Pathophysiology of Anemia

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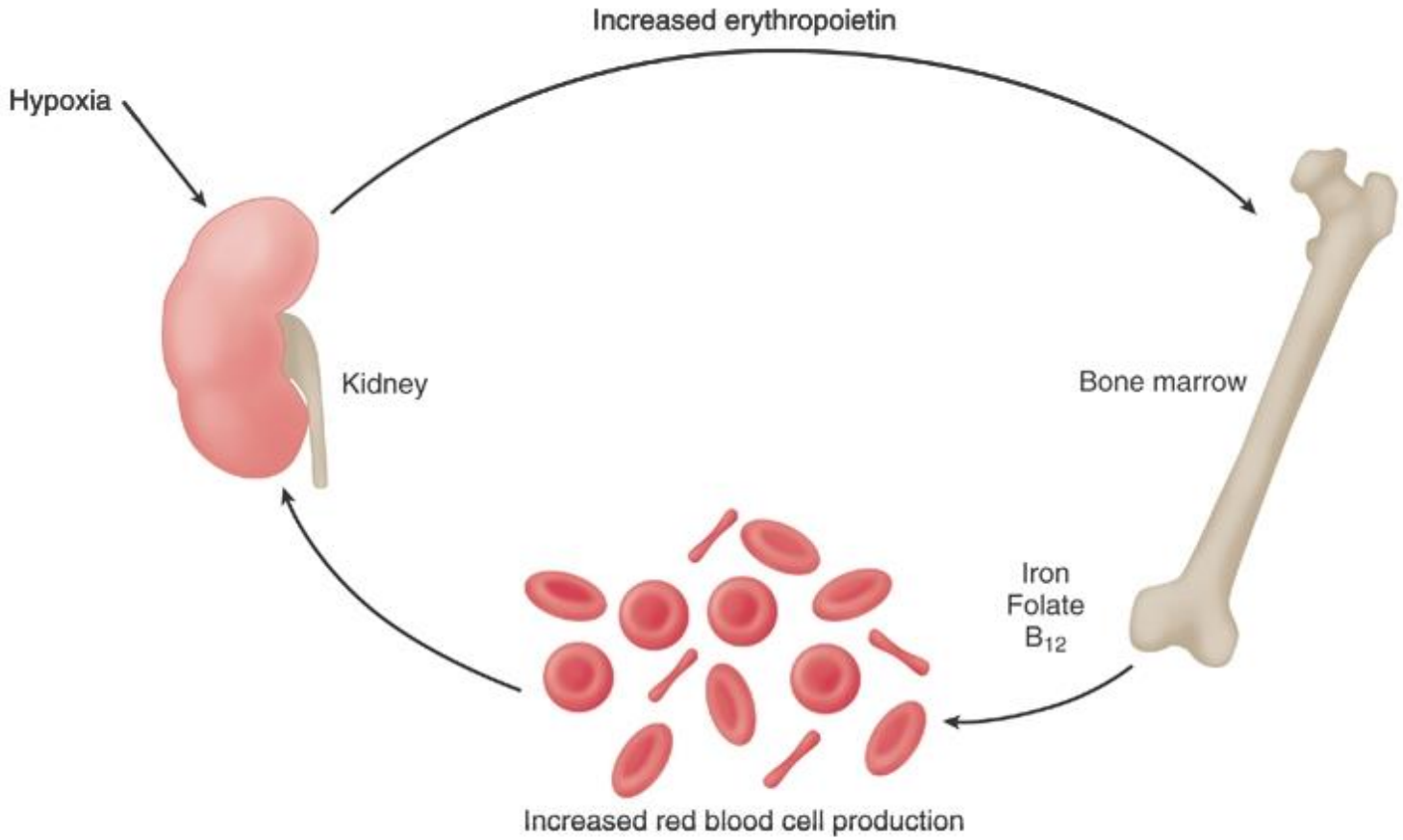
Disclaimer

- None

Objectives

- Define anemia
- Classify anemia according to pathogenesis & clinical significance
- Understand Red cell indices
- Relate the red cell indices with type of anemia
- Interpret CBC to approach diagnosis of anemia
- Diagnosis and management of Iron deficiency anemia

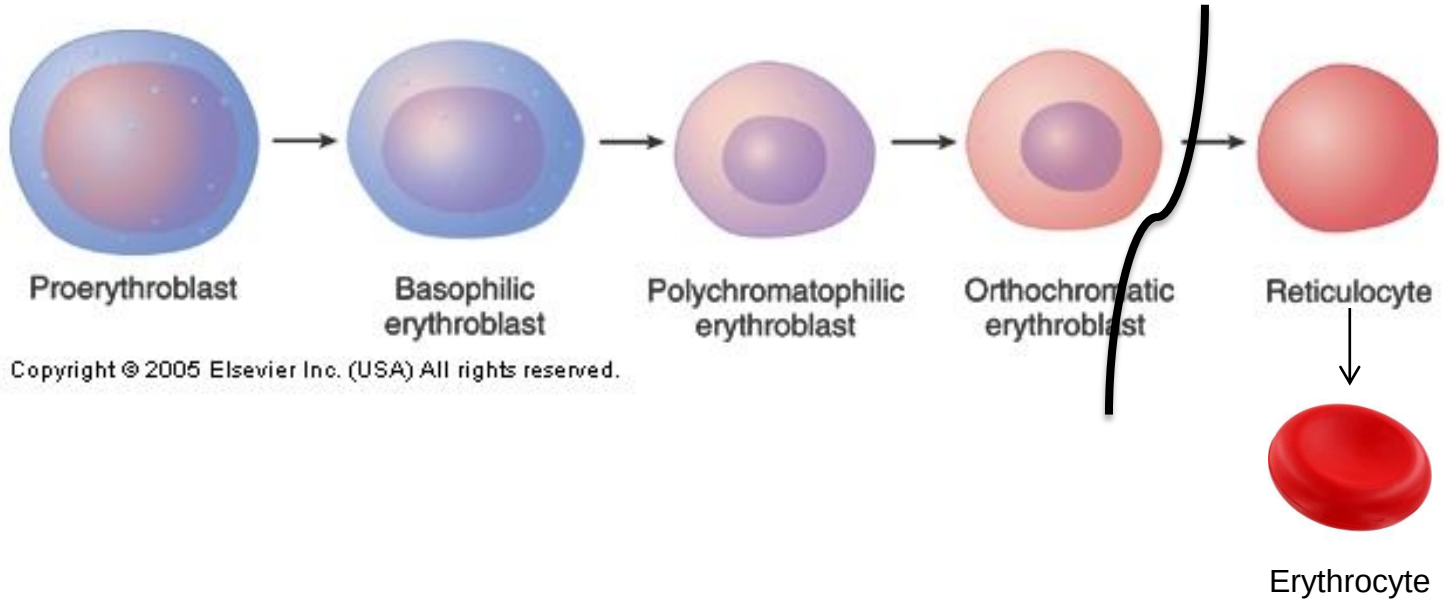
Regulation of Erythropoiesis



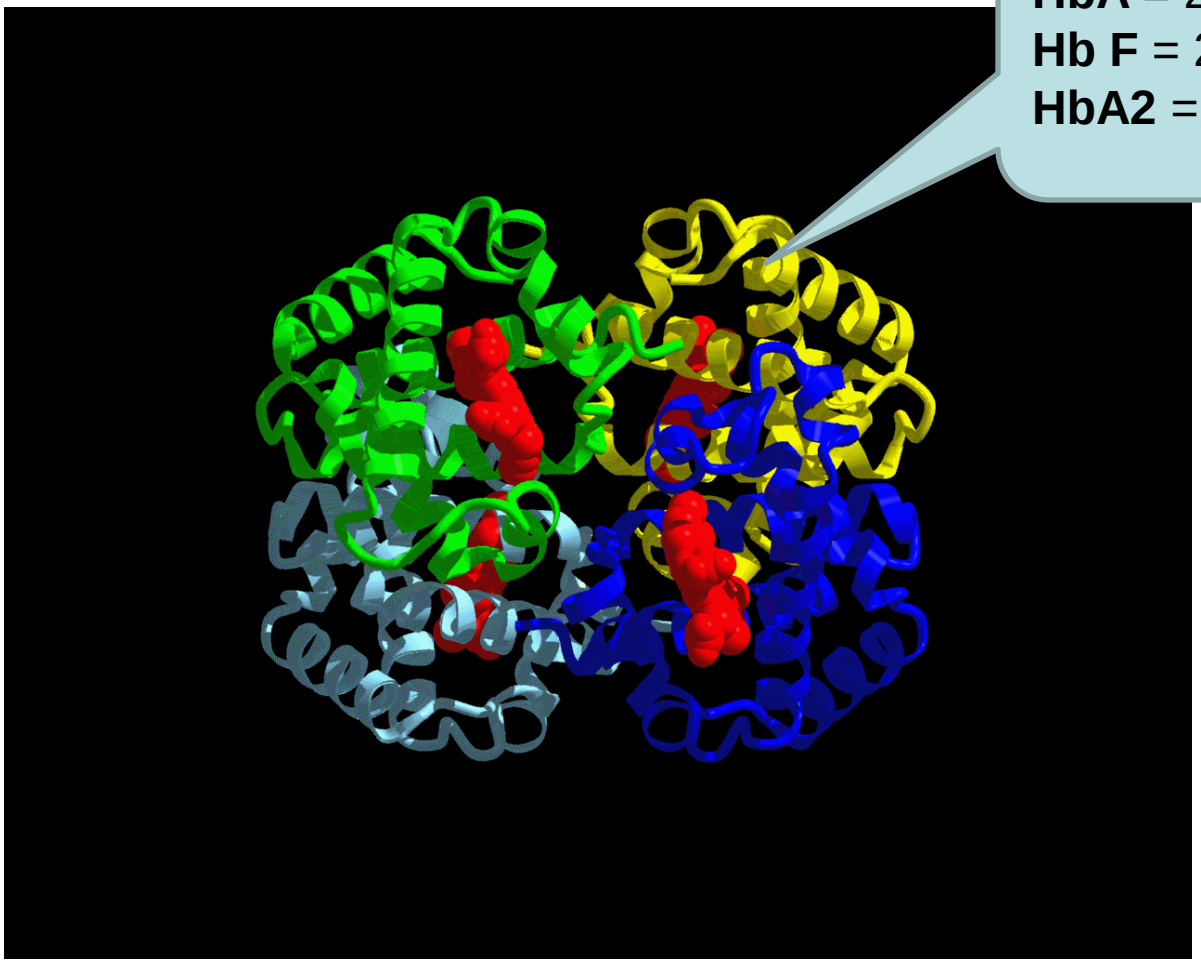
Overview of Erythropoiesis

BONE MARROW

PERIPHERAL BLOOD

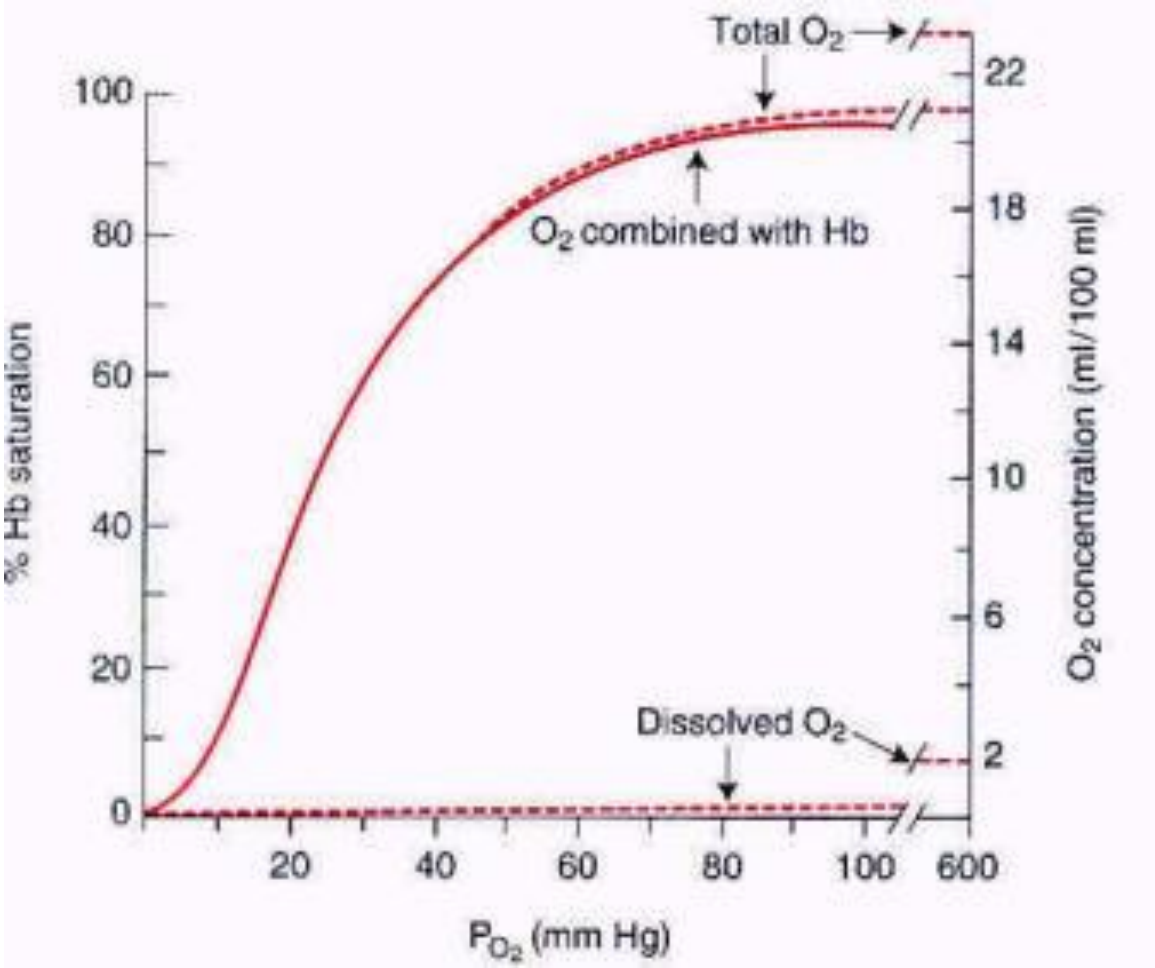


Hemoglobin

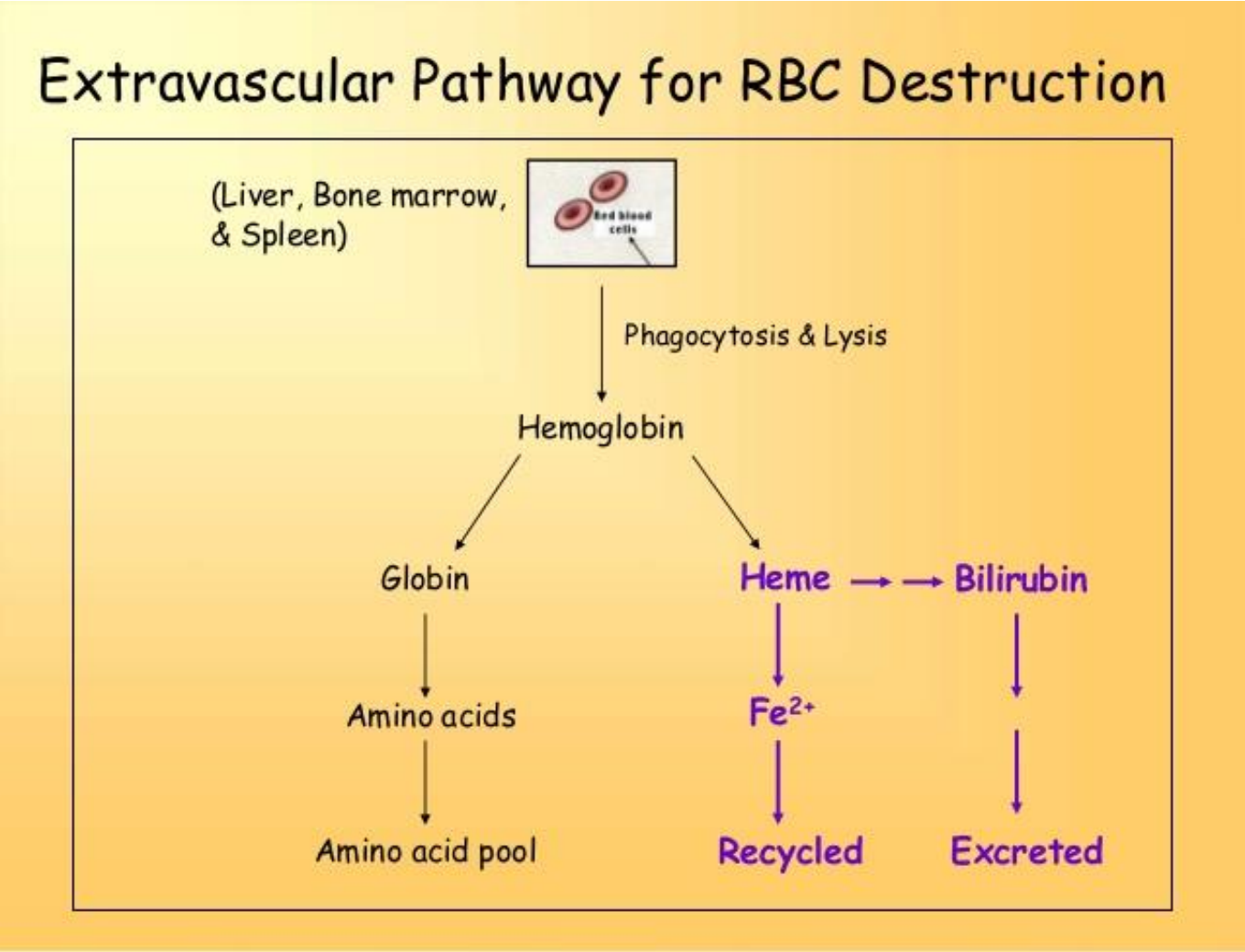


HbA = 2 α+2β
Hb F = 2 α+2ɣ
HbA2 =2 α+2δ

O2 dissociation curve



Metabolism of hemoglobin



Anemia

It is defined as reduction in circulating red cell mass.

It may be defined as decreased oxygen carrying capacity of blood

Clinically, anemia is reduction in hemoglobin or hematocrit below the reference range.

Reference ranges of hemoglobin

- Infants
  - 6 months 9.5-13.5 g/dl
  - 3 yrs 11.0-14.0 g/dl
- Adult male 13.7-16.3 g/dl
- Adult female 11.1-14.5 g/dl

How does the body adapt to anemia?

- Increased cardiac output
- Redistribution of blood flow
- Decreased hemoglobin-oxygen affinity

Classification of anemia

1. Pathogenesis

   according to underlying mechanism

2. Morphological

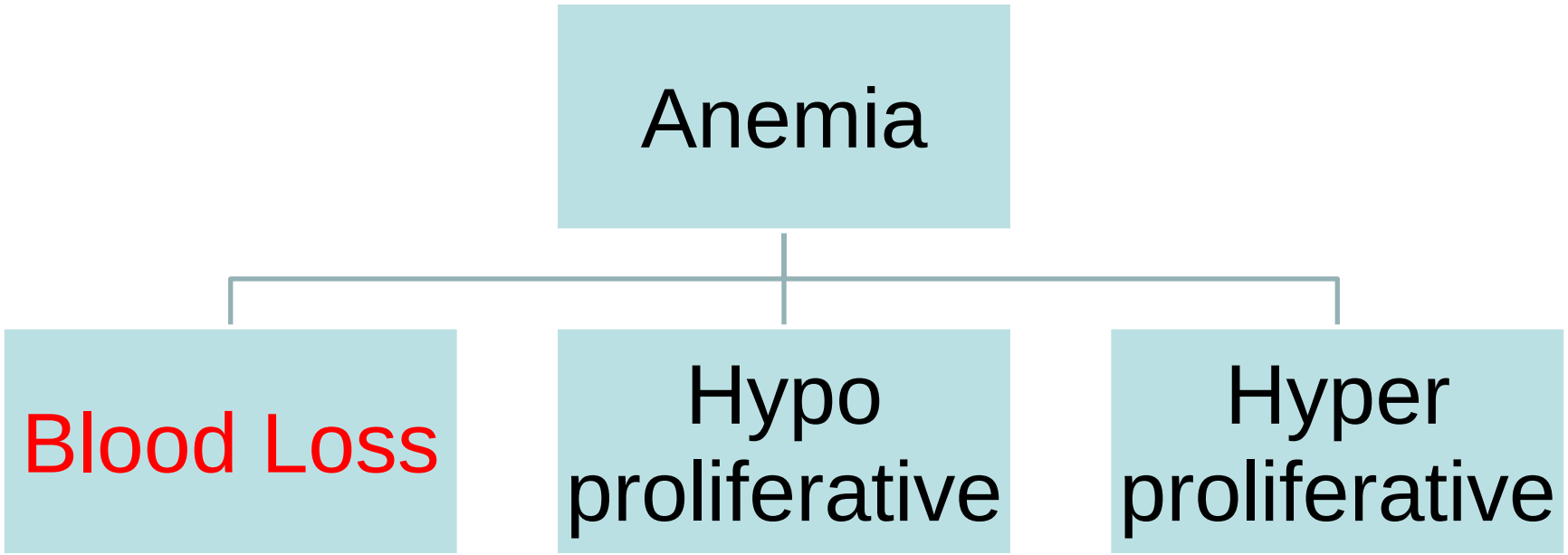
   according to red cell indices

Robbins Pathology 2009 ed

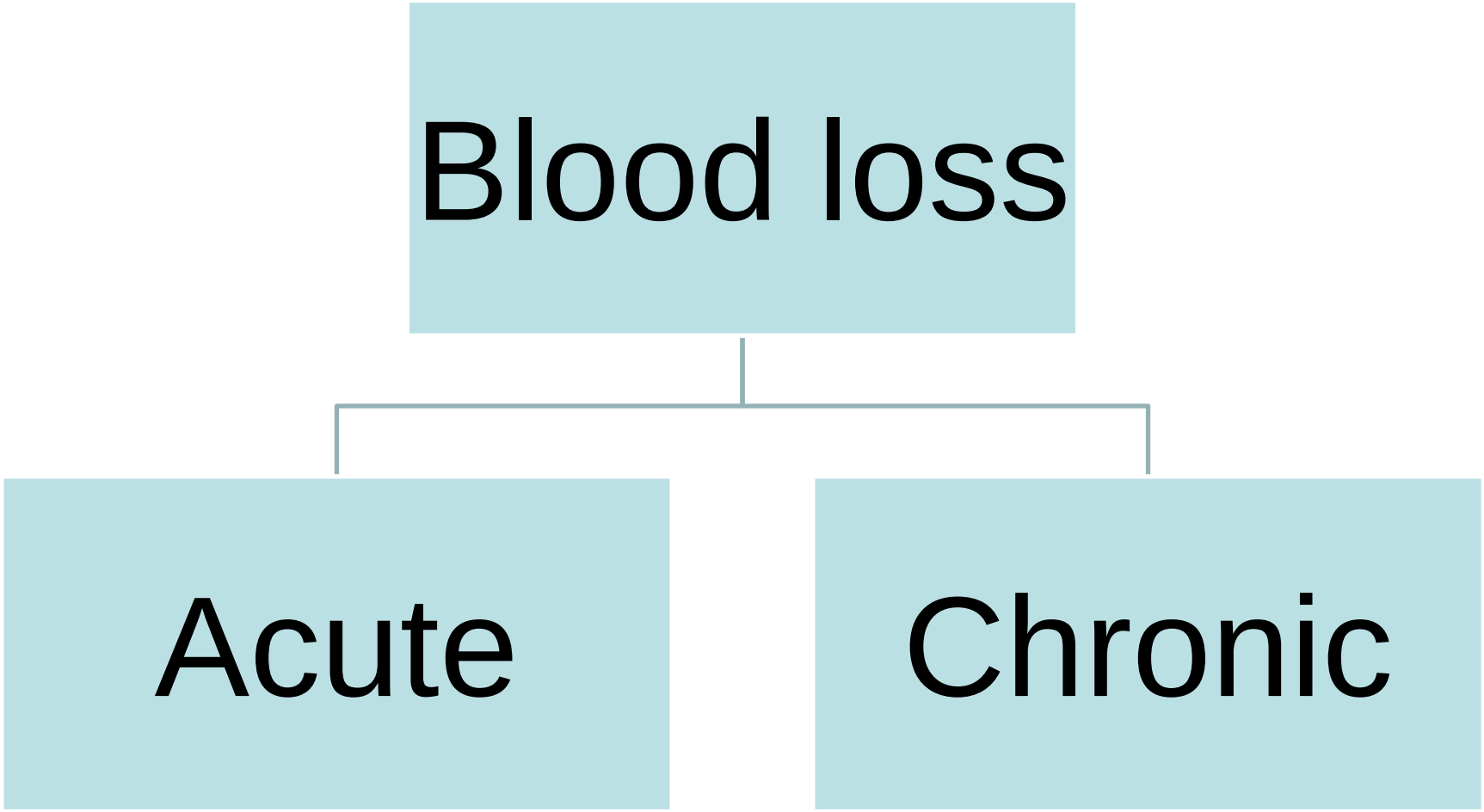
Pathogenesis of Anemia

1. Blood loss
2. Bone marrow failure
3. Rapid destruction of red cells

1. Classification of anemia according to underlying mechanism

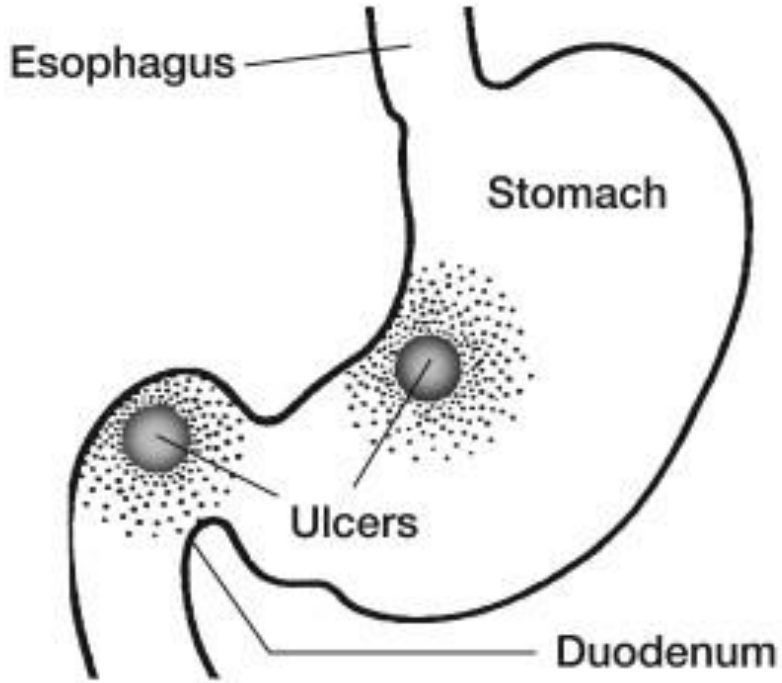


1. Blood loss anemia

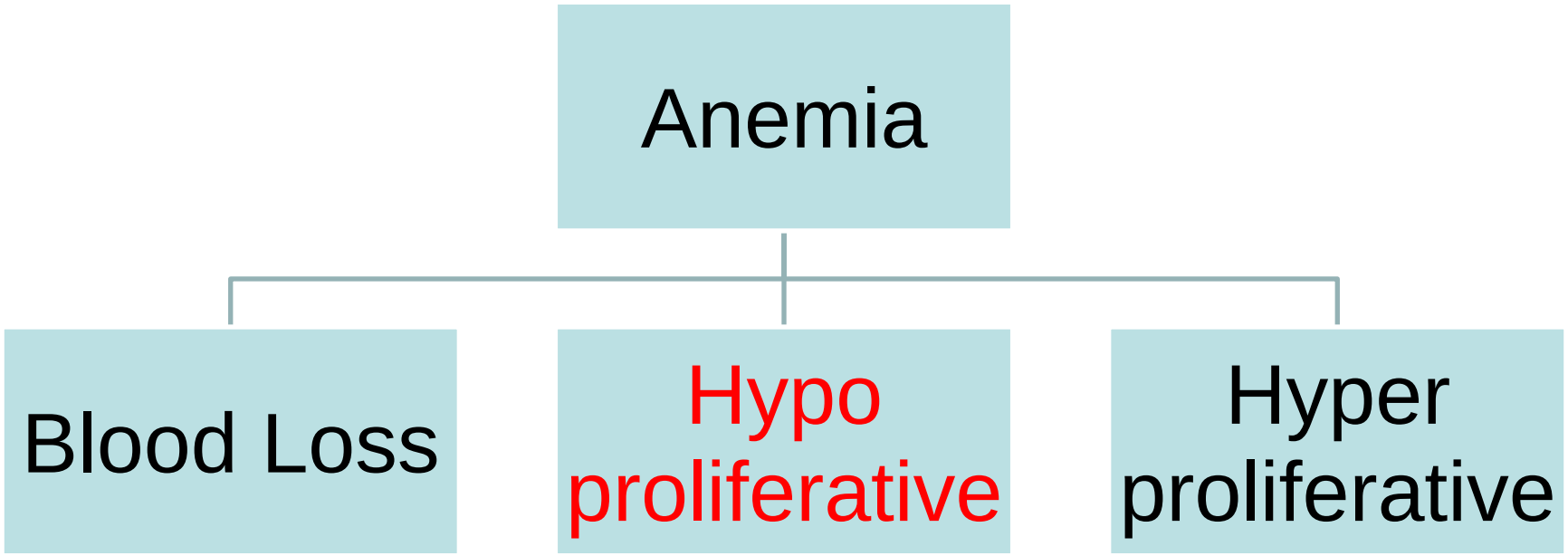


Acute blood loss surgical bleeds

Chronic blood loss
e.g. gastric bleed



Classification of anemia



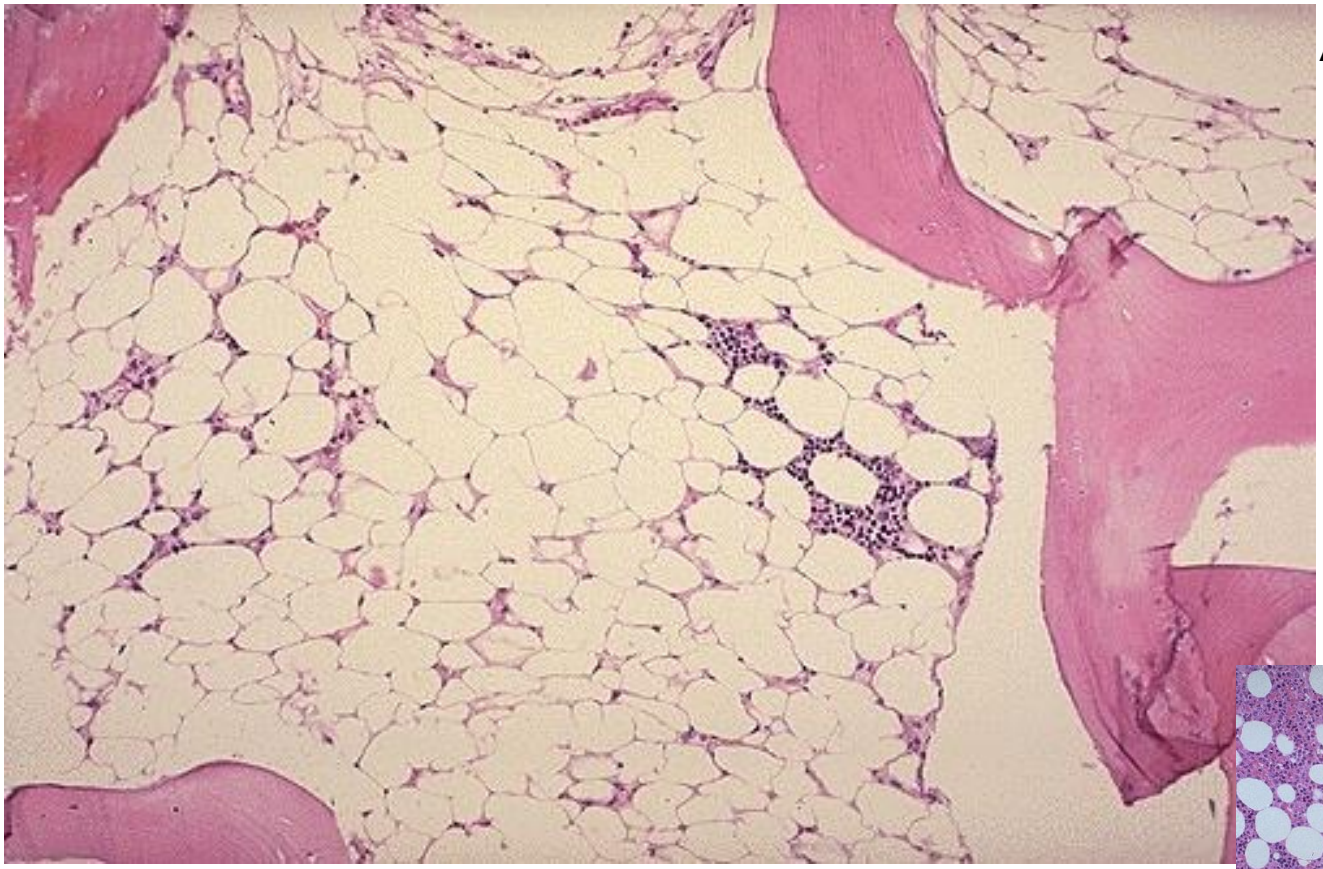
2. Hypoproliferative anemias

There is inability to produce an adequate number of erythrocytes in response to appropriate stimulus.

Types:

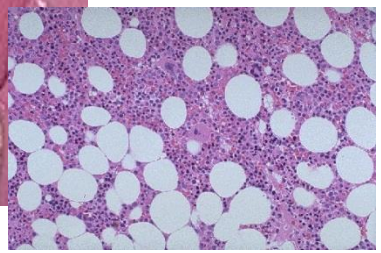
1. Nutritional anemias
2. Anemia of cancers
3. Anemia of renal failure
4. Aplastic anemia

Bone marrow: Aplastic anemia

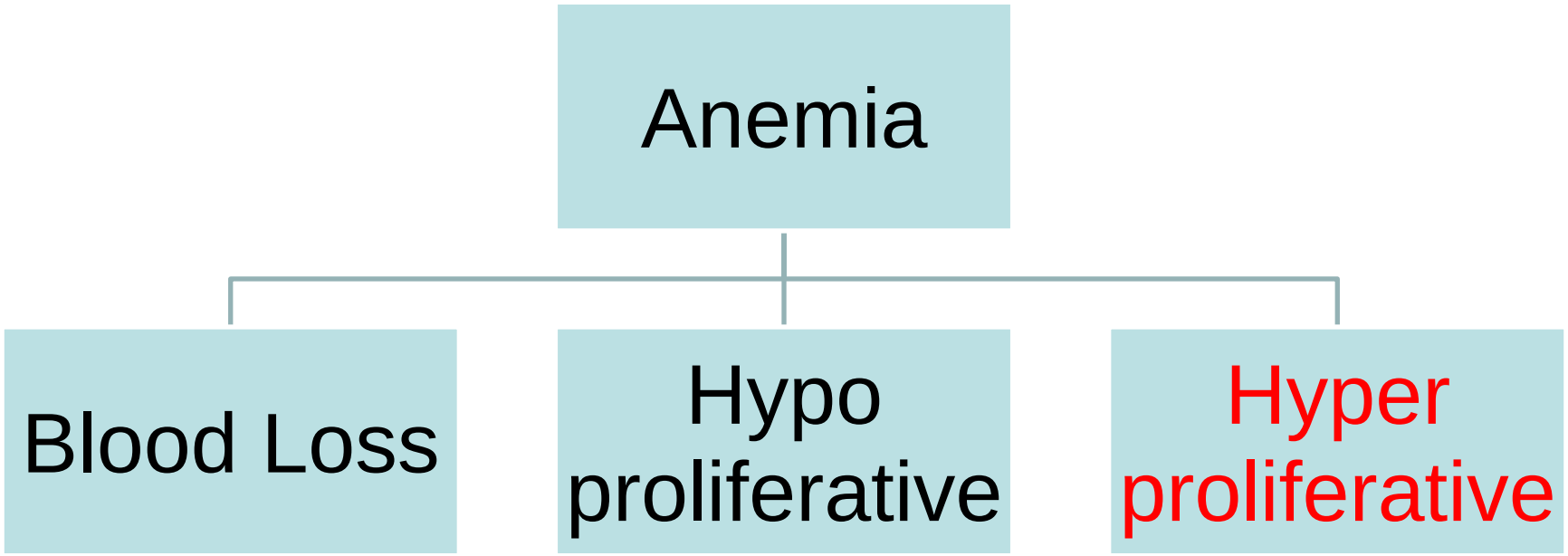


Aplastic

Normal



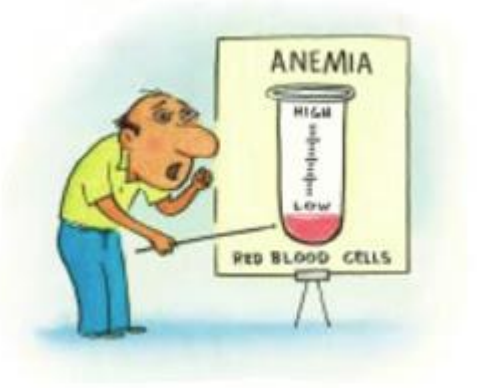
Classification of anemia



3. Hyperproliferative anemia

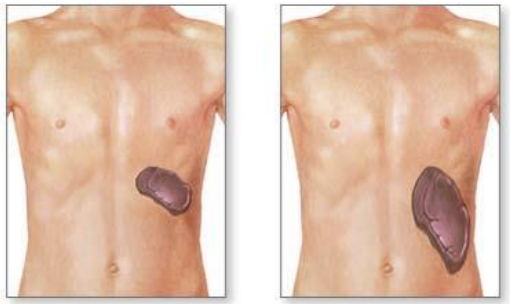
- They are regarded as hemolytic anemias
- Occur due to premature destruction of red cells
- Thalassemia
- Sickle cell disease

Hemolytic anemia: 3 cardinal signs



Anemia

Jaundice



Splenomegaly

Symptoms and signs

- Easy fatigability
- Dizziness
- Headaches
- Pallor
- Increased heart rate
- Breathlessness
- Heart failure

Lab tests in Anemia

1. CBC
    1. Hb
    2. HCT
    3. RBC
    4. Red cell indices
    5. Peripheral film review
2. Reticulocyte

Red cell indices

- MCV
- RDW

Size of red cells

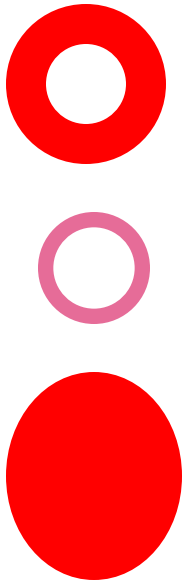
- MCH
- MCHC

Hemoglobin of red cells

Significance of MCV

- It helps in classifying anemia on morphological basis
- Red cells may be:

1. Normocytic
2. Microcytic
3. Macrocytic

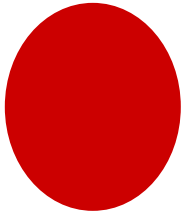


Morphological classification of anemia

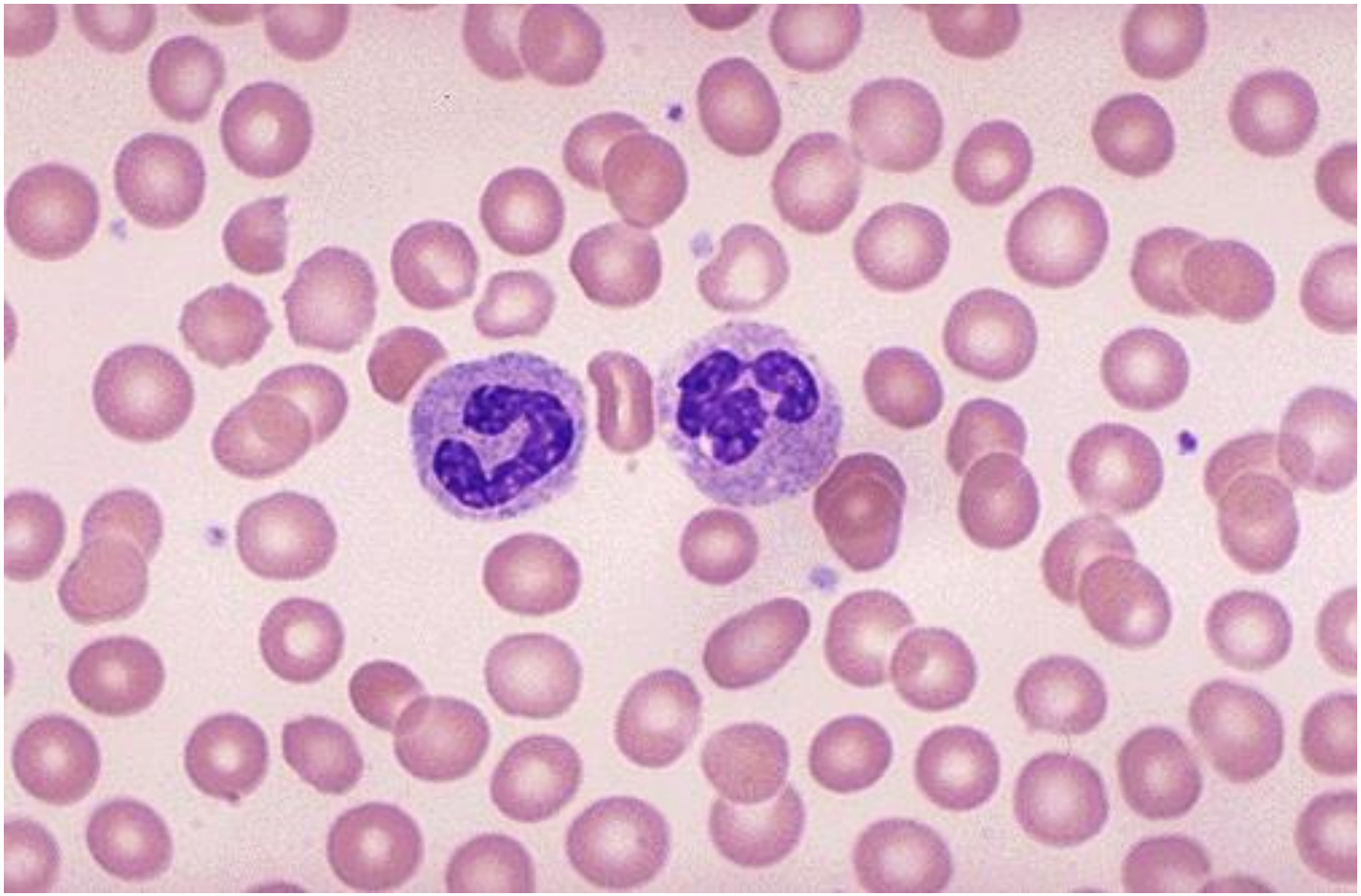
1. Normochromic normocytic anemias
    1. Acute blood loss
    2. Anemia of renal failure

2. Hypochromic microcytic anemias
    1. Iron deficiency anemia
    2. Thalassemia

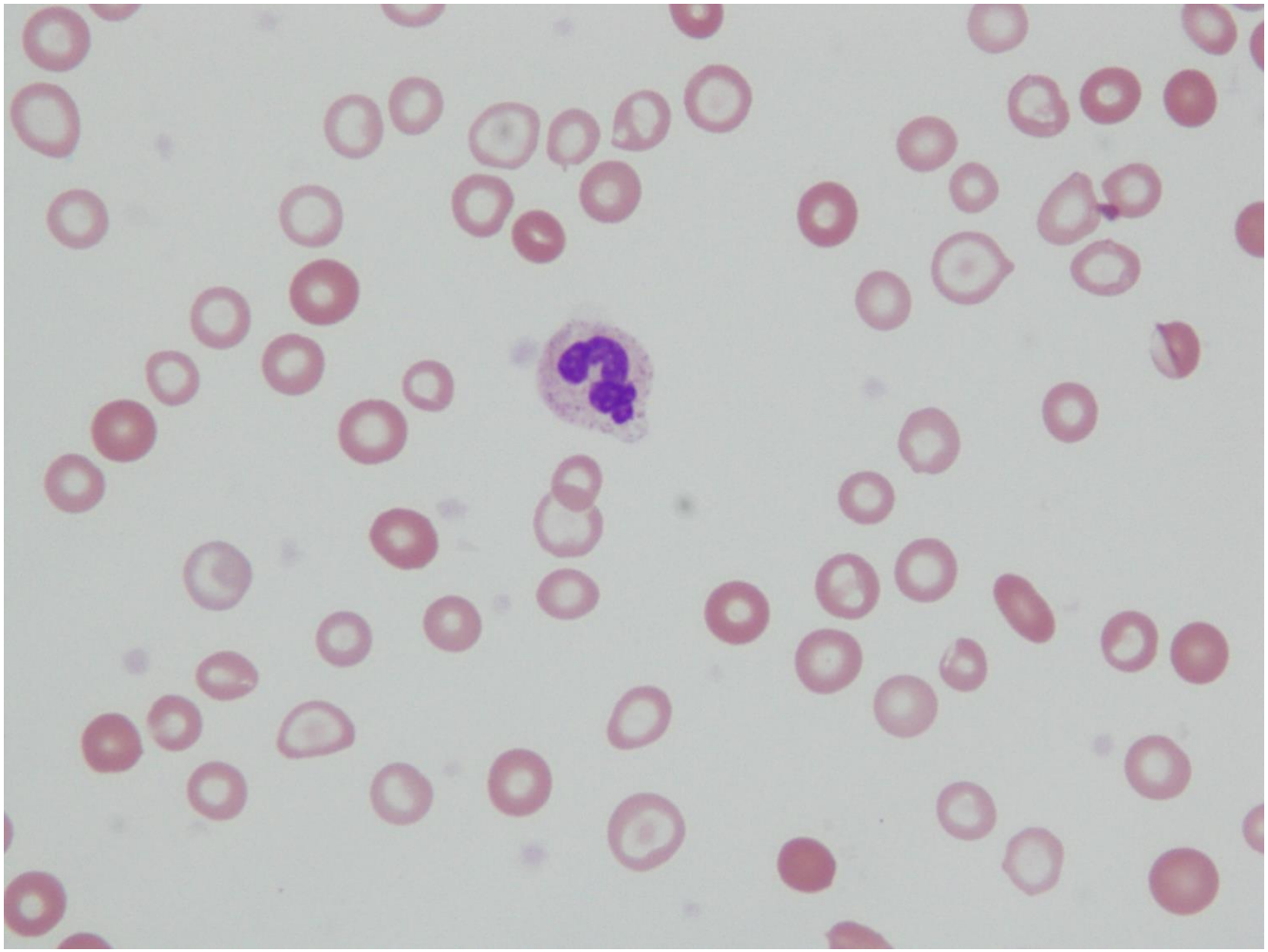
3. Macrocytic anemia
    1. megaloblastic anemia



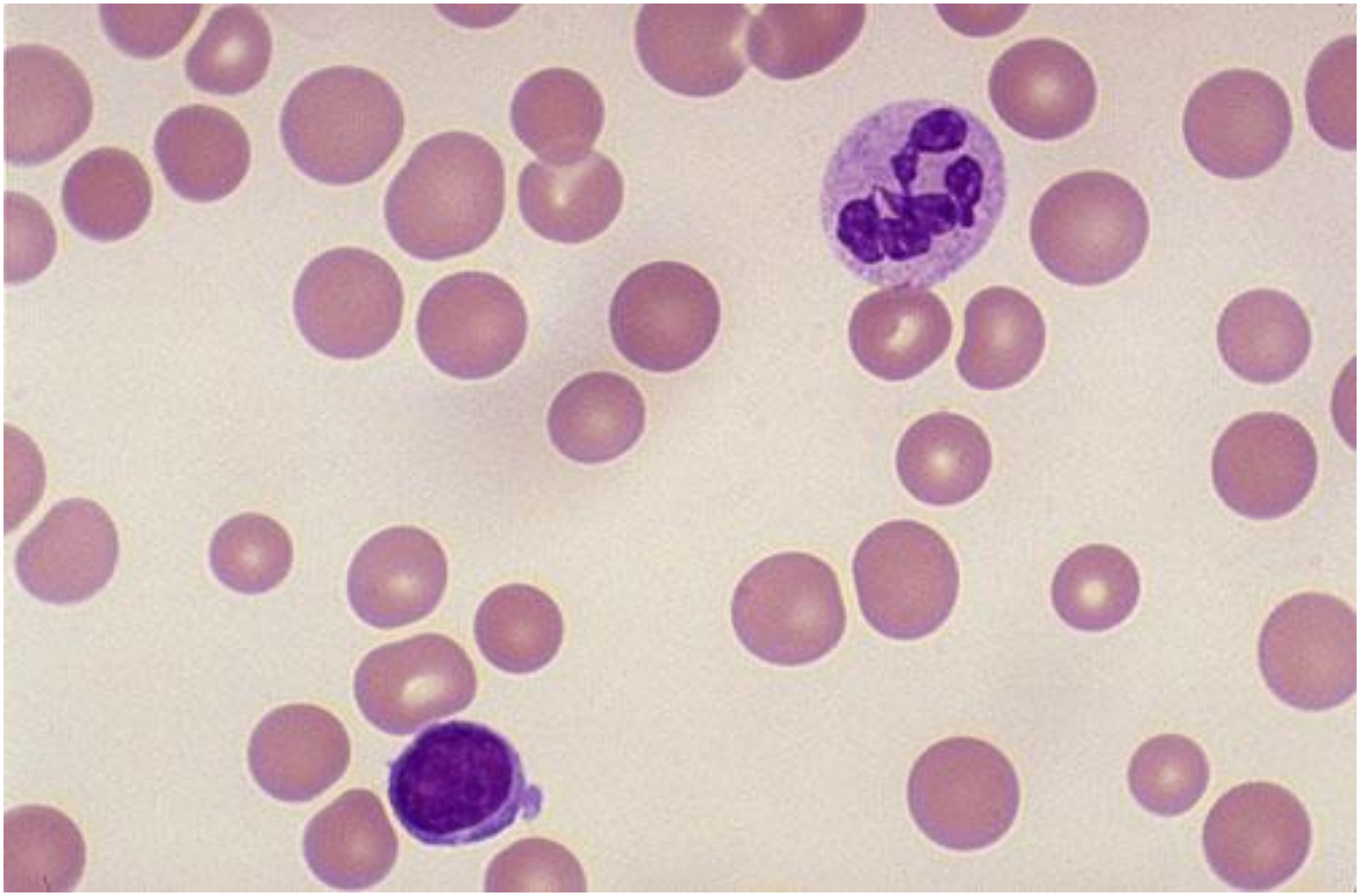
Normochromic normocytic red cells



Hypochromic microcytic anemia



Macrocytic anemia



Interpretation of hemogram

- A 19- year-old girl presented with loss of appetite and pallor.
- Hb=9.0 g/dl [11.1-14.5]
- Hct=18 [33-42]
- MCV=62 fl [76-96]
- MCH=20pg [28-30]
- RDW=30% [12]

Interpretation of hemogram

- A 12-year-old boy presented with anemia, jaundice and splenomegaly
- Hb=8.0 g/dl [13.5-16.3]
- Hct=24 [41.9-48.7]
- MCV=77fl [76-96]
- MCH=30 pg [28-30]

Iron deficiency anemia

Prevalence

- More than a quarter of the world's population is anemic, with about one-half of the burden from iron deficiency. The prevention and treatment of iron deficiency is a major public health goal, especially in women, children, and individuals in low-income countries.

- Challenges in the treatment of iron deficiency include finding and addressing the underlying cause and the selection of an iron replacement product that meets the needs of the patient.

Body Iron Distribution and Storage

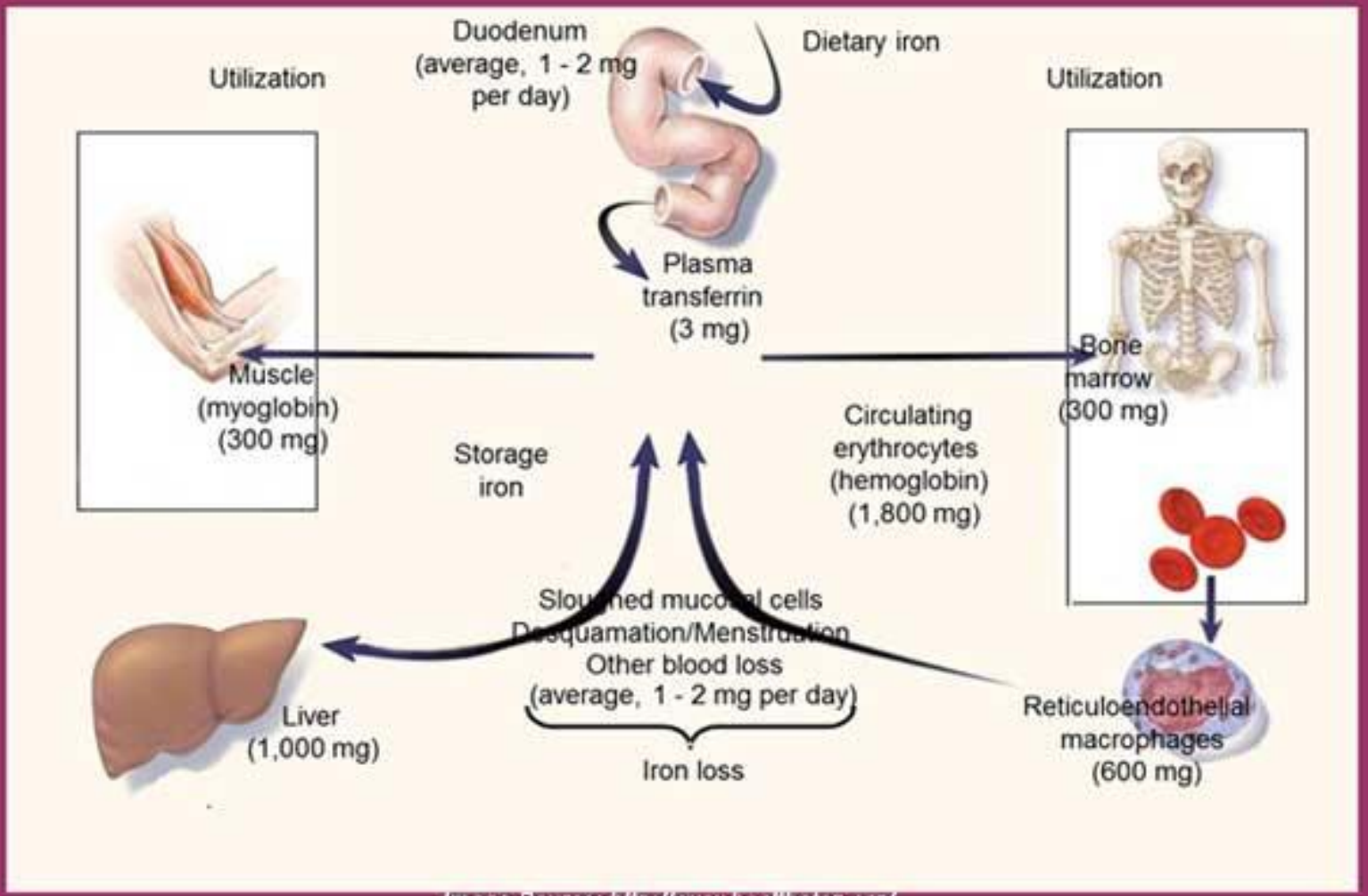
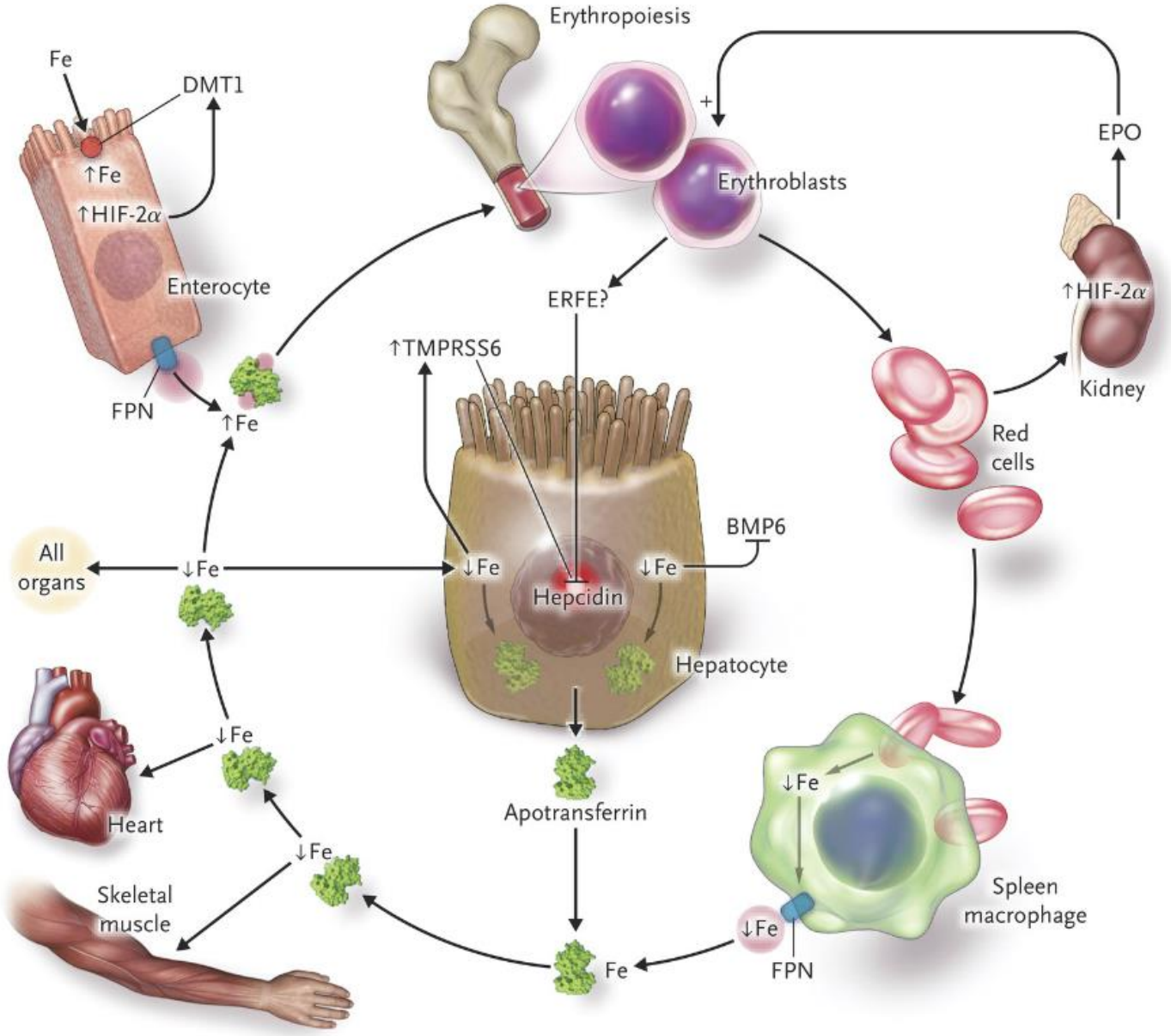


Image Source: http://www.healthatoz.org/



Carla Rothaus • May 8th, 2015

Signs & symptoms

Mood disorders

Strong cravings for sugary foods

Anemia or iron deficiency

Skin ailments

Recurring yeast infections

Bleeding gums

Headaches

Anxiety

Diagnosis

- CBC (Hb, ↓MCV,↓ MCH)
- Reticulocyte count↓
- Serum Iron↓
- Transferrin saturation↓
- Serum TIBC ↑
- Serum ferritin↓

Diagnosis of iron deficiency anemia

- Cause of deficiency
  - Nutritional
  - Low absorption
  - Increased blood loss
  - Increased requirement

Iron deficiency without anemia

- Some individuals with reduced or absent iron stores who have not yet developed anemia may have symptoms such as fatigue or reduced exercise tolerance.
- The approach to therapy is individualized according to etiology and severity of iron deficiency. We replace iron stores in most patients who have iron deficiency without anemia, with the rationale that this treatment is likely to improve symptoms, and failure to treat is likely eventually to result in anemia. These patients are often referred to the hematologist after iron studies reveal iron deficiency as part of screening laboratory tests performed to evaluate fatigue or unexplained microcytosis.

Treatment of IDA

- Regardless of the presence of symptoms, all patients with iron deficiency anemia and most patients with iron deficiency without anemia should be treated [1].
- The rationale is that there is risk for further organ damage/ischemia and progression of anemia unless the underlying cause of the deficiency is addressed and adequate iron stores are replenished. An exception is when iron depletion is used therapeutically (eg, porphyria cutanea tarda, polycythemia vera).

[1] Hem Am Educ Prog 2016

Principle of treatment

- When treatment is indicated, the usual approach is repletion of iron.
  - Diet
  - Oral or iron supplemets
- Blood transfusion should **not** be used a treatment for iron deficiency unless the individual has severe anemia or hemodynamic instability

Approximate Elemental Iron Content of Various Oral Iron Preparations

Drug	Elemental Iron
Ferric pyrophosphate	120 mg/g
Ferrous gluconate	120 mg/g
Ferrous sulfate	200 mg/g
Ferrous sulfate, dried	300 mg/g
Ferrous fumarate	330 mg/g
Ferrous carbonate, anhydrous	480 mg/g
Carbonyl iron	1000 mg/g

www.drug.com

Various IV Iron Preparations

Drug	**Elemental Iron**
Iron dextran	Total dose infusion
Ferrous gluconate	Multiple infusions
Iron sucrose	Multiple infusions
Ferumoxytol	2 doses
Ferric caroboxymaltose	2 doses
Iron Isomaltoside	Single infusion

Oral vs. IV Iron therapy

- There are a number of settings in which the use of IV iron may be preferable to oral iron [1,2]:
- Patients who cannot (or prefer not to) tolerate the gastrointestinal side effects of oral iron.
- Patients who prefer to replete iron stores in one or two visits rather than over the course of several months.
- Ongoing blood loss that exceeds the capacity of oral iron to meet needs (eg, heavy uterine bleeding, mucosal telangiectasias).
- Anatomic or physiologic condition that interferes with oral iron absorption.
- Coexisting inflammatory state that interferes with iron homeostasis.

1 ASH education program 2016
2 NEJM 2015;372: 1832

Advantages and disadvantages of oral versus IV iron

	Advantages	Disadvantages
Oral iron	▪ Effective for most patients ▪ Extremely low risk of serious adverse events ▪ Initial costs very low	▪ Gastrointestinal side effects are common ▪ Compliance may be low ▪ May be inadequate for severe or ongoing blood loss ▪ May require administration for several months ▪ Total costs may be higher
IV iron	▪ Effective for most patients ▪ More rapid correction of anemia and resolution of symptoms ▪ Ability to administer large doses (up to 1000 mg elemental iron) in a single infusion ▪ Compliance is assured ▪ No gastrointestinal side effects	▪ Requires monitored intravenous infusion ▪ Rare cases of allergic or infusion reactions ▪ Requires equipment and personnel to treat allergic or infusion reactions ▪ Initial costs may be higher

Refer to UpToDate content on the management of iron deficiency for further details. Advantages, disadvantages, costs, and burdens for any individual patient may depend on a number of factors.

IV: intravenous.

Severe/life-threatening anemia

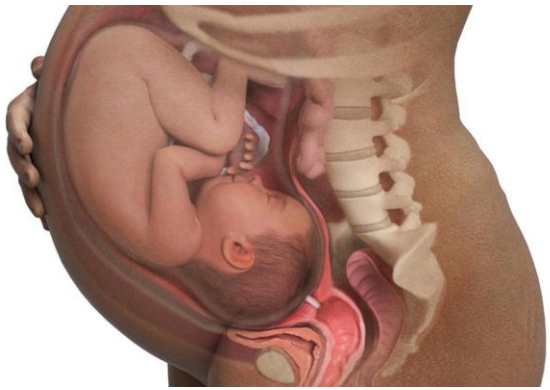
- Patients with severe, severely symptomatic (eg, with symptoms of myocardial ischemia), or life-threatening anemia should be treated with red blood cell (RBC) transfusion because correction of iron deficiency anemia using iron replacement requires time for iron administration and incorporation into RBCs.
- RBC transfusion can be life saving for the patient who is hemodynamically unstable due to active bleeding, and/or when evidence of end-organ ischemia secondary to severe anemia is present. The following may be expected for each unit of packed RBCs transfused to an adult, as long as there is not ongoing bleeding:
- Total volume – 300 mL
- Volume of RBCs – approximately 200 mL
- Iron – 200 mg (in the form of hemoglobin)
- Increase in hemoglobin – approximately 1 g/dL
- Increase in hematocrit – approximately 3 percentage points
- Once the patient is stabilized with transfusion, the need for additional iron supplementation can be determined and evaluation for the cause can be pursued.

Menstruating women

- Normal menstruation does not lead to iron deficiency. However, abnormal uterine bleeding/menorrhagia has been reported to cause iron deficiency anemia in one-fifth to two-thirds of affected women. Approaches to determining the site and cause of bleeding are presented separately.
- Other known bleeding site – Other known bleeding sites include gastrointestinal lesions
- Adults without an obvious source of blood loss – Adults without an obvious source of blood loss must be evaluated for occult gastrointestinal malignancy unless there is a clear reason not to do so. This is especially true for individuals >50 years of age, non-menstruating women, and those at increased risk of colorectal cancer based on family history or other risk factors.

Pregnancy

- Iron requirements increase during pregnancy, to accommodate
  - fetal and placental needs,
  - expansion of the maternal RBC mass,
  - and blood loss during delivery



Blood 2017;129:940

IDA in pregnancy

- A 2011 Cochrane review of randomized trials for the treatment of iron deficiency in pregnancy found that iron supplementation was effective in treating maternal anemia .
- Some studies showed better improvements in anemia with parenteral versus oral iron and others did not. Fetal outcomes were similar with oral versus IV iron repletion.
- From the standpoint of the developing fetus, iron repletion, as well as a more liberal use of IV iron in pregnancy, will likely minimize the chance that the neonate of an iron-deficient woman will also be iron deficient, especially in view of evidence that iron-deficient neonates have delayed growth and development and an increase in behavioral problems that persist up to 10 years after iron repletion.

Cochrane Database Syst Rev 2011

The adverse maternal and fetal effects

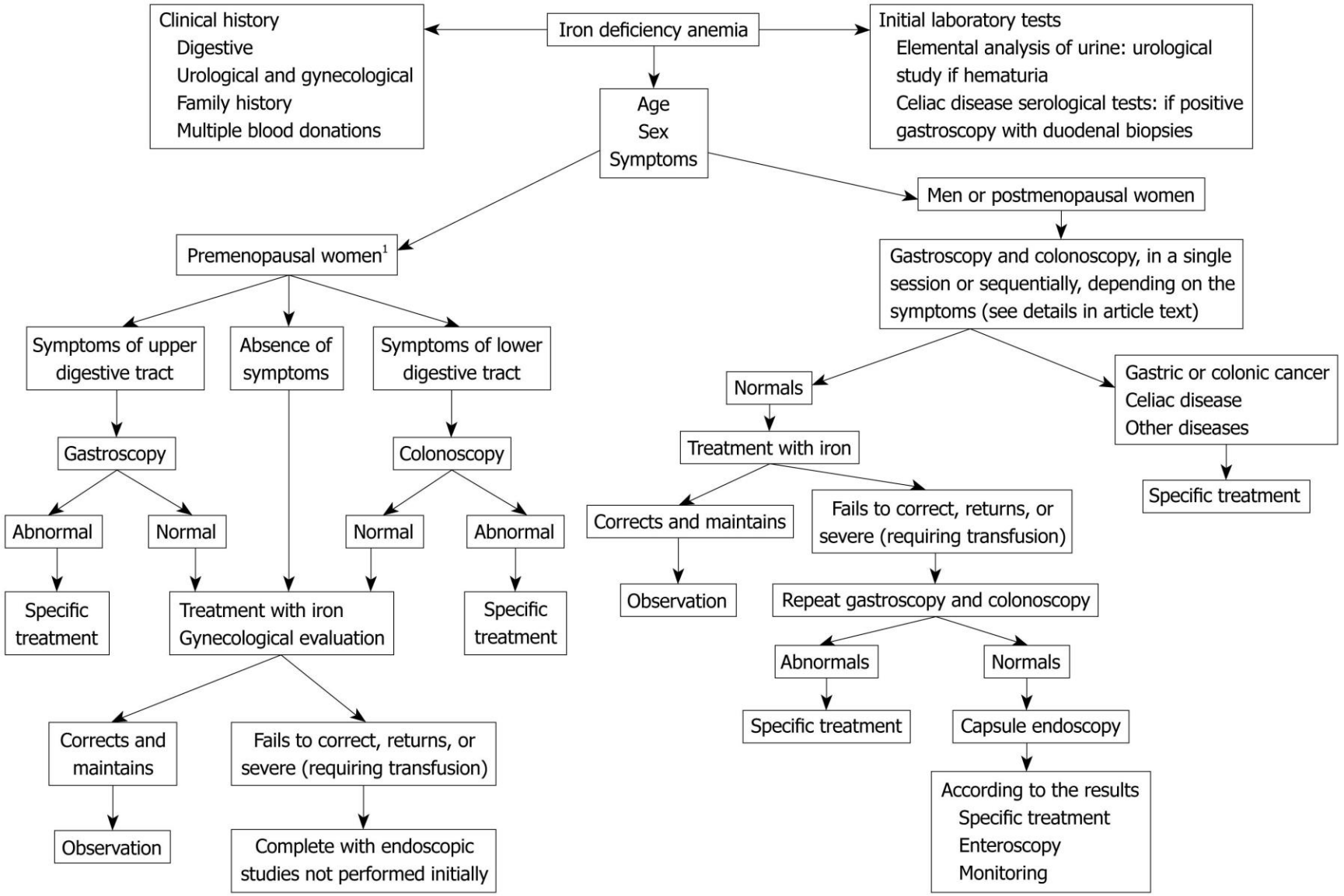
- In a retrospective review of 75,660 term singleton deliveries at a single institution, 7977 of which (11 %) were associated with maternal iron deficiency anemia at presentation for delivery
- Compared with controls, women with iron deficiency anemia were at increased
  - risk of transfusion (odds ratio [OR] 5.48; 95% CI 4.57-6.58),
  - preterm delivery (OR 1.54; 95% CI 1.36-1.76), and
  - cesarean delivery (OR 1.30; 95% CI 1.13-1.49).
  - Increased adverse fetal outcomes included 5-minute Apgar <7 (OR 2.21; 95% CI 1.84-2.64), intensive care admission (OR 1.28; 95% CI 1.04-1.57), macrosomia (OR 1.23; 95% CI 1.12-1.35),
  - and large for gestational age (OR 1.29; 95% CI 1.20-1.39).
- Anemic women were also more likely to be younger and multiparous.

Transfusion 2015;55:2799

IV iron in Pregnancy

- The safety and efficacy of IV iron in pregnancy has been illustrated by a number of small trials and case series that have found IV iron to be as good or better than oral iron without serious adverse events; however, most of these were too small to allow extensive safety evaluation.
- As noted above, we reserve IV iron for the second and third trimesters, as safety during the first trimester has not been established.

Am J Hematol 2011;86:860
Am H Hematol 2016;91:590



Conclusions

- A systematic approach is required to the evaluation of anemia
- Red cell indices and reticulocyte count help in classifying anemia and in diagnosis of the type of anemia.
- Underlying mechanism should be sought for correct diagnosis