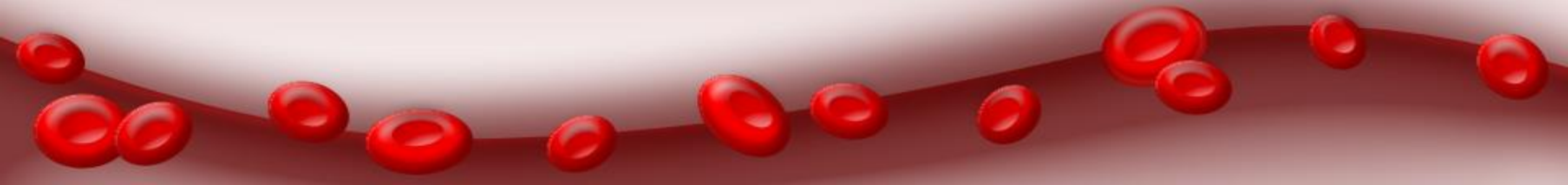


# Control of Erythropoiesis, Iron Metabolism and Hemoglobin

*Dr. Ahmed Alsabih*



# Objectives;

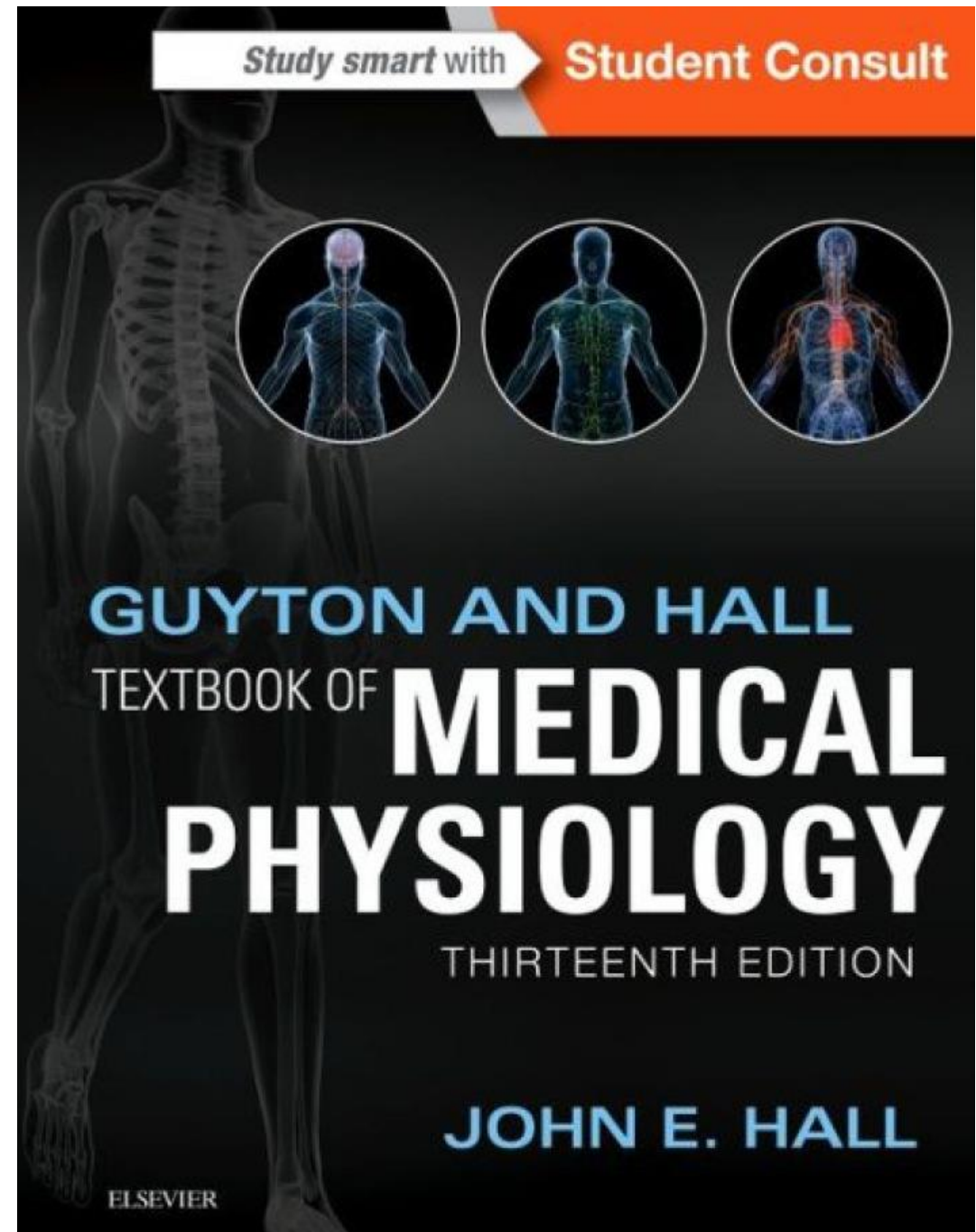
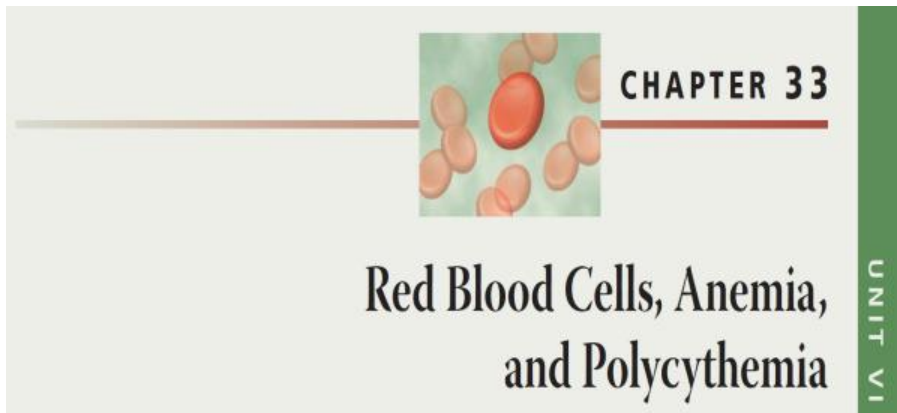
## Intended learning outcomes (ILOs)

**After reviewing the PowerPoint presentation and the associated learning resources, the student should be able to:**

- **Discuss regulation of erythropoiesis**
- **Describe the factors required for normal erythropoiesis and the role of erythropoietin in erythropoiesis**
- **Recognize clinical conditions associated with high level of erythropoietin in the blood**
- **Summarize the synthesis of Hemoglobin**
- **Recognize hemoglobin structure and its functions**
- **Describe metabolism of iron and vitamin B12**
- **Define Anaemia**
- **Classify Anaemia and explain its assessment**
- **Describe the physiological consequences and clinical picture of Anaemia**
- **Define polycythemia**
- **Classify polycythemia**
- **Describe the physiological consequences of polycythemia**

# Learning Resources

- ❑ Guyton and Hall, Textbook of Medical Physiology; 13<sup>th</sup> Edition; Unit VI-Chapter 33.



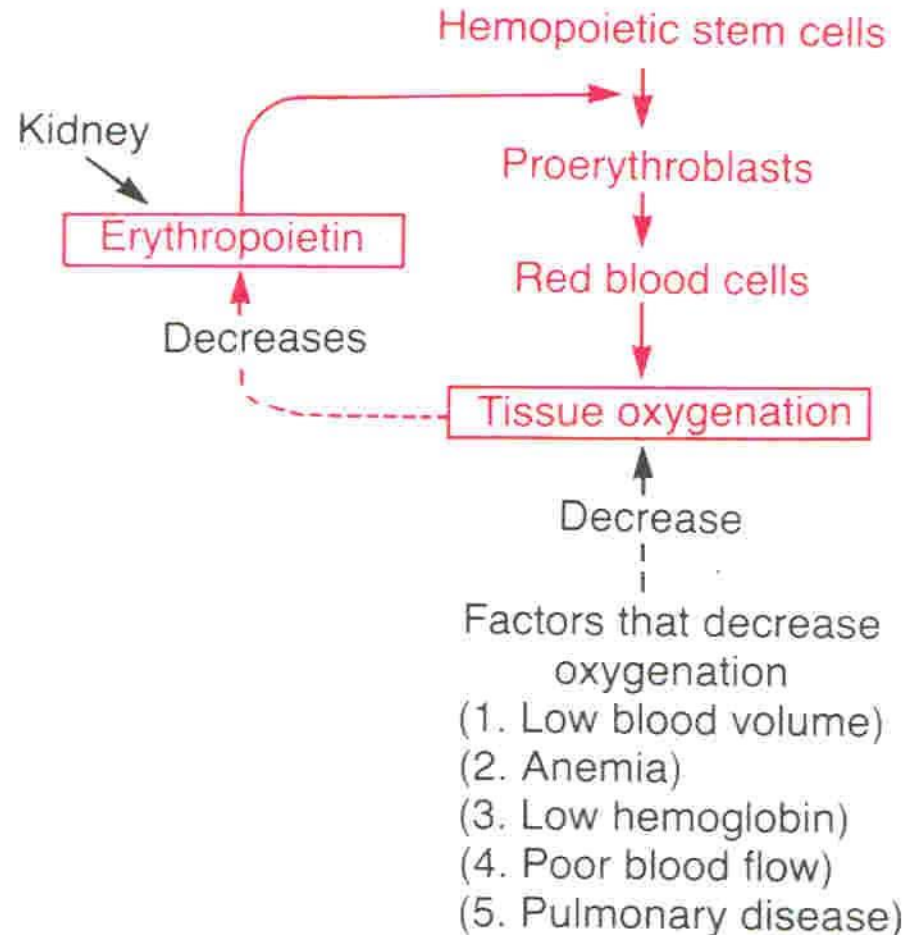
# Regulation of Erythropoiesis

- ❑ Erythropoiesis is under the influence of **erythropoietin**
  
- ❑ **Other Factors Influencing Rate of Erythropoiesis:**
  - ❑ **Hormones:** androgens (testosterone), thyroxin, growth hormone and cortisol stimulate erythropoiesis. Deficiency of any of these hormones results in Anaemia
  
  - ❑ **Adequate diet:**
    - ❑ **Amino acids:** are important for the formation of globin in Hb. Severe protein deficiency → Anaemia
    - ❑ **Iron (Fe):** 60-70% of iron in the body is in the Hb inside the RBCs. Fe is important for the formation of heme in Hb. Iron deficiency → iron-deficiency Anaemia (microcytic hypochromic Anaemia)
    - ❑ **Vitamins:**
      - ❑ Vitamins B<sub>12</sub> and folic acid are important for the synthesis of nucleoproteins (DNA) and final maturation of RBCs. Deficiency of Vitamins B<sub>12</sub>, folic acid → megaloblastic Anaemia. **Pernicious Anaemia** is due to deficiency of Vit. B<sub>12</sub> due to lack of intrinsic factor produced by gastric mucosa, which is needed for Vit B<sub>12</sub> absorption. **Pernicious Anaemia** is an autoimmune condition in which the body's immune system attacks the actual intrinsic factor protein or the parietal cells in the lining of the stomach that make it.
      - ❑ Other vitamins :Vit B<sub>6</sub>, Riboflavin, nicotinic acid, biotin (B<sub>7</sub>), Vit C, Vit E

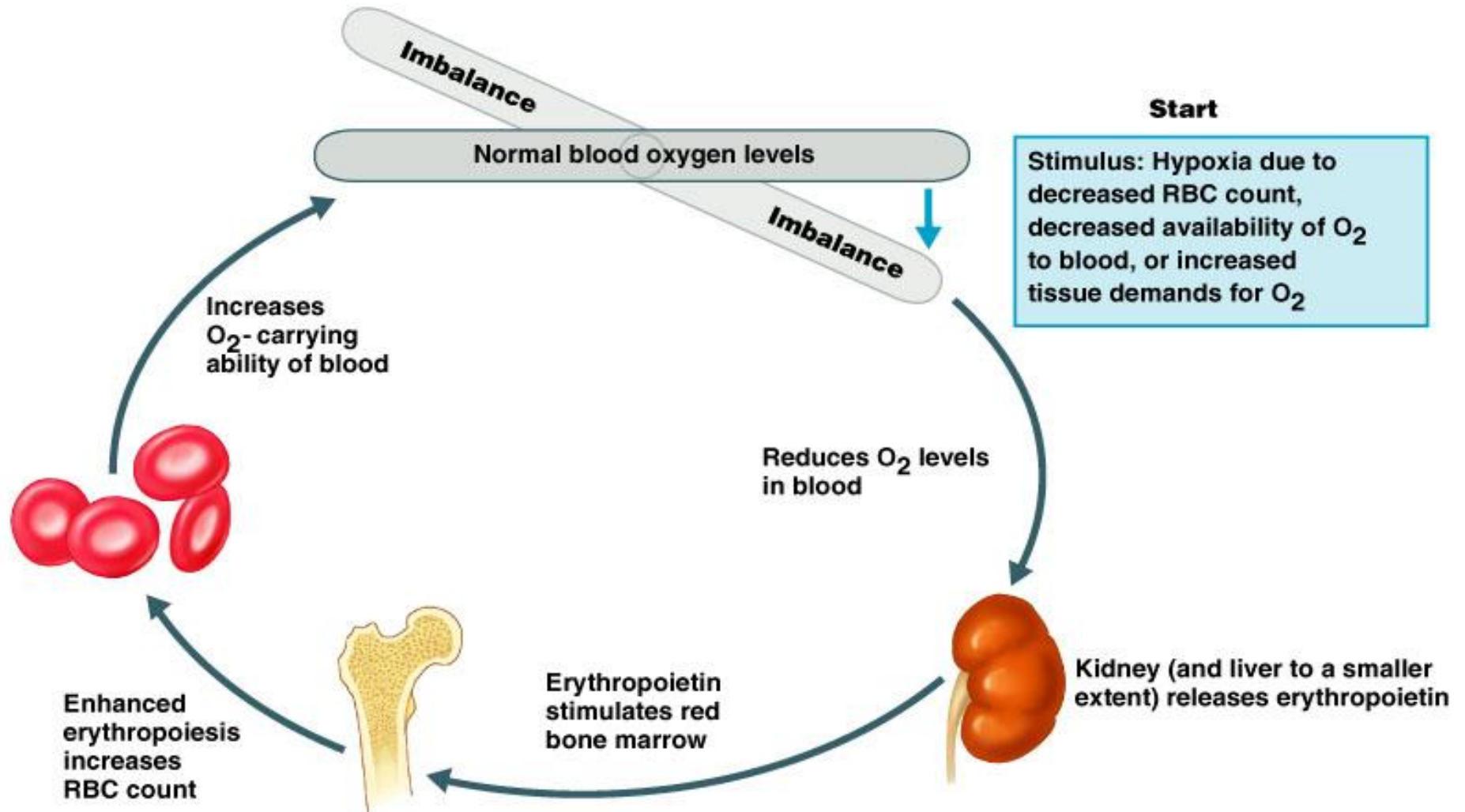
# Erythropoietin

- ❑ Erythropoiesis is stimulated by erythropoietin
- ❑ Erythropoietin is a glycoprotein, which is synthesized from renal cortex (90%) and the liver (10%)
- ❑ Erythropoietin stimulate the production of proerythroblasts from hematopoietic stem cells in the bone marrow. Once the proerythroblasts are formed, erythropoietin causes these cells to pass more rapidly through the different erythroblastic stages and can increase it to perhaps 10 or more times normal
- ❑ Erythropoietin can be measured in plasma & urine
- ❑ High level of erythropoietin are produced in response to hypoxia ( $\downarrow O_2$ ), which can be caused by:
  - ❑ Low RBC count (Anaemia)
  - ❑ Hemorrhage
  - ❑ High altitude
  - ❑ Prolong heart failure
  - ❑ Lung disease

# Feedback Control of Erythropoiesis



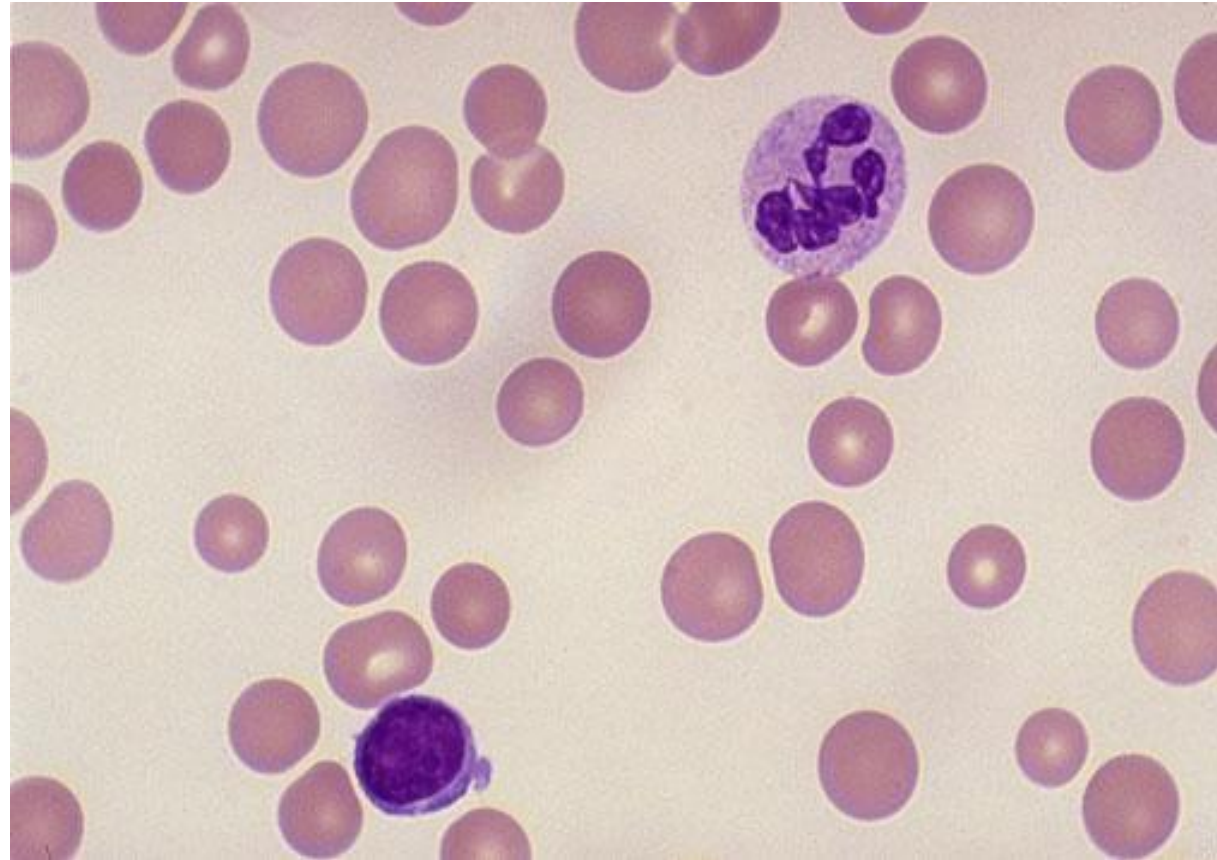
# Feedback Control of Erythropoiesis





# Vitamin B<sub>12</sub> and Folic Acid

- ❑ Important for DNA synthesis and final maturation of RBCs.
- ❑ Dietary sources include: meat, milk, liver, fat, green vegetables.
- ❑ Deficiency leads to:
  - ❑ Failure of nuclear maturation & division
  - ❑ Abnormally large & oval shaped RBCs
  - ❑ Short life span of RBCs
  - ❑ Reduced RBC count & Hb concentration
  - ❑ Macrocytic (megaloblastic) Anaemia



**Note the hypersegmented neutrophil and also that the RBC are almost as large as the lymphocyte. Finally, note that there are fewer RBCs.**



# Causes of Vitamin B<sub>12</sub> Deficiency

## Causes of vitamin B<sub>12</sub> deficiency

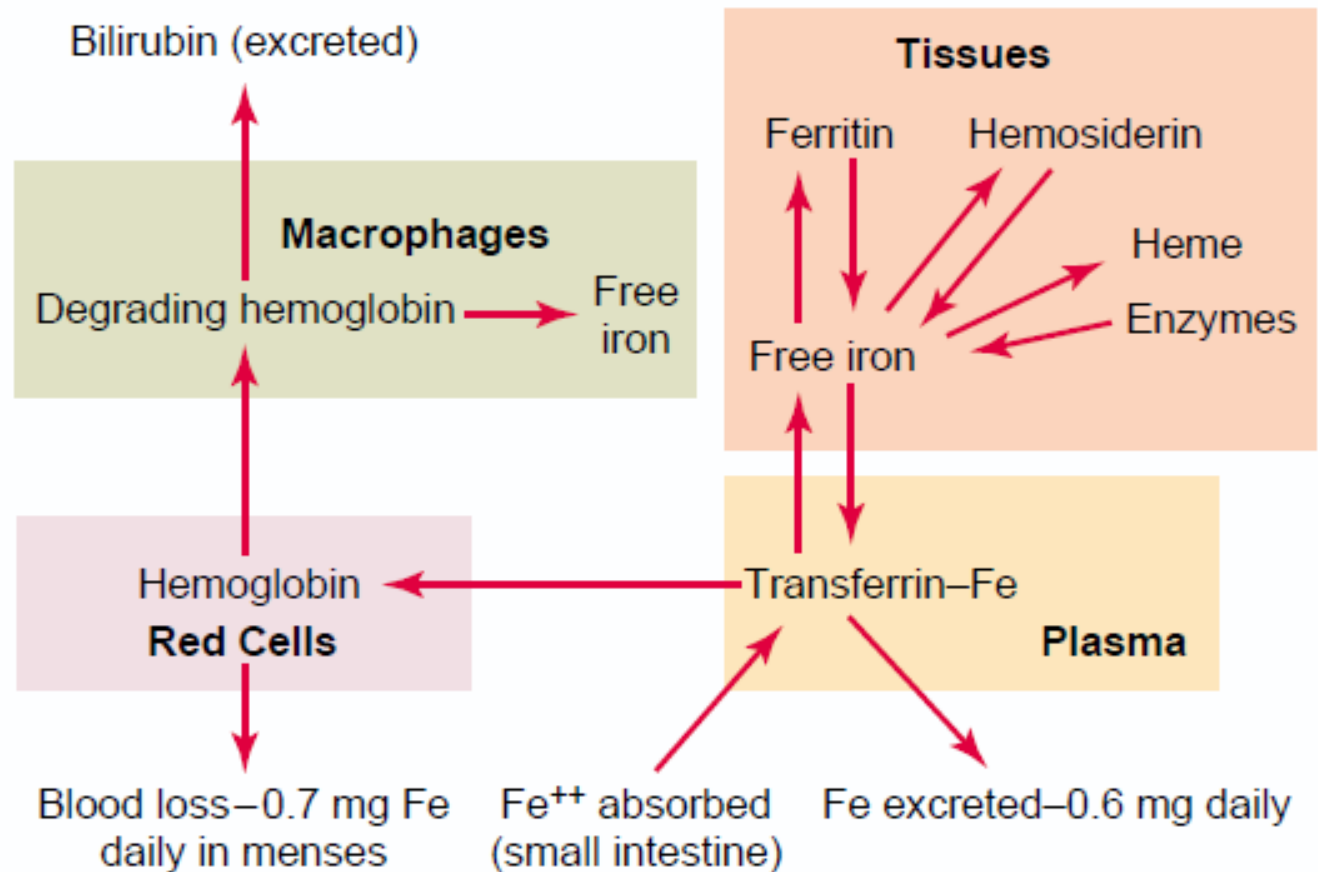
Cause	Particulars
Inadequate intake	Alcohol consumption Vegetarian diet
Malabsorption	Food vitamin B <sub>12</sub> malabsorption Lack of intrinsic factor or parietal cell <ul style="list-style-type: none"><li>• Pernicious anaemia</li><li>• Atrophic gastritis</li><li>• Post-gastrectomy</li></ul> Ileal malabsorption <ul style="list-style-type: none"><li>• Ileal resection</li><li>• Crohn's disease</li></ul> Bacterial overgrowth
Defective transport	Transcobalamin deficiency (genetic)

# Iron Metabolism

- ❑ Iron is needed for the synthesis of hemoglobin, myoglobin, cytochrome oxidase, peroxidase & catalase
- ❑ The total quantity of iron in the body averages 4-5 g
  - ❑ Hemoglobin: 65-75% (3 g)
  - ❑ Stored iron: 15-30%, particularly in the form of ferritin in the liver, spleen and bone marrow.
  - ❑ Myoglobin: 4%
  - ❑ Heme compounds that promote intracellular oxidation (cytochrome): 1%
  - ❑ Plasma iron: (transferrin): 0.1%
- ❑ A man excretes about 0.6 mg of iron each day, mainly into the feces. Additional quantities of iron are lost when bleeding occurs. For a woman, additional menstrual loss of blood brings long-term iron loss to an average of about 1.3 mg/day.
- ❑ Diet provides 10-20 mg iron per day.
- ❑ Only 10% of dietary iron is absorbed (1 – 2 mg ).
- ❑ Iron in food mostly in oxidized form (Ferric,  $F^{+3}$ ). It is better absorbed in reduced form (Ferrous,  $F^{+2}$ ). Iron in stomach is reduced by gastric acid, and Vitamin C.

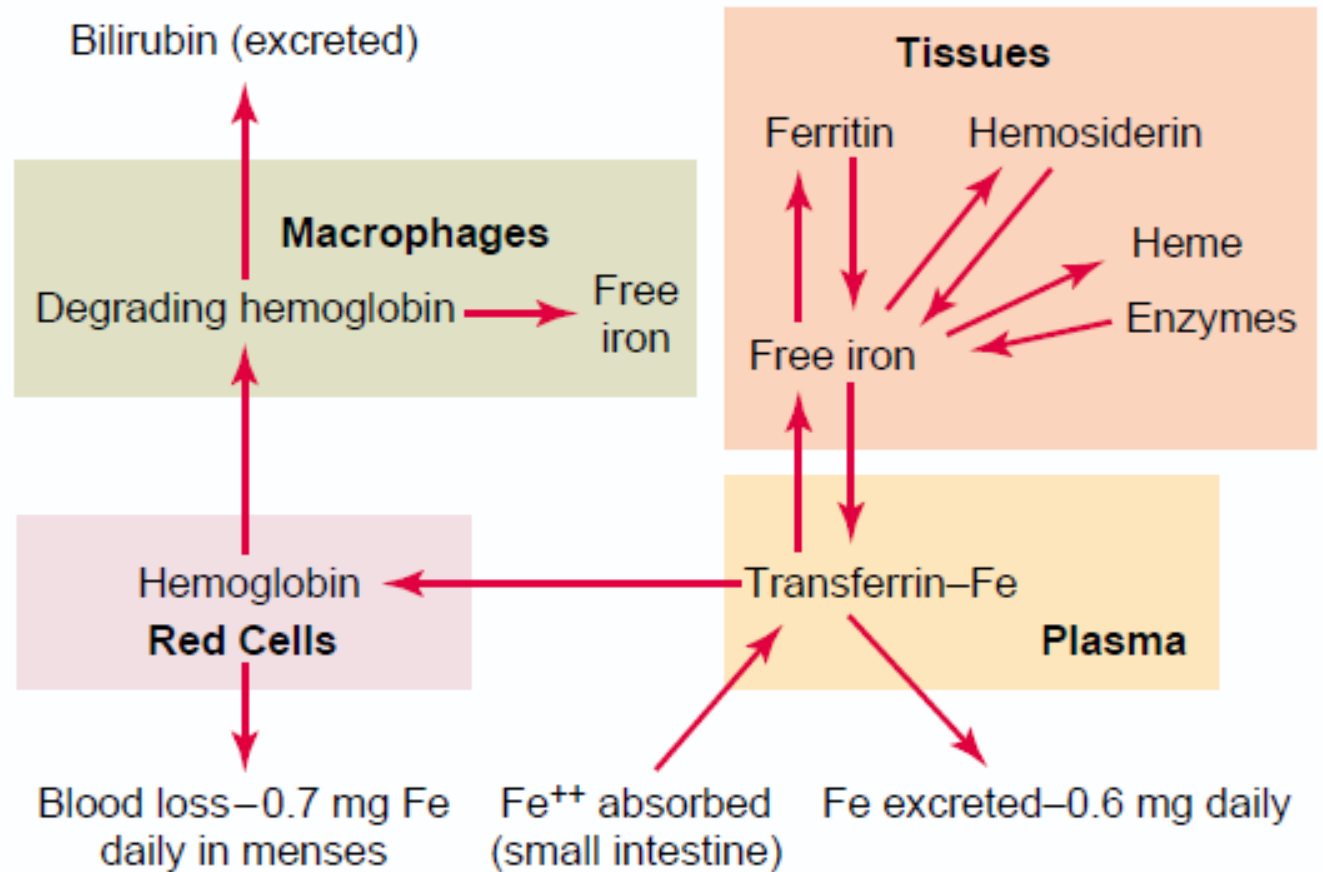
# Iron Absorption, Transport and Metabolism

- ❑ Iron is absorbed from all parts of the small intestine,
- ❑ The liver secretes apotransferrin into the bile.
- ❑ In the duodenum, the apotransferrin binds with iron forming transferrin.
- ❑ The formed transferrin is absorbed into the intestinal epithelial cells by receptor-mediated pinocytosis. This is later released into the blood capillaries in the form of plasma transferrin.
- ❑ Only a few milligrams of iron can be absorbed per day. Thus, even when tremendous quantities of iron are present in the food, only small proportions can be absorbed.



# Iron Absorption, Transport and Metabolism

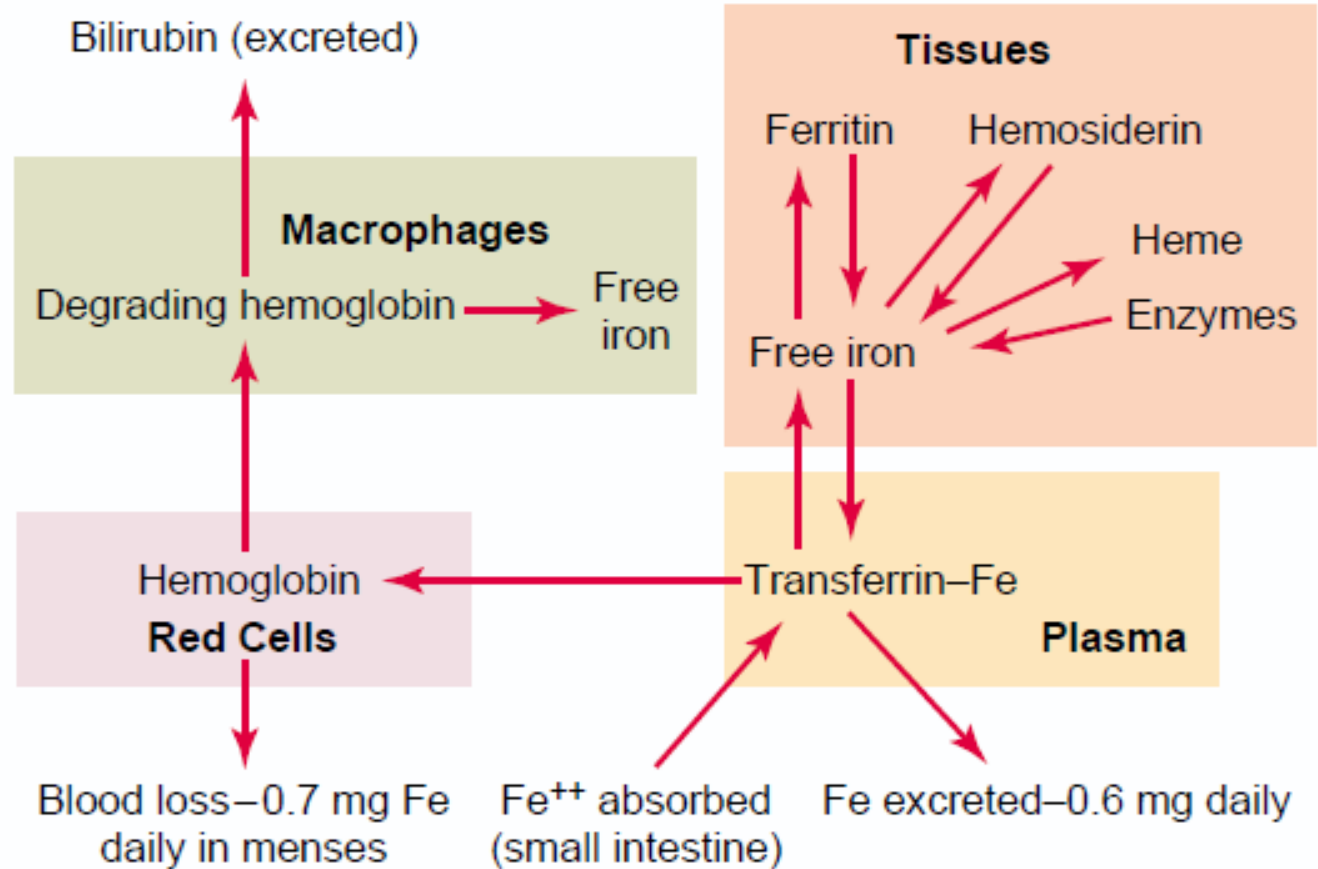
- ❑ When iron is absorbed from the small intestine, it immediately combines in the blood plasma with *apotransferrin*, to form *transferrin*, which is then transported in the plasma.
- ❑ The iron is loosely bound in the transferrin and, consequently, can be released to any tissue cell at any point in the body.
- ❑ Excess iron in the blood is deposited and stored especially in the liver hepatocytes and less in the Reticuloendothelial cells of the bone marrow.



- ❑ In the cell cytoplasm, iron combines mainly with a protein, *apoferritin*, to form *ferritin*. This iron stored as ferritin is called *storage iron*.
- ❑ Smaller quantities of the iron in the storage pool are in an extremely insoluble form called *hemosiderin*. This is especially true when the total quantity of iron in the body is more than the apoferritin storage pool can accommodate.

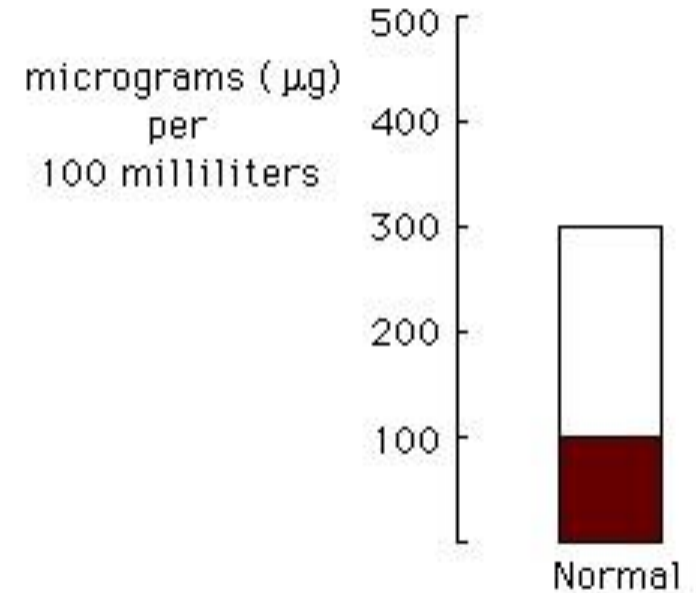
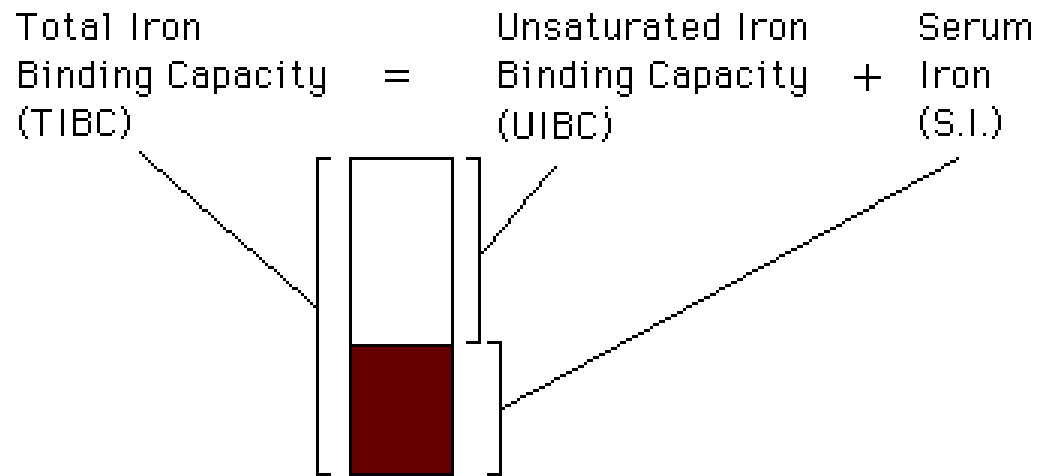
# Iron Absorption, Transport and Metabolism

- ❑ When the body has become saturated with iron so that all apoferritin is already combined with iron, the rate of additional iron absorption from the intestinal tract becomes greatly decreased.
- ❑ Conversely, when the iron stores have become depleted, the rate of absorption can accelerate probably five or more times normal.
- ❑ Thus, total body iron is regulated mainly by altering the rate of absorption.



# Serum Iron and Total Iron Binding Capacity (TIBC)

## Serum Iron and Iron Binding Capacity



- ❑ Normally transferrin in the plasma is 30-40% saturated with iron, giving a plasma iron level of 100-130  $\mu\text{g}/100\text{ml}$
- ❑ When transferrin is 100% saturated with iron  $\rightarrow$  plasma iron level reaches 300  $\mu\text{g}/100\text{ml}$ . This is referred to as Total Iron Binding Capacity (TIBC)



# Anaemia and Polycythemia

**Anaemia** is decrease in RBC mass as determined by Hct or Hb values below reference level for age and gender.

The major causes of anaemia are:

1. RBC Loss without RBC destruction
2. Decreased RBC production
3. Increased RBC destruction over production

**Polycythaemia** is increase in RBC mass as determined by Hct or Hb values above reference level for age and gender

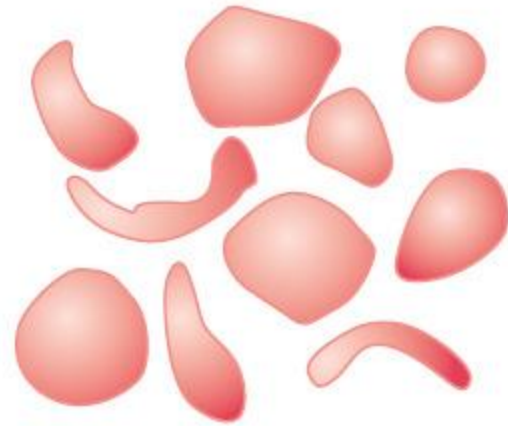
# Anaemia

RBC loss without RBC Destruction	Decreased RBC Production	Increased RBC Destruction over Production (Hemolytic Anaemias)
<ul style="list-style-type: none"> <li>– Hemorrhage               <ul style="list-style-type: none"> <li>Due to trauma</li> <li>Due to disorders: e.g.cancer, ulcers</li> </ul> </li> <li>– Menstrual flow</li> <li>– Gynecological disorders</li> <li>- Parasitism               <ul style="list-style-type: none"> <li>Hookworms</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>– Neoplasia               <ul style="list-style-type: none"> <li>Leukemia</li> </ul> </li> <li>– Myelofibrosis</li> <li>– Pernicious Anaemia</li> <li>– Iron Deficiency Anaemia</li> <li>– Aplastic Anaemia               <ul style="list-style-type: none"> <li>Chloramphenicol administration</li> </ul> </li> <li>–Renal disease (lack of erythropoietin production)</li> </ul>	<ul style="list-style-type: none"> <li>– <b>Intrinsic Abnormalities</b> <ul style="list-style-type: none"> <li>Hereditary Spherocytosis</li> <li>Thalassemia</li> <li>Sickle Cell Anaemia</li> <li>G6PD deficiency</li> <li>Hexokinase deficiency</li> </ul> </li> <li>– <b>Extrinsic Abnormalities</b> <ul style="list-style-type: none"> <li>Infections               <ul style="list-style-type: none"> <li>Malaria</li> <li>Mycoplasma</li> </ul> </li> </ul> </li> </ul>

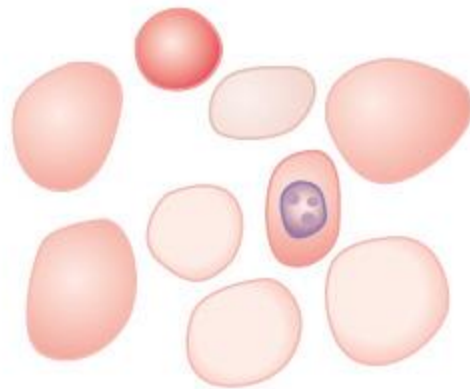
# Anaemia



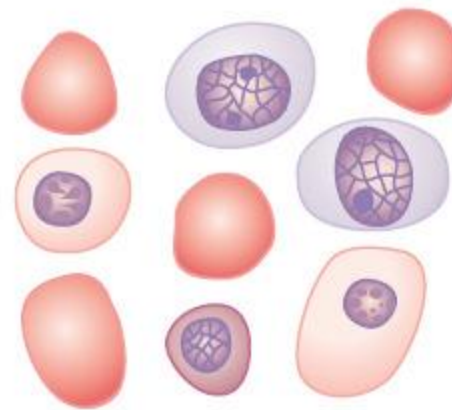
Microcytic,  
hypochromic anemia



Sickle cell anemia



Megaloblastic anemia



Erythroblastosis fetalis

# Basic Evaluation of Anaemia

- ❑ Review of blood count, blood smear and RBC indices (MCV, MCH, MCHC)

*MCV (Mean corpuscular volume) is the most accurate method of measuring red blood cells and most useful in classification of anaemia as:*

- ❑ Reticulocyte index

= reticulocyte count (%) x [observed haematocrit / normal haematocrit] *ie* normalized for hematocrit

- ❑ Reticulocyte index > 2% indicates excessive RBC destruction or loss
- ❑ Reticulocyte index < 2% indicates decreased production

# Effects of Anaemia on Body Functions

- Increased cardiac output, as well as increased pumping workload on the heart, because of decreased viscosity and vasodilation.
- Reduced oxygen-carrying capacity of blood and lack of O<sub>2</sub> for ATP and heat production, manifested mostly during exertion.
- If severe, can lead to heart failure

# Clinical Picture of Anaemia

## Symptoms

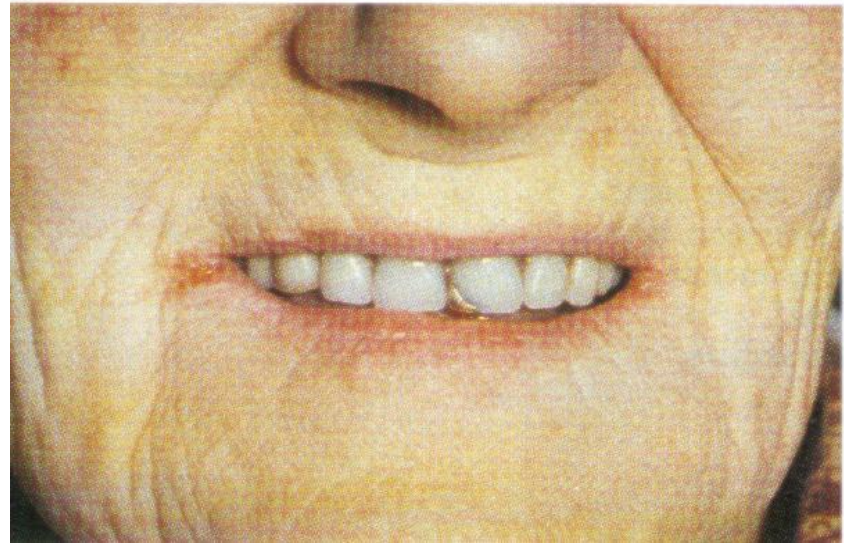
- **fatigue, cold intolerance and paleness**
  - **oxygen-carrying capacity of blood is reduced**
    - **lack of O<sub>2</sub> for ATP and heat production**

## Signs

- Pallor: an abnormal loss of skin or mucous membrane color.**
- Koilonychia: is when the nail curves upwards (becomes spoon-shaped)**
- Angular stomatitis: deep cracks and splits form at the corners of the mouth**
- Glossitis: is inflammation or infection of the tongue**



# Clinical Picture of Anaemia



# Polycythemia

## Types:

### True or absolute

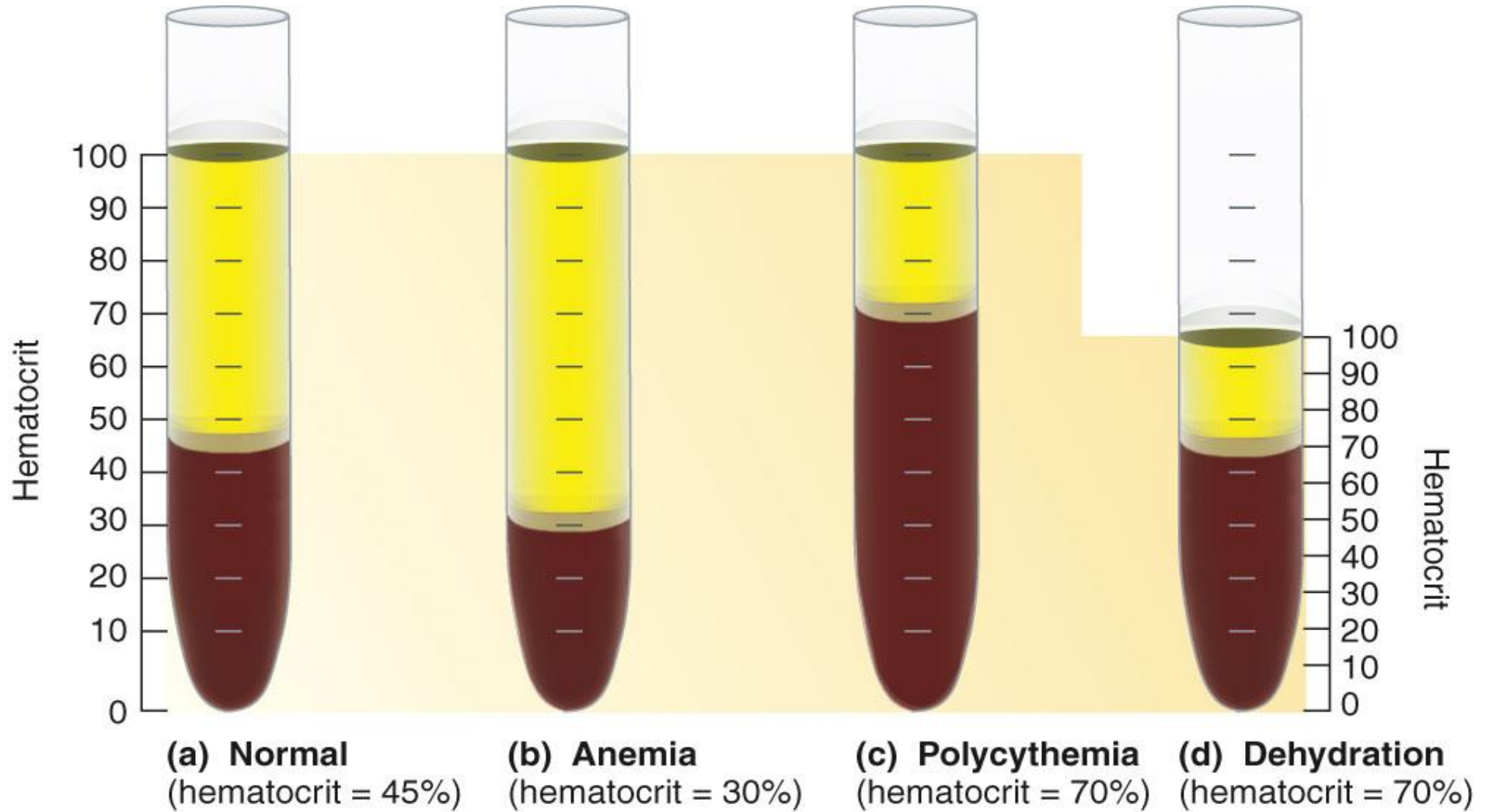
- **Primary (polycythemia rubra vera):**  
uncontrolled RBC production
- **Secondary to hypoxia:** high altitude, chronic respiratory or cardiac disease

### Relative

- **Hemoconcentration:**  
» loss of body fluid in vomiting, diarrhea, sweating

**Complications of polycythemia: hyperviscosity of the blood**

# Hct under various conditions



## KEY



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**Thank You**