In contrast to white blood cells, circulating erythrocytes are anucleate and normally homogeneous in appearance. They have a biconcave shape with peripheral hemoglobinization and a central clear zone of pallor. The biconcave cell shape allows for erythrocyte movement through even the smallest capillaries, while hemoglobin carries oxygen for delivery to tissues.

Erythrocytes are derived from bone marrow orthochromic erythroblasts following extrusion of the nucleus. During development in the bone marrow, erythroid cells increase in RNA content for hemoglobin production; this RNA imparts a grayish color to the cell cytoplasm on Wright-Giemsa stain. As hemoglobin is produced, the cytoplasmic color progressively becomes more orange-pink. Upon release into the circulation, erythrocytes are still slightly immature with slight grayish staining, a finding referred to as polychromasia. These polychromatophilic cells generally represent reticulocytes, although supravital or fluorescent staining of RNA is required for confirmation. In normal patients, reticulocytes mature within 1 or 2 days and only account for about 1% of erythrocytes.

Peripheral blood smear review, in conjunction with CBC, is quite useful in evaluating patients with erythrocyte disorders. In particular, erythrocyte staining characteristics (e.g., polychromasia or hypochromasia), erythrocyte shapes (e.g., schistocytes, spherocytes, bite cells), erythrocyte size (e.g., macrocyte, microcyte), agglutinates, and inclusions (e.g., Pappenheimer bodies, hemoglobin crystals), can assist in determining the underlying etiology. For example, in anemias due to bleeding or red cell destruction (e.g., hemolysis), erythrocytes may be released early from the bone marrow, and polychromatophilic cells may represent an increased proportion of erythrocytes since the bone marrow is properly compensating for the anemia. Cell shapes assist in distinguishing etiologies for anemia; for example, schistocytes are in keeping with microangiopathic hemolytic anemia, spherocytes are seen with autoimmune hemolytic anemia or hereditary spherocytosis, and bite cells may be seen with G-6-PD deficiency. In contrast to those anemias due to blood loss or erythrocyte destruction, lack of increased polychromatophilic cells in an anemic patient suggests an underlying problem with erythrocyte production, as can be seen with nutritional deficiencies, bone marrow failure, or bone marrow replacement disorders.

Red cell size is best assessed by an automated hematology analyzer, although in some cases smear review can detect abnormally small (microcytes) or large (macrocytes) erythrocytes; normal erythrocytes are similar in size to small, mature lymphocytes. Microcytic anemia may be related to iron deficiency, heavy metal toxicity, or thalassemia, while macrocytic anemia may be the result of vitamin B12 or folate deficiency, liver disease, hypothyroidism, or myelodysplasia.
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Erythrocytes are easily recognized by their round contour and pink-red color with central pallor giving them a characteristic donut-shaped appearance in blood smears. Normal mature red blood cells measure 6.7 µm to 7.8 µm in diameter. They circulate in the blood as biconcave disks. The central pallor occupies about one-third the diameter of the cell.

Erythrocytes are usually numerous compared to white blood cells or platelets. The normal circulating erythrocyte is the end product of a complex maturation process, which occurs almost completely in the bone marrow and whose function is primarily to deliver oxygen to cells. A normal red cell takes 7 days to develop in the marrow and then it circulates for 120 days before it is finally trapped in the spleen where it undergoes catabolism with eventual reutilization of its iron.

An erythrocyte contains hemoglobin consisting of four protein subunits ("globin" molecules), each of which is associated with a nonprotein heme group. Heme carries the oxygen, is composed of iron and porphyrin, and is brightly colored (red). Hemoglobin is composed of four globin chains, two alpha and two beta in the adult. Normally, the alpha chain remains constant throughout life, and the beta chain or equivalent (gamma in the neonate, epsilon in the fetus) switches at various stages of development until the normal adult hemoglobin, hemoglobin A, is present as 97% of all hemoglobin by 1 year of age. A reduced rate of hemoglobin production due to a hereditary defect results in disease with symptom severity related to the underlying condition. Decreased production of normal globin results in a thalassemia. Alpha-thalassemia is the result of decreased alpha-globin production, while beta-thalassemia is due to decreased beta-globin production. Abnormal globin chain production (usually an amino acid substitution) results in hemoglobinopathy of which sickle cell anemia is probably the most famous example.

Most of the abnormal red cells described in this section are part of an anemia, which may be due to any of several different causes (detailed in that cell's description). However, more than anemia may be responsible for some of these forms.
The peripheral blood smear is from a 43-year-old man with multiple sclerosis who is receiving G-CSF in preparation for stem cell harvest and bone marrow transplant. The arrowed cell is a normal erythrocyte and was correctly identified by 100% of referees and 99.1% of participants. This cell is anucleate, round in contour, and contains an area of central pallor occupying about one-third of the cell diameter. This field also contains a lymphocyte and a neutrophilic precursor with increased azurophilic granulation, consistent with the patient’s history of G-CSF therapy.

This blood smear is from a 11-year-old girl with asthma. The arrowed cells are normal erythrocytes that are similar in appearance to other erythrocytes in the field. Erythrocytes are biconcave discs that have visible central pallor on the blood smear, usually accounting for about one-third the cell diameter. This appearance is considered normochromic, while cells with increased central pallor are referred to as hypochromic, a finding that can be seen with iron deficiency or thalassemia. Leukocytes in this field include a neutrophil and eosinophil. Mild eosinophilia can be seen in patients with allergic asthma or rhinitis, as well as a variety of other conditions.

The two arrowed erythrocytes demonstrate normal central pallor and the characteristic red color of erythrocytes. In contrast, the three fragmented cells (two in the central part of the field and one in the lower left) do not have any characteristic size or shape and also lack central pallor. Microcytes, for proficiency testing purposes, have increased central pallor. Platelets are decreased in this field.
Acanthocyte (Spur Cell)

The word acanthocyte comes from the Greek term for spike or horn. The shape results from poorly understood alterations in cell membrane lipid content and is irreversible. The most common cause is the postsplenectomy state.

The typical acanthocyte has 3 to 20 spikes with narrow bases and knobby ends. The projections are irregularly distributed over the surface. Acanthocytes have no central pallor, and their spheroidal shape makes them smaller than normal red blood cells. They are usually easily distinguished from echinocytes (burr cells), which have central pallor and uniform smaller and blunter projections, evenly distributed over the surface. Transitional forms exist between acanthocytes and echinocytes, which may blur these distinctions and make absolute diagnosis difficult. For CAP proficiency testing purposes, however, acanthocytes do not have central pallor.

A very rare acanthocyte may be encountered in otherwise normal blood films. They represent older, effete red blood cells approaching their extremes of life (120 days). Acanthocytes are readily found in postsplenectomy states because of diminished removal of such poikilocytes. Large numbers are more characteristically seen in abetalipoproteinemia and advanced liver disease. Acanthocytes form due to derangement in the lipid content of the red cell membrane. In abetalipoproteinemia, the usual lecithin-to-sphingomyelin ratio is reversed. Sphingomyelin is more rigid than lecithin; it selectively expands the outer half of the lipid bilayer producing “wrinkles.” In cirrhosis, the red cell membrane contains 40% to 70% excess cholesterol, producing redundancy in the membrane. Bulges and excrescences develop. (See A Closer Look At…Acanthocyte Formation, page 54, for a more detailed discussion.)
The smear is from a patient with pyruvate kinase deficiency. The arrowed cell is an acanthocyte. It is spheroidal, lacks central pallor, and has irregularly distributed spine-like projections. Acanthocytes in large numbers may elevate the MCHC. Echinocytes exhibit central pallor and tend to have evenly distributed, short blunt spicules. The lack of definitive central pallor favors acanthocyte. It is worth noting that acanthocytes and echinocytes may form part of a morphologic spectrum, and transitional forms between the two can occur. Both acanthocytes and echinocytes may be observed in pyruvate kinase deficiency. Also note the presence of Pappenheimer bodies in many of the RBCs.

This blood smear is from a patient with abetalipoproteinemia. The patient presented with malabsorption, visual impairment, and ataxia. Hemoglobin was 12.5 g/dL and cholesterol 48 mg/dL. The two arrowed cells are acanthocytes. The surface is distorted by small unevenly distributed spicules. Central pallor is lacking. The spicules are short, sharp, and have a narrow base. Other red cells in the field are acanthocytes, echinocytes, and transitional forms between the two. Such diversity is often found in this disorder. The lone leukocyte in the field is a segmented neutrophil.

The arrowed spiculated cell is an acanthocyte. The cell lacks central pallor. The projections are irregular; they vary in length and are unevenly distributed. Some of the cytoplasmic spicules have knobby ends. The leukocyte in the right lower corner is a segmented neutrophil. Platelets are unremarkable.

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A Closer Look At…

Acanthocyte Formation

Acanthocytes are spheroidal dense red cells with multiple irregular thorny projections unevenly distributed over the surface. This change is irreversible and due to alteration of the lipid content of the red cell membrane. Small numbers of acanthocytes are most commonly seen post-splenectomy. Large numbers are found in two types of disorders: abetalipoproteinemia and severe liver disease.

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Abetalipoproteinemia is a very rare genetic disorder that results in defective hepatocyte secretion of apolipoprotein B (apo B). Without apo B, transport of triglycerides from the intestine to the liver is blocked. No very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and chylomicrons enter the plasma. The small bowel is filled with triglyceride droplets. Plasma cholesterol levels are less than 50 mg/dL.

Infants present in the first month of life with steatorrhea, diarrhea, and malabsorption of fat-soluble vitamins (D, A, K, and E). Progressive neurologic abnormalities develop along with blindness due to retinitis pigmentosa. Death may occur by age 30. Diet modification and larger doses of vitamins may assist in managing symptoms and improving life span.

Anemia is mild and the life span of red cells is normal or slightly decreased. The blood contains 50% to 90% acanthocytes. Red cell precursors in the bone marrow are normal. The spiculated shape develops as the red cells age in the peripheral blood. Normal transfused cells also gradually transform into acanthocytes. The shape changes are irreversible.

Red cell membrane lipids are in equilibrium with plasma lipids. Sphingomyelin is a stable, immobile component of the red cell membrane. The lipid abnormalities in abetalipoproteinemia result in a marked increase in red cell membrane sphingomyelin and a decrease in lecithin. Sphingomyelin preferentially collects on the outer half of the lipid bilayer, selectively expanding it and resulting in irregular membrane projections. The underlying spectrin framework of the cells is not disturbed. The abnormal shape reduces the deformability of the red cell somewhat, but not to the degree seen in advanced liver disease. As a result, splenic sequestration and remodeling are minimal and hemolysis is mild.

Advanced liver disease, most commonly due to alcoholic cirrhosis, can lead to lipid abnormalities and the formation of acanthocytes. Unlike abetalipoproteinemia, the acanthocytes have a significantly shorter life span. They are much less deformable and are readily destroyed in the spleen. The resultant hemolytic anemia is progressive and severe. The term spur cell anemia is evoked for this condition.

The red cell membrane normally has a ratio of cholesterol to phospholipid of 1:1. As the amount of cholesterol increases, the surface area of the cell increases. The first step is the formation of broader and flatter cells, which are seen as target cells in peripheral blood smears. In advanced cirrhosis, the damaged liver manufactures an abnormal high-density lipoprotein (HDL) containing a large amount of free (unesterified) cholesterol. The abnormal HDL binds to the red cell membrane and functions as a lipid trap. Large amounts of free cholesterol accumulate in the outer half of the red cell membrane, disturbing the normal cholesterol-to-phospholipid balance. The excess cholesterol first forms target cells, and then, as the amount of membrane increases even more, irregular projections and excrescences develop. In addition, the cholesterol damages the Na+/K+ pump and compromises cell deformity. The spleen continually remodels these cells, eventually producing a subpopulation of small spheroidal acanthocytes with short and sharp thorns. These cells are not deformable and eventually become trapped in the spleen and are destroyed.

**Spur Cell Anemia Due to Liver Failure**

Acanthocytes of liver disease have a short life span leading to severe anemia.

Normal red cell interacts with lipids in the plasma

Target cells form as the red cell membrane accumulates cholesterol

The addition of even more cholesterol produces irregular projections. These thorny cells are remodeled in the spleen and eventually are destroyed.
How Acanthocyte Cells Form

**Normal Red Cell Membrane**

**Acanthocyte Cell Membrane**

**End-Stage Liver Disease**

In cirrhosis, unesterified cholesterol accumulates in the red cell membrane due to interaction with abnormal plasma HDL.

**Abetalipoproteinemia**

A marked amount of sphingomyelin accumulates in the red cell membrane, primarily in the outer layer. Acanthocytes form and comprise 50% or more of circulating erythrocytes.

The anemia is generally mild because these acanthocytes are more deformable; RBC life span is normal or minimally decreased.

Abnormal amounts of lipids accumulate in outer half of lipid bilayer, causing the membrane to evaginate, forming a spicule.

Interactions between plasma lipids and red cell membrane lipids

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