Approach to Anemia

TUCOM
Dep. of Medicine
5th year
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Learning objectives

1. Review the normal structure and function of red blood cell
2. Recognize the normal values for red blood cell measurements and indices
3. Define anemia
4. Review the causes of anemia
5. Clarify the clinical assessment of anemic patient
6. Explain the investigations of anemia
7. List the types of anemia according to mean cell volume (MCV) and low reticulocyte count

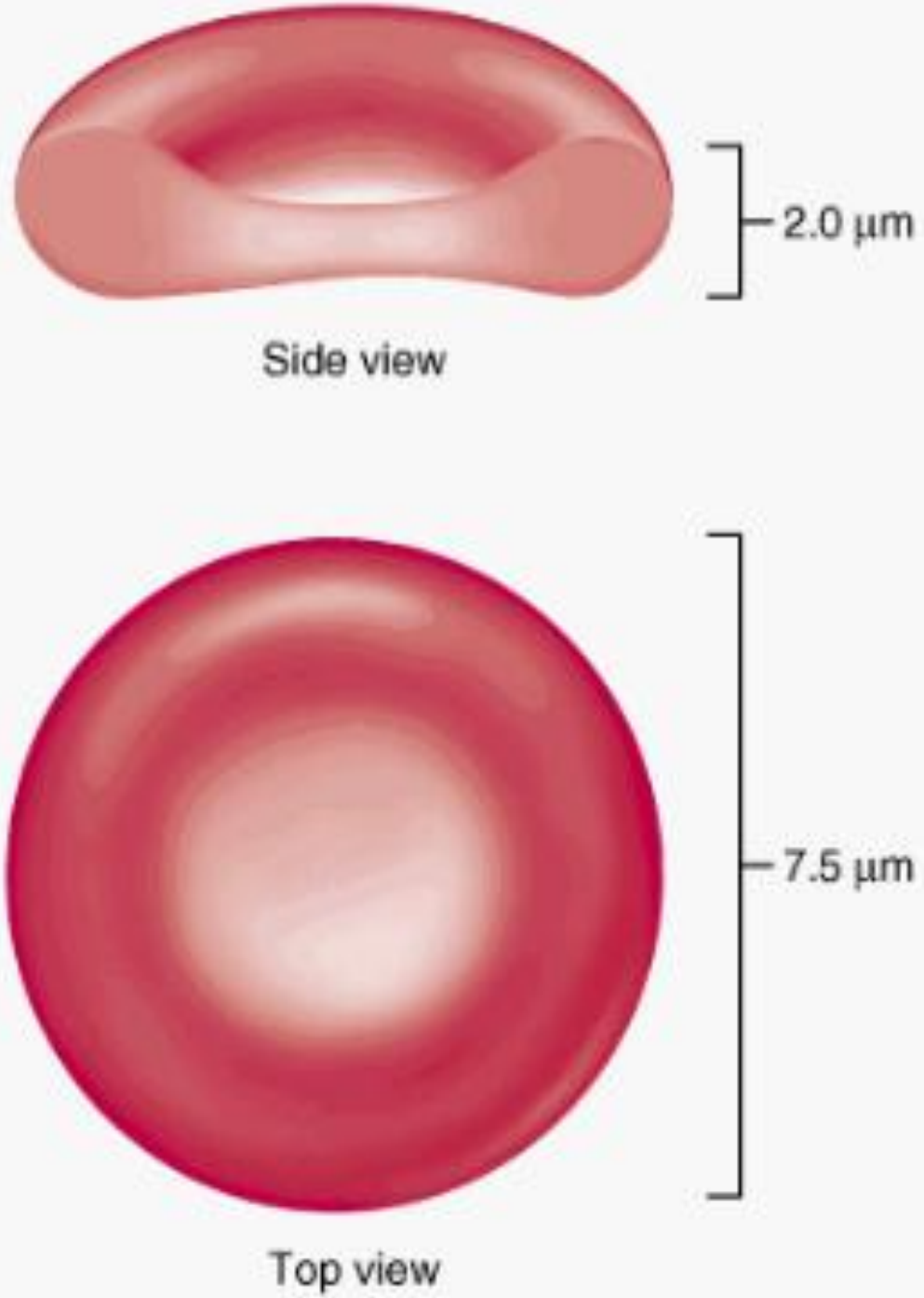
Normal red blood cell structure and function

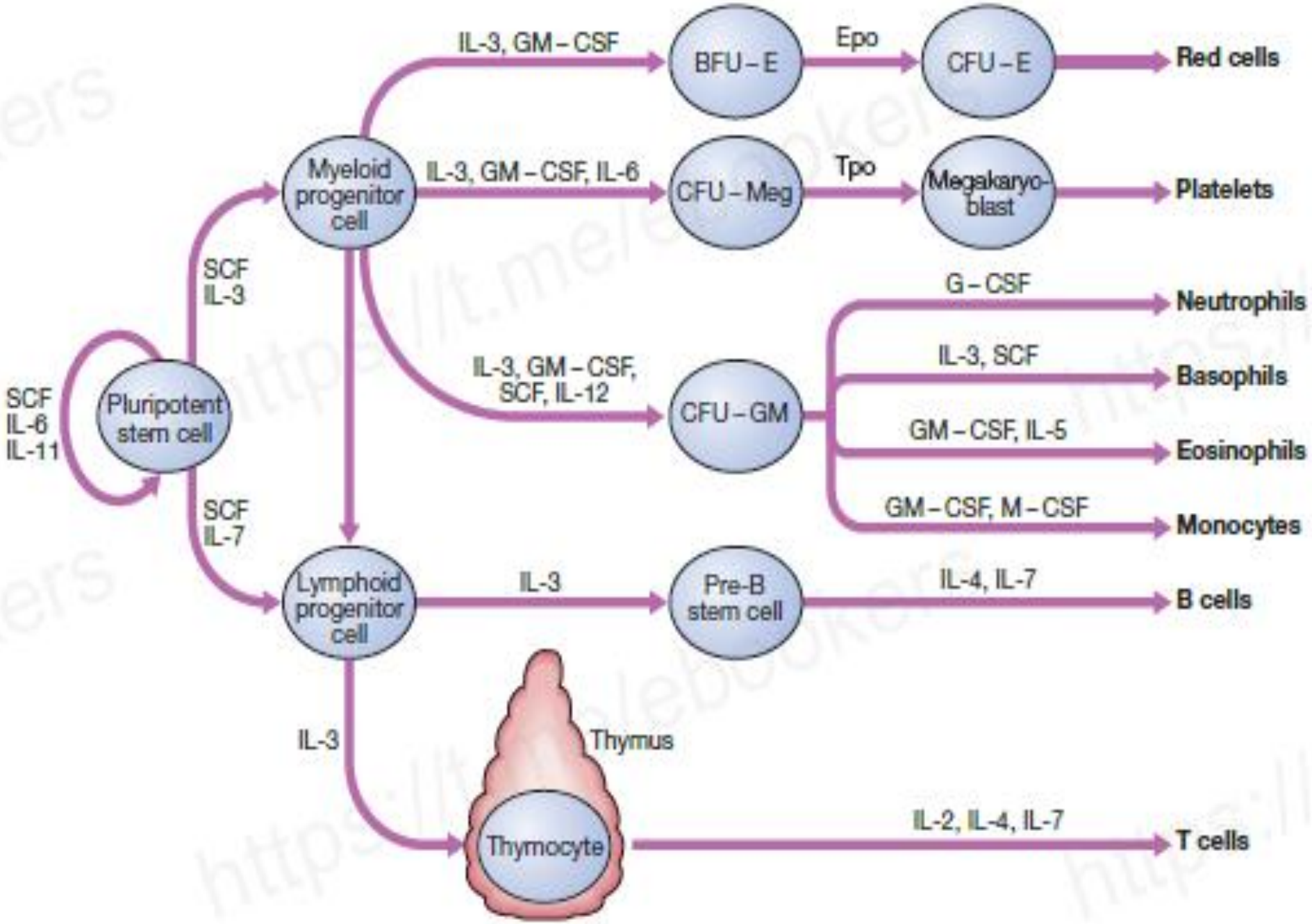
The red blood cells (RBCs, erythrocytes) deliver oxygen to all the tissues in the body and carry carbon dioxide back to the lungs for excretion. The erythrocyte is uniquely adapted to these functions.

Normal mature red cell circulate for about 120 days. It is a 8 µm non-nucleated, non-dividing cell, a biconcave disk shape that maximizes the membrane surface area for gas exchange, and it has a cytoskeleton and membrane structure that allow it to deform sufficiently to pass through the microvasculature.

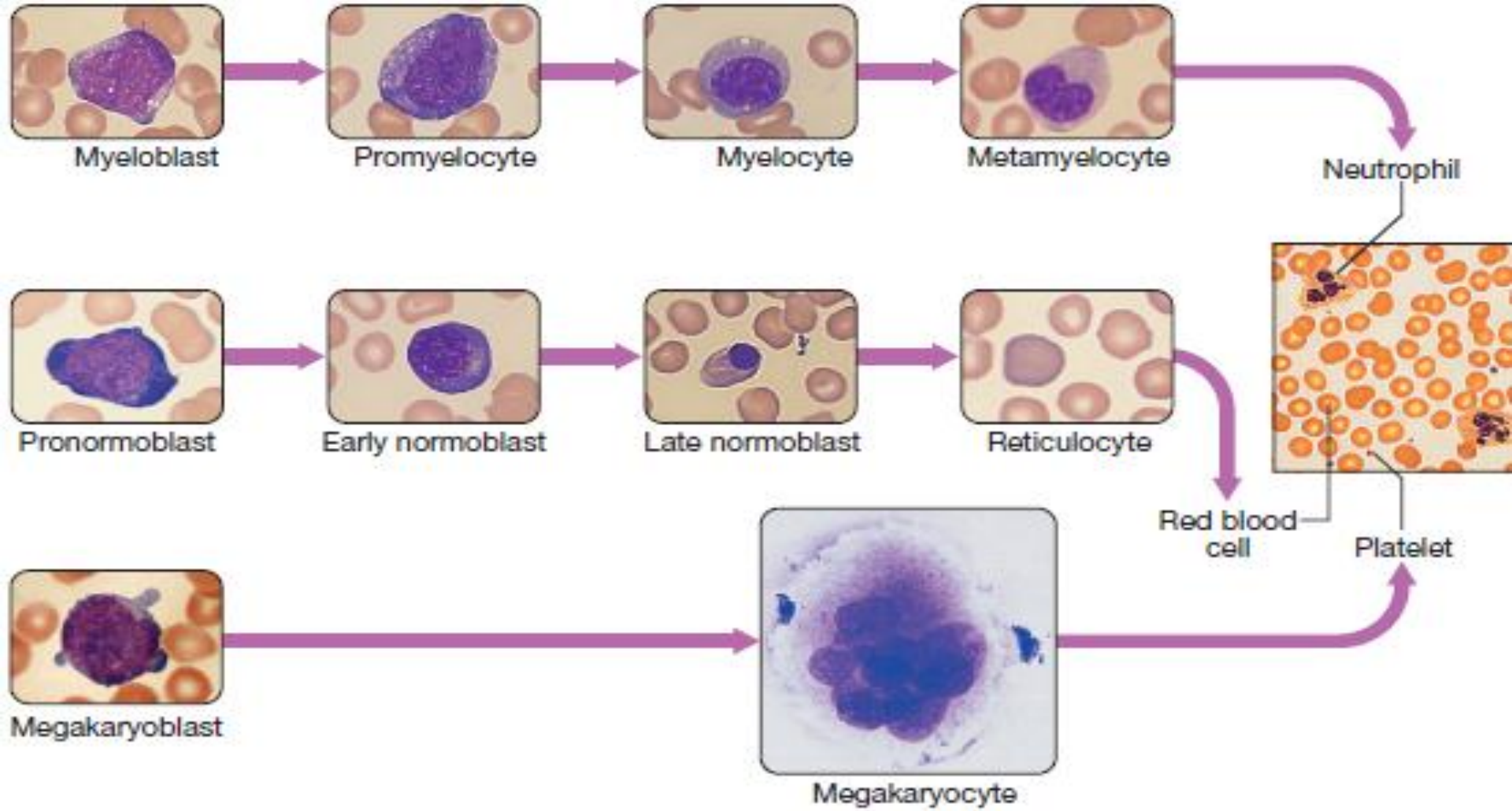
About 98% of the cytoplasmic protein of the mature erythrocyte is hemoglobin. The remainder is mainly enzymatic proteins, such as those required for anaerobic metabolism and the hexose monophosphate shunt.

Normal shape of a red blood cell





Stem cells and growth factors in haematopoietic cell development.

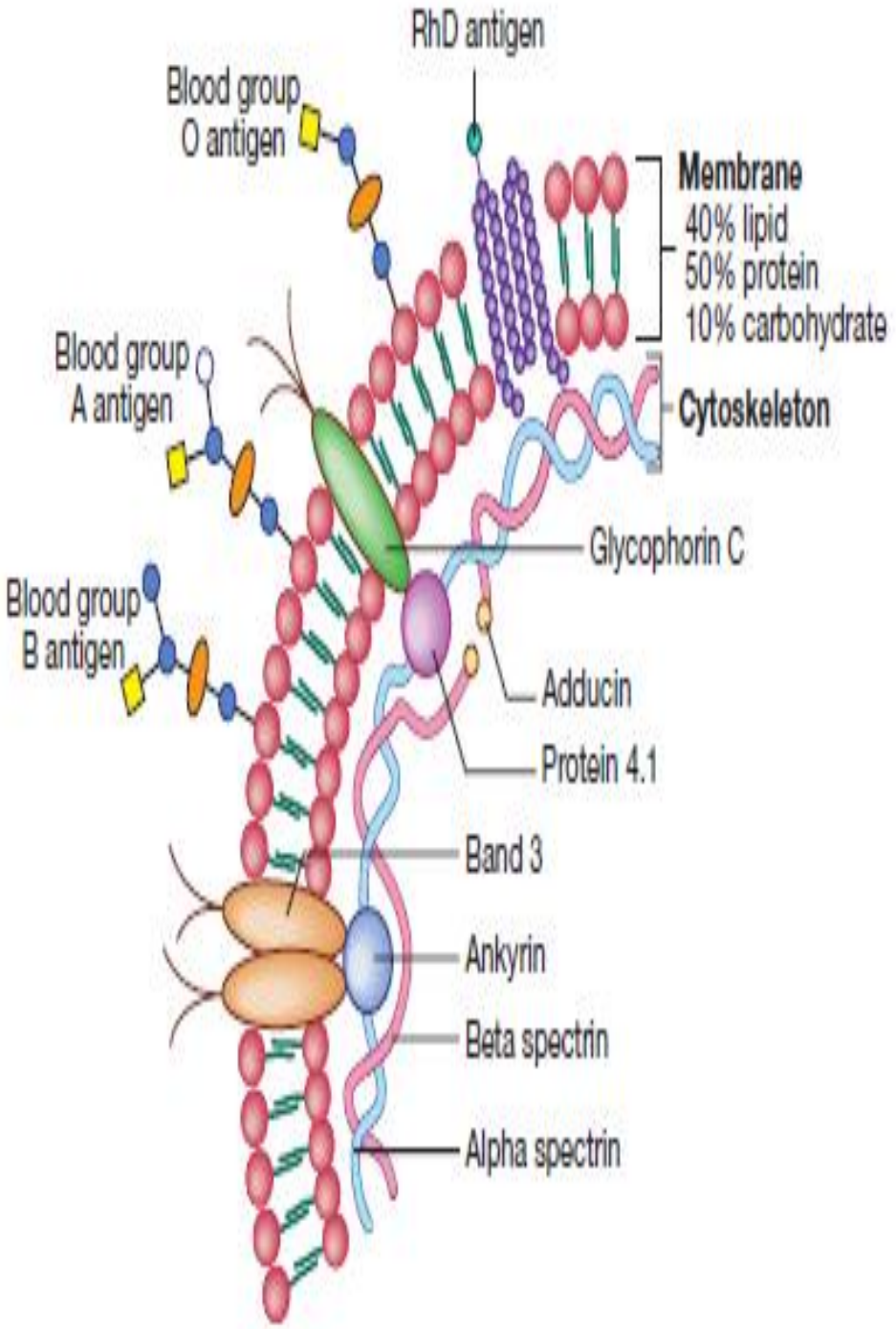


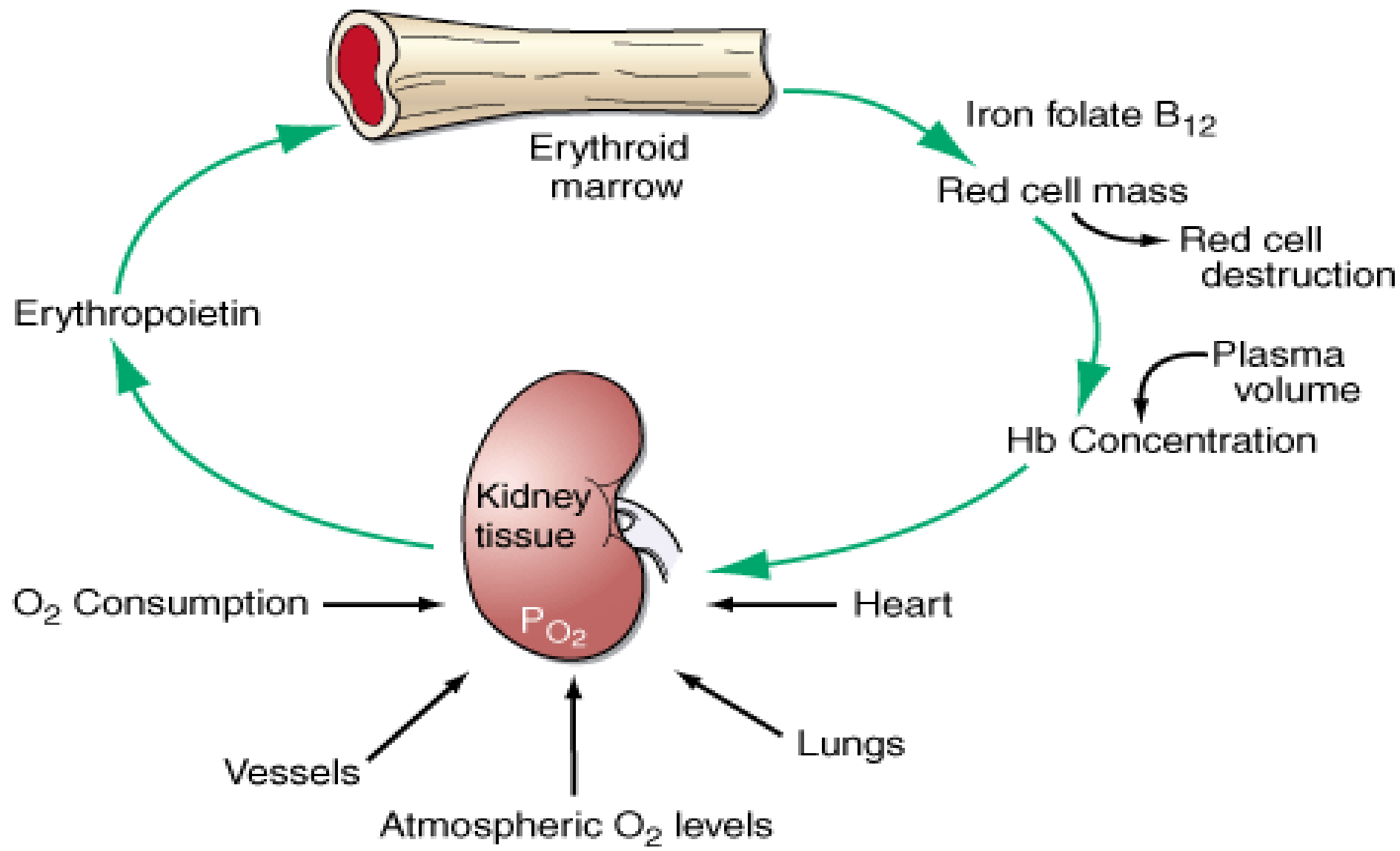
Red cell precursors formed in the bone marrow from the erythroid (CFU–E) progenitor cells are called erythroblasts or normoblasts. The first non-nucleated red cell is a reticulocyte, which still contains ribosomal material in the cytoplasm, giving these large cells a faint blue tinge ('polychromasia'). Reticulocytes lose their ribosomal material and mature over 3 days, during which time they are released into the circulation.

Red cell membrane (lipid bilayer) flexibility is conferred by attachment of cytoskeletal proteins, in order to:

- **Pass through the smallest capillaries**
- **Prevent osmotic destruction in the pulmonary and renal circulation**

Red cell membrane also carry the antigens for ABO blood group and Rhesus system.





Proliferation and differentiation of red cell precursors is stimulated by erythropoietin, a polypeptide hormone produced by renal interstitial peritubular cells in response to hypoxia.

Anemia

Anemia refers to a state in which the level of hemoglobin in the blood is below the reference range appropriate for age and sex. It is not a disease but it is an important sign of different underlying diseases.

Causes of anemia

Decreased or ineffective marrow production

- Lack of iron, vitamin B12 or folate
- Hypoplasia/myelodysplasia
- Invasion by malignant cells
- Renal failure
- Anemia of chronic disease

Normal marrow production but increased removal of cells

- Blood loss
- Hemolysis
- Hypersplenism

Normal values for red blood cell measurements

Measurement		Unit	Normal Range
Hemoglobin		g/dL	Males: 13.5–17.5
			Females: 12–16
Hematocrit		%	Males: 40–52
			Females: 36–48
Red blood cell (RBC) count		× 10^6/µL of blood	Males: 4.5–6.0
			Females: 4.0–5.4
Mean cell volume (MCV)		fL	78–98
Mean cell hemoglobin (MCH)		pg	29–33
Mean cell hemoglobin concentration (MCHC)		g/dL	30–36
Red blood cell size distribution width			
	RDW-CV	%	12–14
	RDW-SD	fL	37–47
Reticulocyte count (absolute number)		No./µL of blood	40,000–100,000
Reticulocyte percentage		% of RBCs	0.5–1.5

Changes in Normal Hemoglobin/Hematocrit Values with Age and Pregnancy

Age/Sex	Hemoglobin g/dL	Hematocrit %
At birth	17	52
Childhood	12	36
Adolescence	13	40
Adult man	16 (±2)	47 (±6)
Adult woman (menstruating)	13 (±2)	40 (±6)
Adult woman (postmenopausal)	14 (±2)	42 (±6)
During pregnancy	12 (±2)	37 (±6)

Clinical presentation

The clinical presentation of anemia depend on its severity and the underlying cause.

- **Acute anemia: due to acute hemorrhage or massive hemolysis may exhibit symptoms of hypovolemic shock.**
- **Chronic anemia: most common, patients complaints are fatigue, pallor, dizziness, headache, decreased exercise tolerance, dyspnea, and palpitations. In patients with coronary artery disease, anemia may precipitate angina.**

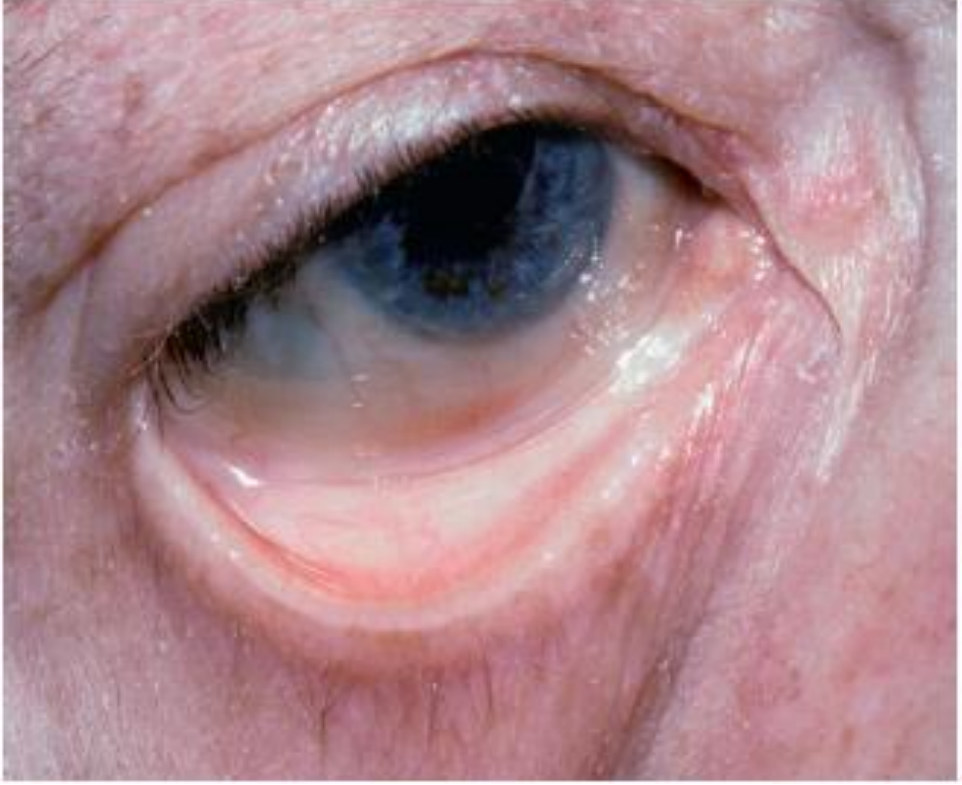
History:

- **Gastrointestinal history, menstrual history or recent pregnancy are to important to looking for iron deficiency anemia (which is the most common type of anemia worldwide).**

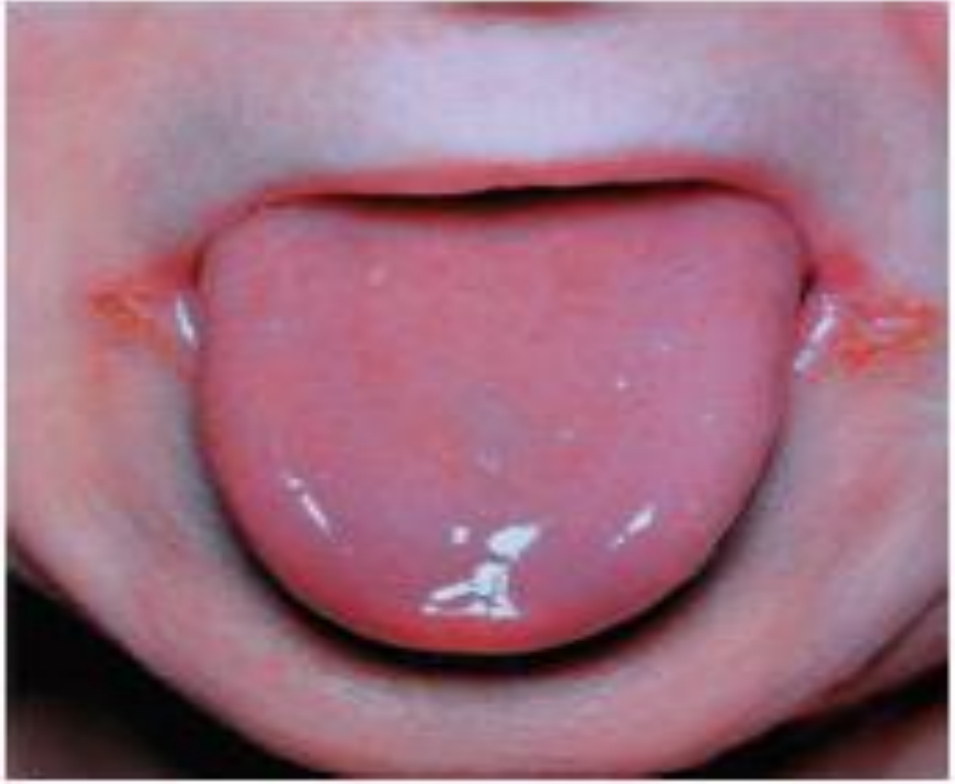
- A dietary history should assess the intake of iron and folate, which may become deficient e.g. in pregnancy or during periods of rapid growth.
- Past medical history: such as rheumatoid arthritis (anaemia of chronic disease), chronic diarrhea or previous surgery (e.g. resection of the stomach or small bowel, which may lead to malabsorption of iron and/or vitamin B12).
- Family history and ethnic background: such as the haemoglobinopathies and hereditary spherocytosis.
- A drug history may reveal the ingestion of drugs which cause blood loss (e.g. aspirin and antiinflammatory drugs), haemolysis (e.g. sulphonamides) or aplasia (e.g. chloramphenicol).
- Recent significant weight loss.

On examination:

- ❑ General physical findings of anemia
- Pallor: of mucous membranes and conjunctiva (Hb < 9 g/dl) or skin creases (Hb < 7 g/dl)
- Tachycardia, systolic flow murmur, wide pulse pressure or features of heart failure
- Rectal digital examination to look for GI bleeding.
- ❑ Specific findings related to the aetiology of the anemia, for example:
- Spooning of the fingernails (koilonychia) due to iron deficiency anemia. Glossitis due to iron, folate and vitamin B12 deficiency.
- Right iliac fossa mass due to an underlying caecal carcinoma.
- Hemolytic anemia can cause jaundice.
- Vitamin B12 deficiency may be associated with neurological signs, including peripheral neuropathy, dementia and signs of subacute combined degeneration of spinal cord.
- Sickle-cell anemia may result in leg ulcers, stroke or features of pulmonary hypertension.
- Splenomegaly, lymphadenopathy and hemorrhagic skin rash due to hematological diseases.

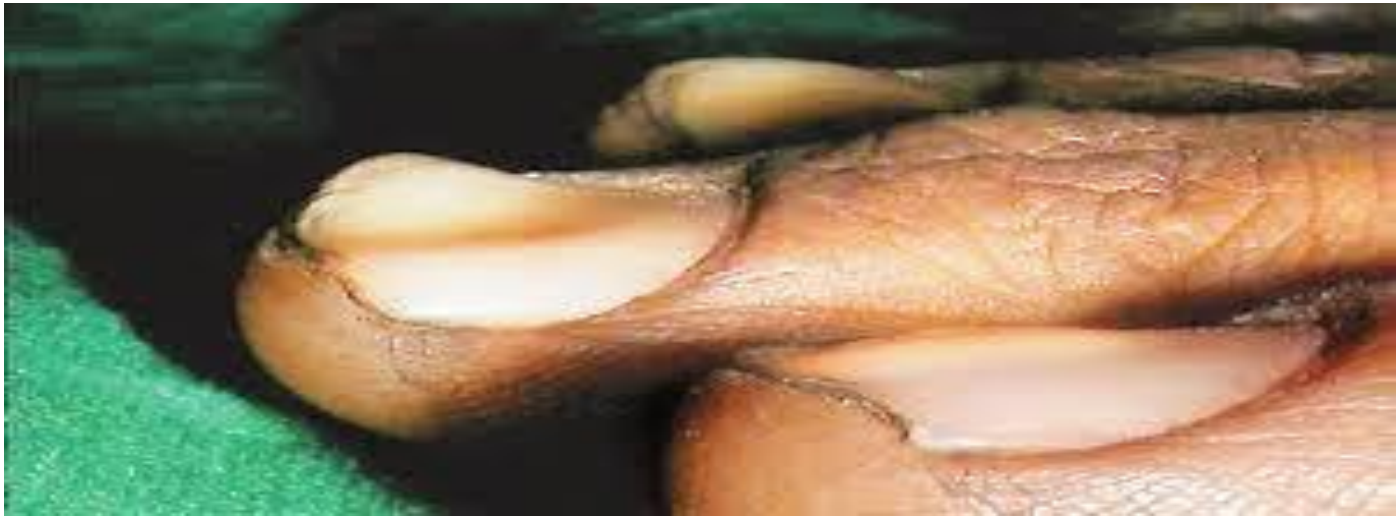


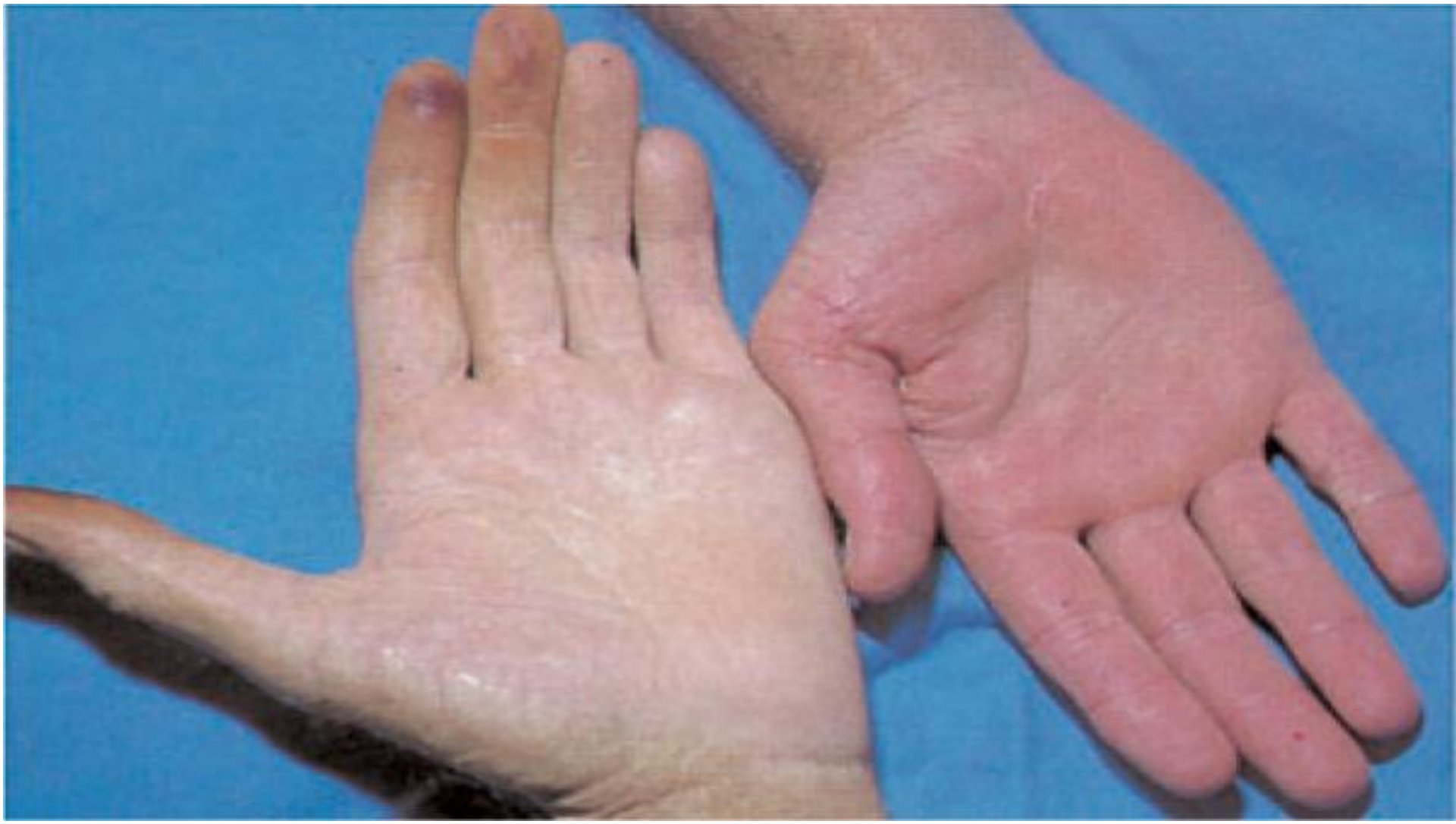
Conjunctival pallor



Smooth red tongue and angular stomatitis

koilonychia





Chronic anemia. Pallor of the hand in anemia is obvious in this patient, especially when compared with the physician's hand on the right. The patient's hemoglobin concentration was 7 g/dL. The hand also shows that the patient was a heavy smoker. His anemia resulted from chronic blood loss from a carcinoma in the esophagus, a site where the risk for carcinoma is increased in smokers.

Investigations

1- Complete Blood Counts: Hemoglobin level and hematocrit, RBC indices and RDW, WBC count and differential, platelet count, and reticulocyte count and percentage.

A- Red blood cell indices:

Index	Normal Value
Mean cell volume (MCV) = (hematocrit x 10)/(red cell count x 10^6)	78- 98 fL
Mean cell hemoglobin (MCH) = (hemoglobin x 10)/(red cell count x 10^6)	29- 33 pg
Mean cell hemoglobin concentration (MCHC) = (hemoglobin x 10)/hematocrit, or MCH/MCV	30- 36 g/dL

Microcytosis is reflected by a lower than normal MCV (<78 fl), whereas high values (>98 fl) reflect macrocytosis.

Decrease in MCH and MCHC reflect defects in hemoglobin synthesis (hypochromia).

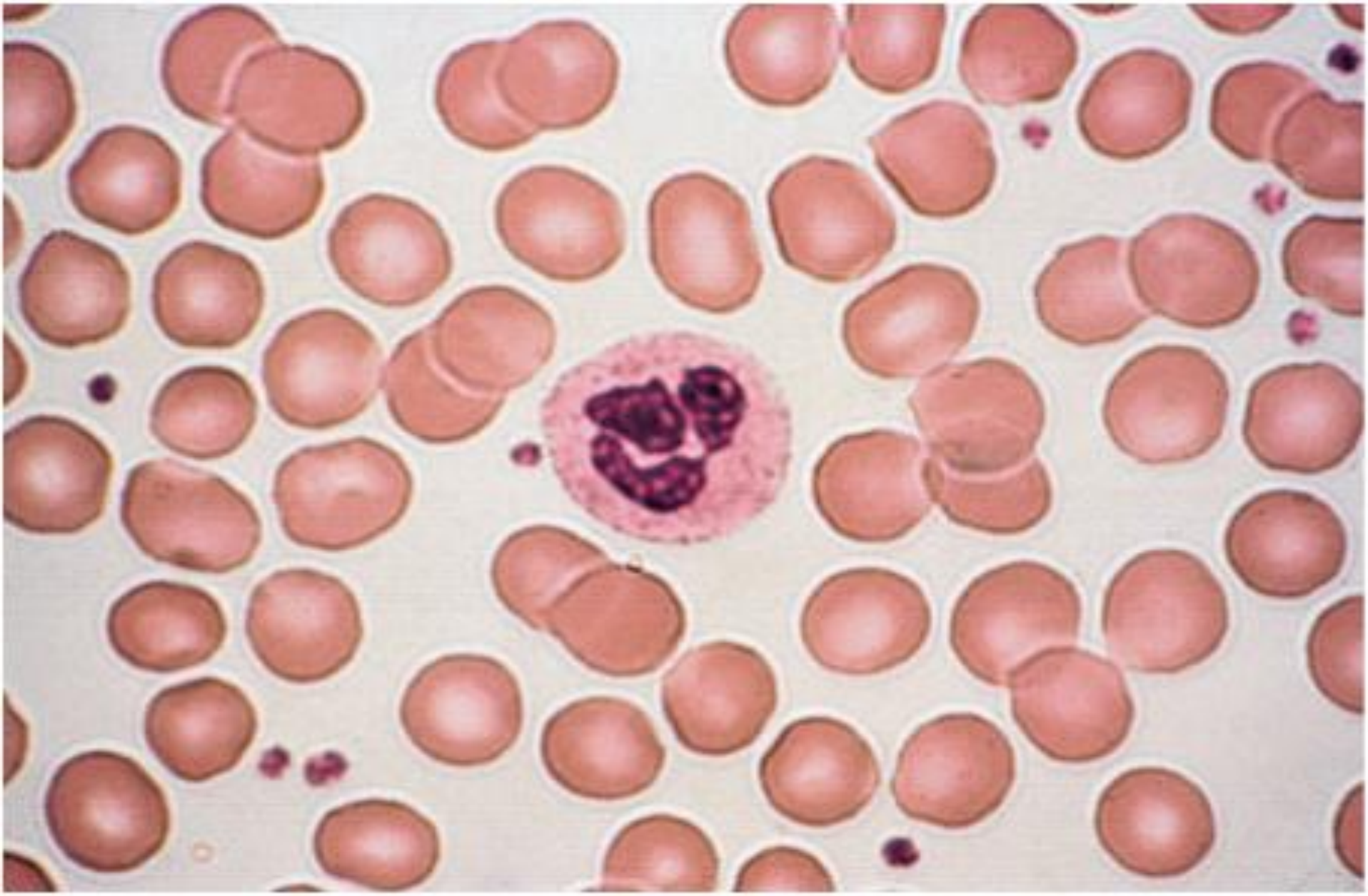
B- Red cell distribution width (RDW): is the measurement of variability of red cell volume or size (anisocytosis). RDW can be reported statistically as coefficient of variation (CV) and/or standard deviation (SD), RDW-CV and/or RDW-SD, respectively.

- It aids in distinguishing between iron deficiency anemia (elevated RDW, low MCV) and thalassemia (normal RDW, low MCV); however, definitive tests are required.
- It can also help distinguish between megaloblastic anemia such as folate or vitamin B12 deficiency anemia (elevated RDW, high MCV) and other causes of macrocytosis (often normal RDW, high MCV).

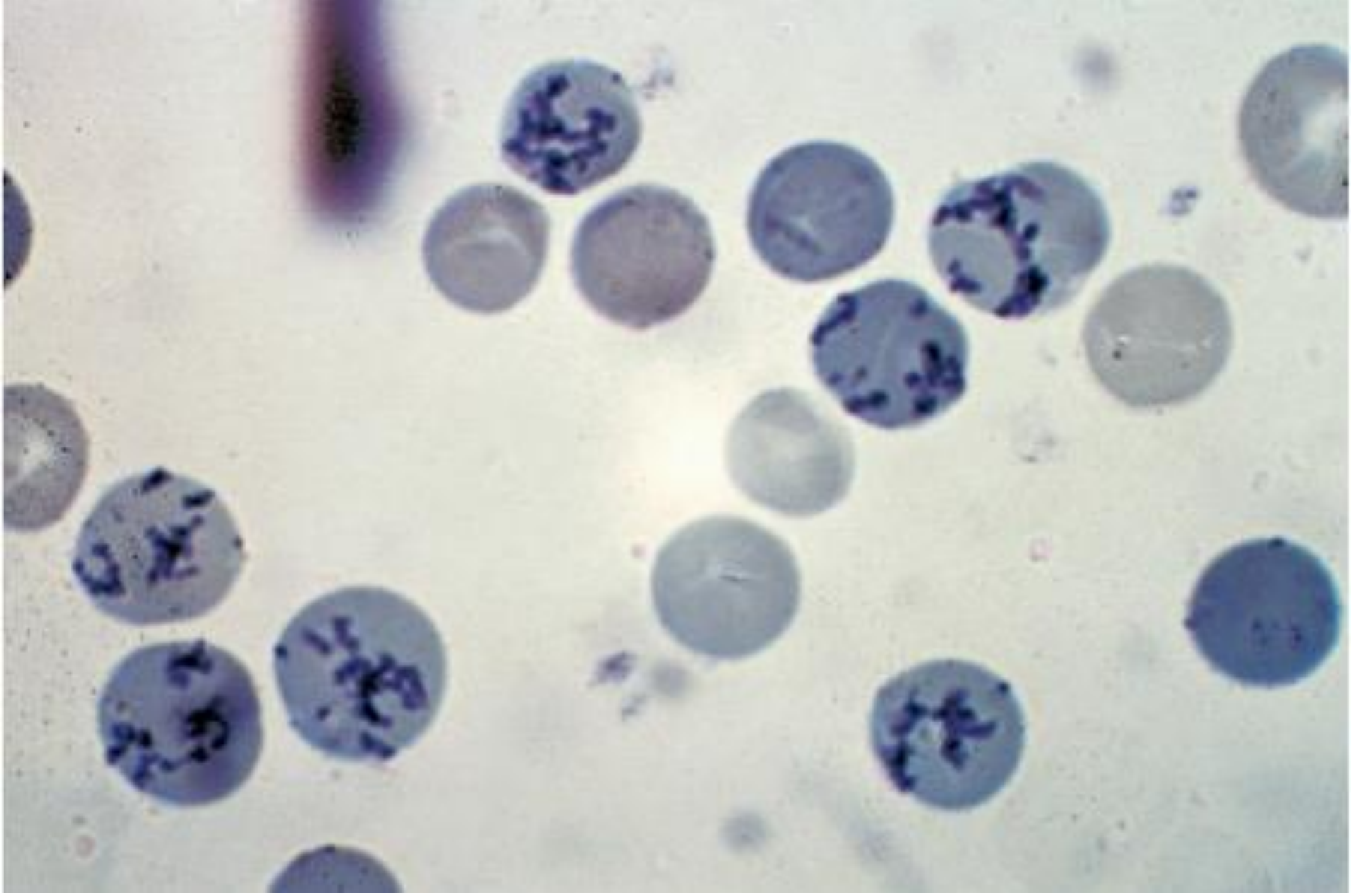
C- The reticulocyte count: allows the critical distinction between anemia arising from a primary failure of red cell production (reticulocyte count not elevated) and anemia resulting from increased red cell destruction or bleeding (reticulocyte count more than 2%).

2- Peripheral Blood Smear: it is complementary to the red cell indices, it may reveals variations in cell size (anisocytosis) and shape (poikilocytosis) and polychromasia (increase reticulocytes). The appearance of nucleated red cells, Howell-Jolly bodies, target cells, sickle cells, and others may provide clues to specific disorders. In addition, examination of myeloid cells and platelets may also be helpful. Hypersegmented neutrophils and large platelets support the diagnosis of megaloblastic anemia, and the presence of immature blast forms may be diagnostic of leukemia.

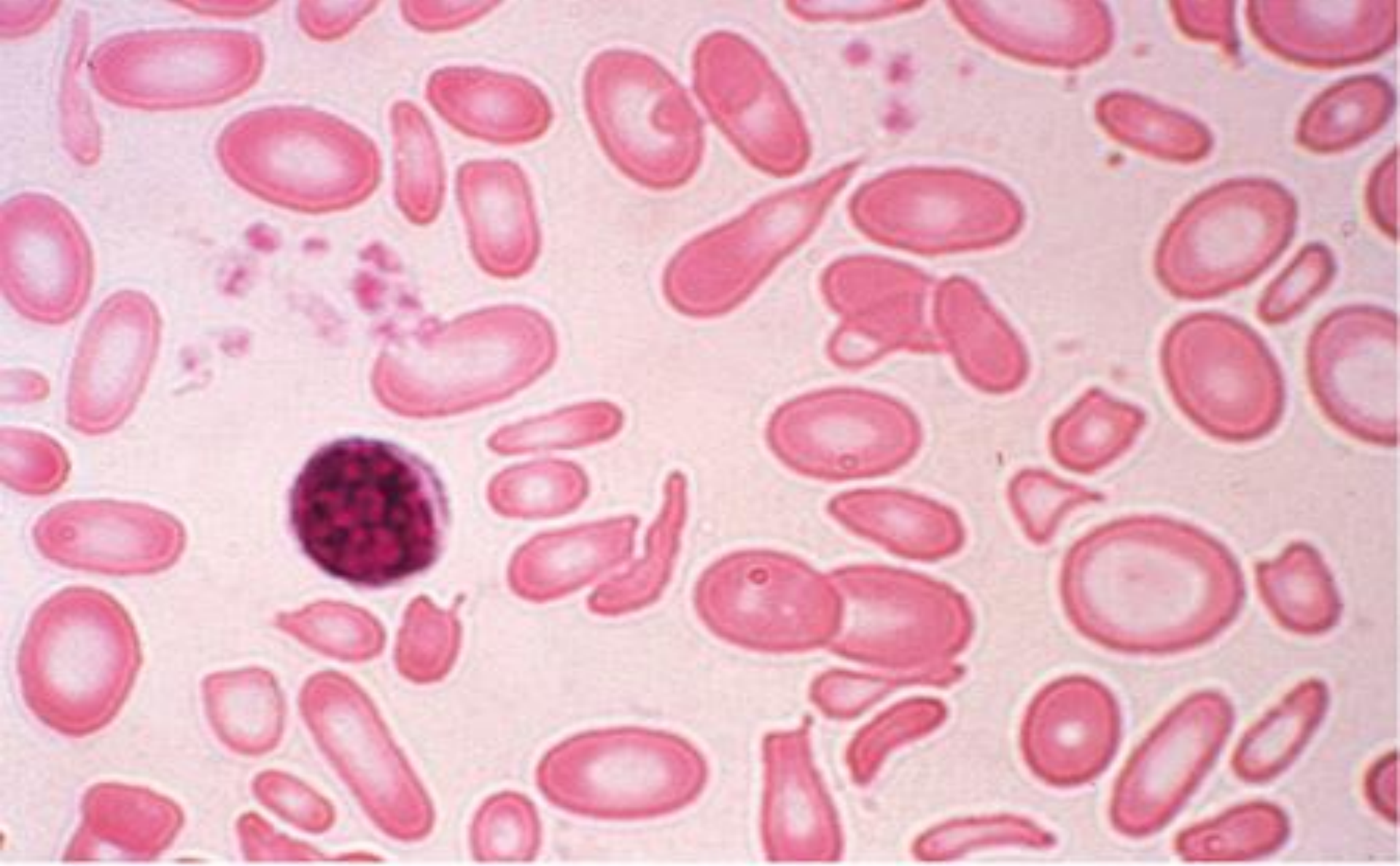
A normal peripheral blood smear indicates the appropriate appearance of red blood cells, with a zone of central pallor occupying about 1/3 of the size of the RBC.



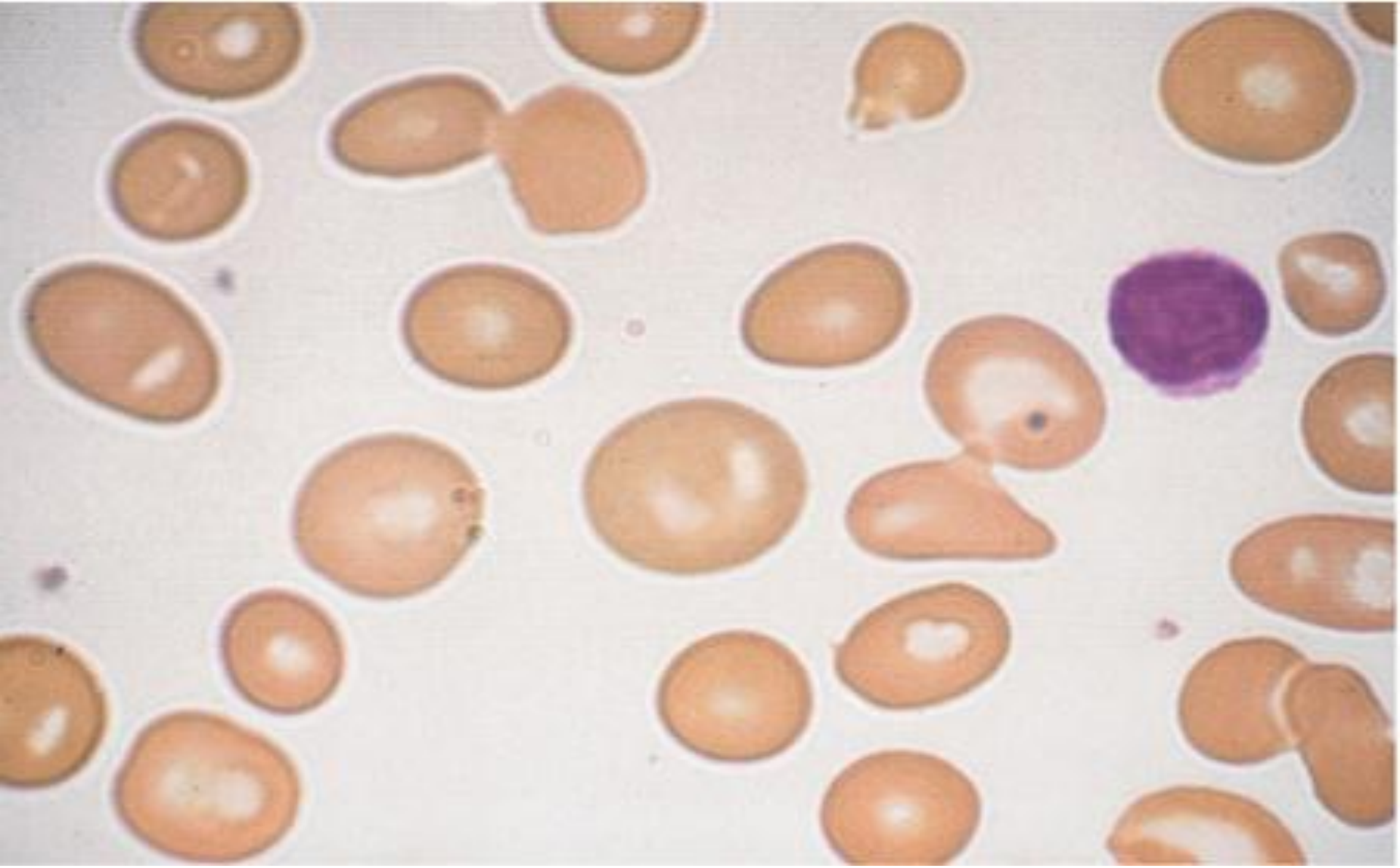
Normal blood smear (Wright's stain). High-power field showing normal red cells, a neutrophil, and a few platelets.



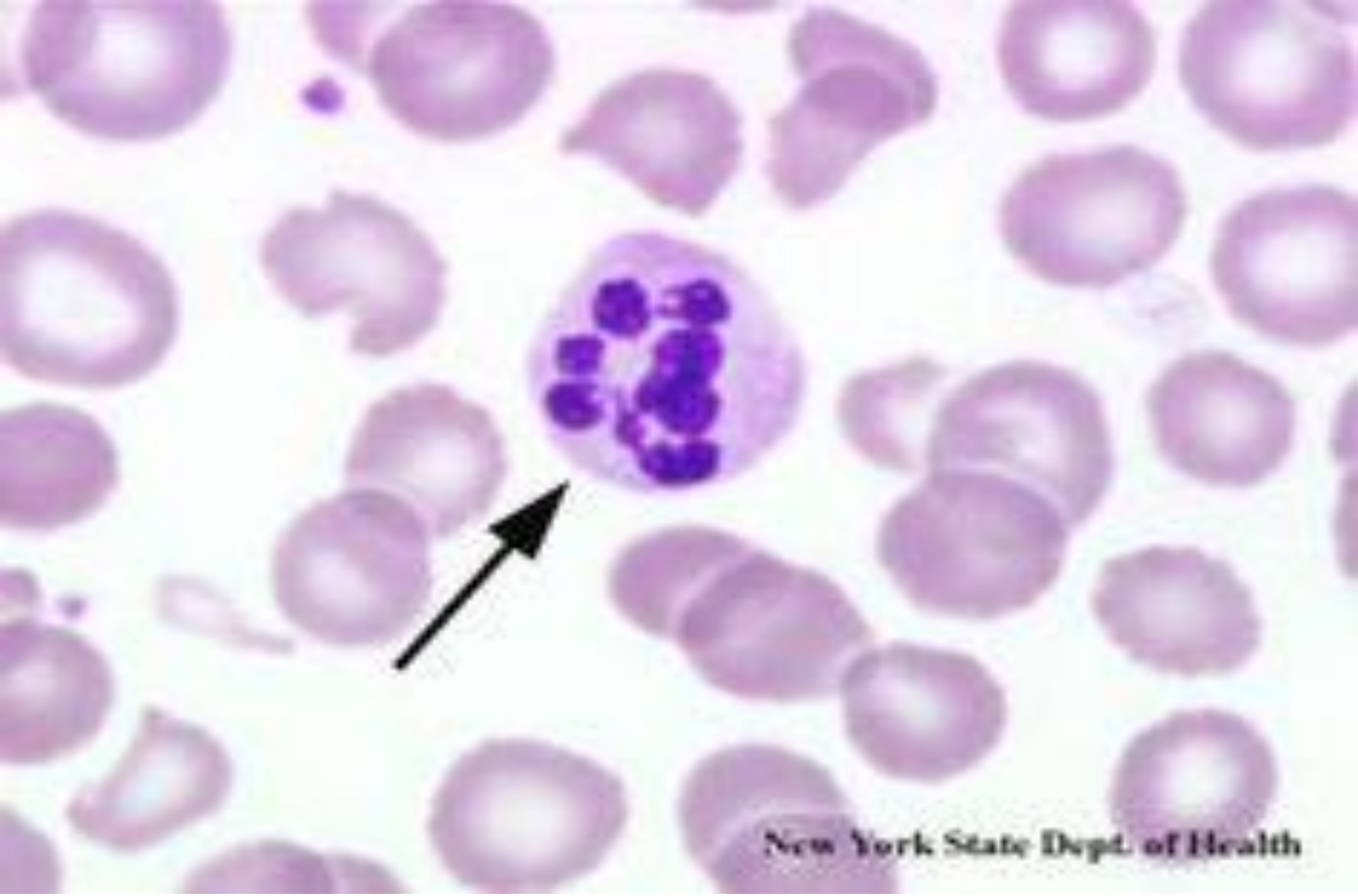
Reticulocytes. Methylene blue stain demonstrates residual RNA in newly made red cells.



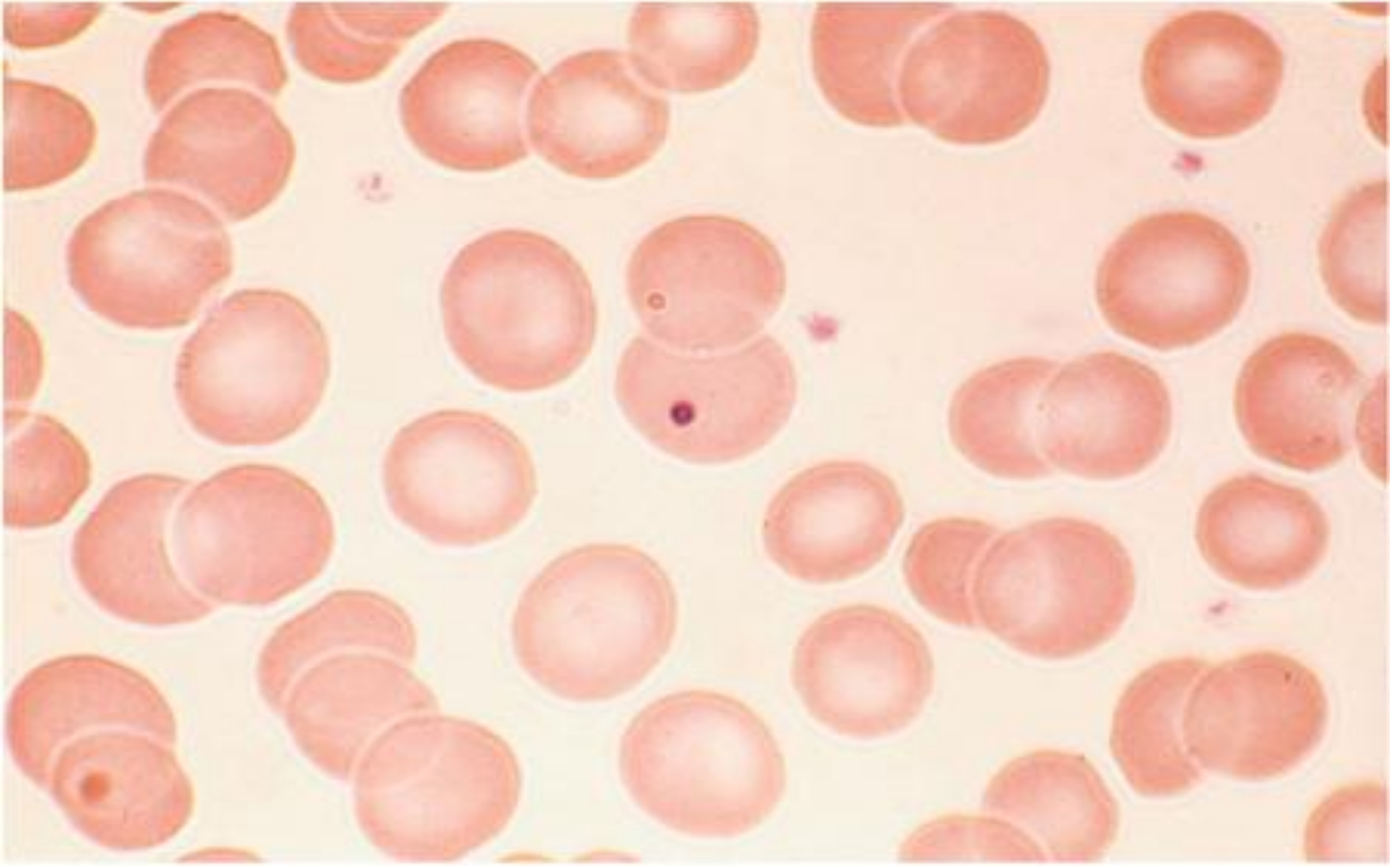
Severe iron-deficiency anemia. Microcytic and hypochromic red cells smaller than the nucleus of a lymphocyte associated with marked variation in size (anisocytosis) and shape (poikilocytosis).



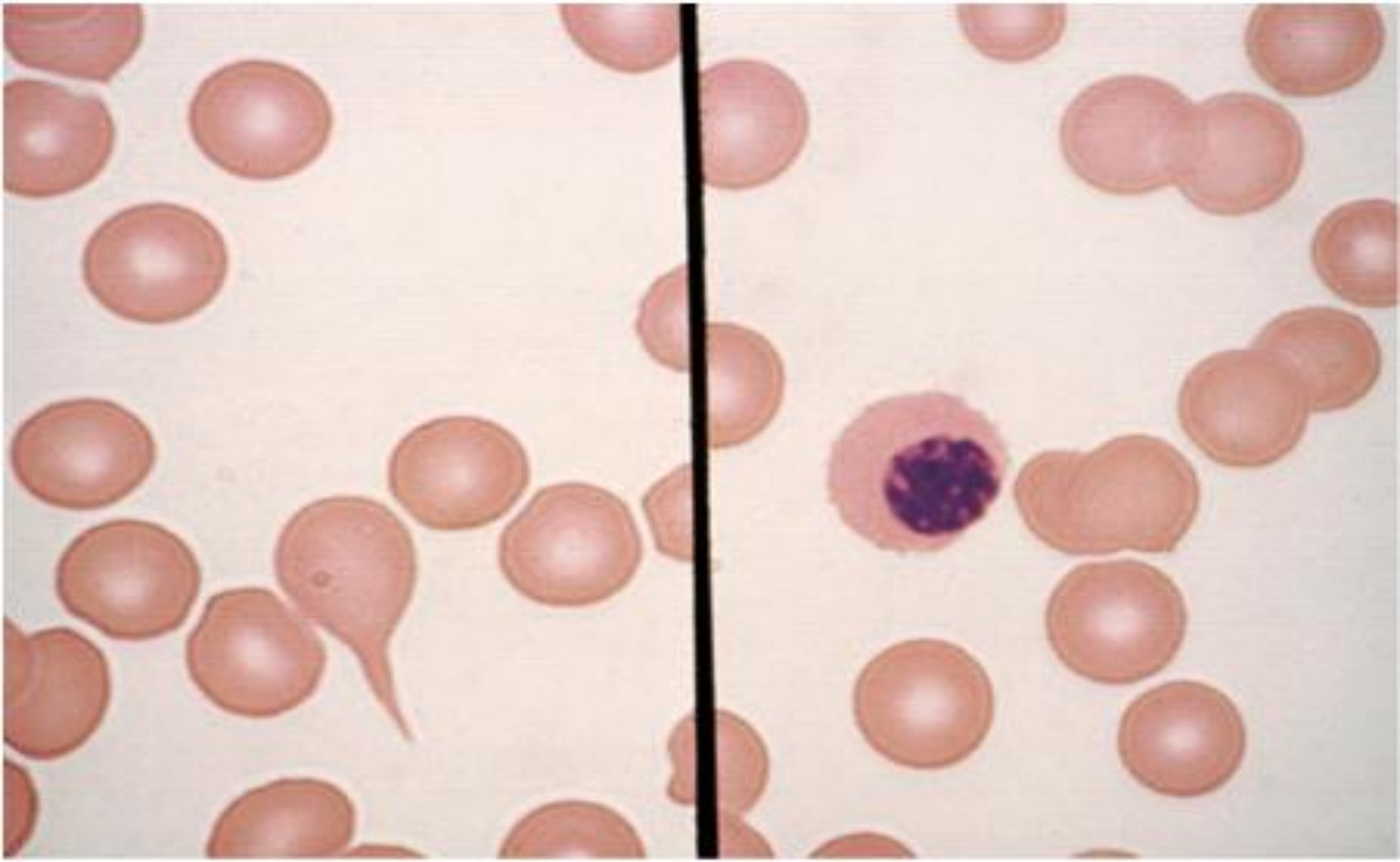
Macrocytosis. Red cells are larger than a small lymphocyte and well hemoglobinized. Often macrocytes are oval-shaped (macroovalocytes).



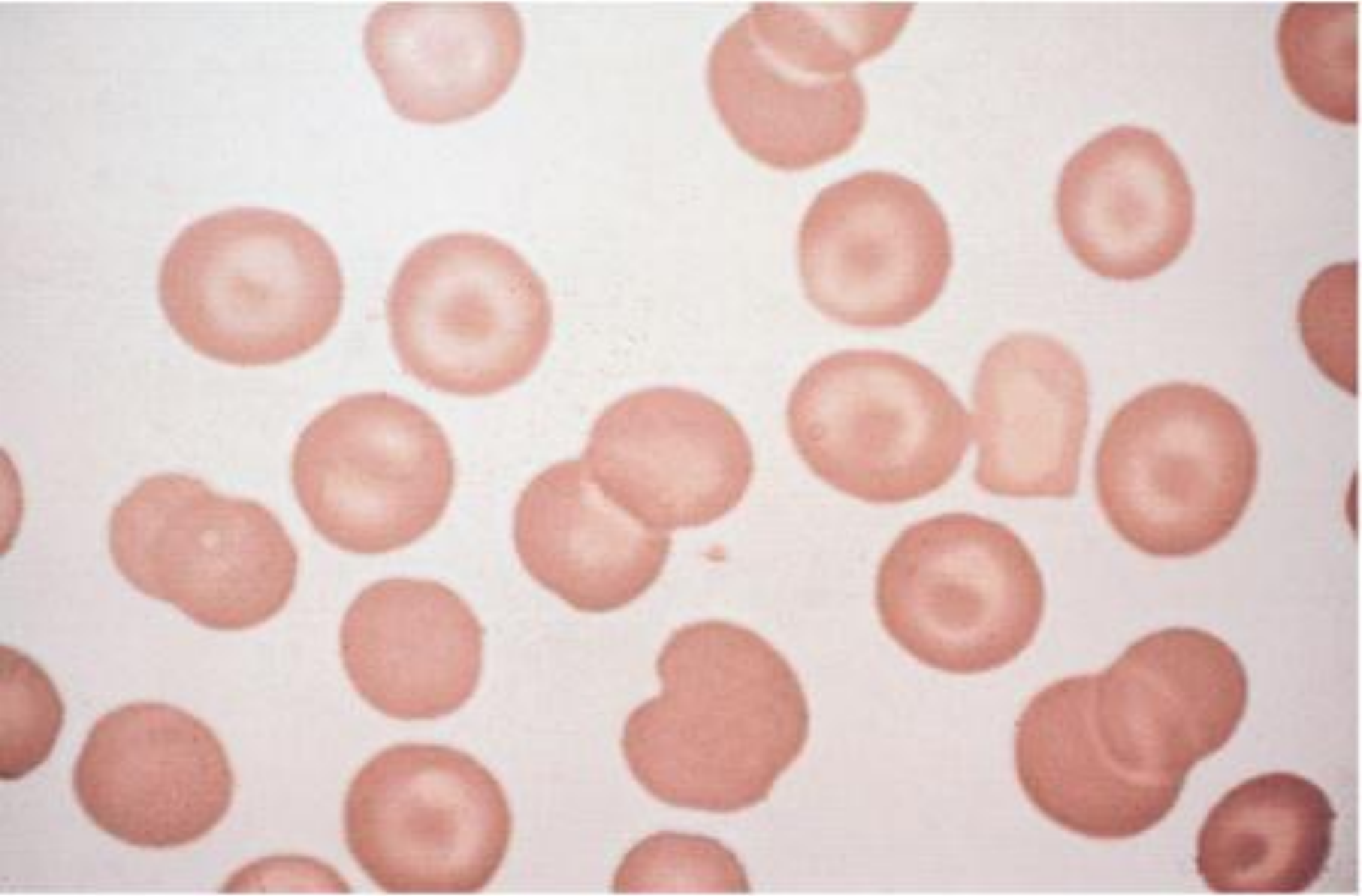
Peripheral blood smear showing hypersegmented neutrophils, characteristic of megaloblastic anemia.



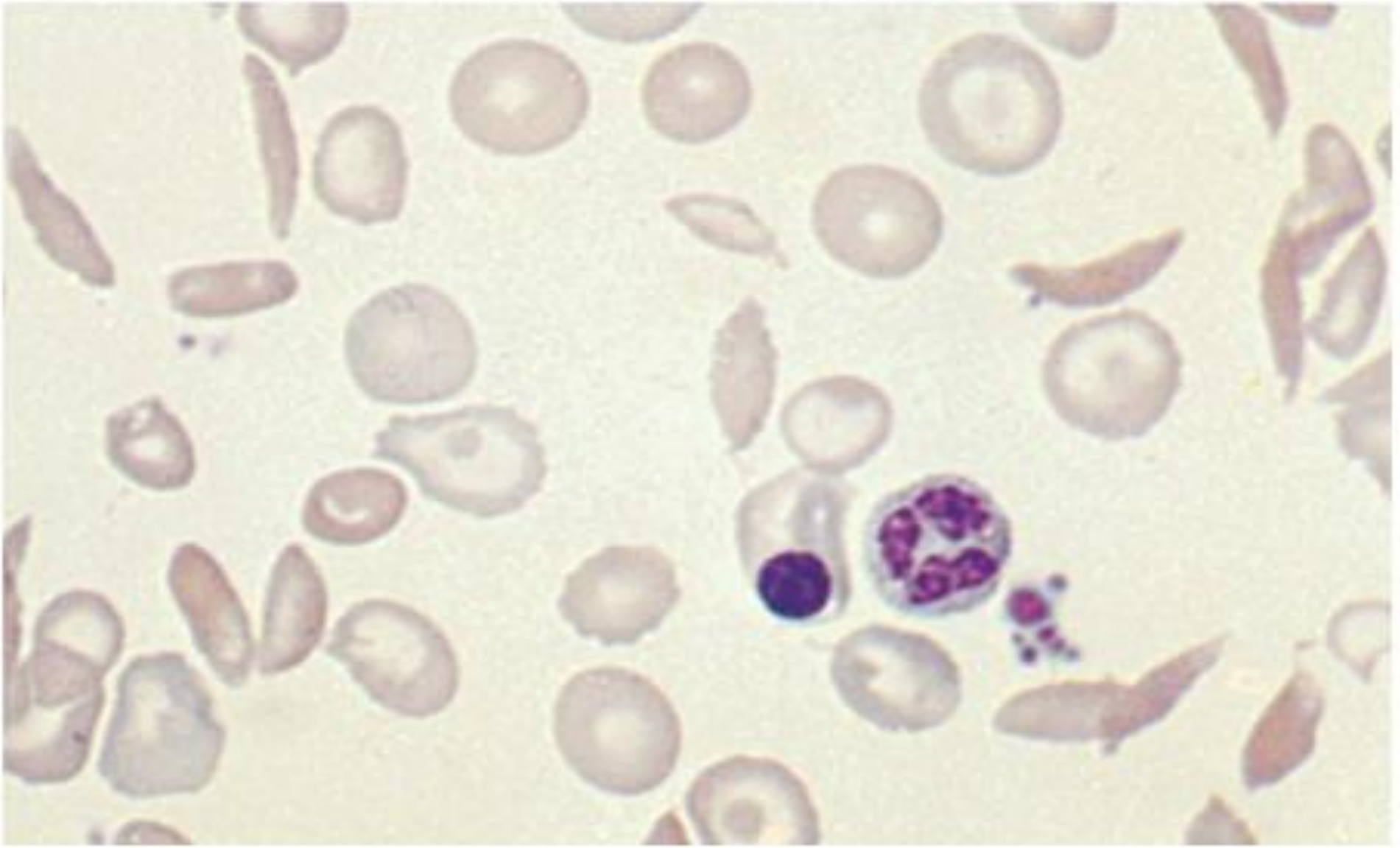
Howell-Jolly bodies. In the absence of a functional spleen, nuclear remnants are not culled from the red cells and remain as small homogeneously staining blue inclusions on Wright stain.



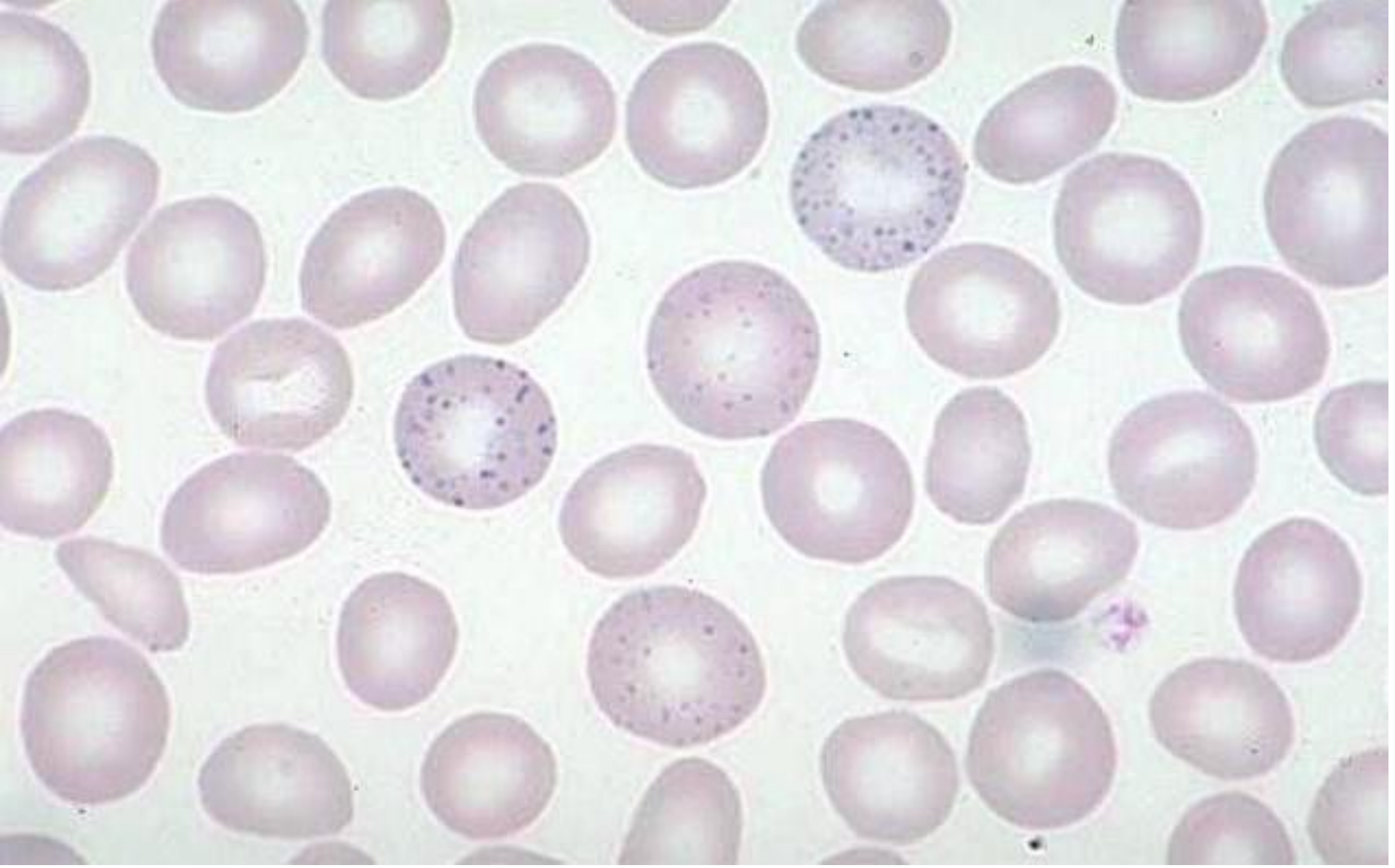
Red cell changes in myelofibrosis. The left panel shows a teardrop-shaped cell. The right panel shows a nucleated red cell. These forms are seen in myelofibrosis with extramedullary hematopoiesis.



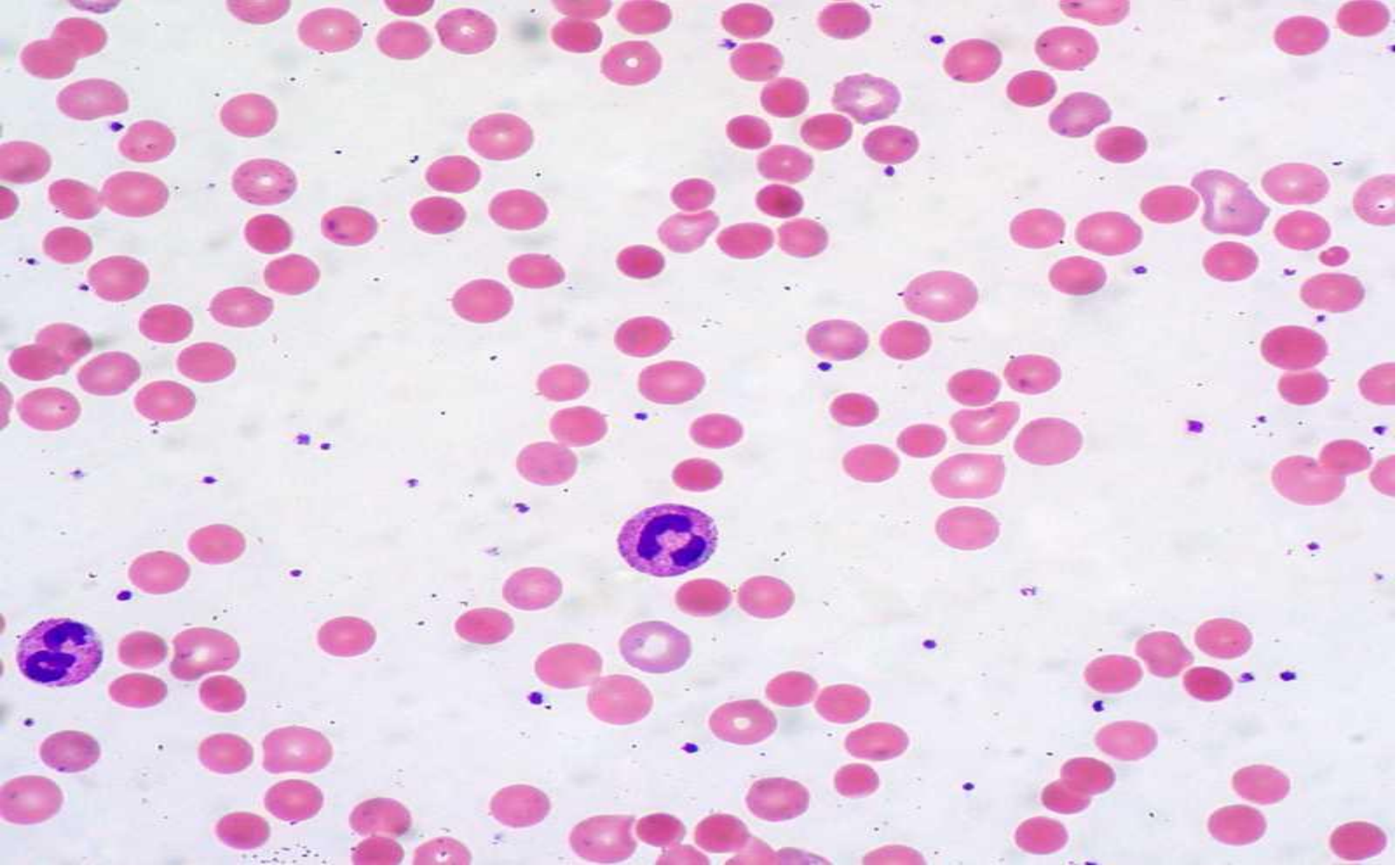
Target cells. Target cells have a bull's-eye appearance and are seen in thalassemia and in liver disease.



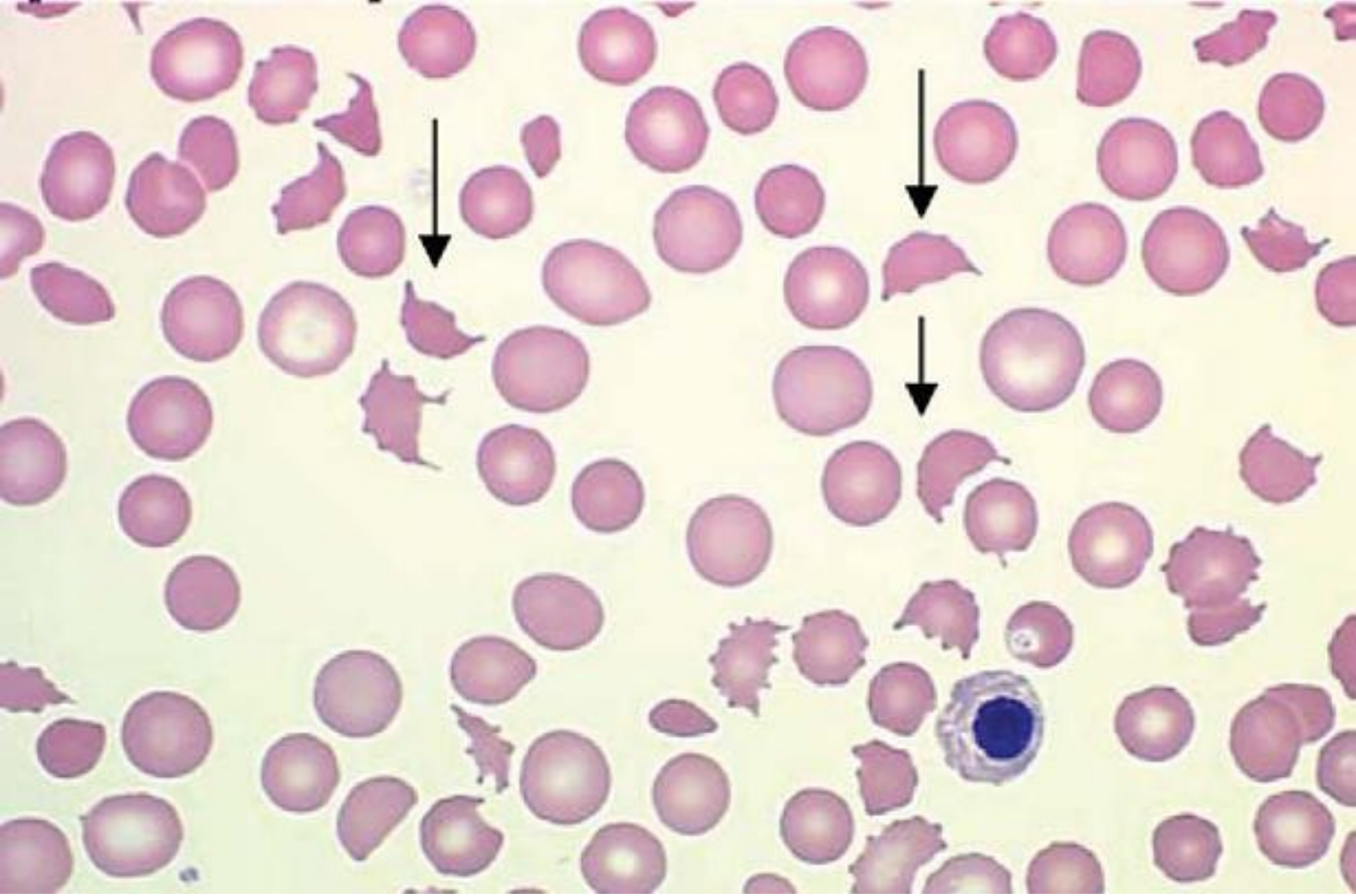
Sickle cell anemia. The elongated and crescent-shaped red blood cells seen on this smear represent circulating irreversibly sickled cells. Target cells and a nucleated red blood cell are also seen.



Basophilic stippling: refers to erythrocytes display small dots at the periphery (visualized ribosomal aggregates) seen in lead poisoning and thalassemia.



Spherocytosis: the red blood cells (RBCs) are sphere-shaped, rather than bi-concave disk shaped. Spherocytes are found in hereditary spherocytosis and autoimmune hemolytic anemia



Microangiopathic hemolytic anemia: A nucleated red blood cell is seen with the fragmented red cells and spherocytes.

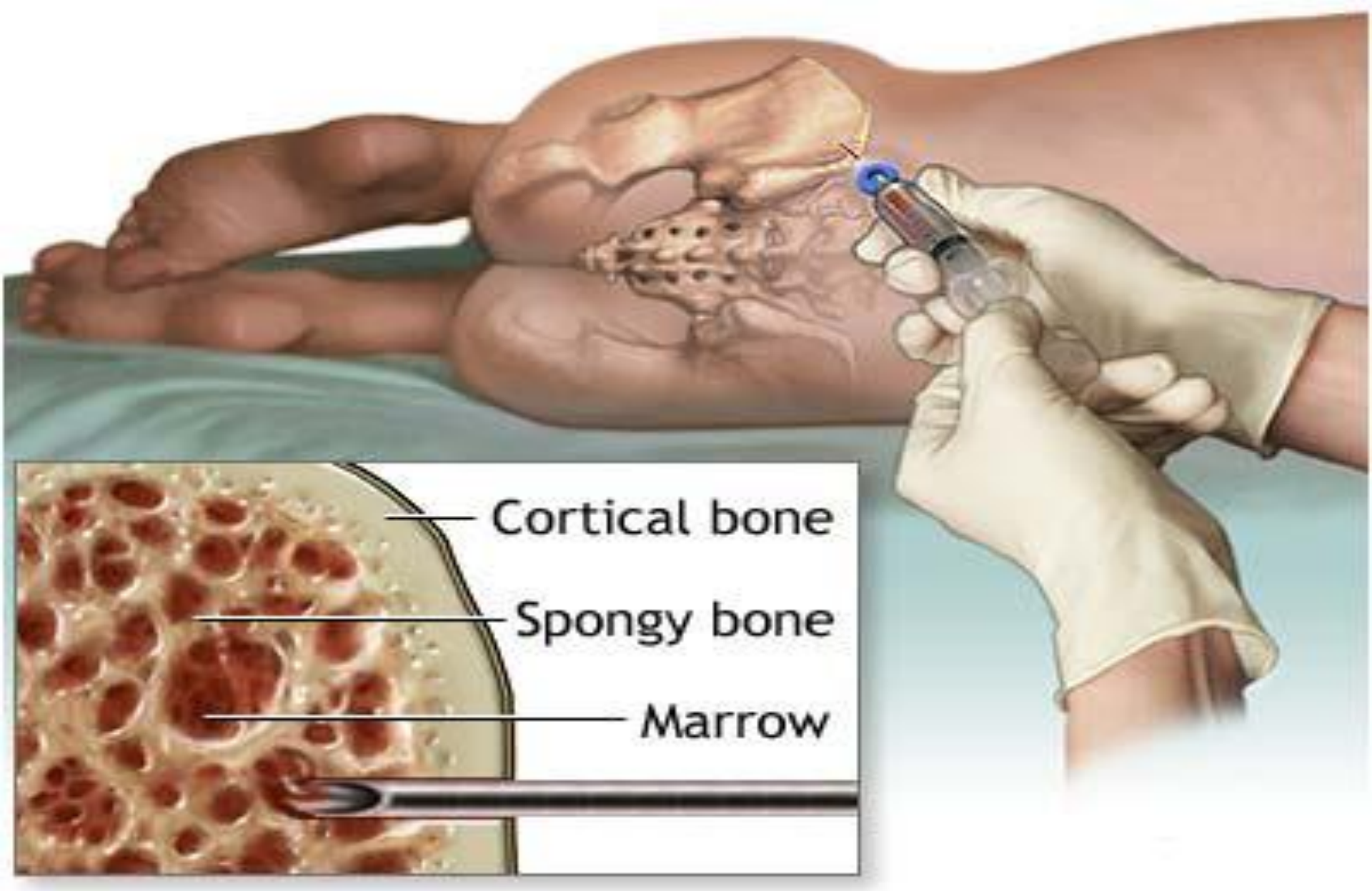
3- Other blood tests for:

- Iron: serum iron, the TIBC, the percent transferrin saturation and serum ferritin.
- Vitamin B12 and folate serum levels.
- Indirect bilirubin.
- Direct Coomb's test.
- Haptoglobin levle.
- Osmotic fragility test.
- Hemoglobin electrophoresis.
- RBC enzyme studies

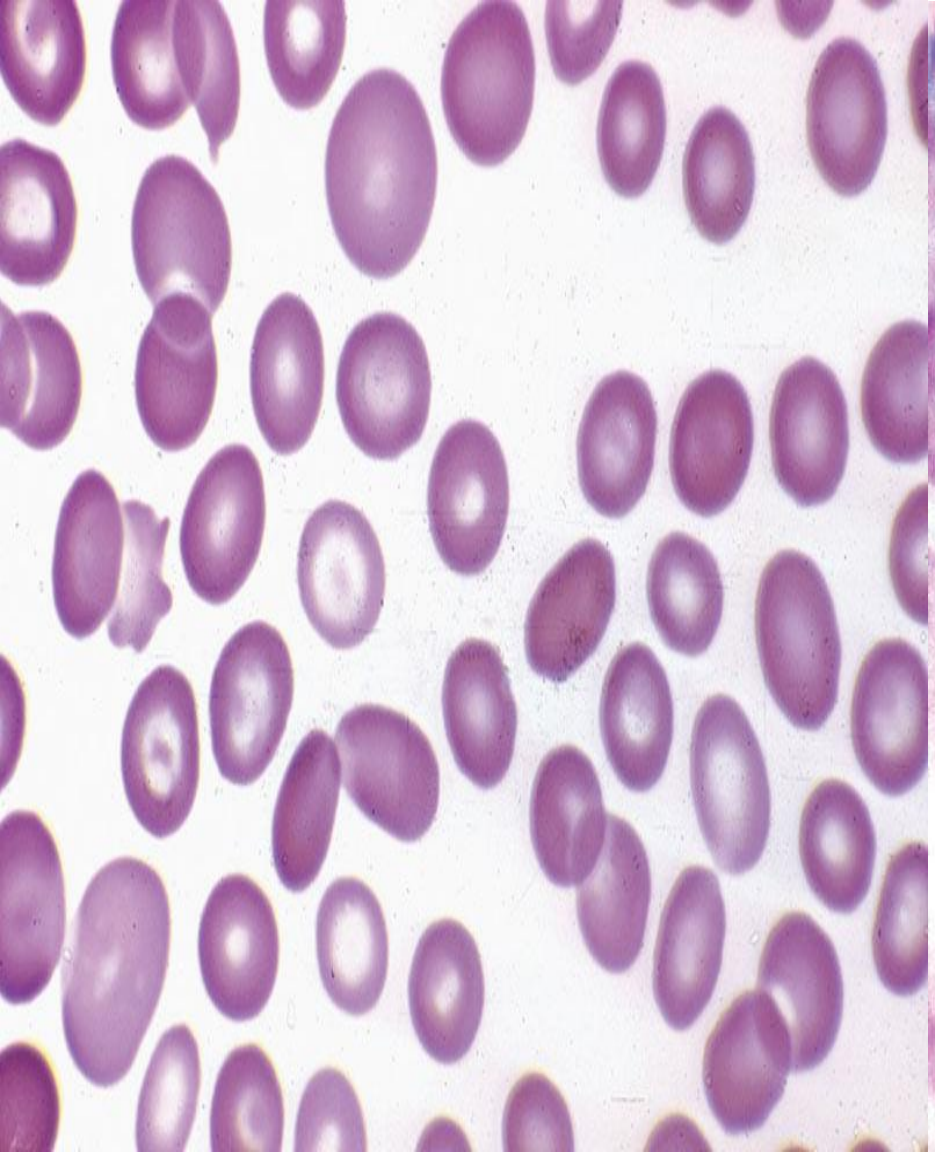
4- Occult blood in stool.

5- Bone Marrow Examination:

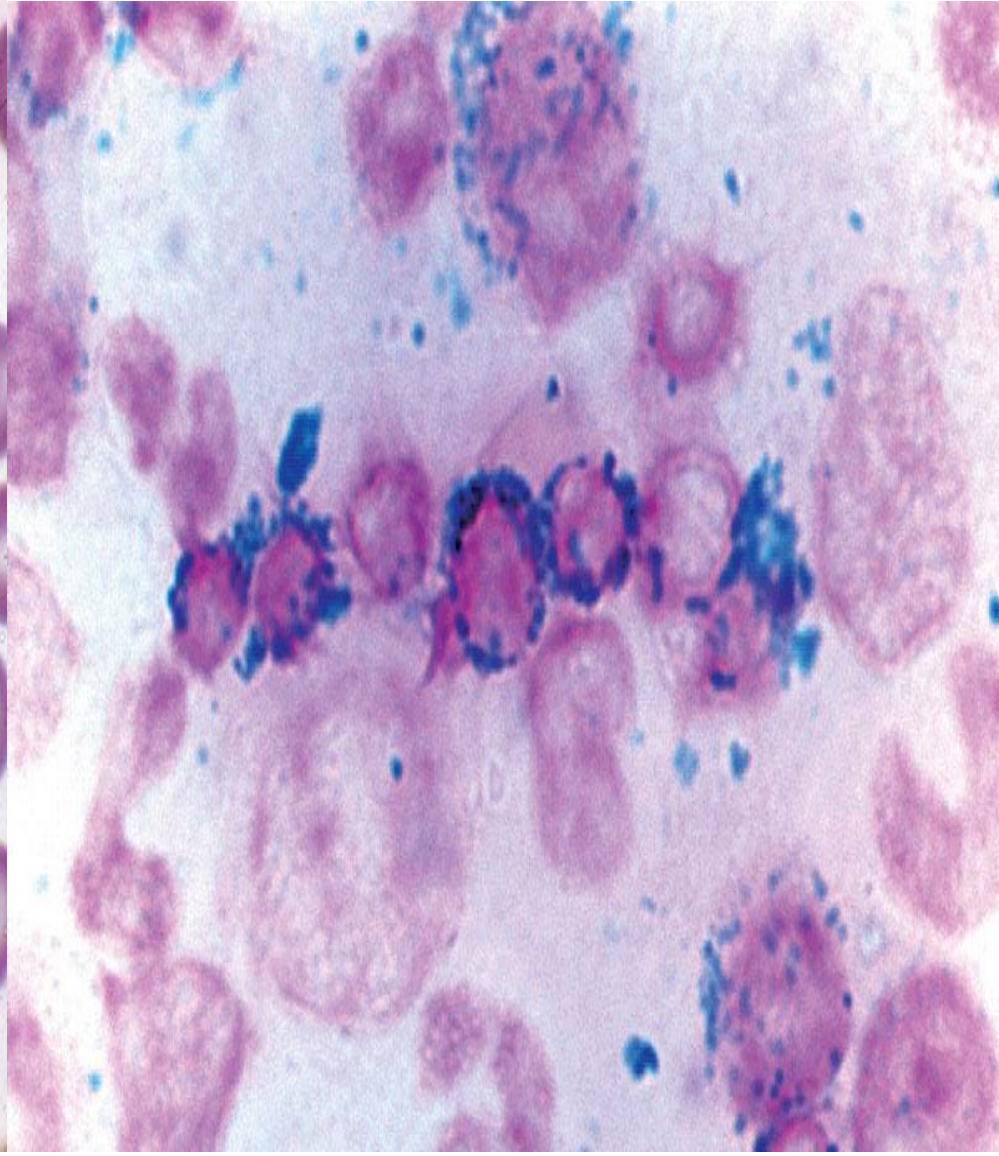
Marrow examination can diagnose primary marrow disorders such as myelofibrosis, a red cell maturation defect, or an infiltrative disease. Marrow biopsy can be stained for the presence of iron stores.



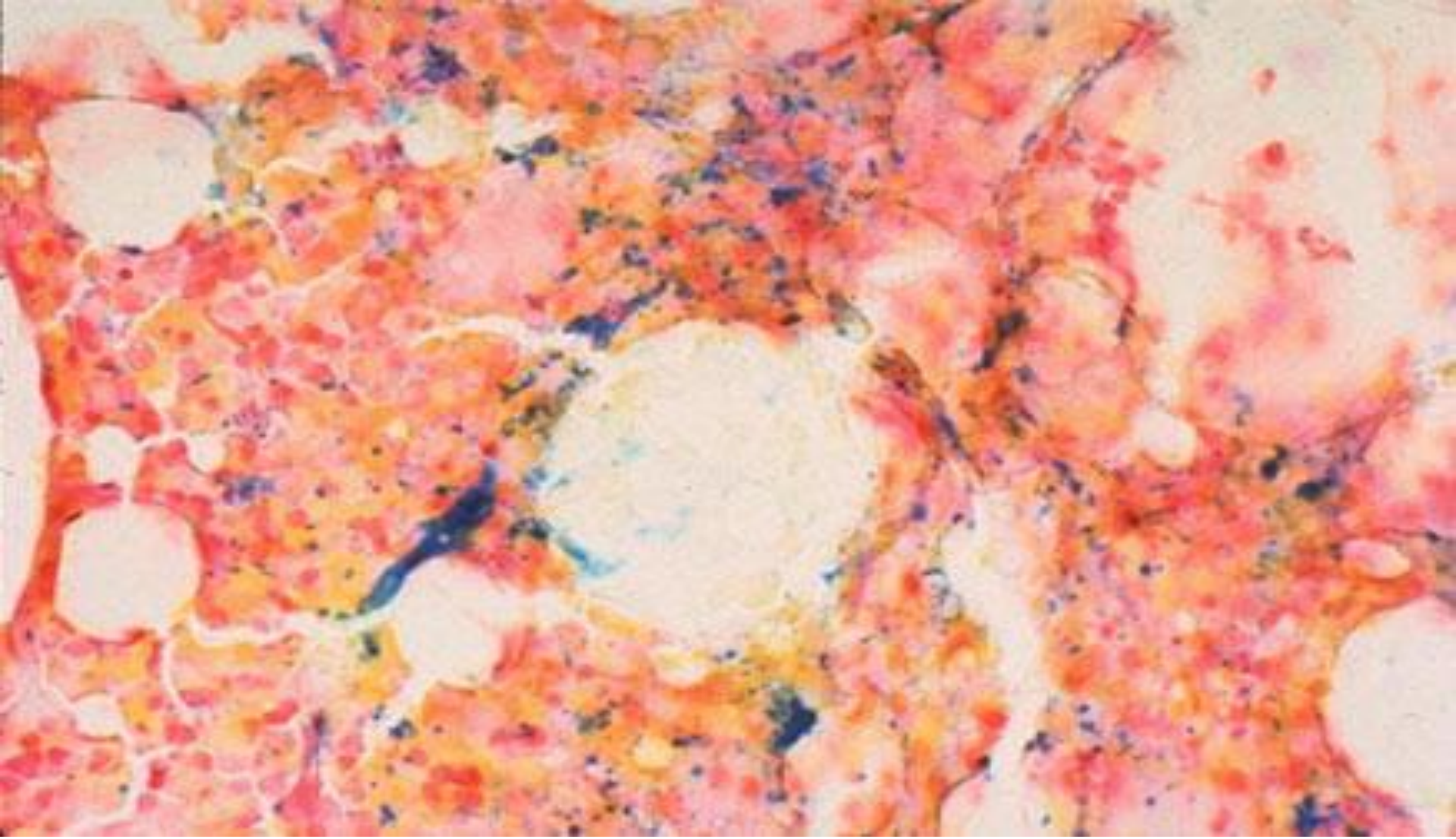
Bone marrow aspiration and trephine biopsy are usually performed on the back of the hip bone on posterior iliac crest.



Refractory anaemia with ring sideroblasts. Blood smear with dimorphic red blood cells and macrocytes



Refractory anaemia with ring sideroblasts. Iron stain of bone marrow aspirate showing numerous ring sideroblasts



Prussian blue stain for iron in a normal bone marrow (the blue staining material is iron within the reticuloendothelial cells in bone marrow). Iron deficiency anemia will develop following depletion of iron stores from the bone marrow.

Differential diagnosis of anemia according to MCV with low reticulocyte count

❖ **Microcytic Anemia (MCV < 78 fl)**

- Iron deficiency
- Thalassemia minor
- Anemia of chronic disease
- Sideroblastic anemia
- Lead poisoning

❖ **Normocytic Anemia (MCV 78-98 fl)**

- Early iron deficiency
- Aplastic anemia
- Endocrinopathies
- Anemia of chronic disease
- Anemia of renal failure
- Mixed nutritional deficiency

❖ **Macrocytic Anemia (MCV > 98 fl)**

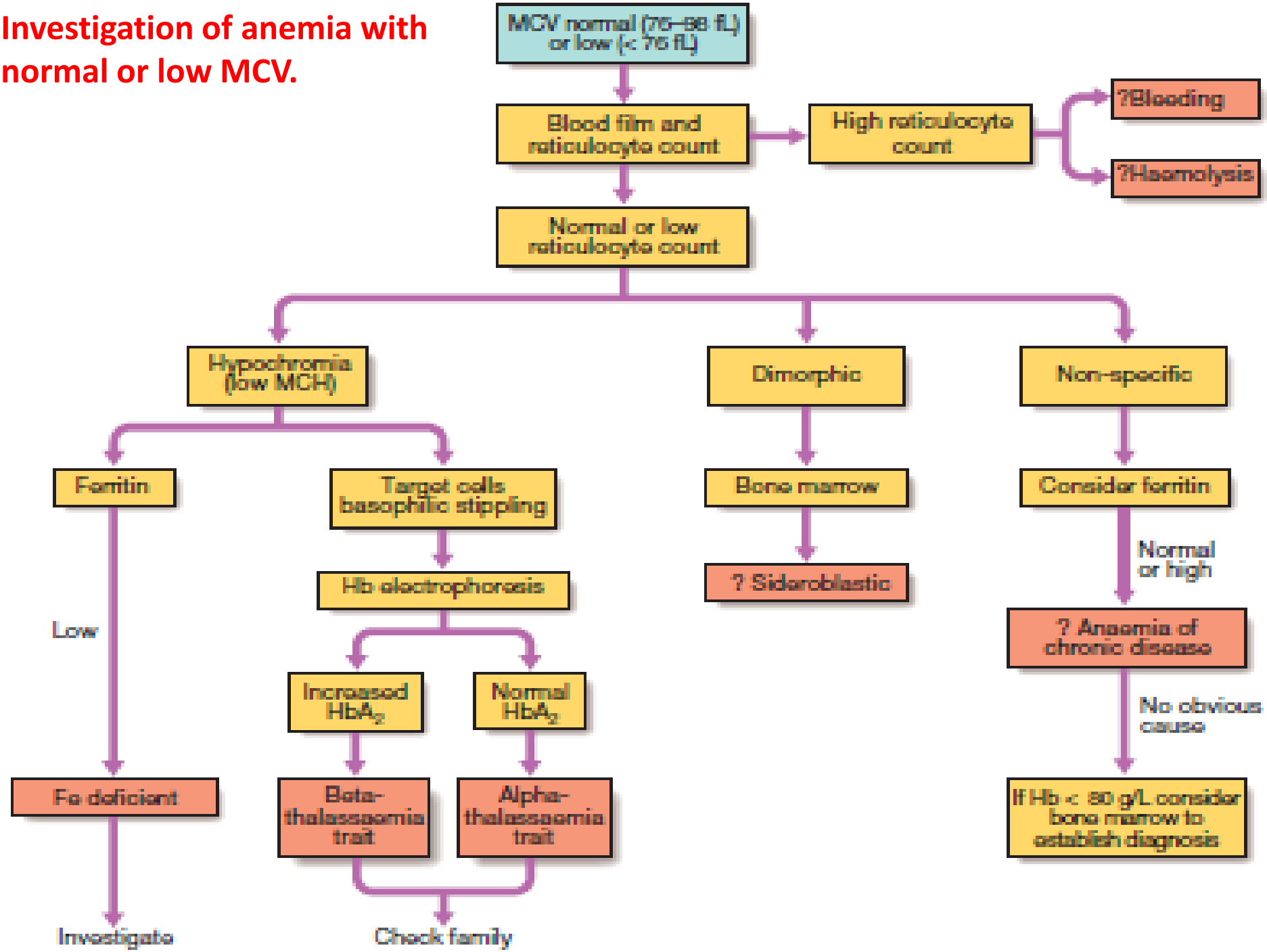
Megaloblastic Anemias

- Folate deficiency
- Vitamin B12 deficiency
- Drug-induced megaloblastic anemia
- Myelodysplasia

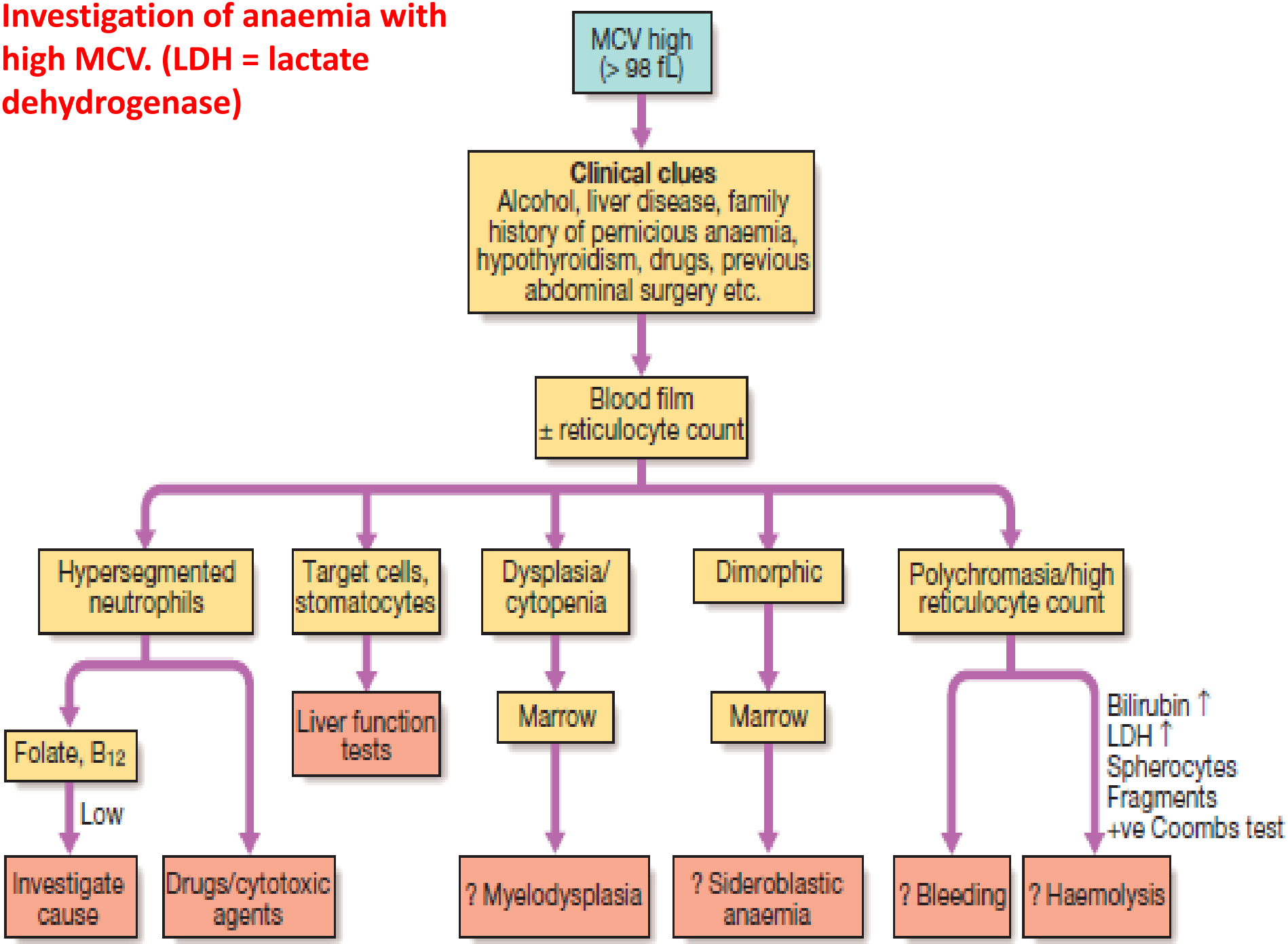
Nonmegaloblastic Macrocytosis

- Liver disease
- Hypothyroidism
- Reticulocytosis

Investigation of anemia with normal or low MCV.



Investigation of anaemia with high MCV. (LDH = lactate dehydrogenase)



Thanks