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M1 - GI Sequence

Micronutrients

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Winter, 2009

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ESSENTIAL MINERAL ELEMENTS

1. Required to maintain normal physiology and health

2. Occur in diet, sometimes as trace elements

3. Variable absorptions may be regulated

4. In steady state intestinal absorption equals body losses

MINERAL ABSORPTION BY SMALL INTESTINE IS AFFECTED BY:

1. Intraluminal pH
2. Redox state of metals
3. Formation of chelates to enhance solubility
4. Formation of insoluble complexes

IRON

1. Essential for oxidative energy metabolism and DNA synthesis

2. Body stores contain about 4 g with 2.5 g in red blood cells

3. To maintain a balance, the gut absorbs 1-2 mg/day from dietary supply of 10-20 mg

CELLULAR IRON HOMEOSTASIS

1. All cells take up iron-transferrin from plasma by transferrin receptor endocytosis.

2. Iron is stored intracellularly complexed to the binding protein ferritin.

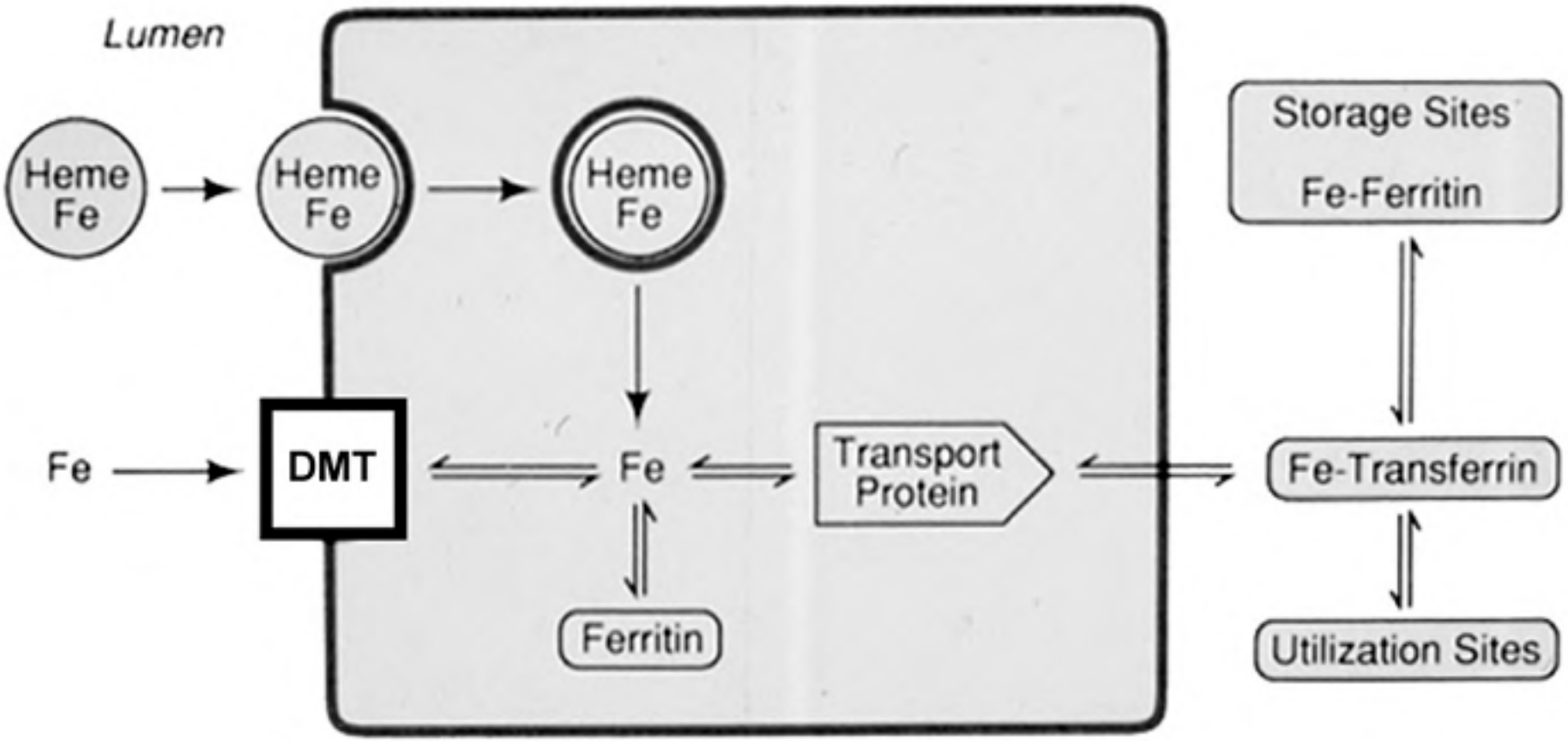
3. Iron regulatory proteins function as cytoplasmic iron sensors and increase Tf Receptors by stabilizing mRNA when more iron is needed.

4. Efflux from cells such as macrophages is by ferroportin.

IRON ABSORPTION

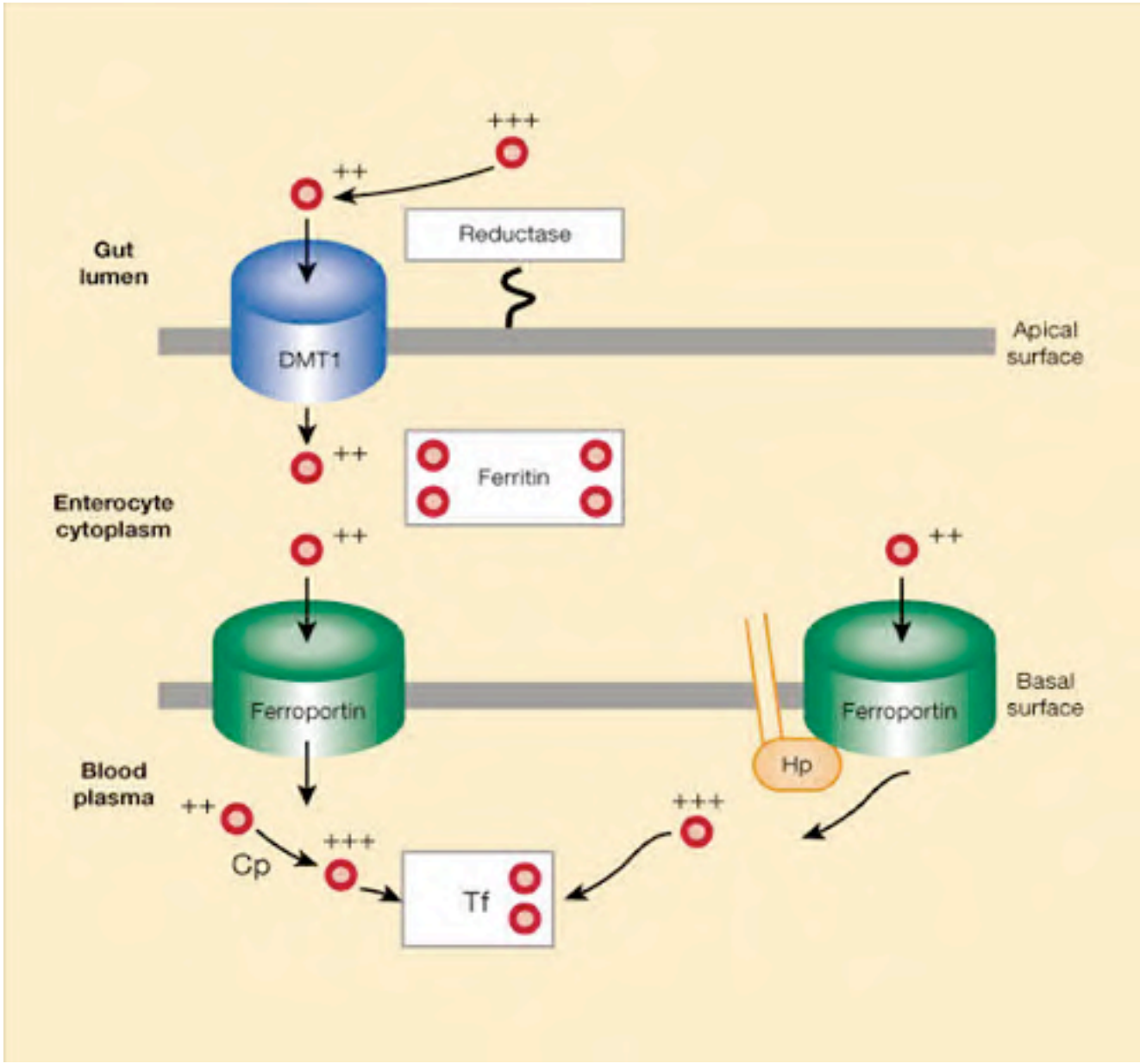
1. Dietary iron present as heme (minor) and nonheme iron compounds (major).
2. Nonheme iron in the Fe^{3+} ferric state requires gastric acid for solubilization.
3. Fe^{3+} mainly reduced to Fe^{2+} (ferrous) prior to absorption.
4. Iron absorption occurs primarily in the duodenum and upper jejunum.

Model for Absorption of Iron by the Small Intestine



PD-INEL Source Undetermined

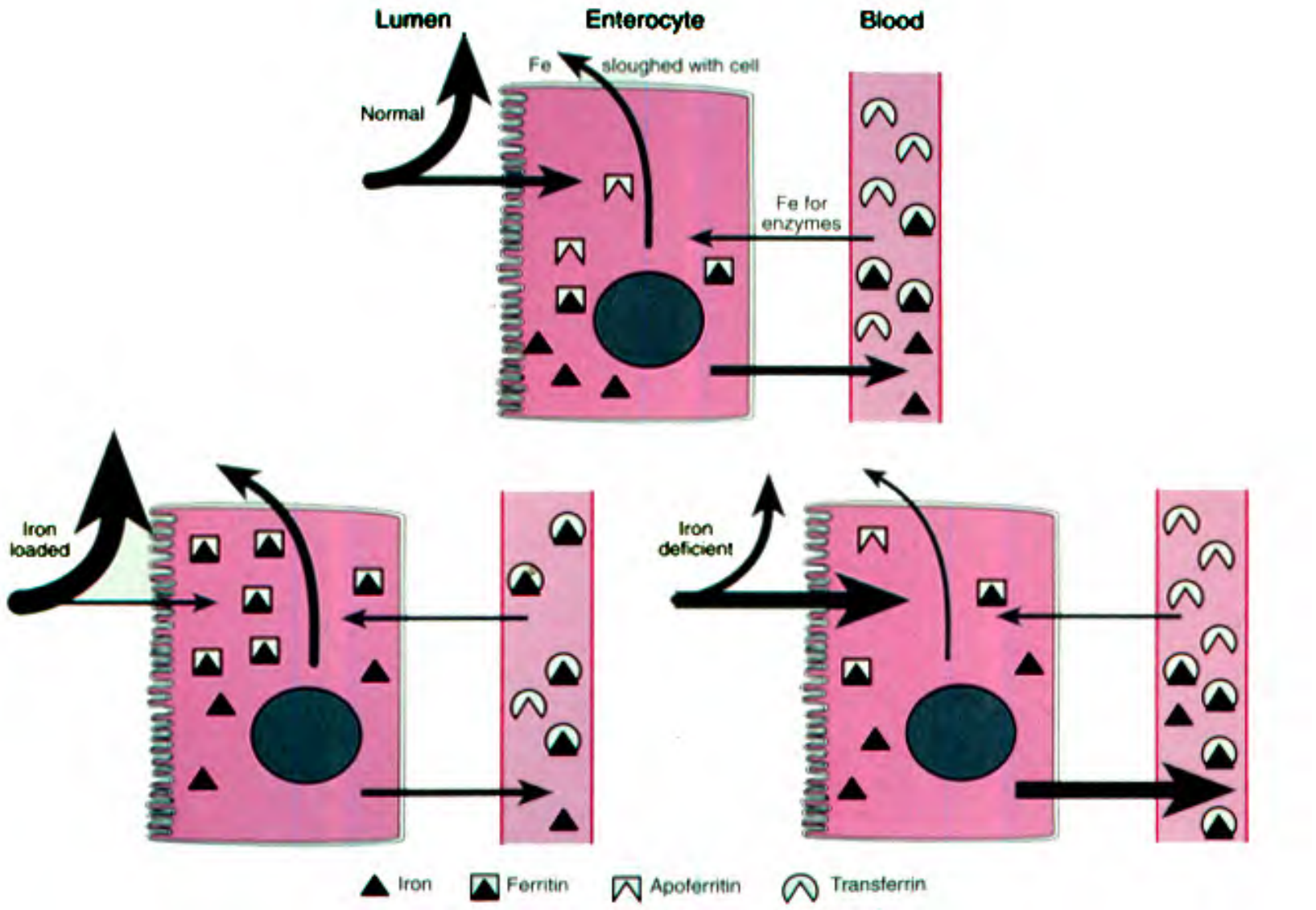
Mechanism of Iron Absorption by Enterocytes



NEW PROTEINS INVOLVED IN IRON ABSORPTION

Ferrireductase	Apical membrane enzyme to reduce iron
DMT-1	Divalent Metal Transporter-1 Apical Membrane Iron Transport
Ferroportin-1	Iron Export Carrier on the Basolateral Membrane
Hephaestin	Basolateral membrane protein which facilitates the transport of iron out of cells

Role of Ferritin in the Regulation of Iron Absorption



PD-INEL Fig. 29-16 Rhoades, R, Tanner, G. *Medical Physiology*. 1995: 568.

Role of Liver in Regulating Iron Absorption

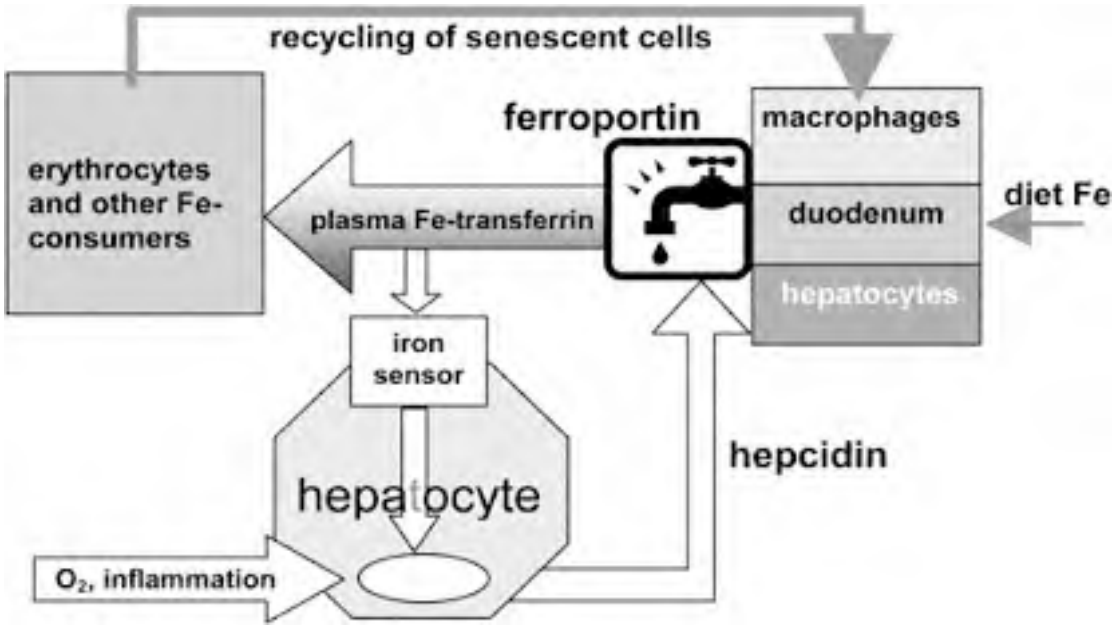
1. Liver is main storage site for excess iron

2. Hepcidin is an antimicrobial peptide secreted by hepatocytes which it acts as an inhibitor of iron absorption by the gut and release from macrophages.

3. Production of hepcidin is decreased by iron deficiency and increased with iron loading and inflammation

4. Hepacidin interacts directly with ferroportin leading to its degradation. This leads to decreased iron absorption and release

ORGANISMAL IRON HOMEOSTASIS



CAUSES OF IRON DEFICIENCY

1. Dietary Deficiency
2. Excess phytate or oxylate in diet
3. Gastric achlorhydria
4. Hookworm infestation
5. Excessive bleeding

CONSEQUENCES OF IRON DEFICIENCY

1. Anemia (microcytic, hypochromic)
2. Poor growth in children
3. Impaired energy metabolism

HEREDITY HEMOCHROMATOSIS

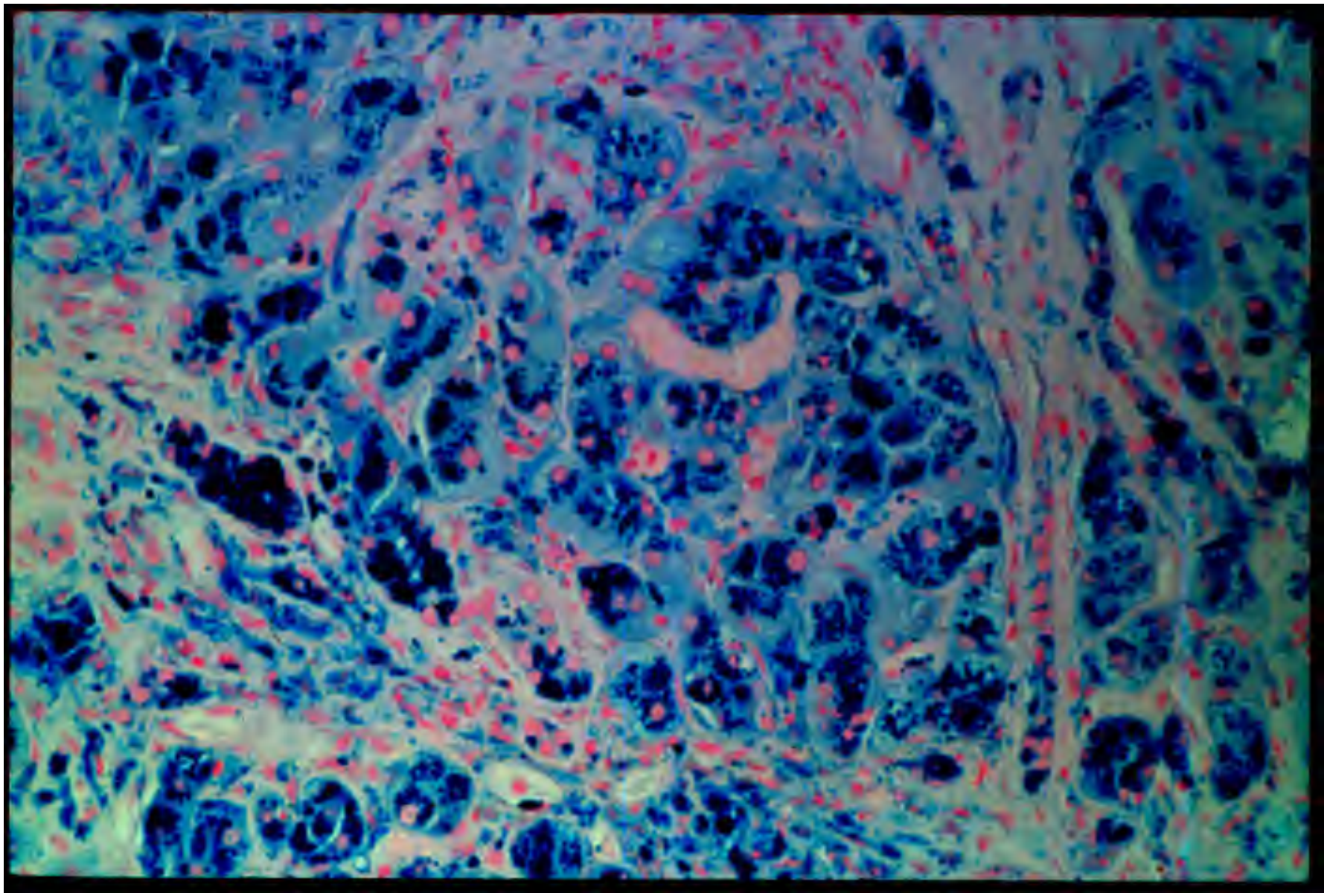
1. Common form is autosomal recessive with gene frequency as high as 1 in 10 in individuals of Northern European descent

2. Excessive mucosal iron absorption relative to need

3. Clinical manifestations are a result of iron deposition in liver, heart, pancreas and joints

4. >80% of patients have a single mutation in HFE protein which leads to decreased plasma hepcidin

Iron Stain of Liver in Hemochromatosis



ABSORPTION OF VITAMINS

1. Water soluble vitamins
    - facilitated diffusion (Na+-coupled)

2. Fat soluble vitamins
    -absorbed same as other lipids

3. Vitamin B_{12}
    -special receptor
    -requires intrinsic factor

WATER SOLUBLE VITAMINS

Thiamine	Pyridoxine	Folate
Riboflavin	Pantothenate	Cobalamin (B_{12})
Niacin	Biotin	Ascorbic Acid

Generally metabolized to forms acting as coenzymes

Vit C functions as a water soluble antioxidant

Structure of Conjugated Folates

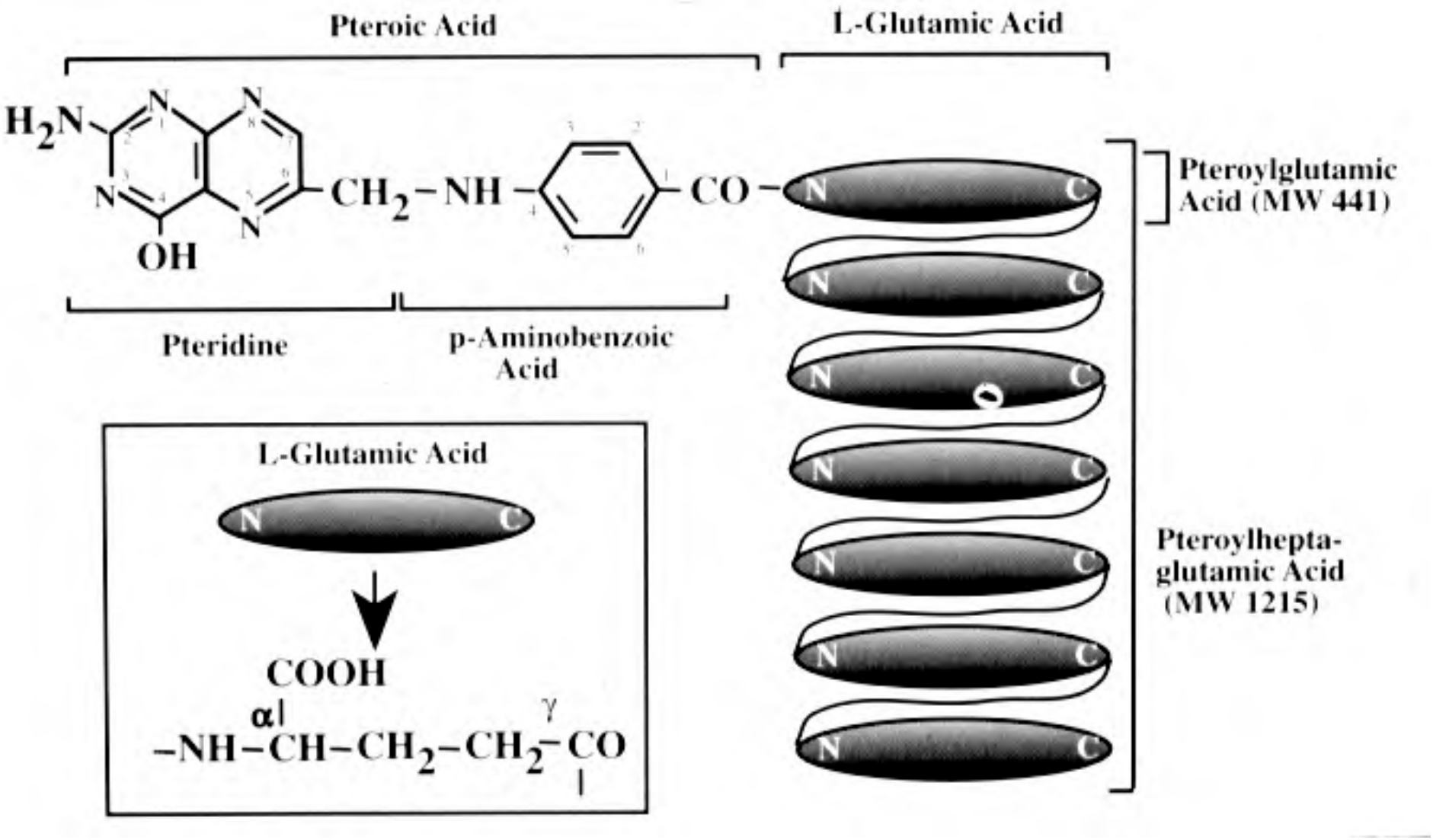


 Fig. 1 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 190.

FOLATE DEFICIENCY

1. Folates function as coenzymes in 1 carbon transfers; important in nucleic acid synthesis and amino acid metabolism
2. Deficiency results in megaloblastic anemia and growth retardation
3. Recent studies show a relationship to neuronal tube birth defects

    PHS recommends women of childbearing age consume 400 µg daily

Metabolism and Absorption of Conjugated Folates

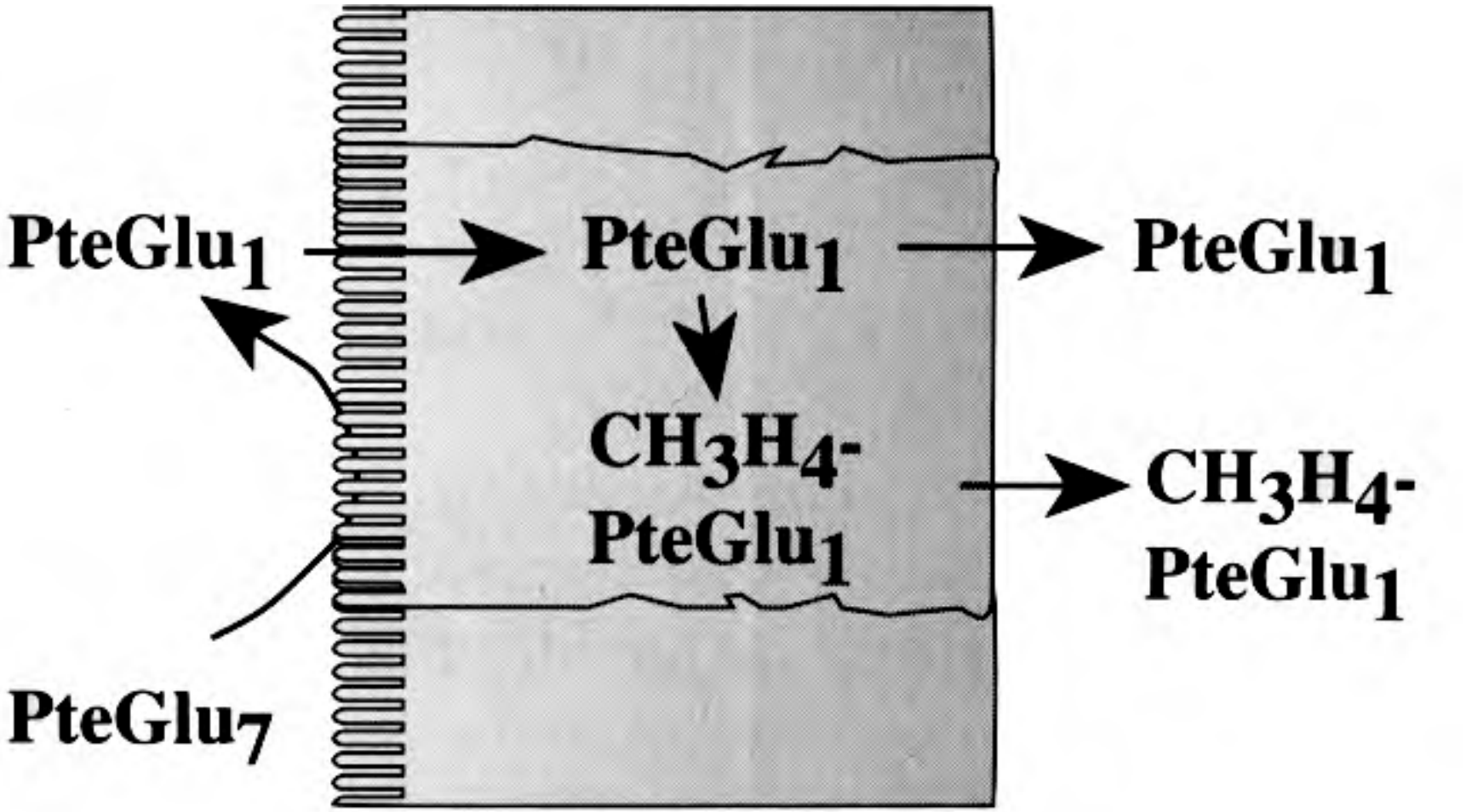


 Fig. 2 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 191.

Polyglutamyl folates must be hydrolyzed to the monoglutamyl form before absorption

A specific enzyme, folate conjugase, is involved which is inhibited by ethanol and some drugs (Dilantin, sulfasalazine)

Absorption is by a saturable mechanism involving a folic acid: OH^- exchange mechanism

Within enterocyte folic acid is reduced and methylated

FAT SOLUBLE VITAMINS

A – Retinol, carotenoids

D – Cholecalciferol (D_3); Ergosterol (D_2)

E – α-Tocopherol

K – Phylloquinone (K_1); Menaquinones (K_2)

VITAMIN E

1. The major lipid soluble antioxidant in plasma and cell membranes

2. Dietary Sources are vegetable oils, wheat germ, nuts, green leafy vegetables. Recommended intake 15 mg/day

3. Absorption varies from 10-80% by passive diffusion and packaging into chylomicrons

4. Role in therapy unclear (macular degeneration, cardiovascular disease, prostate cancer)

VITAMIN K

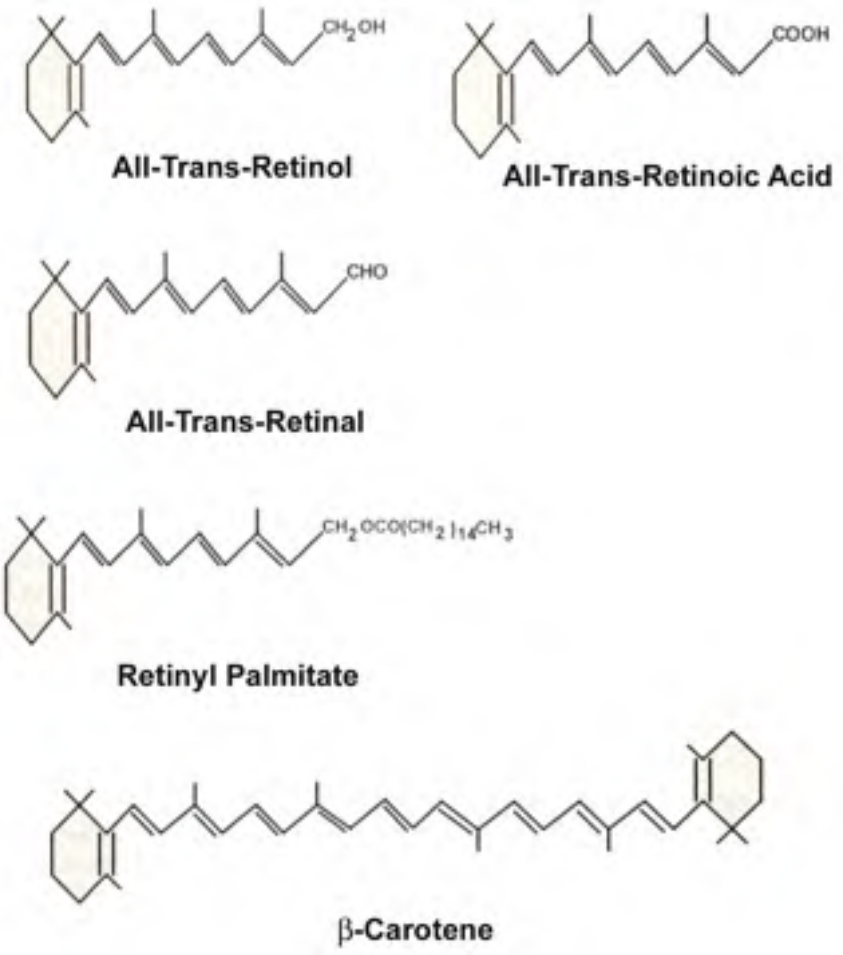
1. Biological function is to serve as a cofactor for essential post-translational modifications essential for certain proteins including blood clotting factors

2. Dietary form (K_1) most abundant in green leafy vegetables

3. Insoluble in water; requires bile salts for absorption

4. Importance of bacterially derived K_2 controversial but prevents severe deficiency in humans unless colonic flora absent

Vitamin A Family

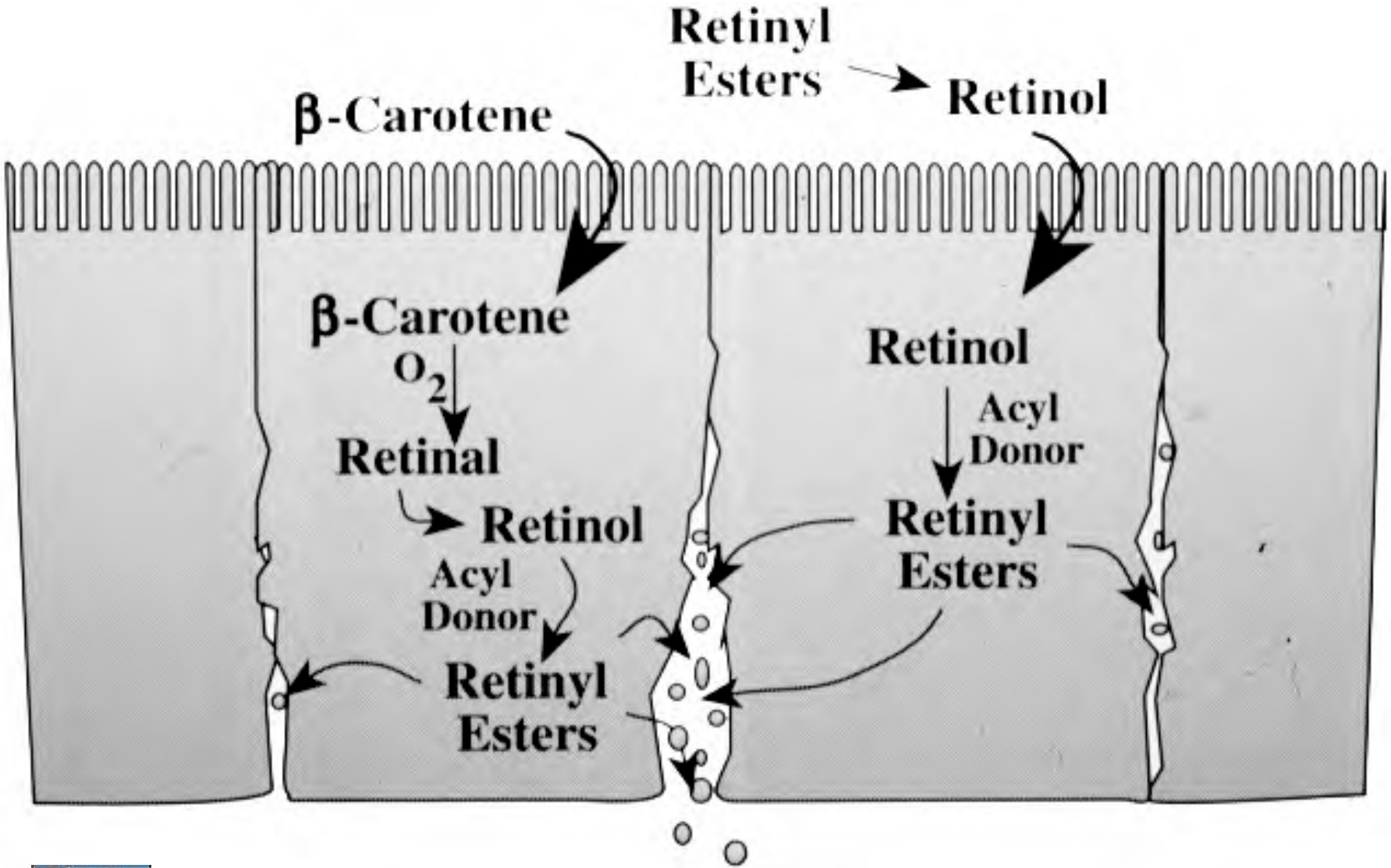


Retinoids present in liver, milk, eggs
Carotenoids present in carrots and green leafy vegetables

DISORDERS OF VITAMIN A HOMEOSTATIS

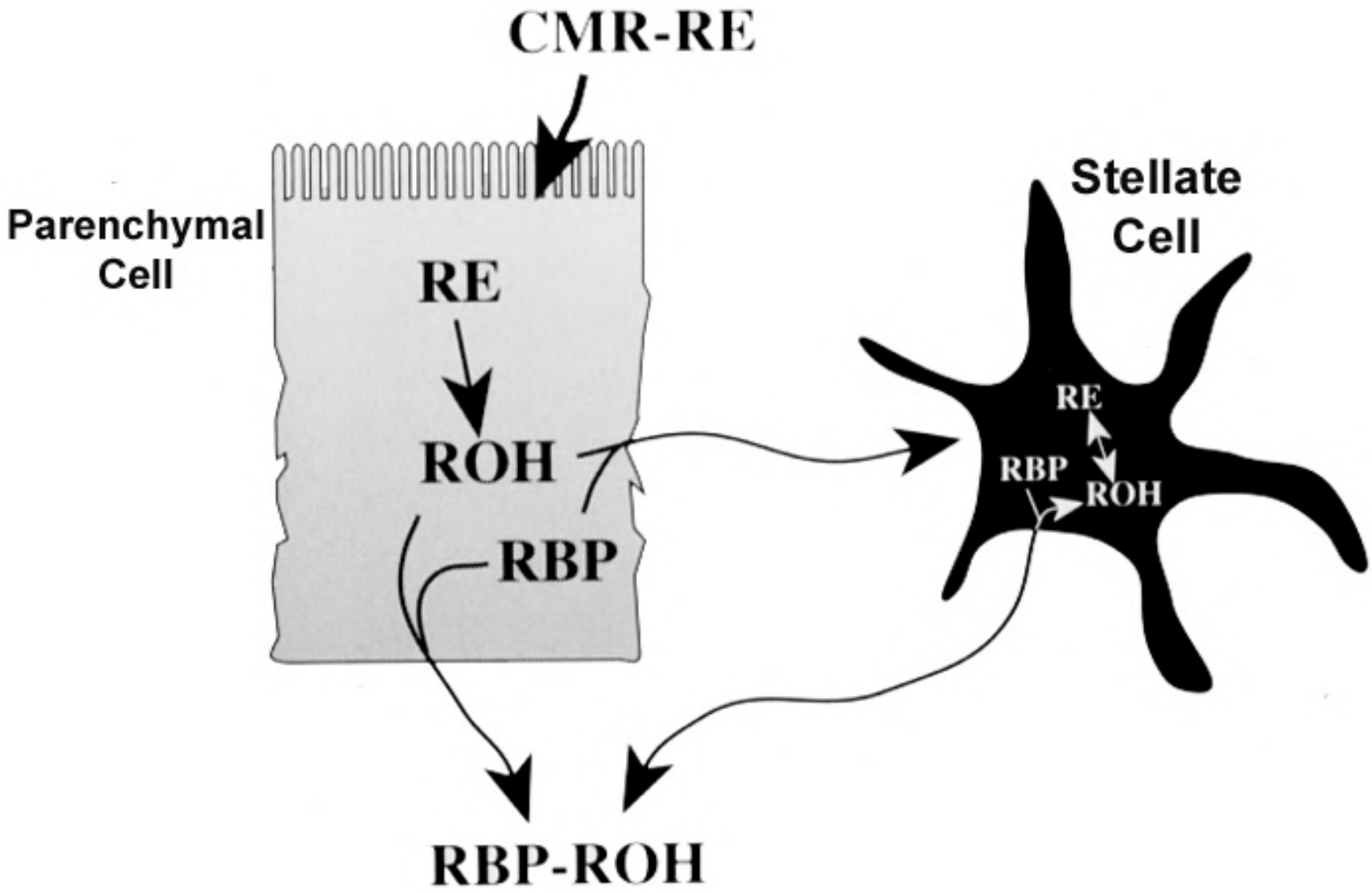
1. Vitamin A deficiency results in xeropthalmia; initially night blindness can progress to total blindness
2. Deficiency also increases susceptibility to infection
3. Recommended daily intake of 1000 µg retinol or 6000 ug beta carotene
4. Hypervitaminosis most commonly due to self-medication; can result in signs and symptoms of increased intracranial pressure, skin lesions and hepatic injury

Intestinal Absorption and Metabolism of Vit. A



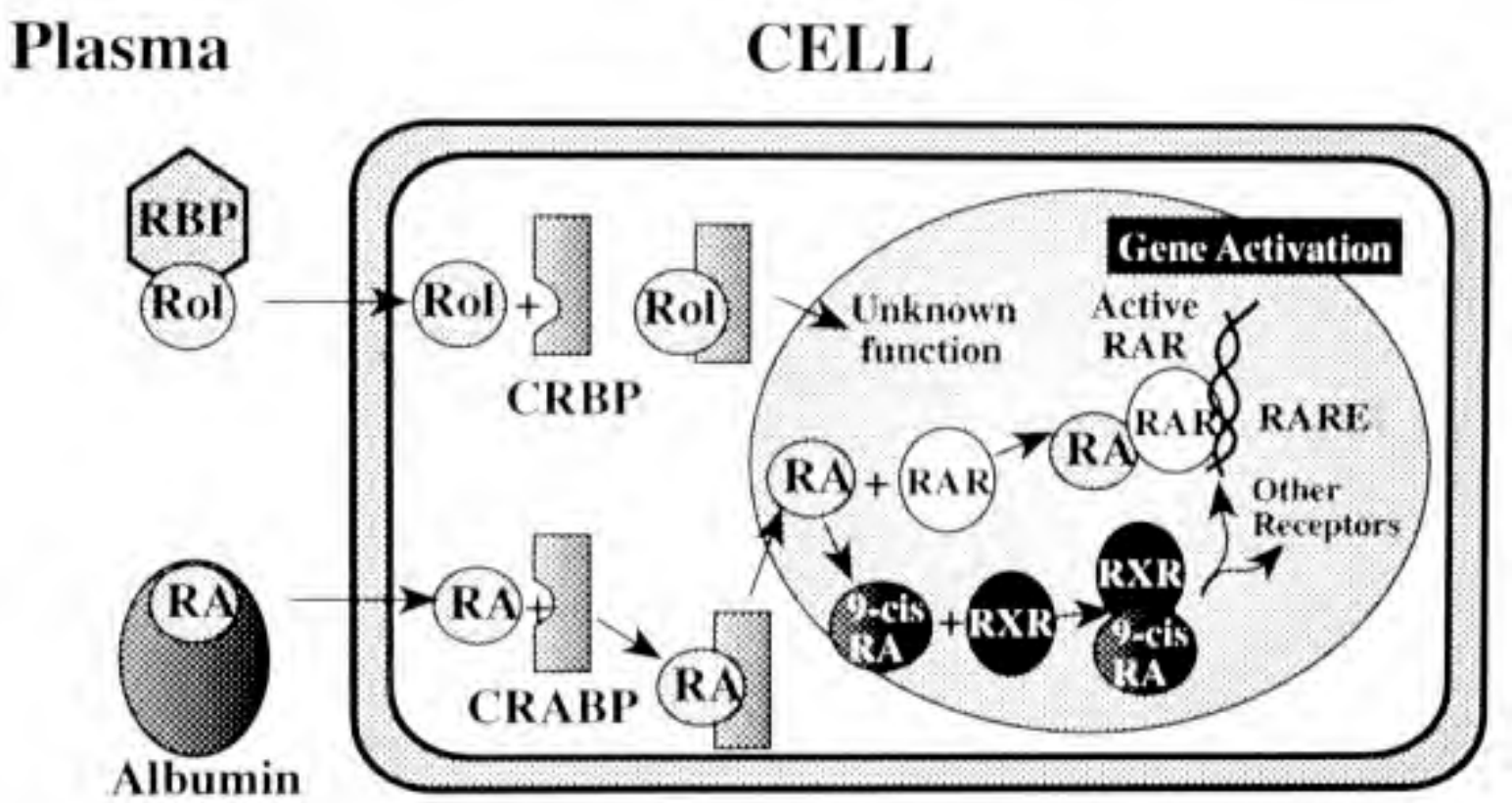
PD-INEL Fig. 3 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 166.

Hepatic Vitamin A Metabolism and Storage



PD-INEL Fig. 6 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 170.

Uptake, Metabolism and Action of Retinol and Retinoic Acid



ROL = Retinol RA = Retinoic Acid
RBP = Serum Retinol Binding Protein
CRABP = Cellular Retinol Binding Protein
RXR = Retinoid X Receptor
RAR = Retinoic Acid Receptor

PD-INEL Fig. 7 Chang, E, Sitrin, M, Black, D. *Gastrointestinal, Hepatobiliary, and Nutritional Physiology.* Lippincott – Raven, Philadelphia, PA; 1996: 171.

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