

# IRON METABOLISM DISORDERS

## ANEMIA *Definition*

- Decrease in the number of circulating red blood cells
- Most common hematologic disorder by far

## ANEMIA

### *Causes*

- Blood loss
- Decreased production of red blood cells (Marrow failure)
- Increased destruction of red blood cells
  - Hemolysis
- Distinguished by reticulocyte count
  - Decreased in states of decreased production
  - Increased in destruction of red blood cells

## ANEMIA

### *Causes - Decreased Production*

- Cytoplasmic production of protein
  - Usually normocytic (MCV 80-100 fl) or microcytic (MCV < 80 fl)
- Nuclear division/maturation
  - Usually macrocytic (MCV > 100 fl)

## ANEMIA

### *Causes - Cytoplasmic Protein Production*

- Decreased hemoglobin synthesis
  - Disorders of globin synthesis
  - Disorders of heme synthesis
- Heme synthesis
  - Decreased Iron
  - Iron not in utilizable form
  - Decreased heme synthesis

## IRON DEFICIENCY ANEMIA

### *Prevalence*

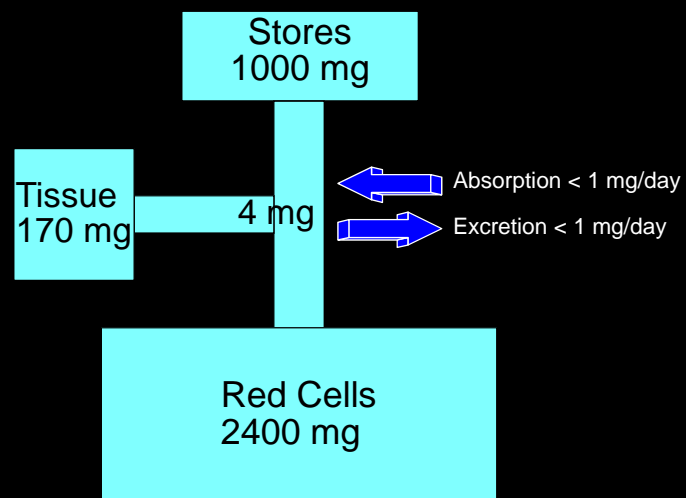
Country	Men (%)	Women (%)	Pregnant Women (%)
S. India	6	35	56
N. India		64	80
Latin America	4	17	38
Israel	14	29	47
Poland			22
Sweden		7	
USA	1	13	

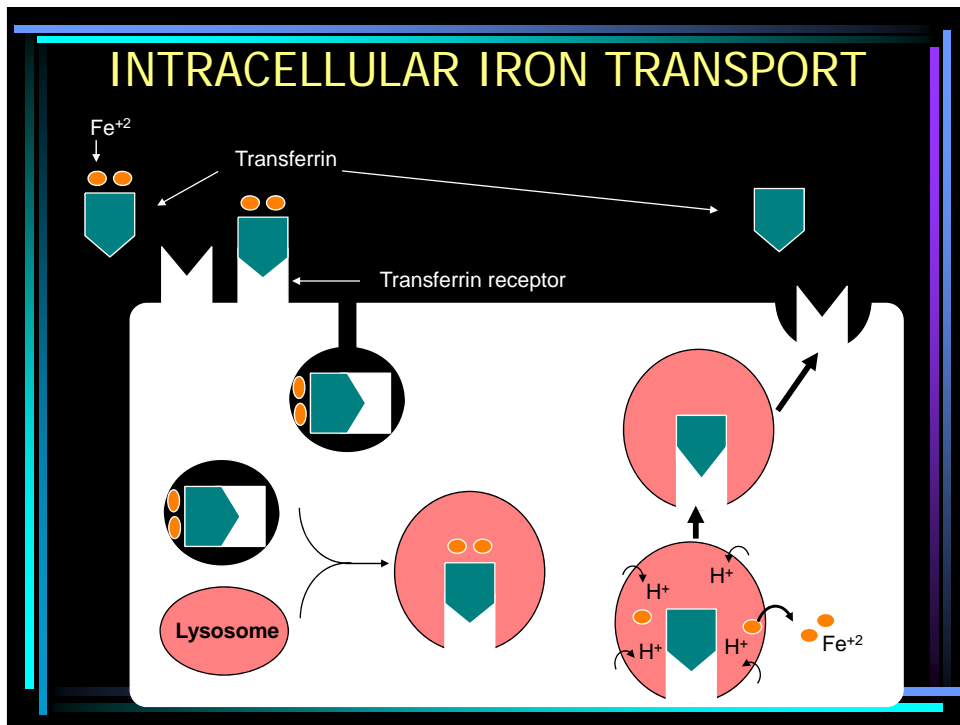
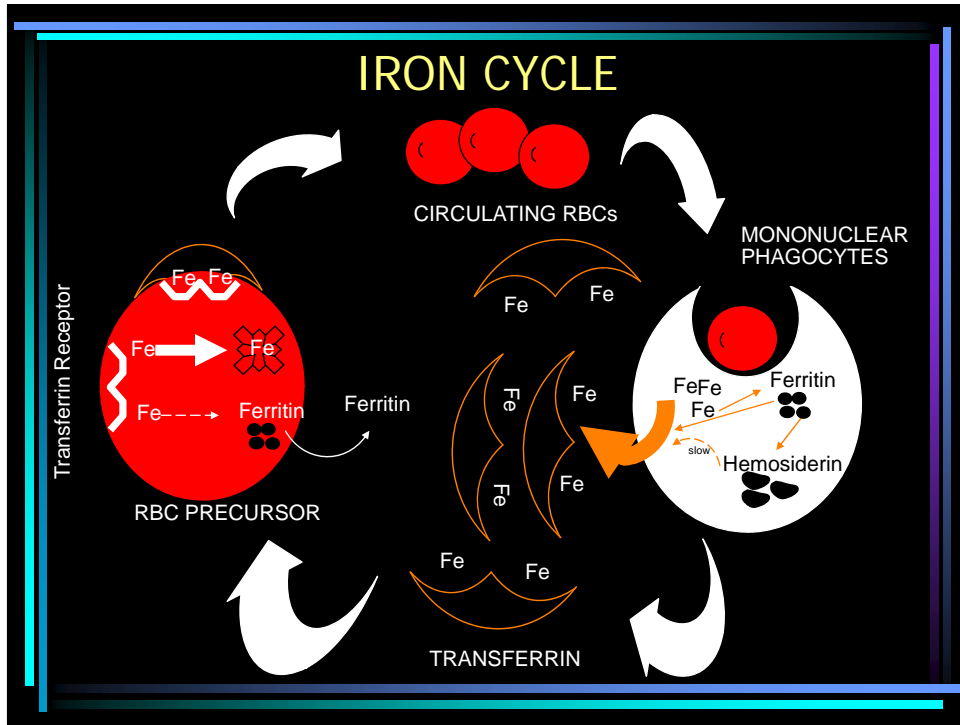
## IRON

- Functions as electron transporter; vital for life
- Must be in ferrous ( $\text{Fe}^{+2}$ ) state for activity
- In anaerobic conditions, easy to maintain ferrous state
- Iron readily donates electrons to oxygen,  $\rightarrow$  superoxide radicals,  $\text{H}_2\text{O}_2$ ,  $\text{OH}\cdot$  radicals
- Ferric ( $\text{Fe}^{+3}$ ) ions cannot transport electrons or  $\text{O}_2$
- Organisms able to limit exposure to iron had major survival advantage

## IRON

*Body Compartments - 75 kg man*



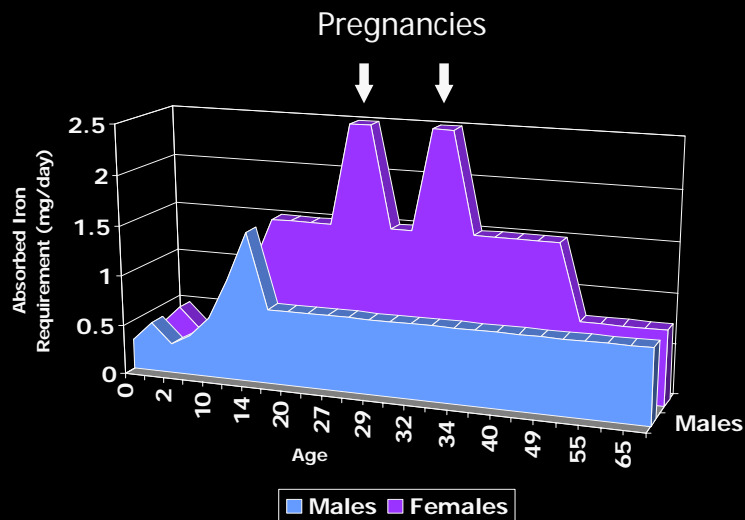


# IRON

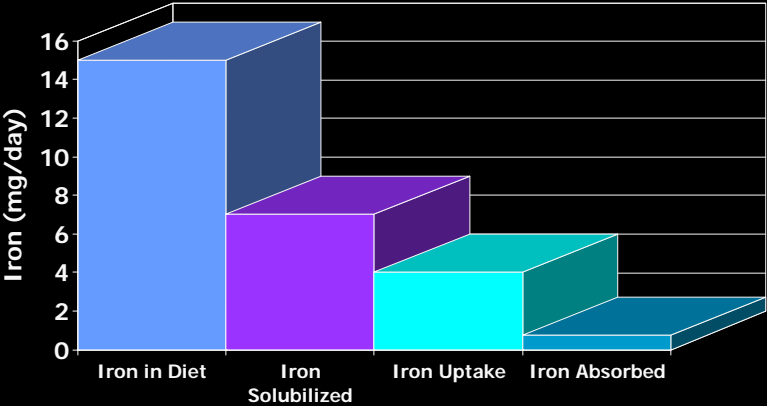
## *Causes of Iron Deficiency*

- Blood Loss
  - Gastrointestinal Tract
  - Menstrual Blood Loss
  - Urinary Blood Loss (Rare)
  - Blood in Sputum (Rarer)
- Increased Iron Utilization
  - Pregnancy
  - Infancy
  - Adolescence
  - Polycythemia Vera
- Malabsorption
  - Tropical Sprue
  - Gastrectomy
  - Chronic atrophic gastritis
- Dietary inadequacy (almost never sole cause)
- Combinations of above

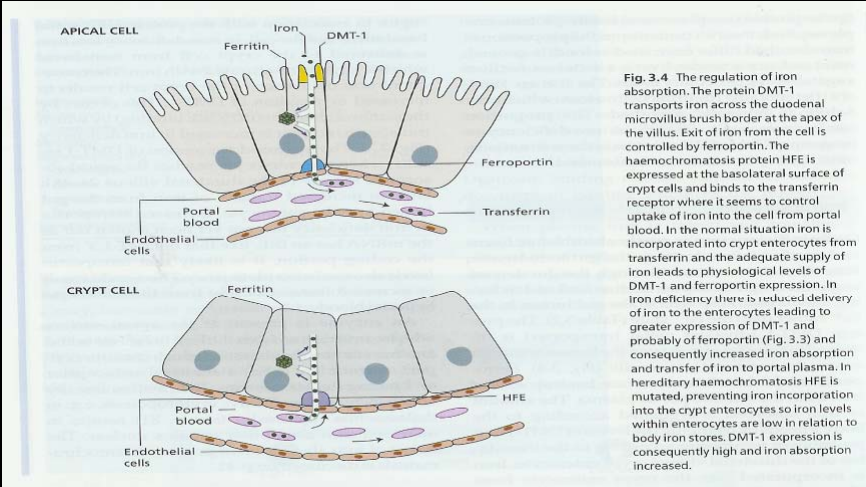
## DAILY IRON REQUIREMENTS



# IRON ABSORPTION



# GI ABSORPTION OF IRON



## FERRITIN/TRANSFERRIN REGULATION

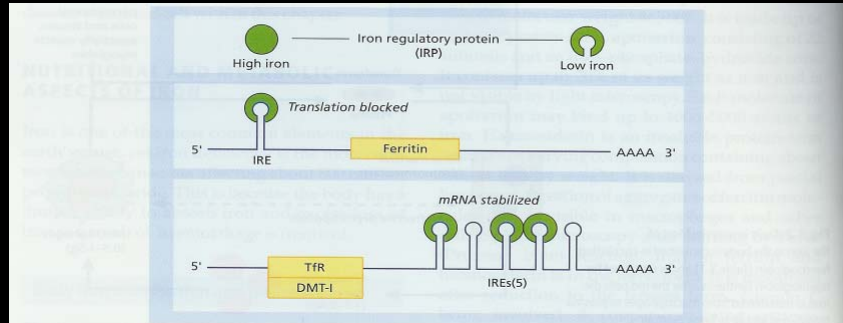
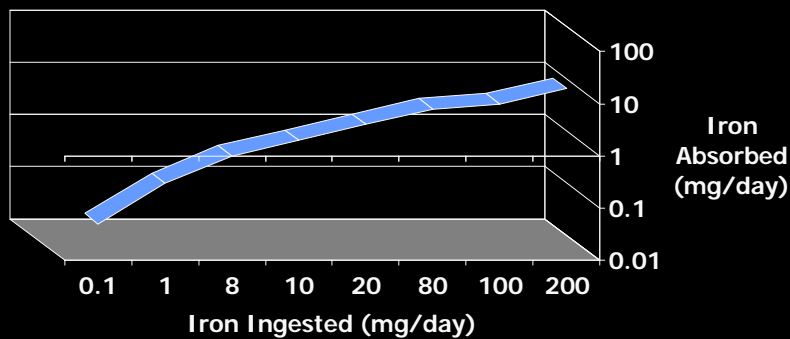


Fig. 3.3 Regulation of transferrin receptor (TfR), DMT-1 (divalent metal transporter), ferroportin and ferritin expression by iron regulatory protein (IRP) sensing of intracellular iron levels. IRPs (●) are able to bind to stem-loop structures called iron response elements (IREs) (U) in transferrin receptor or ferritin messenger RNAs (mRNAs). IRP binding to the IRE within the 3' untranslated region of the former leads to stabilization of mRNA levels and

increased protein synthesis whereas IRP binding to the IRE within the 5' untranslated region of ferritin mRNA reduces translation. IRPs can exist in two states — at times of high iron levels the IRP binds iron and exhibits a reduced affinity for the IREs whereas when iron levels are low the binding of IRPs to IREs is increased. In this way synthesis of TfR, DMT-1 and ferritin is coordinated to physiological requirements.

## IRON ABSORPTION

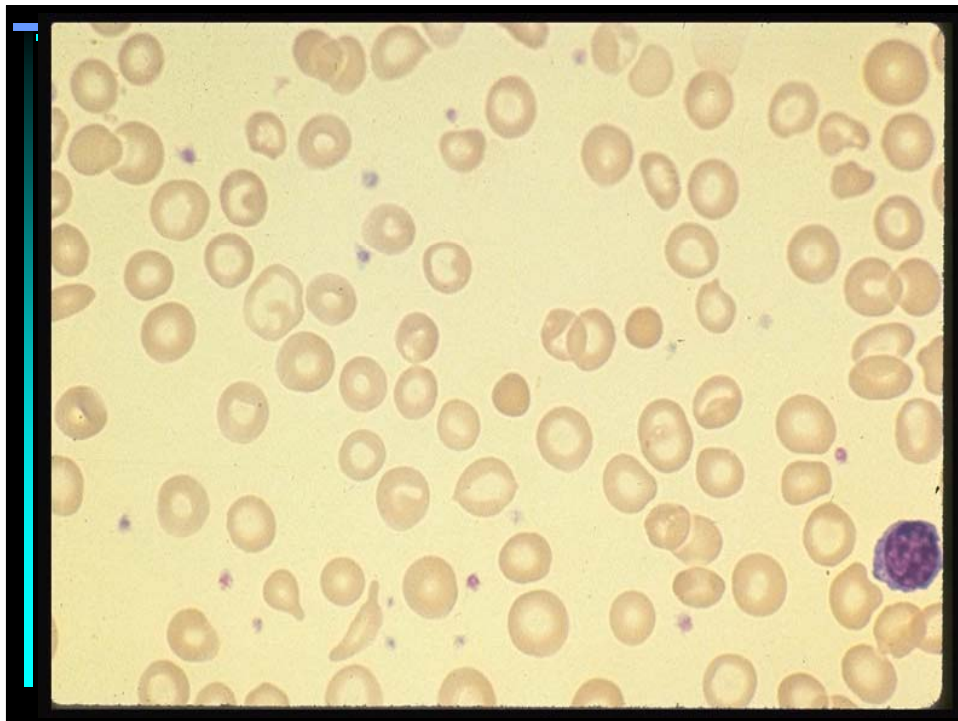


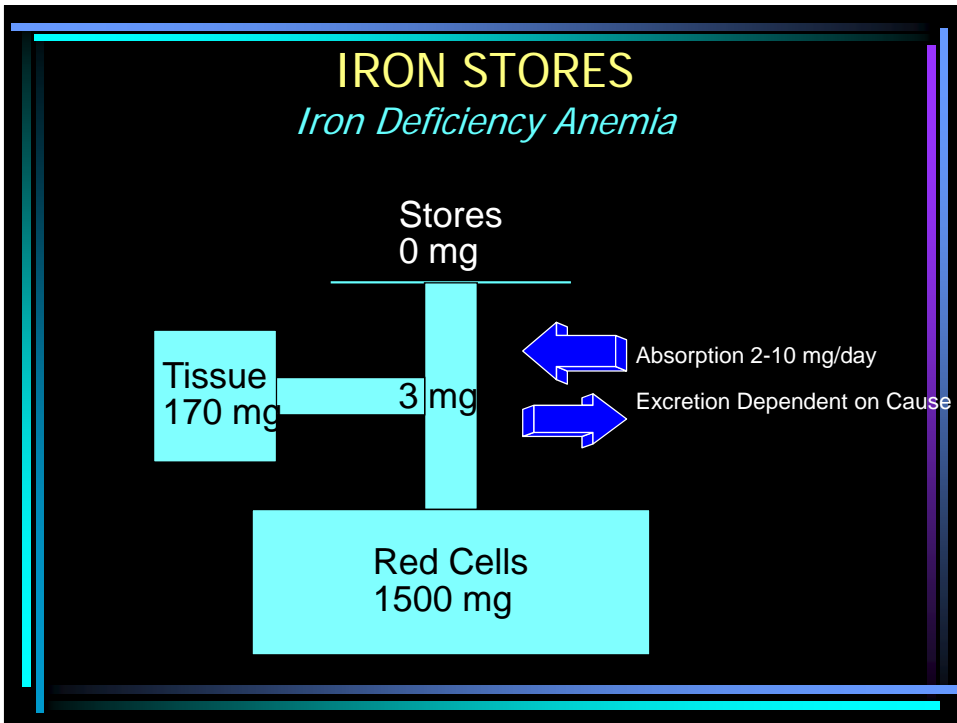
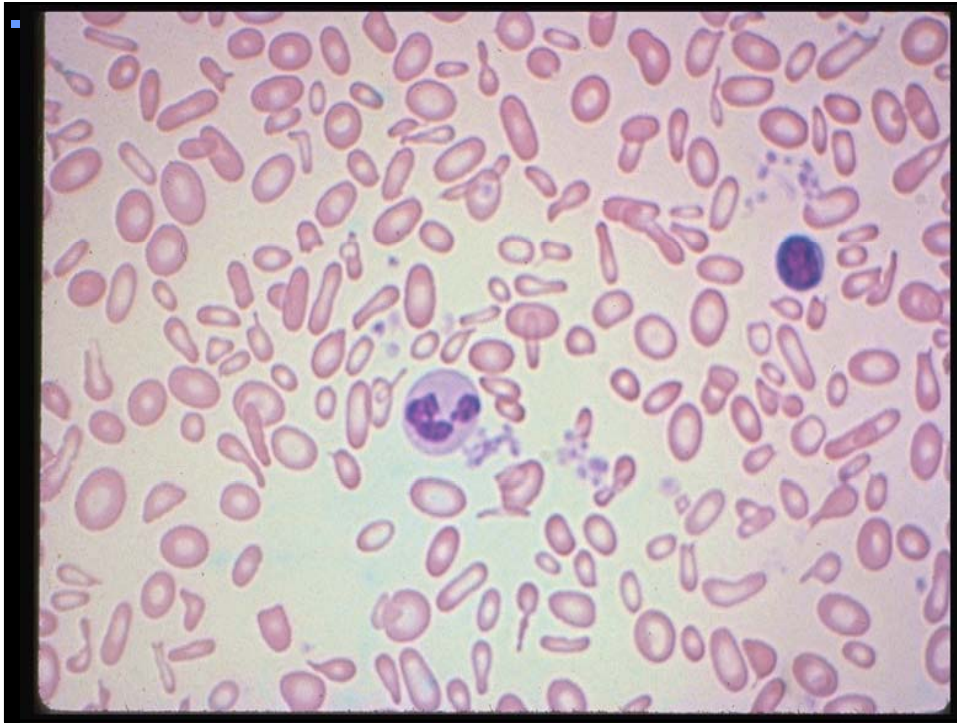


## IRON DEFICIENCY ANEMIA

### *Progression of Findings*

- Stainable Iron, Bone Marrow Aspirate
- Serum Ferritin - Low in Iron Deficiency
- Desaturation of transferrin
- Serum Iron drops
- Transferrin (Iron Binding Capacity) Increases
- Blood Smear - Microcytic, Hypochromic; Aniso- & Poikilocytosis
- Anemia





## IRON DEFICIENCY

### *Symptoms*

- Fatigue - Sometimes out of proportion to anemia
- Atrophic glossitis
- Pica
- Koilonychia (Nail spooning)
- Esophageal Web

## IRON

### *Causes of Iron Deficiency*

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- Increased Iron Utilization
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## IRON REPLACEMENT THERAPY

### Response

- Usually oral; usually 300-900 mg/day
- Requires acid environment for absorption
- Poorly absorbed

## IRON THERAPY

### Response

- Initial response takes 7-14 days
- Modest reticulocytosis (7-10%)
- Correction of anemia requires 2-3 months
- 6 months of therapy beyond correction of anemia needed to replete stores, assuming no further loss of blood/iron
- Parenteral iron possible, but problematic

## Hemochromatosis-1

- Disease of excess iron uptake
- 2% of population has hemochromatosis; inherited as autosomal dominant
- Exists worldwide, but
  - Belt across Northern Europe with increased incidence
    - Ireland, Scandinavia, Russia
- Defects can be in DMT-1, more commonly in HFE (genetic defects only really studied for northern Europeans)
- Can also have acquired hemochromatosis, from transfusion for other illnesses

## Hemochromatosis -2

- Defect in HFE causes decreased iron uptake by crypt enterocytes
- Leads to increased DMT-1, causing increased iron extraction from diet & increased iron delivery to tissues
- Once iron is absorbed, very difficult to remove

## Hemochromatosis-3

- Sequence of events:
  - Increased ferritin
  - Increased transferrin saturation
    - Normal c. 33%; if > 60%, often marker for disease; if > 90-95%, can start to get free iron
- Increased iron binding to other transport proteins
  - Albumin
- Iron deposition in tissues, leading to:

## Hemochromatosis-4

- Diseases
  - Skin darkening
    - Due to iron deposition in skin causing increased melanin production
  - Endocrinopathy
    - Diabetes, hypothyroidism, hypopituitarism
  - Liver damage
    - Can lead to cirrhosis, hepatocellular CA
  - Cardiac damage
    - Cardiomyopathy leading to congestive heart failure

## Hemochromatosis-5

- Treatment
  - Early recognition
  - Phlebotomy
  - Iron chelation – Generally reserved for transfusion-induced hemochromatosis

## ANEMIA OF CHRONIC DISEASE

### *Findings*

- Mild, non-progressive anemia (Hgb c. 10, Hct c. 30%)
- Other counts normal
- Normochromic/normocytic (30% hypochromic/microcytic)
- Mild aniso- & poikilocytosis
- Somewhat shortened RBC survival
- Normal reticulocyte count (Inappropriately low for degree of anemia)
- Normal bilirubin
- EPO levels increased but blunted for degree of anemia

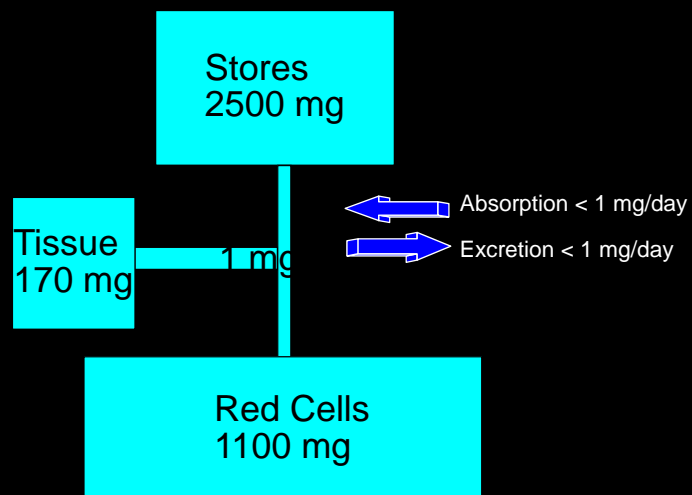
## ANEMIA OF CHRONIC DISEASE

### Causes

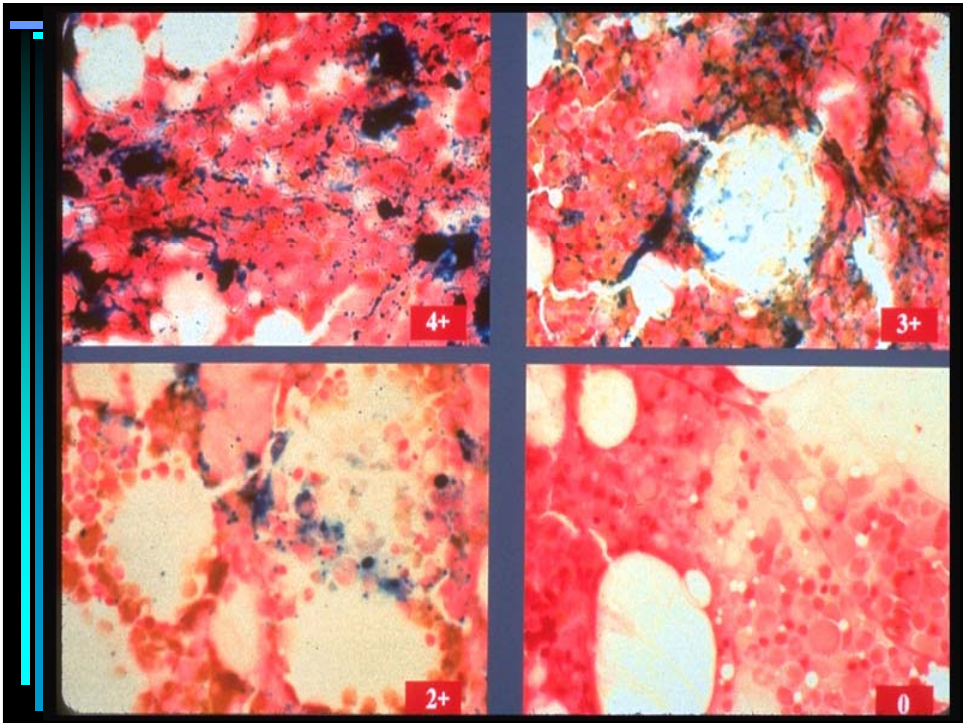
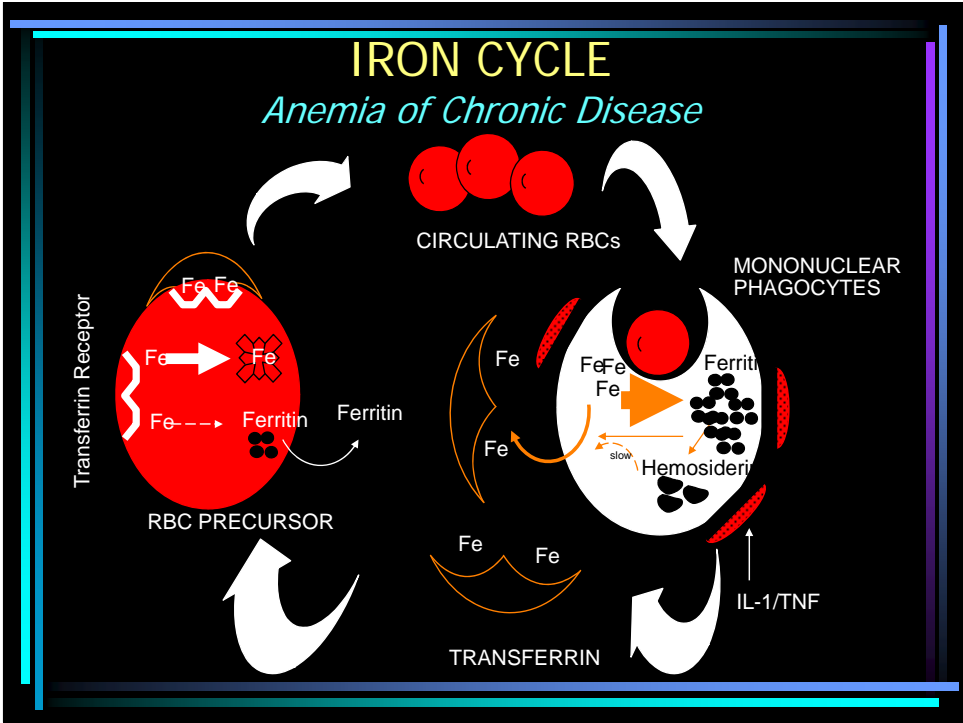
- Thyroid disease
- Collagen Vascular Disease
  - Rheumatoid Arthritis
  - Systemic Lupus Erythematosus
  - Polymyositis
  - Polyarteritis Nodosa
- Inflammatory Bowel Disease
  - Ulcerative Colitis
  - Crohn's Disease
- Malignancy
- Chronic Infectious Diseases
  - Osteomyelitis
  - Tuberculosis
- Familial Mediterranean Fever

## IRON STORES

### Anemia of Chronic Disease







## IRON DEFICIENCY *versus* ACD

	Serum Iron	Transferrin	Ferritin
Iron Deficiency	↓	↑	↓
ACD	↓	↓	↑

### Soluble Transferrin Receptor

- Measure of ferrokinetic activity
- Elevated in iron deficiency
- Not usually elevated in anemia of chronic inflammation (not an acute phase reactant)
- Still not widely available
- Expensive
- May replace iron binding capacity &/or ferritin

## SUMMARY

### *Iron Metabolism Disorders*

- Most common form of anemia
- Symptom of pathologic process
- Primary manifestation is hematologic
- Treatment requires:
  - Replacement therapy
  - Correction of underlying cause (if possible)
- Iron excess more dangerous than iron deficiency