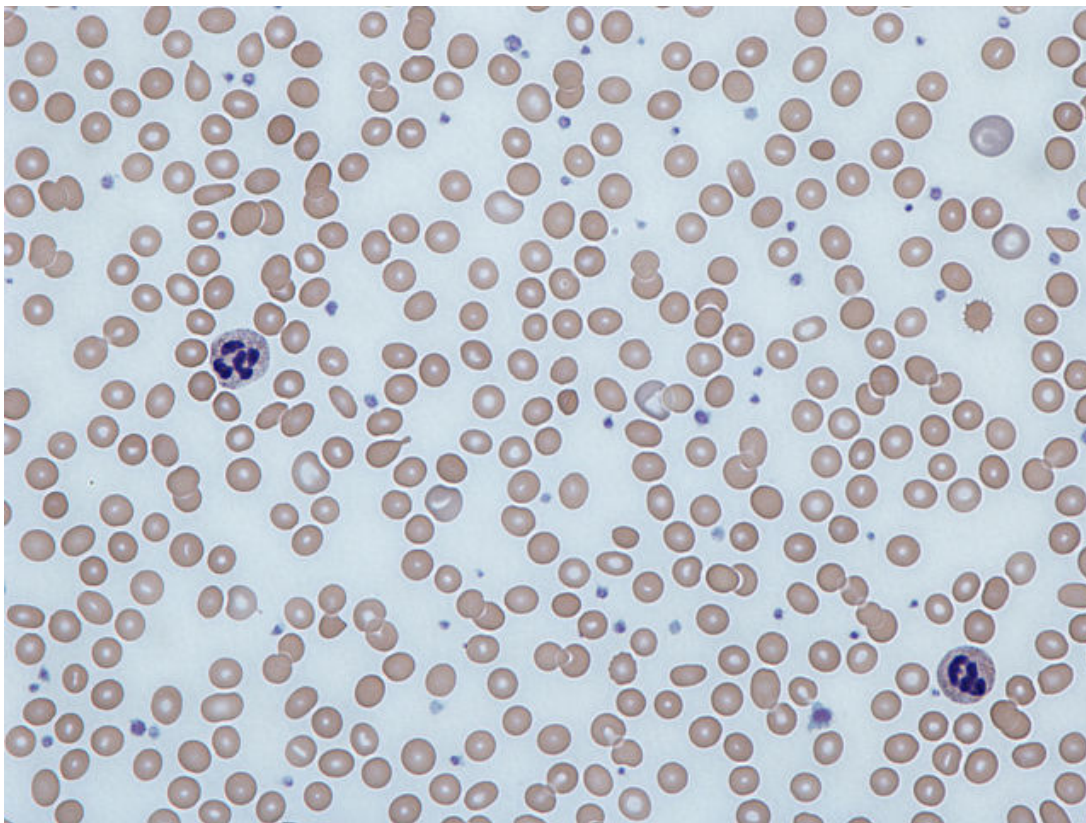


Overview of Anemia: Microcytic, Macrocytic and Normocytic Anemia

[See online here](#)

Anemia is one of the major reasons why patients present with shortness of breath, fatigue, pallor, and weakness. Anemia is a reduction of the oxygen-carrying capacity of the blood, which results in decreased oxygen supply to tissue cells. It is of utmost importance for doctors to rule out anemia as a cause of these symptoms because absence of prompt medical treatment can result in worsening of symptoms and even fatality.



Definitions of Blood Components

Red blood cells

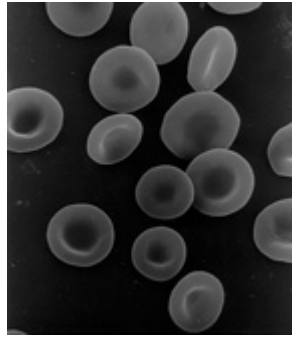


Image: "Red blood cells (eritrociti)" License: Public Domain

Red blood cells, also known as **erythrocytes**, make up the cellular part of blood, giving it its red color and also the ability to **bind and carry oxygen to all parts of the body**. Under a microscope, they appear to be circular and biconcave in shape.

Hemoglobin

Hemoglobin is the **biochemical component of the red blood cells** (RBCs) that is responsible for **binding with oxygen**. It is a **metalloprotein**, with iron being the metal attached to globular protein.

Hematocrit

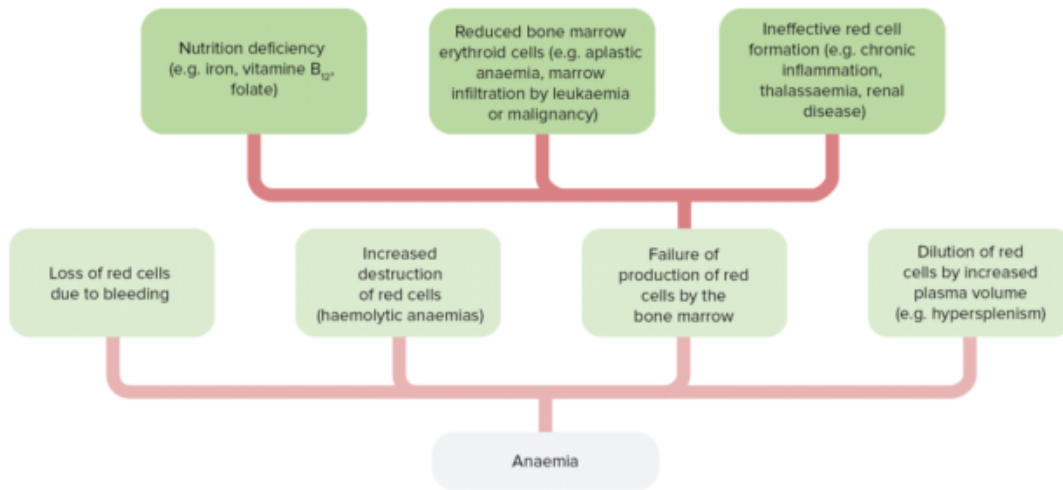
Hematocrit is the **measure of the total volume % of red blood cells** in the blood. The normal value for hematocrit is 45% for men and 40% for women. It is an important component of a patient's complete blood profile.

Mean corpuscular volume

Mean corpuscular volume is the **average volume of red blood cells** and is **reflective of RBC size**. When RBCs increase or decrease in size, the mean corpuscular volume changes; this helps physicians determine the type of anemia and its causes. Normal MCV is **80-96 μm^3** .

Decreased production of red cells

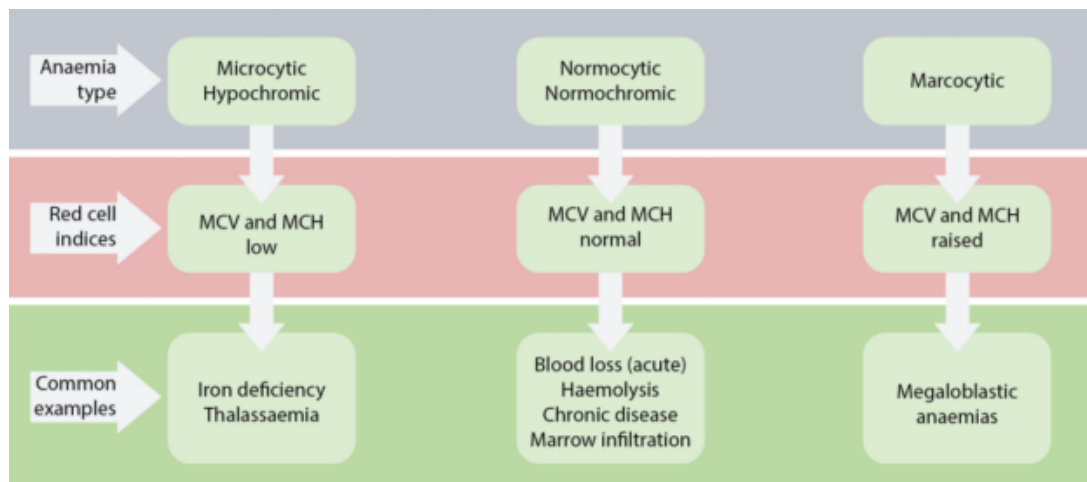
This may occur due to complete bone marrow failure, whereby the production of ALL blood cells is reduced, or it may occur due to disorders that affect only red blood cells. Failure to make red blood cells may be due to nutritional deficiencies of iron or vitamins, inherited disorders of hemoglobin, chronic diseases, or kidney problems.



Decreased production of red cells

The size of the red cell is useful in diagnosis:

- **Microcytic** red cells are seen in iron deficiency and thalassaemia.
- **Normocytic** red cells are observed in bone marrow, inflammatory or renal disorders.
- **Macrocytic** red cells are a feature of vitamin deficiencies.



Epidemiology of Anemia

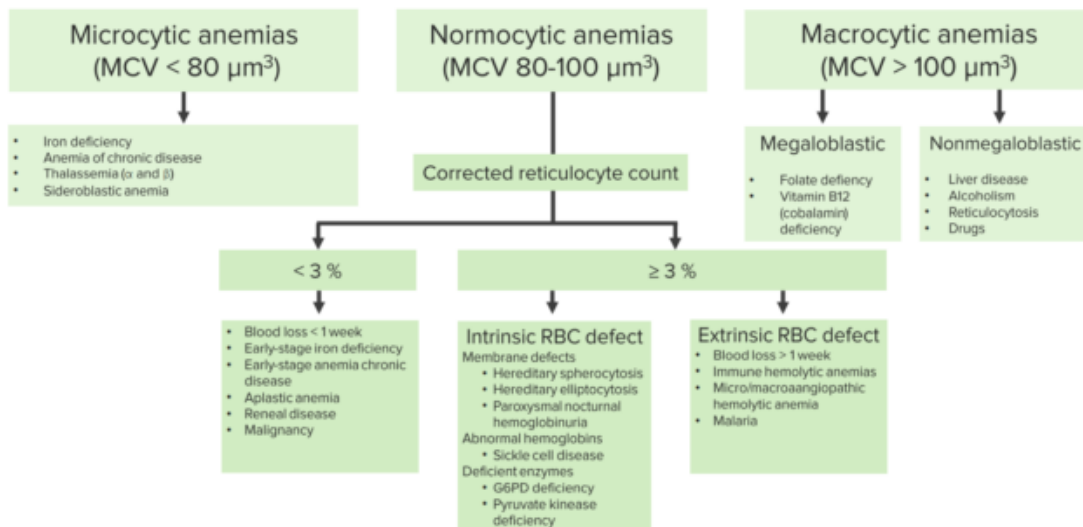
According to the WHO anemia in non-pregnant and otherwise healthy people is characterized by a **hemoglobin value lower than 12.5 g/dL**. Acute anemias affect young adults and people in their 50's. **Females in their reproductive age** (due to menses and pregnancy) are usually more prone to be anemic. Overall, females have twice as much susceptibility to developing anemia than males.

Certain races, due to certain genetic factors, have the prevalence of different types of anemias. For example, thalassaemia is found mainly in the South East Asian region, whereas sickle cell anemia is more prevalent in Africa.

Age	Mean hemoglobin (g/L)	Lower limit of normal (g/L)
Birth (cord blood)	165	135
1-3 days (capillary)	185	145

1 month	140	100
2-6 month	115	95
6 month-2 years	120	105
2-6 years	125	115
6-12 years	135	115
12-18 years: female	140	120
male	145	130
Adult female	140	115
male	155	135

Types of Anemia



Categorized by mean corpuscular volume, anemia can be differentiated into microcytic, macrocytic and normocytic anemias. Normocytic anemia can be further divided into intrinsic and extrinsic RBC defect and blood loss.

Try out the entire course for free: [Hematology basics](#)

Microcytic Anemia

In this type of anemia, the **MCV is lower than 80 μm^3** . This is caused by problems in hemoglobin synthesis. There are **three types of microcytic anemia**.

Iron deficiency anemia

Iron is the main component of hemoglobin, **lack of iron results in decreased synthesis of hemoglobin**, resulting in a **reduction in the size of red blood cells**. It can be due to four reasons:

1. **Decreased intake of iron:** Infants younger than 6 months of age can develop iron deficiency due to the absence of iron in breast milk.
2. **Increased iron demand in the body:** Children and adolescents during their rapid growth phase as well as pregnant women develop this type of iron deficiency due to increase in blood volume and the need to produce more hemoglobin.
3. **Decrease iron absorption:** [Stomach](#) acids and the [small intestines](#) are involved

in the release and absorption of iron from food. Gastrectomy or duodenal diseases, like [celiac disease](#), lead to reduced absorption of iron and cause iron deficiency.

4. **Blood loss: In young women, heavy menstruation is the leading cause of iron deficiency. Blood loss in males is commonly due to [peptic ulcer](#) diseases. In older patients, colon cancer can be the underlying cause of blood loss leading to iron deficiency. In developing countries, it is also necessary to rule out hookworm infection as a cause of iron deficiency anemia.**

Symptoms

Along with usual anemia symptoms of **fatigue, shortness of breath, weakness, and pallor**, patients with iron deficiency anemia also show **signs of pica** (the urge to eat inedible objects), koilonychia (spooning of nails), **Plummer-Vinson syndrome** (esophageal web and glossitis), and restless leg syndrome.

Lab reports show a decrease in serum iron, iron saturation, and serum ferritin and an increase in total iron binding capacity.

Diagnostics — iron studies

Iron studies play a vital diagnostic role in determining the types of anemia and many other diseases that involve iron metabolism. It is composed of four main values:

- **Ferritin: It is the iron-binding storage protein. Its purpose is to store iron in a non-toxic form. Bone marrow macrophages are one of the storage sites of ferritin. Low ferritin levels are a diagnostic feature of iron deficiency anemia. Ferritin synthesis increases in anemia of chronic disease and iron overload disease.**
- **Serum iron:** Iron that is bound to transferrin; transferrin is the binding protein for iron in the blood and is synthesized in the [liver](#)
- **Total iron binding capacity:** This is the concentration of transferrin. Total iron binding capacity is always inversely proportional to ferritin levels.
- **Iron saturation:** Percentage of available binding sites on transferrin

Anemia of chronic disease

Anemia of chronic disease is strongly associated with **inflammatory diseases**. In a chronic inflammatory state, the liver produces a protein called hepcidin. It works to stop iron absorption in the duodenum and prevents iron recycling by inhibiting the breakdown of old RBCs. **Reduction in serum iron** results in [anemia of chronic disease](#).

Therapy

Treatment of the underlying cause (inflammation due to infection, malignancy autoimmune disorder, etc.).

- **Diagnostics**
 - Normal or increased serum ferritin level
 - Decreased total iron binding capacity (TIBC)
 - Decreased % transferrin saturation (serum iron/TIBC ratio)
 - Decreased serum iron level

Sideroblastic anemia

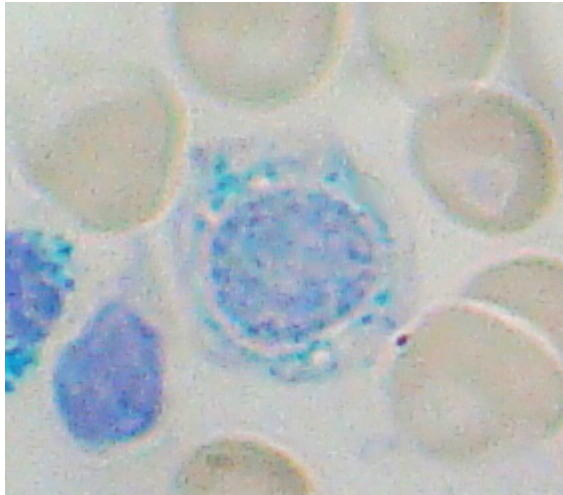


Image: "Sideroblast, as seen in sideroblastic anemia."
Original by Paulo Henrique Orlandi Mourao, zooming in and minor modification by Mikael Häggström. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Sideroblastic anemia occurs due to **abnormalities in the synthesis of protoporphyrin**, which results in **decreased synthesis of hemoglobin**. This happens because protoporphyrin along with iron makes heme (which combines with globular protein to make hemoglobin).

Iron accumulates in the cells because it is not being utilized to make heme due to the absence of protoporphyrin. This results in the characteristic ring sideroblast - iron-laden mitochondria making a ring around the nucleus of the RBC precursor cells.

Laboratory

Serum ferritin level, along with serum iron level and % saturation is increased. Total iron binding capacity is decreased.

Thalassemia

Thalassemia occurs due to **abnormalities in the synthesis of the globular chains** that attach to heme to make hemoglobin. There are two types of thalassemias:

- **Alpha thalassemia:** Occurs because of gene deletion
 - 3 gene deletion: HbH, this is because beta chains start making tetramers in the absence of alpha chains; symptoms are apparent after birth.
 - 4 gene deletion: Hb Bart, incompatible with life; fetus dies in utero due to **hydrops fetalis**. This is due to tetramers formed by gamma chains because there are no alpha chains.
- **Beta thalassemia:** Occurs due to gene mutation; there are 2 types:
 - Minor: Mild, asymptomatic
 - Major: Normal in fetus; severe anemia after birth

Symptoms

Severe anemia, **extramedullary hematopoiesis** leading to **hepatosplenomegaly** and a chipmunk appearance of the face are symptoms of thalassemia.

Overview of microcytic anemia

Test	Iron Deficiency Anemia	Anemia of Chronic Disease	Thalassemia	Sideroblastic Anemia
RBC Count	↓	↓	↑	↓
MCV	↓	N/↓	↓	↓
RDW	↑	N	N/↑	N
Ferritin	↓	N/↑	N	↑
Serum Iron	↓	↓	N	↑
TIBC	↑	↓	N	↓
Tfn Saturation	↓	↓	N	↑

Macrocytic Anemia

In this type of anemia, the **mean corpuscular volume is greater than 96 μm^3** .

Megaloblastic anemia

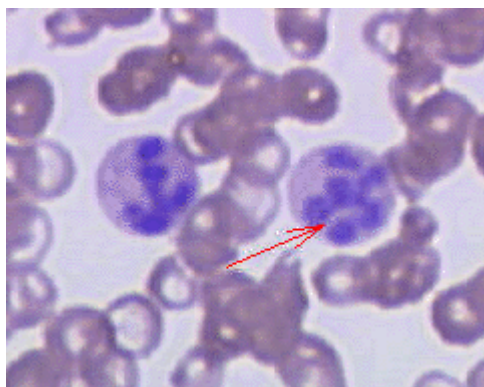


Image: "Hypersegmented neutrophils seen in megaloblastic anemia" by United States Department of Veterans Affairs. License: Public Domain

Megaloblastic anemia is the most common form of macrocytic anemia and is caused specifically by vitamin B12 and/or folate deficiency. It is characterized by **MCV > 100** and **hypersegmented neutrophils** and megaloblastic changes in all rapidly dividing cells of the body, for example, the cells of the tongue.

Etiology

Alcoholism and liver disease are both causes of the megaloblastic anemia, as well as drugs like 5-fluorouracil. There are no hypersegmented neutrophils or megaloblastic changes in the rapidly dividing cells found here.

Vitamin B12 deficiency

Vitamin B12 is a water-soluble vitamin found in animal-derived proteins. The most common cause of vitamin B12 deficiency is **pernicious anemia**, which is **autoimmune-mediated destruction of the parietal cells of the stomach** that decreases the production of hydrochloric acid and intrinsic factor, both of which are needed for absorption of vitamin B12.

Other causes include **pancreatic insufficiency** (as pancreatic enzymes are needed to free vitamin B12) and damage to the part of the small intestine (terminal ileum) where vitamin B12 is absorbed.

Vitamin B12 has two biochemical functions: it takes the methyl group from methylated tetrahydrofolate and gives it to homocysteine, which in turn converts into methionine. Tetrahydrofolate can now be utilized for [DNA synthesis](#). The second biochemical function is the conversion of methylmalonic acid into succinyl CoA.

Due to these functions, vitamin B12 deficiency results in increased homocysteine and methylmalonic acid in the blood. The latter can also contribute to subacute combined degeneration of the spinal cord because methylmalonic acid accumulates and degenerates the myelin in the spinal cord. Other symptoms include **glossitis, megaloblastic anemia, and hypersegmented neutrophils**.

Folate deficiency

Folate is derived from green leafy vegetables like asparagus and broccoli. The body doesn't have large stores of folate so an **increased demand or poor diet can result in folate deficiency within a month**. The symptoms and lab values of folate deficiency and vitamin B12 deficiency in megaloblastic anemia are the same except that for folate deficiency, **methylmalonic acid levels are normal**.

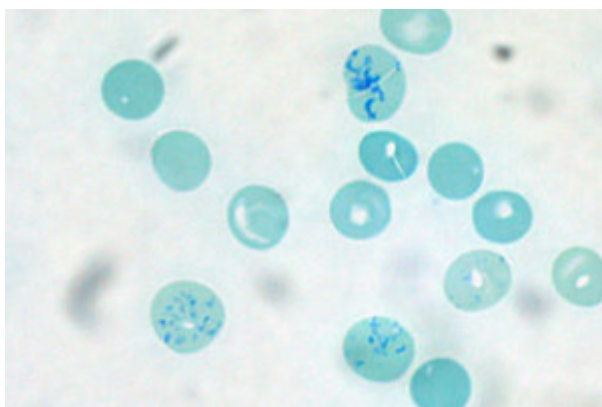
Nonmegaloblastic anemia

Nonmegaloblastic anemia is a less common cause of macrocytic anemia. Alcoholism and liver disease are both causes of nonmegaloblastic macrocytic anemia, as well as drugs like 5-fluorouracil. There are no hypersegmented neutrophils or megaloblastic changes in the rapidly dividing cells found here.

Normocytic Anemia

The mean corpuscular volume in normocytic anemia is within the range of **80-96 μm^3** .

Reticulocyte count



[Image](#): "Reticulocytes seen in peripheral blood smear of a patient with hemolytic anemia" by Ed Uthman, MD. License: [CC-BY 3.0](#)

Reticulocytes are young red blood cells which are large and stain blue due to the presence of RNA. The reticulocyte count is of great clinical significance as it reflects the nature of anemia. Normal reticulocyte count without any underlying pathology is **1-2%**.

In case of normocytic anemia, if the reticulocyte count is...

- **...more than 3 %:** Indicative of bone marrow functioning normally. Therefore, in this case, anemia is not due to underproduction of red blood cells.
- **...less than 3 %:** Indicative of abnormality in the bone marrow. Therefore, there is an underproduction of red blood cells leading to anemia.

Reticulocytes are observed in the peripheral blood smear of a patient with [hemolytic anemia](#). Normocytic anemia occurs in three conditions:

- **Acute blood loss:** Reticulocyte count > 3 %
- **Intrinsic defect of RBC:** Reticulocyte count < 3 %
- **Extrinsic defect of RBC:** Reticulocyte count < 3 %

Extrinsic defect in red blood cells



[Image:](#) "Peripheral blood smear: patient with thrombotic thrombocytopenic purpura" by Erhabor Osaro. License: [CC BY-SA 3.0](#)

This includes the following types of blood disorders:

1. **Immune hemolytic anemias:** IgG- or IgM-mediated destruction of RBCs; direct and indirect Coombs tests are used for diagnostic purposes.
2. **Micro/macroangiopathic hemolytic anemias:** RBCs getting damaged due to micro or macro thrombi, resulting in schistocytes (fragmented RBCs). Diseases include thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation (DIC).
3. **Malaria: Destruction of RBCs by Plasmodium species transmitted by the female Anopheles mosquito.**

Clinical findings of an extrinsic defect in RBCs

- Anemia
- Splenomegaly - due to an increased burden on the [spleen](#) to destroy so many abnormal RBCs.
- Jaundice - due to increased destruction of defective RBCs by the spleen and raised total bilirubin levels; this may also increase the risk of developing gallstones.

Intrinsic defect in red blood cells

This includes membrane defects, abnormal hemoglobin, and enzymatic defects.

Membrane defects

- **Hereditary spherocytosis:** Inherited defect in the proteins that maintain the integrity of the RBC membrane, leading to round, small cells with no central pallor; diagnosed with osmotic fragility test.
- **Paroxysmal nocturnal hemoglobinuria: Inherited abnormalities/absence of surface proteins that protect the RBCs from complement; increased oxidative stress (e.g, acidosis during sleeping) results in the destruction of RBCs overnight and dark-colored urine (containing hemoglobin) in the morning. Diagnosed with**

sucrose and acidified serum test.

Abnormal hemoglobin



Normal capillary



Sickle Cell Anemia

Image: "Sickle Cell Anemia" by BruceBlaus. License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/) The picture is cropped.

Sickle cell anemia is a genetic defect in the synthesis of hemoglobin chain. Glutamic acid gets substituted by valine, resulting in HbS, which sickles (polymerizes) when deoxygenated. Sickling can lead to a range of severe symptoms:

- Vaso-occlusion leading to tissue infarction (for example, dactylitis – swollen hands due to vaso-occlusion of hand bones)
- Auto-splenectomy occurs if spleen gets infarcted; this increases chances of acquiring infections and is the main cause of death in children.
- Extreme pain
- Acute chest syndrome: Infarction of lung vessels; causes death in adults with sickle cell anemia.
- Renal papillary necrosis – occlusion of renal blood vessels – results in visible hematuria and leaking of proteins into the urine.

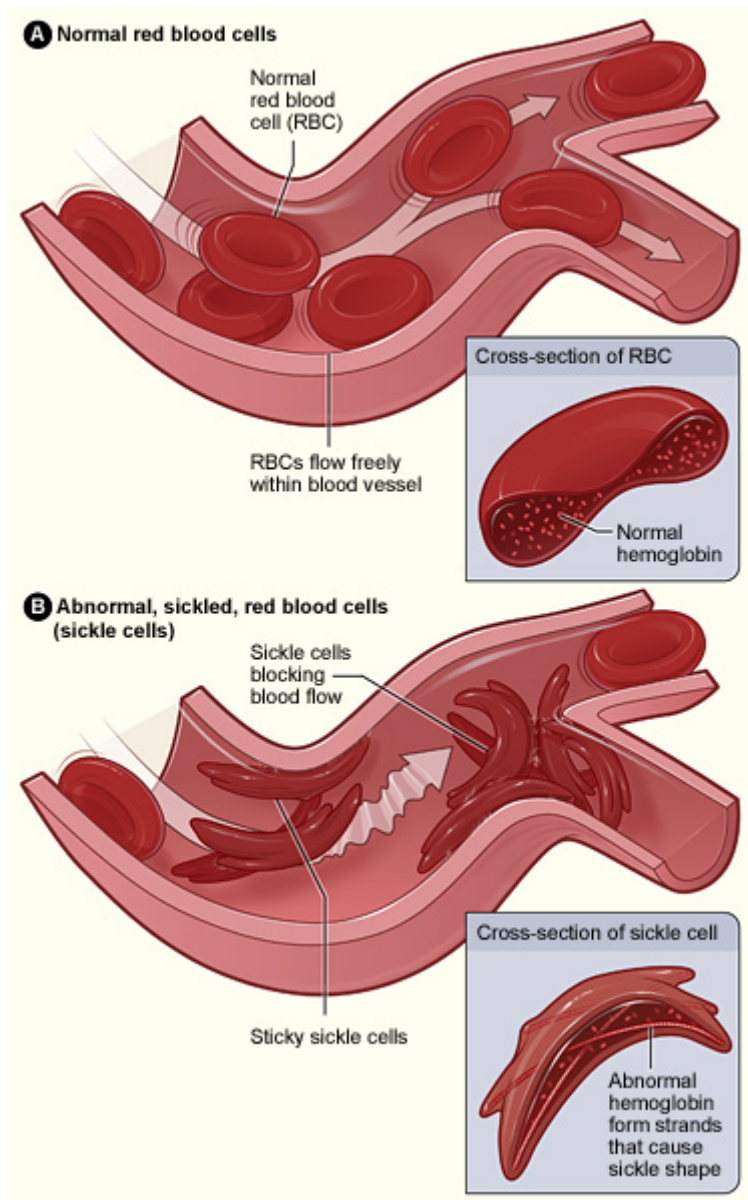


Image: "Figure A shows normal red blood cells flowing freely in a blood vessel. The inset image shows a cross-section of a normal red blood cell with normal hemoglobin. Figure B shows abnormal, sickled red blood cells blocking blood flow in a blood vessel. The inset image shows a cross-section of a sickle cell with abnormal (sickle) hemoglobin forming abnormal strands." by The National Heart, Lung, and Blood Institute. License: Public Domain

Enzymatic defects

Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency) leads to reduced production of NADPH, which is needed to reduce oxidized glutathione. Glutathione is oxidized while protecting the RBCs from hydrogen peroxide. Therefore, G6PD deficiency results in destruction of RBCs by oxidative stress.

Heinz bodies are characteristic of this disorder. When they are removed by splenic macrophages, we see "bite cells." Symptoms include hemoglobinuria and back pain (due to nephrotoxicity of the Heinz bodies).

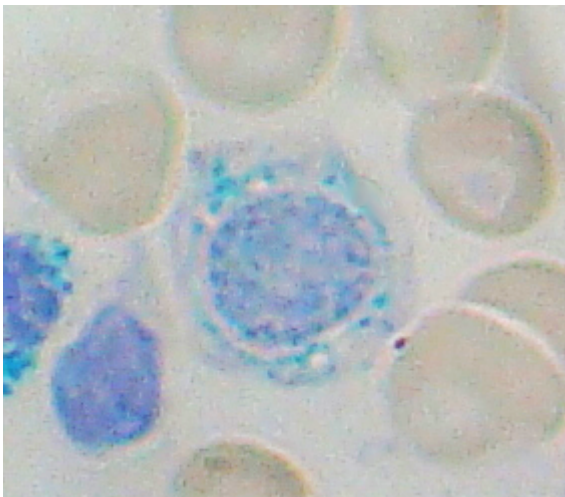
Review Questions

The correct answers can be found below the references.

1. A 34-year-old man went on a business trip to India. On his return, he presented in the clinic with jaundice, painful splenomegaly, and fever spikes. A direct Coombs test is negative. Patient's MCV is within the range of 80-100 μm^3 . The reticulocyte count is discovered to be $> 3\%$. The case complicates further when gross hematuria is observed in the urine bag. A peripheral blood smear shows a sausage-shaped body in the red blood cells. Which of the following is the most likely diagnosis?

- A. *Plasmodium falciparum* malaria
- B. Sickle cell anemia
- C. G6PD deficiency
- D. Autoimmune hemolytic anemia
- E. Disseminated intravascular coagulation

2. A 4-year-old boy presents in the clinic with shortness of breath, pallor, and fatigue. His mean corpuscular volume is 67 μm^3 . On reviewing the patient's history, the patient's mother tells the doctor that she often finds him eating scraped-off paint from the wall. The patient also suffers from colicky abdominal pain and vomiting. Lead poisoning is diagnosed by the doctor. The following image shows the peripheral blood smear. Which of the following best describes the type of anemia observed in this patient?



- A. Microangiopathic anemia
- B. Megaloblastic Anemia
- C. Sideroblastic Anemia
- D. Thalassemia
- E. Sickle Cell Anemia

References

[Red Blood Cell](#) via britannica.com

[Anemia](#) via emedicine.medscape.com

<http://www.mayoclinic.org/diseases-conditions/anemia/symptoms-causes/dxc-20183157>

[Anemia - Symptom and Causes](#) via nhlbi.nih.gov.

[What Is Sickle Cell Disease?](#) via msdmanuals.com

[Hemolytic Anemia](#) via med-ed.virginia.edu

Correct answers: 1A, 2C

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Notes