CBC

Kenneth Alonso, MD, FACP

Hematology instruments

- Hematology instruments measure the numbers of red and white cells, platelets, hemoglobin, and the size of red cells and platelets.
- Hematocrit, MCH, MCHC are calculated.
- White cells are differentiated by size and electrical activity.
- Stains are infrequently applied.
- A Giemsa-Wright stained peripheral smear must be examined microscopically to evaluate cellular morphology.
- Reticulocytes are measured separately.

Red cell indices

- MCV refers to the average size of the RBCs constituting the sample.
- The reference interval for adults is typically 80 - 100 fL.
- Mean cell hemoglobin (MCH) refers to the average weight of hemoglobin in the RBCs in the sample.
- The reference interval for adults is typically 26 - 32 pg.
- Mean cell hemoglobin concentration (MCHC) refers to the average concentration of hemoglobin in the RBCs contained within the sample
- Reference interval for adults is typically 32 - 36 g/dL.

Red cell distribution width

- RDW reflects the variability in the size of the red blood cells.
- The reference range for RDW is 11.5 to 14.5 percent.
- A wide RDW suggests the presence of two red cell populations.

Hemoglobin as screening tool

- The incidence of previously undetected hemoglobin abnormalities in women ranges from 6-13%.
- The incidence of previously undetected hemoglobin abnormalities in men rises to 6% after age 60.
- The WHO defines anemia as a hemoglobin <13.0 g/dl in men; 12.0 g/dl in women.

Diagnostic clues

- Low MCV (microcytic)
- Iron deficiency
- Lead poisoning
- Thalassemia
- Normal MCV (normocytic)
- Sudden blood loss
- Kidney failure
- Hemolytic anemia
- Nutritional deficiencies
- Anemia of chronic disease
- Rheumatoid arthritis
- Giant cell arteritis

Diagnostic clues

- High MCV (macrocytic)
- Vitamin B12 deficiency
- Folate deficiency Liver disease
- Alcoholism
- Hypothyrodisim
- Medications such as chemotherapy drugs and retroviral therapies for HIV

Diagnostic clues

- High RDW and low MCV (microcytic):
- Iron deficiency anemia
- Sickle cell anemia
- High RDW and normal MCV (normocytic):
- Iron deficiency anemia
- Combined anemias
- Hemorrhage (a few days post event)
- Hemoglobin variants

Diagnostic clues

- High RDW and high MCV (macrocytic):
- Vitamin B12 deficiency
- Folate deficiency
- Cold agglutinin disease
- Myelodysplastic syndrome
- Immune hemolytic anemia

Diagnostic clues

- Normal RDW and high MCV:
- Liver disease (chronic)
- Aplastic anemia
- Alcohol-related
- Normal RDW and low MCV:
- Anemia of chronic disease
- Some types of thalassemia
- Some abnormal hemoglobins

Diagnostic clues

- Low MCHC (hypochromic)
- Iron deficiency anemia
- High MCHC (hyperchromic)
- Autoimmune hemolytic anemia
- Hereditary spherocytosis

Diagnostic clues

- Low MPV with low platelet count
- Decreased marrow production
- Low MPV with normal platelet count
- Renal disease
- Low MPV with high platelet count
- Viral infection
- Leukemia

Diagnostic clues

- Low MPV with variable platelet count
- Viral infection
- Heparin
- Rapid clearance by the spleen
- Autoimmune hemolysis
- Inflammatory bowel disease
- Rheumatoid arthritis
- Systemic lupus erythematosis

Diagnostic clues

- High MPV with low platelet count
- Platelet destruction
- Immune thrombocytopenia
- Pre-eclampsia
- High MPV with normal platelet count
- Hyperthyroidism
- Vitamin D deficiency
- Cancer
- CML
- High MPV with elevated platelet count
- Increased marrow production

Acute anemia

- Acute anemia usually results from blood loss or intravascular hemolysis.
- Intravascular hemolysis generally follows transfusion with (usually ABO) incompatible blood. There is release of free hemoglobin. There may be a sense of doom, acute back pain, free hemoglobin in the plasma and urine, and renal failure. The transfusion must be stopped. Saline diuresis is begun to limit precipitation of hemoglobin in renal tubules. Pressors may be required; heparinization is begun if DIC is present.

Acute anemia

- Hypovolemia dominates the clinical picture in acute blood loss. Hematocrit and hemoglobin levels do not reflect the volume of blood lost.
- With acute loss of 10–15% of the total blood volume, hypotension and diminished organ perfusion are present. Peripheral vasoconstriction and redistribution of organ blood flow are present.
- With acute loss of >30% of the blood volume is lost suddenly (>2.0-3.0 g/dL hemoglobin lost), usual physiologic responses are impaired. Postural hypotension and tachycardia are evident.

Acute anemia

- Shock with confusion, dyspnea, diaphoresis, hypotension, and tachycardia predominate if the volume of blood lost acutely is >40%. Immediate volume replacement is indicated.

Autoimmune hemolytic anemia

- 50% have complement fixing IgG antibodies reactive at 37C. Often due to drugs such as penicillins or cephalosporins or quinidine that bind to cell surface.
- α-methyldopa induces production of antibodies to red cell antigens, principally Rh type.
- Occasionally antibodies are of IgA type.
- Direct Coombs positive.
- Up to 30% associated with IgM antibodies reactive below 37C (usually 0-4C). May follow infection.
- IgG antibodies to the P blood group are reactive below 37C as well. May follow infection.

Chronic anemia

- RDW is the mean of distribution of red cell sizes and is an indicator of the chronic nature of the anemia. A wide RDW suggests the presence of two red cell populations.
- The usual cause of chronic anemia is uncompensated blood loss. Menstruation, gastrointestinal bleeding, or bleeding in the urinary tract must also be explored.
- In elderly patients this may represent myelodysplastic syndrome. Bone marrow examination may be required for diagnosis.

Chronic anemia

- Fatigue and loss of stamina are prominent.
- Total blood volume is normal or increased in chronic anemia. Cardiac output is maintained. Redistribution of organ blood flow away from the skin, gastrointestinal tract, and kidney compensates for loss of Oxygen carrying capacity.

Chronic anemia

- The skin and mucous membranes may be pale if the hemoglobin is <8.0–10.0 g/dL (positive likelihood ratio of pallor of conjunctival rim, LR+, 16.7). If the palmar creases are lighter in color than the surrounding skin when the hand is hyperextended, the hemoglobin level is usually <8 g/dL (LR+, 8).
- In the younger patient, symptoms may not be present until the anemia is severe (hemoglobin of <7.0 g/dL).
- The bone marrow normally responds by increasing erythroid cell production.

Normochromic, normocytic anemia

- An MCV between 80-100 fl is seen in anemia related to acute blood loss.
- Generally there is an adequate reticulocyte response (>2.5%).
- An elevated LDH and a depressed haptoglobin level are diagnostic of hemolysis.
- A direct Coombs test to detect red cells coated with immunoglobulin as well as an indirect Coombs test to detect complement sensitivity may be required to evaluate hemolysis.

Normocytic, normochromic anemia

- Non-immune causes of hemolysis include pyruvate kinase deficiency, hereditary elliptocytosis, and hereditary spherocytosis. G6PD deficiency is commonly associated with hemoglobinopathy.
- If a chronic condition, consider anemia of chronic disease (iron sequestration), pure red cell aplasia, chronic renal insufficiency (erythropoietin loss), liver disease, and androgen deficiency.

Microcytic, hypochromic anemia

- 60 days are required for changes in hemoglobin levels to reflect uncompensated blood loss. Cell size, reflected in the MCV, is the first parameter to change.
- Iron deficiency is the most common cause of an MCV <80 fl. Low serum ferritin levels are diagnostic (positive likelihood ratio, LR+, 25-50).
- 20% of women are iron deficient.
- Search for source of bleeding loss. (Colonoscopy in the absence of symptoms, upper gastrointestinal endoscopy if colonoscopy negative even in women over 50 years of age.)

Microcytic, hypochromic anemia

- Hb <8 g/dL suggests a cause for anemia that is not that of chronic disease.
- If ferritin levels are normal but RDW >15%, anemia of chronic disease is likely.
- If ferritin levels are normal as is the RDW, the thalassemias must be considered. Target cells may be present.
- Lead intoxication (>10 µg/dL) and siderobalstic anemia are also causes of microcytic anemia.

Therapy of Iron deficiency anemia

- The intestine cannot absorb more than 50-60 mg/d of elemental Iron.
- An individual with a normally functioning marrow and appropriate erythropoietin stimulus should absorb 50 mg/d if receiving a daily oral dose of 200–300 mg of ferrous sulfate. This should double red cell production.
- 1 mg/d (men), 1.4 mg/d (women) normal iron need.

Therapy of Iron deficiency anemia

- Sustained treatment for a period of 6–12 months after correction of the anemia will be necessary to provide stores of at least 0.5–1.0 g of iron.
- The reticulocyte count should begin to increase within 4–7 days after initiation of therapy and peak at 1½ weeks. It may reach 15%.

Macrocytic anemia

- MCV >100 fl is associated with inadequate levels of either Folic Acid or Vitamin B_{12} or both.
- May be nutritional in origin: vegetarian diet, alcohol abuse. Common in older persons.
- May reflect malabsorption. May reflect liver disease. May be tapeworm.
- Methotrexate, zidovudine as other causes.
- May reflect autoimmune hypothyroidism. Anti-parietal cell antibody may be present.
- With elevated LDH, intravascular hemolysis.
- Any disorder associated with reticulocytosis will elevate measured MCV.

Macrocytic anemia

- Both folic acid and vitamin B_{12} levels should be determined in evaluating patients with elevated MCV. The assays are interdependent.
- (In cobalamin deficiency, the methylation of homocysteine to methionine is impaired. Methylation requires the methyl group of the folate intermediate, 5-methyl tetrahydrofolate. 5-MTHF enters the cell from the plasma and accumulates. It is the first step in the pathway that generates all other intracellular folate coenzymes. THF, the substrate on which all other intracellular folate intermediates depend, falls, impairing DNA synthesis, leading to megaloblastic change. Hypersegmented neutrophils found.)

Macrocytic anemia

- RBC folate determinations correlate with long term folate levels but offer little additional information. (Serum folate is elevated in B_{12} deficiency while intracellular folate is low.) Methylmalonic acid elevation compatible with B_{12} deficiency.
- Little need for Schilling test in view of low cost of vitamin B_{12} therapy.
- MCV >100 fl with normal folic acid and vitamin B_{12} levels may indicate pyridoxine deficiency. Bone marrow examination will be necessary to diagnose myelodysplastic syndrome.
- In the older patient, myelodysplastic syndrome should be considered.

Treatment of macrocytic anemias

- Replenishment of body stores of vitamin B12 should be complete with six 1000-mg IM injections of hydroxocobalamin given at 3- to 7-day intervals.
- There is no evidence that more frequent injections produce a better response in patients with neuropathy.
- For maintenance therapy, 1000 mg hydroxocobalamin IM once every 3 months is satisfactory. (Cyanocobalmin is not as well absorbed.)
- Oral doses of 5–15 mg folic acid daily are satisfactory to treat folic acid deficiency..

Hypoproliferative anemia

- Pure red cell aplasia is rare.
- Acquired acute transient hypoproliferative anemia in adults as well as children is usually caused by a viral infection, often parvovirus B19.
- Chronic acquired hypoproliferative anemia involving red blood cells is generally associated with thymoma and has an autoimmune basis. Reticulocytes are rare.
- Hypoproliferation may be associated with chronic renal disease as well as a chemotherapy related change.

Treatment of hypoproliferative anemias

- Endogenous erythropoietin levels are inappropriately low in the hypoproliferative anemias.
- Iron stores must be restored to obtain optimal effects from erythropoietin.
- Hemoglobin levels of 10–12 g/dL are usually reached within 4–6 weeks if iron levels are adequate.
- Once a target hemoglobin level is achieved, the erythropoietin dose can be decreased.

Treatment of hypoproliferative anemias

- >90% of those with chronic renal disease respond to erythropoietin therapy. However, only 60% of cancer patients respond to erythropoietin therapy.
- There is an increased risk of vascular thrombosis with erythropoietin therapy.
- A fall in hemoglobin level occurring in the face of erythropoietin therapy usually signifies the development of an infection or iron depletion.

Treatment of hypoproliferative anemias

- Aluminum toxicity and hyperparathyroidism can also compromise the erythropoietin response in dialysis patients.
- When an infection intervenes, it is best to interrupt the erythropoietin therapy and rely on transfusion to correct the anemia until the infection is adequately treated.

Red cell morphology

- Agglutination refers to aggregation or clumping of red cells.
- This is seen in paraproteinemia as well as in autoimmune hemolytic anemia.
- Rouleaux formation refers to red cells lying in single rows as if they were stacked.
- This reflects abnormal serum protein levels.
- Anisocytosis refers to variation in cell size.
- Poikilocytosis refers to variation in cell shape.

Red cell morphology

- Cells are either normal in color (normochromic) or pale (hypochromic).
- If too much hemoglobin is produced, the cells become larger, not darker.
- Polychromatophilia is the persistence of a bluish hue to the cytoplasm, reflecting the presence of ribosomes actively producing hemoglobin in a young cell.
- Basophilic stippling refers to the diffuse fine or coarse blue dots in the cytoplasm representing nucleic acid residue.
- It is a common finding in lead poisoning.

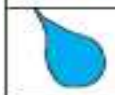
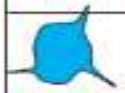
Red cell morphology

- Erythroid cells mature in 4.5 days.
- They are released into the circulation on the final day of maturation with RNA still present in the cytoplasm (reticulocytes).
- In anemia, erythroid precursors are released early.
- At hematocrits of 35%, reticulocytes may circulate for 1.5 days; at 15%, 2.5 days.
- A correction for this shift reflecting early release is incorporated into the reported reticulocyte count.
- Nucleated red cells are those released from the marrow prior to maturation and may reflect myelofibrosis.

Red cell morphology

- Marked anisocytosis and poikilocytosis with polychromatophilia and basal stippling suggest a maturation disorder.
- The reticulocyte count is low.
- Howell-Jolly bodies are dense blue circular inclusions that represent DNA remnants.
- Their presence points to functional hyposplenia
- Conspicuous erythrocyte inclusions suggest malaria.
- Supravital stains are necessary to see precipitated hemoglobin called Heinz bodies.
- These may be seen in α-thalassemia (hemoglobin H disease), G6PD deficiency, or liver disease.

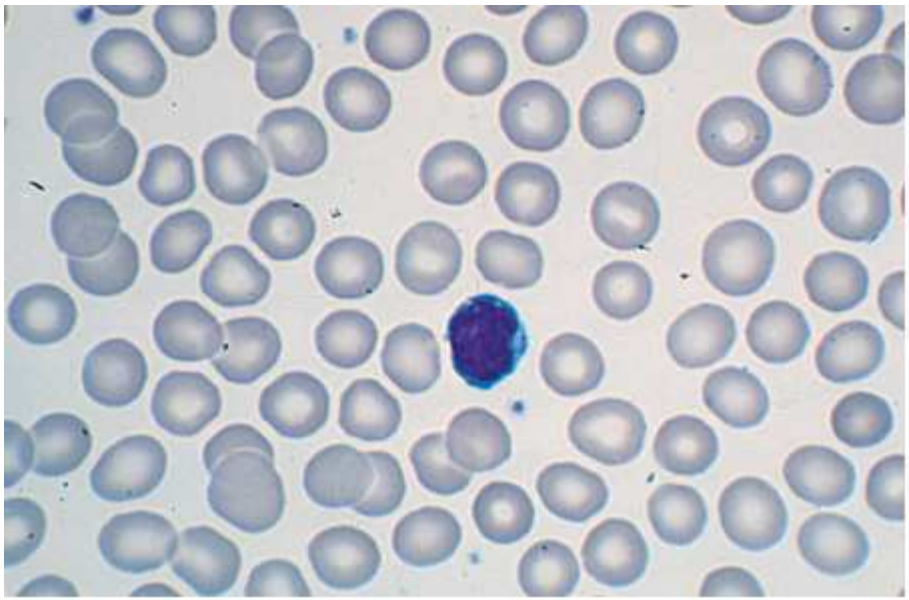
Abnormal red cell morphology

	Name	Characteristic	Also seen in
	Spherocyte	Hereditary spherocytosis Immune hemolytic anemia	Clostridial sepsis, hemolytic anemia of Wilson disease, hemoglobin CC disease
	Elliptocyte	Hereditary elliptocytosis (HE)	Iron deficiency, MDS megaloblastic anemia, thalassemias,
	Dacrocyte	Hemolytic hereditary elliptocytosis, hereditary pyropoikilocytosis	Severe iron deficiency, megaloblastic anemia, thalassemias, myelofibrosis, MDS
	Schistocyte	Microangiopathic and fragmentation hemolytic anemias	
	Echinocyte	Renal failure, malnutrition	Common in vitro artifact after blood storage
	Acanthocyte	Spur cell anemia, abetalipoproteinemia	Splenectomy
	Target cell	Cholestasis, hemoglobin C trait and CC disease	Iron deficiency, thalassemias
	Stomatocyte	Hereditary stomatocytosis	Alcoholism

Source: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology*, 7th Edition: http://www.accessmedicine.com

Fig. 2-5
Accessed 03/01/2010

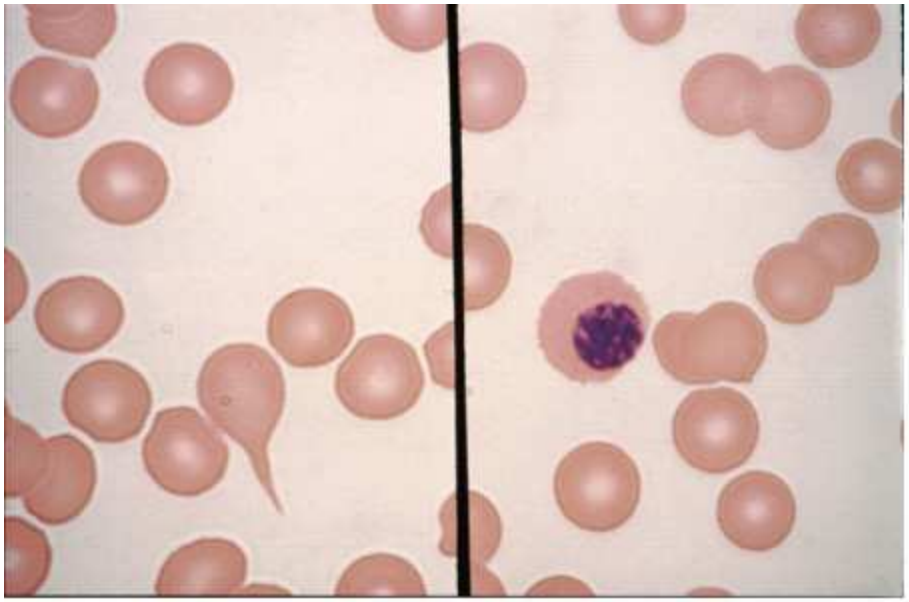
Normal red cell morphology



The normal red cell is slightly smaller than the small lymphocyte.

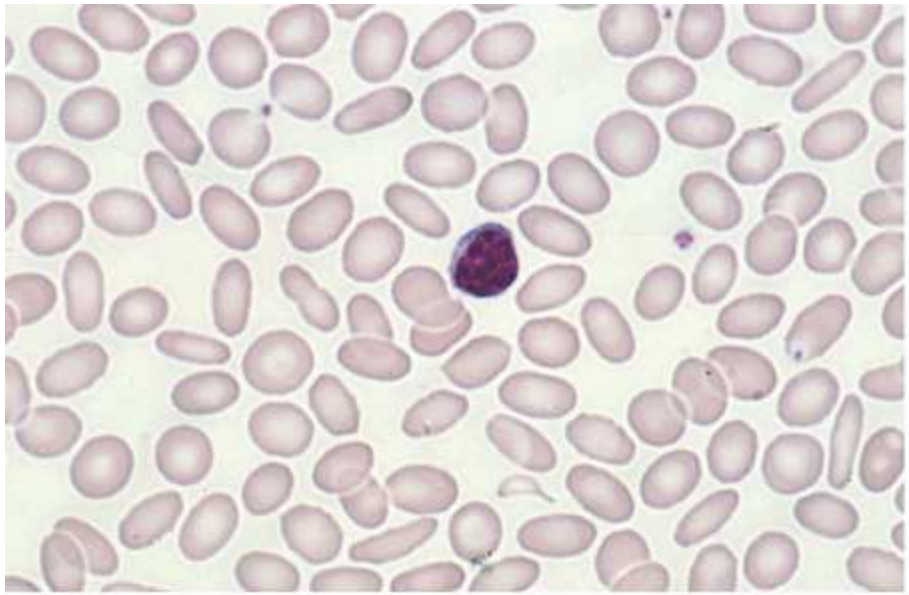
Fig. e11-1
Accessed 03/01/2010

Abnormal red cell morphology



A teardrop-shaped red blood cell (left panel) and a nucleated red blood cell (right panel) as typically seen with myelofibrosis and extramedullary hematopoiesis.

Abnormal red cell morphology

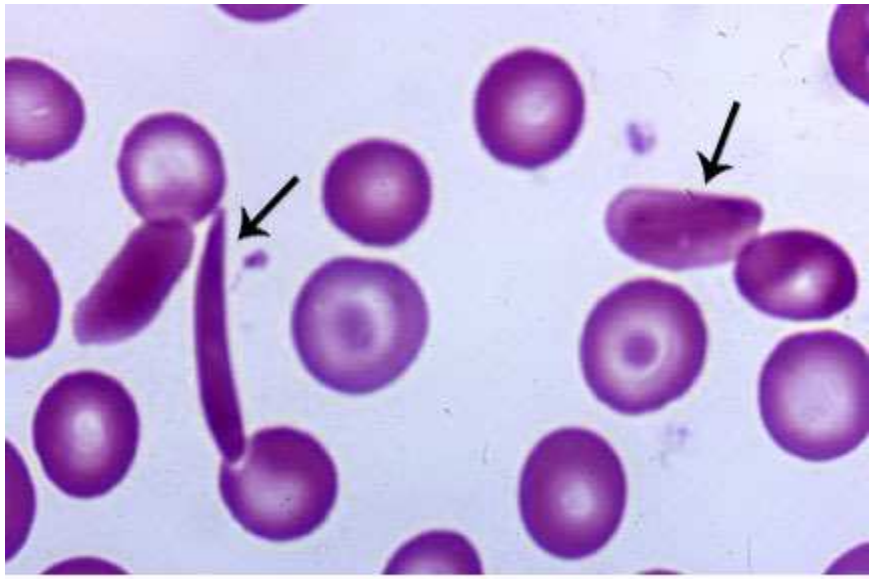


In elliptocytosis the elliptical shape of red cells is related to weakened membrane structure, usually due to mutations in spectrin.

Fig. e11-18
Accessed 03/01/2010

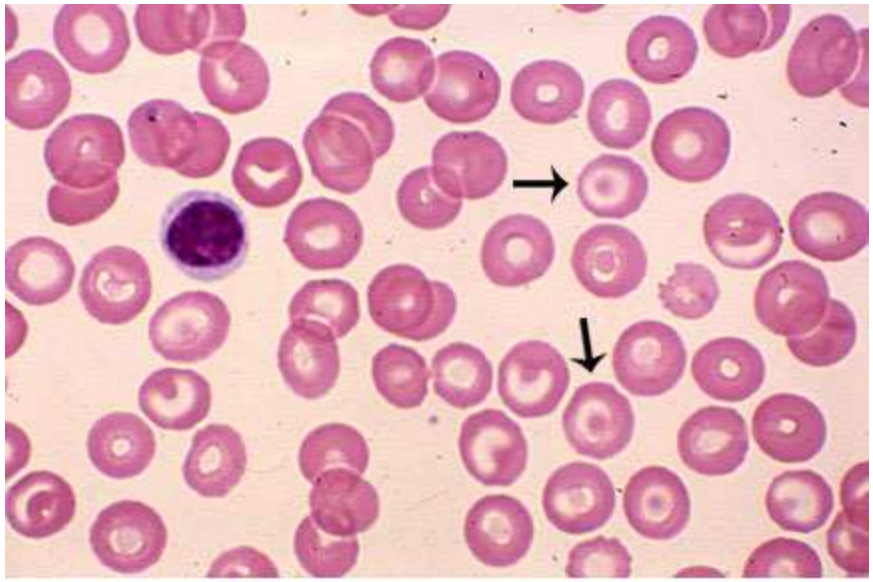
Abnormal red cell morphology

- Sickle Cells (HbS)



Source: Lichtman MA, Shafer MS, Felgar RE, Wang N:
Lichtman's Atlas of Hematology: http://www.accessmedicine.com

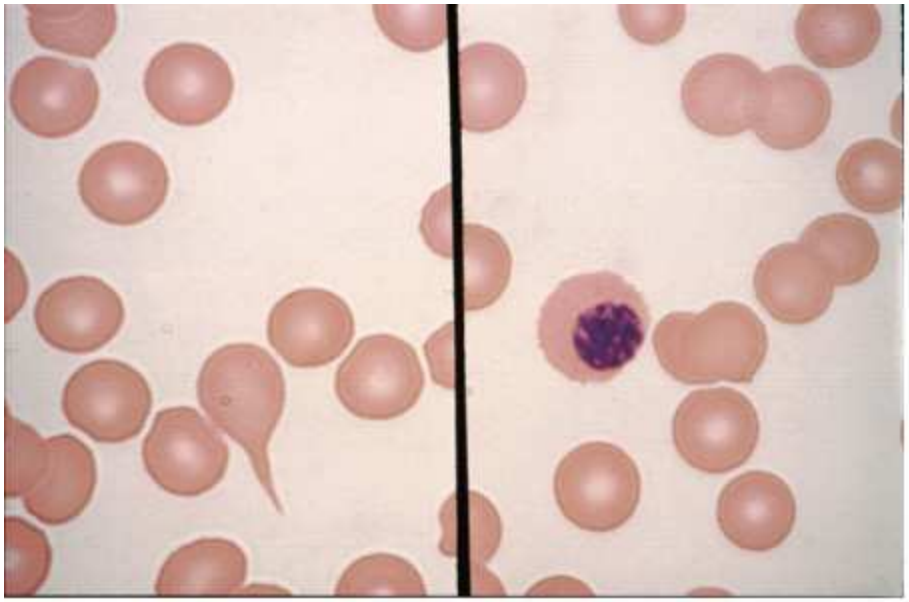
Target Cells (Hb C)



Source: Lichtman MA, Shafer MS, Felgar RE, Wang N:
Lichtman's Atlas of Hematology: http://www.accessmedicine.com

Figs. I.A.26 and I.A.30
Accessed 03/01/2010

Myelofibrosis



A teardrop-shaped red blood cell (*left panel*) and a nucleated red blood cell (*right panel*) as typically seen with myelofibrosis and extramedullary hematopoiesis.

Red cell membrane exoskeleton

- Spectrin consists of two polypeptide chains (α, β) which form helical flexible heterodimers. The “head” region of spectrin dimers self-associate to form tetramers. The “tail” region associates with actin oligomers. Each actin oligomer binds multiple spectrin tetramers.
- Ankyrin (band 4.2) binds spectrin to the transmembrane ion transporter (band 3). Protein 4.1 binds the “tail”region of spectrin to the transmembrane protein, glycophorin A.

Hereditary spherocytosis

- 75% autosomal dominant; remainder result from inheritance of two different defects (compound heterozygosity) and present as more severe form.
- Highest prevalence in northern Europe
- Mutations common in tethering proteins ankyrin and spectrin. Plasma membrane unstable; fragments loss as red cell ages. Osmotically fragile.
- Anemia, splenomegaly, jaundice are characteristic features. May see gallstones as well.
- Red cells are spherical (lack central zone of pallor).
- Parvovirus may produce aplastic crisis.

G6PD deficiency

- G6PD reduces NADP to NADH while oxidizing G6P.
- NADH provides protons required for conversion of oxidized glutathione to reduced glutathione. Reduced glutathione protects the cell against oxidant injury.
- G6PD deficiency is X-linked recessive trait. Two major forms noted: west African (less severe) and Mediterranean.
- As enzyme levels fall (aging), hemolysis results. Globin chains cross-link sulfhydryl groups, precipitate, and are membrane bound (Heinz bodies).

G6PD deficiency

- Fava beans and primaquine are known oxidant stresses.
- Oxidant exposure precipitates intravascular hemolysis. Self-limited when only enzyme rich young red cells remain.
- Anemia, hemoglobinemia, hemoglobinuria noted.

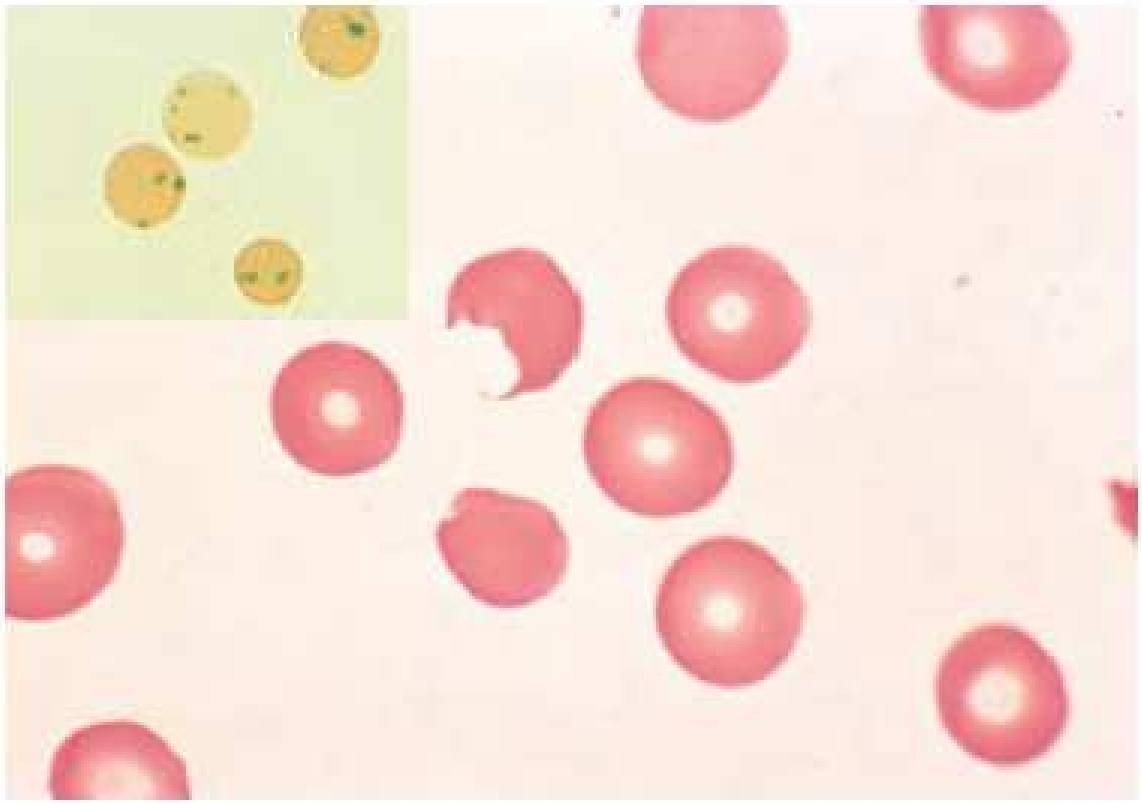


Figure 14-6 Glucose-6-phosphate dehydrogenase deficiency: effects of oxidant drug exposure (peripheral blood smear). *Inset*, Red cells with precipitates of denatured globin (Heinz bodies) revealed by supravital staining. As the splenic macrophages pluck out these inclusions, "bite cells" like the one in this smear are produced. (Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Paroxysmal nocturnal hemoglobinuria

- May be asymptomatic or mild (<10% cells affected)
- Commonly present with anemia, headache, esophageal spasm and/or erectile dysfunction (free hemoglobin scavenges nitric oxide, blocking relaxation), or renal failure (hemoglobinuria)
- >50% cells affected (flow cytometry)
- Arterial thrombosis may be present
- Venous thrombosis in 40% (hepatic, renal, cerebral veins frequently).
- Retinal changes
- Up to 10% will develop myelodysplastic syndrome.

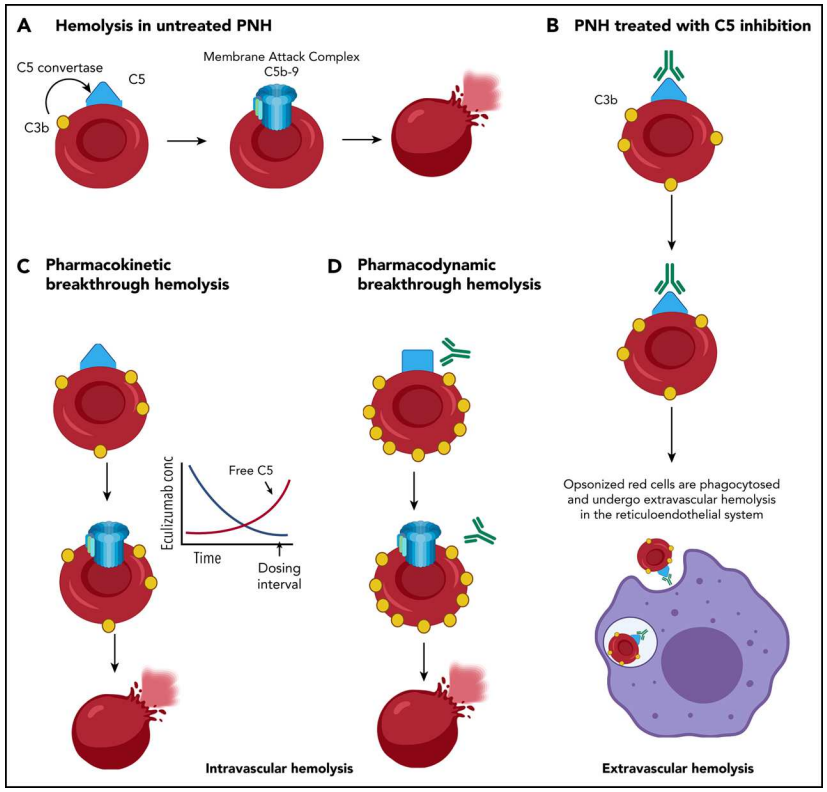
Paroxysmal nocturnal hemoglobinuria

- Mutation in phosphatidylinositol glycan complementation group A (PIGA) gene. Glycosylphosphatidyl inositol protein produced by the PIGA gene serves to covalently link transmembrane proteins in plasma membrane.
- X-linked
- Affected cells lack complement decay accelerating factor (CD55); membrane inhibitor of reactive lysis (CD59), a potent inhibitor of C3 convertase; and C8 binding protein. Cells sensitive to C5b-C9 membrane attack complex.

Paroxysmal nocturnal hemoglobinuria

- GPI-anchor protein deficiency on stem cells leads to a conditional survival advantage of PNH stem cells compared with normal stem cells in the setting of autoimmunity.
- Immunologic escape, alone or in combination with other somatic mutations, allows for the clonal expansion PNH blood cells
- Acidosis that normally results when asleep increases complement activity, leading to intravascular hemolysis.

How I treat paroxysmal nocturnal hemoglobinuria



Robert A. Brodsky, How I treat paroxysmal nocturnal hemoglobinuria, Blood, 2021,

Paroxysmal nocturnal hemoglobinuria

- Anticoagulation with heparin or low-molecular-weight heparin is still the first action to take in the setting of an acute thrombotic event.
- Complement inhibitors that target terminal complement are begun to limit further thrombosis (Eculizumab, ravulizumab)
- Pregnancy changes in C3b may block C5 inhibitors
- Pegcetocoplan is a C3 inhibitor capable of blocking both intravascular and extravascular hemolyis
- Danicopan blocks Factor D (alternative pathway)
- Iptacopan blocks the amplification loop of C3b
- Marrow transplantation curative.

Hemoglobinopathy

- Hemoglobinopathy may be associated with anemia.
- Hemoglobin S or C is seen in those with tropical African or South Mediterranean or coastal Indian Ocean ancestry.
- Hemoglobin E is principally found in Indochina.
- Single point mutations are noted in β-globin.
- Hemoglobin electrophoresis only identifies Hemoglobins A, C, F, and S.
- MCV elevated in sickle cell disease while depressed in thalassemia.

Hemoglobinopathy

- Valine substitution for glutamate in the sixth codon of β-globin permits hemoglobin molecules to polymerize when deoxygenated. (Hemoglobin S)
- Deoxygenated hemoglobin S forms needle-like fibers in red cells, leading to sickle deformation.
- Hemoglobin C involves a lysine for glutamate in the sixth codon.
- Hemolysis, microvascular occlusion facilitated by dehydration, acidosis, and long transit time in microvascular beds.

Hemoglobinopathy

- Herniation of HbS polymers through the red cell membrane leads to $^{Ca2}+$ entry and activation of a K^{+}-efflux ion channel with resultant intracellular dehydration. Oxygen binding lost.
- Sickle cells express elevated levels of adhesion molecules as well as induce endothelial activation. Free hemoglobin released from lysed cell binds nitric oxide, contributing to further vascular constriction and platelet activation.
- Hemolytic anemia, reticulocytosis common. Splenomegaly early in disease course; late in the disease course, little splenic function noted.

Hemoglobinopathy

- Vascular occlusive crises commonly involve bones, lungs, liver, brain, spleen, and penis.
- Aplastic crises precipitated by Parvovirus B19 infection.
- Sequestration crisis results from splenic trapping of red cells with marked hypovolemia being noted.
- Acute chest syndrome presents with fever, cough, chest pain, and pulmonary infiltrates. Systemic hypoxemia may result.
- Hydroxyurea inhibits DNA synthesis and leads to increased HbF levels, limiting hemoglobin polymerization.

Hemoglobinopathy

- In thalassemia, production of the globin chain is affected. A decrease in α-globins allows for greater tetrameric hemoglobin formation by β-chains (and vice versa).
- Two loci encode the β-chain on chromosome 11; four loci encode the α-chain on chromosome 16.
- The severity of α-thalassemia is correlated with the number of affected loci. If all loci are affected, the fetus dies. If three loci are affected, hemoglobin H disease results. Higher Oxygen binding occurs, resulting in poor Oxygen delivery to tissue. Two loci are associated with trait.

Hemoglobinopathy

- Mutations in β-thalassemia are characterized as to whether they prevent (β^0) or permit (β^+) formation of β-chains.
- Splicing, promoter region mutations common in β^+ disease.
- Chain termination mutations common in β^0 disease.
- Tetramers do not form. Excess α-globins bind red cell membranes, producing membrane damage, and, at high concentrations, form toxic aggregates.
- Anemia, aniso and poikilocytosis, hypochromia, basophilic stippling noted. Expansion of hematopoietic marrow (with new bone formation in a sunburst appearance) as well as extramedullary hematopoiesis noted.

Hemoglobinopathy

- Thalassemia is seen in those with tropical or coastal African, South Mediterranean, coastal Indian Ocean, or South Asian ancestry.
- It is possible to have β-thalassemia and Hb S together.
- Elevated Hemoglobin F is suggestive of β-thalassemia. Hemoglobin A2 is often elevated as a percentage of A. Measure Hemoglobin A2 by column chromatography.

Hemoglobinopathy

- Hemoglobin H is found in α-thalassemia; it is unstable. Hemoglobin A2 levels are low. -/- -/α genotype.
- -/- α/α genotype noted in Asia; -/α -/α genotype noted in Africa. May be asymptomatic.
- Single mutation is carrier state; four mutations are lethal.

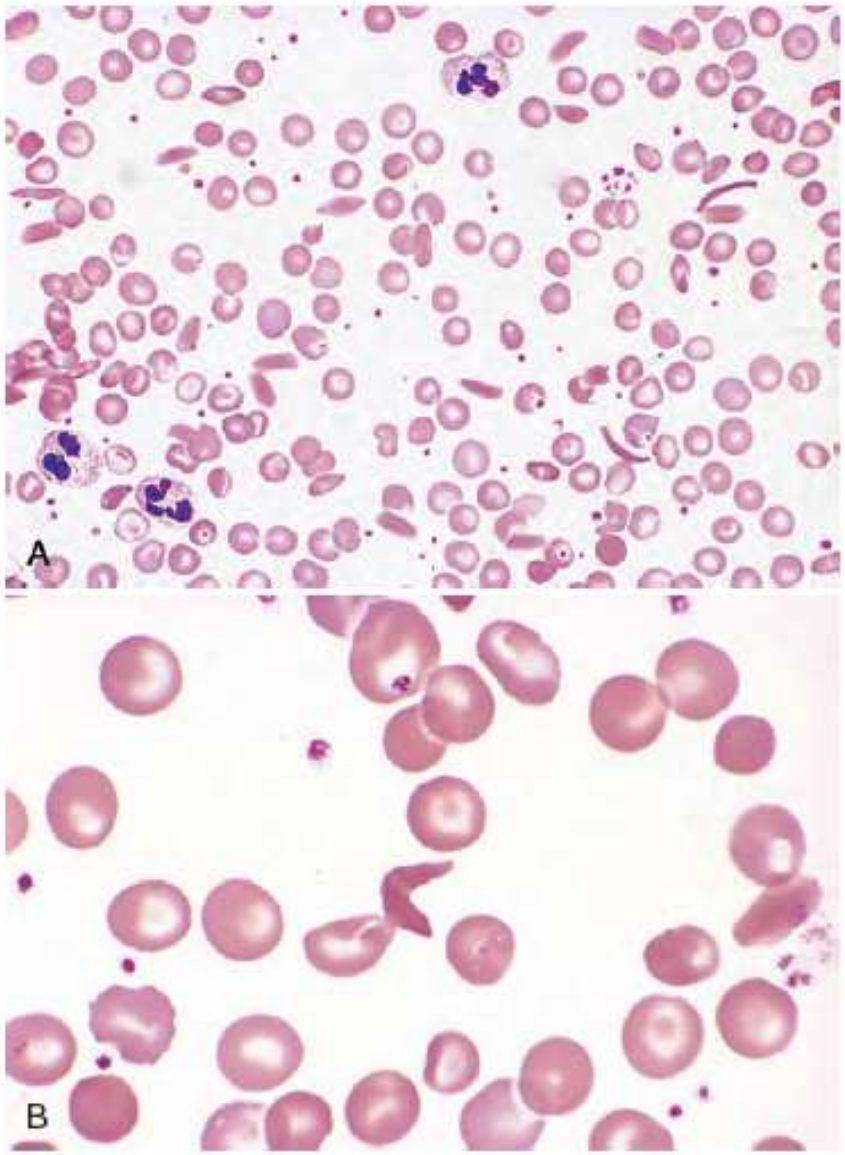


Figure 14-8 Sickle cell disease (peripheral blood smear). **A,** Low magnification shows sickle cells, anisocytosis, and poikilocytosis. **B,** Higher magnification shows an irreversibly sickled cell in the center. (Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Elevated red cell counts

- Chronic tobacco use, chronic lung disease, residence at high altitude are associated with low arterial oxygen tension and may lead to elevated red cell counts.
- Elevated erythropoietin levels require a search for tumor source (renal carcinoma or cyst, cerebellar hemangioblastoma, uterine leiomyoma, hepatoma).
- Polycythemia vera, part of the spectrum of myelodysplastic syndrome, is diagnosed with determination of red cell mass and bone marrow examination. Erythropoietin levels are low.

Therapy of polycythemia vera

- Polycythemia vera patients generally present following a thrombotic or hemorrhagic event.
- Headache, weakness, epigastric distress, and pruritis may be present.
- Phlebotomy is recommended to maintain the hematocrit <45 % (<42 % in women).
- Low dose daily aspirin (81mg) is begun.
- Allopurinol is reserved for those with hyperuricemia.
- Consider hydroxyurea (begin 15-20 mg/kg/d) in those >60 years old with a history of a previous thrombosis. If compliance is a problem, ^{32}P administration should be considered. Both are leukemogenic.

White blood cell counts as screening tool

- Fewer than 0.5% of asymptomatic patients whose primary disease is not associated with leukocytosis will have an abnormal white blood cell count.
- Among patients whose total white blood cell count is normal, a white blood cell differential contributes to patient care in only 2.8%.

White cell counts

- High white cell counts are associated with acute inflammation, often bacterial in origin.
- There is an associated rise in the number of neutrophils reported.
- Elderly patients may not show elevations of white counts.
- Examination of a peripheral blood smear may demonstrate the presence of >4% band forms.
- Low white counts may be associated with marijuana ingestion, viral infection (with lymphocytosis), chemotherapy, or proliferative disorders.

White cell counts

- An absolute neutrophil count above 500 is associated with protection against bacterial or fungal infection.
- The presence of 4-7% eosinophils is associated with an allergic response.
- The presence of >10% eosinophils is consistent with helminthic infection.
- The presence of >3% basophils is associated with a hypersensitivity reaction.

White cell counts

- An increased absolute monocyte count is consistent with myelodysplasia.
- Elevation of the monocyte count above 7% indicates an immune defense reaction.
- An elevated absolute monocyte cell count accompanied by a drop in absolute cell counts in other series suggests monocytic leukemia.

White cell counts

- An infant with a low white count and 100% lymphocytosis with morphologically normal lymphocytes probably has an infection with B. pertussis.
- Chickenpox, measles, brucellosis associated with lymphocytosis and normal white cell counts.
- Constitutional relative lymphocytosis can reach up to 60% and occurs without apparent reason
- Principally in asthenic teenagers

White cell counts

- Hyperthyroidism and Addison disease
- Absolute granulocytopenias with relative lymphocytosis
- Chronic lymphocytic leukemia (CLL), which is always accompanied by absolute and relative lymphocytosis, usually with high cell counts.

White cell counts

- Transformed, “stimulated” lymphocytes may be seen with:
- Toxoplasmosis (normal white cell counts)
- Rubella (normal or low white cell counts)
- Hepatitis (normal or low white cell counts).
- The most extreme lymphocyte transformation is observed in mononucleosis (Epstein–Barr virus (EBV) or cytomegalovirus (CMV) infection)

White cell life spans

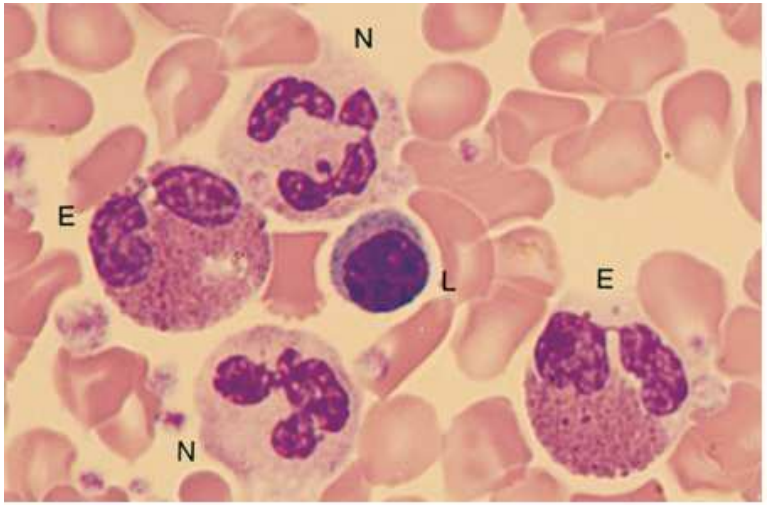
- Neutrophil 2- 3 days

  (50% of the neutrophils are in the freely flowing pool, composed of those cells that are in the blood and not in contact with the endothelium).
- Eosinophil 3- 6 days
- Basophil 6-12 days
- Monocyte 1- 3 days

White cell life spans

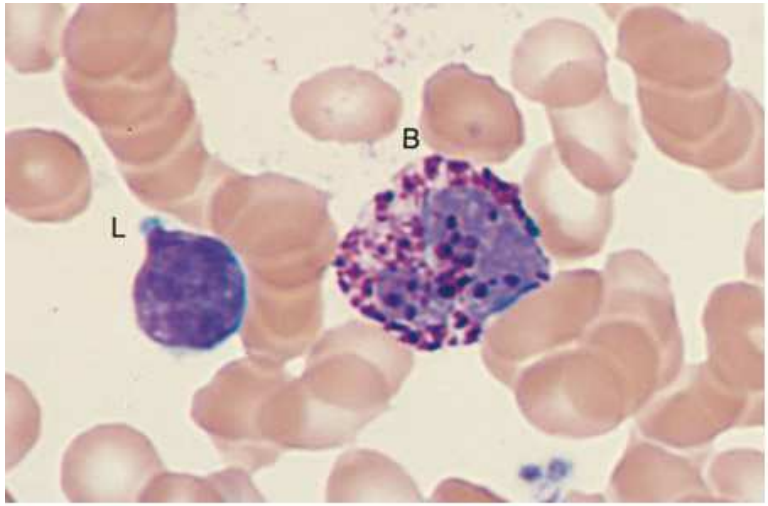
- B-lymphocyte (circulating) 10-14 days
- T-cell (in contact with antigen) 15 weeks
- Plasma cell (if no B-lymphocyte memory cell present) >1 year
- Platelets 10-14 days

White blood cells

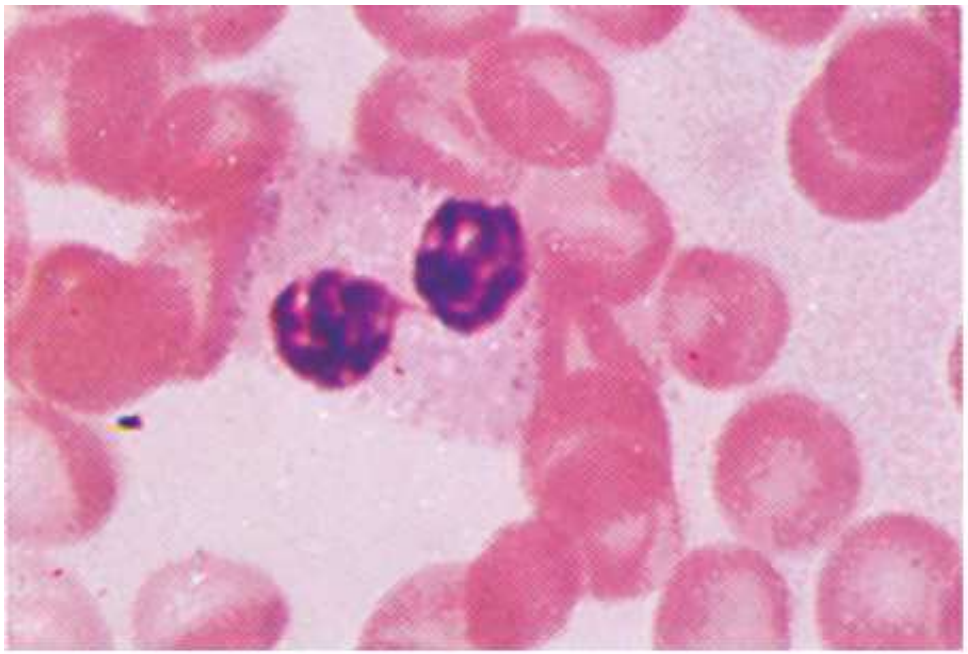


Figs. e11-25, e11-26
Accessed
02/01/2010

L, lymphocyte; N, neutrophil;
E, eosinophil; B, basophil



Pelger-Hüet anomaly



The Pelger-Huet anomaly is an hereditary segmentation anomaly of granulocytes that results in rod shaped nuclei. The same appearance in a non-hereditary syndrome is associated with stress (Pel-Ebstein fever, Murchison's syndrome) or myelodysplasia.

Fig. e11-28 Accessed 02/01/2010

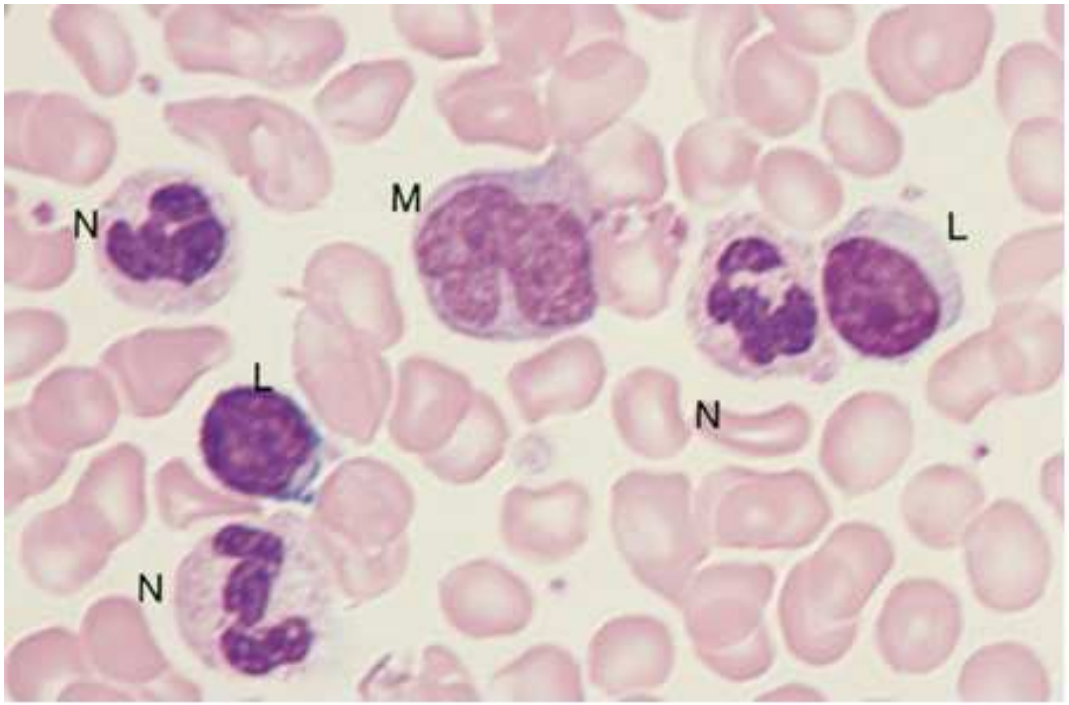
White blood cell inclusions

- Vacuolated neutrophils are noted in bacterial sepsis.
- Döhle bodies are small blue cytoplasmic inclusions associated with inflammation. They represent aggregates of rough endoplasmic reticulum.
- Toxic granulations stain red with a Wright-Giemsa stain.
- They are larger than normal neutrophil granules
- They are associated with systemic inflammation.
- Large misshapen granules may reflect the inherited Chédiak-Higashi syndrome.

Mononuclear cells

- Small lymphocytes have a small dark nucleus and scant cytoplasm.
- They are the lymphocytes most commonly found in the peripheral blood.
- They are the size of a red cell.
- Large granular lymphocytes contain blue granules in a light blue cytoplasm.
- Monocytes are the largest white blood cells.
- The nucleus can take on a variety of shapes but usually appears to be ovoid, folded, irregular in outline.
- The nuclear chromatin is fine.
- The cytoplasm is gray.

Mononuclear cells



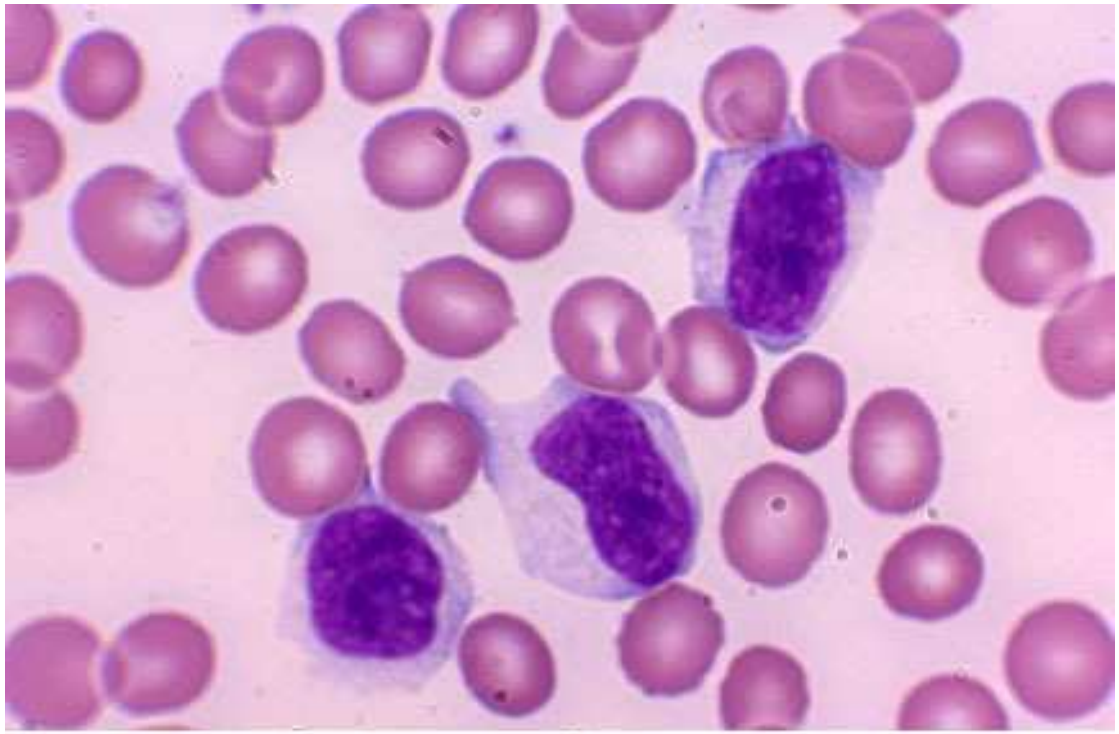
L, lymphocyte; M, monocyte; N, neutrophil

Fig. e11-27 Accessed 02/01/2010

Mononuclear cells

- Reactive lymphocytes are found in the presence of viral infections.
- The lymphocytes are the size of a neutrophil, have abundant cytoplasm and a less condensed nuclear chromatin.
- Smudge cells are rare in the absence of chronic lymphoid leukemia.
- These are small lymphocytes ruptured in making the blood smear, leaving a smudge of nuclear material without a surrounding cytoplasm or cell membrane.

Atypical lymphocytes



Source: Lichtman MA, Shafer MS, Felgar RE, Wang N:
Lichtman's Atlas of Hematology: http://www.accessmedicine.com

Cytoplasmic periphery conforms to red cell outlines. Nuclear shape not a strict circle but elongated or irregular.

Fig. II.G.9
Accessed 02/01/2010

Platelet indices

- Mean platelet volume (MPV) is the measure of platelet size (and, reactivity)
- The reference range is between 7.2 fL and 11.8 fL in adults.
- A low MPV is associated with increased bleeding risk
- A high MPV is associated with thrombosis risk
- A prognostic marker
- Platelet distribution width (PDW) reflects the variability in platelet size
- A wide PDW suggests the presence of two platelet populations.

Platelets

- Only mature platelets occur in blood.
- Produced by budding off megakaryocytes.
- Each megakaryocyte produces 5-10,000 platelets.
- Platelets are smaller than red cells, with blue gray cytoplasm, and lack a nucleus.
- They contain RNA, mitochondria, actin-myosin, lysozomes, dense bodies (ADP, Ca^{2+}, serotonin, histamine), and α-granules (fibrinogen, factor V, VWF, vitronectin, thrombosponin).

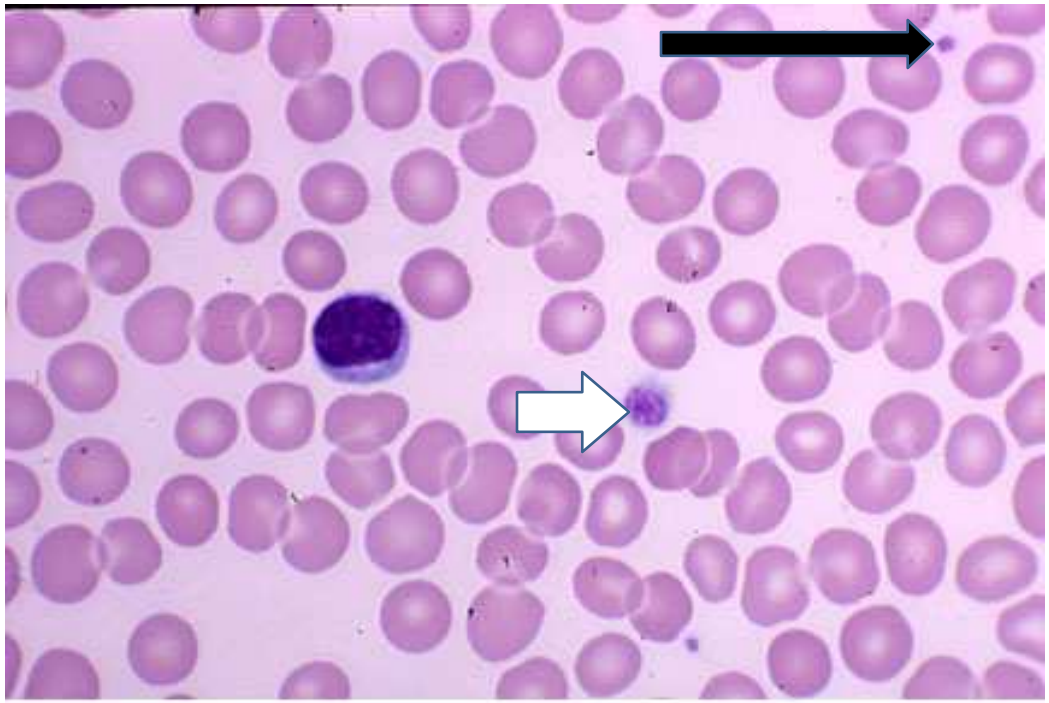
Platelets

- They circulate one week and are then destroyed in the spleen (and by Kupffer cells in the liver).
- Abnormalities present before anemia in megaloblastic disorders.
- MPV elevated in hemolytic disorders.

Platelets

- Elevated platelet counts usually reflect iron deficiency anemia.
- Counts over one million may be associated with hyperparathyroidism, malignancy, or myelodysplastic syndrome.
- Low platelet counts may reflect:
- Viral illness (usual).
- Heparin or quinine use, splenomegaly with platelet sequestration, ITP, TTP (anemia, schistocytes, elevated LDH), bone marrow failure, DIC (schistocytes) must also be considered.
- Bone marrow examination or skin biopsy is necessary to distinguish ITP and TTP.

Giant platelets



A normal platelet (black arrow) and giant platelet (white arrow) are shown. A lymphocyte is present for size comparison.

Fig. IV.A.2 Accessed 02/01/2010