Red Cell Disorders
Anemia

Ghadeer AlMuhaisen, M.D.
Consultant hematopathologist
Mutah University

Anemia

Definition:

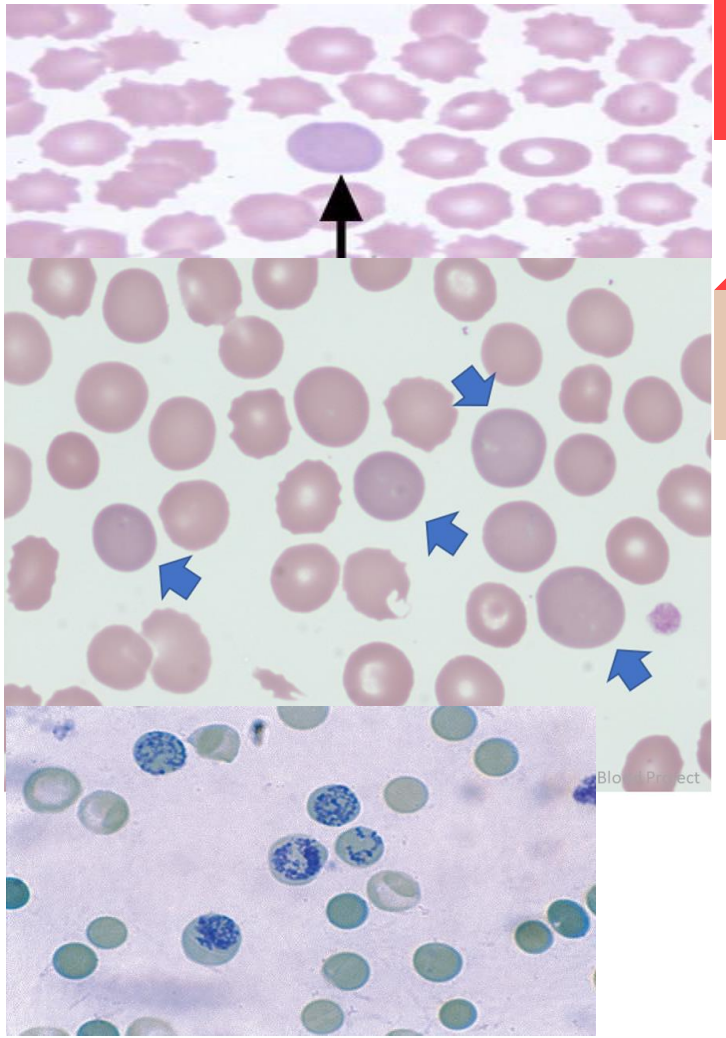
- Reduction in the oxygen-transporting capacity of blood, resulting from a decrease in the red cell mass to subnormal levels.
- Anemia can stem from bleeding, increased red cell destruction, or decreased red cell production. Which could be used for classification

Erythropoietin :

- A growth factor secreted from specialized cells in the kidney (peritubular fibroblasts).
- Decreased in tissue oxygen tension in anemia triggers increased production of erythropoietin → a compensatory hyperplasia of erythroid precursors in the bone marrow.
- In well-nourished persons who become anemic because of acute bleeding or increased red cell destruction (hemolysis), the compensatory response can increase the production of red cells 5X-8X

Reticulocytes

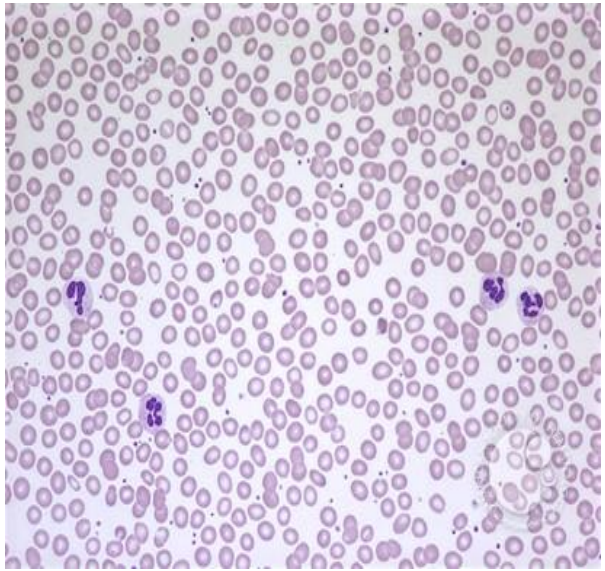
- The rise in marrow output due to erythropoietin → the appearance of increased numbers of newly formed red cells (reticulocytes) in the peripheral blood.
- In contrast, anemia caused by decreased red cell production is associated with subnormal reticulocyte counts



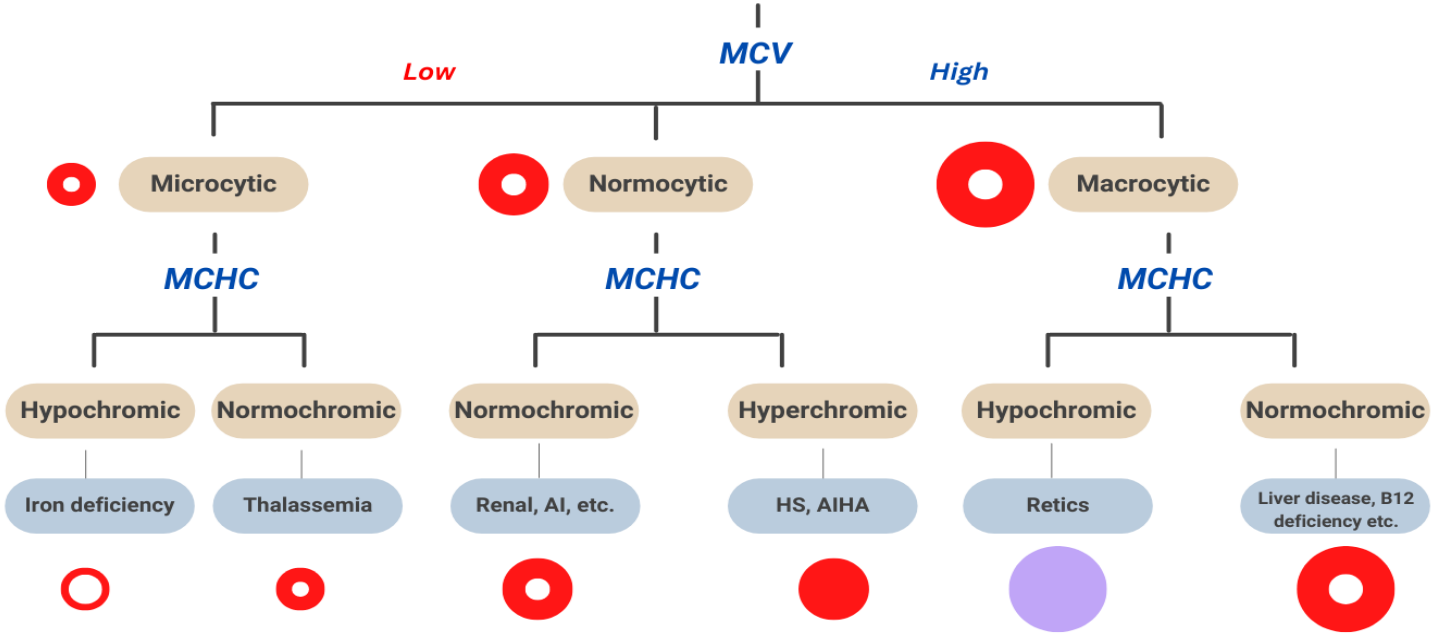
Blood component	Abbreviation used	Reference range	SI Reference range
White blood cells	WBC	4500-11,000/mm^3	4.5-11.0 x 10^9/L
Red blood cells*	RBC	Male: 4.3-5.9 million/mm^3 Female: 3.5-5.5 million/mm^3	Male: 4.3-5.9 x 10^{12}/L Female: 3.5-5.5 x 10^{12}/L
Hemoglobin*	HGB	Male: 13.5-17.5 g/dL Female: 12.0-16.0 g/dL	Male: 2.09-2.71 mmol/L Female: 1.86-2.48 mmol/L
Hematocrit*	HT	Male: 41%-53% Female: 36%-46%	Male: 0.41-0.53 Female: 0.36-0.46
Mean corpuscular volume	MCV	80-100 μm^3	80-100 fl
Mean corpuscular hemoglobin	MCH	25.4-34.6 pg/cell	0.39-0.54 fmol/cell
Mean corpuscular hemoglobin concentration	MCHC	31%-36% Hb/cell	4.81-5.58 mmol Hb/L
Platelets	Platelets	150,000-400,000/mm^3	150-400 x 10^9/L

Anemia also can be classified based on red cell morphology. Features that provide etiologic clues include the size, color, and shape of the red cells. Judged subjectively by visual inspection of peripheral smears and expressed quantitatively using the following indices:

Mean cell volume (MCV):	the average volume per red cell, expressed in femtoliters (cubic micrometer)
Mean cell hemoglobin (MCH)	the average mass of hemoglobin per red cell, expressed in picograms
Mean cell hemoglobin concentration (MCHC)	the average concentration of hemoglobin in a given volume of packed red cells, expressed in grams per deciliter
Red cell distribution width (RDW)	the coefficient of variation of red cell volume



Morphologic Classification of Anemia



https://www.thebloodproject.com/

Microcytic anemia

- Small, often hypochromic, red blood cells in a peripheral blood smear and is usually characterized by a low MCV (< 80 fl).
- Iron deficiency is the most common cause of microcytic anemia.
- Other causes include anemia of chronic disease, sideroblastic anemia, and thalassemia.

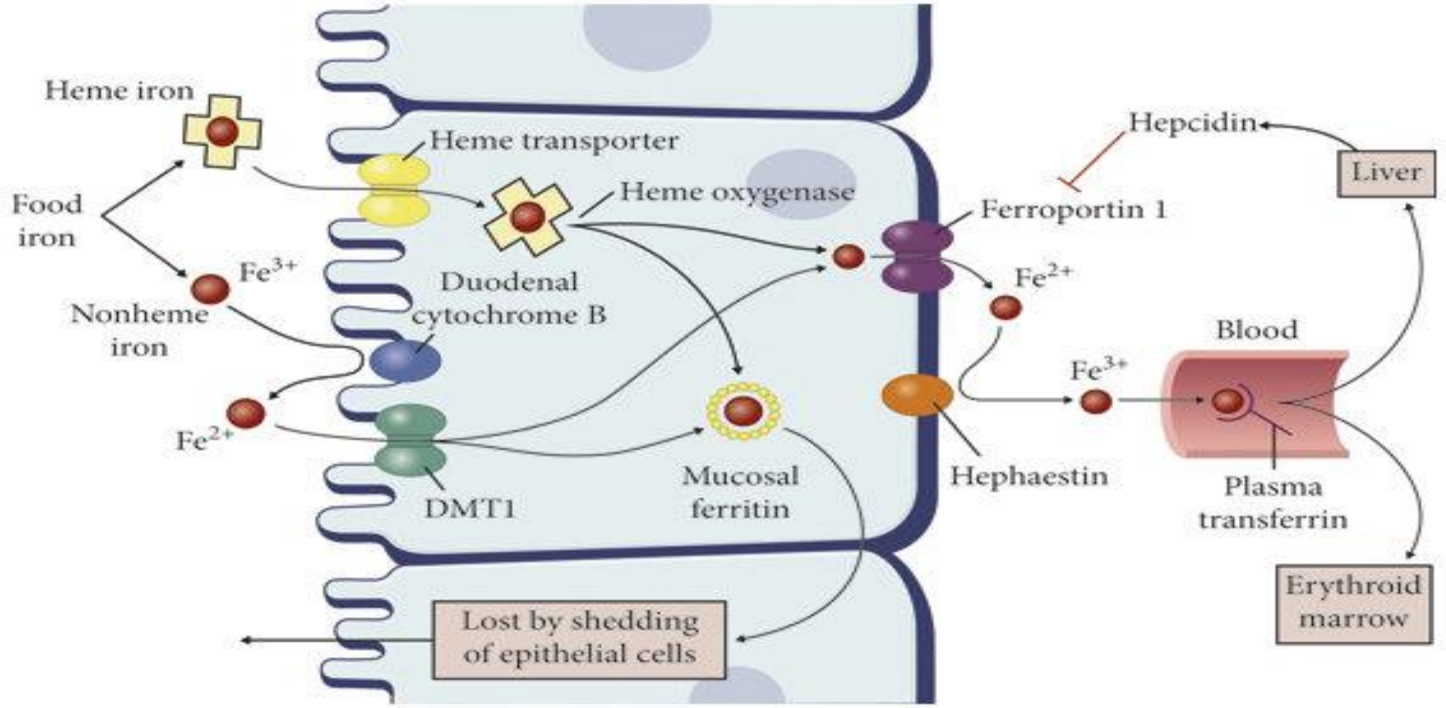
Iron Deficiency Anemia (IDA)

- The most common nutritional deficiency in the world
- 80% of functional body iron is present in hemoglobin, and 20% in the iron storage pool (hemosiderin and **ferritin-bound iron** in the cells in the liver, spleen, bone marrow, and skeletal muscle)
- So serum ferritin level is good measure of iron stores.
- Iron is transported in plasma bound to the protein transferrin (Normally 33% saturated)
- Regulation of iron absorption occurs within the duodenum: through

1. DMT1 (apical side)
2. ferroportin (basolateral).

- Then it binds to transferrin in the plasma to be transported to BM and liver.

Hepcidin, a small peptide that is synthesized and secreted from the liver in an iron-dependent fashion.



DOI:10.1155/2020/7373498

Pathogenesis of Iron deficiency

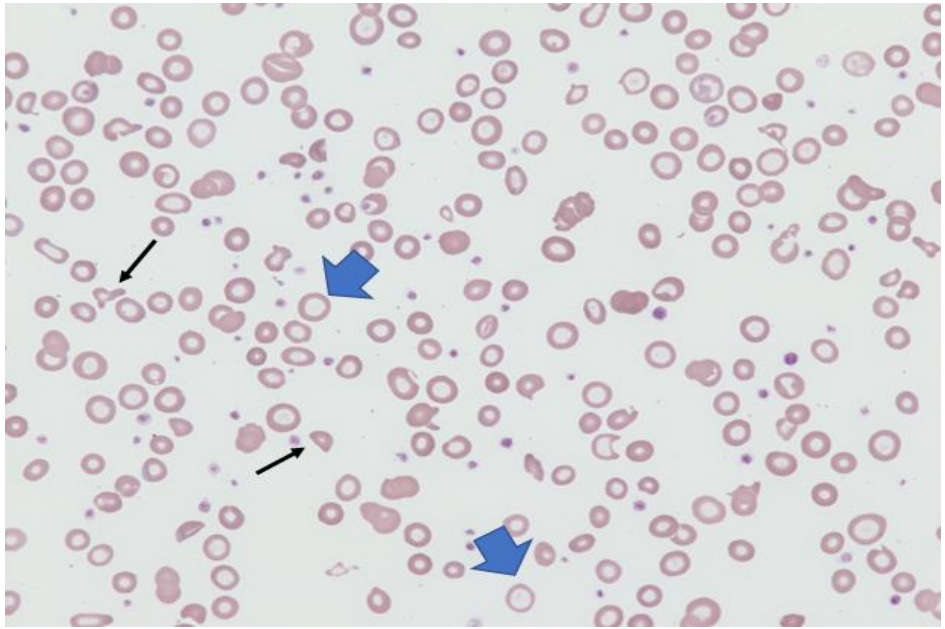
- Chronic blood loss: GI bleeding (e.g., peptic ulcers, colon cancer, hemorrhoids) and the female genital tract (e.g., menorrhagia, endometrial cancer).
- Low intake and poor bioavailability (predominantly vegetarian diets) ..most common cause in developing world
- Increased demands not met by normal dietary intake: pregnancy and infancy.
- Malabsorption: e.g.; celiac disease or after gastrectomy.

Clinical manifestation

- Usually develops insidiously (starts mild or asymptomatic)
- Or with non-specific manifestations in severe cases: weakness, listlessness, and pallor
- Long-standing anemia, abnormalities of the fingernails (thinning, flattening, and “spooning,”) and pica.

Laboratory manifestation

- ↓↓ Iron storage (Serum ferritin) → ↓↓ serum iron → ↑↑ transferrin (TIBC) → microcytic anemia (↓MCV, ↓MCHC, ↑RDW)
- Peripheral blood smear: red cells are microcytic and hypochromic



Anemia of chronic inflammation

- The most common form of anemia in hospitalized patients.
- Arises from the suppression of erythropoiesis by systemic inflammation

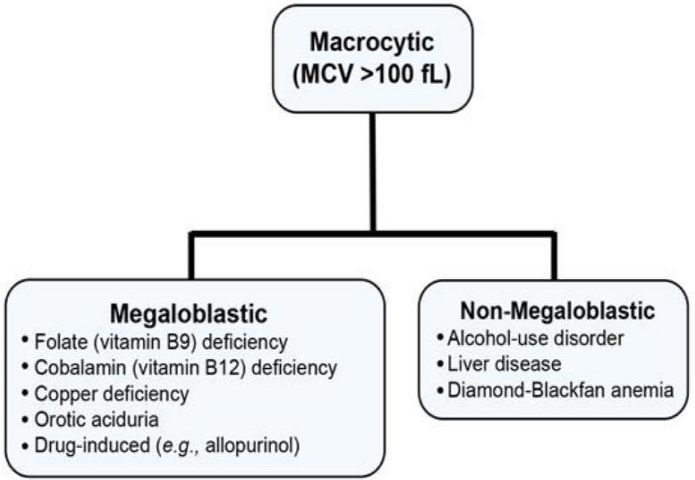
1. Chronic microbial infection (osteomyelitis, endocarditis).
2. Chronic immune disorders (RA).
3. Neoplasms (Carcinoma or lymphoma)

- Anemia of chronic inflammation stems from:

1- high levels of plasma hepcidin, which blocks the transfer of iron to erythroid precursors by downregulating ferroportin in macrophages and duodenum.
The elevated hepcidin levels are caused by proinflammatory cytokines such as IL-6 (increase hepatic hepcidin synthesis)
2-Chronic inflammation blunts erythropoietin synthesis by the kidney

Macrocytic anemia

- Large cells with MCV>100 fL
- Most commonly megaloblastic anemia (delayed nuclear maturation).
- The principal causes of megaloblastic anemia are folate & vit. B12 deficiencies.
- Both are required for DNA synthesis, & effects of their deficiency on hematopoiesis are identical.



Megaloblastic anemia

- Megaloblastic anemia stems from metabolic defects that lead to inadequate biosynthesis of thymidine.
- Thymidine deficiency causes abnormalities in rapidly dividing cells throughout the body, but the hematopoietic marrow is most severely affected the synthesis of RNA and cytoplasmic elements proceeds at a normal rate and thus outpaces that of the nucleus, the hematopoietic precursors show nuclear-cytoplasmic asynchrony
- Many red cell progenitors are so defective in DNA synthesis that they undergo apoptosis in the marrow (ineffective hematopoiesis).
- Granulocyte and platelet precursors also are affected (not as severely) most patients present with pancytopenia (anemia, thrombocytopenia, and granulocytopenia)

Folate (Folic Acid) Deficiency Anemia

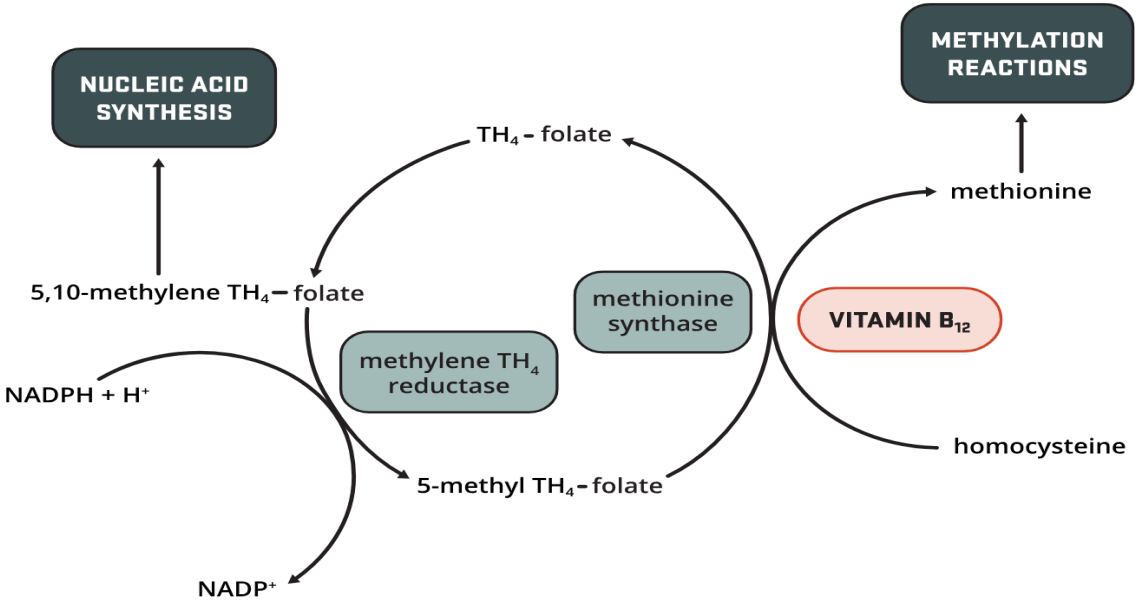
- Usually, the result of inadequate dietary intake, sometimes complicated by increased metabolic demands.
- The risk is highest:

1. a poor diet (poverty & the elderly).
2. increased metabolic needs (pregnant women and patients with chronic hemolytic anemias; e.g; sickle cell disease).

- Deficiency may stem from problems with absorption or metabolism.

- Absorption is inhibited by acidic foods and substances found in beans & other legumes.
- Drugs: interferes with -absorption (phenytoin) or -inhibit folate metabolism (methotrexate).
- Malabsorptive disorders (celiac disease and tropical sprue) may also impair folate uptake. (jejunum)

Tetrahydrofolate acts as an acceptor and donor of one-carbon units in several reactions that are required for the synthesis of synthesized DNA molecules leading to megaloblastic anemia.



The Linus Pauling Institute's Micronutrient Information Center

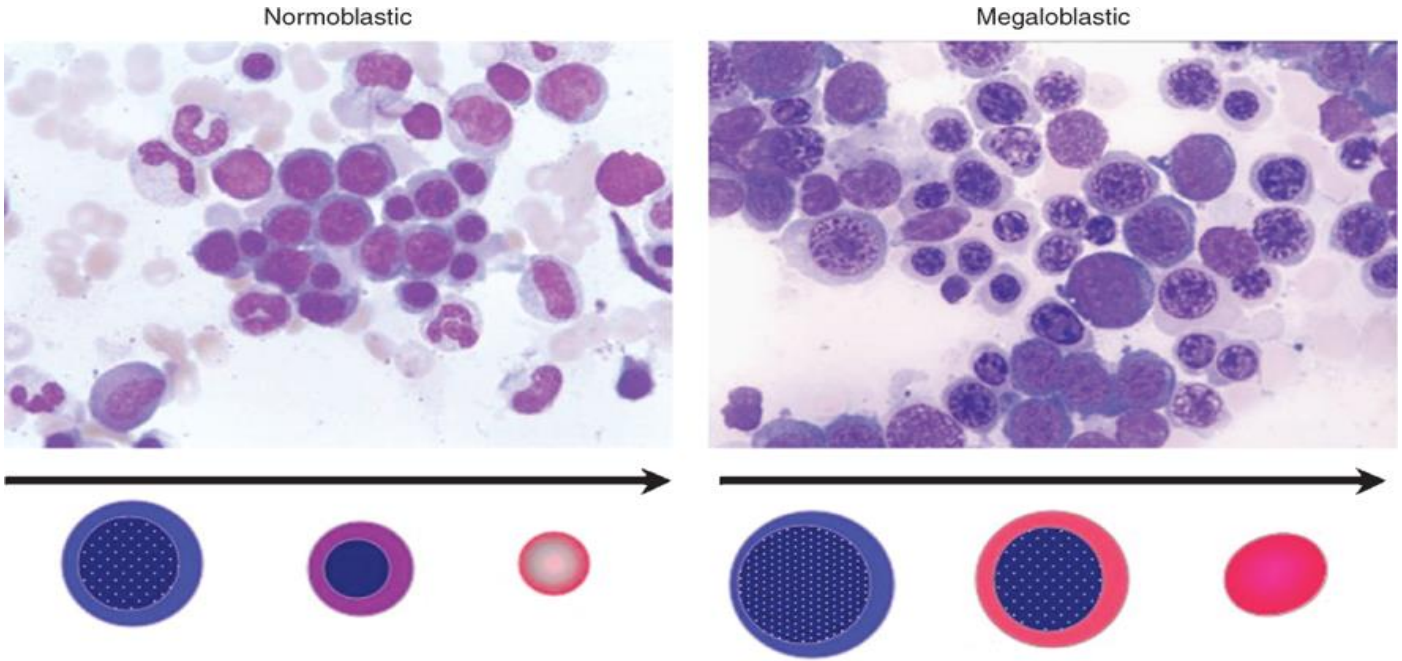
Vitamin B12 (Cobalamin) Deficiency Anemia

- Virtually never caused by inadequate intake except in vegetarians who avoid milk & eggs. Typically arise from abnormalities that interfere with absorption.
- It is stored in the liver, which normally contains reserves sufficient for 5-20 years→ clinical presentations typically follow years of unrecognized malabsorption.
- The most frequent cause vit.B12 deficiency is pernicious anemia, an autoimmune attack on the gastric mucosa that suppresses the production of intrinsic factor (e.g; chronic atrophic gastritis) .
- Intrinsic factors are produced by parietal cell of gastric fundic mucosa & facilitate B12 absorption in distal ileum.
- Other causes of B12 malabsorption includes: gastrectomy, ileal resection, distal ileum disorders (Crohn disease, tropical sprue, & Whipple disease), or pancreatic insufficiency.

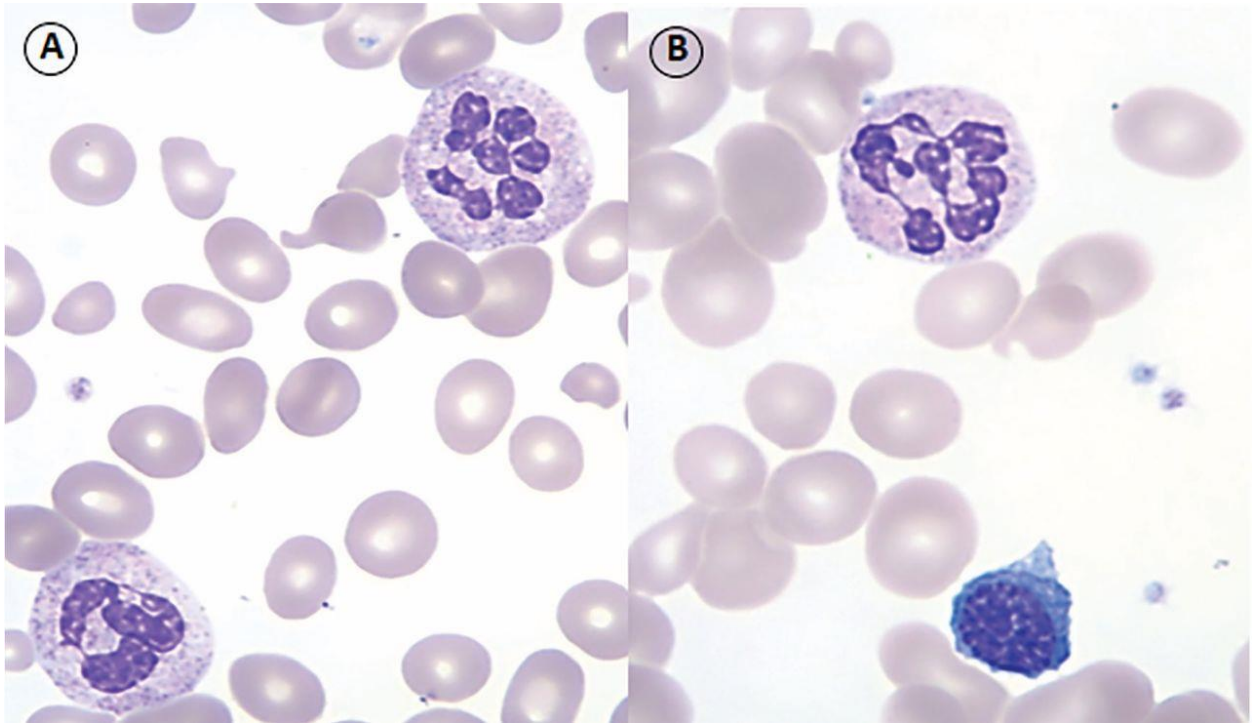
Morphology of megaloblastic anemia

- Bone marrow (BM) is markedly hypercellular with numerous megaloblastic erythroid & granulocytic progenitors
- Megaloblasts: larger than normal progenitors with delicate, finely reticulated nuclear chromatin (indicative of nuclear immaturity).
- As they differentiate and acquire hemoglobin, the nucleus retains its finely distributed chromatin and fails to undergo the chromatin clumping → a classic example of nuclear-cytoplasmic asynchrony.
- In the peripheral blood (PB): the earliest change is the appearance of hypersegmented neutrophils (>=5) → which appear before the onset of anemia.
- The red cells typically include large, eggshaped macroovalocytes; the MCV often is greater than 110 fL (normal, 82–96 fL)

Morphology of megaloblastic anemia - BM



Morphology of megaloblastic anemia - PB



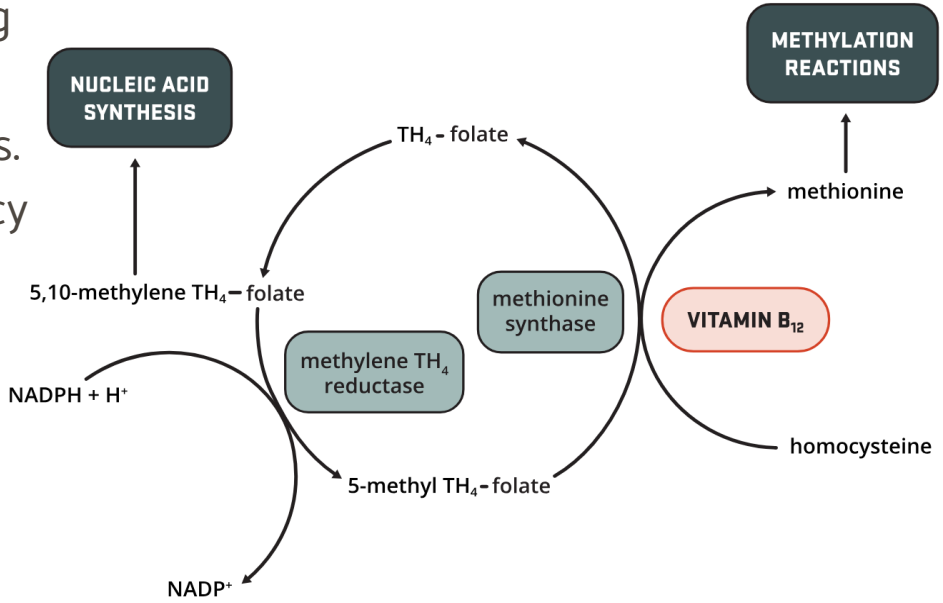
https://doi.org/10.3949/ccjm.87a.19072

Clinical manifestation of megaloblastic anemia

- The manifestations are nonspecific. As with all anemias include pallor, easy fatigability, and, in severe cases, dyspnea and even congestive heart failure.
- Megaloblastic changes in the oropharyngeal epithelium may produce a beefy red tongue.
- In B12 def. The main neurologic lesions are demyelination of the posterior & lateral columns of the spinal cord: clinically begins with symmetric numbness, tingling, & burning in the feet or hands, followed by unsteadiness of gait and loss of position sense, particularly in the toes.
- Although the anemia responds dramatically to parenteral vitamin B12, the neurologic manifestations often fail to resolve.

The metabolic defects responsible for the anemia of vitamin B12 deficiency are intertwined with folate metabolism

- Vitamin B12 is required for recycling tetrahydrofolate, which is the form of folate that is needed for DNA synthesis.
- the anemia of vitamin B12 deficiency is reversed with the administration of folate.
- By contrast, folate administration does not prevent and may in fact worsen certain neurologic symptoms that are specific to vitamin B12 deficiency



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Aplastic Anemia

- The multipotent myeloid stem cells are suppressed, leading to bone marrow failure and pancytopenia.
- Must be distinguished from pure red cell aplasia → only erythroid progenitors are affected & anemia is the only manifestation.
- **The pathogenesis is not fully understood. There are two major etiologies:**

1. **An extrinsic, immune-mediated suppression of marrow progenitors.**

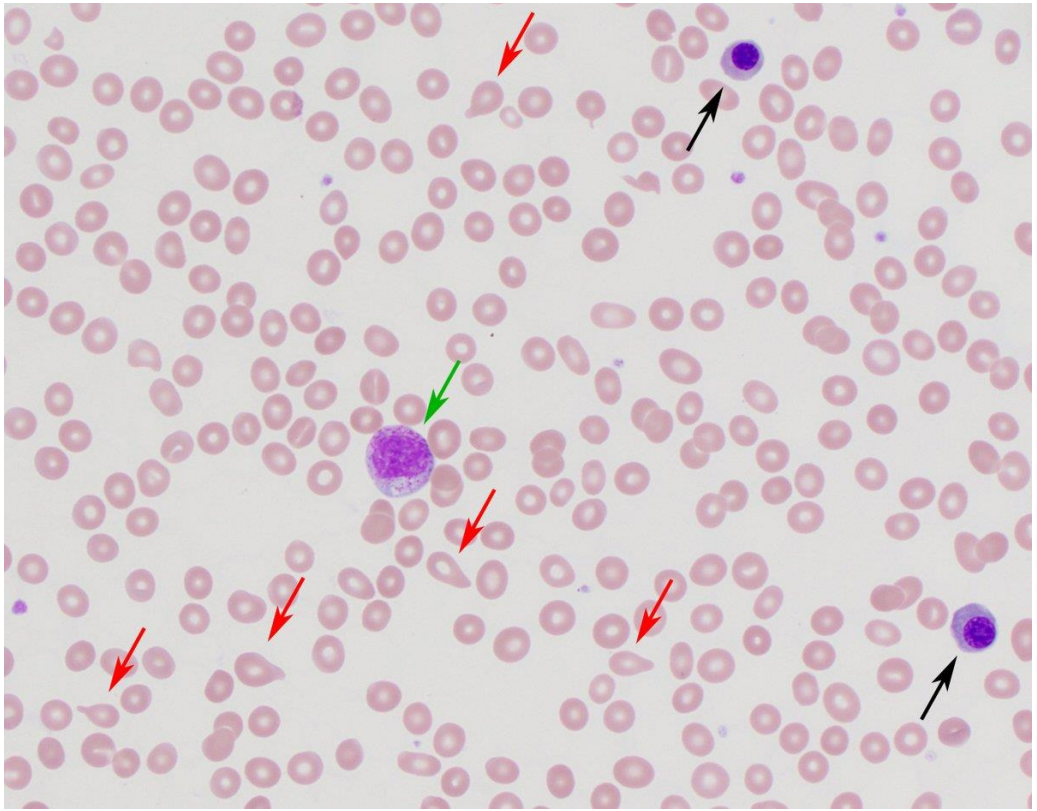
- Stem cells are antigenically altered by exposure to drugs, infectious agents, or other environmental insults → a cellular immune response → activated TH1 cells produce cytokines (IFN-γ and TNF) that suppress & kill hematopoietic progenitors.
- This scenario is supported by experience with immunosuppressive therapy directed against T cells, which restores hematopoiesis in 60-70% of patients

2. **An intrinsic abnormality of stem cells.**

Myelophthisic Anemia

- **Myelophthisic anemia is caused by extensive infiltration of the marrow by tumors or other lesions.**
- Most commonly associated with metastatic breast, lung, or prostate cancer.
- Advanced tuberculosis, lipid storage disorders, and osteosclerosis may produce a similar clinical picture.
- The principal manifestations include anemia and thrombocytopenia; in general, the white cell series is less affected.
- PB: Characteristically misshapen red cells, some resembling teardrops, are seen. Immature granulocytic and erythrocytic precursors also may be present (**leukoerythroblastosis**) along with mild leukocytosis.
- Treatment is directed at the underlying condition

Leukoerythroblastosis



Thank you