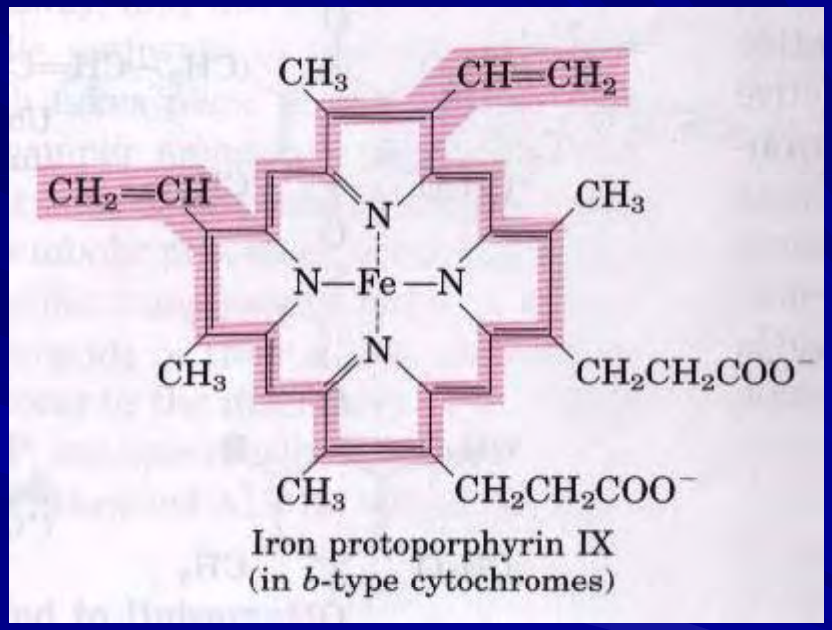
IRON METABOLISM

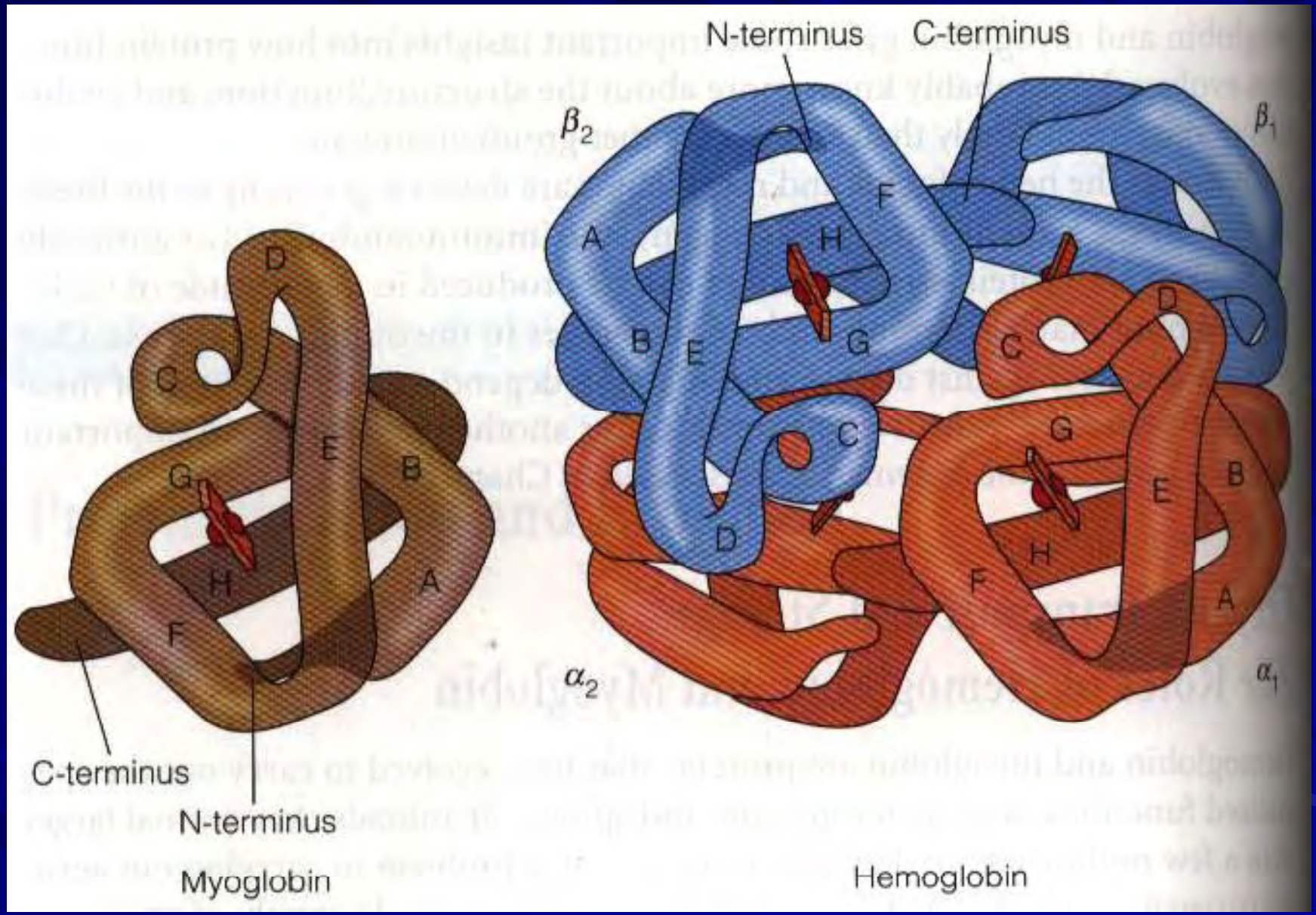
R. Mohammadi
Biochemist (Ph.D.)
Faculty member of Medical Faculty

HEMPROTEINS

- Hemoglobin
- Myoglobin
- Cytochromes
- Peroxidases
- Trp Pyrrolase
- PG Synthase
- NO Synthase
- Guanylate Synthase



Iron protoporphyrin IX
(in *b*-type cytochromes)


N-terminus
C-terminus
β_2
β_1
A
B
C
D
E
F
G
H
α_2
α_1
C-terminus
N-terminus
Myoglobin
Hemoglobin

NON-HEME PROTEINS

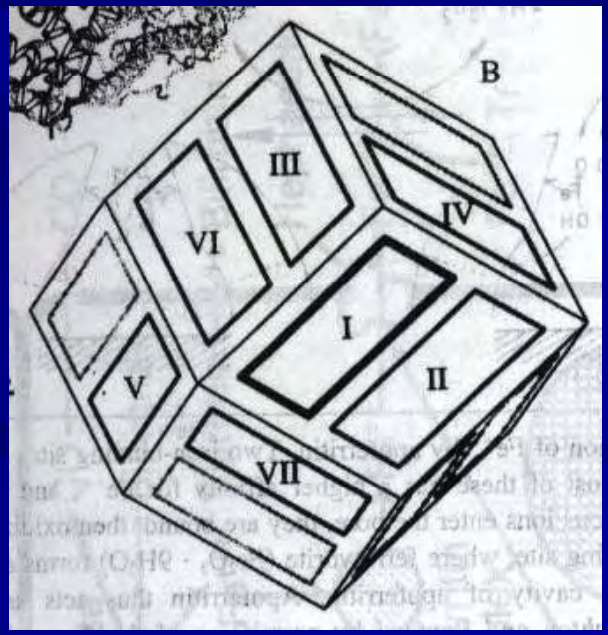
- Transferin
- Ferritin
- Hemsiderin
- Lactoferrin
- Iron-Sulfur Proteins

TRANSFERIN (Tf)

- Is Iron Binding Protein In Circulation
- Is a 75 kDa β_1-Glycoprotein
- Is a Negative Acute Phase Protein
- Increases During Pregnancy
- Apotransferin Binds to Two Fe^{3+}

FERRITIN IS THE MAIN STORAGE FORM OF IRON IN BODY

- **Ferritin is a Spherical Protein, Having**
  - ***1) Apoferritin Shell (24 Subunit)***
  - ***2) Ferrihydrite (FeOOH) Crystal Core***



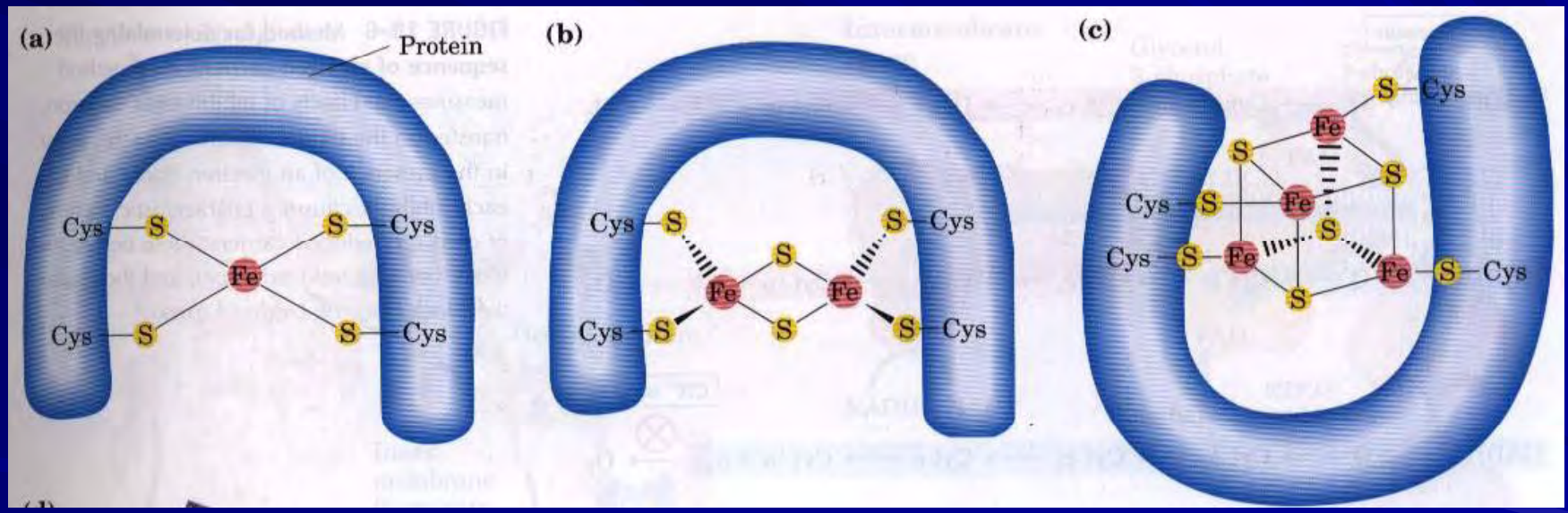
HEMOSIDERIN

- *Consists of Aggregates of Ferrihydrite Core Crystals, Largely Devoid of Appoferritin*
- *It Is Water-Insoluble*

LACTOFERRIN

- Is Transferrin-like Protein
- Is Present in Granulocytes, Milk and Mucous Secretions
- Has Bacteriostatic function
- Facilitate Iron Transport and Storage in Milk

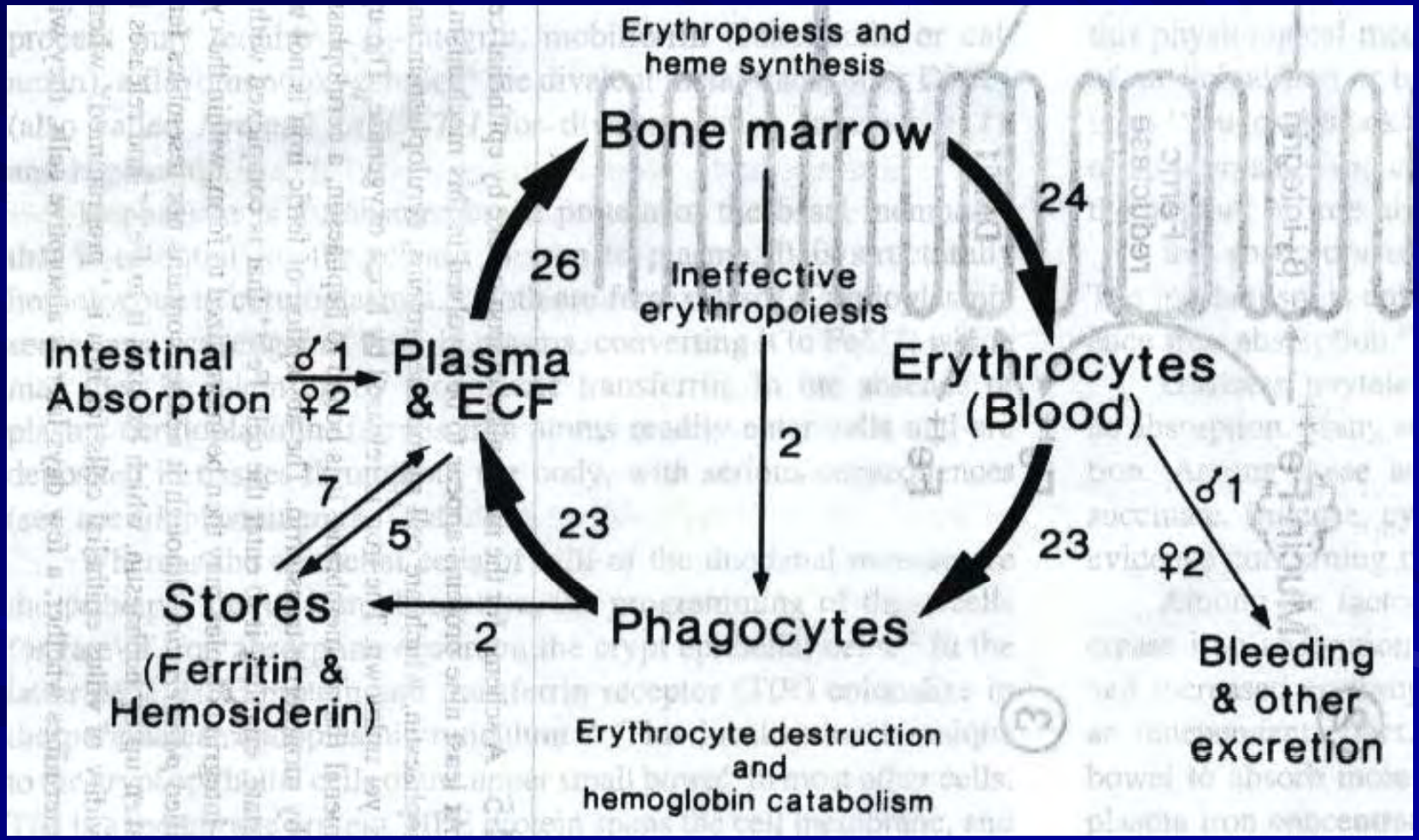
Fe –S CENTER



IRON DISTRIBUTION IN BODY

- *Hemoglobin (2500 mg)*
- *Myoglobin (130 mg)*
- *Tissue Iron (Enzymes & Coenzymes; 8 mg)*
- *Storage as Ferritin & Hemosiderin (Up to 1000 mg)*
- *Labile Pool (80 mg)*

IRON METABOLISM OCCURS IN A CLOSED CYCLE



DIFFERENT PROTEINS INVOLVE IRON METABOLISM

FERRIREDUCTASES

- *DCytb*
- *Streap3*

FERROXIDASES

- *Hephaestin*
- *Ceruloplasmin*

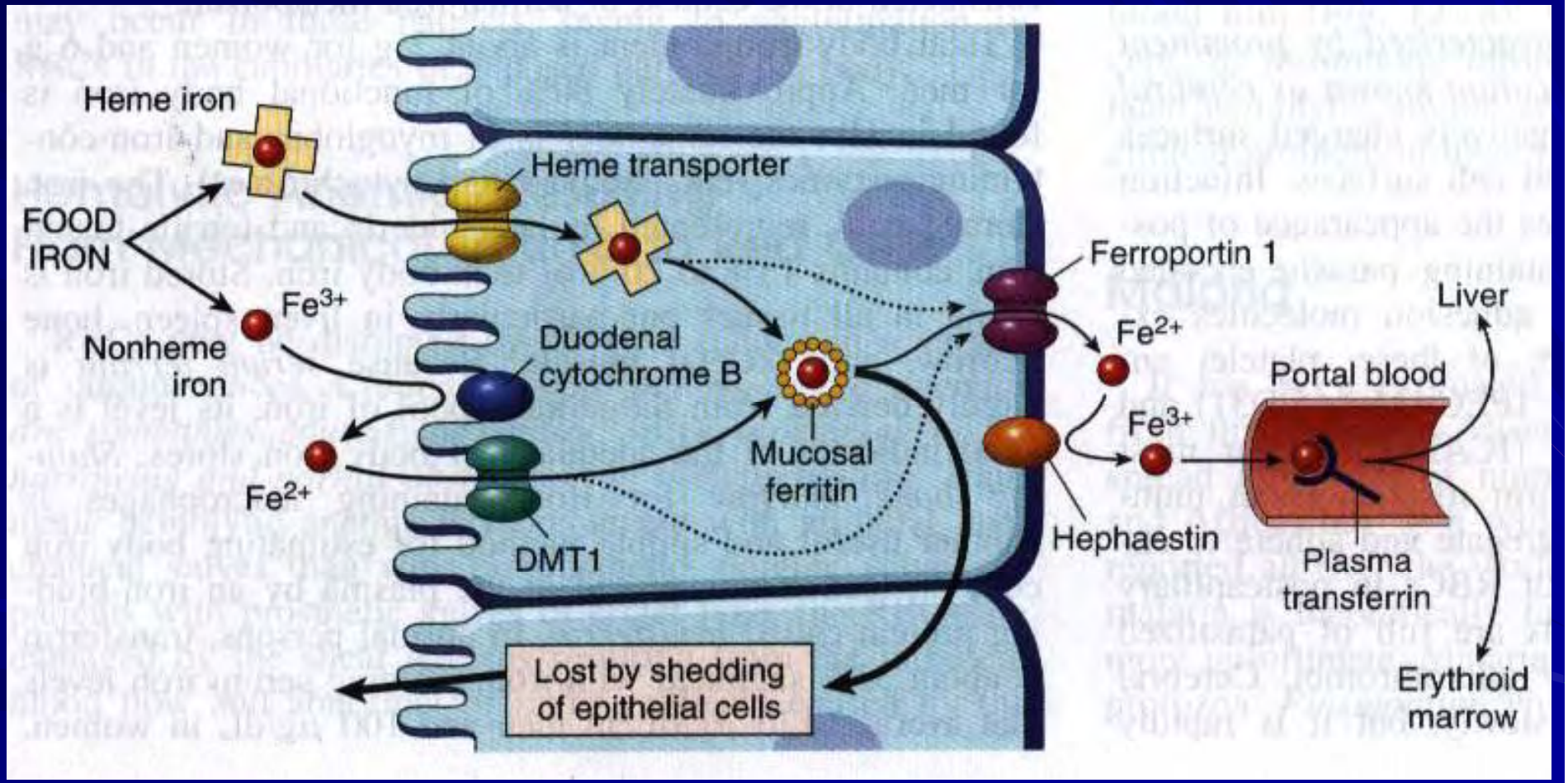
TRANSPORTERS

- *DMT-1*
- *Ferroportin*
- *TfR1*
- *Mitoferrin*

REGULATORS

- *Hepcidin*
- *Hemojuvelin*
- *TfR2*
- *HFE*
- *IL-6*

INTESTINAL ABSORPTION IS THE MAIN WAY IN BODY IRON REGULATION



IRON ABSORPTION IS AFFECTED BY

ACCELARATORS:

- *Gastric Juice*
- *Ascorbate*
- *Cysteine*
- *Sorbitol*
- *Fructose*

INHIBITORS:

- *Phosphtes*
- *Phytates*
- *Tannic Acid*

REGULATION OF HEPCIDIN SYNTHESIS

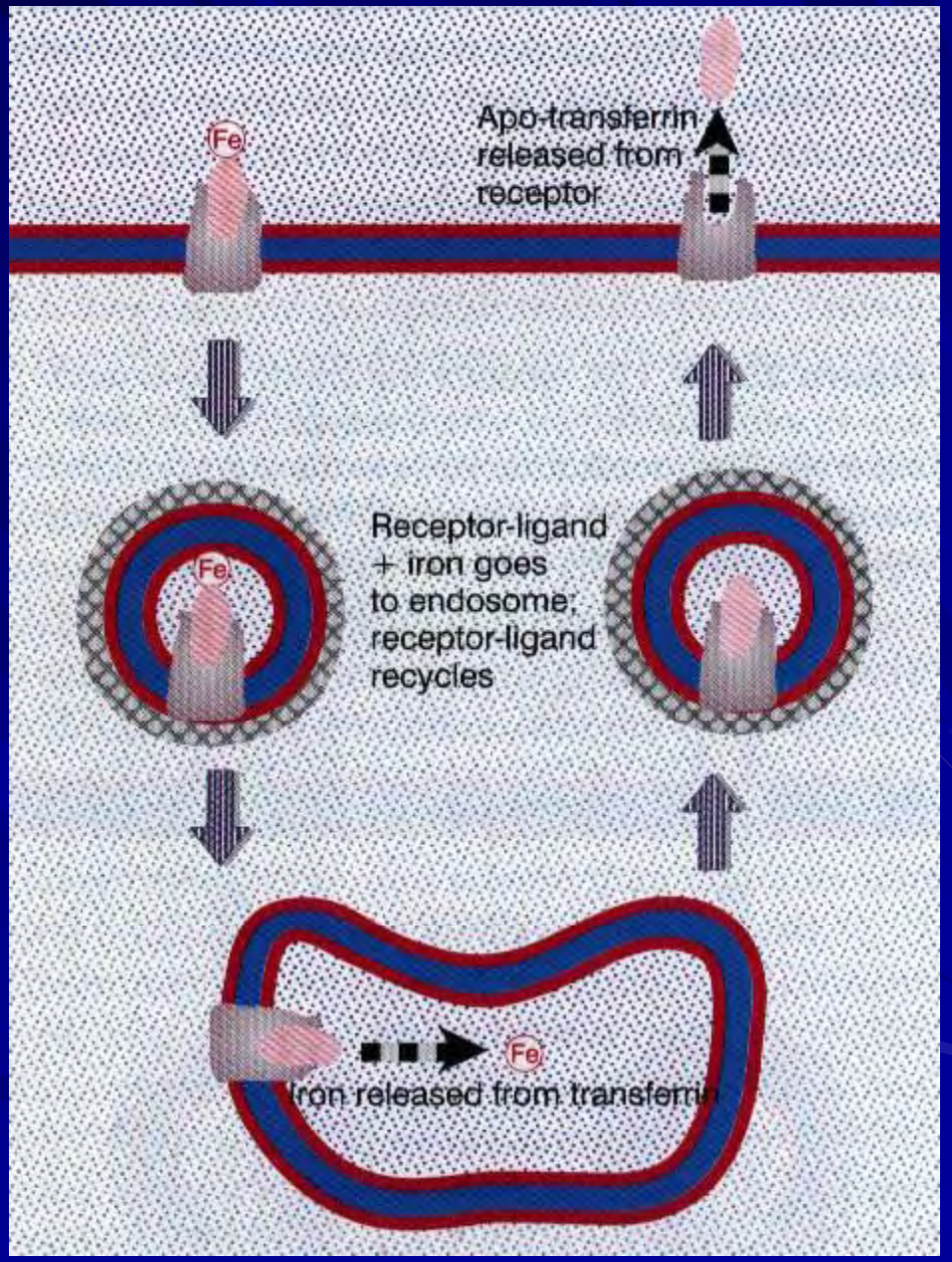
ACCELARATORS:

- ***Iron Excess Through HJV, HFE, TfR2***
- ***Infection and Inflammation Through IL-6***

INHIBITORS:

- ***Hypoxia***
- ***Erythpoiesis***

CELLULAR UPTAKE OF IRON OCCURES THROUGH RECEPTOR-MEDIATED ENDOCYTOSIS OF TRANSFERIN



INTRACELLULAR REGULATION OF IRON METABOLISM

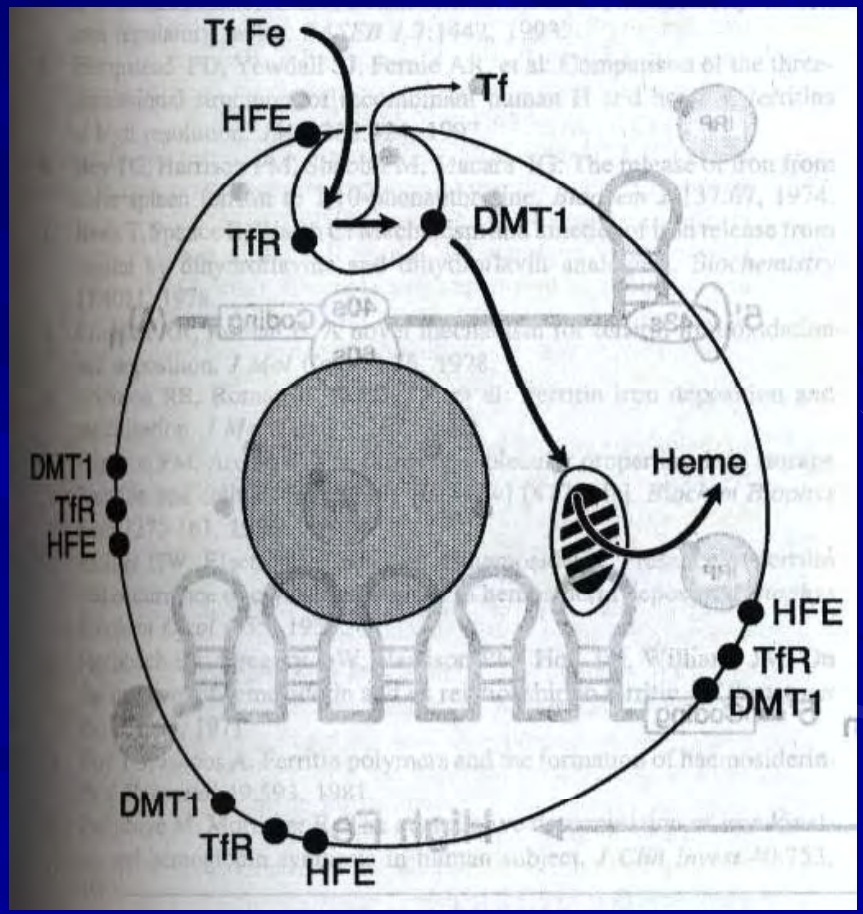
Occures Through Regulation of Synthesis Proteins Such as:

Apotransferin

Transferin Receptor

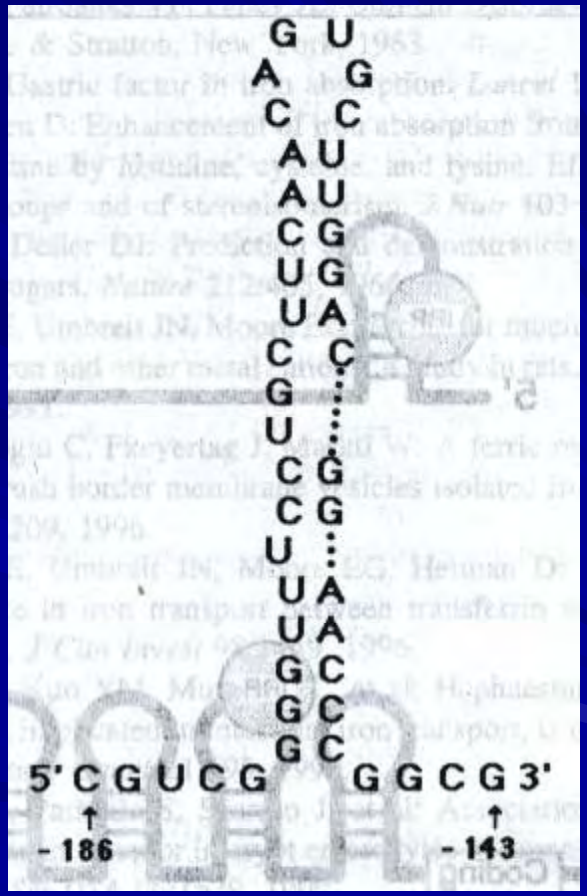
Apoferritin

DMT1

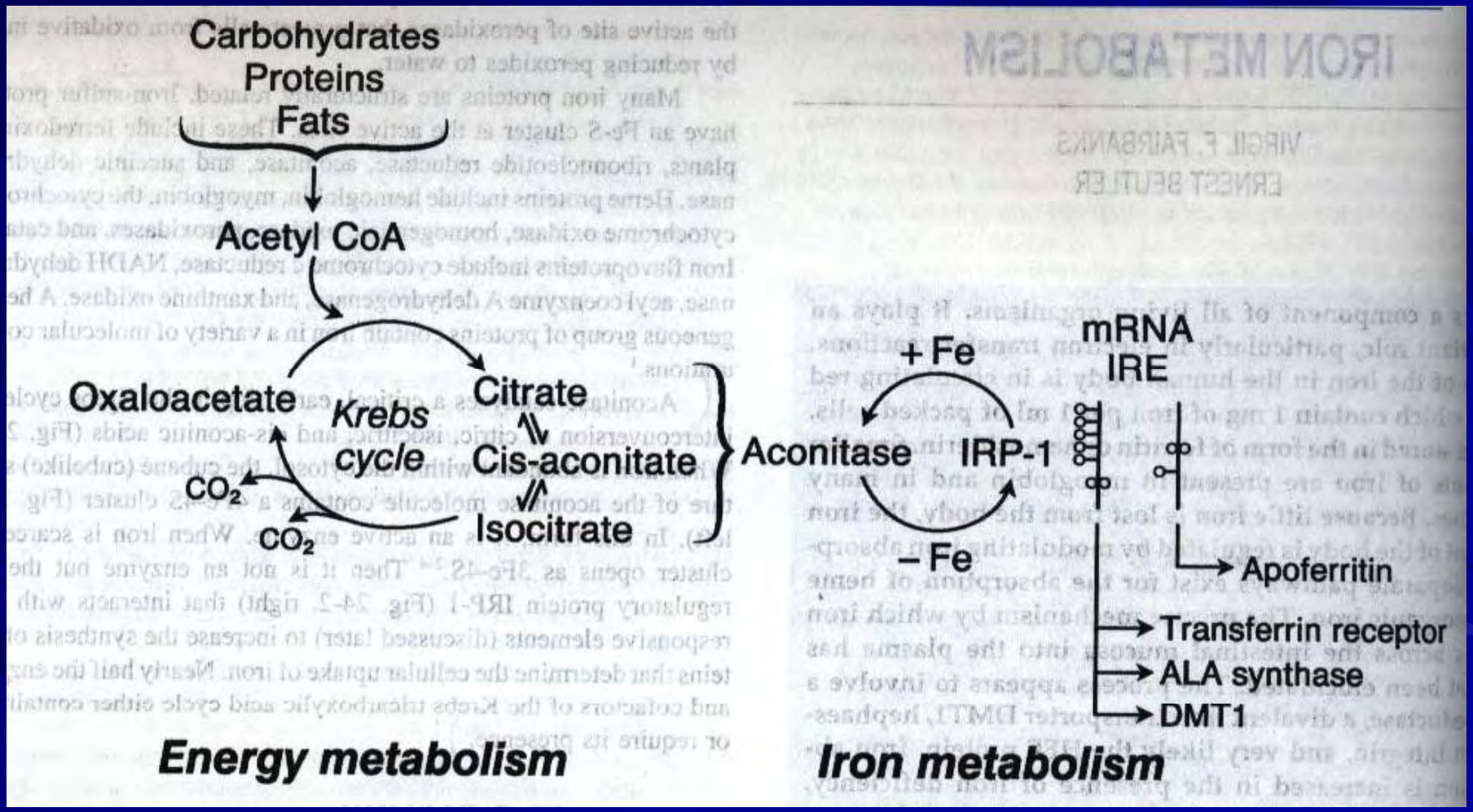


STEM-LOOP STRUCTURE IN mRNAs

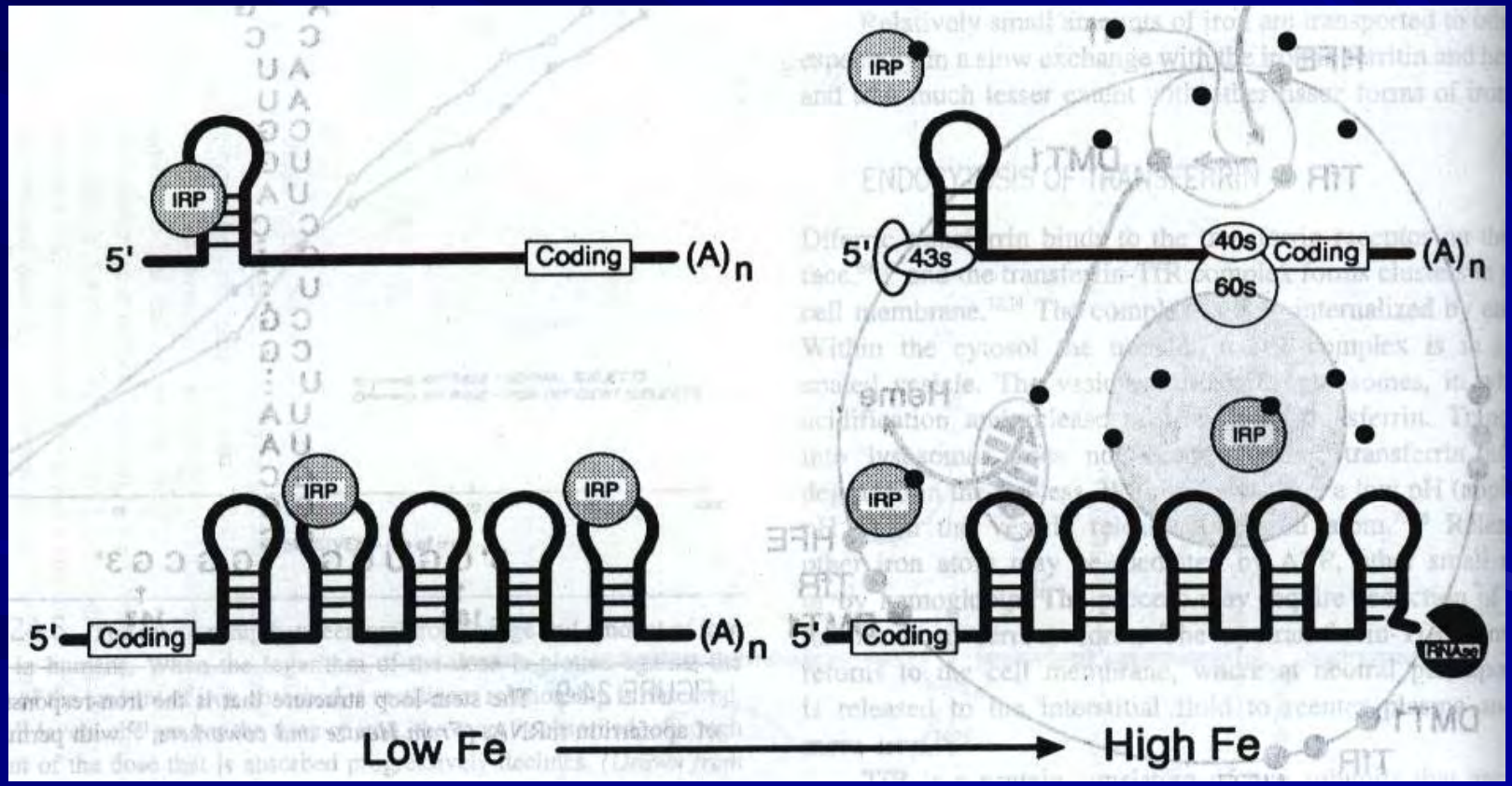
- Iron Response Elements *(IREs)*
- Iron Regulatory Protein 1 *(IRP-1)*



IRP-1 IS ACONITASE IN IRON-DEPLETED STATE



IREs IN mRNAs OF FERRITIN (*above*) AND TRANSFERIN RECEPTOR (*blow*)



IRP-1 Binding to IREs and Regulation of mRNA Translation

- **IRE in 5' end of mRNA**
  1) Its binding to IRP-1 results in mRNA degradation
  2) It is present in mRNA of Apoferritin, TfR2 and ALA synthase
- **IRE in 3' end of mRNA**
  1) Its binding to IRP-1 results in mRNA translation
  2) It is present in mRNA of Apotransferin, TfR1 and DMT-1

ABNORMALITIES IN IRON METABOLISM

ABNORMALITIES IN IRON METABOLISM

- **Iron Deficiency**
  - ***Iron Deficiency Anemia***
  - ***Anemia of Chronic Disease***
- **Iron Overload**
  - ***Hemosiderosis***
  - ***Hemochromathosis***
  - ***Sideroblastic Anemia***

IRON DEFICIENCY ANEMIA IS

- *Most Common Form of Nutritional Deficiencies in Both Developed and Developing Countries*
- *Most Common Organic Disorders in Clinical Medicine*
- *Most Common Anemia*

ETIOLOGIC FACTORS

- *Decreased Iron Intake*
- *Increased Iron Loss*
- *Increased Requirments*
- *Unknown*

DECREASED IRON INTAKE

- ***Inadequate Diet***
- ***Impaired Absorption***
  1) **Decreased Gastric Acid**
  2) **Gastric Surgery**
  3) **Celiac disease**
  4) **Pica**

INCREASED IRON LOSS

- *GI Bleeding due to Neoplasm, Hemorrhoids, Peptic Ulcer, Hookworm,…*
- *Excessive Menstural Flow*
- *Disorders of Hemostasis*

INCREASED IRON REQUIRMENTS

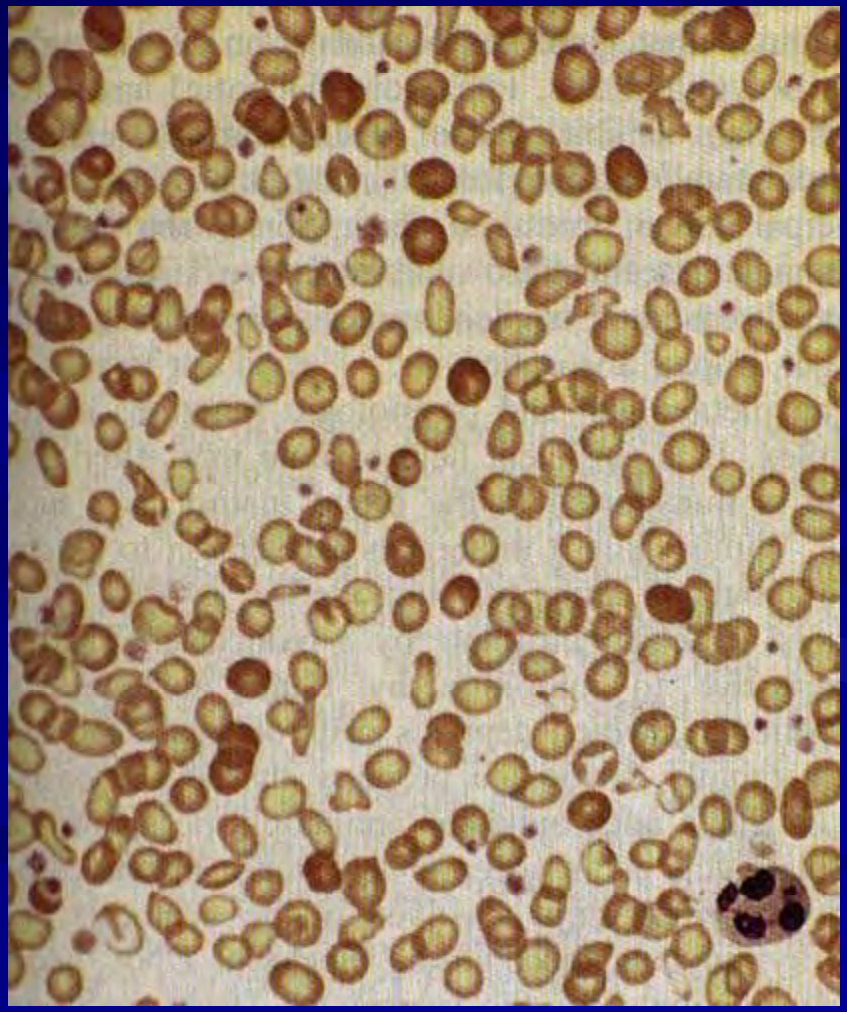
- ***Pregnancy***
- ***Lactation***
- ***Infancy***

LABORATORY DIAGNOSIS

- Blood Examination
- Bone Marrow Examination
- Serum Iron Determination
- Serum Transferin Determination
- Serum Ferritin Determination
- Serum Transferin Receptor Determination
- Erythrocyte Porphyrines Determination

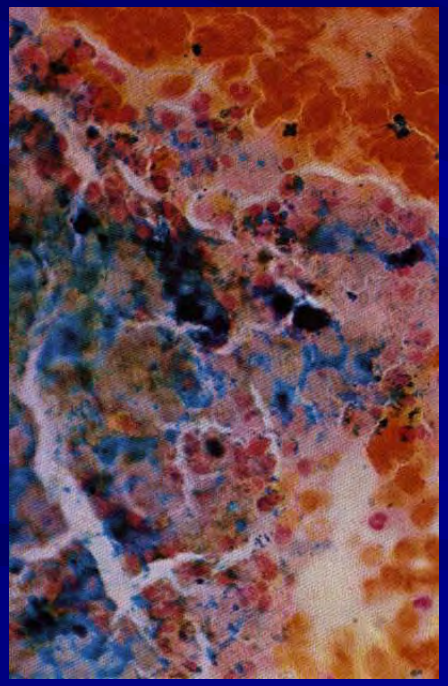
BLOOD EXAMINATION

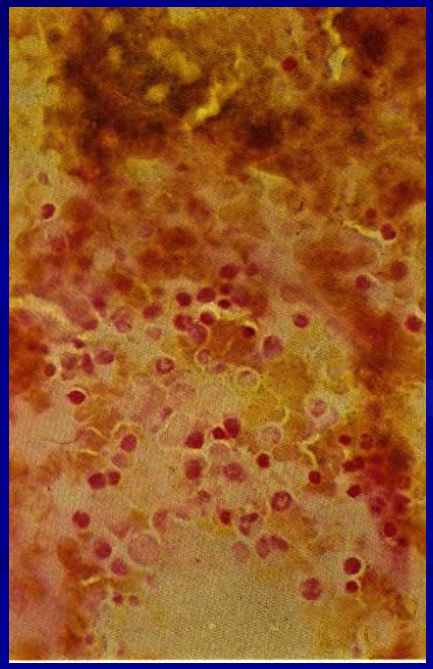
- Microcytic Hypochromic Anemia with Anisocytosis, Microcytosis, Poikilicytosis
- Reduced Hct, Hb, MCV, Retic
- Increased RDW
- Normal or Slightly Reduced Leukocyte Count with Granulocytopenia



BONE MARROW EXAMINATION

- Severly Reduced Iron Storage



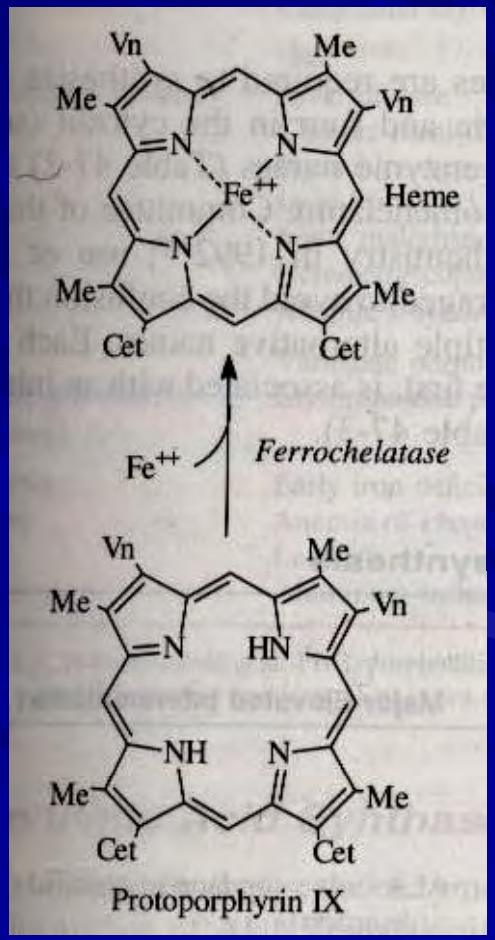


SERUM DETERMINATION OF

- IRON
- TRANSFERIN
- FERRITIN
- TRANSFERIN RECEPTOR

PORPHYRIN DETERMINATION

- Free Erythrocytic Porphyrines (FEP)
- Zinc Porotoporphyrines (ZPP)
- ZPP/H Ratio



ANEMIA OF CHRONIC DISORDERS (ACD)

GENERAL CHRACTERS

- *ACD Is Mild to Moderate Anemia That Is Often Observed in Patients with Infectious, Inflammatory or Neoplastic Diseases that Persist for More than 1 to 2 Months*
- *ACD Is Common and Occurs in 50% Hospitalized Patients*
- *According to Underlying Disorder, Clinical Manifestations Vary Widely*

CONDITIONS ASSOCIATED WITH ACD

- **Chronic Infections**
  - ***Pulmonary Infection***
  - ***Subacute Bacterial Endocarditis***
  - ***Chronic Urinary Tract Infection***
  - ***Human Immunodeficiency Virus***
  - ***Osteomyelitis***

- **Chronic Immune Disorders**
  - ***Rheumatoid Arthritis***
  - ***Systemic Lupus Erythmatosus***
  - ***Regional Enteritis***
  - ***Vasculitis***

- **Neoplasms**

  Carcinoma of Lung, Breast, …

  Hodgkin Disease

  Leukemia

  Multiple Myloma

- **Miscellaneous**

  Alcoholic Liver Disease

  Congestive Heart Failure

  Ischemic Heart Disease

PHATHOGENESIS

THERE ARE THREE PRINCIPAL ABNORMALITIES

- **Shortened Erythrocyte Survival**
- **Impaired Marrow Response**
- **Abnormal Iron Metabolism**

PHATHOGENESIS

CYTOKINE PRODUCTION IS COMMON PATHOGENIC FACTOR SHARED BY VARIOUS CONDITIONS ASSOCIATED WITH ACD

CYTOKINES MOST OFTEN IMPLICATED ARE:

1) Interleukin-1 (IL-1)

2) Tumor Necrosis Factor (TNF)

3) Interferons

SHORTENED ERYTHROCYTE SURVIVAL

- **IL-1**
- **TNF**
- **Clearance of Minimally Damaged Erythrocytes by Activated Macrophages**
- **Production of Hemolysins by Certain Tumors**
- **Localized Erythrocyte Destruction**

IMPAIRED MARROW RESPONSE

- **Inappropriately Low Erythropoietin Secretion**
- **Diminished Marrow Response to Erythropoietin**
- **Iron-Limited Erythropoiesis**

ABNORMAL IRON METABOLISM

- **There Is a Fuctional Iron Deficiency**
- **There Is a Shift of Iron from a Transferrin-bound to Ferritin-incorporated**
- **Three mechanisms Can Be Mentioned:**
  - ***1) Reduction of Transferin Synthesis***
  - ***2) Increased Ferritin Synthesis***
  - ***3) Release of Lactoferrin***

LABORATORY DIAGNOSIS

- Blood Examination
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- Serum Iron Determination
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IRON OVERLOAD

- Hemosiderosis
- Hemochromatosis
- Sideroblastic Anemia