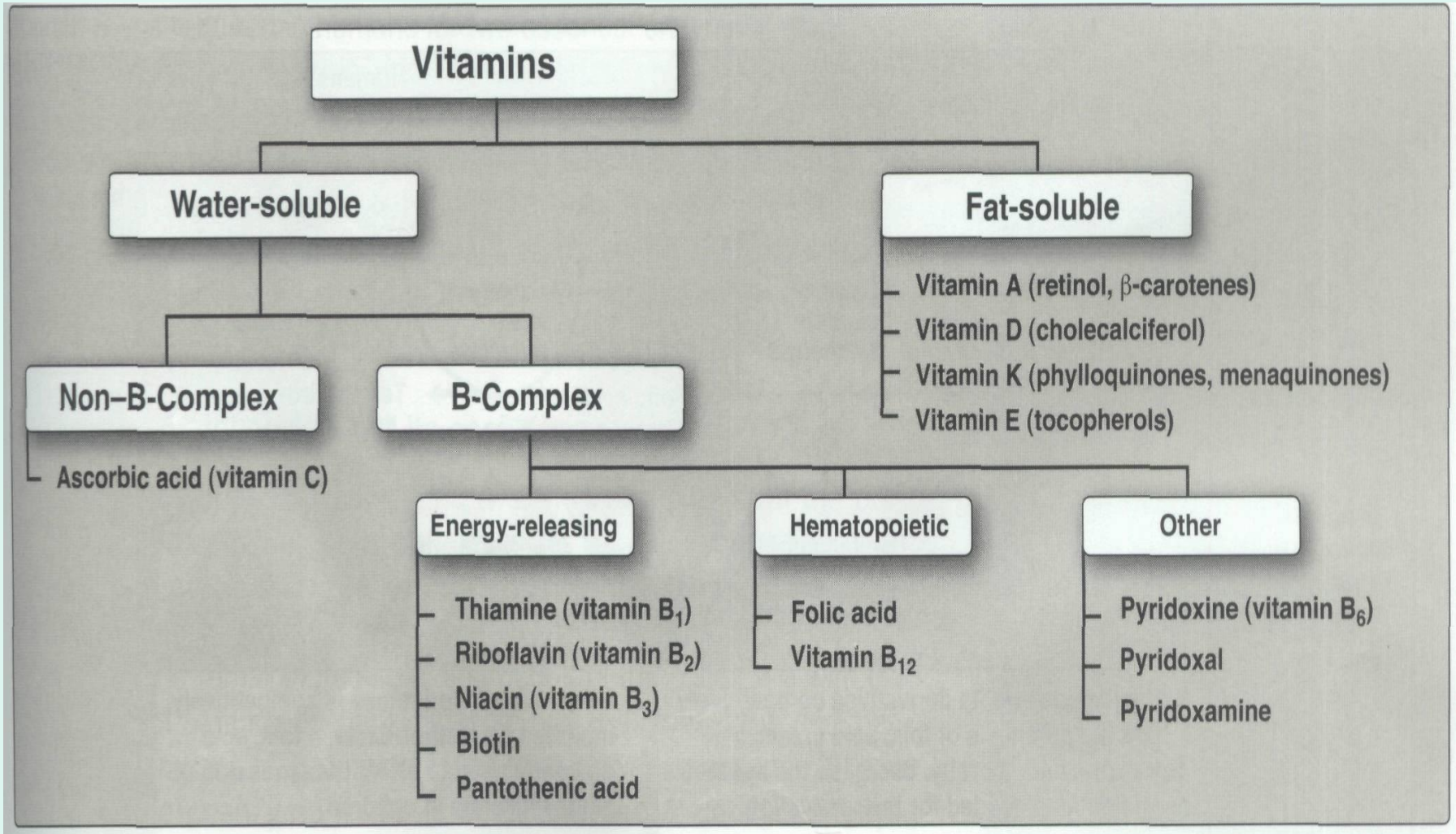


Figure 28.1
Classification of the vitamins.

	Fat soluble vitamins	Water soluble vitamins
Absorption	First into lymph and then into blood	Directly into blood
Storage	Stored in the liver and in fat	Not stored in the body (except vit B12)
Toxicity	Excess intake leads to toxic manifestation	Toxicity is rarely seen because they can be excreted in urine

RECOMMENDED DAILY ALLOWANCE (RDA)

Amount of the vitamin needed daily to maintain good nutrition in most healthy people.

FAT SOLUBLE VITAMINS

Objectives to learn:

- Chemistry
- Sources
- Biochemical functions
- Recommended daily allowance
- Deficiency manifestations [Hypovitaminosis]

VITAMIN A

Vitamin A

Synonyms:

- Anti-night blindness vitamin

Or

- Anti-xerophthalmic vitamin

Vitamin A

Structure:

- Vitamin A does not occur in plants, but many plants contain **carotenoids such as beta-carotene** that can be converted to vitamin A within the intestine and other tissues.

The term retinoids includes both natural and synthetic forms of vitamin A that may or may not show vitamin A activity.

RETINOIDS

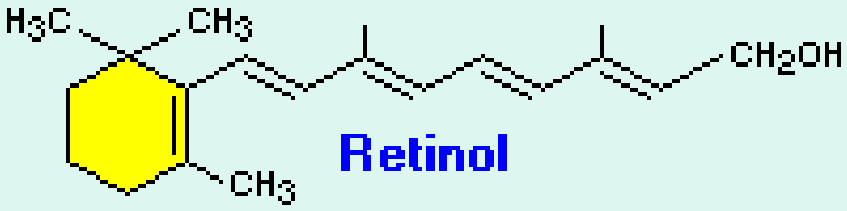
- A family of molecules that are related to retinol (vitamin A), are essential for vision, reproduction, growth, and maintenance of epithelial tissues. **Retinoic acid,** derived from oxidation of dietary retinol, mediates most of the actions of the retinoids, except for vision, which depends on **retinal,** the aldehyde derivative of retinol.

- **Retinol:** A primary alcohol containing aB-ionone ring with an unsaturated side chain. It is found in animal tissues as retinyl ester with long-chain fatty acids.

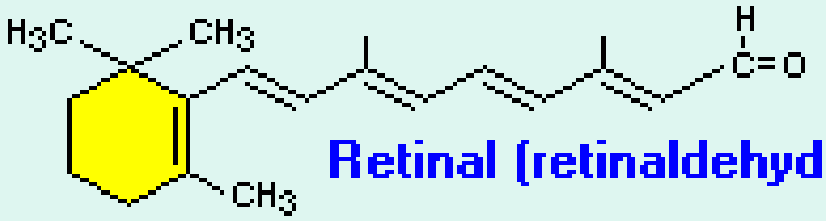
- **Retinal:** The aldehyde derived from the oxidation of retinol. Both are readily interconverted.

- B-carotene (provitamin A): It is present in plant foods, which can be oxidatively cleaved in the intestine to yield two molecules of retinal.

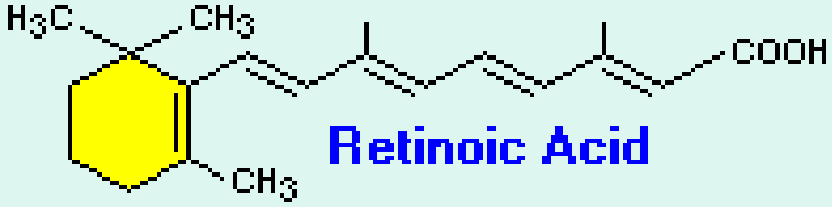
- **Retinoic acid:** The acid derived from oxidation of retinal. It cannot be reduced in the body so cannot give rise to retinol or retinal.



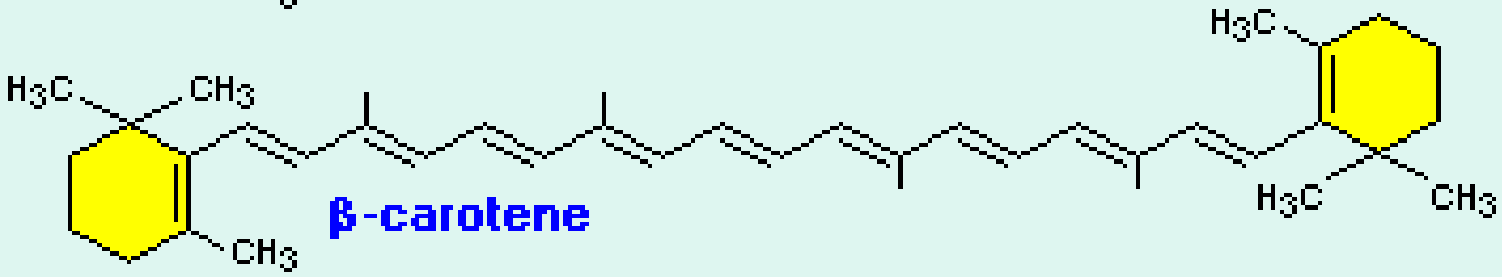
Retinol



Retinal (retinaldehyde)



Retinoic Acid



β-carotene

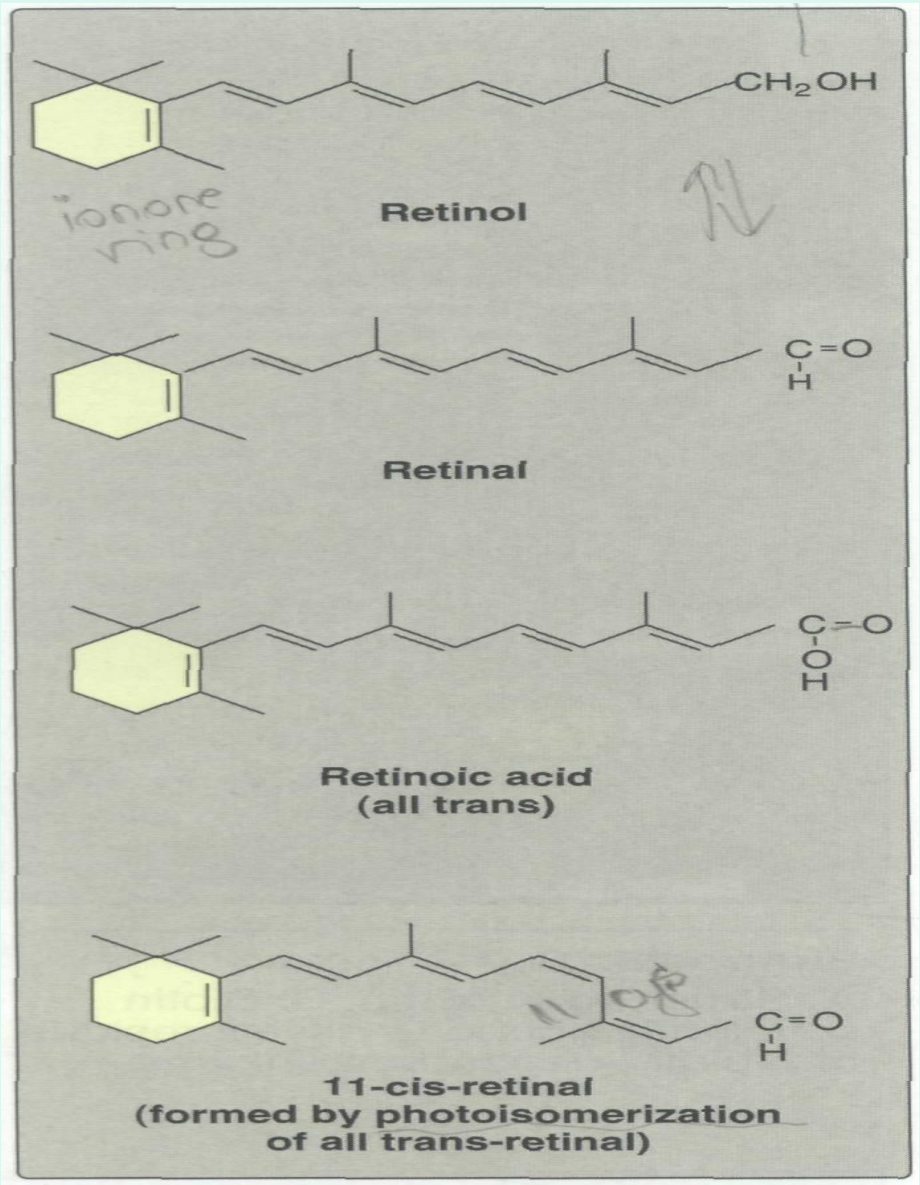


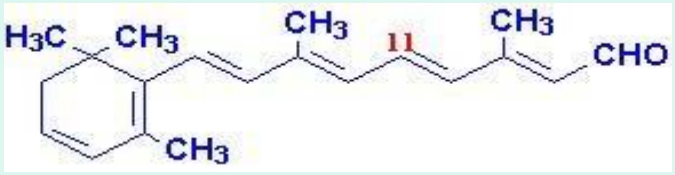
Figure 28.18
Structure of the retinoids.

Vitamin A

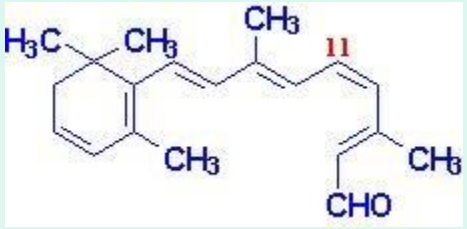
Vitamin A consists of three biologically active molecules,

retinol, retinal (retinaldehyde) and **retinoic acid.**

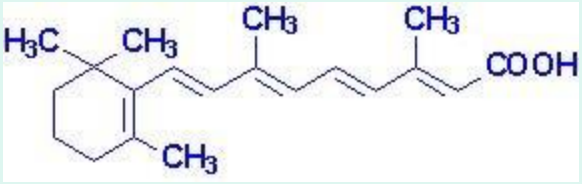
- **All-*trans*-retinal**



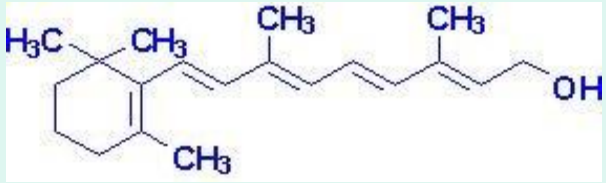
11-*cis*-retinal



Retinoic Acid



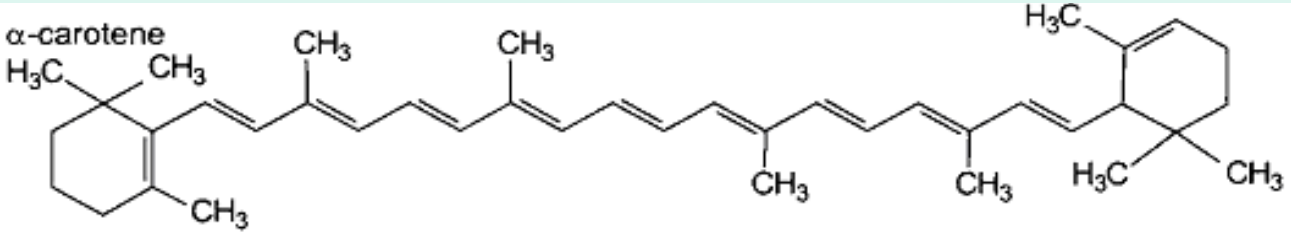
Retinol



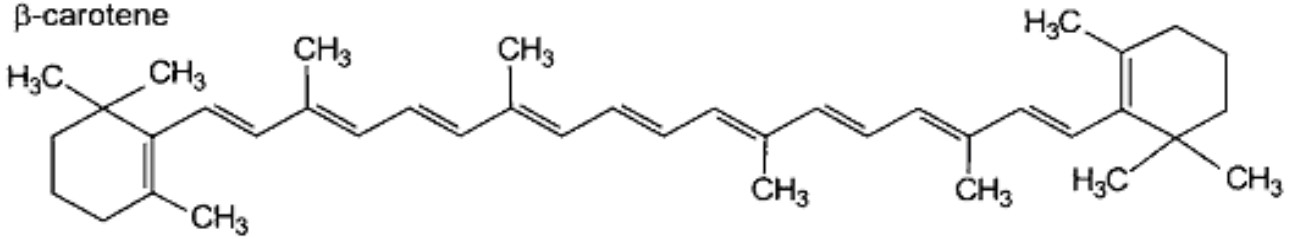
Chemistry of Vitamin A

- The provitamin or precursors of vit. A are carotenoids α, ß, ɣ carotene and cryptoxanthine containing ß -ionone ring.
- All carotenes are formed from two ring (A and B ring) connected together by 18 carbon atoms.
- A ring in all carotenes is ß -ionone ring.
- At the other B ring end there is:
- α-ionone ring in α-carotene.
- ß-ionone ring in ß-carotene.
- ɣ-ionone ring in ɣ-carotene.
- Hydroxy ß-ionone ring in cryptoxanthine.

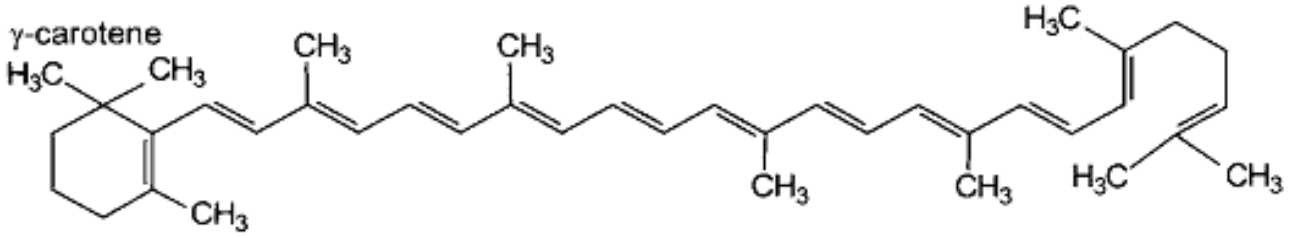
α-carotene



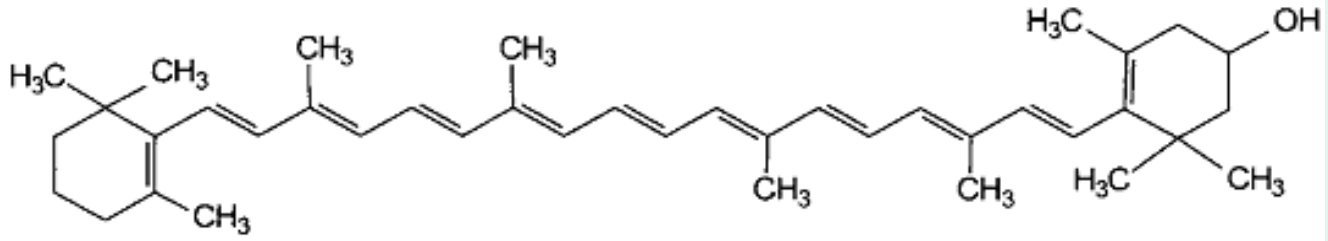
β-carotene



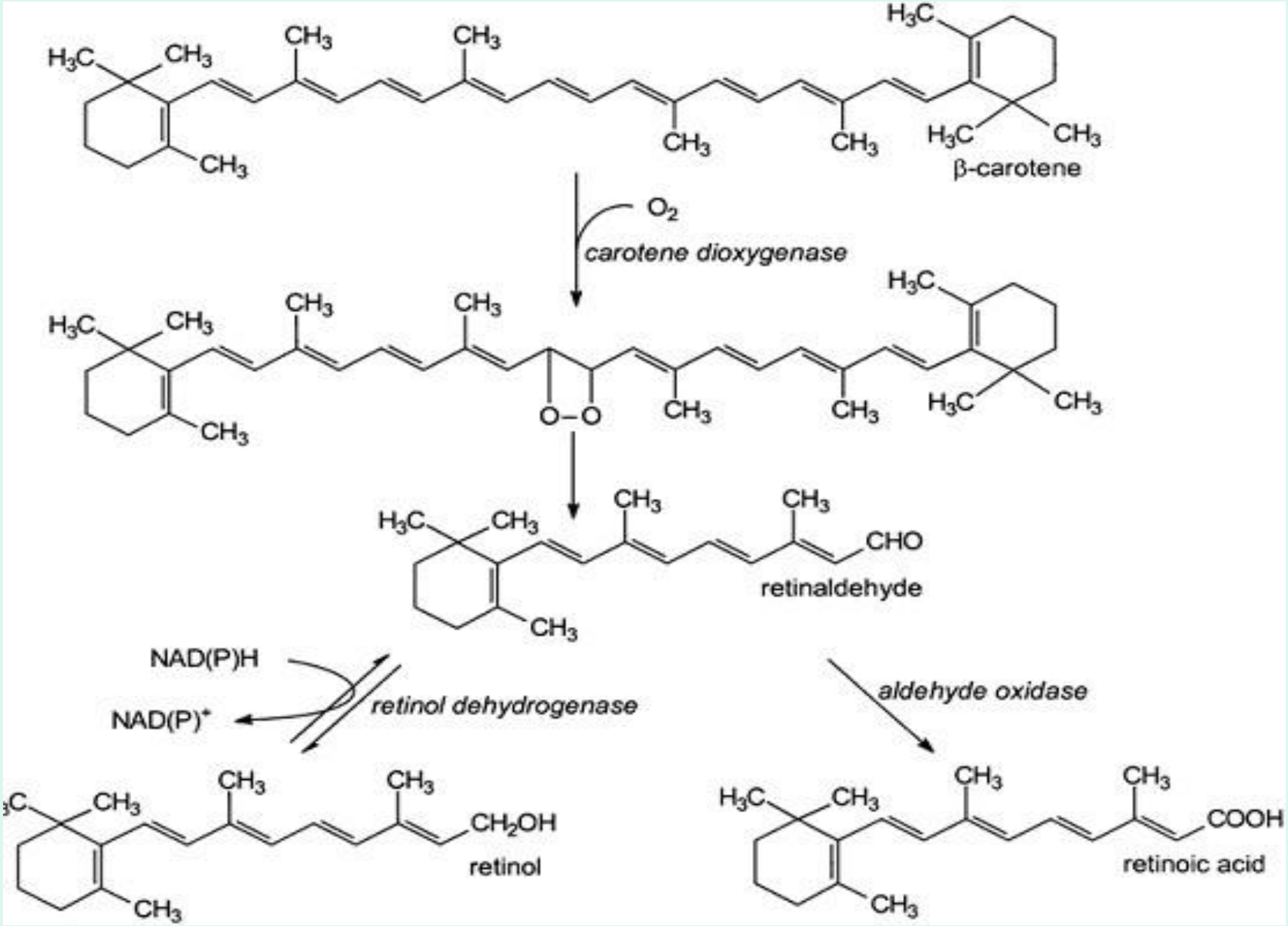
γ-carotene



β-cryptoxanthine (3-hydroxy-β-carotene)



- Carotenes by carotenase give vitamin A aldehyde(retinal) by oxidation of the central double bond.
- Retinal by reduction give vitamin A alcohol(retinol).
- ß-carotene is the most useful type give two molecules of vitamin A1(because it is asymmetrical molecule) while the other give only one molecule of vitamin A1.


β-carotene
O2
carotene dioxygenase
retinaldehyde
NAD(P)H
NAD(P)+
retinol dehydrogenase
aldehyde oxidase
retinol
retinoic acid

Absorption and transport of vitamin A

Transport to the liver:

- **Retinol esters present in the diet are hydrolyzed in the intestinal mucosa, releasing retinol and free fatty acids.**

- **Retinol derived from esters and from the cleavage and reduction of carotenes is reesterified to long-chain fatty acids in the intestinal mucosa and secreted as a component of chylomicrons into the lymphatic system.**
- **Retinol esters contained in chylomicrons are taken up by, and stored in, the liver.**

Release from the liver:

- **Retinol** is released from the liver and transported to extrahepatic tissues by the **plasma retinol-binding protein** (RBP).
- The complex attaches to specific receptors on the surface of the cells of peripheral tissues, permitting retinol to enter.

- Many tissues contain a **cellular retinol-binding protein** that carries retinol to sites in the nucleus where the vitamin acts in a manner analogous to steroid hormones.

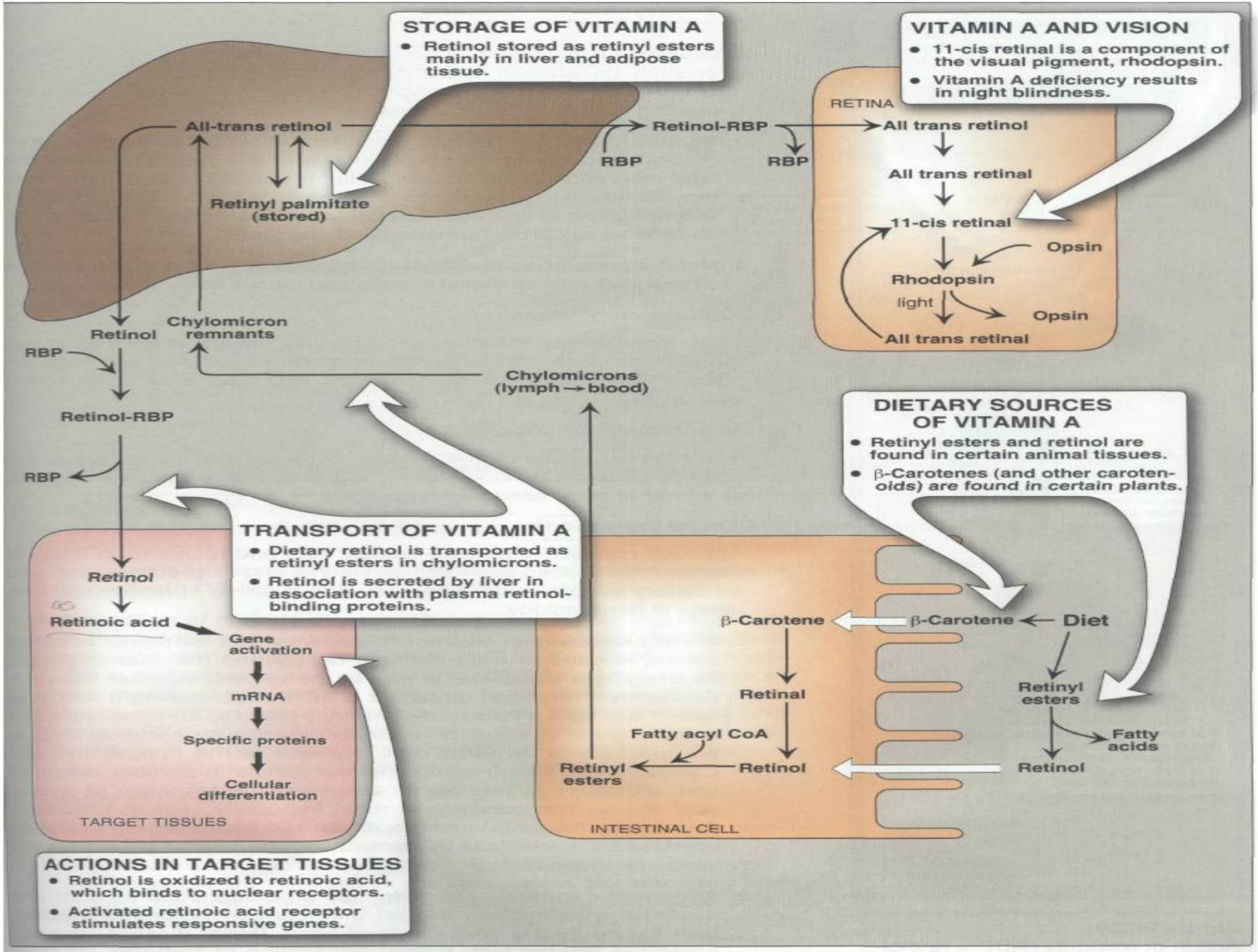


Figure 28.19
Absorption, transport, and storage of vitamin A and its derivatives. RBP = retinol-binding protein.

Mechanism of action of vitamin A

- Retinol is carried in the circulation on a retinol binding protein (RBP).

- The RBP complex attaches itself to specific receptors on the surface of cells of peripheral tissues permitting retinol to enter.

- Inside the cell, retinol is oxidized to retinoic acid. It may also have specific carriers inside some cells, cellular retinol binding protein (CRBP), that carries it to sites in nucleus.

- Retinoic acid binds with high affinity to specific receptor on nucleus. Then the activated receptors stimulate certain genes on the DNA and are transcribed into mRNA and then translated into specific proteins which increase cellular differentiation and regulate keratin genes.

- For example, retinoids control the expression of the keratin gene in most epithelial tissues of the body.
- The specific retinoic acid-receptor proteins are part of the superfamily of transcriptional regulators that includes the steroid and thyroid hormones and 1,25 dihydroxycholecalciferol.

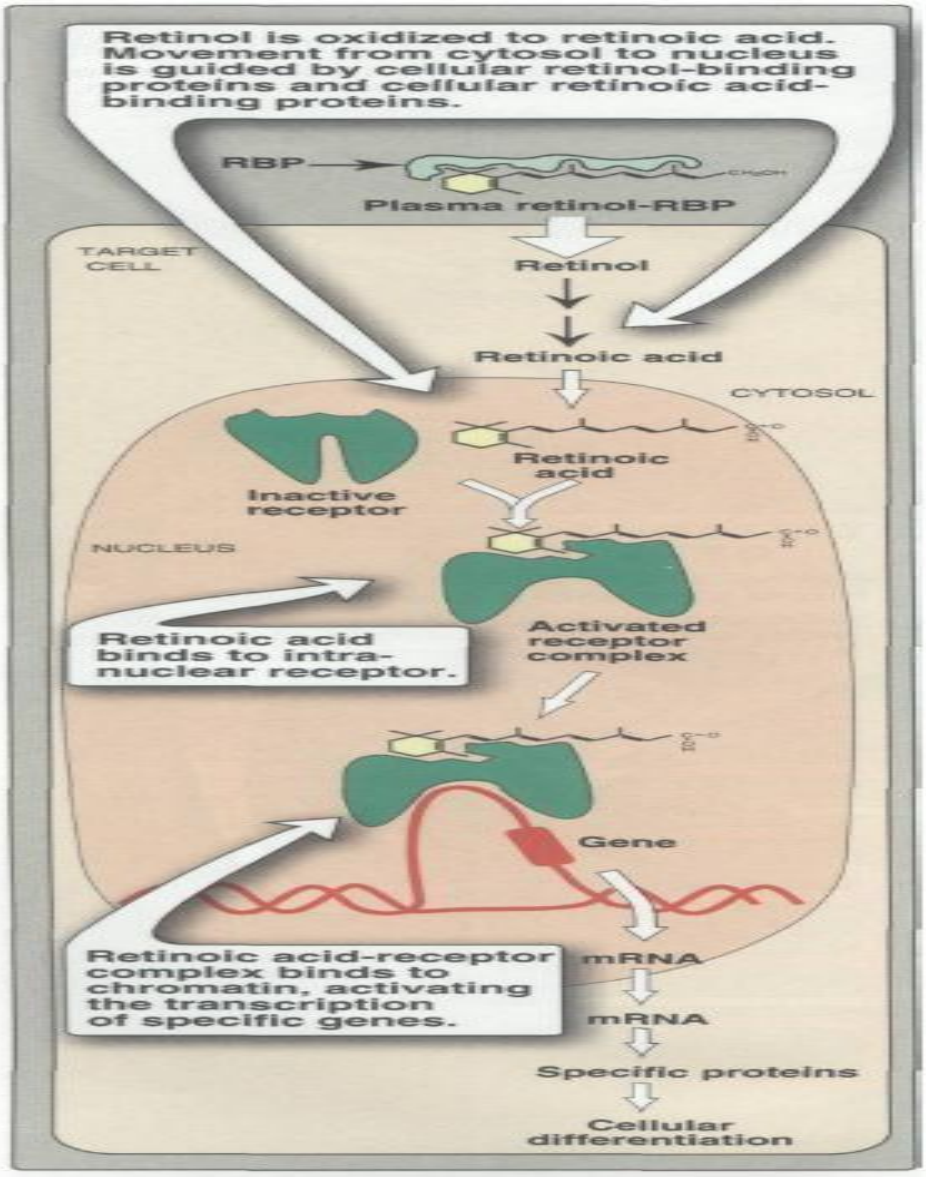


Figure 28.20
Action of retinoids (RBP = retinol-binding protein).

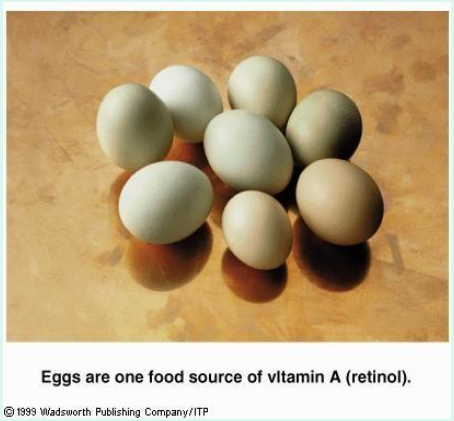
Distribution of vitamin A

- Liver, kidney, cream, butter, and egg yolk are good sources of preformed vitamin A.
- Yellow and dark green vegetables and fruits are good dietary sources of the carotenes, which serve as precursors of vitamin A.

SOURCES OF VITAMIN A

- **Preformed vitamin A (retinyl esters, free vitamin A):**

  Egg yolk, butter, milk, cod liver oil and liver



Eggs are one food source of vitamin A (retinol).

Provitamin A (β carotene)– **Carrot, papaya, mangoes,tomatoes, pumpkin,**

Requirement for vitamin A

The RDA for adults is 1000 retinol equivalents (RE) for males and 800 RE for females.

One RE = 1μg of retinol, 6 μg of β-carotene, or 12 μg of other carotenoids.

RECOMMENDED DAILY ALLOWANCE FOR VITAMIN A

Infants - 400 Retinol Equivalent (RE)

Children - 400 – 700 RE

Adults - Males - 1000 RE

- Females - 800 RE

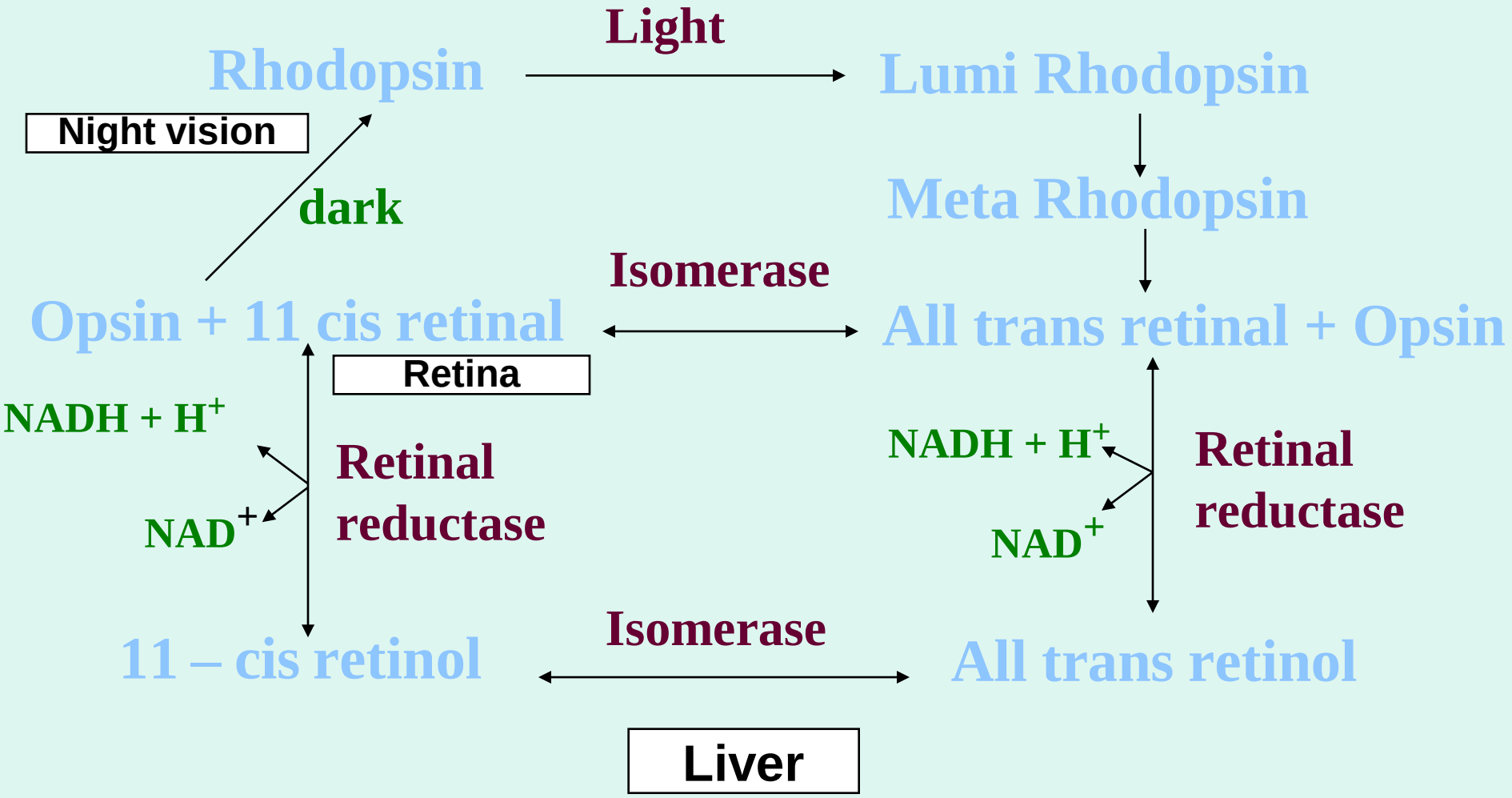
- Pregnancy- 1000 RE

- Lactation - 1200 RE

1 Retinol Equivalent = 1 micro gram of retinol (or) 6 micro gram of β carotene

FUNCTIONS OF VITAMIN A

1. Role in vision (Wald's visual cycle) Rhodopsin **is the visual pigment present in the retina of eye.It is made of opsin and retinal (vitamin A– 11 – cis retinal)**



Explanation of Wald's cycle:

- **Rhodopsin is a photosensitive pigment present in the rod cells and is involved in dim light vision.**
- **When light falls on the rod cells a series of reaction takes place converting the 11 –Cis retinal to Lumi then to meta rhodopsin and finally to All trans retinal.**

Regeneration of 11- cis –retinal:

- **can occur in the retina itself or may go to liver there it is converted to All trans retinol by retinal reductase and then isomerised to 11- cis retinol and carried to retina where it is oxidised to 11 cis retinal.**

- Vitamin A is essential for the differentiation and maintenance of epithelial cells [Retinoic acid] .
- Role in glycoprotein synthesis [Retinoic acid].
- Bone remodeling – Vitamin A is required for sulfation of the muco-polysaccahride in the matrix of bone.

- Essential for normal reproduction [Retinol]
- Retinoic acid is an important regulator of gene expression.
- May act as an antioxidant especially carotenoids, they trap peroxyl and free radicals

Additional Role of Retinol

- Retinol also functions in the synthesis of certain glycoproteins and mucopolysaccharides necessary for mucous production and normal growth regulation.

- This is accomplished by phosphorylation of retinol to **retinyl phosphate** which then functions similarly to dolichol phosphate

Functions of Vit A

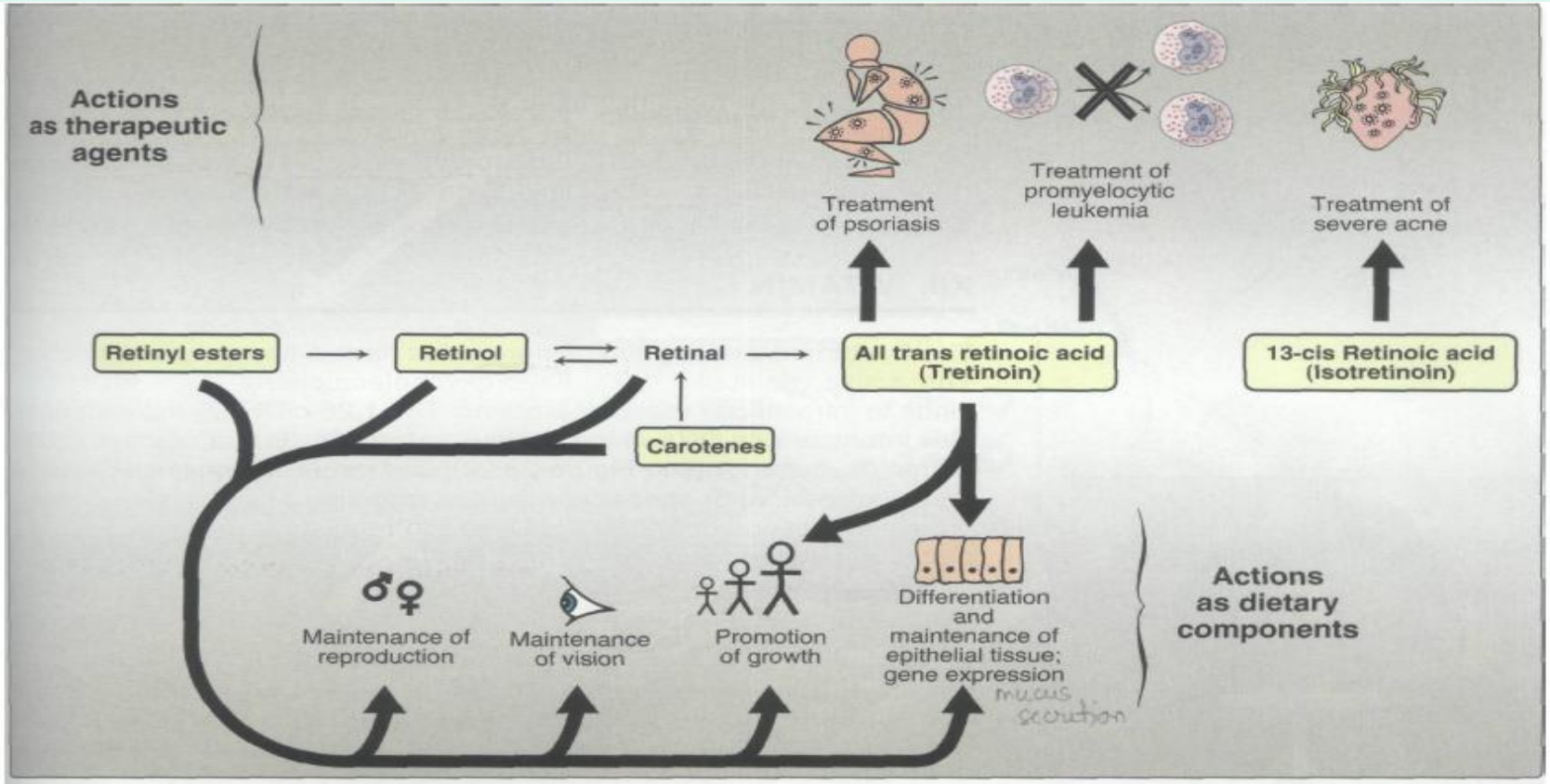


Figure 28.21
Summary of actions of retinoids. Compounds in boxes are available as dietary components or as pharmacologic agents.

Dietary deficiency

- Vitamin A, administered as retinol or retinyl esters, is used to treat patients deficient in the vitamin.
- **Night blindness** is one of the earliest signs of vitamin A deficiency. The visual threshold is increased, making it difficult to see in dim light.
- Prolonged deficiency leads to an irreversible loss in the number of visual cells.

- Severe vitamin A deficiency leads to **xerophthalmia,** a pathologic dryness of the conjunctiva and cornea.
- If untreated, xerophthalmia results in corneal ulceration and, ultimately, in blindness because of the formation of opaque scar tissue.

Clinical Significances of Vitamin A Deficiency

- Vitamin A is stored in the liver and deficiency of the vitamin occurs only after prolonged lack of dietary intake.
- The earliest symptoms of vitamin A deficiency are **night blindness**.
- Additional early symptoms include follicular hyperkeratinosis, increased susceptibility to infection and cancer and anemia equivalent to iron deficient anemia.
- Prolonged lack of vitamin A leads to deterioration of the eye tissue through progressive keratinization of the cornea, a condition known as xerophthalmia.

- The increased risk of cancer in vitamin deficiency is thought to be the result of a depletion in B-carotene.
- Beta-carotene is a very effective antioxidant and is suspected to reduce the risk of cancers known to be initiated by the production of free radicals. Of particular interest is the potential benefit of increased B-carotene intake to reduce the risk of lung cancer in smokers.

Vitamin A Deficiency Is a Major Public Health Problem Worldwide

- Vitamin A deficiency is the most important preventable cause of blindness. The earliest sign of deficiency is a loss of sensitivity to green light, followed by impairment to adapt to dim light, followed by **night blindness.**
- More prolonged deficiency leads to **xerophthalmia:** keratinization of the cornea and blindness.

- Vitamin A also has an important role in differentiation of immune system cells, and even mild deficiency leads to increased susceptibility to infectious diseases.
- Also, the synthesis of retinol binding protein is reduced in response to infection (it is a negative **acute phase protein**), decreasing the circulating concentration of the vitamin, and further impairing immune responses.

Deficiency disease

- Night blindness.
- Xerophthalmia.
- keratinization of skin.

Vitamin A Is Toxic in Excess

- There is only a limited capacity to metabolize vitamin A, and excessive intakes lead to accumulation beyond the capacity of binding proteins, so that unbound vitamin A causes tissue damage.

Symptoms of toxicity affect:

1. The central nervous system (headache, nausea, ataxia, and anorexia, all associated with increased cerebrospinal fluid pressure)
2. The liver (hepatomegaly with histologic changes and hyperlipidemia).
3. Calcium homeostasis (thickening of the long bones, hypercalcemia, and calcification of soft tissues).
4. The skin (excessive dryness, desquamation, and alopecia).

Toxicity of retinoids

- Excessive intake of vitamin A produces a toxic syndrome called hypervitaminosis A.
- Amounts exceeding 7.5 mg/day of retinol should be avoided.
- Early signs of chronic hypervitaminosis A are reflected in the skin, which becomes dry and pruritic, the liver, which becomes enlarged and can become cirrhotic, and in the nervous system, where a rise in intracranial pressure may mimic the symptoms of a brain tumor.
- Pregnant women particularly should not ingest excessive quantities of vitamin A because of its potential for causing congenital malformations in the developing fetus.

References:

1. Lippincott's review of biochemistry, 3rd edition.
1. Biochemistry Stryer 5th edition.
2. Harper,s Biochemistry 28 edition.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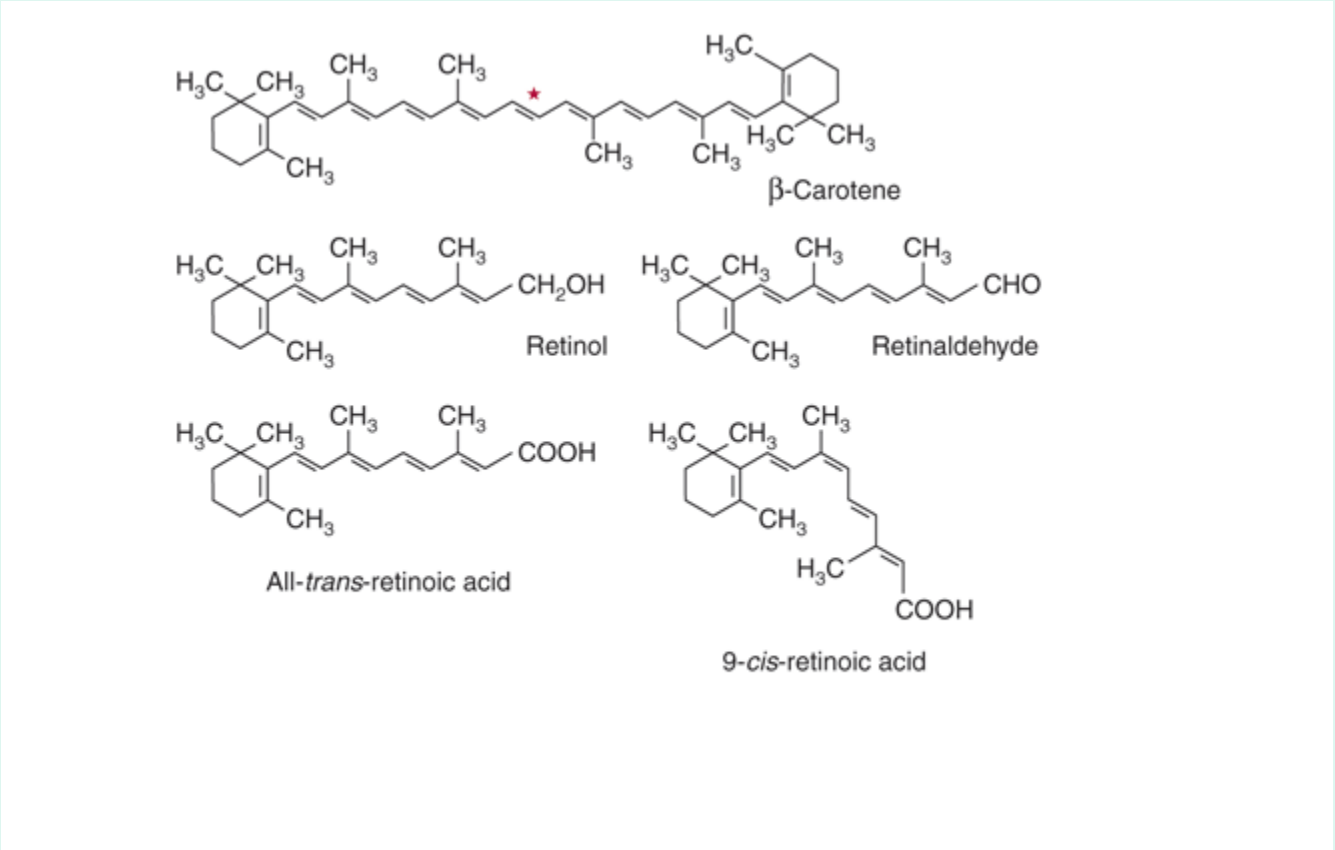
Retinoic Acid Has a Role in the Regulation of Gene Expression and Tissue Differentiation

- A major role of vitamin A is in the control of cell differentiation and turnover. All-*trans*-retinoic acid and 9-*cis*-retinoic acid (Figure 44–1) regulate growth, development, and tissue differentiation; they have different actions in different tissues. Like the thyroid and steroid hormones and vitamin D, retinoic acid binds to nuclear receptors that bind to response elements of DNA and regulate the transcription of specific genes. There are two families of nuclear retinoid receptors: the retinoic acid receptors (RAR) bind all-*trans*-retinoic acid or 9-*cis*-retinoic acid, and the retinoid X receptors (RXR) bind 9-*cis*-retinoic acid. Retinoid X receptors also form dimers with vitamin D, thyroid, and other a nuclear acting hormone receptors. Deficiency of vitamin A impairs vitamin D function because of lack of 9-*cis*-retinoic acid to form receptor dimers, while excessive vitamin A also impairs vitamin D function, because of formation of RXR-homodimers, meaning that there are not enough RXR available to form heterodimers with the vitamin D receptor.

Retinoic Acid Has a Role in the Regulation of Gene Expression and Tissue Differentiation



UNIT – IV
NUCLEIC ACIDS

Nucleic acids are long-chain polymeric molecules, the monomer (the repeating unit) is known as the nucleotides and hence sometimes nucleic acids are referred to as polynucleotides.

Nucleic acids consist of a sugar (pentose), nitrogenous bases (purines and pyrimidines), and phosphoric acid. A nucleic acid molecule is a linear polymer in which nucleotides are linked together by means of phosphodiester 'bridges' or bonds.

These bonds link the 3′ carbon in the pentose of one nucleotide to the 5′ carbon in the pentose of the adjacent nucleotide. Thus the backbone of a nucleic acid consists of alternating phosphates and pentoses. The nitrogenous bases are attached to the sugars of this backbone.

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are two major types of nucleic acids. DNA and RNA are responsible for the inheritance and transmission of specific characteristics from one generation to the other. There are prominently two types of nucleic acids known to us.

Deoxyribonucleic Acid (DNA)

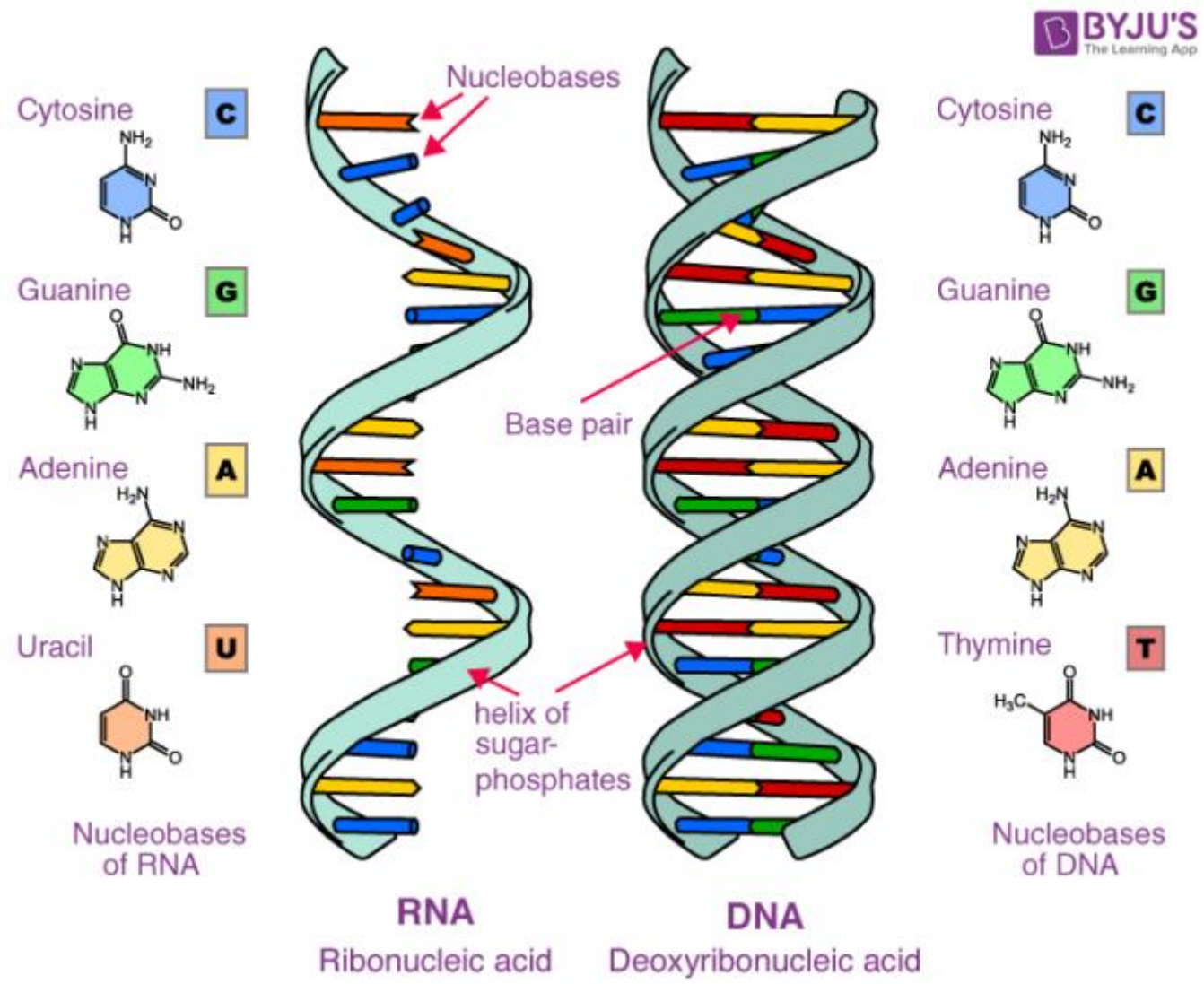
Chemically, DNA is composed of a pentose sugar, phosphoric acid and some cyclic bases containing nitrogen. The sugar moiety present in DNA molecules is β-D-2-deoxyribose. The cyclic bases that have nitrogen in them are adenine (A), guanine (G), cytosine(C) and thymine (T). These bases and their arrangement in the molecules of DNA play an important role in the storage of information from one generation to the next one. DNA has a double-strand helical structure in which the strands are complementary to each other.

Ribonucleic Acid (RNA)

The RNA molecule is also composed of phosphoric acid, a pentose sugar and some cyclic bases containing nitrogen. RNA has β-D-ribose in it as the sugar moiety. The heterocyclic bases present in RNA are adenine (A), guanine (G), cytosine(C) and uracil (U). In RNA the fourth base is different from that of DNA. The RNA generally consists of a single strand which sometimes folds back; that results in a double helix structure. There are three types of RNA molecules, each having a specific function:

1. **messenger RNA (m-RNA)**
2. **ribosomal RNA (r-RNA)**

3. **transfer RNA (t-RNA)**



The Functions of Nucleic Acids

1. Nucleic acids are responsible for the transmission of inherent characters from parent to offspring.
2. They are responsible for the synthesis of protein in our body
3. DNA fingerprinting is a method used by forensic experts to determine paternity. It is also used for the identification of criminals. It has also played a major role in studies regarding biological evolution and genetics.

The Differences between DNA and RNA

DNA	RNA
DNA is deoxyribonucleic acid.	RNA is ribonucleic acid.
DNA is located in the mitochondria which are in the nucleus of the cell.	RNA is located in the cytoplasm, ribosome, and nucleus.
DNA is also known to be a double-stranded molecule.	The function of RNA is to transmit the genetic code needed to create protein.
DNA cans self replicate.	RNA is known to be a single-stranded molecule.
The sharing and transmission of genetic information is the primary function of DNA.	RNA cannot self replicate; it needs to be synthesized from DNA.

Nucleotides

A nucleotide is an organic molecule with a basic composition of a nitrogenous base, pentose sugar and phosphate.

DNA and RNA are polynucleotides, which contain a chain of nucleotides monomers with different nitrogenous bases.

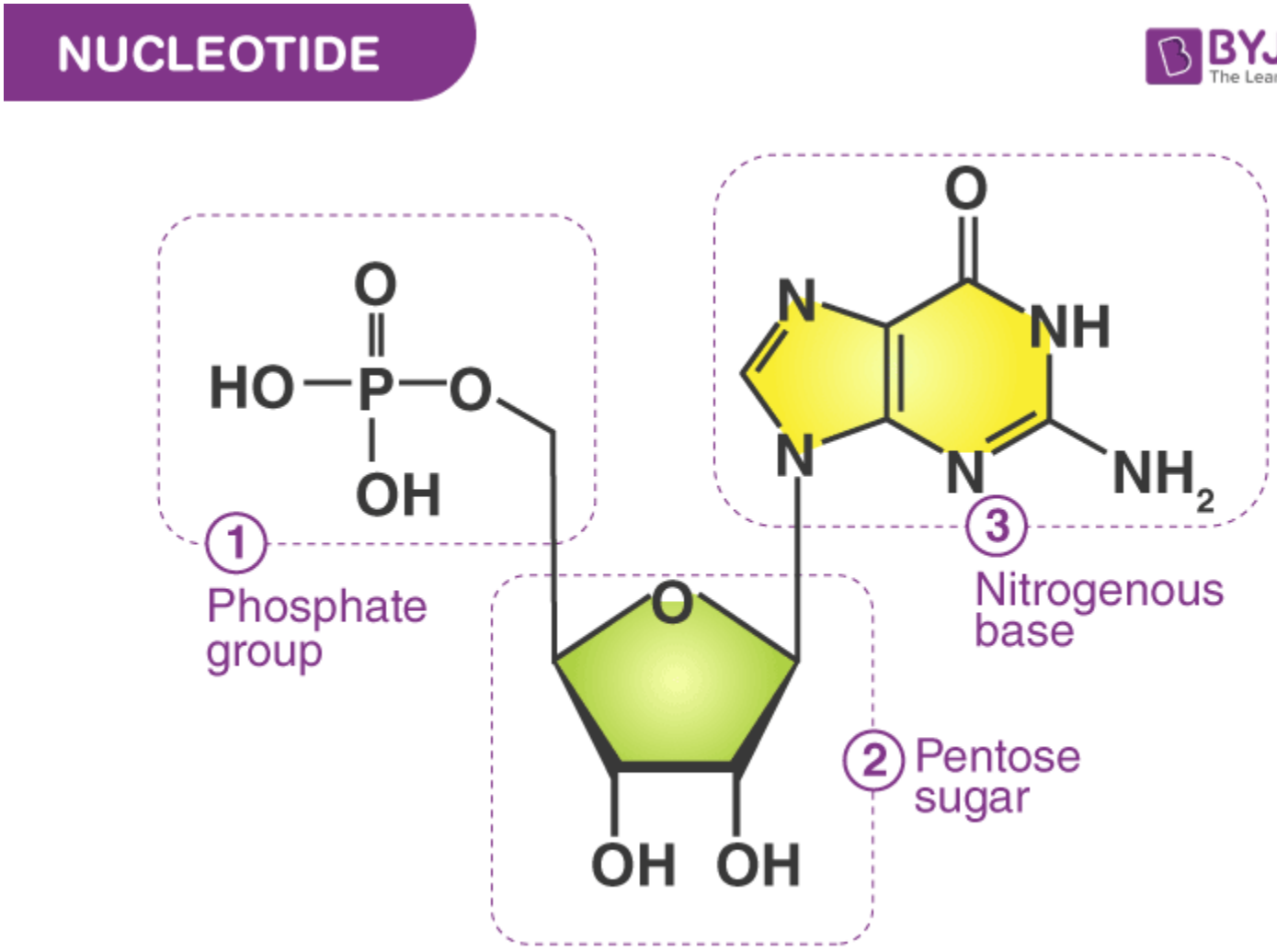
Nucleotides are essential for carrying out metabolic and physiological activities.

ATP (Adenosine triphosphate) acts as the energy currency of cells. Nucleotides form various coenzymes and cofactors, such as NAD, NADP, FAD, coenzyme A, etc. and are essential for many metabolic processes.

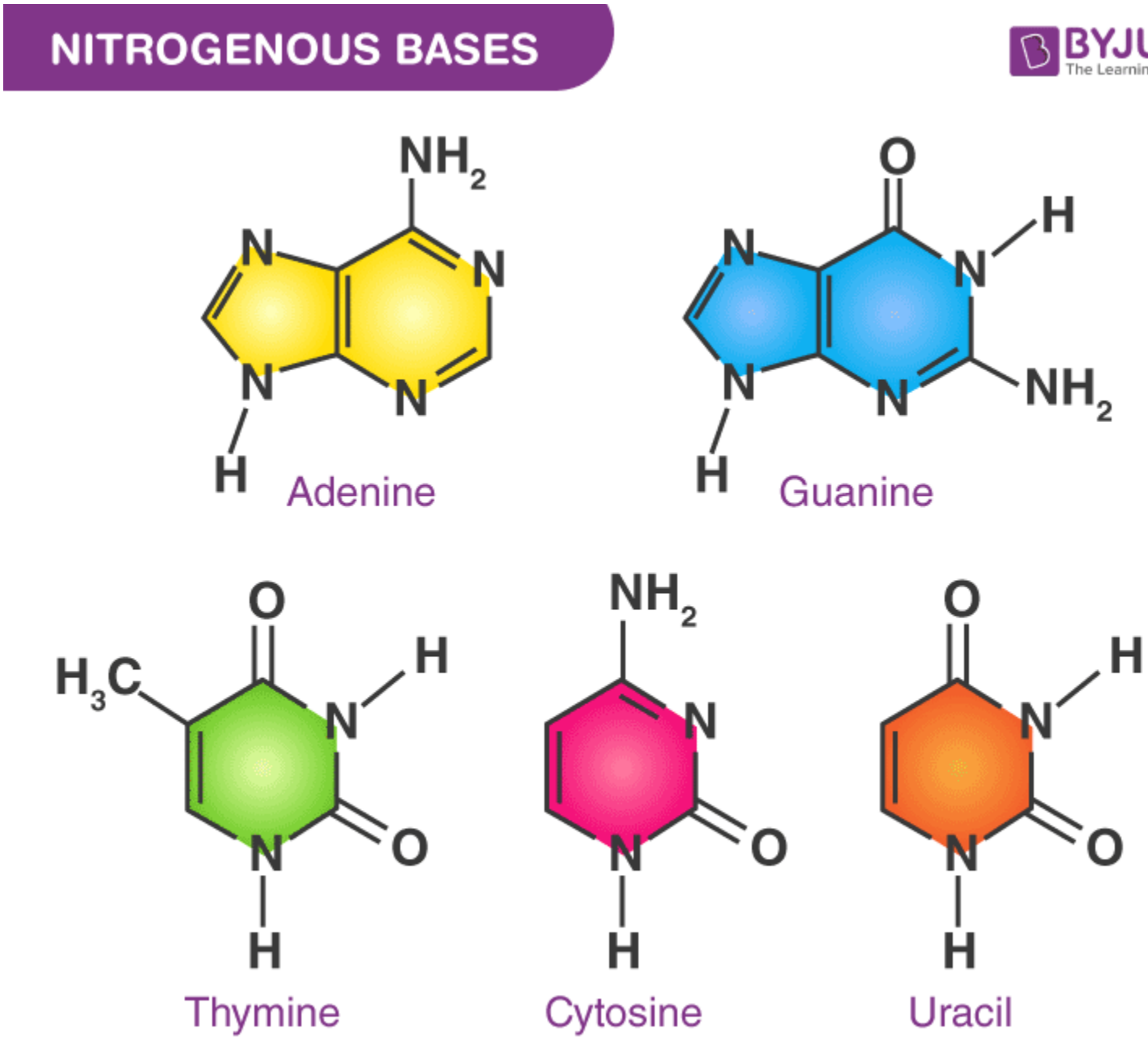
Nucleotide Structure

A nucleotide consists of three units, which are covalently linked. They are:

1. Nitrogenous bases – Purine and Pyrimidine
2. Pentose Sugar – Ribose and Deoxyribose
3. Phosphate – monophosphate, diphosphate, triphosphate



1. Nitrogenous Base: They contain purine or pyrimidine base. DNA contains adenine (A), guanine (G), thymine (T) and cytosine (C), whereas RNA contains adenine, guanine, uracil (U) and cytosine.



2. Sugar: A nucleotide contains a pentose sugar. DNA (Deoxyribonucleic acid) contains deoxyribose sugar and RNA (Ribonucleic acid) contains a ribose sugar.

A Nitrogenous base attached with the sugar is called **"Nucleoside".**

3. Phosphate: Phosphate is attached to the sugar of nucleoside by an ester bond with the 5thC hydroxyl group. Nucleotides at least contain one phosphate group.

Phosphate of one nucleotide attaches to the 3rd C-OH group of the sugar of the 2nd nucleotide, thereby forming 5' → 3' linkage.

In DNA (double helix) there are two antiparallel strands of polynucleotides that are linked together by hydrogen bonds between nitrogenous bases. Purine pairs with pyrimidine base, A pairs with T and G pairs with C by two and three hydrogen bonds respectively.

In RNA instead of thymine (T), A pairs with U.

Phosphate group interlinks the sugar molecules of two nucleotides forming a chain. DNA and RNA are polynucleotides. Sugar phosphate chain forms the backbone of a polynucleotide chain.

When the phosphate group attaches to the hydroxyl group of the same sugar, it forms cyclic nucleotide; they are present as a single monomer, e.g. cAMP, cGMP used in intracellular signal transduction processes.

How do nucleotides and nucleosides differ?

Nucleoside = Nitrogenous base + Sugar

Nucleosides are named as Adenosine, Guanosine, Thymidine, Cytidine, Uridine

Nucleotide = Nucleoside + Phosphate

Nucleotides are named as Adenylic acid, Guanylic acid, Thymidylic acid, Cytidylic acid and Uridylic acid.

Nucleotides are also named as nucleoside mono, di or triphosphate, based on the number of phosphate groups attached to it, e.g. Adenosine monophosphate (AMP), Adenosine diphosphate (ADP) or Adenosine triphosphate (ATP).
DNA and RNA only contain nucleotides.

Nucleotide Function

- Nucleotides are the building block of DNA and RNA. They contain genetic information
- Nucleotides act as coenzymes, which are required to catalyse many biochemical reactions by enzymes
- Energy is stored in our body as ATP. When there is a need for the energy they get converted to ADP or AMP. ATP also acts as a coenzyme
- NAD, NADP has an essential role to play in many redox reactions, they act as an electron carrier
- cAMP helps in transporting chemical signals and metabolic regulation