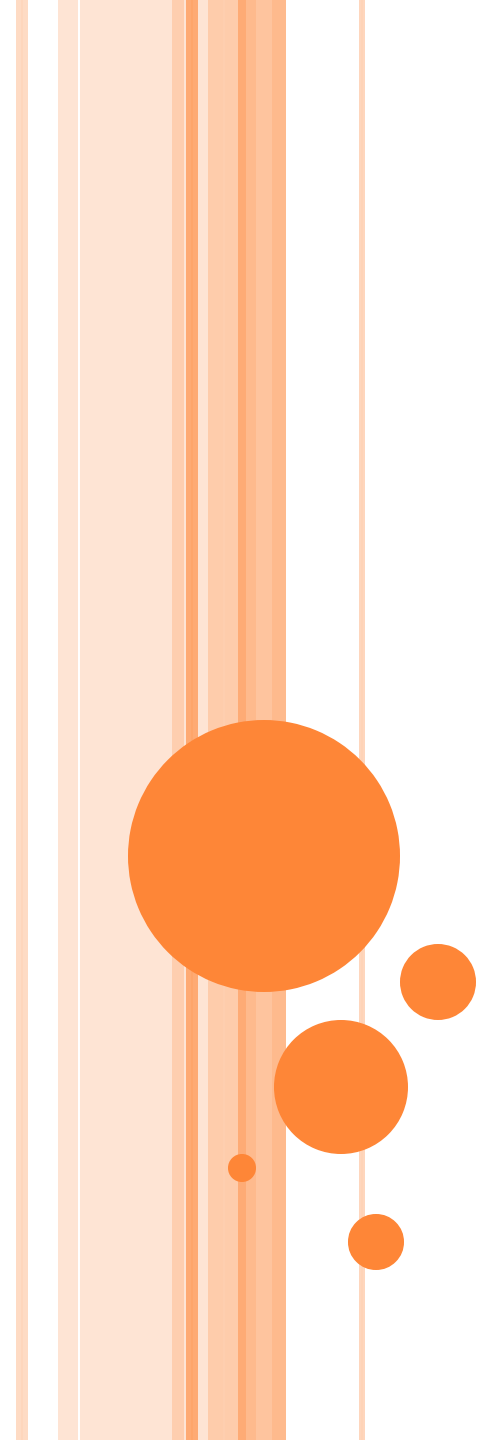




Pathology lab- Anemia

Red cell line: erythrocytes

Location

During embryogenesis/fetal development

Week 3–8: yolk sac

Week 6–birth: liver

Week 10–28: spleen

After week 18: red bone marrow

After birth: red bone marrow

In children: diaphyses of long bones (e.g., femur, tibia)

In adults: mainly plain bones (pelvis, cranium,
vertebrae, sternum) and metaphyses of long bones



Duration: approx. 1 week (production and maturation)

Regulation: primarily EPO, along with other hematopoietic growth factors, including GM-CSF, stem cell factor, and IL-3

Stages

In bone marrow

Hematopoietic stem cell (erythroid progenitor cell)

Proerythroblast: large cells with basophilic cytoplasm and a large nucleus

Erythroblast: smaller nucleus than proerythroblasts; no nucleoli

Normoblast: increasingly acidophilic cytoplasm with a compact nucleus

Reticulocyte: acidophilic cytoplasm with granules composed of cytoplasmic ribosomal RNA (enabling reticulocytes to be stained with methylene blue)



In blood

Reticulocytes are released into the blood.

The peripheral reticulocyte count reflects erythropoietic activity.

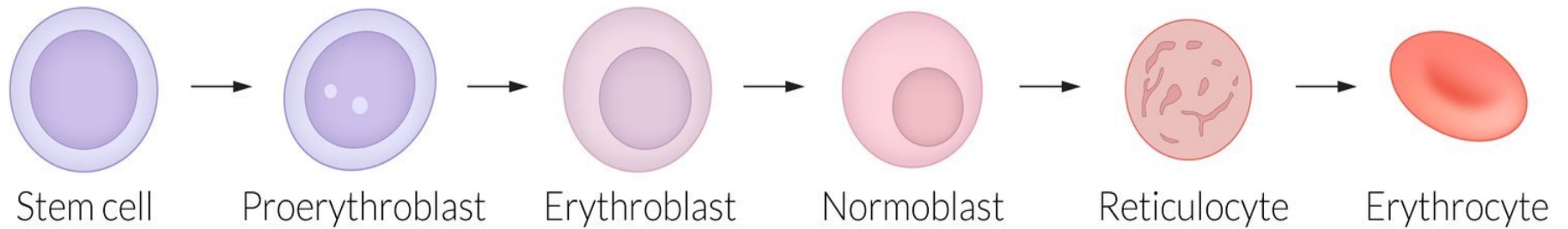
Increased reticulocytes indicate increased erythropoiesis (e.g., due to hemolysis).

Decreased reticulocytes indicate decreased erythropoiesis (e.g., due to aplastic anemia).

After 1–2 days, reticulocytes mature into erythrocytes.



Erythropoiesis



Erythrocyte morphology

Normal morphology

No nucleus, cell organelles, or granules

Biconcave shape

Maintained by spectrin, a cytoskeletal protein

Leads to a large surface area to volume ratio, enabling rapid gas exchange

Provides great flexibility, allowing for easy movement through narrow vessels and capillaries

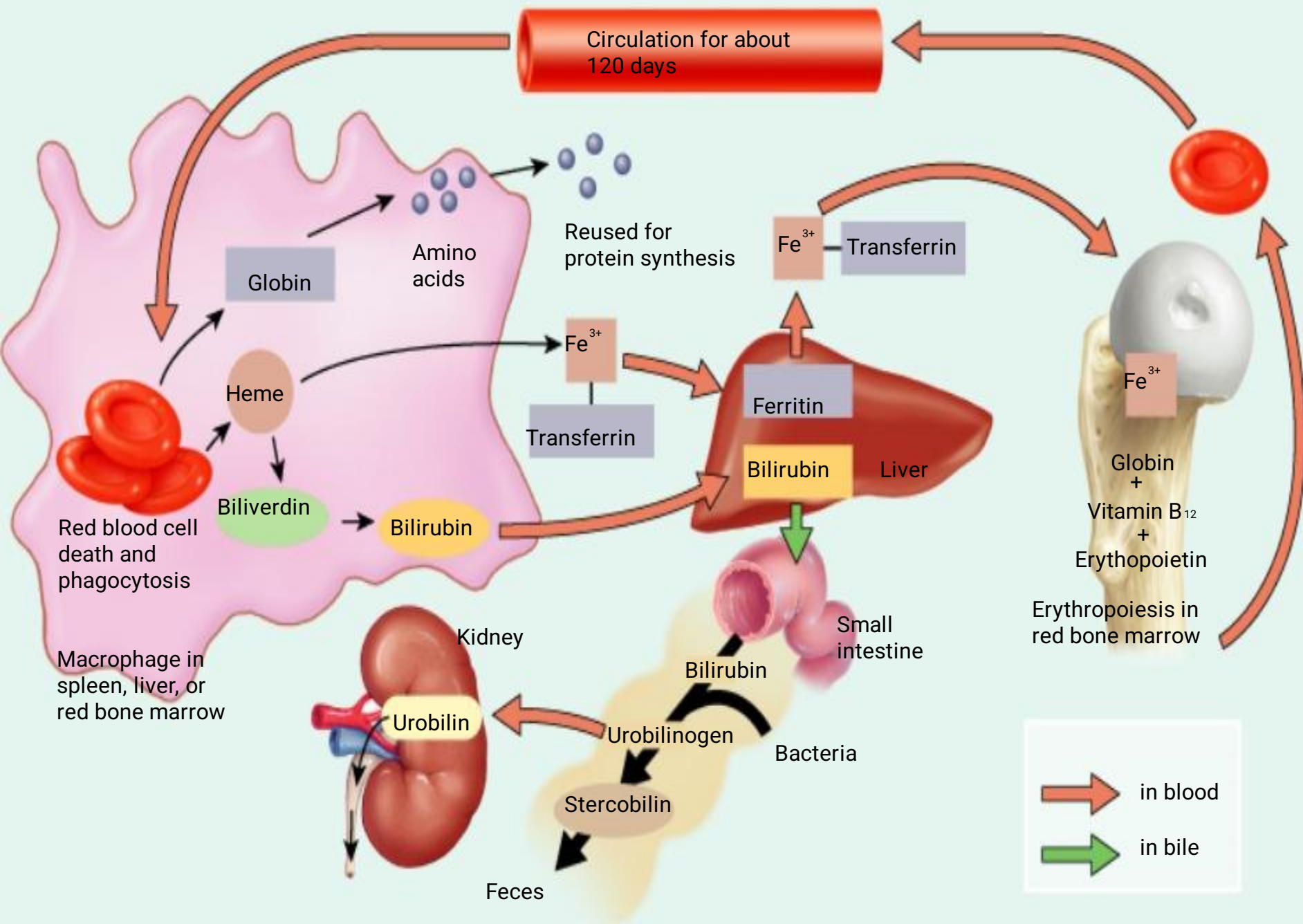
Contain hemoglobin, which leads to acidophilic cytoplasm



Dysmorphic RBCs

- ✓ Anisocytosis: the presence of RBCs of varying sizes
- ✓ Poikilocytosis: the presence of RBCs of abnormal shapes





Haemoglobin synthesis

Each normal adult Hb molecule (HbA) consists of two α and two β globin polypeptide chains

Haemoglobin synthesis occurs in the mitochondria of the developing red cell.

The major rate-limiting step is the conversion of glycine and succinic acid to δ -aminolaevulinic acid (ALA) by ALA synthase.

Vitamin B6 is a coenzyme for this reaction, which is inhibited by haem and stimulated by erythropoietin. Two molecules of δ -ALA condense to form a pyrrole ring (porphobilinogen).

These rings are then grouped in fours to produce protoporphyrins and with the addition of iron haem is formed.

Haem is then inserted into the globin chains to form a haemoglobin molecule.



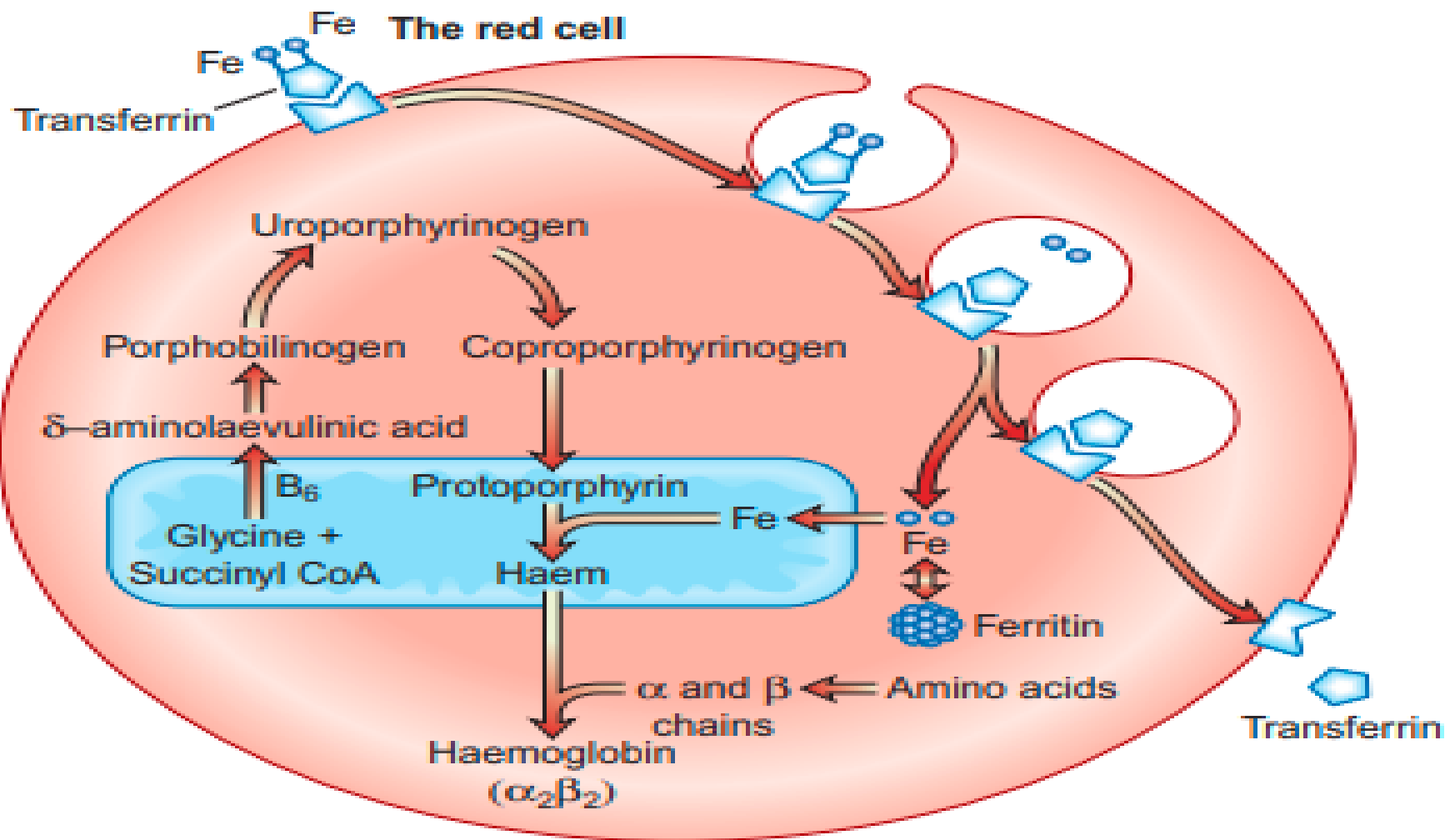


Figure 8.2 Haemoglobin synthesis. Transferrin attaches to a surface receptor on developing red cells. Iron is released and transported to the mitochondria, where it combines with protoporphyrin to form haem. Protoporphyrin itself is manufactured from glycine and succinyl-CoA. Haem combines with α and β chains (formed on ribosomes) to make haemoglobin.

Definition

Definition: a decrease in the absolute number of circulating RBCs; exact cutoffs vary from source to source.

WHO criteria for anemia

Men: Hb < 13 g/dL

Women: Hb < 12 g/dL

Pregnant women: Hb < 11 g/dL

Children

6–59 months: < 11 g/dL

5–11 years: < 11.5 g/dL

12–14 years: < 12.0 g/dL



Classification

Anemia may be classified into several subtypes based on the following methods:

RBC size and morphology

- ✓ The most widely used classification



Classification of anemia by morphology

	Microcytic anemia	Normocytic anemia	Macrocytic anemia
<u>MCV</u> (fL)	< 80	80–100	> 100
Mechanism	Insufficient <u>hemoglobin</u> production	Decreased blood volume and/or decreased <u>erythropoiesis</u>	- Insufficient nucleus maturation relative to <u>cytoplasm</u> expansion due to - Defective <u>DNA synthesis</u> - Defective <u>DNA repair</u>
<u>Etiology of anemia</u>	- Defective <u>heme synthesis</u>: e.g., <u>IDA</u>, <u>lead poisoning</u> - Defective <u>globin</u> chain (↓ <u>Globin</u> → ↓ <u>hemoglobin</u> → ↓ <u>MCV</u>): e.g., thalassemia	<u>Hemolytic anemia</u> - Intrinsic defects: e.g., hemoglobinopathies, enzyme deficiencies - Extrinsic defects: e.g., <u>AIHA</u>, <u>MAHA</u>, <u>Nonhemolytic</u> anemia: e.g., blood loss, <u>aplastic anemia</u>, <u>anemia of chronic disease</u>	- Megaloblastic anemia: impaired <u>DNA synthesis</u> and/or repair with <u>hypersegmented neutrophils</u> (e.g., <u>Vitamin B12</u> or <u>folate deficiency</u>) - Nonmegaloblastic anemia: normal <u>DNA synthesis</u> without <u>hypersegmented neutrophils</u> (e.g., <u>liver</u> disease)

Severity

✓ Mild anemia

Hb level: below normal range based on age and sex, but > 10–11 g/dL

Presentation: usually asymptomatic; clinical features of anemia may be present

✓ Moderate anemia

Hb level: ~ 7–10.9 g/dL

Presentation: clinical features of anemia may or may not be present.

✓ Severe anemia

Hb level: ~ 7–8 g/dL

Presentation: clinical features of anemia typically present; hemodynamic compromise may be present.



Other classifications

Time course: acute vs. chronic

Inheritance: inherited vs. acquired

Etiology: primary vs. secondary

RBC proliferation: hypo proliferative (decreased RBC production) vs. hyperproliferative (increased RBC destruction or blood loss)



Hematological parameters

Complete blood count (CBC)

A laboratory test that measures:

Red blood cell (RBC) count

Hemoglobin (Hb)

Hematocrit (Hct)

Mean corpuscular volume (MCV)

Mean corpuscular hemoglobin (MCH)

Mean corpuscular hemoglobin concentration (MCHC)

White blood cell (WBC) count

Platelet count

In a CBC with differential, the percentage of WBC subtypes (e.g., neutrophils, lymphocytes, etc.) is also included.



RBC parameters

RBC indices

A set of calculated RBC parameters that comprises MCV, MCH, MCHC, and RBC distribution width

Used to determine the cause of anemia



Overview of RBC parameters

Parameter	Reference range	Description	Common causes of elevation	Common causes of reduction
RBC count	• : 4.3–5.9 million/mm³ (4.3–5.9 x 10¹²/L) • : 3.5–5.5 million/mm³ (3.5–5.5 x 10¹²/L)	• Absolute number of <u>RBCs</u> contained in a certain volume of blood		• <u>Anemia</u>:
Hemoglobin (<u>Hb</u>)	• : 13.5–17.5 g/dL (2.09–2.71 mmol/L) • : 12–16 g/dL (1.86–2.48 mmol/L)	• Oxygen-transporting protein found in <u>RBCs</u> • Contains <u>heme</u>	• <u>Polycythemia vera</u> • <u>Relative polycythemia</u> (e.g., due to <u>severe dehydration</u>) • Increased <u>erythropoietin</u> (EPO) synthesis, e.g., due to: • Chronic <u>hypoxia</u> (e.g., in <u>COPD</u> or <u>CHF</u>) • Malignancies (<u>paraneoplastic</u> effect) • EPO doping	• <u>Anemia</u>: • <u>Porphyria</u> • <u>Methemoglobinemia</u> • <u>Iron deficiency</u> • <u>Lead poisoning</u>

Hematocrit (<u>Hct</u>)	: 41%–53% (0.41–0.53) : 36%–46% (0.36–0.46)	<u>Ratio</u> of <u>RBC</u> volume to total blood volume	- Same as for elevated <u>Hb</u> and <u>RBC count</u> <u>Dehydration</u>	<u>Anemia</u>: See “<u>Classification of anemia</u>.”
Mean corpuscular volume (<u>MCV</u>)	80–100 μm^3 (80–100 fL)	Average volume of an <u>RBC</u>	<u>Megaloblastic anemia</u>, e.g., caused by: <u>Vitamin B₁₂ deficiency</u> <u>Folate deficiency</u>	<u>Microcytic anemia</u>, e.g., due to: <u>Iron deficiency</u> <u>Thalassemia</u>
Mean corpuscular hemoglobin (<u>MCH</u>)	25.4–34.6 pg/cell (0.39–0.54 fmol/cell)	Average mass of <u>hemoglobin</u> in each <u>RBC</u>	<u>Nonmegaloblastic macrocytic anemia</u>, e.g., caused by: <u>Liver</u> disease - Alcohol use <u>Diamond-Blackfan anemia</u> <u>Hypothyroidism</u>	- Hypochromic <u>anemia</u>, e.g., due to: <u>Iron deficiency</u> <u>Thalassemia</u>
Mean corpuscular hemoglobin concentration (<u>MCHC</u>)	31–36% <u>Hb</u>/cell (4.81–5.58 mmol <u>Hb</u>/L)	<u>MCHC</u> = <u>Hb</u>/<u>Hct</u> - Measure for the <u>hemoglobin concentration</u> of all <u>RBCs</u>.	<u>Spherocytosis</u>	

Rule of 3

- $\text{Hgb} = 3 \times \text{Red Blood Cell Count}$
- $\text{Hct} = 3 \times \text{Hgb Normal Values}$

$\text{RBC} = 5 \text{ million cells/ul}$

$\text{Hgb} = 15\text{g/dl}$

$\text{Hct} = 45\%$



Reticulocyte count	• 0.5–1.5% (0.005–0.015)	• Percentage of all <u>RBCs</u> that are <u>reticulocytes</u> • Represents erythropoietic activity		
Absolute <u>reticulocyte count</u>	• $50\text{--}100 \times 10^9 / \text{L}$ ^[1]	• Absolute number of <u>reticulocytes</u> contained in a certain volume of blood • In cases of <u>anemia</u>, more accurate than <u>reticulocyte count</u> expressed as a percent	• Increased <u>erythropoiesis</u>, e.g. secondary to: • <u>Hemolysis</u> • Blood loss	• Insufficient <u>erythropoiesis</u>, e.g., caused by • <u>Aplastic anemia</u> • <u>Chronic kidney disease</u>



Corrected reticulocyte count	• Same range as <u>reticulocyte count</u>	• Used in cases of <u>anemia</u>: evaluates the <u>reticulocyte count</u> in context of <u>hematocrit</u> • Calculation: <u>reticulocyte count</u> (in %) x (patient <u>Hct</u> / normal <u>Hct</u>)
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Reticulocyte production index (<u>RPI</u>)	• Individuals without <u>anemia</u>: 1 • Individuals with <u>anemia</u> • ≥ 2 is a normal value. • < 2 is an abnormal value.	• Measures adequate <u>erythrocyte</u> production in response to <u>anemia</u> • Calculation: <u>corrected reticulocyte count</u> / <u>reticulocyte maturation time</u> • <u>Reticulocyte maturation time</u>: estimated value (in days), ranging from 1 to 2.5, correlating with <u>hematocrit</u>
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Red blood cell
distribution width
(RDW)

- 11–15%

• Measures the
variation in RBC
volumes

- Anisocytosis
- Vitamin B₁₂
deficiency
- Folate deficiency
- Iron deficiency
- Sideroblastic
anemia
- Anemia of chronic
disease
- Hereditary
spherocytosis
- Conditions
associated with
reticulocytosis (e.g.,
recent hemorrhage)

WBC parameters

WBC count and differential

Granulocytes make up the largest portion of WBCs:
1,500–8,500/ μ L.

An increase (granulocytosis) or decrease (granulocytopenia) in granulocytes (especially neutrophils) usually contributes the most to changes in the total WBC count.



Overview of WBC parameters

Parameter	Reference range	Common cause of elevation	Common cause of reduction
<u>WBC count</u>	4,500–11,000/mm³ (4.5–11.0 x 10⁹/L)	- Leukocytosis: <u>WBC count</u> > 11,000/mm³ - Causes - Infections <u>Sepsis</u> <u>Leukemia</u>: leads to increased release of premature <u>leukocytes</u> into the blood <u>Acute myeloid leukemia (AML)</u> <u>Acute lymphocytic leukemia (ALL)</u> <u>Chronic myeloid leukemia (CML)</u> <u>Chronic lymphocytic leukemia (CLL)</u> - Autoimmune reactions <u>Drugs</u>: e.g., <u>lithium</u>	- Leukopenia: <u>WBC count</u> < 4,500/mm³ - Causes <u>Malignancy</u> (e.g., <u>leukemia</u>, <u>myelodysplastic syndrome</u>) - Infections: mainly viral (e.g., <u>HIV</u>) <u>Sepsis</u> - Drug toxicity (e.g., <u>clozapine</u>, interaction between <u>allopurinol</u> and <u>azathioprine</u>) <u>Aplastic anemia</u> <u>Bone marrow</u> irradiation (e.g., from <u>chemotherapy</u>) - Autoimmune disease (e.g., <u>SLE</u>, <u>rheumatoid arthritis</u>) - Inherited <u>immunodeficiencies</u> (e.g., <u>SCID</u>)

Segmented neutrophil count

- 54–62% (0.54–0.62)

Band neutrophil count

- 3–5% (0.03–0.05)

- Neutrophilia : > 65%
- Causes^[6]
 - Bacterial infections (especially pyogenic, due to, e.g., S. aureus, S. pneumoniae)
 - Inflammation (e.g., in burns, after myocardial infarction)
 - Physical stress (e.g., surgery, exercise, generalized seizures)
 - Drugs, e.g.:
 - Glucocorticoids: cause neutrophilia via demargination
 - Catecholamines
 - Myeloproliferative neoplasms (e.g., CML)
 - Smoking
 - Asplenia

- Neutropenia: < 51% or < 1500/mm³^[7]
 - Mild: 1,000–1,500 cells/mm³
 - Moderate: 500–1,000 cells/mm³
 - Severe: < 500 cells/mm³ (characterized by severe infections; see “Agranulocytosis”)
- Causes
 - Bone marrow damage/ suppression (e.g., aplastic anemia, chemotherapy, radiation)
 - Drugs (e.g., carbimazole, clozapine)
 - Autoimmune diseases (e.g., SLE, Crohn disease, granulomatosis with polyangiitis)^[8]
 - Rarely: bacterial infection (e.g., typhoid fever, sepsis, postinfectious state)
 - Immune deficiencies (e.g., Kostmann syndrome)
 - Viral infections (e.g., hepatitis, EBV infection)
 - Benign ethnic neutropenia (not pathological)

Neutrophil left shift

Definition: increase in immature leukocytes (e.g., band cells, metamyelocytes) in the peripheral blood

Causes

Infections (especially bacterial infections)

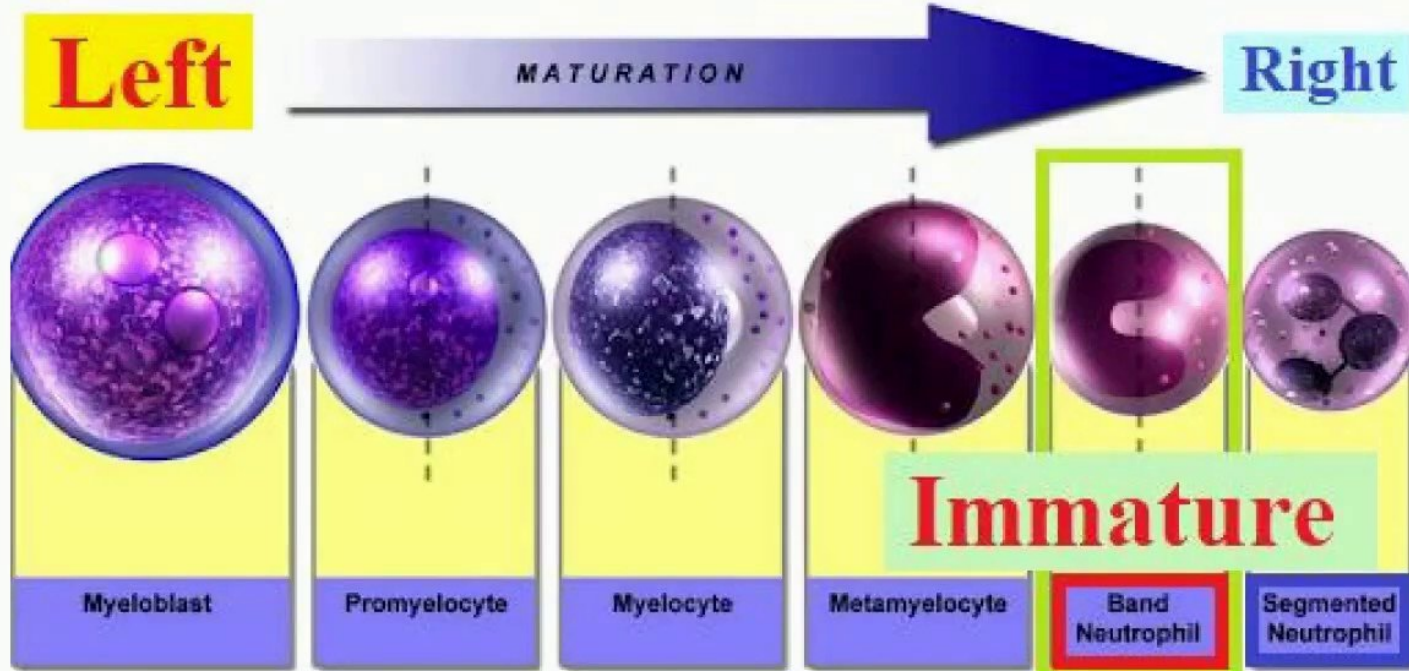
Acute inflammation

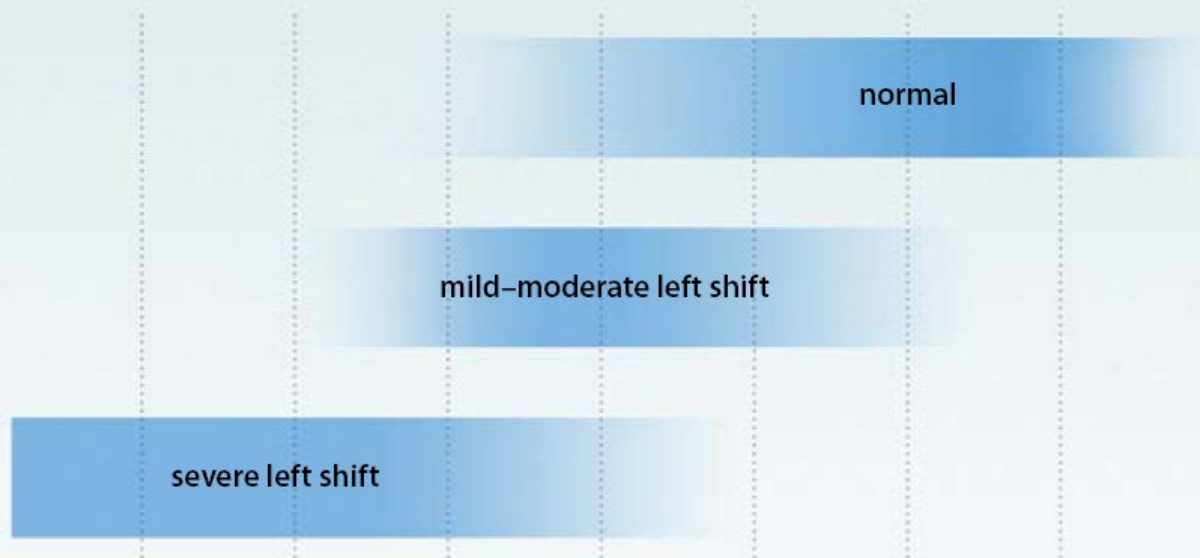
Severe anemia

Bone marrow infiltration

Necrosis







Increasing Neutrophil Maturity →



Iron studies

Iron is a trace element that is essential for hematopoiesis. Iron is required for the synthesis of heme and, subsequently, of hemoglobin.

Iron studies are particularly important in the differential diagnosis of anemia



Serum iron	• Male: 65–175 µg/dL • Female: 50–170 µg/dL	• Measurement of circulating <u>iron</u>, most of which is bound to <u>transferrin</u> • <u>Serum iron</u> levels are subject to physiological daily fluctuation and can be influenced by dietary intake.	• Iron overload, e.g., due to: • <u>Hemochromatosis</u> • Repeated <u>transfusions</u> • Ineffective <u>erythropoiesis</u> (e.g., in <u>thalassaemia</u>) • Increased <u>iron</u> intake (e.g., due to oversupplementation) • <u>Iron poisoning</u> • <u>Sideroblastic anemia</u>	• <u>Iron deficiency</u>, e.g., due to: • Hemorrhage • <u>Malnutrition</u> • Increased demand (e.g., in <u>pregnancy</u>) • <u>Anemia of chronic disease</u>
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Ferritin	• Male: 20–250 ng/mL • Female: 10–120 ng/mL	• Main storage protein for <u>iron</u>	• <u>Acute phase reaction</u> • <u>Anemia of chronic disease</u> • Iron overload • <u>Sideroblastic anemia</u>	• <u>Iron deficiency</u>: <u>Ferritin</u> is the parameter of choice in diagnosing <u>iron deficiency</u>.
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Transferrin *	• 200–360 mg/dL	• Transport protein for <u>iron</u> • Can be reported as <u>total iron binding capacity (TIBC)</u>	• <u>Iron deficiency</u> • <u>Pregnancy</u>	• <u>Inflammation: Transferrin is a <u>negative acute phase reactant</u>.</u> • Iron overload
Total iron binding capacity (<u>TIBC</u>)	• 250–400 µg/dL	• Indirect measure of <u>transferrin</u> (same diagnostic value)		• <u>Anemia of chronic disease</u> • Iron overload



Transferrin saturation (<u>TfS</u>)	20–50%	<u>Ratio</u> of <u>serum iron</u> to <u>TIBC</u>	- Iron overload <u>Sideroblastic anemia</u>	<u>Iron deficiency</u> <u>Pregnancy</u>
Soluble transferrin receptor (<u>sTfR</u>)	- Male: 2–5 mg/L - Female: 1.9–4.4 mg/L	- Part of the transferrin receptor of erythroid precursor cells of the <u>bone marrow</u> - Serum levels reflect the <u>erythropoiesis</u> rate.	<u>Iron deficiency</u> - Other conditions associated with erythroid <u>hyperplasia</u> (e.g., chronic <u>hemolytic anemia</u>)	- Conditions associated with erythroid <u>hypoplasia</u>, e.g.: <u>Aplastic anemia</u> <u>Anemia of chronic kidney disease</u> - No elevation in <u>anemia of chronic disease</u>

In combination with an elevated TIBC, low hemoglobin, ferritin, and iron levels are diagnostic of iron deficiency anemia.

Elevated ferritin levels do not rule out iron deficiency anemia. Ferritin can be elevated in response to simultaneous chronic inflammation.



Etiology

Microcytic anemia

Defective heme synthesis

Iron deficiency anemia (IDA): the most common

Lead poisoning

Anemia of chronic disease (late phase)

Sideroblastic anemia

Defective globin chain: Thalassemia



	Serum laboratory findings in microcytic anemia					
	<u>Iron</u>	<u>Ferritin</u>	<u>Transferrin</u> saturation (<u>TfS</u>)	<u>Transferrin</u> or <u>TIBC</u>	<u>Reticulocyte</u> count	<u>Red cell</u> distribution width (<u>RDW</u>)
<u>Iron deficiency</u>	↓	↓	↓	↑	↓	↑
<u>Anemia of chronic disease</u>	↓	↑	Normal to ↓	↓	↓	Normal
<u>Thalassemia</u>	Normal to ↑*	Normal to ↑*	Normal to ↑*	Normal to ↓*	↑	Normal (occasionally ↑)
<u>Sideroblastic anemia</u>	↑	↑	↑	↓	↓	↑
<u>Pregnancy</u> or use of <u>oral contraceptive pills</u>	Normal to ↓	Normal	↓	↑	Normal	Normal

* If there is iron overload (e.g., due to multiple transfusions, ineffective erythropoiesis, increased GI iron absorption)

Macrocytic anemia

✓ Megaloblastic anemia

Vitamin B₁₂ deficiency

Folate deficiency

Medications

Phenytoin

Sulfa drugs

Trimethoprim

Hydroxyurea

MTX

6-mercaptopurine

Fanconi anemia

Orotic aciduria

✓ Non megaloblastic anemia

Liver disease

Alcohol use

Diamond-Blackfan anemia

Myelodysplastic syndrome

Multiple myeloma

Hypothyroidism



Normocytic anemia

Hemolytic anemia

Intrinsic defects

Hemoglobinopathies

Sickle cell anemia

HbC disease

Enzyme deficiencies

Pyruvate kinase deficiency

G6PD deficiency

Membrane defects

Paroxysmal nocturnal hemoglobinuria

Hereditary spherocytosis



Extrinsic defects

Autoimmune hemolytic anemia

Microangiopathic hemolytic anemia

Macroangiopathic hemolytic anemia

Infections

Mechanical destruction

Nonhemolytic normocytic anemia

Blood loss

Aplastic anemia

Anemia of chronic kidney disease

Iron deficiency anemia (early phase)

Anemia of chronic disease (early phase)

Dilutional anemia of pregnancy



Aplastic anemia

Pancytopenia caused by bone marrow insufficiency
Should not be confused with aplastic crisis, a condition
in which erythropoiesis is temporarily suppressed (e.g.,
due to parvovirus B19 infection in patients with
hemolytic anemias)



Etiology

Idiopathic in > 50% of cases

Possibly immune-mediated

May follow acute hepatitis (hepatitis-associated aplastic anemia)

Medication side effects: carbamazepine, methimazole, NSAIDs, chloramphenicol, propylthiouracil, sulfa drugs, cytostatic drugs (esp. alkylating agents and antimetabolites)

Toxins: benzene, cleaning solvents, insecticides, toluene

Ionizing radiation

Viruses: HBV, EBV, CMV, HIV



Fanconi anemia

- ✓ Hereditary autosomal recessive disorder due to a DNA crosslink repair defect resulting in bone marrow failure
- ✓ Skeletal and organ abnormalities: short stature, hypo- and hyperpigmentation, cafe-au-lait spots, microcephaly, developmental delay, thumb and forearm malformations, kidney, GI, heart, eye, and ear abnormalities
- ✓ Laboratory tests show pancytopenia and normocytic or macrocytic anemia.
- ✓ ~ 50% of patients with Fanconi anemia will develop acute myeloid leukemia or myelodysplastic syndromes in early adulthood.





Figure 2 Palmar view of the right hand with thumb polydactyly. The



Clinical features

Fatigue, malaise

Pallor

Purpura, petechiae, mucosal bleeding

Infection

Diagnostics

CBC:

Pancytopenia (in contrast to aplastic crisis characterized by anemia only)

Normocytic or macrocytic anemia

Reticulocyte count: low

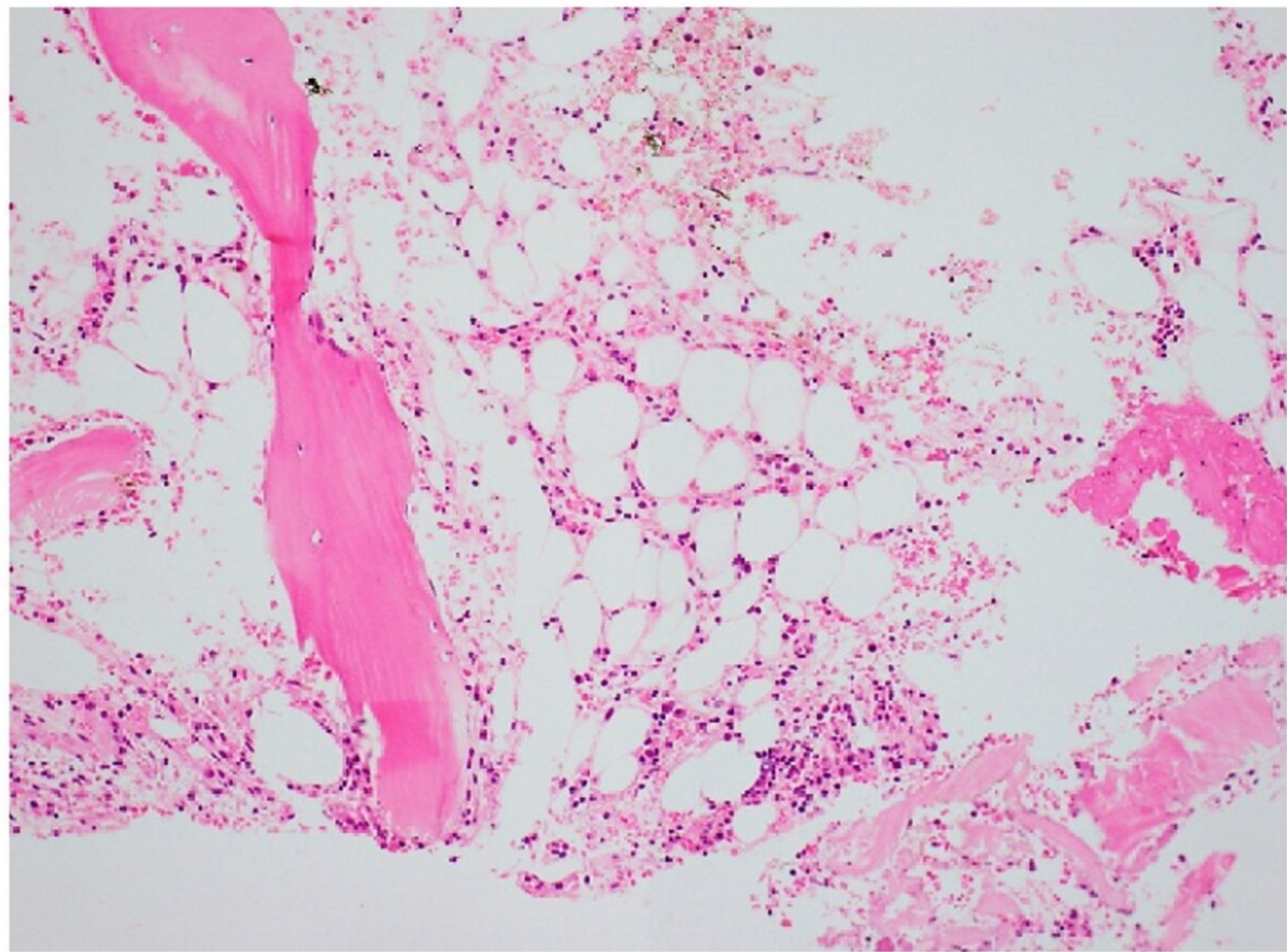
EPO level: high

Bone marrow biopsy findings

Hypocellular fat-filled marrow (dry bone marrow tap)

RBCs normal morphology





Anemia of chronic disease

Description: anemia due to chronic inflammation

Epidemiology: second most common anemia

Pathophysiology: inflammation → increase in cytokines (esp. IL-6) and hepcidin → results in the outcomes listed below:

Reduced iron release from macrophages in the reticuloendothelial system and reduced intestinal iron absorption → reduced iron available systemically

Reduced response (of production) to erythropoietin (EPO) and relative reduction of EPO levels → reduced RBC synthesis

Reduced erythrocyte survival and lifespan



Hepcidin

- Acute phase protein
- Produced in liver
- Has anti-bacterial properties
- Affects iron metabolism
- Inhibits iron transport
- Binds to ferroportin in enterocytes, macrophages
- Iron trapped in cells as ferritin
- Contributes to anemia of chronic disease
- Key finding ACD: ↑ ferritin



Etiology

Inflammation (e.g., rheumatoid arthritis, systemic lupus erythematosus)

Malignancy (e.g., lung cancer, breast cancer, lymphoma)

Chronic infections (e.g., tuberculosis)

Diagnostics

CBC: normocytic anemia (early phase) → microcytic anemia (later phase)

Low iron

Low iron saturation

Low total iron binding capacity (TIBC)

High serum ferritin (• Iron trapped in storage form •
Ferritin is acute phase reactant • Increase may not
represent increased storage iron)

Low reticulocyte count



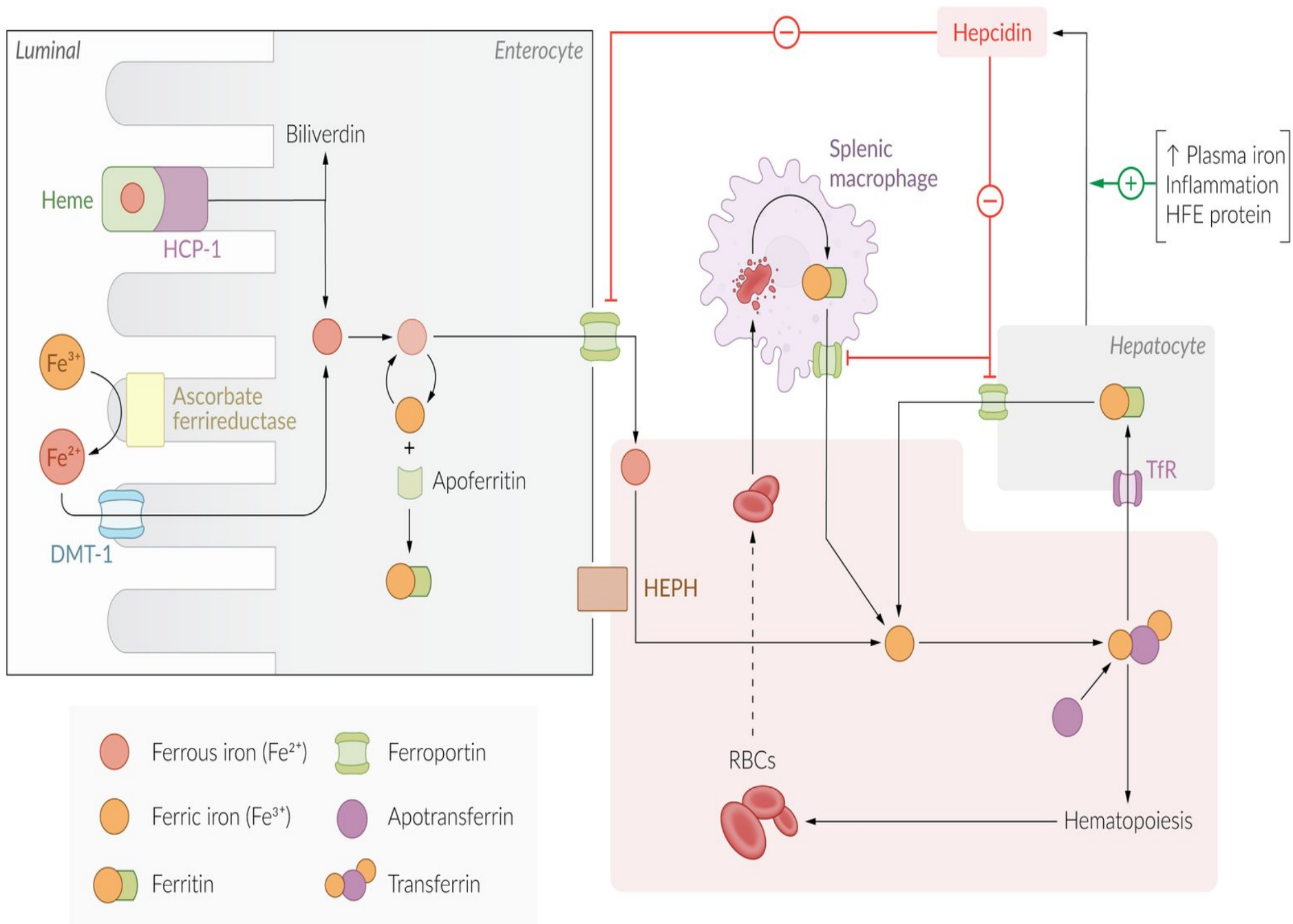
Treatment:

Treat the underlying cause

Blood transfusion if required

EPO in chronic incurable diseases (e.g., chronic kidney disease)





Anemia of chronic kidney disease

Pathophysiology: ↓ synthesis of erythropoietin → ↓ stimulation of RBC production → normocytic, normochromic anemia

Laboratory findings

↓ Hemoglobin (Hb)

MCV is usually normal

✓ MCV may be low if there is concurrent iron deficiency.



In patients > 15 years of age with CKD, anemia is defined as an Hb level of < 13.0 g/dL in male individuals and < 12.0 g/dL in female individuals.



EPO Erythropoietin

- Synthesized in the kidney
- Interstitial cells peritubular capillary
- Found in cortex of the kidney
- Released in response to hypoxia
- Decreased production in renal failure
- Results in a normocytic anemia



Sideroblastic anemia

Description: anemia caused by defective heme metabolism, which leads to iron trapping inside the mitochondria

Etiology

Inherited: X-linked sideroblastic anemia due to a δ -ALA-synthase gene defect

Acquired

Vitamin B₆ deficiency

Lead poisoning

Alcohol use disorder

Drugs (e.g., chloramphenicol, isoniazid , linezolid)

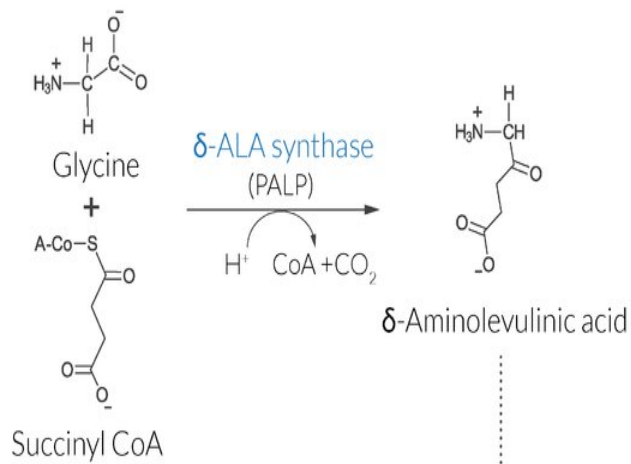
Copper deficiency

Myelodysplastic syndrome

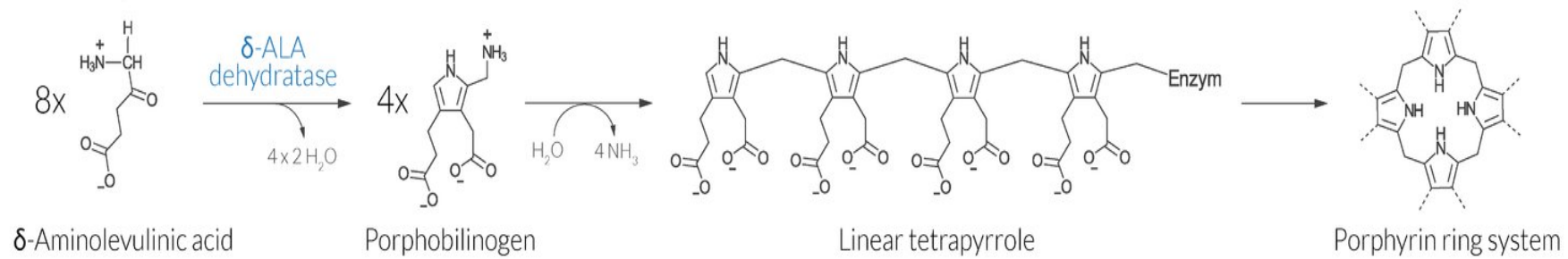
Malignancy



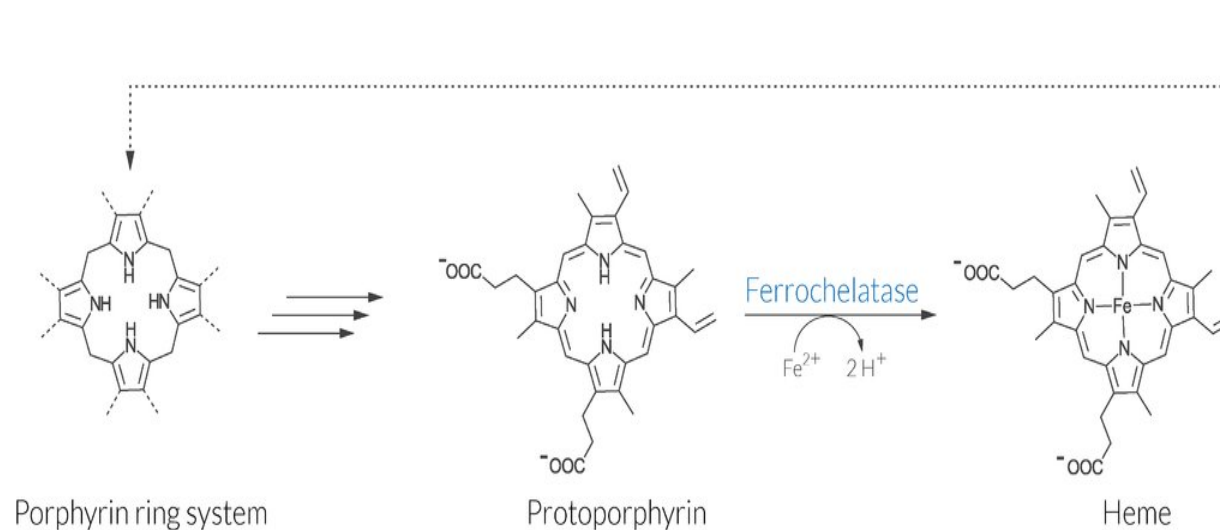
Mitochondrion



Cytoplasm



Mitochondrion



Diagnostics

CBC: microcytic anemia

Serum iron studies

High ferritin

High iron (The only anemia in which the iron level is elevated)

High transferrin saturation

Normal/low TIBC



Peripheral blood smear

Basophilic stippling of RBCs

Normocytes/macrocytes (more common in acquired etiologies)

Prussian blue staining of bone marrow: ringed sideroblasts

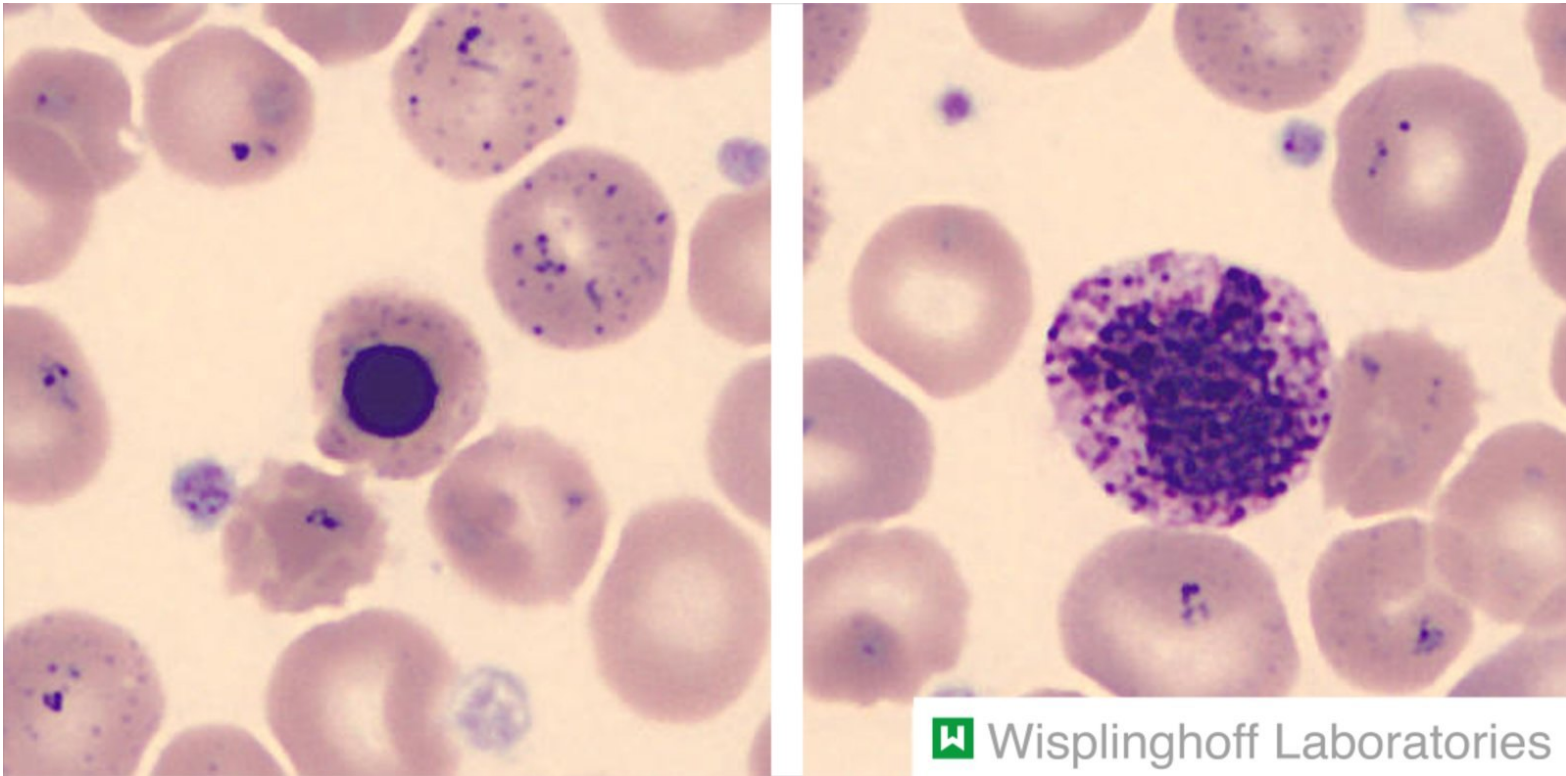
Treatment

Cessation of the offending agent

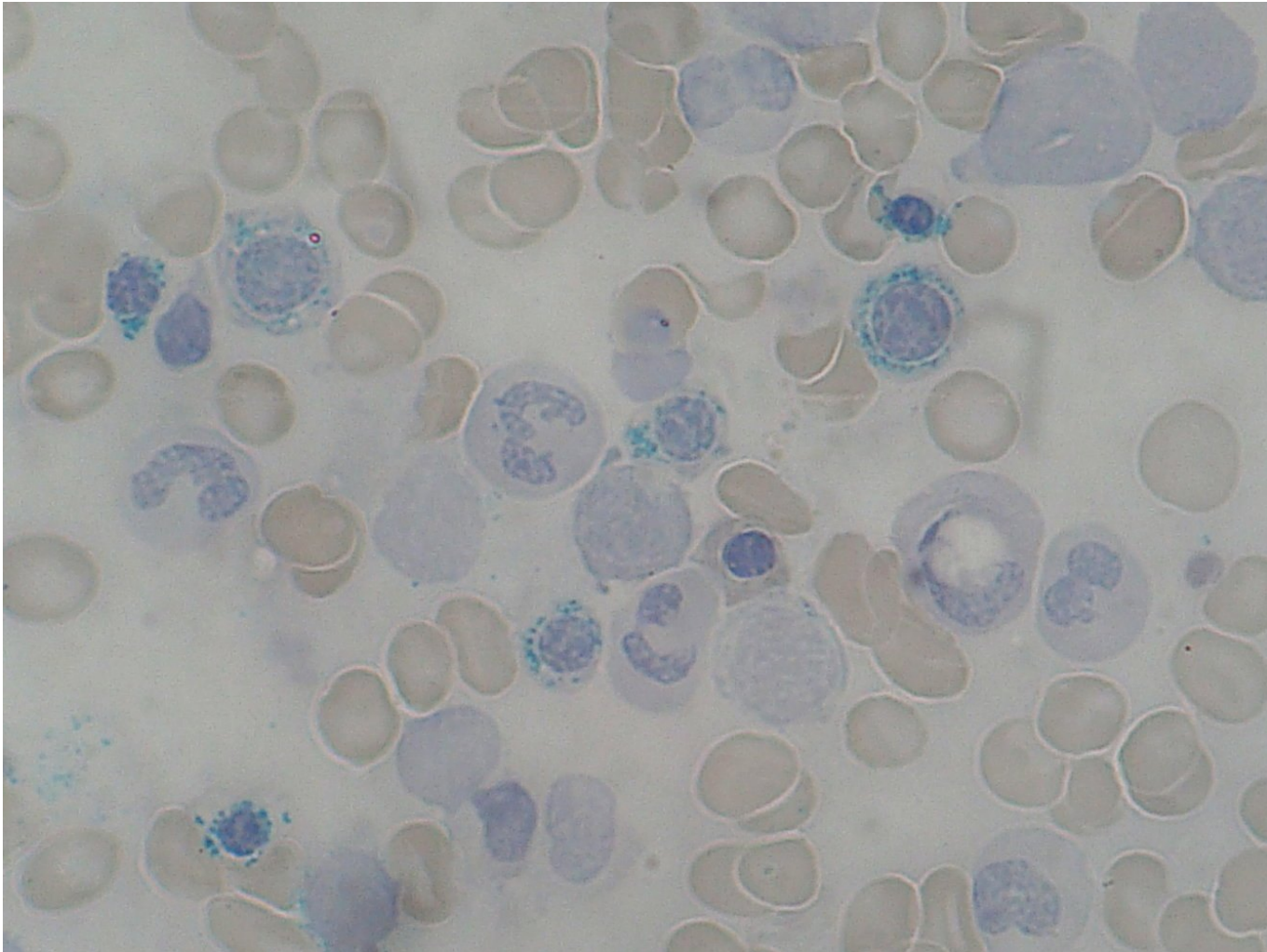
Pyridoxine (B₆) supplementation (a cofactor for δ-ALA synthase)

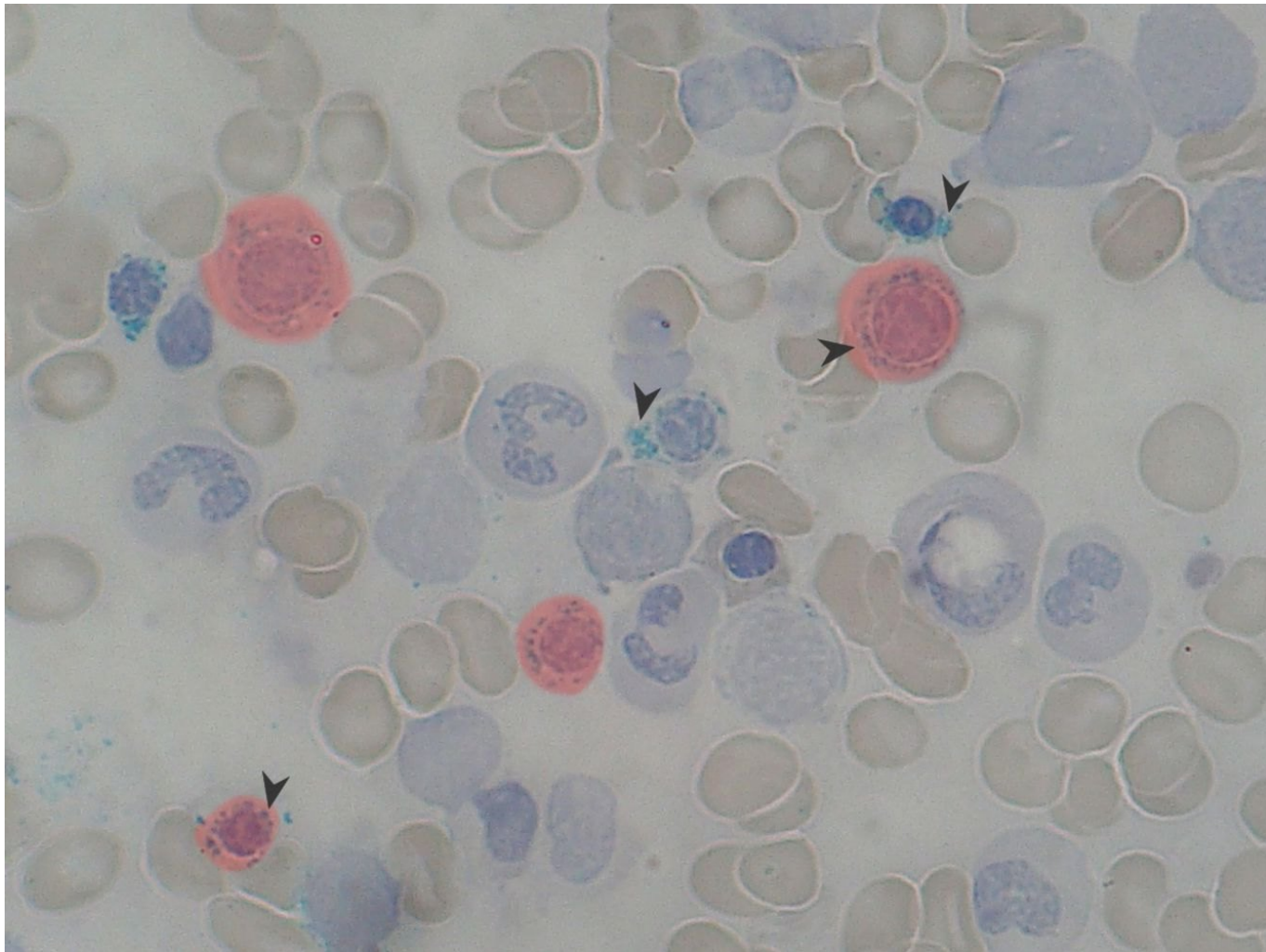


Basophilic stippling of erythrocytes



Sideroblasts





Sideroblastic anemia is due to ineffective heme synthesis, which may be congenital (X-linked defect in the δ -ALA synthase gene) or acquired (e.g., vitamin B₆ deficiency, or lead poisoning leading to sequential inhibition of δ -ALA dehydratase and ferrochelatase).



Lead Poisoning

- Exposure to lead:
 - Adults: Inhalation from industrial work (battery factory)
 - Children: Eating lead paint (old house)
- Inhibits heme synthesis via two enzymes in RBCs
- Delta-aminolevulinic acid (δ -ALA) dehydratase
- Ferrochelatase
- $\downarrow$ heme synthesis $\rightarrow$ microcytic, hypochromic anemia
- Iron studies: normal or low



ALA Synthase: Rate-limiting Step

↓ Heme → ↑ ALA Synthase

Build up of: δ -ALA, Protoporphyrin

Diagnosis

- Plasma lead level
- ↑ delta-aminolevulinic acid (δ -ALA)
- ↑ erythrocyte protoporphyrin
- Basophilic stippling of erythrocytes on peripheral blood smear (lead inhibits RNA degeneration)

Residual RNA often remains visible as blue stipples, but they might not be found in all cases of lead poisoning.



Protoporphyrin

- Heme = Iron + protoporphyrin
- Erythrocyte protoporphyrin level
- Rarely used blood test
 - Will be elevated in iron deficiency
- No Fe for protoporphyrin to bind with
 - Also elevated in lead poisoning
- Inhibits addition of iron to protoporphyrin
- Major uses: screening
- Iron deficiency or lead poisoning



Symptoms

- Abdominal pain (“lead colic”)
- Constipation
- Headache
- “Lead lines”

Blue pigment at gum-tooth line

Caused by reaction of lead with dental plaque

- Nephropathy

Injury to proximal tubules (Fanconi-type syndrome)

Glucose, amino acids, and phosphate wasting

- Neuropathy

Common symptom: Drop wrist and foo



- Children may have prominent neurologic effects
- Behavioral issues
- Developmental delay
- Failure to reach milestones (i.e. language)
- Many states screen children with lead level testing
- Usually at 1-2 years of age



Burton line

The gums and teeth of a 7-year old boy

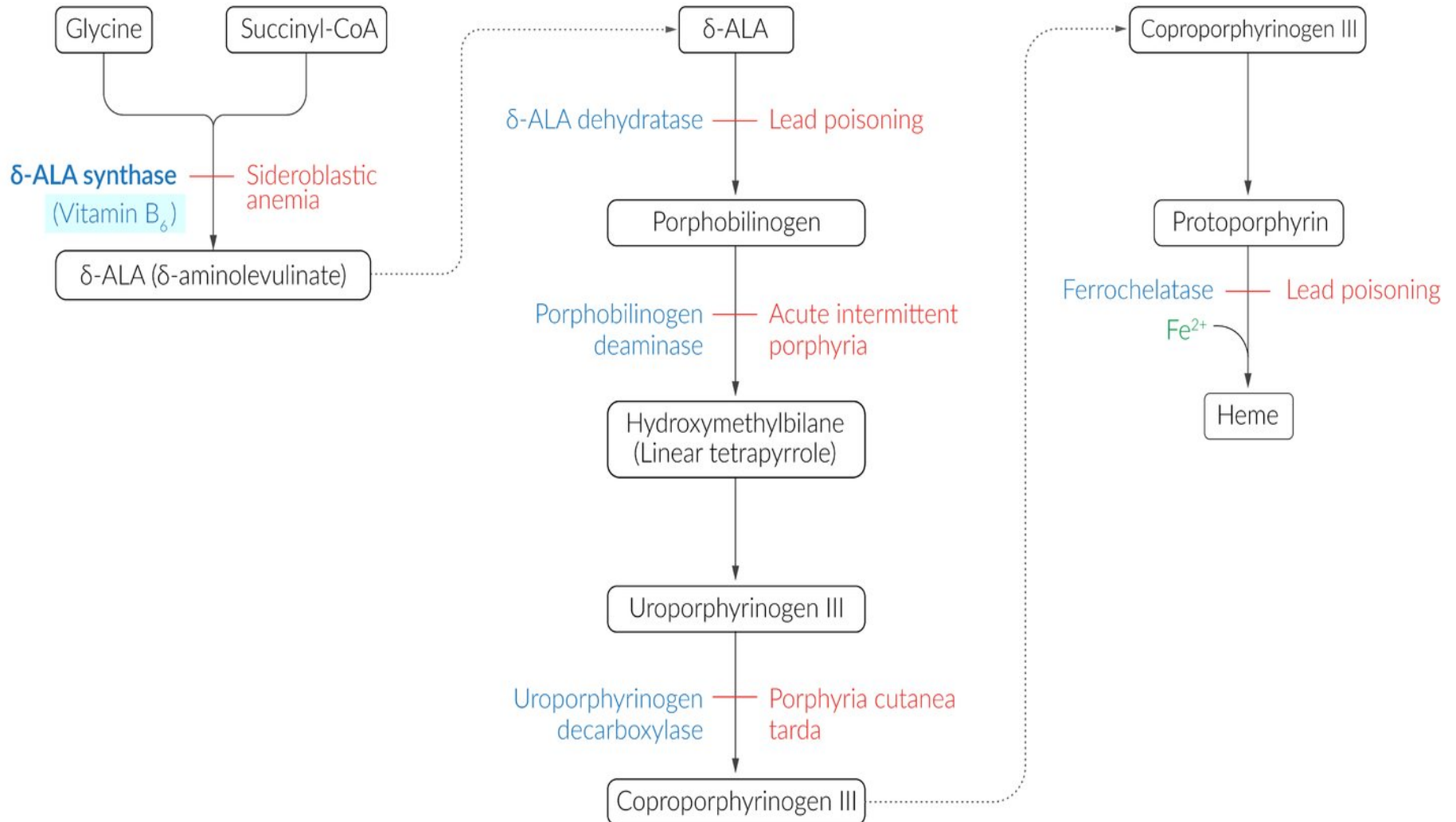
A purplish-blue line is visible at the margin of the gums.



Mitochondria

Cytosol

Mitochondria



Pure red cell aplasia

General

Description: normocytic, normochromic anemia characterized by a severe reduction in circulating reticulocytes and marked reduction or absence of erythroid precursors in the bone marrow

Pathophysiology: thought to be related to abnormal T-cell function and IgG antibodies that target erythroblasts and erythropoietin



Etiology

Acquired

Most often idiopathic

Possible associated conditions

Thymoma

Myelodysplastic syndrome

Adverse drugs effects (e.g., from phenytoin, chloramphenicol)

Parvovirus B19 infection

Autoimmune disorders (e.g., type 1 diabetes, thyroiditis, rheumatoid arthritis)

Congenital: Diamond-Blackfan anemia (DBA)



Diagnostics

Low reticulocyte count

Bone marrow biopsy shows marked reduction or absence of erythroid precursors.

Treatment

Treatment of the underlying cause (e.g., cessation of possible offending agents, thymectomy)

Red blood cell transfusion for symptomatic patients

Immunosuppressive and/or cytotoxic agents (e.g., glucocorticoids, cyclosporine, cyclophosphamide)



Diamond-Blackfan anemia

Description

Intrinsic defect of erythroid progenitor cells → ↑ apoptosis

Usually autosomal dominant inheritance or associated with impaired ribosome synthesis mutations

Rapid onset of macrocytic (non megaloblastic) anemia in infancy (usually diagnosed within the first year of life)



Additional clinical features : physical abnormalities manifest in ~50% of affected individuals

Fatigue, poor feeding

Short stature, webbed neck

Upper extremity malformations (e.g., triphalangeal thumbs)

Microcephaly, micrognathia

Hypertelorism, flat nasal bridge, cleft palate

Congenital cataracts or glaucoma

Atrial and ventricular septal defects



Diagnostics

Electrophoresis

Elevated HbF levels

Low total Hb levels

Specific laboratory findings

Elevated erythrocyte adenosine deaminase levels (eADA)

Increased expression of i antigen in RBCs



Treatment

Corticosteroids (first-line treatment)

Chronic red cell transfusions: individuals who do not respond to corticosteroids

Hematopoietic stem cell transplantation

Complications

Increased risk of malignancy: acute myelogenous leukemia, myelodysplastic syndrome, solid tumors (e.g., colon cancer, osteogenic sarcoma)

Treatment-associated complications: iron overload due to repeated transfusions, corticosteroid-induced hyperglycemia

Endocrine dysfunction: adrenal insufficiency, hypogonadism, vitamin D deficiency



Triphalangeal thumb





Thank You