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Anemias

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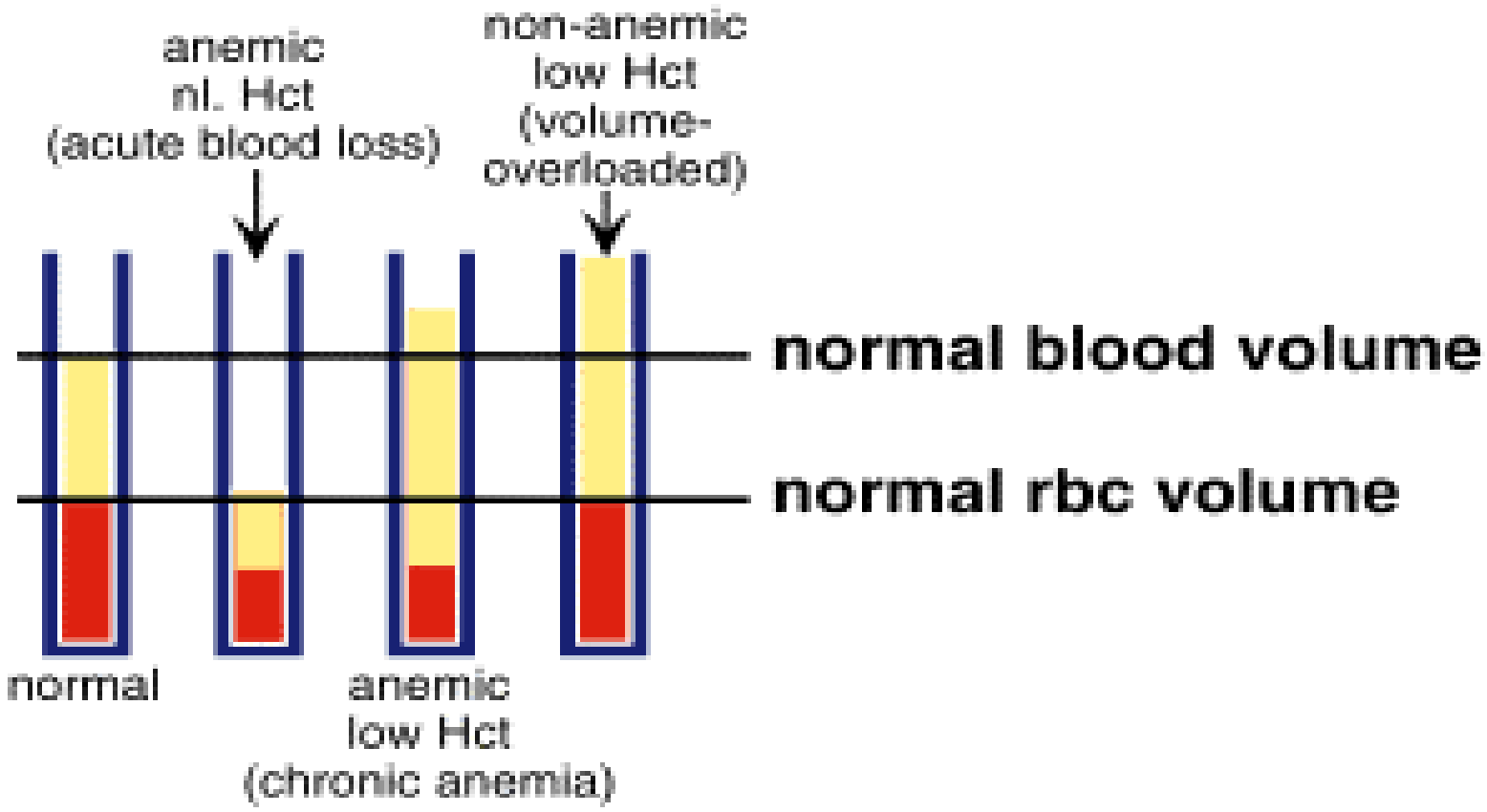
Definition of anemia

- Anemia is best defined in relation to H&H (hemoglobin [Hb] and hematocrit [HCT]) levels below the normal reference range, because a patient's symptoms and physiologic consequences are the result of decreased oxygen-carrying capacity of the blood.
- According to World Health Organization (WHO) criteria, anemia is diagnosed in males when Hb is <130 g/L (13 g/dL) and HCT is <0.39 (39%); in nonpregnan females, when Hb is <120 g/L (12 g/dL) and HCT is <0.36 (36%).

Hematocrit evaluation in anemia



The diagram illustrates that a person can have a low hematocrit and not be anemic. This occurs when a patient is overhydrated, typically as a result of overenthusiastic intravenous fluid therapy.

Pathological classification of anemias

- **Blood loss**
  - ✓ Acute
  - ✓ Chronic
- **Decreased production**
  - ✓ Deficiency anaemias
    - ✓ Iron deficiency
    - ✓ Vitamin B12 and Folate deficiency
  - ✓ Bone marrow disease/infiltration
- **Increased destruction**

✓Inherited (Membrane, enzyme, Hb defects)

✓Acquired (immune and non-immune)

Classification of anemias by mean cell volume (MCV)

TABLE 5. Morphological Classification of Anemias*

Microcytic (MCV <80 fL)	
Commonly microcytic	Occasionally microcytic
Iron deficiency	Anemia of chronic disease
Thalassemia	Hemoglobinopathies
Hereditary sideroblastic anemia	
Macrocytic (MCV >100 fL)	
Commonly macrocytic	Occasionally macrocytic
Folic acid deficiency	Hypoproliferative anemia
Vitamin B_{12} deficiency	Refractory anemia
Liver disease	
Hemolytic anemia	
Blood loss anemia	
Normocytic (MCV 80–100 fL)	
Commonly normocytic	Occasionally normocytic
Hypoproliferative anemia	Early iron deficiency
Secondary anemia in malignancies	
Refractory anemia in myelodysplasia	
Hemolytic anemia	
Hemoglobinopathies	
Blood loss anemia	
Anemia of chronic disease	
Acquired sideroblastic anemia	

http://www.hem-aids.ru/system/files/attachments/646/anemii_anemii_pdf_008.pdf

Classification of anemias by mean cell hemoglobin (MCH)

- MCH represents the average content of Hb in average RBC.

I. Hypochromic anemia <27 picograms/cell

II. Hyperchromic anemia >31 picograms/cell

III. Normochromic anemia 27 - 31 picograms/cell

Classification of anemia according to the degree of severity

1. Mild - hemoglobin - 120-90 g /l
2. Moderate - hemoglobin - 90-70 g /l
3. Severe - hemoglobin - less than 70 g / l

Anisocytosis and poikilocytosis

- Normally all red blood cells are relatively uniform in size and shape.
- Variation in size is referred to as “anisocytosis”
- Variation in shape is is referred to as “poikilocytosis”

IRON DEFICIENCY
and
IRON DEFICIENCY ANAEMIA

Definition

- Iron deficiency will result from any condition in which dietary iron intake does not meet the body's demands.
- Iron deficiency anemia is characterized by a defect in hemoglobin synthesis, resulting in red blood cells that are abnormally small (microcytic) and contain a decreased amount of hemoglobin (hypochromic).

Epidemiology

- Iron deficiency anemia (IDA) is a disease that is potentially exposed to people of all ages, both sexes, all socio-economic classes and geographic regions.
- However, the most prone to IDA are pregnant women, women of reproductive age and children under school age, and patients with low socio-economic status.
- According to the report of the World Health Organization anemia affects 1.6 billion people, accounting for 24.8% of the global population.
- The highest prevalence of IDA in the world has seen in Africa and South East Asia.
- In India, for example, up to 88% of pregnant and 74% of non-pregnant women are affected. Throughout Africa, about 50% of pregnant and 40% of non-pregnant women are anaemic. West Africa is the most affected, and southern Africa the least.

International Statistical Classification of Diseases (ICD-10)

Iron deficiency is coded as:

- (E61.1) Iron deficiency

Iron deficiency anemia is coded as:

- (D50) Iron deficiency anaemia
- (D50.0) Iron deficiency anaemia secondary to blood loss (chronic)
- (D50.1) Sideropenic dysphagia
- Kelly-Paterson syndrome
- Plummer-Vinson syndrome
- (D50.8) Other iron deficiency anaemias
- (D50.9) Iron deficiency anaemia, unspecified

Classification

Causes of Iron Deficiency and Iron Deficiency Anaemia

Increased Requirements	Decreased Intake
• Growing infants and children • Menstruating women • Pregnancy • Lactation • Multiparity • Parturition	• Low socioeconomic status • Vegetarian diet • Lack of balanced diet or poor intake • Alcoholism • Elderly • High risk ethnic groups *(First Nations, Indo-Canadians*)*
Increased Loss	**Decreased Absorption**
• Menorrhagia • GI bleeding • Regular blood donors • Post-operative patients with significant blood loss • Hematuria • Intestinal parasites (travel or immigration from an endemic area) • Hemolytic anemias • Extreme physical exercise (endurance athletes)	• Dietary factors *(tannins, phytates in fibre, calcium in milk, tea, coffee, carbonated drinks)* • Upper GI Pathology: • Chronic gastritis • Gastric lymphoma • Celiac disease • Crohn's disease • Medications that decrease gastric acidity or bind iron • Gastrectomy or intestinal bypass • Duodenal pathology • Chronic renal failure

10.17 Hookworm infection is the most common cause of iron-deficiency anaemia worldwide. The worms are seen attached by their buccal capsules to the villi of the small intestine, where they feed by sucking blood (up to 0.2 ml per day per worm). In gross hookworm infection, severe iron-deficiency anaemia may result.

Iron exchange

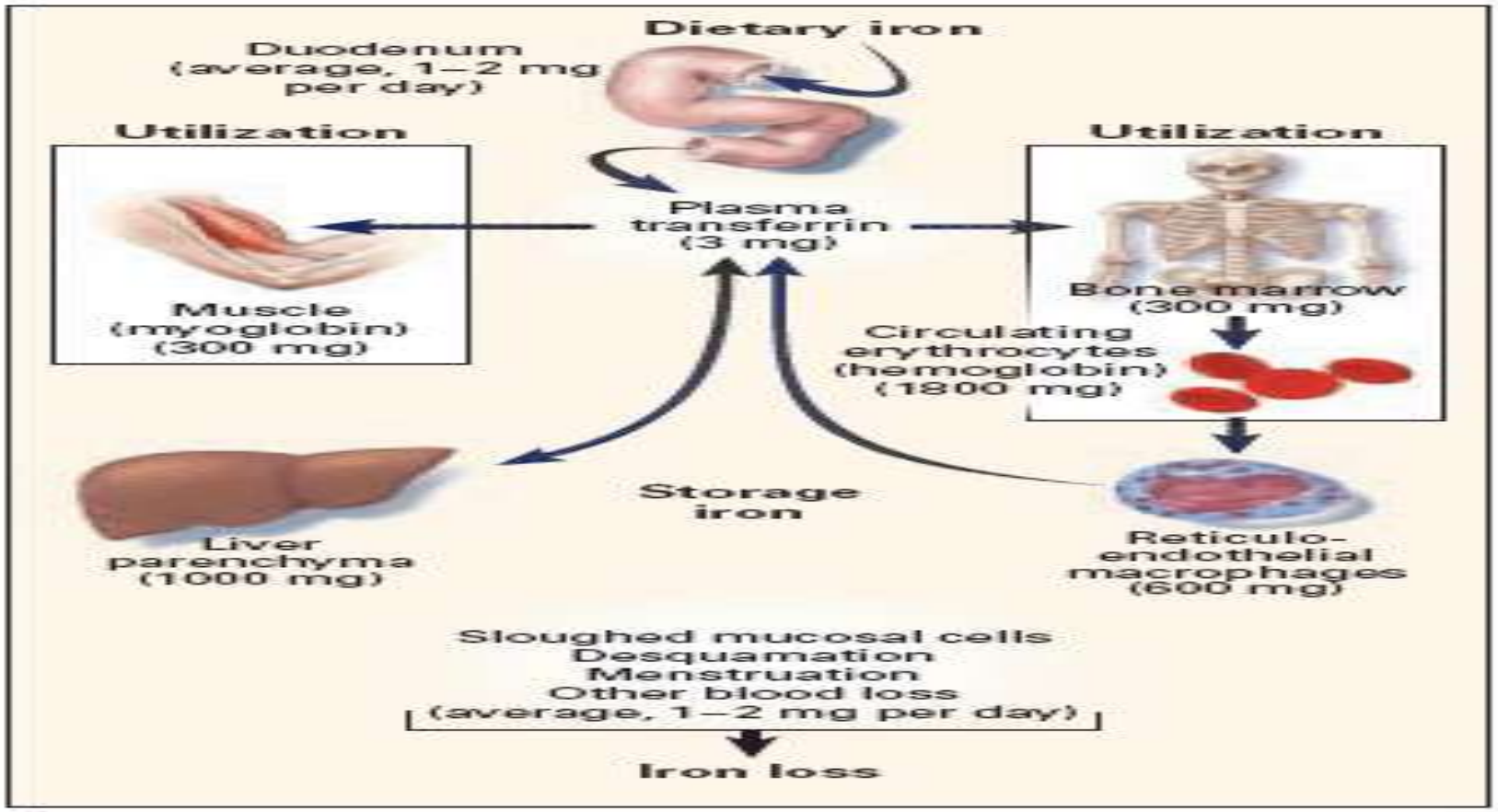
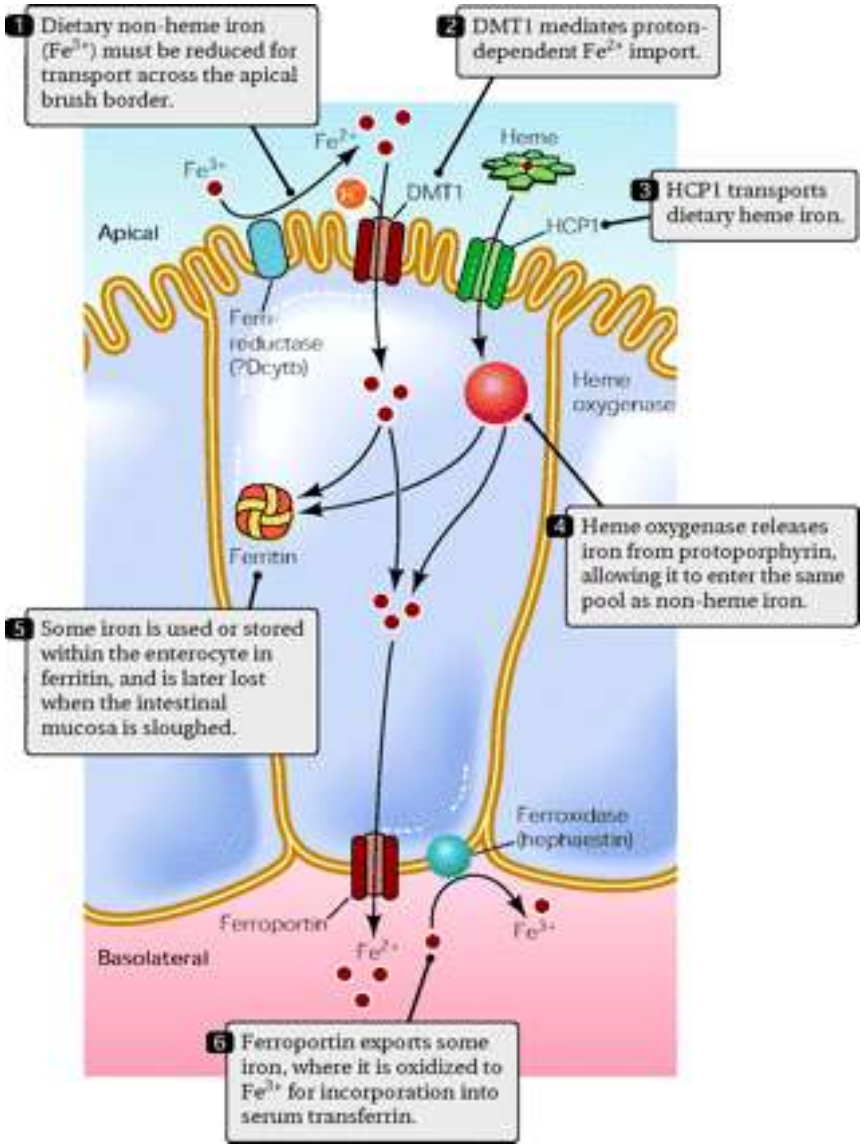


Figure 1. Distribution of Iron in Adults.
In the balanced state, 1 to 2 mg of iron enters and leaves the body each day. Dietary iron is absorbed by duodenal enterocytes. It circulates in plasma bound to transferrin. Most of the iron in the body is incorporated into hemoglobin in erythroid precursors and mature red cells. Approximately 10 to 15 percent is present in muscle fibers (in myoglobin) and other tissues (in enzymes and cytochromes). Iron is stored in parenchymal cells of the liver and reticuloendothelial macrophages. These macrophages provide most of the usable iron by degrading hemoglobin in senescent erythrocytes and reloading ferric iron onto transferrin for delivery to cells.

Iron balance

- Iron enters the body by absorption from dietary sources in the duodenum. Iron circulates bound to transferrin and is delivered primarily to the bone marrow for erythropoiesis . Senescent erythrocytes are phagocytosed by reticuloendothelial macrophages to recycle iron back into the circulation. Iron storage and release also occur in hepatocytes.Sloughing of enterocytes and bleeding are the only siginificant means for removing iron from the body. On average, approximately 1-2 mg of iron is provided on a daily basis by intestinal absorption, and this is balanced by an equal amount of iron loss by epithelial shedding in the gastrointestinal tract and blood loss in menstruating women. Most of the iron required for erythropoiesis, approximately 20-25 mg/d, is provided by iron recycling from senescent erythrocytes. The circulation pool of transferrin-bound iron is much smaller, approximately 3 mg, and therefore must be turned over every few hours to ensure an adequate supply of iron for erythropoiesis.

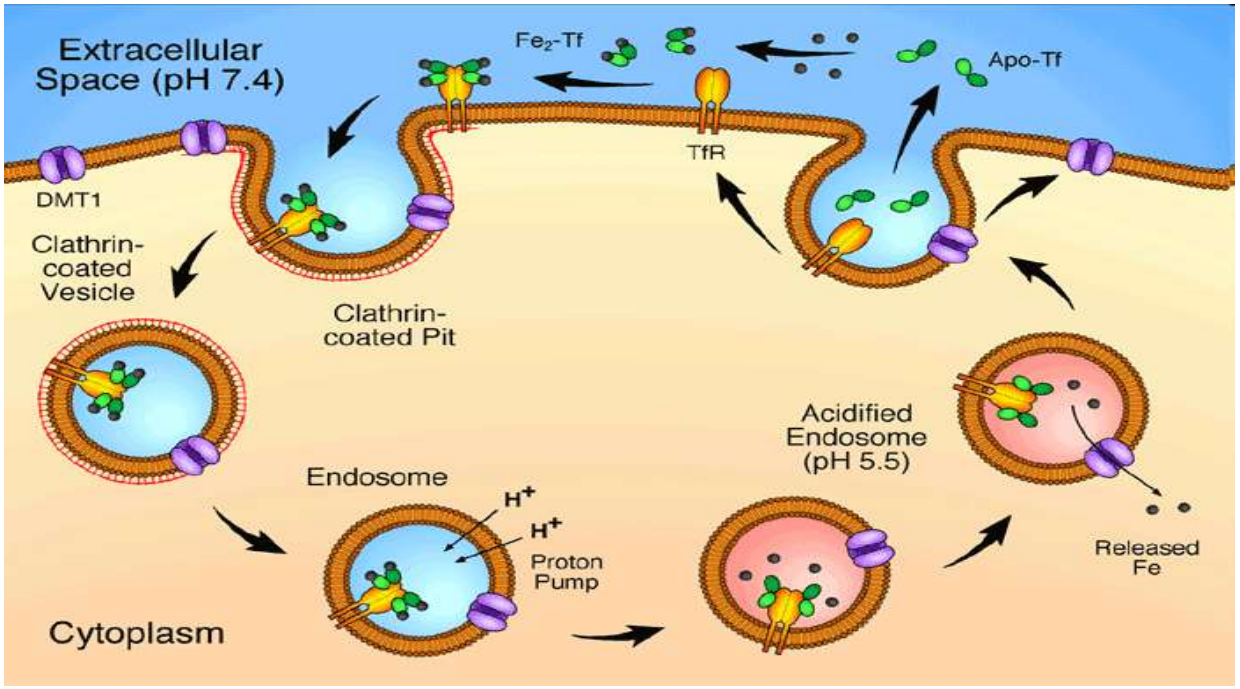
Intestinal iron absorption



- An individual enterocyte is depicted.
- Dietary non-heme iron (Fe3+) must be reduced for transport across the apical brush border. DMT1 mediates proton-dependent Fe2+ import.
- Dietary heme iron is transported by HCP1.
- Once inside the cell, heme oxygenase releases iron from protoporphyrin, presumably allowing it to enter the same pool as non-heme iron.
- Some iron is used or stored within the enterocyte in ferritin. This iron is later lost from the body when the intestinal mucosa is sloughed.
- Some iron is exported across the basolateral membrane by ferroportin and oxidized to Fe3+ for incorporation into serum transferrin.

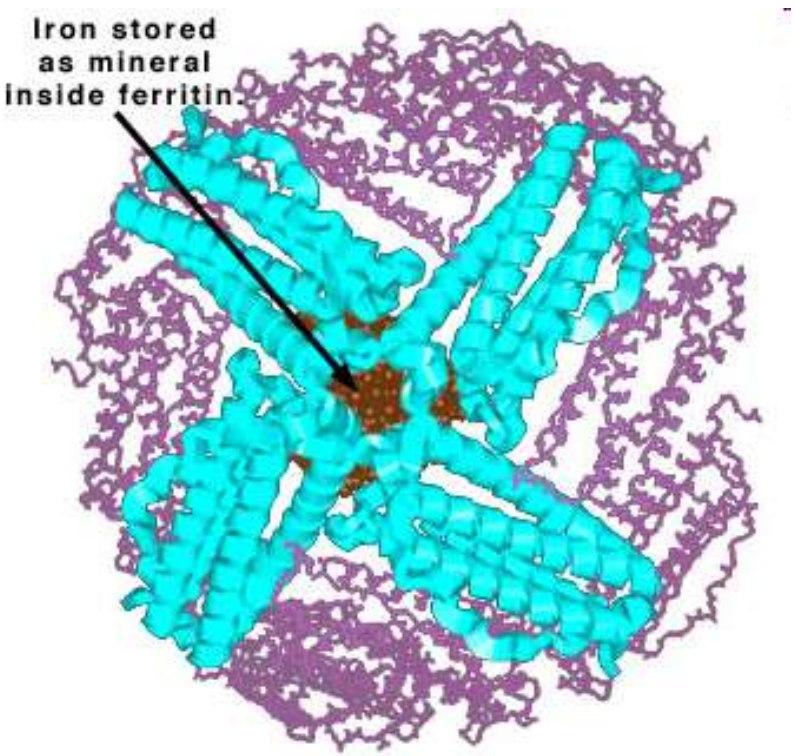
The Transferrin Cycle

- The liver synthesizes transferrin and secretes it into the plasma. Transferrins are produced locally in the testes and CNS. These two sites are relatively inaccessible to proteins in the general circulation (blood:testis barrier, blood:brain barrier)
- When not bound to iron, it is known as "apotransferrin“
- Each transferrin molecule has the ability to carry two iron ions in the ferric form (Fe3+).
- A transferrin binds to a transferrin receptor on the surface of a cell (e.g., to erythroid precursors in the bone marrow). Then it is transported into the cell in a vesicle by receptor-mediated endocytosis. The pH of the vesicle is reduced by hydrogen ion pumps (H+ ATPases) to about 5.5, causing transferrin to release its iron ions. The receptor (with its ligand, transferrin, bound) is then transported through the endocytic cycle back to the cell surface, ready for another round of iron uptake.



Ferritin

- Ferritin is a globular protein complex consisting of 24 protein subunits and is the primary intracellular iron-storage protein, keeping iron in a soluble and non-toxic form.
- Ferritin that is not combined with iron is called apoferritin.
- Each ferritin complex can store about 4500 iron (Fe3+) ions.
- The heavy chain of Ferritin also possesses ferroxidase activity, this involves the conversion of iron from the ferrous (Fe2+) to ferric (Fe 3+) forms. This limits the deleterious reaction which occurs between ferrous iron and hydrogen peroxide known as the Fenton reaction which produces the highly damaging hydroxyl radical.



Protective compensatory mechanism in chronic hypoxia

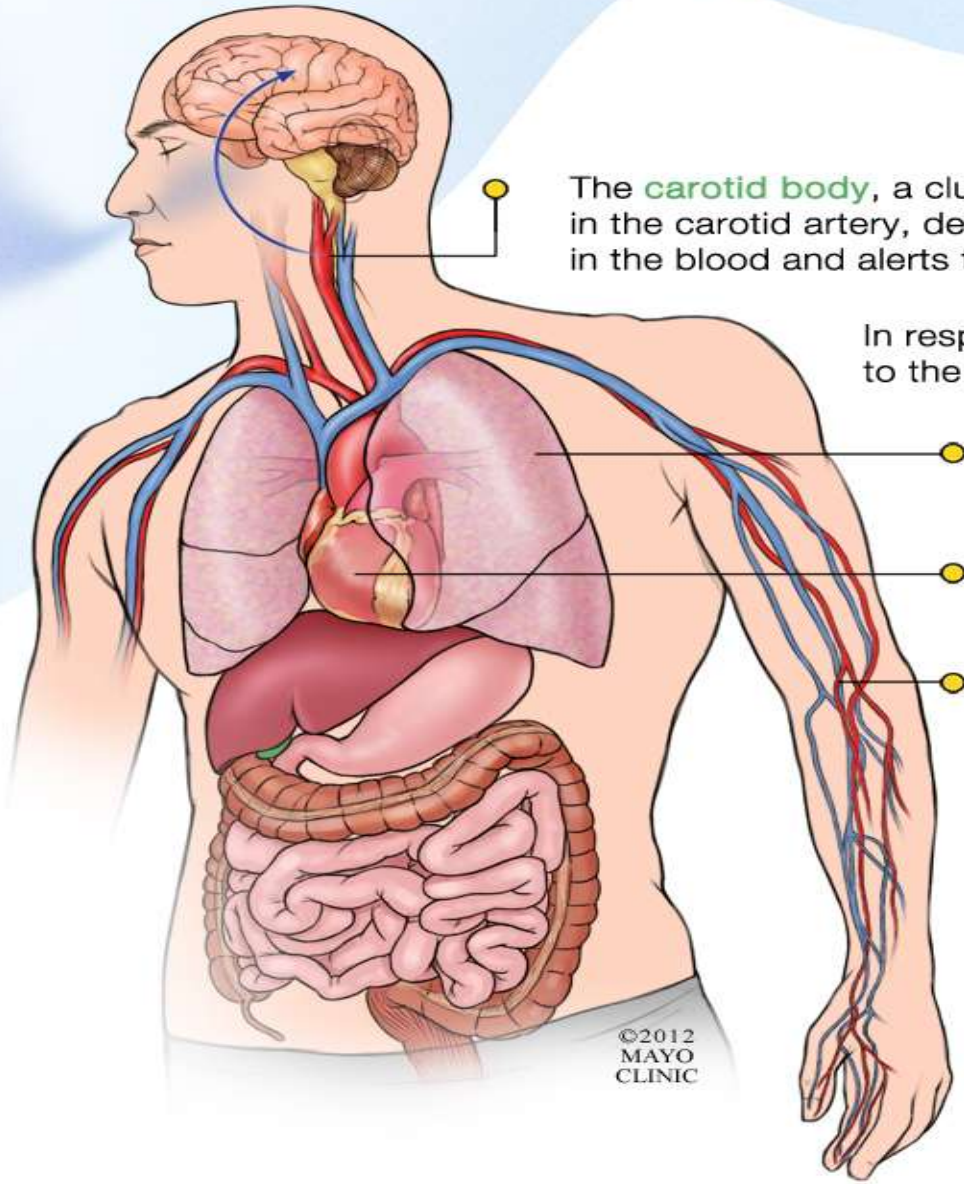
There are several protective compensatory mechanism in chronic hypoxia followed by IDA:

1. **Activation of the protein complex - hypoxia-inducible factor 1 (HIF-1),** which provides a physiological compensatory response to hypoxic stress by regulating the synthesis of erythropoietin, transferrin, and vascular endothelial growth factor, and the optimization of oxidative phosphorylation in the mitochondria.
2. **Activation of chemoreceptors and sympathetic-dependent vasoconstriction.** Hypoxemia causes activation of chemoreceptors of carotid sinus, which in turn reflexively activate sympathetic-adrenal system. This leads to the release of catecholamines and arteriolar narrowing the skin, mucous membranes, muscles, abdomen and kidneys in order to reallocate tissue perfusion from'' no'' vital to vital organs (brain, heart).
3. **Increase cardiac output by increasing stroke output and increase in heart rate.** This explains the often observed in IDA tachycardia. Initial oxygen starvation and an additional increase in oxygen demand of the heart with tachycardia provoke exacerbation of chronic heart disease, up to anginal attacks.

Effects of Hypoxia

(hi-pok´se-ah)
: a condition in which the body as a whole or a region of the body is deprived of adequate oxygen supply.
/hy·pox·ia/ - noun

Low oxygen pressure at high altitude



The carotid body, a cluster of specialized cells in the carotid artery, detects low oxygen levels in the blood and alerts the brain.

In response, the brain sends signals to the rest of the body to...

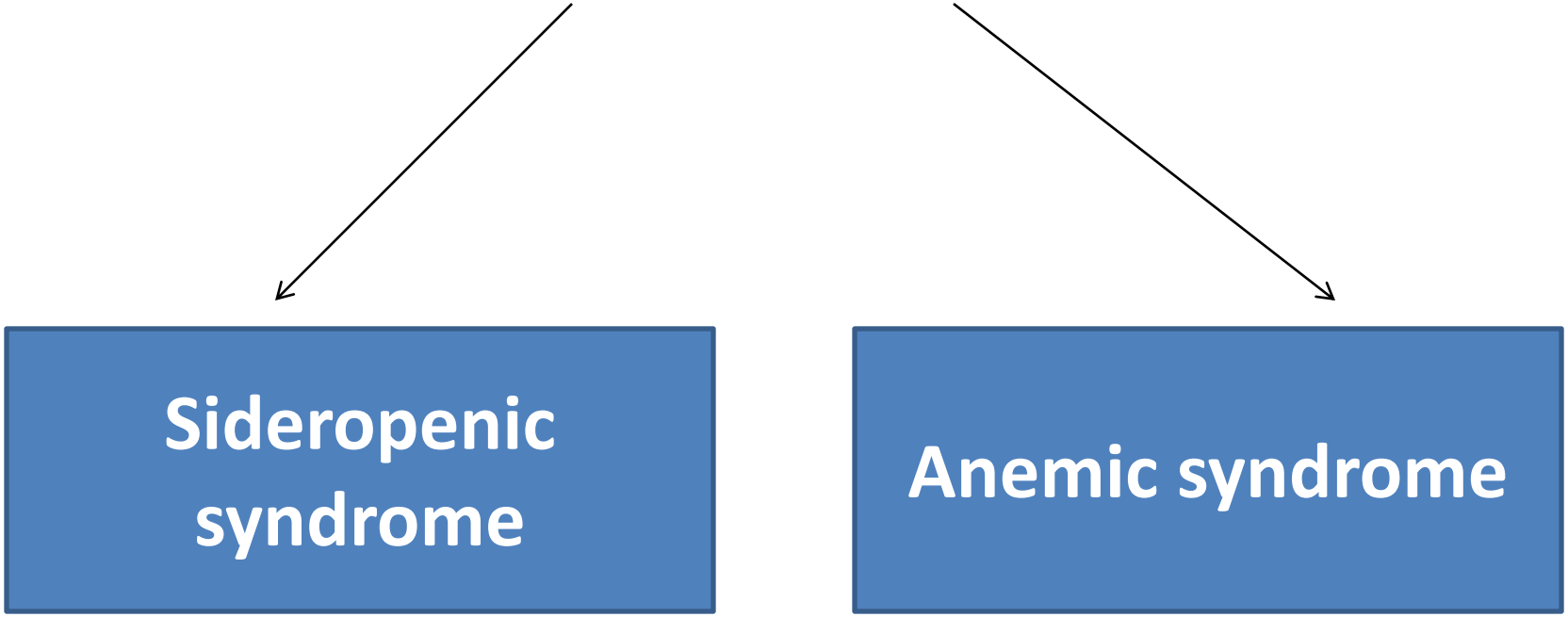
- increase breathing rate and constrict vessels in the lung
- increase heart rate
- dilate peripheral blood vessels in arms, legs, hands, and feet

Consequences of hypoxia

Variety of metabolic disorders during hypoxia reduces to the basic pathogenic mechanisms such as:

- Decrease of ATP synthesis as a result of failure of oxidative phosphorylation in the mitochondria.
- As a result of deficit of ATP violation of all energy-dependent cellular processes take place: synthesis of proteins, lipids, nucleic acids, the work of membrane ion channels, antioxidant protection.
- Hypoxia is always accompanied by acidosis (due to the accumulation of lactic acid, pyruvate, etc.), which itself aggravates hypoxia - a vicious cycle develops.

Clinical picture of ID and IDA



Anemic syndrome

Three pathogenetic mechanisms contribute to the anemic syndrome:

1. Hemic hypoxia: refers to the decrease in amount of Hb in the blood.
2. Tissue hypoxia which is the reduction of oxygen supply to a tissue below physiological levels despite adequate perfusion of the tissue by blood.
3. Decreased viscosity of blood (systolic murmur at the apex and noise in the jugular veins)

Symptoms of anemic syndrome

Organs and systems	Hemic hypoxia	Tissue hypoxia
Respiratory system	•Dyspnea	Dyspnea
Cardiovascular system	-	•Heart pain •Palpitations •Heart failure
Central and peripheral nervous system	-	•Feeling of lack of air, especially in unventilated areas •Fatigue •Headaches •Daytime sleepiness •Dizziness •Fainting
Skin and mucous layers	•Pallor	•Hypersensitivity to cold •Chilliness
Skeletal muscles	-	•Weakness •Fatigue during exercise

Conjunctival pallor

Due to vasoconstriction of the arterioles of the skin and mucous membranes a pallor of skin, palmar creases and conjunctiva appears.

Pale conjunctiva. Note that the color of the pale anterior rim and the posterior part of the conjunctiva are the same.

Normal conjunctiva. Note the full reddness of the anterior rim and its dissimilarity to the posterior aspect of the conjunctiva

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1497067/figure/fig2/

Sideropenic syndrome

Sideropenic syndrome is caused by reduction in the synthesis of iron-containing proteins (hemoglobin, myoglobin, ferritin, hemosiderin, etc.) and decreased activity of iron-containing enzymes (cytochrome c reductase, succinate dehydrogenase, myeloperoxidase, etc.). This results in a dystrophic and atrophic processes followed in almost all cells.

The symptoms are:

- Symptoms of lesion of rapidly dividing cells: mucous membranes, skin and bone marrow
- Pica chlorotica
- Sideropenic dysphagia or Plummer-Vinson syndrome
- Sideropenic fever (some patients have long-term temperature increase to subfebrile values)
- Central and peripheral nervous systems symptoms such as irritability, poor memory, poor concentration, intolerance to areas with limited air circulation, restless leg syndrome.
- Deep iron deficiency may be accompanied by muscle atrophy, decreased muscle strength, hypotension, sphincter deficiency (frequent urge to urinate, nocturnal enuresis, urinary incontinence when laughing or coughing).

Symptoms of sideropenic syndrome

Symptoms of lesion of rapidly dividing cells

The epithelium of the skin and skin appendages	The epithelium of lining mucosa	Bone marrow cells
•Dry, exfoliating, itchy skin• • Tendency to cracked skin •Poorly healing wounds and injuries •Angular stomatitis - inflammation in the corners of the mouth• •Fragility, loss, early graying of hair• •Thinning, brittle, dull nails, koilonychia	•Sideropenic dysphagia or Plummer-Vinson syndrome • Atrophic glossitis • Atrophic gastritis • Atrophic rhinitis •Atrophy of the intestinal mucosa	•Decreasing the amount of hemoglobin in red blood cells • Decreasing the amount of red blood cells • Reduction of the phagocytic activity of neutrophils • Reduce the number of T-lymphocytes and/or reduction of their function

Symptoms of sideropenic syndrome

Pica chlorotica

- Taste perversion or pica chlorotica characterized by an overwhelming desire to eat inedible (chalk, clay, sand, ice, salt, etc.).
- Manifestations of the syndrome also include sideropenic perversion of the sense of smell - addiction to smells, which by most others are perceived as unpleasant (gasoline, kerosene, acetone, dyes, shoe polish, naphthalene, etc.).
- The term «pica» comes from the Latin «pica» - magpie - a bird known for its indiscriminate eating habits. It is believed that the term was first introduced Byzantine physician Etius of Amide in the 6th century AD, in his textbook on obstetrics. Etius said: "At about the second month of pregnancy, there is a disorder called Pica, and derived from the names of magpie ... Women want different: some spicy foods, other – salty."
- One should note that pica in most cases is a manifestation of iron deficiency, but sometimes it is a manifestation of zinc deficiency or mental disorders.

Plummer-Vinson syndrome

Sideropenic dysphagia

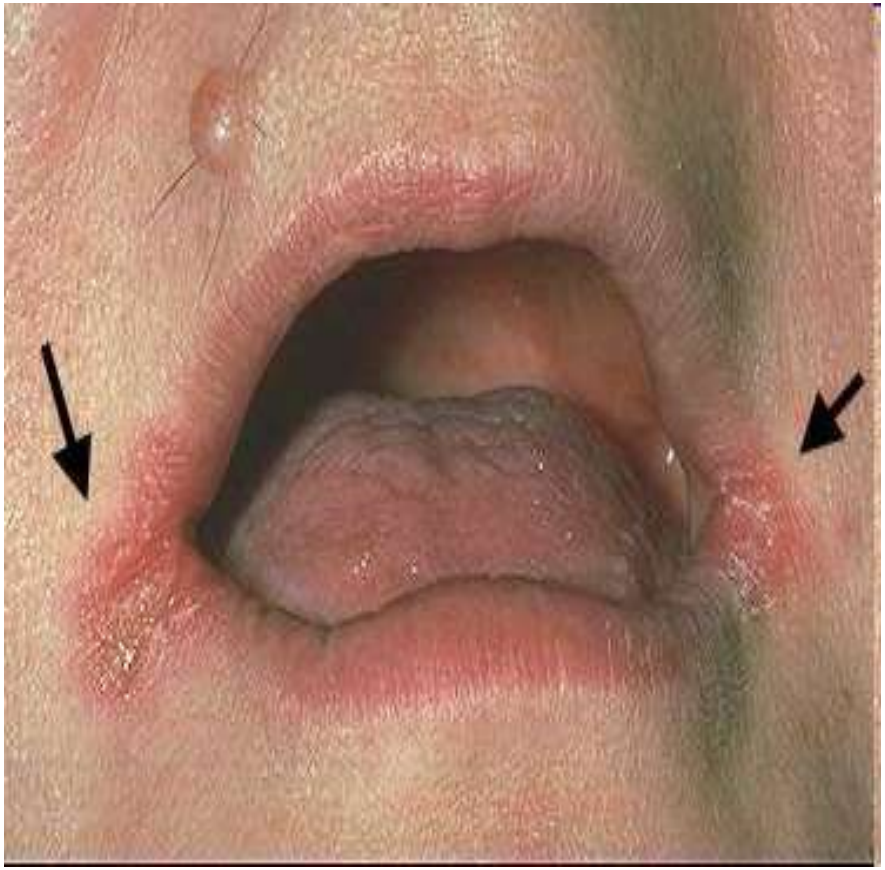
The syndrome is association with:

- Dysphagia (difficulty swallowing), due to upper esophageal webs
- Iron deficiency anemia t it is not associated with anemia.

The presence of mucous membranes and webs in the upper third of the esophagus.

Angular cheilitis
(synonims: angular stomatitis, bridou)

Angular cheilitis is an inflammatory lesion at the labial commissure, or corner of the mouth, and often occurs bilaterally. The condition manifests as deep cracks or splits.



http://sdk-center.ru/lechenie_stomatita.html

Cheilitis

Cheilitis is a medical condition involving inflammation of the lip

http://www.graphicshunt.com/health/images/plummer-vinson_syndrome-2219.htm

Sideropenic glossitis

Glossitis is inflammation of the tongue

http://flipper.diff.org/app/items/info/1626

Koilonychia

Koilonychia, also known as "spoon nails", is a nail disease that can be a sign of hypochromic anemia, especially iron-deficiency anemia.

It refers to abnormally thin nails (usually of the hand) which have lost their convexity, becoming flat or even concave in shape.

http://mrishaanshareef.blogspot.com/2008/10/finger-nails-to-predict-health.html

486. Ложкообразные ногти (койлонихия). Ногти вогнуты настолько, что в них можно налить несколько капель воды. Ложкообразные ногти встречаются при железодефицитной анемии. Тяжелое общее состояние также нередко сопровождается нарушением роста ногтей и их вогнутостью. У детей младшего возраста ложкообразные ногти — вариант нормы.

Koilonychia

Sideropenic skin changes
Poorly healing wounds and injuries

Sideropenic skin changes

Dry, exfoliating, itchy skin

Diagnostics

Stages of Iron Deficiency

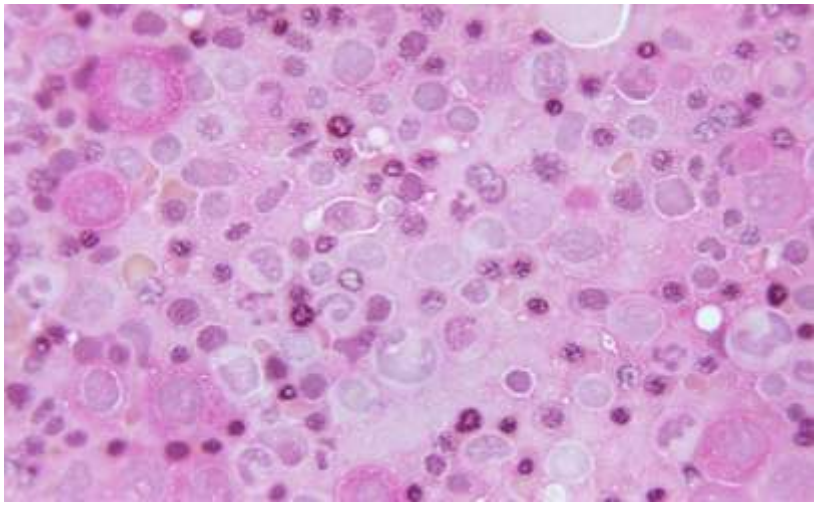
Stage	Description	Laboratory findings
Stage 1 Pre-latent iron deficiency Depleted iron stores	There are depleted iron stores but increased iron absorption and normal serum iron and capacity to bind iron and transport in around the body.	•Low ferritin •Depletion of bone marrow iron
Stage 2 Latent iron deficiency	There are decreased iron serum levels and there is an increase in the capacity of binding and transporting iron.	•Low transferrin saturation • Low serum iron • Raised serum transferrin • Normal haemoglobin
Stage 3 Iron deficiency anemia	Features of stages 1+stages 2+anemia	•Low haemoglobin

Pre-latent iron deficiency laboratory markers

Marker	Advantages	Limitations	Normal range
Serum ferritin	Quantitative , well standardized	Affected by inflammation, liver disease	45-340 ng/mL
Bone-marrow iron	Well established, high specificity	Affected by EPO treatment, invasive, expensive	

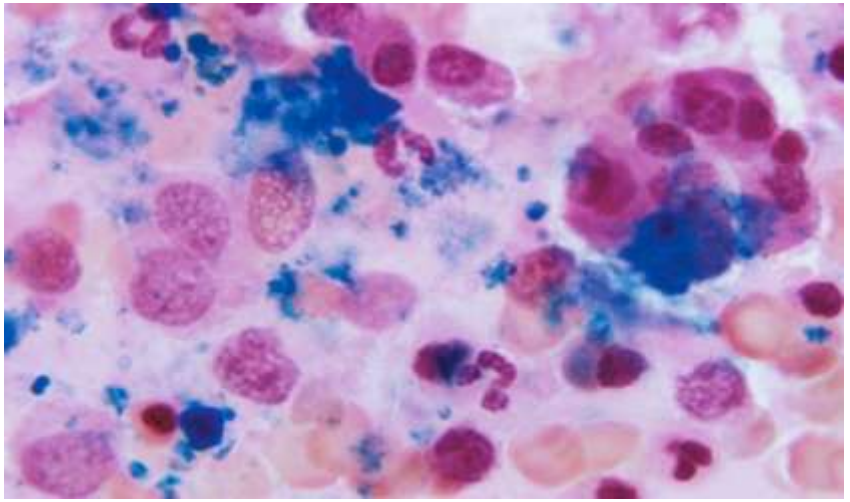
Examination of bone marrow

- The examination of Prussian blue–stained bone marrow aspirate for the presence or absence of histiocytic iron granules has been considered the "gold standard"
- Iron appears as variously sized intracellular blue granules or wispy amorphous intracellular deposits. The complete absence of staining is considered to represent iron deficiency.



There is no stainable iron.
The specimen is diffusely pale red/pink, which is the color of the counterstain on this slide.

http://www.rightdiagnosis.com/phil/html/iron-deficiency-anemia/2656.html



Normal iron stores are seen as dark blue-staining material in the bone marrow.

http://www.rightdiagnosis.com/phil/html/iron-deficiency/2657.html

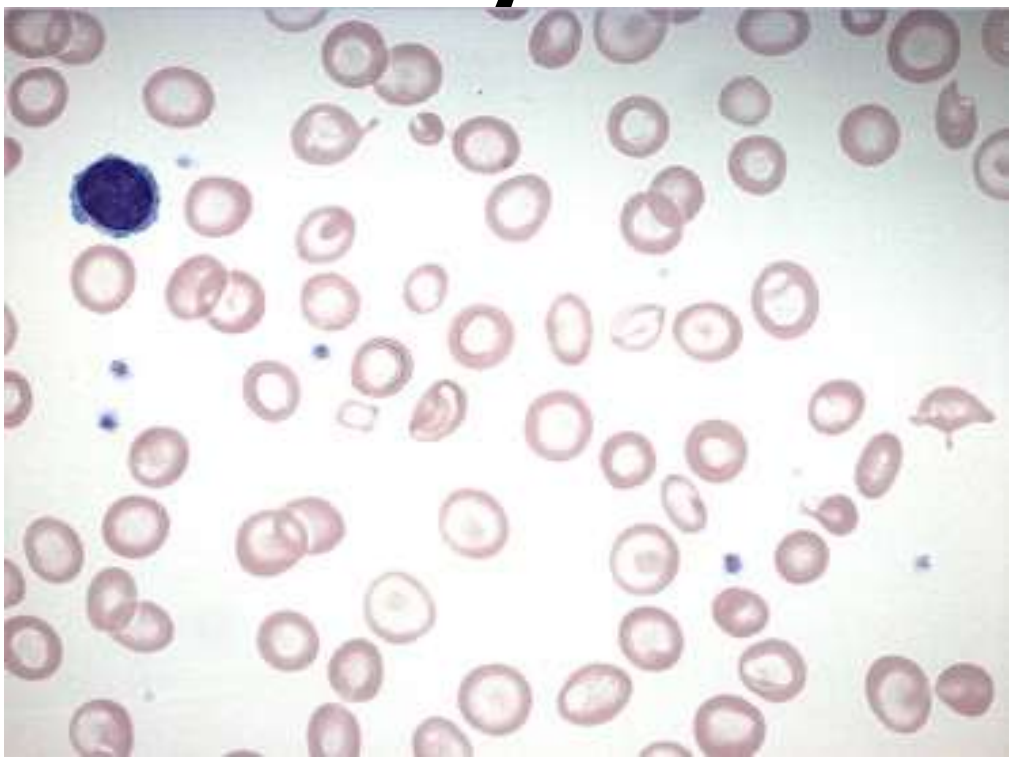
Latent iron deficiency laboratory markers

Marker	Changes in ID	Advantages	Limitations	Normal range
Soluble transferrin receptor (sTfR), serum	Increase	Quantitative (tissue deficiency) unaffected by inflammation	Patients with hemolysis or recent blood loss may have falsely elevated sTfR levels	1.8 – 4.6 mg/L
Transferrin, serum	Increase due to an increase in synthesis.		High levels can be seen in pregnancy and during estrogen administration.	200-400 mg/dL
Transferrin Saturation	Decrease less than 20%	Inexpensive Well established	Wide diurnal variation, Low specificity	Transferrin is 20-45% saturated with iron.
Serum iron (should always be interpreted in the context of other markers of ID)	Decrease		Serum iron alone is unreliable due to physiologic diurnal variations	50-150 ug/dL

Iron deficiency anemia laboratory markers

Marker	Changes in ID	Normal range
Erythrocyte count	Decrease	3.8-5.2 x 1012 /liter (female) 4.4-5.9 x 1012 /liter (male)
Hemoglobin	Decrease	12-140 g/dL (female) 130-150 g/dL (male)
Hematocrit	Decrease	36-45% (female) 42-50% (male)
Mean Cell Volume (MCV)	Decrease Microcytosis	80-100 femtoliters (fl)
Mean cell hemoglobin (MCH) **is the average mass of hemoglobin per red blood cell**	Decrease Hypochromic	27 to 31 picograms/cell

Peripheral blood smear in iron-deficiency anemia



Microcytosis with hypochromasia (100× oil). Hypochromic and microcytic red blood cells are seen with occasional target cells. The small, mature lymphocyte can be used to size the red blood cells. Many of the red blood cells have increased central pallor (hypochromia).

http://www.sciencedirect.com/science/article/pii/S0740257011000979

Hemoglobin levels

Haemoglobin levels to diagnose anaemia at sea level (g/l) (WHO 2010)

Population	Non-Anaemia*	Anaemia*		
		Mild[2]	Moderate	Severe
Children 6 - 59 months of age	110 or higher	100-109	70-99	lower than 70
Children 5 - 11 years of age	115 or higher	110-114	80-109	lower than 80
Children 12 - 14 years of age	120 or higher	110-119	80-109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	lower than 80
Pregnant women	110 or higher	100-109	70-99	lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	lower than 80

Revised Hemoglobin levels

In 2006, Ernest Beutler and Jill Waalen criticized existing since 1968 the lower limit of normal hemoglobin for women and men, proposed by WHO. Based on the research database the third revision of the National Register of Health, USA (NHANES-III) and its own database Scripps-Kaiser, gathered in San Diego from 1998 to 2002, they have proposed new lower limits of hemoglobin for adults of different by sex and race

Proposed lower limits of normal for hemoglobin concentration of the blood for white and black adults

Group	Hemoglobin, g/L
White men, y	
20-59	137
60+	132
White women, y	
20-49	122
50+	122
Black men, y	
20-59	129
60+	127
Black women, y	
20-49	115
50+	115

http://bloodjournal.hematologylibrary.org/content/107/5/1747.full.pdf

Management of iron deficiency

Three main strategies can be applied in order to improve iron status in individuals and populations:

- **Dietary modification**
- **Food fortification**
- **Iron supplemetation**

Determine and treat underlying cause

Dietary modification

- **Dietary iron sources include meat, fish and poultry, lentils, dried beans, grain products, vegetables, dried fruit, and molasses.**

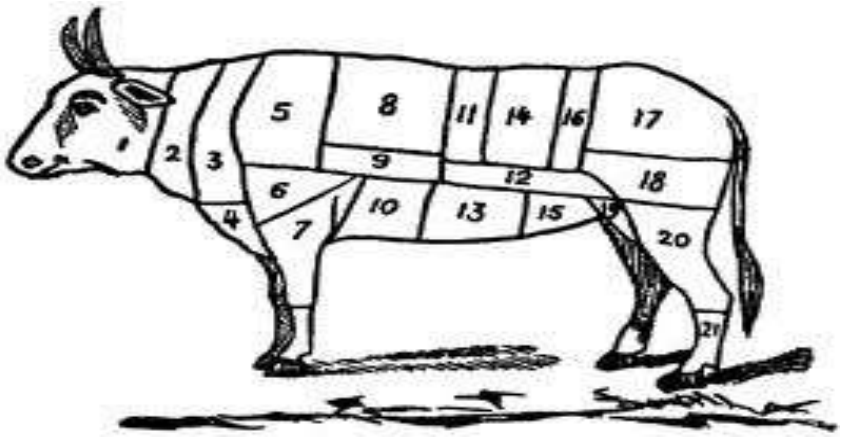
Dietary Factors That Enhance and Inhibit Iron Absorption

Enhance:

- Gastric acid
- Ascorbic acid
- Malic acid
- Citric acid

Inhibit:

- Phosphate
- Calcium
- Tea (tannic acid)
- Coffee
- Colas
- Soy protein
- High doses of minerals
- Bran/fiber



Oral iron medicines representing different iron salts

Percentage and amount of iron in some commonly used oral iron preparations

Preparation	**Iron compound (mg/tab)**	**Elemental iron mg/tab (%)**
Fe-sulfate(hydrous)	300	60 (20%)
Fe-sulfate(dried)	200	65 (32.5%)
Fe-fumarate	200	66 (33%)
Fe-gluconate	300	36 (12%)
Fe-succinate	100	35 (35%)
Fe-bisglycinate	300	60 (20%)
Carbonyl iron	100	98 (98%)
Na-feredetate	231	33 (14%)

Side-effects after oral iron intake

- The oral administration of iron can cause gastrointestinal side-effects in some individuals such as epigastric discomfort, nausea, vomiting, constipation, and diarrhea.
- The frequency of these side-effects is directly related to the dose of iron or % of elemental iron in tablet.
- In addition, iron consumed with a meal is better tolerated than when it is taken on an empty stomach, although the amount of iron absorbed is reduced.
- Also blackening of teeth and faeces may occur due to formation of iron sulfide and metallic taste.

Doses of oral iron supplements for the treatment of IDA (WHO)

Patients	Treatment (daily dose, mg)	Prophylaxis (daily dose, mg)	Duration /months
Adults	120	60	3
Pregnant	120	60	3

Iron poisoning

- After aspirin, the second commonest cause of accidental poisoning among small children is iron.
- Most deaths occur in children, particularly 12 to 14 months. As little as 1 to 2 gm of iron may cause death.
- The colored sugar coating of many commercially available tablets may attract the child and he may consume them.

http://www.ijmps.com/files/documents/2.3.2.pdf

Parenteral iron therapy

- **Parenteral medicines contain only trivalent iron.**
- **Indication for parenteral iron medicines are:**

1. intolerance to oral iron preparations
2. severe iron deficiency where a rapid
3. therapeutic effect is needed
4. functional iron deficiency where the iron demand for haemoglobin synthesis exceeds the amount that can be mobilised from filled iron stores, e.g.
5. anaemia of inflammation
6. iron deficiency, where oral iron therapy is insufficient because of chronic blood loss
7. malabsorption of iron due to intestinal disorders
8. poor compliance to oral iron treatment
9. risk of drug-drug interactions between
10. oral iron and concomitant medication.

There are three parenteral iron products:

1. Iron dextran (Cosmofer, DexFerrum, Infed). A notable side effect is allergic reaction, which occurs in less than 1 on 100 treated patients, but may cause severe, sometimes fatal, complications, including loss of consciousness, collapse, difficulty breathing, hives, swelling, convulsions and severe low blood pressure (hypotension).
2. Iron sucrose (Venofer) has an occurrence of allergic reactions of less than 1 in 1000. A common side effect is taste changes, especially a metallic taste. Doses can be given up to 3 times a week.
3. Iron carboxymaltose (trade name Ferinject) is a newer formulation of parenteral iron which is dextran free with the shell being fully metabolised in the body to simple sugars. The most common side effect are headaches which occur in 3.3%. It can be given over 15 minutes in doses up to 1,000 mg and has been adopted in many hospitals due to the increased number of patients that can be treated as no test dose is required and the patient does not need to be monitored after a dose has been administered.

- **Parenteral iron causes the same therapeutic response as oral iron but can cause adverse effects, such as anaphylactoid reactions, serum sickness, thrombophlebitis and pain.**

Transfusion

- Blood transfusions are helpful in the context of life threatening anaemia with haemoglobin level less that 50 g/dl.
- The repeated use of blood transfusions needs a careful appraisal. Iron overload, immune modulation and sensitization to HLA antigens may occur. [6]

Prognosis

- Prediction of iron deficiency and IDA depends on the cause. If iron deficiency and IDA are caused by alimentary deficiency - the prognosis is favorable, ie with adequate compensation for iron, a complete recovery.
- However, the prognosis is poor, if the IDA is due to a untreatable disease such as gastrointestinal tumors.
- When iron deficiency and IDA occur in the fetus and young children then the prognosis is poor - there are intrauterine growth retardation, delayed neuro-psychological and physical development in young children
- Chronic IDA is rarely the cause of death, but severe hypoxia may aggravate concomitant pulmonary or cardiac disease.
- Very rarely severe anemia causes anemic coma, when patients refuse from blood transfusions for religious reasons.

Prevention

- Prevention of IDA is divided into primary and secondary.
- Primary prevention - is iron intake by persons at risk in order to prevent the development of IDA.
- Secondary prevention - is iron intake by persons with IDA and persons with irremovable cause of IDA, in order to prevent recurrence of IDA.

Anemia of chronic disease

Definition

- Anaemia of chronic disease (ACD) is the second most prevalent after anaemia by iron deficiency.
- It is characterized by inadequate erythrocyte production in the setting of low serum iron, low iron binding capacity, low transferrin, but normal or high serum ferritin with a preserved or even increased macrophage iron stores in the bone marrow.
- The erythrocytes are usually normocytic and normochromic, but long standing anaemia can give rise to microcytic and hypochromic blood picture .

Causes of anaemia of chronic disease

Infections:

- Tuberculosis
- Viral infections including human immunodeficiency
- viruses infection
- Bacterial
- Parasitic
- Fungal

Cancer

- Haematologic
- Solid tumours

Autoimmune

- Rheumatoid arthritis
- Systemic lupus erythematosus
- and connective tissue disorders
- Vasculitis
- Sarcoidosis
- Inflammatory bowel disease

Chronic renal disease and inflammation

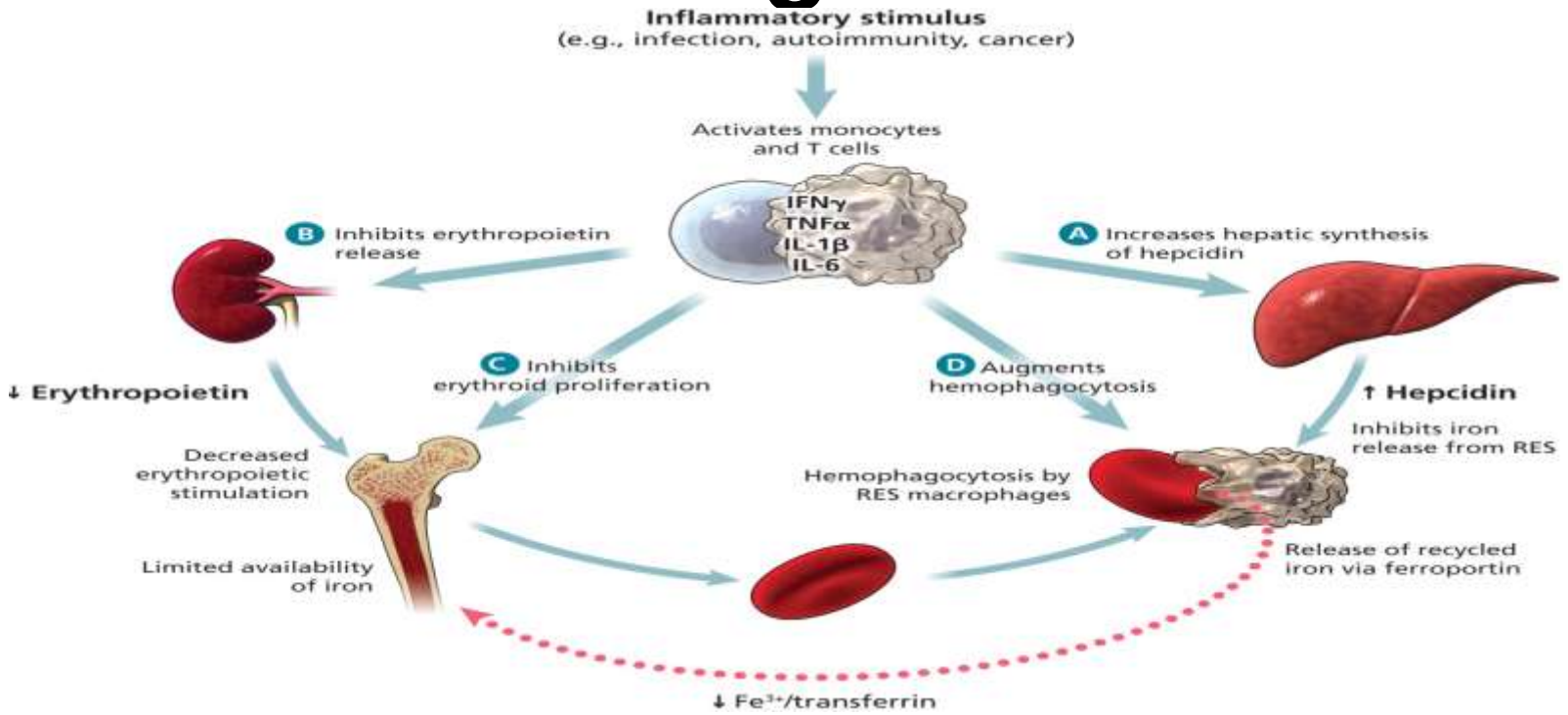
Miscellaneous

- Chronic rejection after solid – organ transplantation

Pathogenesis

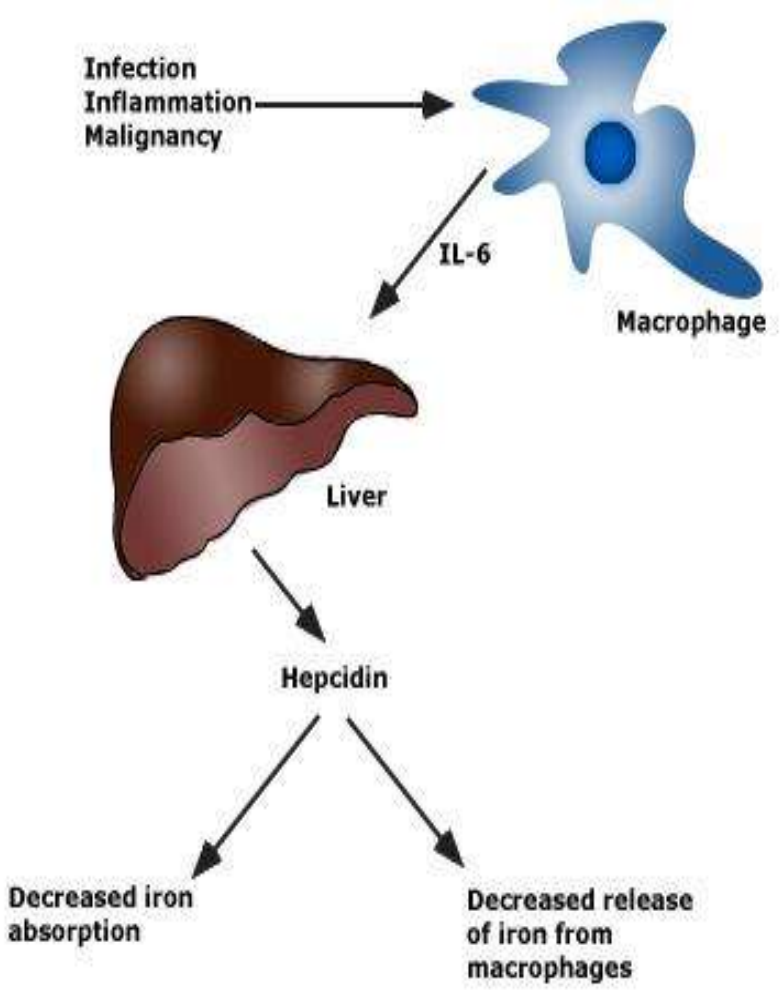
- A hall mark of anaemia of chronic disorder is an increased uptake and retention of iron within cells of the reticuloendothelial system.
- This leads to subsequent limitation of the availability of iron for erythroid cells , and iron-restricted erythropoiesis.

Pathogenesis



Cytokines released by activated leukocytes and other cells exert multiple effects that contribute to the reduction in hemoglobin levels: (A) Induction of hepcidin synthesis in the liver (especially by interleukin-6 [IL-6].
(B) Inhibition of erythropoietin release from the kidney (especially by interleukin-1β [IL-1β] and tumour necrosis factor α [TNFα]).
(C) Direct inhibition of the proliferation of erythroid progenitors.
(D) Augmentation of erythrophagocytosis by reticuloendothelial macrophages (by TNFα).

Pathogenesis



A proposed mechanism for the anemia of chronic disease (ACD) is shown here. In the presence of infection, inflammation, or malignancy, the macrophage is stimulated to produce Interleukin-6 (IL-6), which induces the production of hepcidin by the liver. Hepcidin, in turn, through its interaction with the iron export protein ferroportin, inhibits iron absorption from the gastrointestinal tract and decreases release of iron from macrophages. Both effects lead to the reduced plasma iron levels (hypoferremia) characteristic of ACD.

Protective mechanism of ACD

- Iron is an essential nutrient for proliferating microorganisms, and the sequestration of iron from microorganisms or tumour cells into the reticuloendothelial system is believed to be a potentially effective defense strategy to inhibit the growth of pathogen.

Clinical manifestation

- Most often the sign and symptoms seen in patients with ACD are referable to the underlying disease.
- Common symptoms elicited from the history include weight loss, anorexia, fever,chills, myalagias and arthralgias.
- The anaemia usually occurs insidiously over a period of approximately 3 to 4 weeks and therafter remains stable or unchanged.

Laboratory Evaluation

- ACD is a normochromic, normocytic anaemia that is characteristlcally mild (hameoglobin level ,9.5 g per deciliter) to moderate (haemoglobin level , 8 g per deciliter). Hematocrit: 28 ~ 32%.
- ↓ Iron (hypoferremia)
- ↓ Iron-binding capacity
- ↓ Transferrin saturation
- ↑ Ferritin
- ↓ soluble transferrin receptor conc.
- ↑ Hemosiderin within mactophages

Table 1: Differentiation Between Anemia of Chronic Disease and Iron-Deficiency Anemia[9]

Variable	Anemia of Chronic Disease	Iron Deficiency Anemia
Serum Iron	Reduced	Reduced
Transferrin	Reduced to normal	Increased
Transferrin saturation	Reduced	Reduced
Ferritin	Normal to increased	Reduced
Soluble transferrin receptor	Normal	Increased
Ratio of soluble transferrin receptor to log ferritin	Low (<1)	High (>2)
Cytokine levels	Increased	Normal

Adapted from Weiss G, Goodnough LT. *N Engl J Med*. 2005;352:1016.

Treatment

- Iron therapy: does not correct the anemia!
- Recognition and correction of underlying disorders!
- Erythropoietin administration. Purified recombinant erythropoietin (epoetin alfa) is effective for treatment of the anemia of renal failure and other secondary anemias such as anemia related to cancer or inflammatory disorders (eg, rheumatoid arthritis).

Vitamin B 12 deficiency anemia

Epidemiology

- The prevalence of pernicious anemia ranges from 50 to 4000 cases per 100,000 persons, depending on the diagnostic criteria.
- All age groups are affected, but the median age range in large series is 70 to 80 years.
- Pernicious anemia is more common in persons of African or European ancestry.

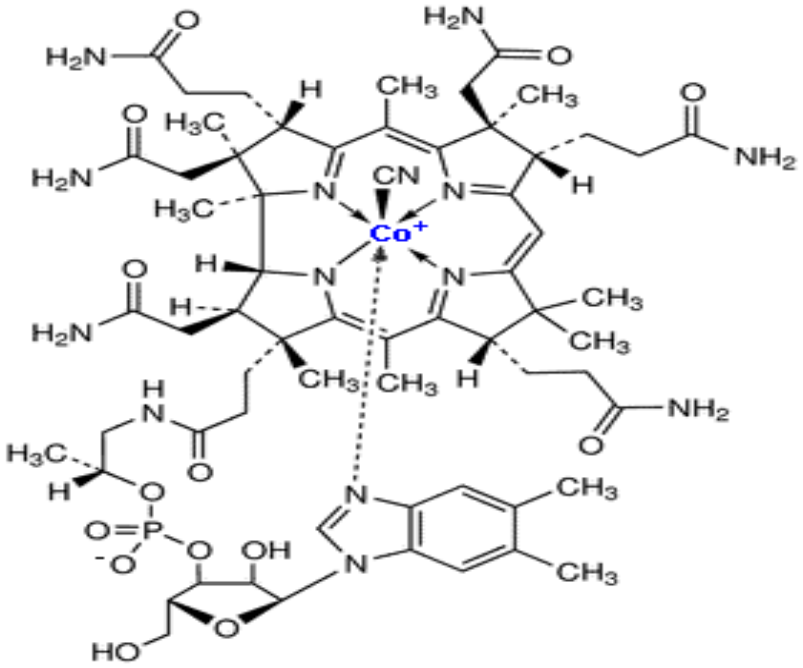
Pernicious anemia

- Pernicious anemia is an autoimmune gastritis resulting from the destruction of gastric parietal cells and the associated lack of intrinsic factor to bind ingested vitamin B12. The immune response is directed against the gastric H/K–ATPase, which accounts for associated achlorhydria.

Causes B 12 deficiency

Cause
Severe malabsorption
Pernicious anemia (autoimmune gastritis)
Total or partial gastrectomy
Gastric bypass or other bariatric surgery
Ileal resection or organ reconstructive surgery (ileal conduit diversion and ileocystoplasty)
Inflammatory bowel disease, tropical sprue
Imerslund–Gräsbeck and other syndromes‡
Mild malabsorption
Protein-bound vitamin B_{12} malabsorption
Mild atrophic gastritis
Use of metformin[14]
Use of drugs that block stomach acid
Dietary deficiency
Adults
Vegan or vegetarian diet, or diet low in meat and dairy products
Infants
Breast-feeding in infants with vitamin B_{12}–deficient mothers[15,16]

Sources of vitamin B12



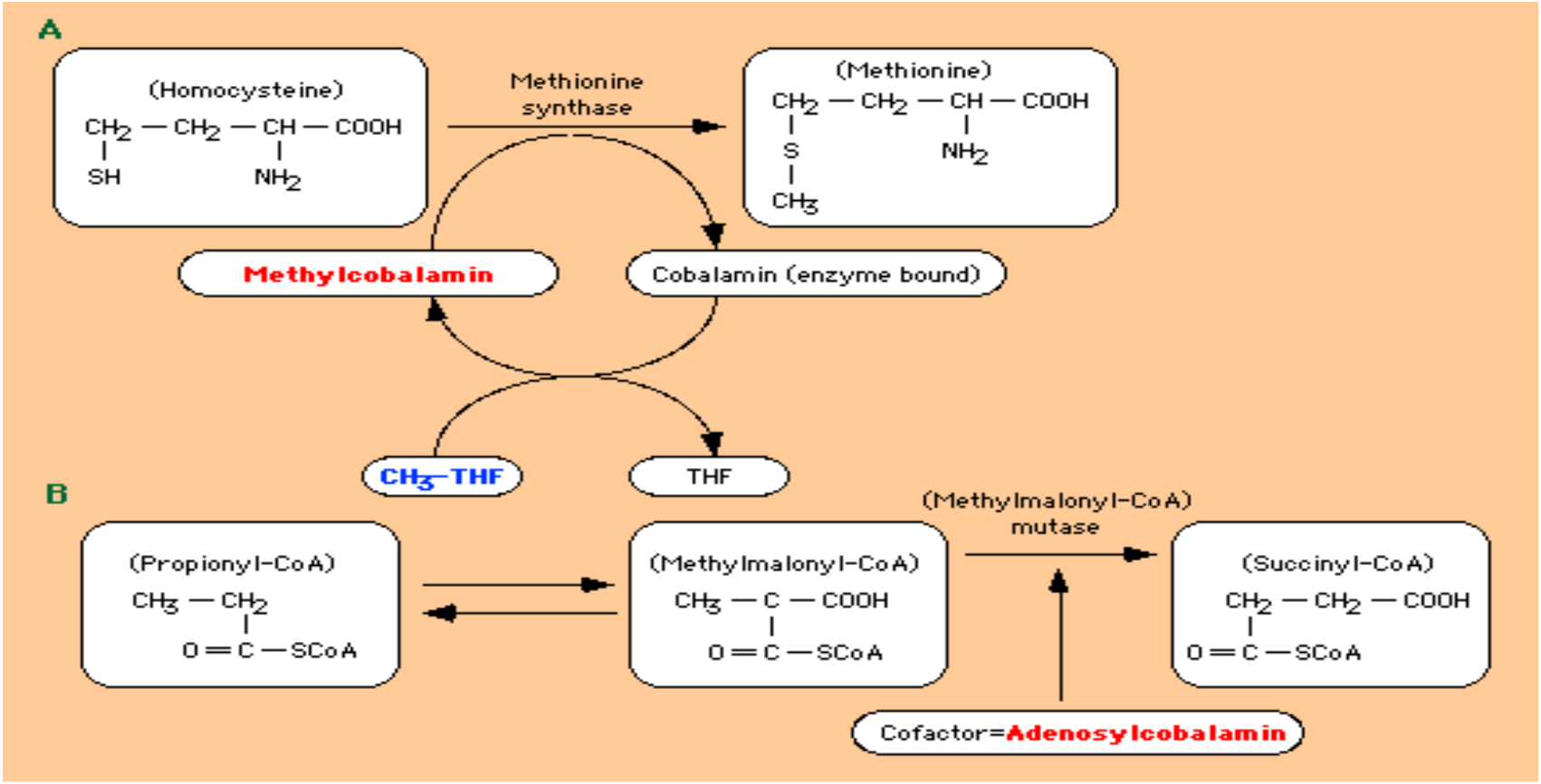
Vitamin B12 contains cobalt in its structure and a cyano group, each together forming a cyanocobalamin.
The human body does not synthesize B12.

- Vitamin B12 is produced by soil microbes that live in symbiotic relationships with plant roots
- Vitamin B12 is found only in foods of animal origin in meat, liver, kidney, eggs, cheese, milk.
- B12 in human milk is contained in the form of methylcobalamin (the main form of the vitamin in the body).

Body`s demands for vitamin B

- The daily requirement of vitamin B12 has been set at 2.4 µg
- Total stores of B12 in the adult human body is about 2-5 mg.
- Stores B12 in the body are large, so that the deficit occurs only after 5-6 years after decrease of intake
- The daily intake is about 9.6 mg
- The daily output is about 2.5 mg with urine and feces.
- Principal place of deposit of vitamin B12 is the liver. Large amount is absorbed as the spleen and kidney, somewhat less - muscles.

Folate/B12 DNA Synthesis



Actions of cobalamin Role of cobalamin in homocysteine and methylmalonic acid metabolism. Panel A – Methylcobalamin is a cofactor in the synthesis of methionine from homocysteine. Panel B – Adenosylcobalamin is a cofactor in the synthesis of succinyl-CoA from methylmalonyl-CoA. Tetrahydrofolate (THF) participates in homocysteine but not methylmalonic acid (MMA) metabolism. Thus, cobalamin deficiency is characterized by elevations in the serum levels of both homocysteine and MMA, while only homocysteine levels are elevated in folate deficiency. (Reproduced with permission from Tefferi, A, Pruthi, RK. The Biochemical Basis of Cobalamin Deficiency. Mayo Clin Proc 1994; 69:181).

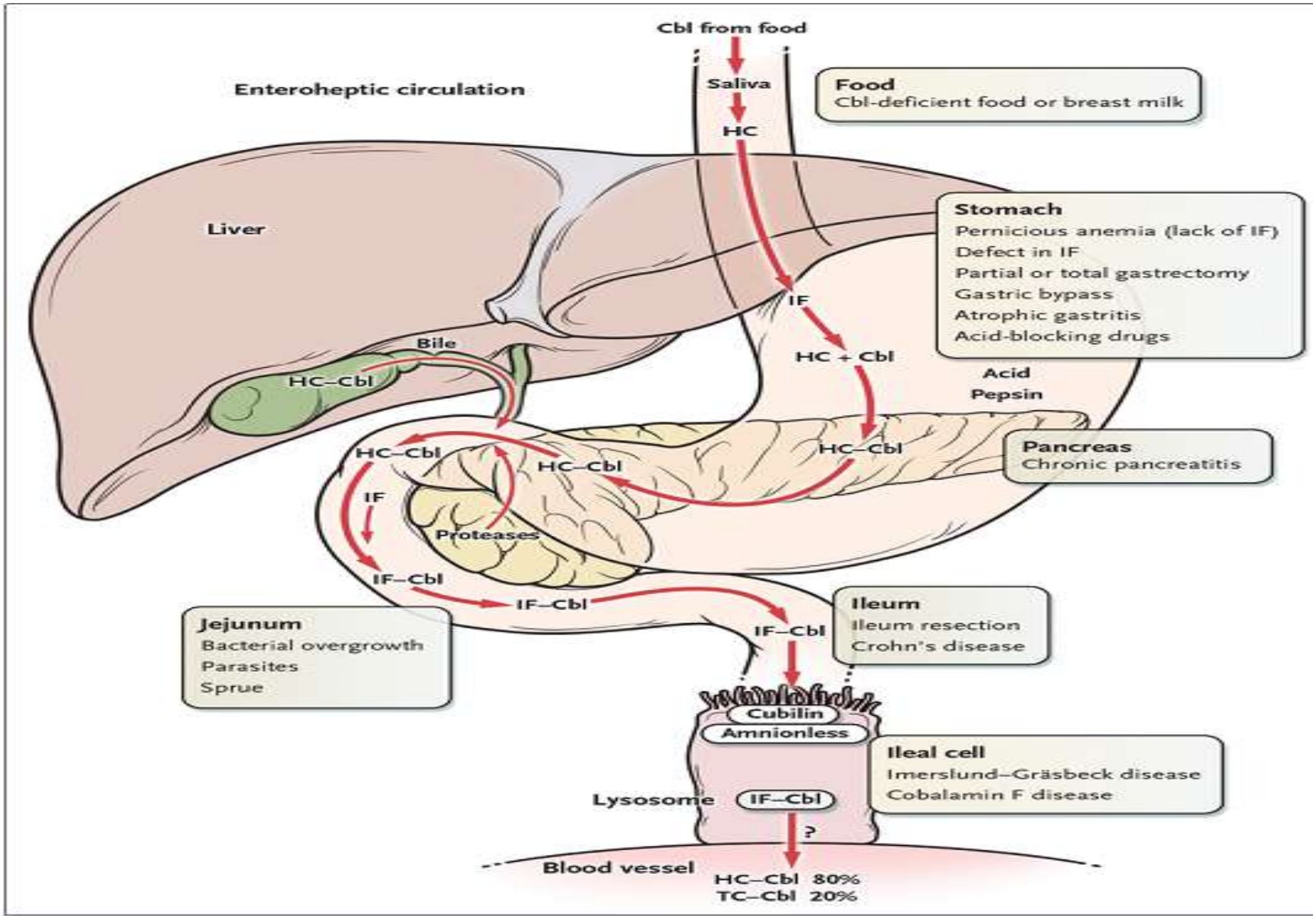
Methylmalonic acid

- Patients with cobalamin deficiency have increased concentrations of MMA in their serum (S-MMA) because 5'-deoxyadenosylcobalainin is required for the enzymatic conversion of l-methylmalonyl-CoA to succinyl-CoA by methylmalonyl-CoA mutase.
- An increased concentration of MMA in serum and its excessive urinary excretion are believed to be direct measures of tissue stores of cobalamin and thus provide an indication of functional cobalamin deficiency.

Absorption of Vitamin B12

- Dietary B-12 binds to haptocorrin (HC) (R factor) in saliva and gastric juices.
- Haptocorrin is produced by the salivary glands of the oral cavity, in response to ingestion of food
- The essential function of haptocorrin is protection of the acid-sensitive vitamin B12 while it moves through the stomach.
- In duodenum, pancreatic enzymes promote dissociation from HC to bind to Intrinsic Factor (IF)
- IF-B12 complex taken up by ileal receptor cubilin.
- Released into plasma bound to transcobalamines TC I, II, III and haptocorrin.
- Haptocorrin binds approximately 80% of circulating B12, rendering it unavailable for cellular delivery by Transcobalamin II.

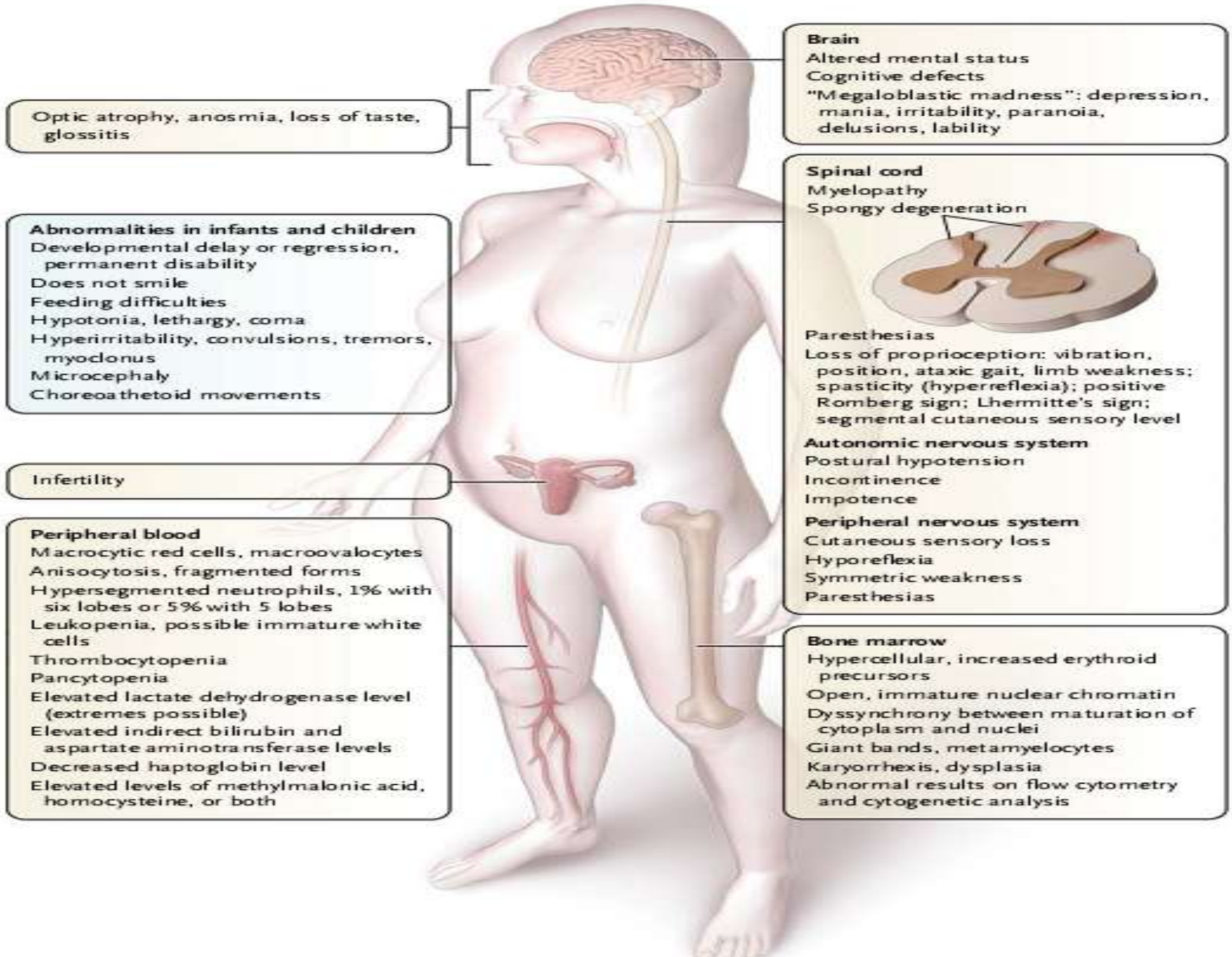
Absorption of Vitamin B12



Clinical signs

The Triad:

1. Blood disturbances
2. Gastrointestinal lesions
3. Damage of CNS and PNS


Brain
Altered mental status
Cognitive defects
"Megaloblastic madness": depression, mania, irritability, paranoia, delusions, lability
Optic atrophy, anosmia, loss of taste, glossitis
Spinal cord
Myelopathy
Spongy degeneration
Paresthesias
Loss of proprioception: vibration, position, ataxic gait, limb weakness; spasticity (hyperreflexia); positive Romberg sign; Lhermitte's sign; segmental cutaneous sensory level
Autonomic nervous system
Postural hypotension
Incontinence
Impotence
Peripheral nervous system
Cutaneous sensory loss
Hyporeflexia
Symmetric weakness
Paresthesias
Abnormalities in infants and children
Developmental delay or regression, permanent disability
Does not smile
Feeding difficulties
Hypotonia, lethargy, coma
Hyperirritability, convulsions, tremors, myoclonus
Microcephaly
Choreoathetoid movements
Infertility
Peripheral blood
Macrocytic red cells, macroovalocytes
Anisocytosis, fragmented forms
Hypersegmented neutrophils, 1% with six lobes or 5% with 5 lobes
Leukopenia, possible immature white cells
Thrombocytopenia
Pancytopenia
Elevated lactate dehydrogenase level (extremes possible)
Elevated indirect bilirubin and aspartate aminotransferase levels
Decreased haptoglobin level
Elevated levels of methylmalonic acid, homocysteine, or both
Bone marrow
Hypercellular, increased erythroid precursors
Open, immature nuclear chromatin
Dyssynchrony between maturation of cytoplasm and nuclei
Giant bands, metamyelocytes
Karyorrhexis, dysplasia
Abnormal results on flow cytometry and cytogenetic analysis

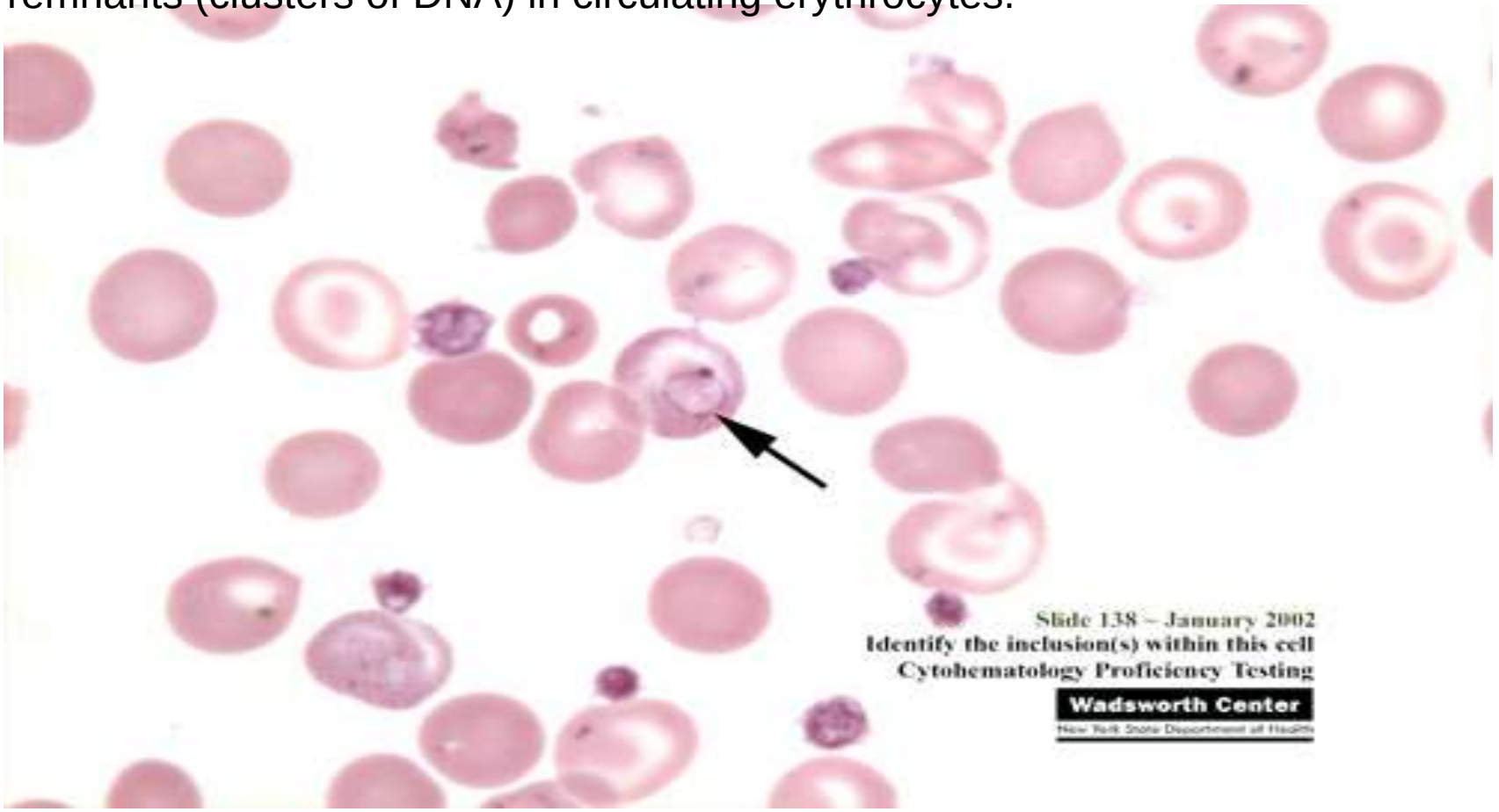
Diagnostics

Changes in blood

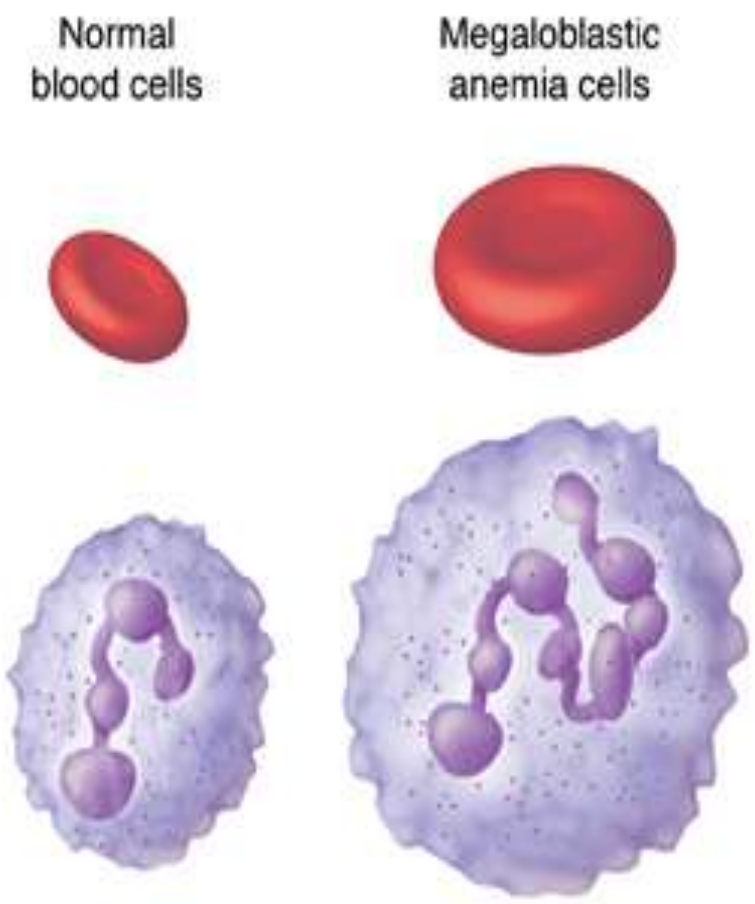
1. Reduction in the number of erythrocytes and decrease of hemoglobin level
2. Prevalence of macrocytes (diameter> 8 mcm, MCV> 100 fl) and megalocytes (diameter of 10 to 12 mcm) in blood smear
3. The increase in color index greater than 1.0 (hyperchromic RBC, MCH> 34 pg).
4. Cabot rings and Howell–Jolly bodies
5. Anisocytosis, poikilocytosis
6. Large number of makroovalocytes.
7. Reduced number of reticulocytes
8. Leukopenia
9. Neutropenia with a shift to the right (presence of overmature hypersegmented neutrophils > 5%)
10. Eosinopenia
11. Monotsitopeniya and relative lymphocytosis
12. Thrombocytopenia

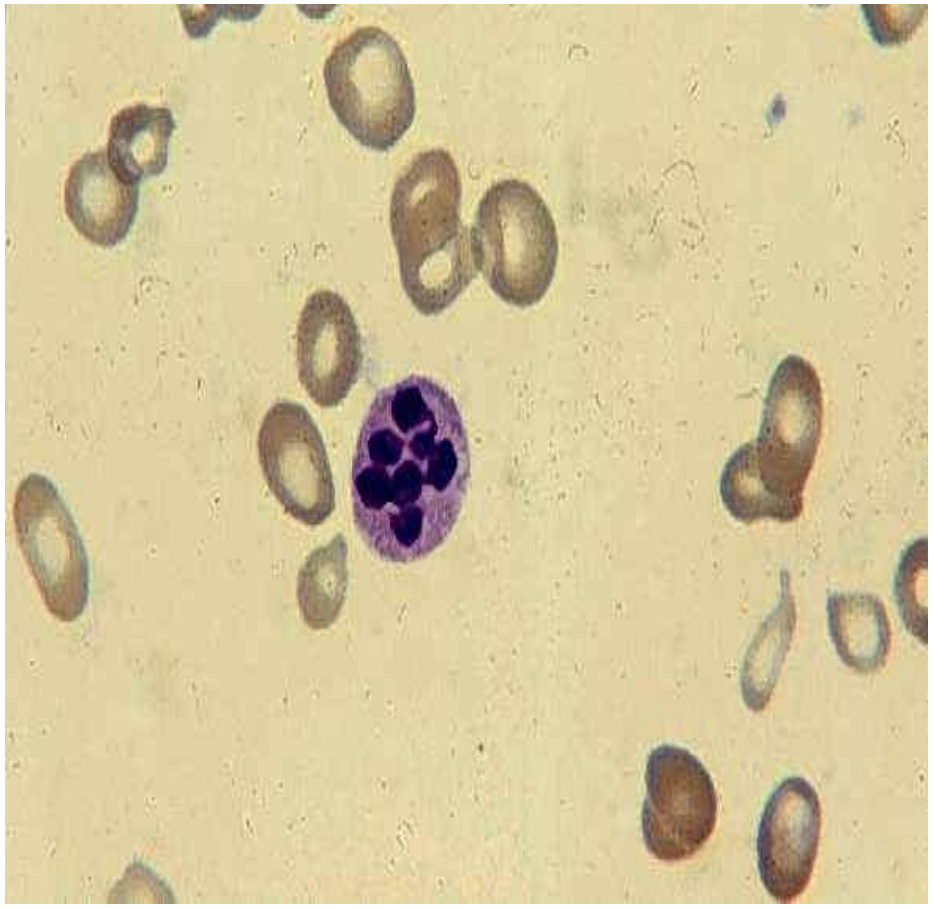
Cabot rings and Howell–Jolly bodies

•**Cabot rings** are thin, red-violet staining, threadlike strands in the shape of a loop or figure-8 that are found on rare occasions in erythrocytes.
•**Howell–Jolly bodies** are histopathological findings of basophilic nuclear remnants (clusters of DNA) in circulating erythrocytes.

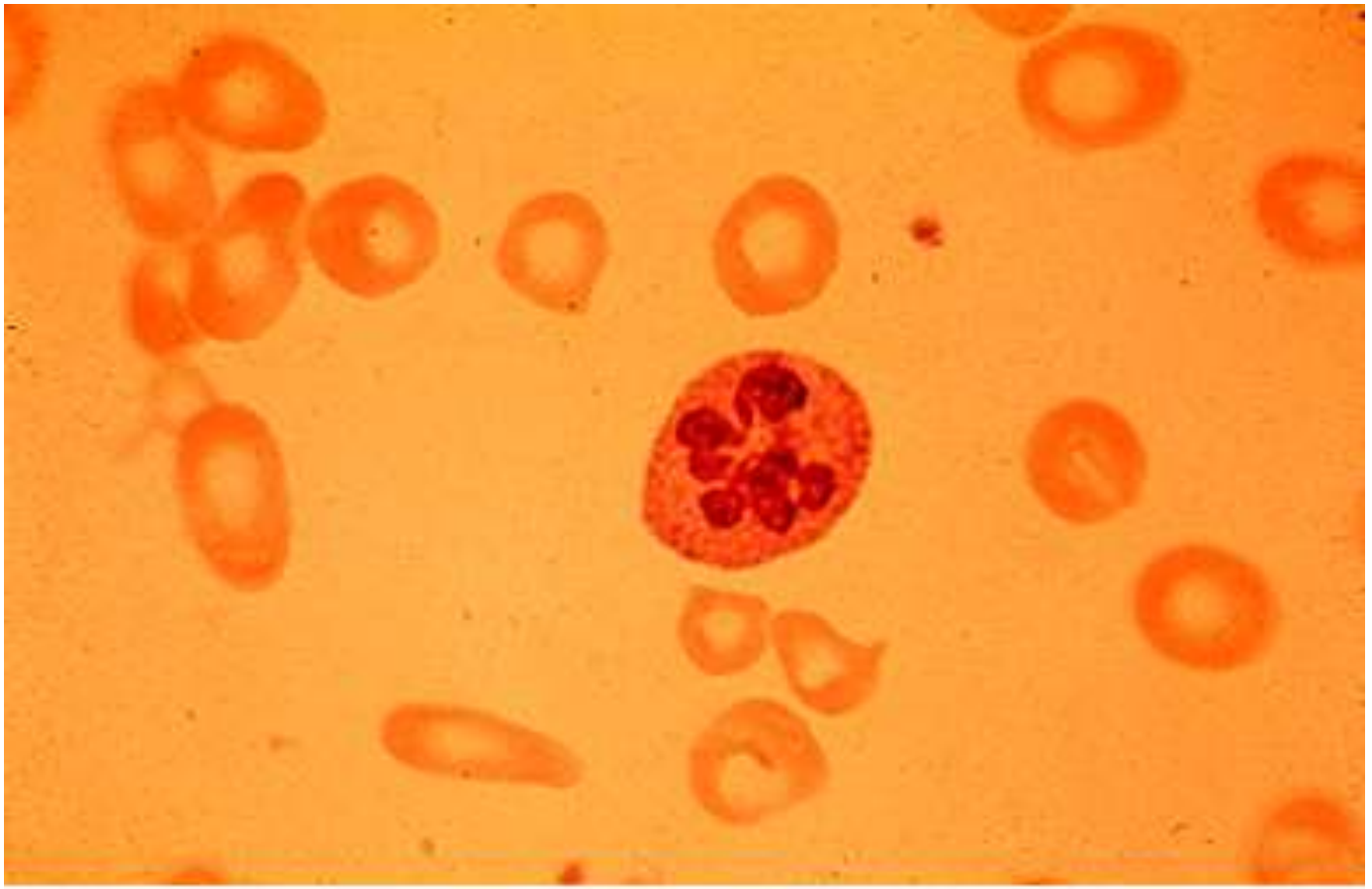


Hypersegmented neutrophil



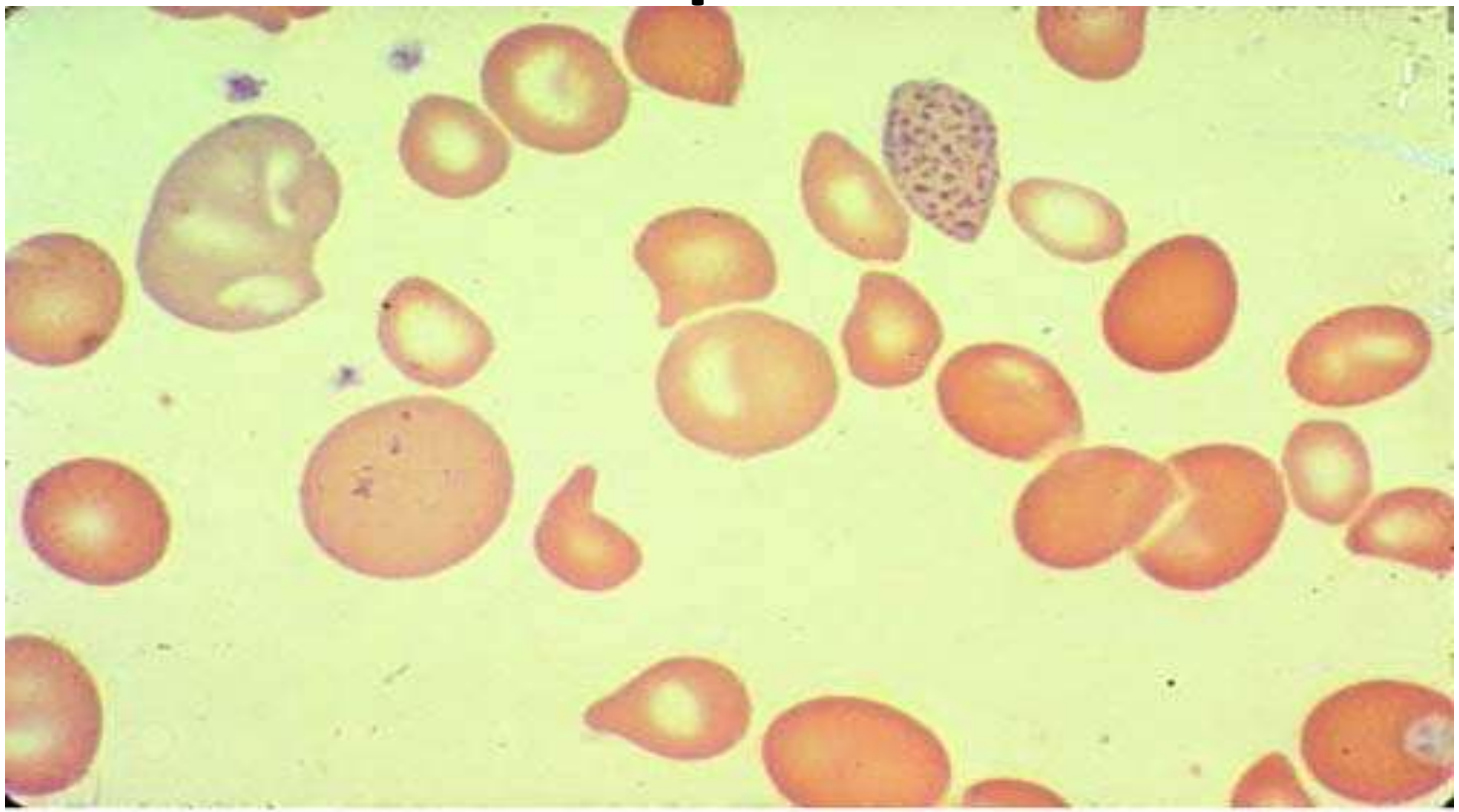


Hypersegmented neutrophil



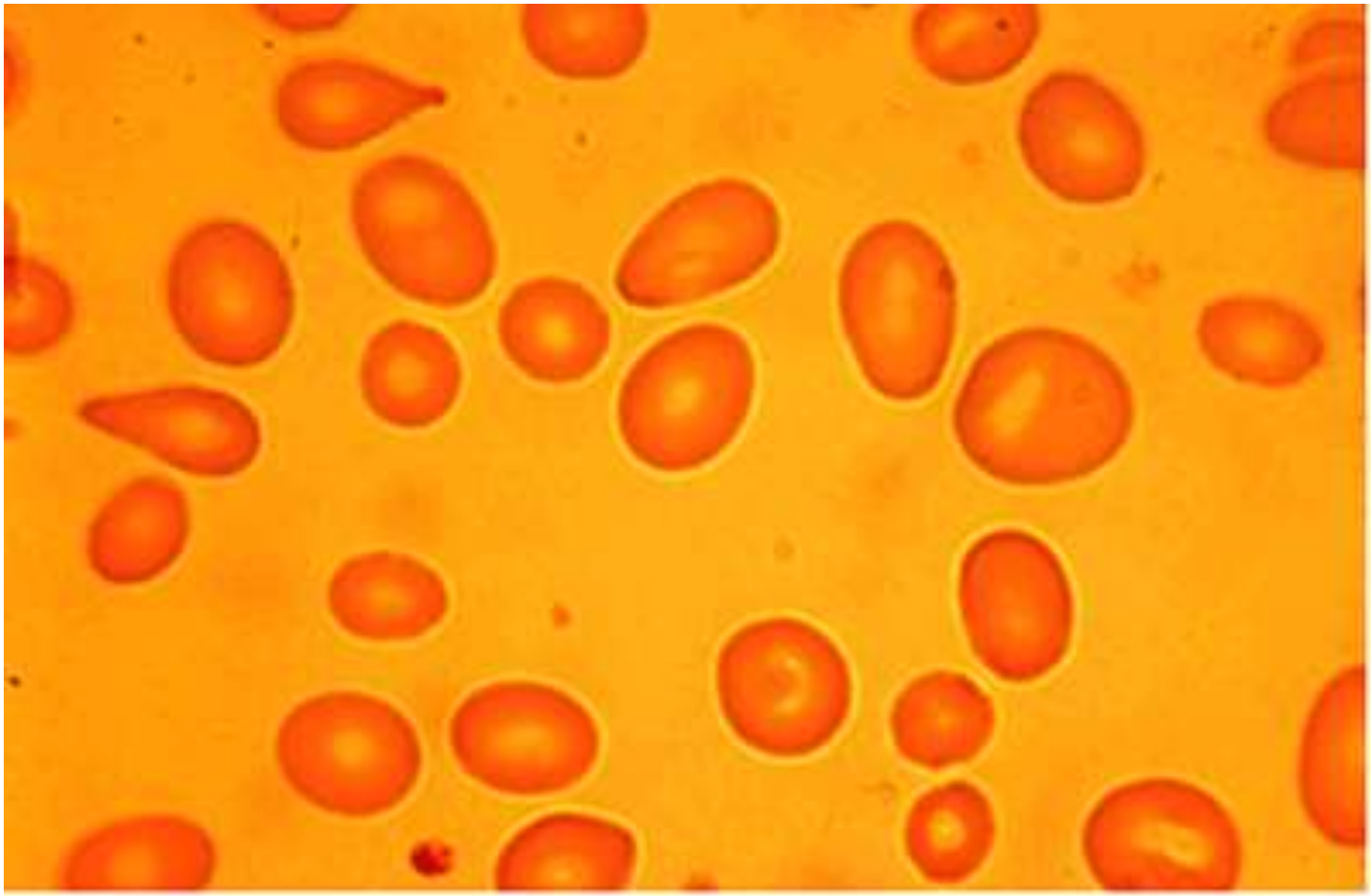
Megaloblastic blood picture Peripheral blood smear showing a hypersegmented neutrophil (7 lobes) and macroovalocytes, a pattern that can be seen with cobalamin or folate deficiency. Courtesy of Stanley L Schrier, MD.

Macro-ovalocytes, basophilic stippling, and bizarre-shaped red cell forms



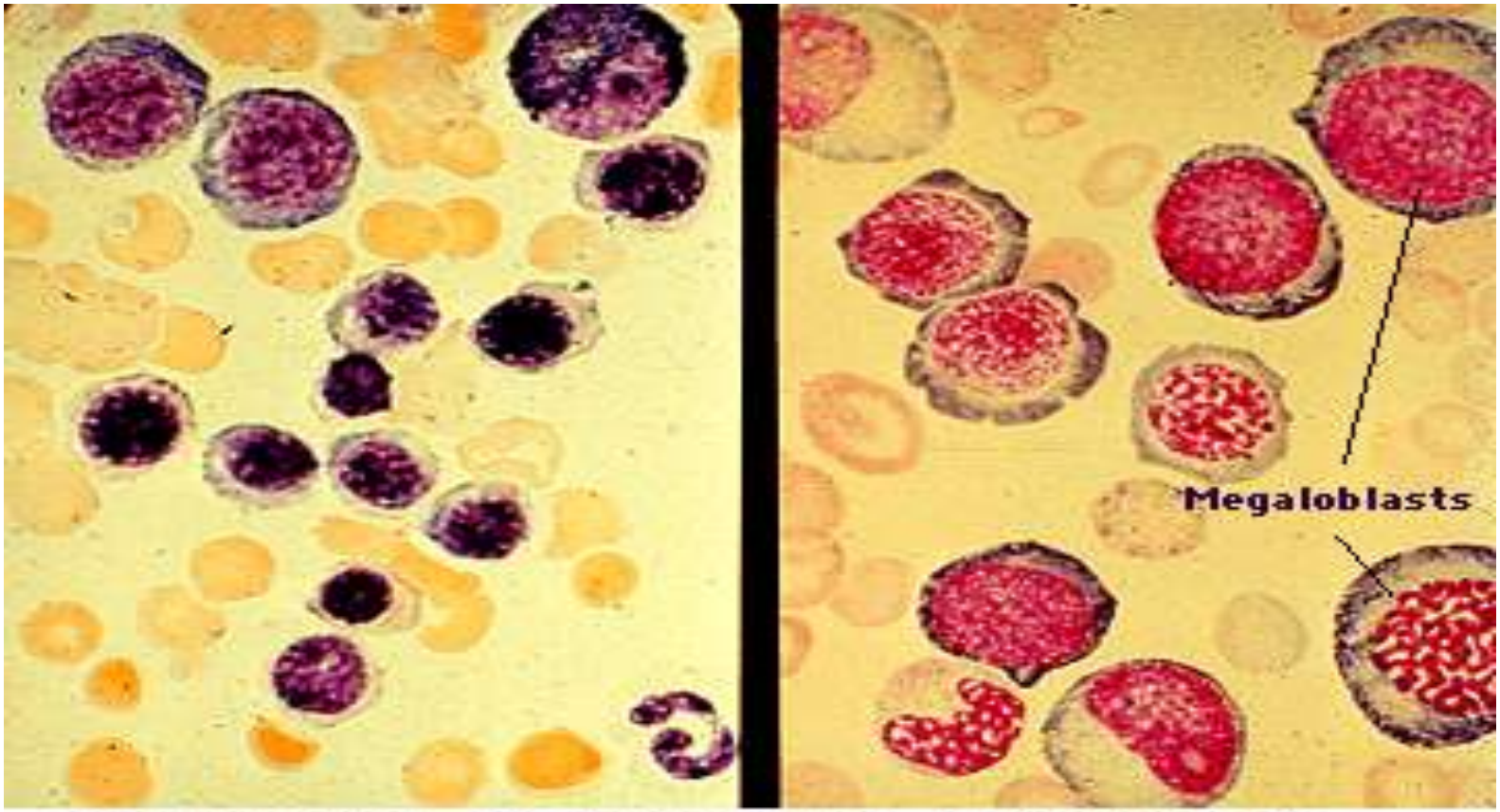
Vitamin B12 deficiency. (Peripheral blood, 100 x.) Shown are several hallmark features of vitamin B12 deficiency, including macro-ovalocytes, basophilic stippling, and bizarre-shaped red cell forms. (Courtesy of L Damon.)

Macroovalocytosis



Macroovalocytosis Peripheral smear shows marked macroovalocytosis in a patient with vitamin B12 deficiency. Courtesy of Stanley L Schrier, MD.

Megaloblastic erythropoesis



Megaloblastic erythropoiesis Comparison of normal and megaloblastic erythropoiesis with respect to erythroid precursors in the bone marrow. Left panel: Normal erythropoiesis. Right panel: Megaloblastic erythropoiesis. Courtesy of Stanley L Schrier, MD.

Laboratory confirmation of diagnosis

Marker	B12-anemia	Norm
Serum vitamin B12	< 200 pg/ml	200-900 pg/ml
Serum methylmalonic acid	>0.75 µmol/l	0.07 - 0.27 µmol/l
Serum or plasma total homocysteine	>21 µmol/liter	2.2 - 13.2 µmol/l

Tests to determine cause of deficiency

Marker	B12-anemia	Norm
Anti–intrinsic factor antibodies	Present	Absent
Anti–parietal-cell antibodies	Present	Absent
Fasting high serum gastrin level	>100 pmol/liter	
Low level of serum pepsinogen I	<30 µg/liter	

Treatment

Saturation phase 4-6 weeks	Fixating phase 6 month	Maintenance phase lifelong

- Vitamin B12 is administered orally, intramuscularly, intravenously and intralumbarly.
- Different forms of vitamin B12 can be used, including cyano,- hydroxy,- and methylcobalamin.

Injected Vitamin B12

- About 10% of the injected dose (100 of 1000 µg) is retained.
- Patients with severe abnormalities should receive injections of 1000 µg at least several times per week for 1 to 2 weeks, then weekly until clear improvement is shown, followed by monthly injections.

High-Dose Oral Treatment

- High-dose oral treatment is effective and is increasingly popular.
- 0.5 to 4% of radioactively labeled oral vitamin B12 can be absorbed by passive diffusion in both normal controls and patients with pernicious anemia.
- Thus, oral doses of 1000 µg deliver 5 to 40 µg, even if taken with food.

Response to treatment

- Hematologic response is rapid, with an increase in the reticulo-cyte count in 1 week and correction of megalo-blastic anemia in 6 to 8 weeks.

The end