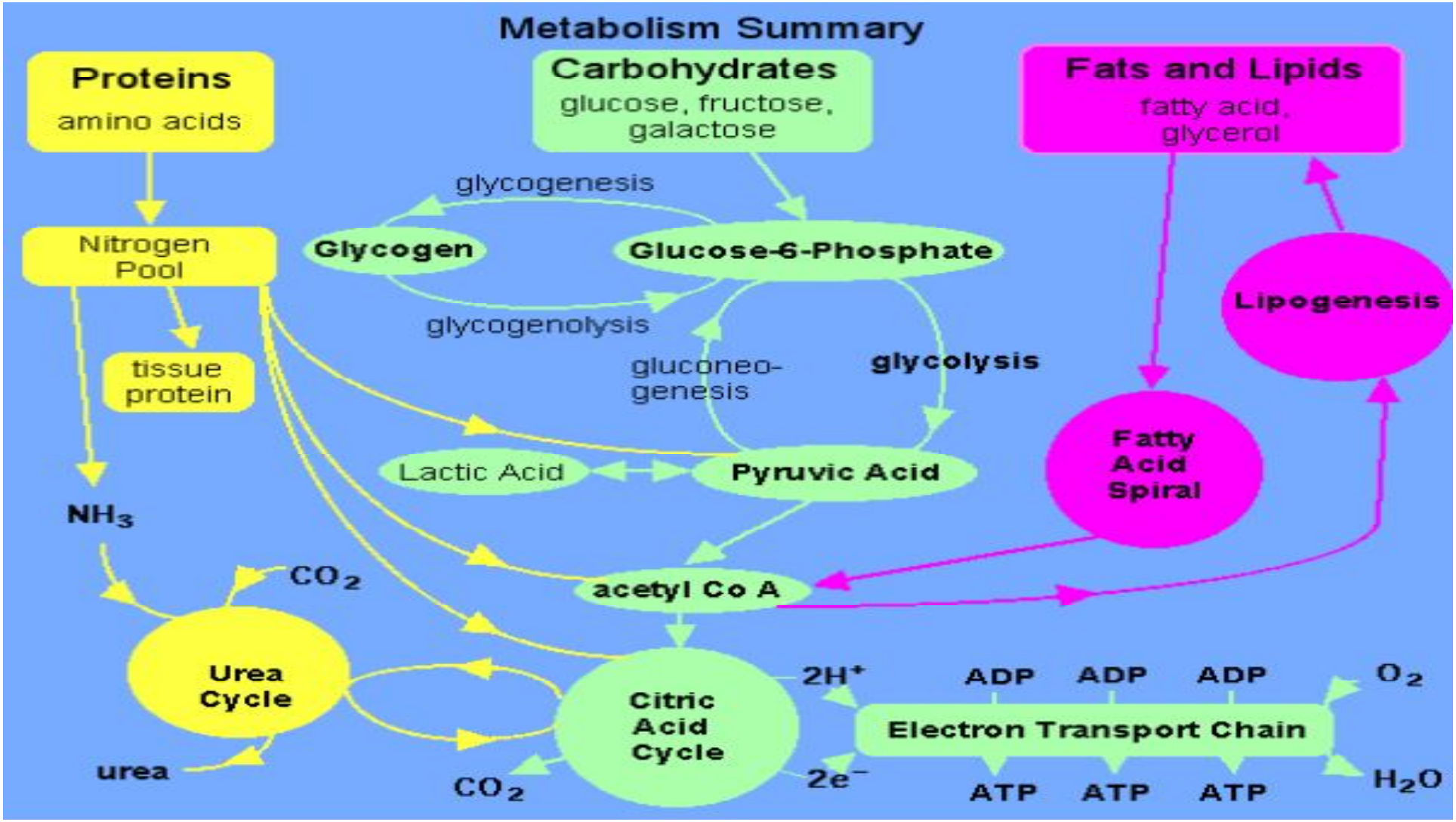
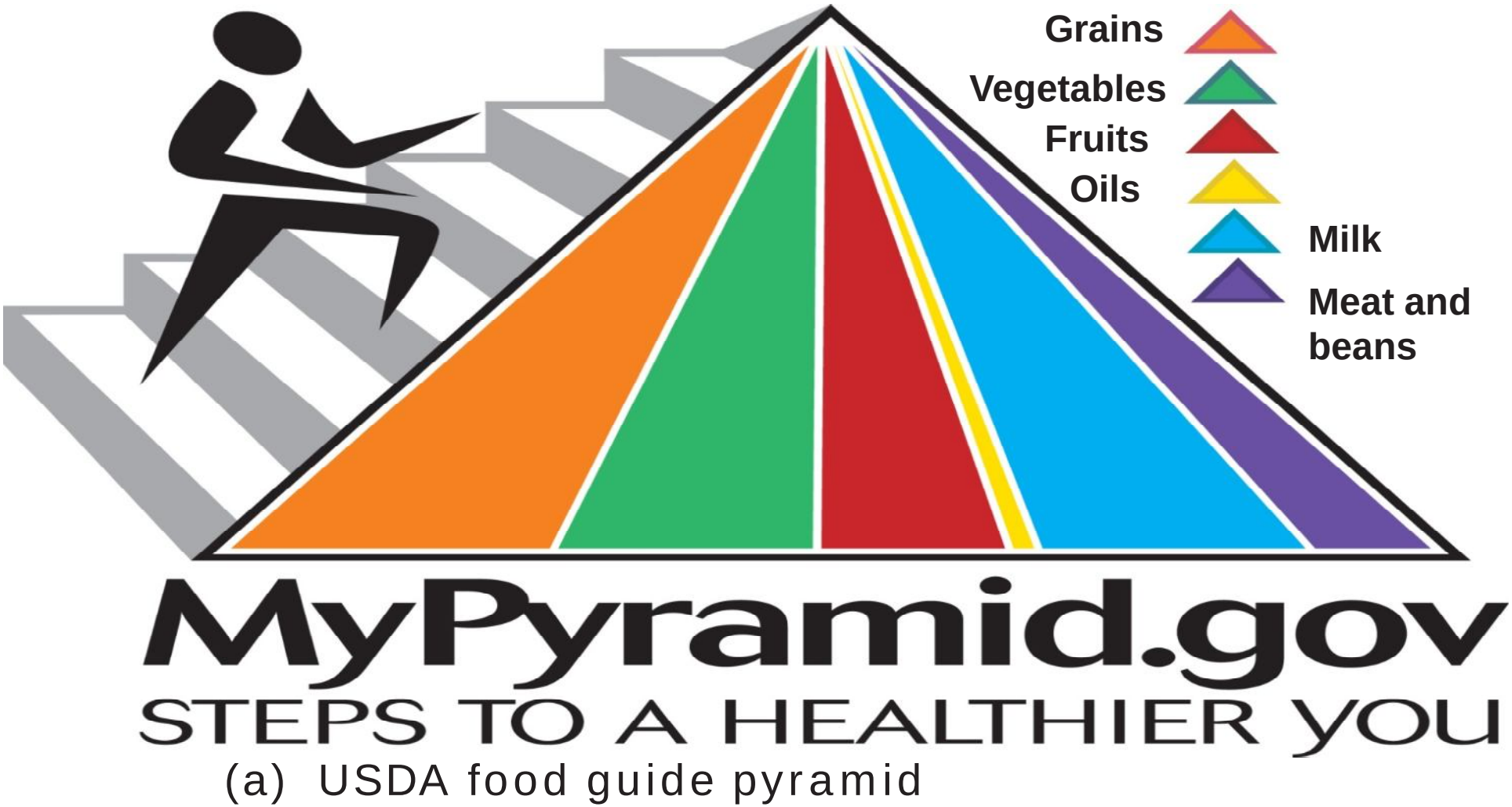
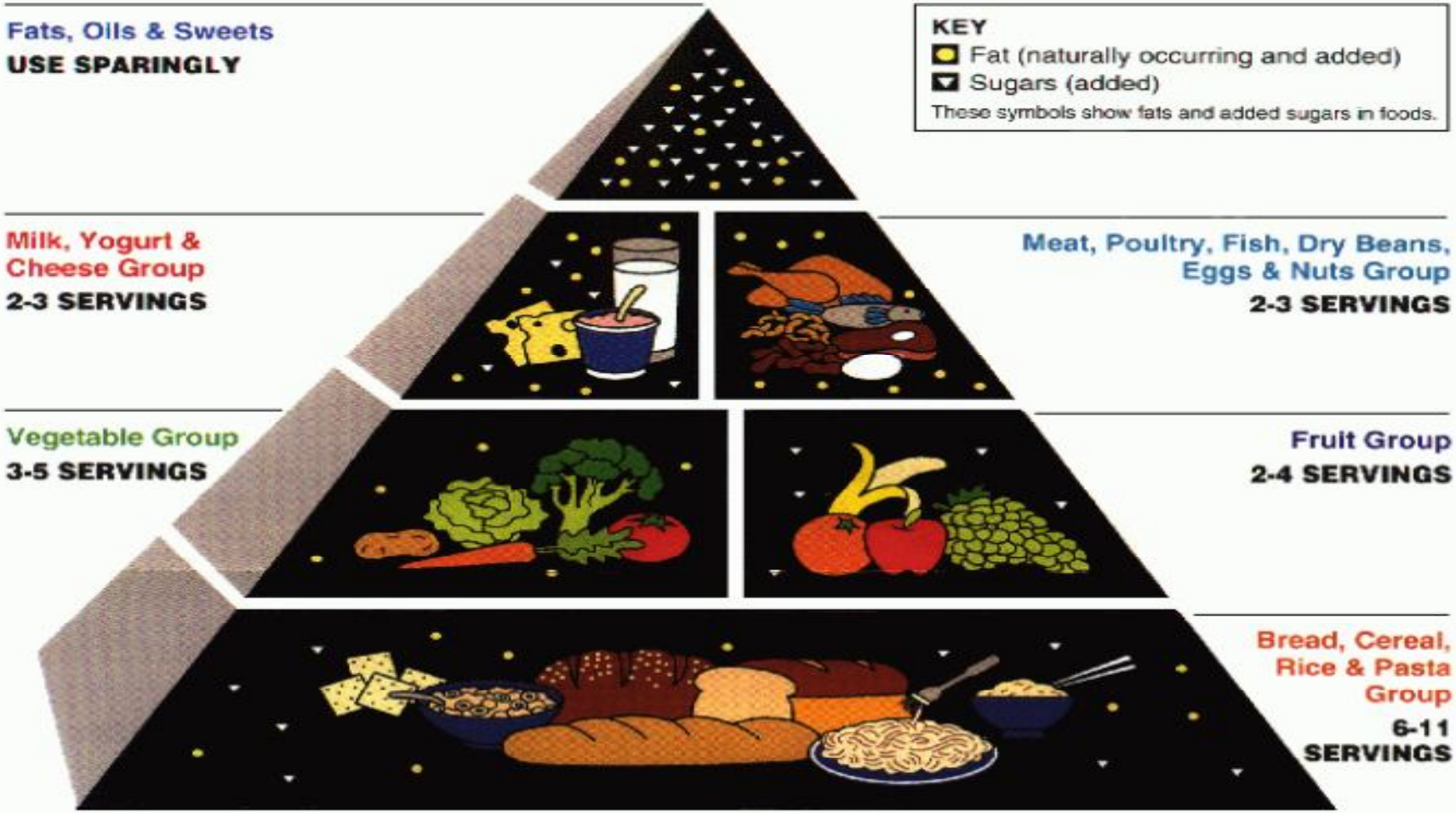
NUTRITION METABOLISM


Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose, fructose, galactose
Fats and Lipids
fatty acid, glycerol
glycogenesis
Nitrogen Pool
Glycogen
Glucose-6-Phosphate
Lipogenesis
glycogenolysis
tissue protein
gluconeo-genesis
glycolysis
Fatty Acid Spiral
Lactic Acid
Pyruvic Acid
NH3
CO2
acetyl Co A
Urea Cycle
Citric Acid Cycle
2H+
ADP ADP ADP
O2
Electron Transport Chain
urea
CO2
2e−
ATP ATP ATP
H2O



(a) USDA food guide pyramid

Figure 24.1a


Fats, Oils & Sweets
USE SPARINGLY
KEY
Fat (naturally occurring and added)
Sugars (added)
These symbols show fats and added sugars in foods.
Milk, Yogurt & Cheese Group
2-3 SERVINGS
Meat, Poultry, Fish, Dry Beans, Eggs & Nuts Group
2-3 SERVINGS
Vegetable Group
3-5 SERVINGS
Fruit Group
2-4 SERVINGS
Bread, Cereal, Rice & Pasta Group
6-11 SERVINGS

Digestion

- Carbohydrate digestion starts in the mouth
- Protein digestion starts in the stomach
- Nucleic acids & fats start in the small intestine
- Everything completely digested and absorbed by the end of the small intestine

Metabolism sites

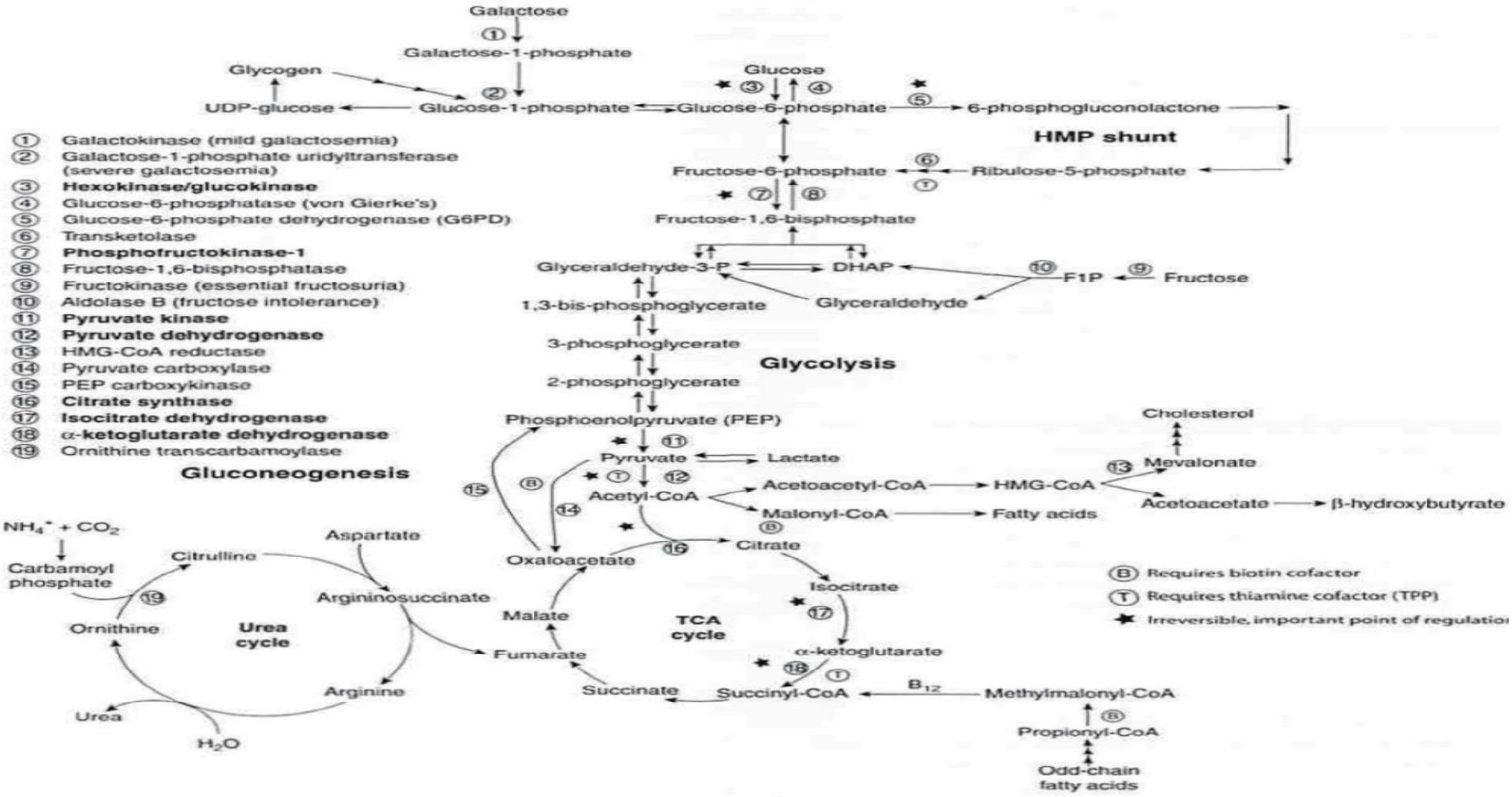
Mitochondria	Fatty acid oxidation (β-oxidation), acetyl-CoA production, TCA cycle, oxidative phosphorylation.	
Cytoplasm	Glycolysis, fatty acid synthesis, HMP shunt, protein synthesis (RER), steroid synthesis (SER).	
Both	Heme synthesis, Urea cycle, Gluconeogenesis.	HUGs take **two.**

Enzyme terminology

An enzyme's name often describes its function. For example, glucokinase is an enzyme that catalyzes the phosphorylation of glucose using a molecule of ATP. The following are commonly used enzyme descriptors:

1. Kinase—uses ATP to add high-energy phosphate group onto substrate (e.g., phosphofructokinase)
2. Phosphorylase—adds inorganic phosphate onto substrate without using ATP (e.g., glycogen phosphorylase)
3. Phosphatase—removes phosphate group from substrate (e.g., fructose-1,6-bisphosphatase)
4. Dehydrogenase—oxidizes substrate (e.g., pyruvate dehydrogenase)
5. Carboxylase—adds 1 carbon with the help of biotin (e.g., pyruvate carboxylase)

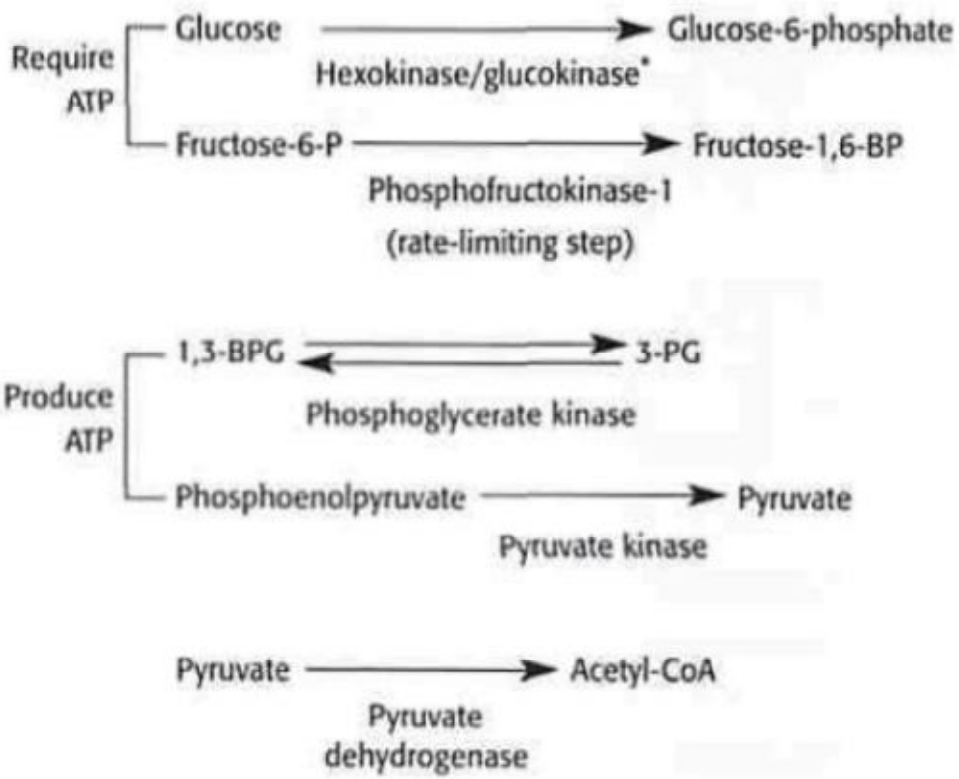
Summary of pathways



Glycolysis
Regulation,
key enzymes

Net glycolysis (cytoplasm):

$$\text{Glucose} + 2\ P_i + 2\ ADP + 2\ NAD^+ \rightarrow 2\ \text{pyruvate} + 2\ ATP + 2\ NADH + 2H^+ + 2H_2O$$



Glucose-6-P ⊖.

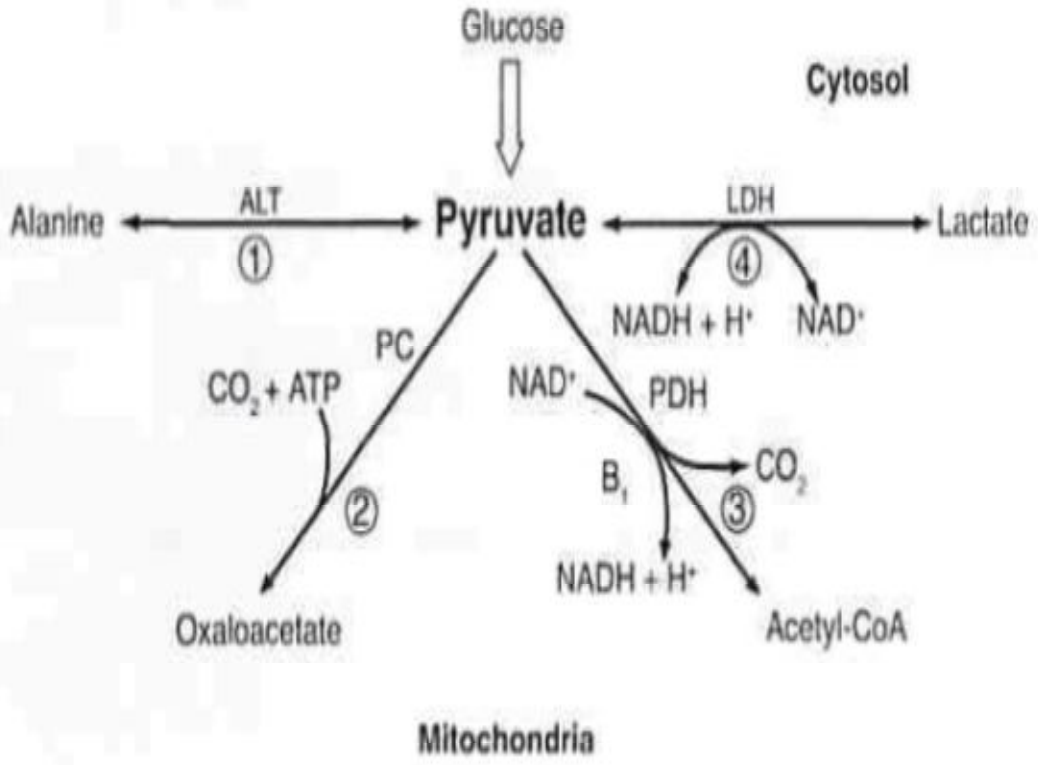
ATP ⊖, AMP ⊕, citrate ⊖, fructose-2,6-BP ⊕.

ATP ⊖, alanine ⊖, fructose-1,6-BP ⊕.

ATP ⊖, NADH ⊖, acetyl-CoA ⊖.

* Glucokinase in liver; hexokinase in all other tissues.

Pyruvate metabolism



Functions of different pyruvate metabolic pathways:

1. Alanine carries amino groups to the liver from muscle
2. Oxaloacetate can replenish TCA cycle or be used in gluconeogenesis
3. Transition from glycolysis to the TCA cycle
4. End of anaerobic glycolysis (major pathway in RBCs, leukocytes, kidney medulla, lens, testes, and cornea)

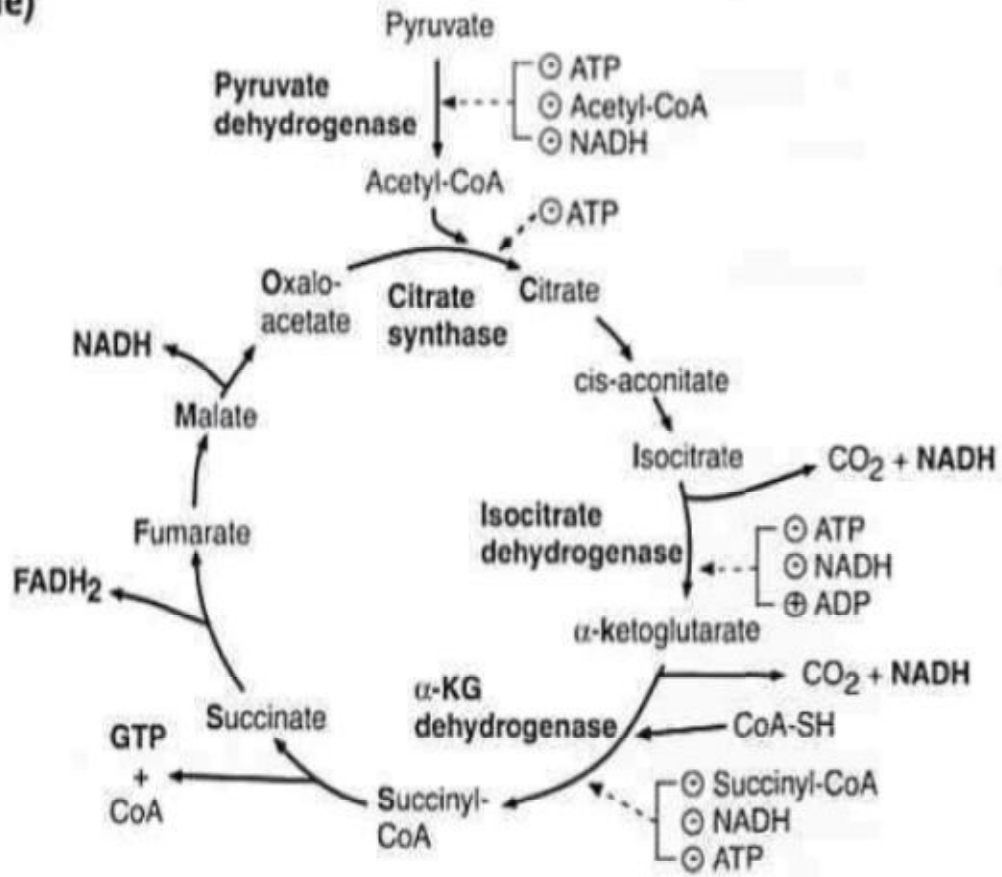
- The **citric acid cycle** — also known as the **tricarboxylic acid cycle** (**TCA cycle**), the **Krebs cycle**, or more rarely, the **Szent-Györgyi-Krebs cycle**,— is a series of **enzyme-catalysed chemical reactions**,
- central importance in all living cells that use oxygen as part of cellular respiration.
- In eukaryotic cells, the citric acid cycle occurs in the matrix of the **mitochondrion.**

- In aerobic organisms, the citric acid cycle is **part of a metabolic pathway involved in the chemical conversion of carbohydrates, fats and proteins into carbon dioxide and water to generate a form of usable energy**.

- Other relevant reactions in the pathway include those in glycolysis and pyruvate oxidation before the citric acid cycle, and oxidative phosphorylation after it.
- In addition, it provides precursors for many compounds including some amino acids and is therefore functional even in cells performing fermentation.

TCA cycle (Krebs cycle)

Pyruvate → acetyl-CoA produces 1 NADH, 1 CO_2.



* Enzymes in boldface are irreversible.

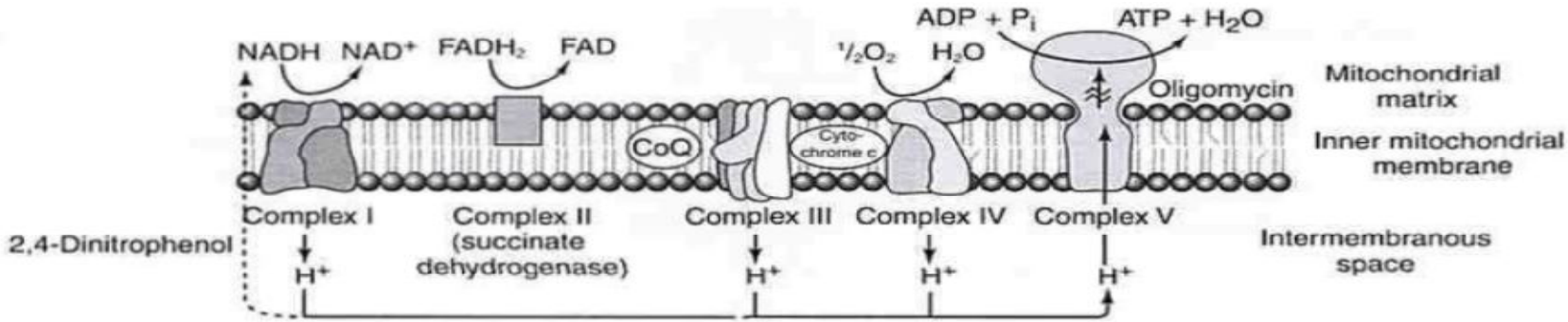
The TCA cycle produces 3 NADH, 1 $FADH_2$, 2 CO_2, 1 GTP per acetyl-CoA = 12 ATP/acetyl-CoA (2× everything per glucose). TCA cycle reactions occur in the mitochondria.

α-ketoglutarate dehydrogenase complex requires the same cofactors as the pyruvate dehydrogenase complex (B_1, B_2, B_3, B_5, lipoic acid).

Citrate Is Krebs' Starting Substrate For Making Oxaloacetate.

Electron transport chain and oxidative phosphorylation

NADH electrons from glycolysis and the TCA cycle enter mitochondria via the malate-aspartate or glycerol-3-phosphate shuttle. $FADH_2$ electrons are transferred to complex II (at a lower energy level than NADH). The passage of electrons results in the formation of a proton gradient that, coupled to oxidative phosphorylation, drives the production of ATP.

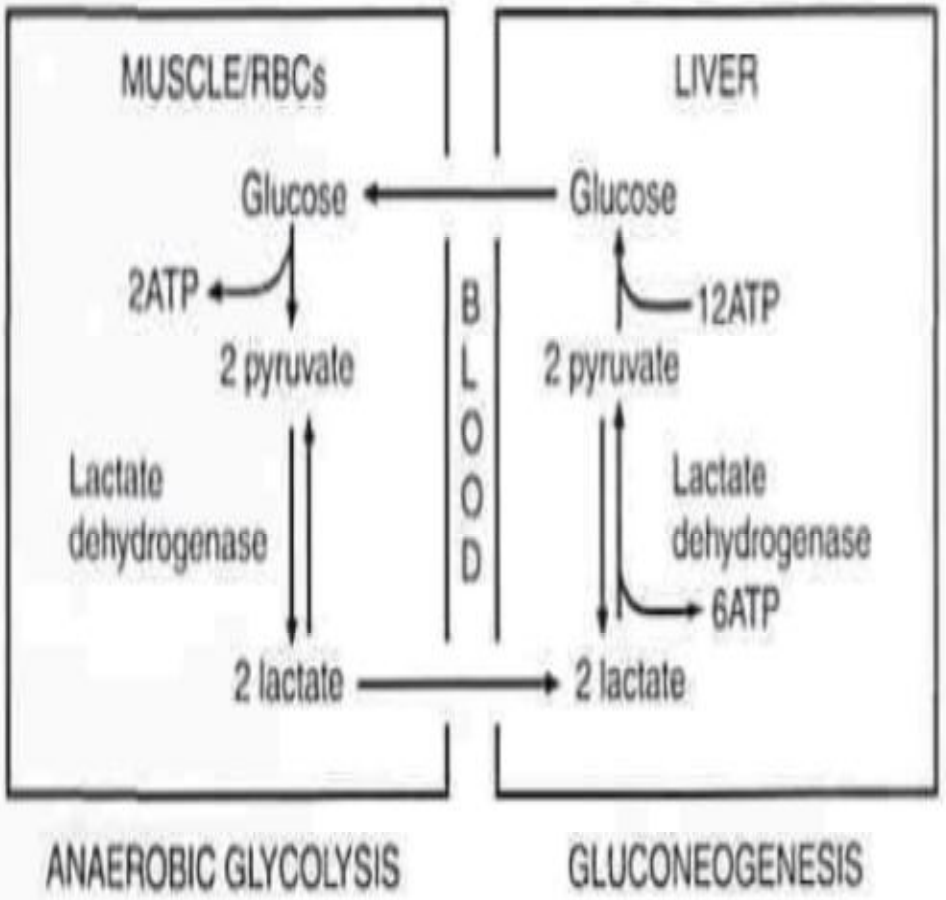


ATP produced via ATP synthase: 1 NADH → 3 ATP; 1 $FADH_2$ → 2 ATP.

Oxidative phosphorylation poisons

Electron transport inhibitors	Directly inhibit electron transport, causing a ↓ proton gradient and block of ATP synthesis.	Rotenone, CN^-, antimycin A, CO.
ATPase inhibitors	Directly inhibit mitochondrial ATPase, causing an ↑ proton gradient. No ATP is produced because electron transport stops.	Oligomycin.
Uncoupling agents	↑ permeability of membrane, causing a ↓ proton gradient and ↑ O_2 consumption. ATP synthesis stops, but electron transport continues. Produces heat.	2,4-DNP, aspirin (fevers often occur after aspirin overdose), thermogenin in brown fat.

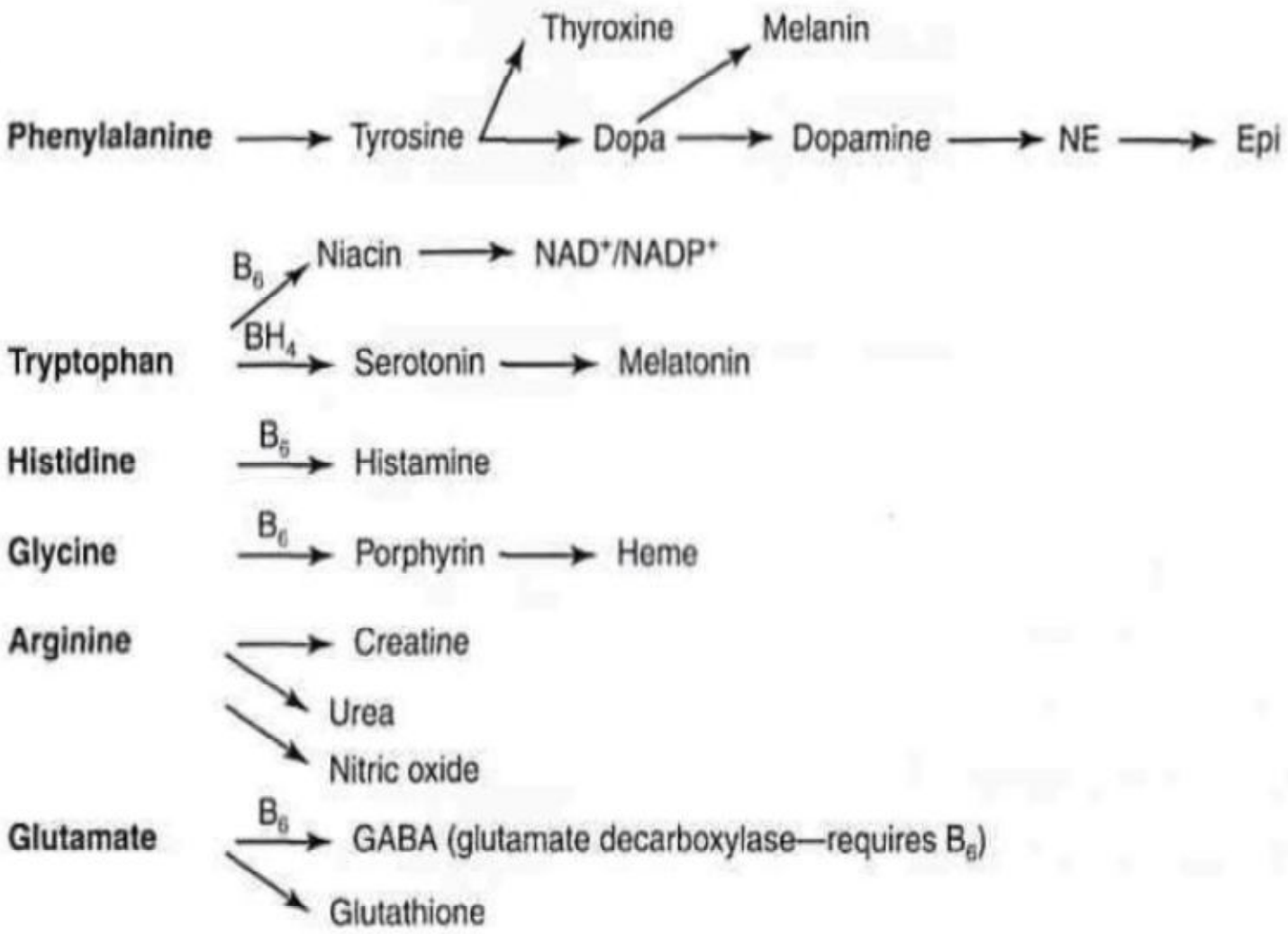
Cori cycle



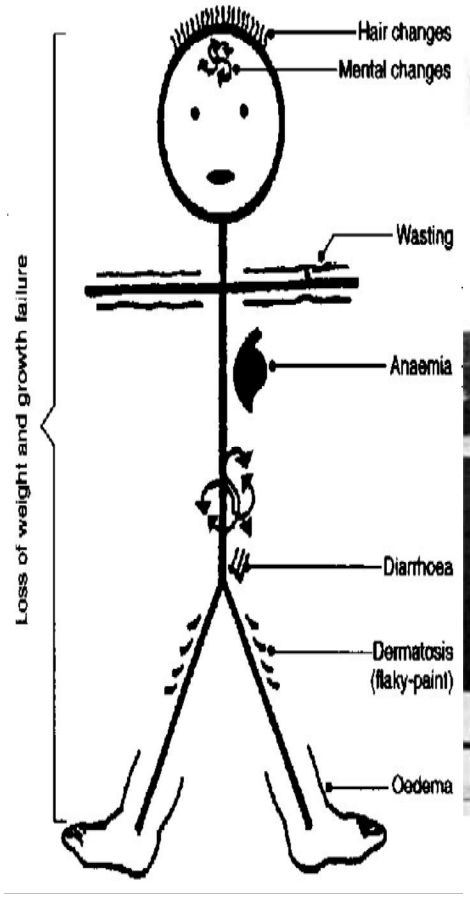
The Cori cycle allows lactate generated during anaerobic metabolism to undergo hepatic gluconeogenesis and become a source of glucose for muscle/RBCs. This come at the cost of a net loss of 4 ATP/cycle.

Shifts metabolic burden to the liver.

Amino acid derivatives



Kwashiorkor vs. marasmus



Kwashiorkor—protein malnutrition resulting in skin lesions, edema, liver malfunction (fatty change due to ↓ apolipoprotein synthesis). Clinical picture is small child with swollen belly.

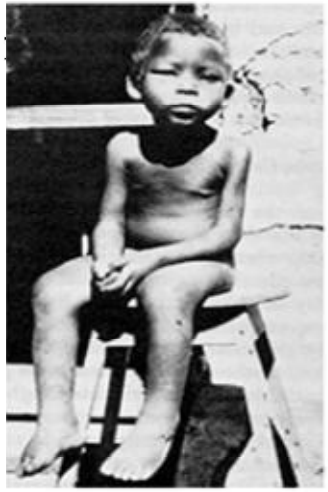
Marasmus—energy malnutrition resulting in tissue and muscle wasting, loss of subcutaneous fat, and variable edema.

Kwashiorkor results from a protein-deficient MEAL:

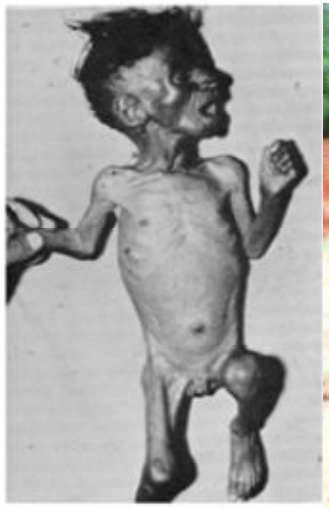
- Malnutrition
- Edema
- Anemia
- Liver (fatty)

Marasmus results in

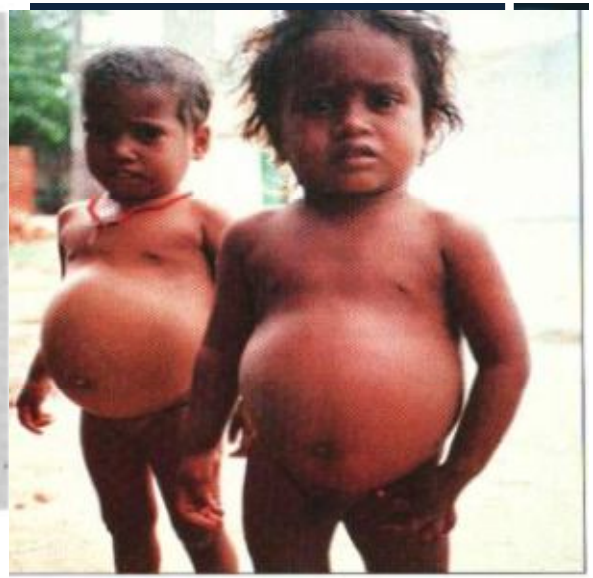
- Muscle wasting.



kwashiorkor



marasmus

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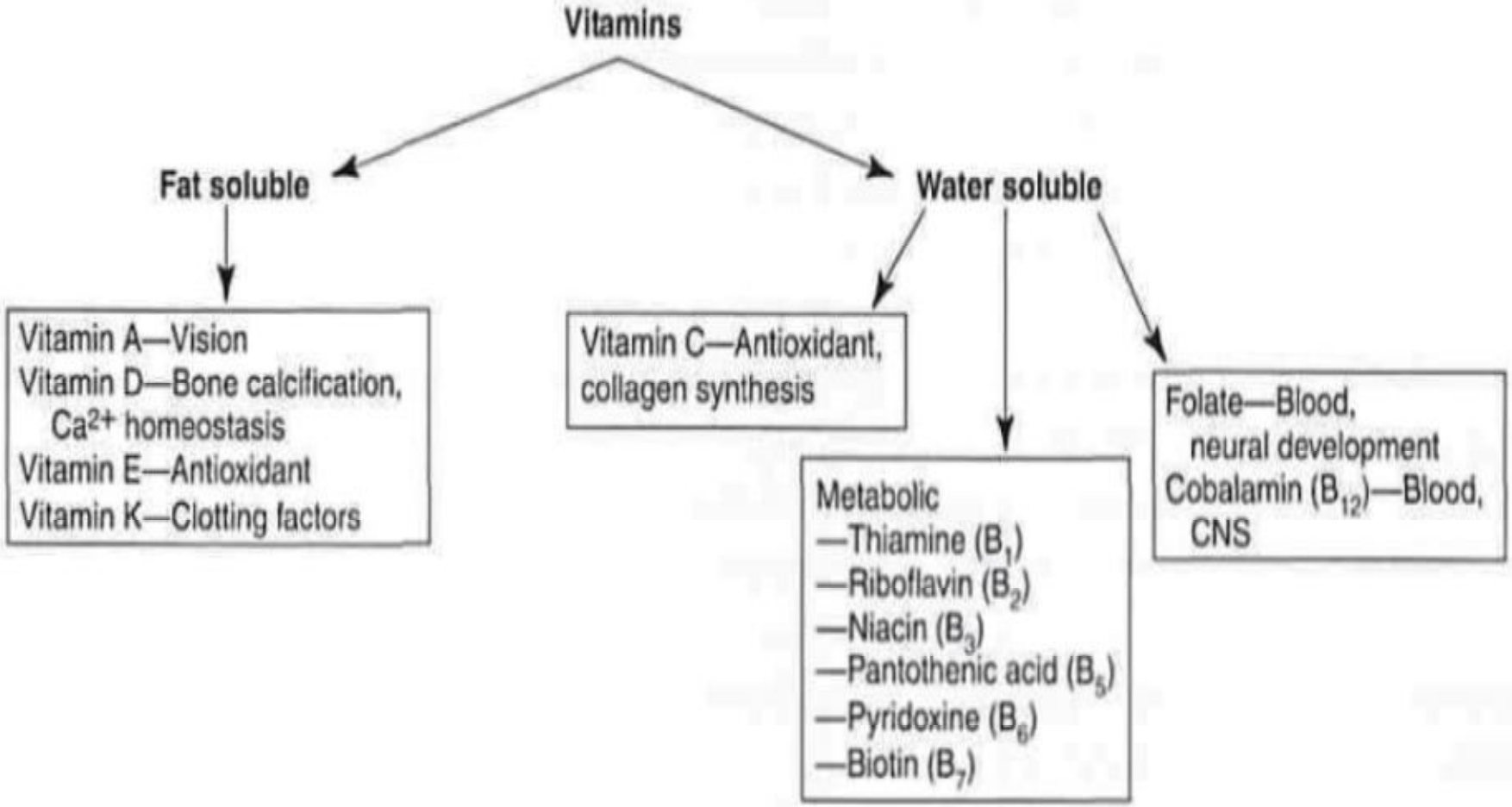
Vitamins


Vitamins
Fat soluble
Water soluble
Vitamin A—Vision
Vitamin D—Bone calcification, Ca^{2+} homeostasis
Vitamin E—Antioxidant
Vitamin K—Clotting factors
Vitamin C—Antioxidant, collagen synthesis
Metabolic
—Thiamine (B_1)
—Riboflavin (B_2)
—Niacin (B_3)
—Pantothenic acid (B_5)
—Pyridoxine (B_6)
—Biotin (B_7)
Folate—Blood, neural development
Cobalamin (B_{12})—Blood, CNS

Vitamins: water soluble	B_1 (thiamine: TPP) B_2 (riboflavin: FAD, FMN) B_3 (niacin: NAD^+) B_5 (pantothenic acid: CoA) B_6 (pyridoxine: PLP) B_{12} (cobalamin) C (ascorbic acid) Biotin Folate	All wash out easily from body except B_{12} and folate (stored in liver). B-complex deficiencies often result in dermatitis, glossitis, and diarrhea.

Vitamins: fat soluble	A, D, E, K. Absorption dependent on gut (ileum) and pancreas. Toxicity more common than for water-soluble vitamins, because these accumulate in fat.	Malabsorption syndromes (steatorrhea), such as cystic fibrosis and sprue, or mineral oil intake can cause fat-soluble vitamin deficiencies.

Vitamin A (retinol)

Function	Antioxidant; constituent of visual pigments (retinal); essential for normal differentiation of epithelial cells into specialized tissue (pancreatic cells, mucus-secreting cells).	**Retinol** is vitamin **A**, so think **Retin-A** (used topically for wrinkles and acne). Found in liver and leafy vegetables.
Deficiency	Night blindness, dry skin.	
Excess	Arthralgias, fatigue, headaches, skin changes, sore throat, alopecia. Teratogenic (cleft palate, cardiac abnormalities), so a pregnancy test must be done before isotretinoin is prescribed for severe acne.	

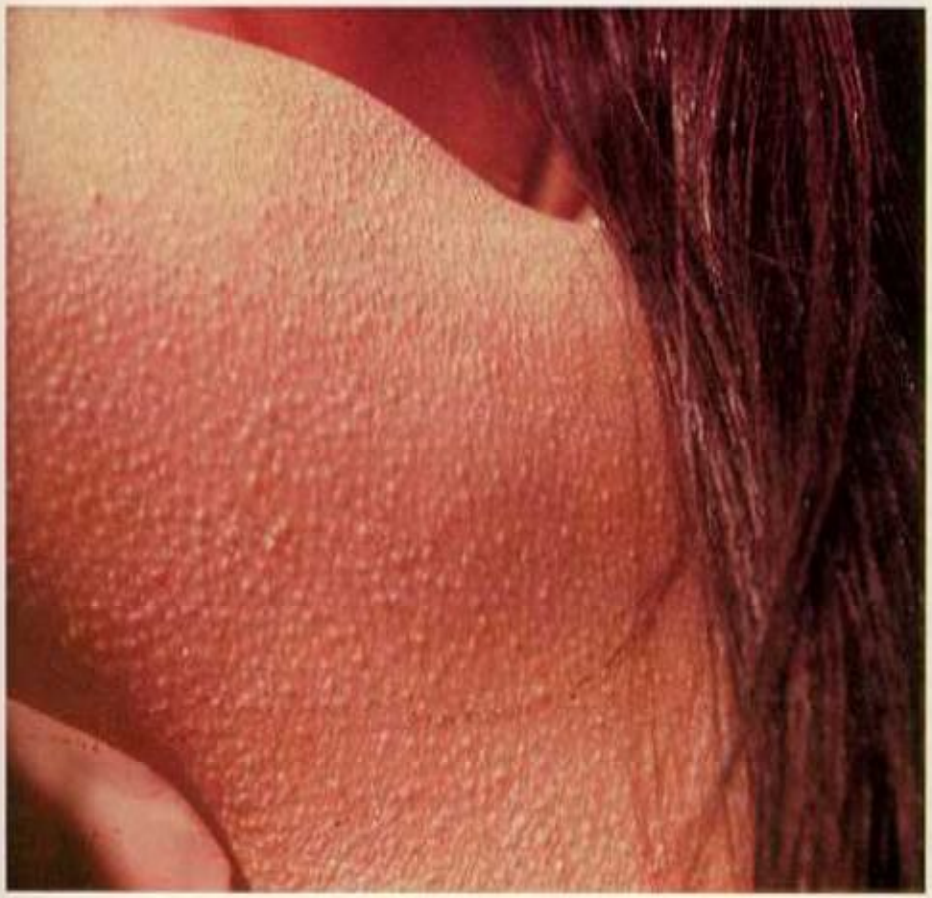


Fig. 4 Follicular hyperkeratosis resulting from vitamin A deficiency resembles "gooseflesh" but can be distinguished from it because the bumps do not disappear when the skin is rubbed. These lesions commonly appear on the lateral surface of the arm and extensor surface of the thigh.

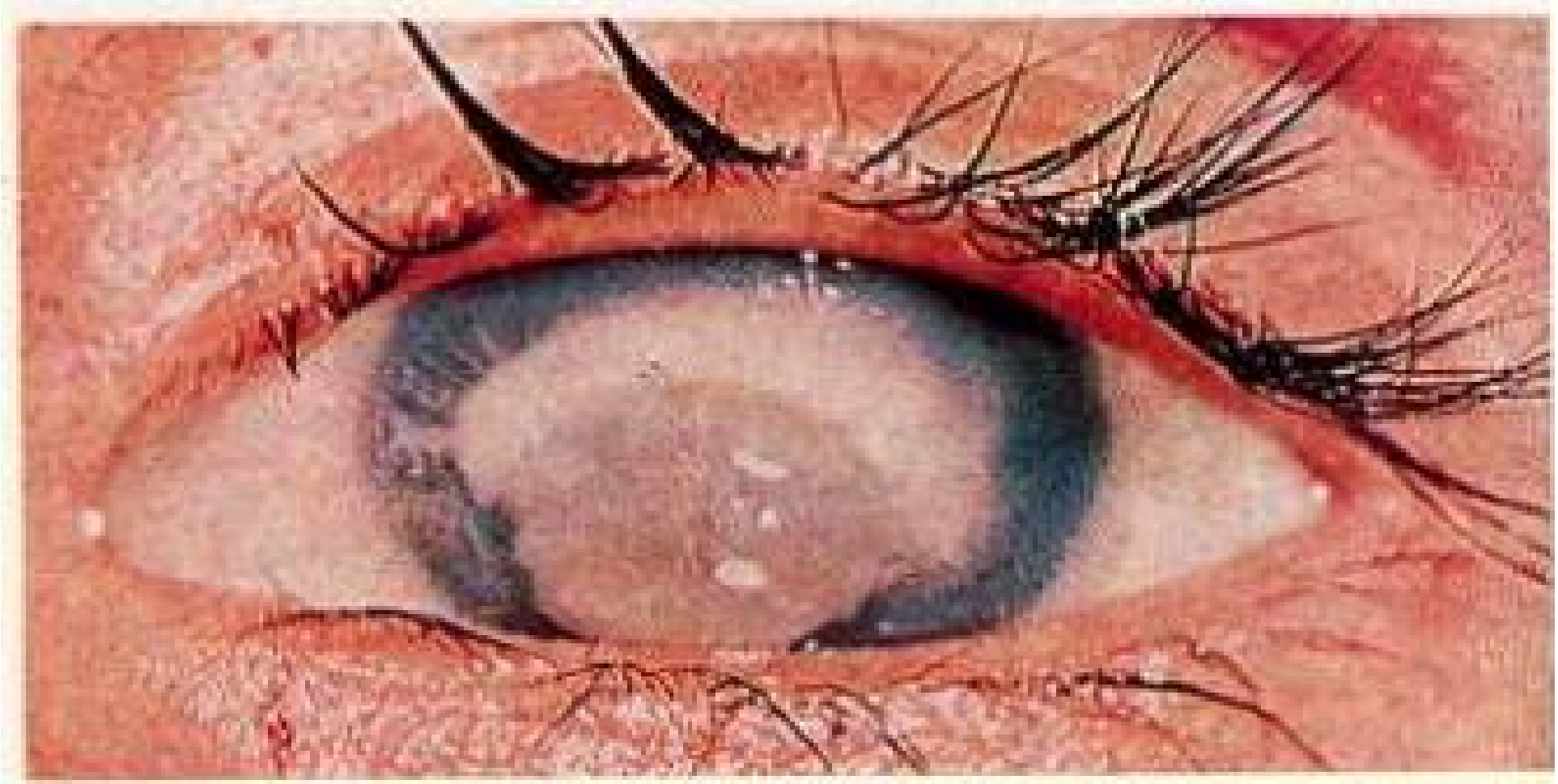


Fig. 3 Keratomalacia in a young child.

Vitamin B_1 (thiamine)

Function	In thiamine pyrophosphate (TPP), a cofactor for several enzymes: 1. Pyruvate dehydrogenase (glycolysis) 2. α-ketoglutarate dehydrogenase (TCA cycle) 3. Transketolase (HMP shunt) 4. Branched-chain AA dehydrogenase	Spell beriberi as Ber1Ber1.
Deficiency	Impaired glucose breakdown → ATP depletion; highly aerobic tissues (brain and heart) are affected first. Wernicke-Korsakoff syndrome and beriberi. Seen in malnutrition as well as alcoholism (2° to malnutrition and malabsorption).	Wernicke-Korsakoff—confusion, ophthalmoplegia, ataxia + memory loss, confabulation, personality change. Dry beriberi—polyneuritis, symmetrical muscle wasting. Wet beriberi—high-output cardiac failure (dilated cardiomyopathy), edema.

Vitamin B_2 (riboflavin)

Function	Cofactor in oxidation and reduction (e.g., $FADH_2$).	FAD and FMN are derived from riboFlavin (B_2 = 2 ATP).
Deficiency	Cheilosis (inflammation of lips, scaling and fissures at the corners of the mouth), Corneal vascularization.	The 2 C's.

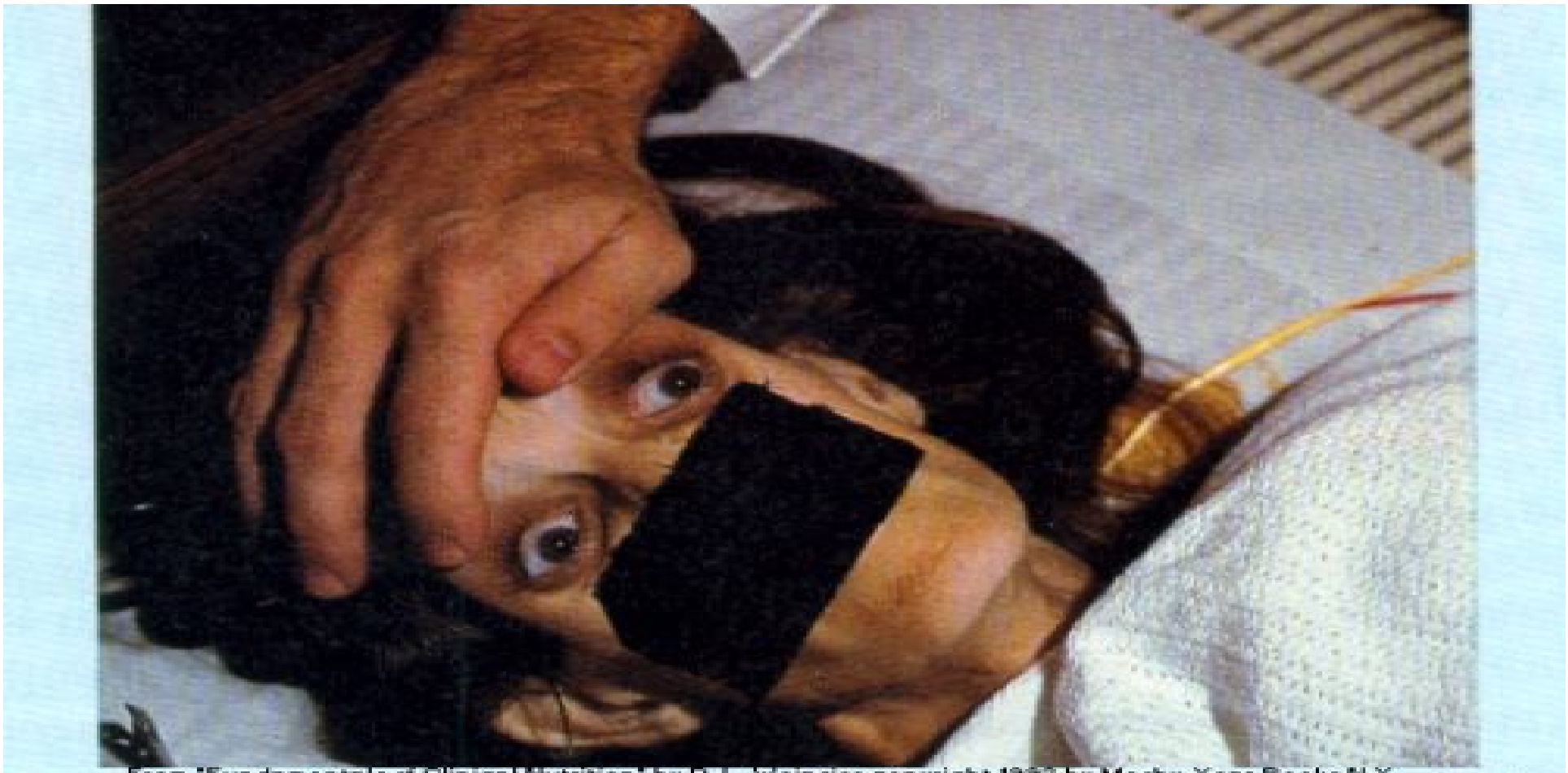


Fig. 6-11 Inability to follow a light source (ophthalmoplegia) due to thiamin deficiency and phosphorus deficiency.

Vitamin B_3 (niacin)		
Function	Constituent of NAD^+, $NADP^+$ (used in redox reactions). Derived from tryptophan. Synthesis requires vitamin B_6.	NAD derived from Niacin (B_3 = 3 ATP).
Deficiency	Glossitis. Severe deficiency leads to pellagra, which can be caused by Hartnup disease (↓ tryptophan absorption), malignant carcinoid syndrome (↑ tryptophan metabolism), and INH (↓ vitamin B_6).	The 3 D's: of pellagra: Diarrhea, Dermatitis, Dementia.
Excess	Facial flushing (due to pharmacologic doses for treatment of hyperlipidemia).	Vitamin B_3 in corn not absorbable unless treated. Excess untreated corn in diet can lead to pellagra.
Vitamin B_5 (pantothenate)		
Function	Essential component of CoA (a cofactor for acyl transfers) and fatty acid synthase.	Pantothen-A is in Co-A.
Deficiency	Dermatitis, enteritis, alopecia, adrenal insufficiency.	
Vitamin B_6 (pyridoxine)		
Function	Converted to pyridoxal phosphate, a cofactor used in transamination (e.g., ALT and AST), decarboxylation reactions, glycogen phosphorylase, cystathionine synthesis, and heme synthesis. Required for the synthesis of niacin from tryptophan.	
Deficiency	Convulsions, hyperirritability, peripheral neuropathy (deficiency inducible by INH and oral contraceptives), sideroblastic anemias.	

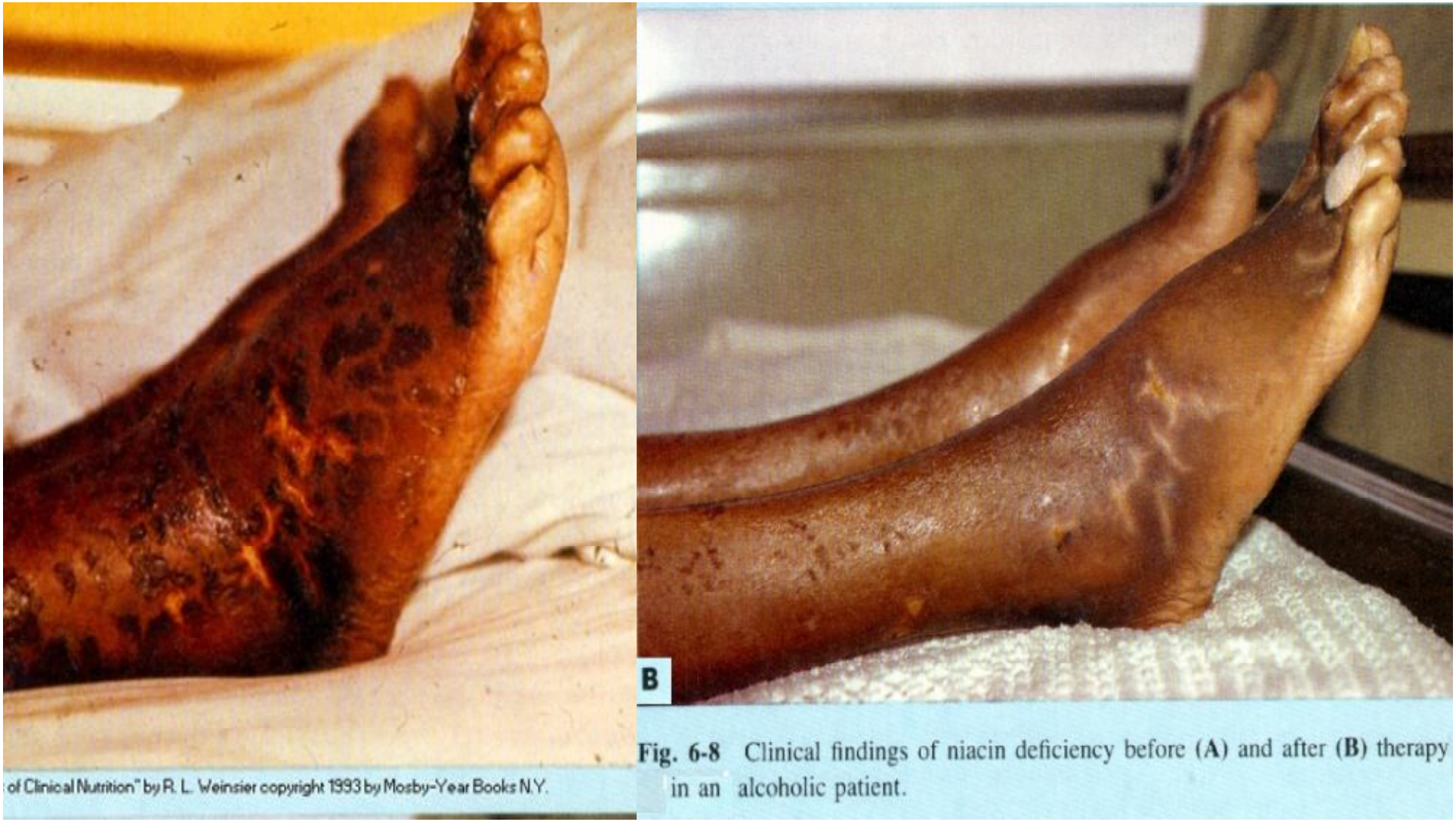


Fig. 6-8 Clinical findings of niacin deficiency before **(A)** and after **(B)** therapy in an alcoholic patient.

Folic acid

Function	Converted to tetrahydrofolate (THF), a coenzyme for 1-carbon transfer/methylation reactions. Important for the synthesis of nitrogenous bases in DNA and RNA.	FOLate from FOLiage. Small reserve pool stored primarily in the liver. Eat green leaves.
Deficiency	Macrocytic, megaloblastic anemia; no neurologic symptoms (as opposed to vitamin B_{12} deficiency). Most common vitamin deficiency in the United States. Seen in alcoholism and pregnancy.	Deficiency can be caused by several drugs (e.g., phenytoin, sulfonamides, MTX). Supplemental folic acid in early pregnancy reduces neural tube defects.

Vitamin B_{12} (cobalamin)

Function	Cofactor for homocysteine methyltransferase (transfers CH_3 groups as methylcobalamin) and methylmalonyl-CoA mutase.	Found in animal products. Synthesized only by microorganisms. Very large reserve pool (several years) stored primarily in the liver.
Deficiency	Macrocytic, megaloblastic anemia, hypersegmented PMNs, neurologic symptoms (paresthesias, subacute combined degeneration) due to abnormal myelin. Prolonged deficiency leads to irreversible nervous system damage.	Deficiency is usually caused by malabsorption (sprue, enteritis, *Diphyllobothrium latum*), lack of intrinsic factor (pernicious anemia, gastric bypass surgery), or absence of terminal ileum (Crohn's disease). Use Schilling test to detect the etiology of the deficiency.

$$\text{Homocysteine + N-methyl THF} \xrightarrow{B_{12}} \text{Methionine + THF}$$

$$\text{Methylmalonyl-CoA} \xrightarrow{B_{12}} \text{Succinyl-CoA}$$

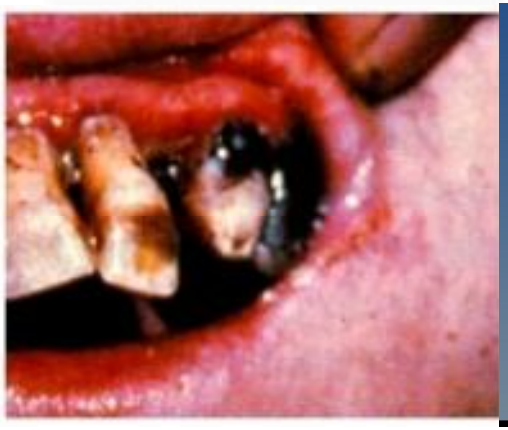
Vitamin C (ascorbic acid)

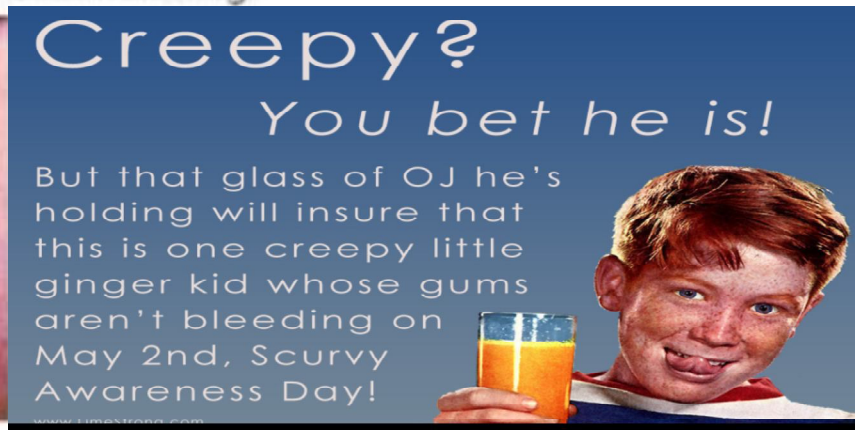
Function — Antioxidant. Also:

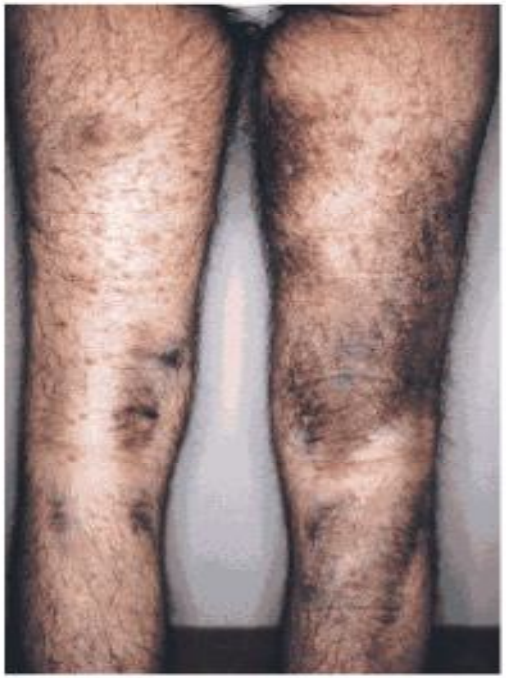
1. Facilitates iron absorption by keeping iron in Fe^{2+} reduced state (more absorbable)
2. Necessary for hydroxylation of proline and lysine in collagen synthesis
3. Necessary for dopamine β-hydroxylase, which converts dopamine to NE

Found in fruits and vegetables. British sailors carried limes to prevent scurvy (origin of the word "limey").

Deficiency — Scurvy—swollen gums, bruising, anemia, poor wound healing.







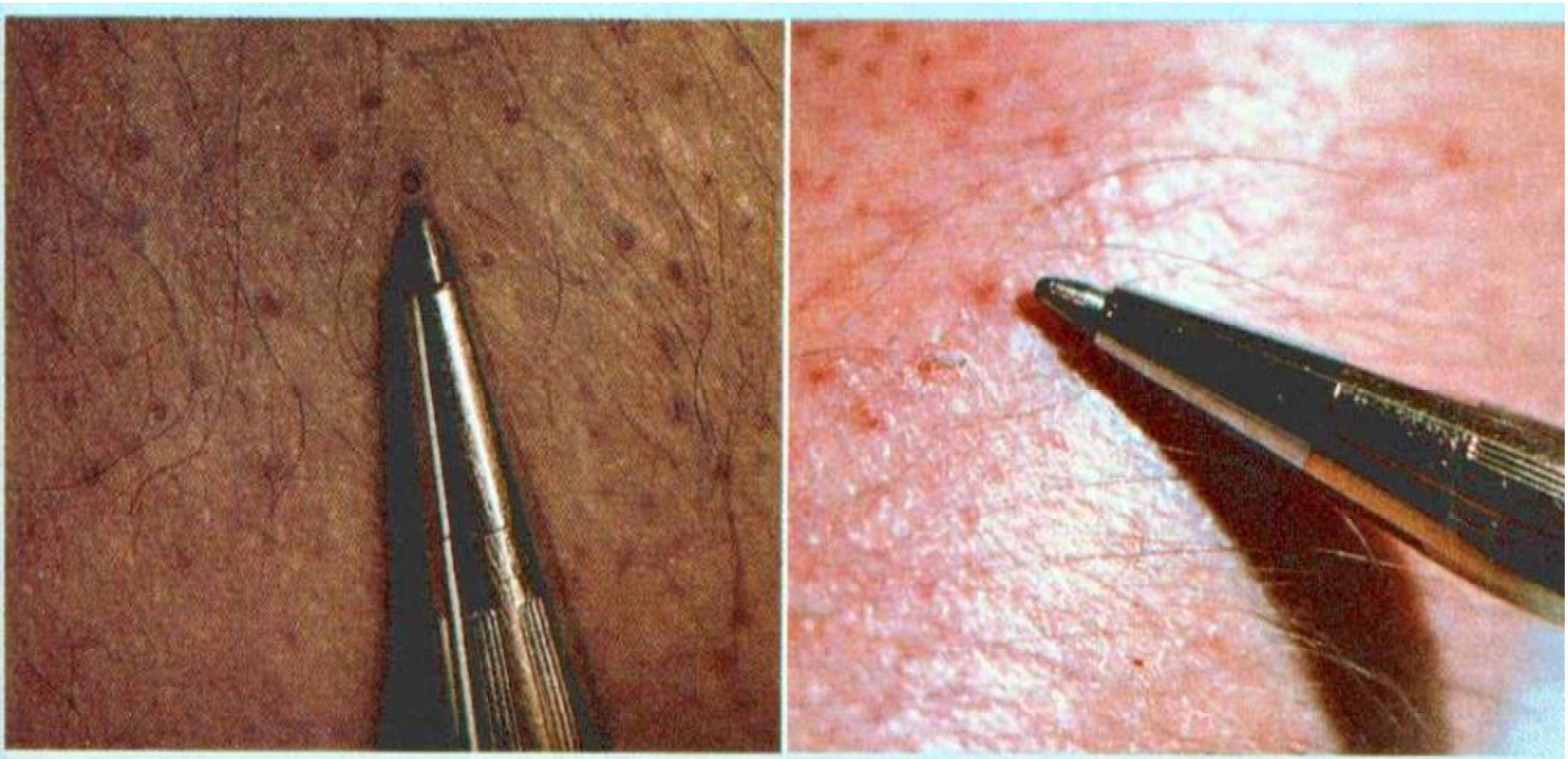
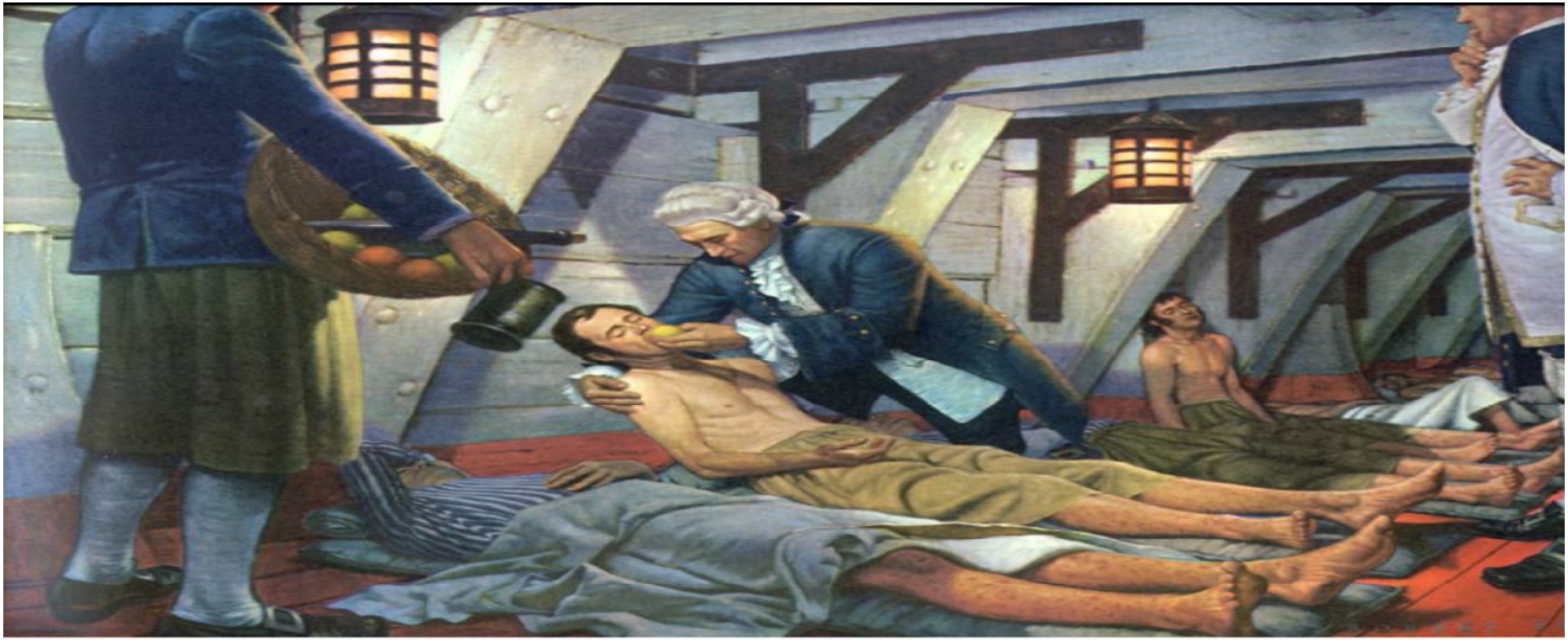


Fig. 6-2 **A,** Corkscrew hairs in scurvy. **B,** Perifollicular petechiae in scurvy.



James Lind, a surgeon in the Royal Navy, conducted clinical tests that proved that citrus fruits and their juices would cure and prevent scurvy, the disease which killed a million seamen between 1600 and 1800. In this painting he is shown aboard HMS *Salisbury* in 1747. Lind published his paper, *A Treatise on the Scurvy* was published in 1751. He later became Chief Surgeon of the Royal Naval Hospital and published many more papers on how to safeguard the health of sailors.

Image from *A History of Medicine in Pictures*, published by Parke, Davis & Co. in 1960; Artist: Robert A.Thom

Vitamin D	D_2 = ergocalciferol—ingested from plants, used as pharmacologic agent. D_3 = cholecalciferol—consumed in milk, formed in sun-exposed skin. 25-OH D_3 = storage form. 1,25-$(OH)_2$ D_3 (calcitriol) = active form.	Drinking milk (fortified with vitamin D) is good for bones.
Function	↑ intestinal absorption of calcium and phosphate, ↑ bone resorption.	
Deficiency	Rickets in children (bending bones), osteomalacia in adults (soft bones), hypocalcemic tetany.	
Excess	Hypercalcemia, hypercalciuria, loss of appetite, stupor. Seen in sarcoidosis (↑ activation of vitamin D by epithelioid macrophages).	
Vitamin E		
Function	Antioxidant (protects erythrocytes and membranes from free-radical damage).	E is for Erythrocytes.
Deficiency	↑ fragility of erythrocytes (hemolytic anemia), muscle weakness, neurodysfunction.	

Vitamin K

Function	Catalyzes γ-carboxylation of glutamic acid residues on various proteins concerned with blood clotting. Synthesized by intestinal flora.	K for Koagulation. Necessary for the synthesis of clotting factors II, VII, IX, X, and protein C and S. Warfarin—vitamin K antagonist.
Deficiency	Neonatal hemorrhage with ↑ PT and ↑ aPTT but normal bleeding time (neonates have sterile intestines and are unable to synthesize vitamin K). Can also occur after prolonged use of broad-spectrum antibiotics.	Neonates are given vitamin K injection at birth to prevent hemorrhage.

Zinc

Function	Essential for the activity of 100+ enzymes. Important in the formation of zinc fingers (transcription factor motif).
Deficiency	Delayed wound healing, hypogonadism, ↓ adult hair (axillary, facial, pubic), dysgeusia, anosmia. May predispose to alcoholic cirrhosis.

Biotin

Function	Cofactor for carboxylation enzymes (which add a 1-carbon group): 1. Pyruvate carboxylase: Pyruvate (3C) → oxaloacetate (4C) 2. Acetyl-CoA carboxylase: Acetyl-CoA (3C) → malonyl-CoA (4C) 3. Propionyl-CoA carboxylase: Propionyl-CoA (3C) → methylmalonyl-CoA (4C)	"AVIDin in egg whites AVIDly binds biotin."
Deficiency	Relatively rare. Dermatitis, alopecia, enteritis. Caused by antibiotic use or excessive ingestion of raw eggs.	