INTRODUCTION — The spleen is a hematopoietic organ capable of supporting elements of the erythroid, myeloid, megakaryocytic, lymphoid, and monocyte-macrophage (ie, reticuloendothelial) systems [1]. As such, it is important in the following situations:

- The spleen participates in cellular and humoral immunity through its lymphoid elements. (See "The adaptive cellular immune response" and "The humoral immune response".)

- The spleen is involved with the removal of senescent red blood cells, bacteria, and other particulates from the circulation through elements of the monocyte-macrophage system. An increase in this function (ie, hypersplenism) may be associated with varying degrees of cytopenia, while removal of the spleen may render the patient susceptible to bacterial sepsis, especially with encapsulated organisms. (See "Extrinsic nonimmune hemolytic anemia due to mechanical damage: Fragmentation hemolysis and hypersplenism", section on 'Extravascular nonimmune hemolysis due to hypersplenism' and "Clinical features and management of sepsis in the asplenic patient").

- Splenectomy in patients with various hematologic disorders (eg, polycythemia vera, essential thrombocythemia, thalassemia, stomatocytosis) has been associated with an increased incidence of vascular complications, including venous and arterial thrombosis and pulmonary hypertension [2].

- Normally, about one-third of circulating platelets are sequestered in the spleen, where they are in equilibrium with circulating platelets. (See "Approach to the adult patient with thrombocytopenia", section on 'Dilutional thrombocytopenia' and "Approach to the adult patient with thrombocytopenia", section on 'Distributional thrombocytopenia caused by splenomegaly'.)

- Under abnormal circumstances, the spleen may become the site of extramedullary hematopoiesis and contain developing erythroid, myeloid, and megakaryocytic precursors. (See "Clinical manifestations and diagnosis of primary myelofibrosis", section on 'Extraduillary hematopoiesis'.)

This topic review will discuss the approach to a patient whose spleen is enlarged on physical examination (ie, splenomegaly) or is more than minimally enlarged on ultrasound, x-ray, nuclear medicine liver–spleen colloid study, CT scan, or magnetic resonance imaging. However, it should be remembered that the diagnostic criteria for various disease states have historically been built on long experience with the physical examination, while scanning procedures have been available for a shorter period of time. Thus, the clinical or diagnostic significance of a spleen that is modestly enlarged on scan but is not palpable (ie, "scanomegaly") is uncertain.

As an example, in polycythemia vera, palpable splenomegaly was a major diagnostic criterion
According to the Polycythemia Vera Study Group. However, a spleen enlarged on a scanning procedure has been considered to be only a minor criterion using other diagnostic algorithms. (See "Diagnostic approach to the patient with suspected polycythemia vera").

An approach to the child with splenomegaly is discussed separately. (See "Approach to the child with an enlarged spleen").

**SPLENIC DISORDERS**

**Normal splenic function** — The spleen lies within the peritoneal cavity in the posterior portion of the left upper quadrant, below the diaphragm and adjacent to the 9th to the 11th ribs, stomach, colon, and left kidney, with its hilum in close approximation to the tail of the pancreas. The spleen weighs 80 to 200 grams and 70 to 180 grams in the normal adult male and female, respectively, averaging about 150 grams, or approximately 0.2 percent of body weight [3]. It is not usually palpable, but may be felt in children, adolescents, and some adults, especially those of asthenic build.

The spleen is a major lymphopoietic organ, containing approximately 25 percent of the total lymphoid mass of the body; this component, as well as components of the monocyte-macrophage system, can react and enlarge quickly after the onset of infection or inflammation. Under such circumstances, a spleen enlarged to scan but not palpably enlarged may be a nonspecific marker of inflammation similar to an elevated erythrocyte sedimentation rate or other acute phase reactants. (See "Acute phase reactants").

A major function of the spleen is to remove particulates (eg, opsonized bacteria, antibody-coated cells) from the blood stream [4]. This function is most apparent when the spleen has been removed, since splenectomized patients are susceptible to bacterial sepsis, especially with encapsulated organisms. This function is also associated with trapping and destruction antibody-coated platelets or red cells in patients with autoimmune thrombocytopenia or hemolytic anemia, respectively. (See "Clinical features and management of sepsis in the asplenic patient", section on 'Role of the spleen in host defense' and "Treatment and prognosis of immune (idiopathic) thrombocytopenic purpura in adults", section on 'Splenectomy' and "Treatment of autoimmune hemolytic anemia: Warm agglutinins", section on 'Splenectomy'.)

The spleen also serves as a quality control mechanism for red cells, removing senescent and/or poorly deformable red cells from the circulation. This "culling" function is taken advantage of when splenectomy is employed as treatment for hereditary spherocytosis. (See "Hereditary spherocytosis: Clinical features; diagnosis; and treatment", section on 'Splenectomy'.)

As part of this quality control function, the spleen also removes particles from within circulating red cells (ie, its "pitting" function), such as nuclear remnants (Howell-Jolly bodies), insoluble globin precipitates (Heinz bodies), and normally-occurring endocytic vacuoles. Of clinical importance, Howell-Jolly bodies appear in circulating red cells when the spleen has been surgically removed or has reduced function (ie, hyposplenism), and subsequently disappear when and if splenic function returns, as in the following circumstances:

- **Splenosis due to the growth of splenic implants resulting from the spillage of cells from the splenic pulp during splenectomy.** (See 'Splenosis' below.)
- **Growth of a preexisting accessory spleen following splenectomy, classically (albeit rarely) described in patients with ITP undergoing a late relapse after successful splenectomy.** (See "Chronic refractory immune (idiopathic) thrombocytopenic purpura in adults", section on 'Accessory splenectomy'.)
- **Improvement in splenic function, as seen in some patients with sickle cell anemia following successful allogeneic hematopoietic cell transplantation** [5] or institution of a chronic transfusion program in children or young adults [6,7].
Hypersplenism — Normally, about one-third of the platelet mass is sequestered in the spleen, where it is in equilibrium with circulating platelets. Splenic sequestration of platelets can be increased to 90 percent in cases of extreme splenomegaly, although total platelet mass and overall platelet survival remain relatively normal (figure 1) [8].

Patients with cirrhosis, portal hypertension, and splenomegaly may have significant degrees of "apparent" thrombocytopenia (with or without leukopenia and anemia), but rarely have clinical bleeding, since their total platelet mass is usually normal. (See "Extrinsic nonimmune hemolytic anemia due to mechanical damage: Fragmentation hemolysis and hypersplenism", section on 'Extravascular nonimmune hemolysis due to hypersplenism'.)

Hyposplenism and asplenia — Splenic functions are lost when the spleen is congenitally absent, has been surgically removed, has atrophied following repeated infarction (eg, sickle cell disease), or following splenic artery thrombosis.

Splenic function is reduced in the neonate and may be abnormally reduced (called hyposplenism or functional asplenia) when it is engorged with blood (eg, splenic sequestration crisis associated with sickle cell disease, malaria, splenic vein thrombosis), or infiltrated (sarcoidosis, amyloidosis, tumors, cysts) [9-11].

Functional asplenia has also been described in autoimmune disease, celiac disease, and inflammatory bowel disease; the mechanism in these latter settings is unclear [12-15]. (See "Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults", section on 'Hyposplenism'.)

Subjects with hyposplenism or functional/surgical asplenia may show any or all of the following [15,16] (see "Overview of the clinical manifestations of sickle cell disease", section on 'Reduced or absent splenic function'):

- Sepsis with encapsulated organisms, especially in children. (See "Clinical features and management of sepsis in the asplenic patient", section on 'Incidence'.)
- Mild degrees of thrombocytosis (table 1) and leukocytosis.
- The presence of Howell-Jolly bodies in circulating red cells, along with increased numbers of target cells and misshapen red cells (picture 1 and picture 2). Howell-Jolly bodies can be quantitated to provide an estimate of the degree of splenic hypofunction [17,18]. (See "Evaluation of the peripheral blood smear", section on 'Howell Jolly bodies'.)
- Increased number of erythrocyte "pits" and Heinz bodies. Demonstration of these abnormalities requires special techniques such as interference microscopy and supravital dyes, respectively. Quantitation of the number of pitted erythrocytes has been used to estimate the volume and function of splenic tissue remaining after splenectomy [19].
- Depending upon the degree of hypofunction, imaging studies may demonstrate decreased or absent uptake of radioactive colloid, red cells, white cells, and/or platelets by the spleen [9-11,13].

Splenosis — Splenic implants may result from the spillage of cells from the splenic pulp following injury or splenectomy, a condition called splenosis. These implants, which are often multiple, can be located anywhere in the peritoneal cavity, and may be confused with neoplasms or endometriosis [20,21]. If traumatic splenic rupture is accompanied by a diaphragmatic tear, implants can also be present within the pleural or pericardial cavities [22-24].

These implants, which consist of normal splenic tissue, can be diagnosed via tissue biopsy techniques or non-invasively through radioisotope scanning, using either Tc99m sulfur colloid or labeled, heat-denatured red cells [25,26]. If the patient has had a prior splenectomy, a presumptive diagnosis of splenic implants can be made if the peripheral smear no longer shows the presence of Howell-Jolly bodies (see 'Hyposplenism and asplenia' above) [24].
**Splenic abscess** — Splenic abscess is an uncommon infection that typically results from endocarditis or seeding from some other site of infection [27-31]. The frequency of this complication was evaluated in a review of 564 patients with documented endocarditis in whom 27 (4.8 percent) developed splenic abscess [28].

Typical clinical manifestations are fever that may be recurrent or persistent despite antimicrobial therapy and left upper quadrant pain with or without splenomegaly [28,29,31]. However, some patients lack these classic features [32]. Splenic abscess may be accompanied by a left-sided pleural effusion [31] or by splenic infarction if due to septic emboli [27].

A splenic abscess can usually be seen on CT scan [27,28], although the lesion may be incorrectly called an infarct [28] which also can be a complication of bacterial endocarditis [27]. (See 'Symptoms' below.)

Splenic abscess is usually managed by a combination of antibiotic therapy and splenectomy [27-29,32]. CT-guided percutaneous aspiration is occasionally successful, but this approach has not replaced splenectomy as the standard of care [32].

**Splenic infarction** — Splenic infarction occurs when the splenic artery or one or more of its sub-branches become occluded with an infected or bland embolus or clot. Affected patients classically present with acute left upper quadrant pain and tenderness, although atypical presentations are common. As an example, in a study of 26 patients with splenic infarction seen at a single medical center, the following clinical and laboratory features were noted [33]:

- Left-sided abdominal pain: 48 percent; abdominal pain was absent in 16 percent
- Fever >38°C: 36 percent
- Left upper quadrant abdominal tenderness: 36 percent; abdominal tenderness was absent in 32 percent
- Nausea or vomiting: 32 percent
- Splenomegaly: 32 percent
- Elevated serum lactate dehydrogenase (LDH): 71 percent
- White blood cell count >12,000/microL: 56 percent

Splenic infarction can occur in a variety of settings [34]:

- Presence of a hypercoagulable state (eg, malignancy, antiphospholipid syndrome) [35]
- Embolic disease (eg, atrial fibrillation, patent foramen ovale, atheromatous disease, infective endocarditis) [27,36,37]. Splenic artery embolization has been therapeutically employed in order to reduce splenic blood flow in some patients with severe portal hypertension, prior to laparoscopic splenectomy in order to diminish intraoperative blood loss, as well as for the treatment of splenic injury [38]. (See "Treatment of diuretic-resistant ascites in patients with cirrhosis", section on 'Splenic artery embolization' and "Hereditary spherocytosis: Clinical features; diagnosis; and treatment", section on 'Splenectomy'.)
- Underlying myeloproliferative disorder with associated (often massive) splenomegaly (eg, polycythemia vera, essential thrombocythemia, primary myelofibrosis)
- Underlying hemoglobinopathy, especially sickle cell disease [39-41]. (See "Hepatic manifestations of sickle cell disease", section on 'Computerized tomography' and 'Hyposplenism and asplenia' above.)
- Any condition associated with marked splenomegaly (eg, Gaucher disease, splenic lymphoma). (See "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis", section on 'Visceral disease'.)
- Trauma to the spleen which compromises its vascularity. Splenic hematoma and laceration may also occur following blunt abdominal trauma. This subject is discussed in detail separately. (See "Liver, spleen, and pancreas injury in children with blunt abdominal
Splenic arterial torsion, as seen in the "wandering spleen" syndrome. (See "Differential diagnosis of abdominal pain in adults", section on 'Wandering spleen syndrome'.)

Splenic infarction and splenic rupture are uncommon complications of infectious mononucleosis. (See "Clinical manifestations and treatment of Epstein-Barr virus infection", section on 'Splenic rupture'.)

Splenic calcification and cysts — With the increase in ultrasound and imaging procedures, patients are being referred who have abnormalities in splenic architecture that frequently have nothing to do with the patient's complaints. This has lead to patient anxiety and multiple extensive and repetitive further imaging studies at considerable expense and little apparent clinical benefit. Two such findings are splenic calcification and splenic cysts.

Calcification — Splenic calcification may be noted on conventional imaging techniques, and may or may not be associated with splenomegaly. A vast number of abnormal conditions may be associated with such calcifications, including phleboliths, splenic artery aneurysm, sickle cell disease [42], tumors (eg, hemangioma, hemangiosarcoma, lymphoma), and infections (eg, histoplasmosis, brucellosis, echinococcosis, candidiasis, tuberculosis) [43-51].

Gamma-Gandy bodies are fibro-siderotic nodules impregnated with iron pigment (hemosiderin) and calcium that may appear in the spleen in congestive splenomegaly, sickle cell anemia, and hemochromatosis [52]. They likely represent areas of organized hemorrhage.

Cysts and pseudocysts — A splenic cyst (or multiple cysts) may be noted as an incidental finding on conventional imaging techniques, or as a result of evaluation of a patient with left upper quadrant pain, left shoulder pain, abdominal enlargement, or splenomegaly. A vast number of abnormal conditions, many of which are rare, may be associated with such cysts, including [53,54]:

- Post-traumatic cysts/pseudocysts, including cystic splenosis
- Hydatid (echinococcal) cysts
- Congenital cysts
- Epidermoid, mesothelial cysts
- Hemangioma, lymphangioma
- Polycystic kidney disease with splenic cysts
- Splenic peliosis
- Cystic metastasis to the spleen

Some splenic cysts may remain unchanged for many years, while others may enlarge slowly, enlarge to massive proportions, rupture, bleed, or become secondarily infected. Since non-parasitic splenic cysts are rare, there is no evidence-based information regarding their optimal surgical management [55].

For those with symptomatic cysts, or cysts that are enlarging over time, a number of radiologic and surgical procedures are available for investigating the probable diagnosis [55-57]. Available options for those with non-parasitic cysts include percutaneous procedures (eg, biopsy, aspiration, drainage), or more direct surgical interventions such as decapsulation/cyst wall unroofing, partial or total splenectomy. However, only splenectomy provides diagnostic certainty, which is rarely clinically justified.

Treatment of echinococcal cysts is discussed separately. (See "Treatment and prevention of echinococcosis".)

Splenic rupture

Traumatic splenic rupture — Blunt abdominal trauma most often results in injury to the
spleen, which in over 60 percent of cases is the only damaged intraperitoneal structure. Delayed splenic rupture can occur. This subject is discussed separately.

- (See "General approach to blunt abdominal trauma in adults".)
- (See "Diagnosis and management of splenic injury in the adult trauma patient".)
- (See "Surgical management of splenic injury in the adult trauma patient".)
- (See "Child abuse: Injuries of the thorax; abdomen; retroperitoneum; and pelvis".)
- (See "Liver, spleen, and pancreas injury in children with blunt abdominal trauma", section on 'Spleen'.)

**Atraumatic splenic rupture** — Splenic rupture in the absence of trauma is uncommon, but may be life-threatening. In a systematic review of 845 cases from the literature, in which the mortality was 12 percent, six major causes were described [58]:

- Neoplasm (eg, leukemia, lymphoma) — 30 percent
- Infection (eg, infectious mononucleosis, CMV, HIV, endocarditis, malaria) — 27 percent
- Inflammatory disease/non-infectious disorders (eg, acute and chronic pancreatitis, primary amyloidosis) — 20 percent
- Drug and treatment related (eg, anticoagulation, G-CSF, thrombolytic therapy, dialysis) — 9 percent
- Mechanical causes (eg, pregnancy-related, congestive splenomegaly) — 7 percent
- Idiopathic (normal spleen) — 7 percent

Risk factors for mortality included splenomegaly, age >40 years, and the presence of a neoplastic disorder. Splenectomy was performed in 84 percent of the cases, with conservative measures taken in the remainder.

**Splenectomy** — Splenic artery aneurysms are the third most common aneurysms found within the abdomen, after those of the aorta and iliac arteries. They are clinically important because of the possibility of rupture, which is associated with a high mortality rate, especially during pregnancy and/or in patients with portal hypertension [59,60]. They are often calcified and may be mistaken for lesions of the distal pancreas [61]. (See "Approach to abdominal pain and the acute abdomen in pregnant and postpartum women", section on 'Splenic artery aneurysm' and "Pregnancy in women with pre-existing chronic liver disease", section on 'Cirrhosis and portal hypertension'.)

Treatment options include surgical resection with vascular reconstruction, stenting of the vessel or endovascular coil/glue ablation techniques [62-64].

**Symptoms** — The presence or absence of symptoms due to an enlarged spleen depends on many factors, such as the acuteness and nature of the underlying illness, as well as the size of the spleen. Thus, a minimally enlarged spleen secondary to an acute viral infection may be quite tender, while a markedly enlarged spleen in one of the chronic myeloproliferative disorders (eg, polycythemia vera, primary myelofibrosis) may be totally asymptomatic unless there is an episode of splenic infarction.

When present, symptoms of an enlarged spleen may include one or all of the following:

- Pain, a sense of fullness, or discomfort in the left upper quadrant
- Pain referred to the left shoulder
- Early satiety, due to encroachment on the adjacent stomach

Acute pleuritic-like pain and tenderness in the left upper quadrant in the presence of fever suggests the presence of perisplenitis or splenic abscess, most likely due to infection originating elsewhere in the body (eg, sepsis, infective endocarditis). Splenic abscess may be accompanied by a left pleural effusion [31] or by splenic infarction if due to septic emboli [27]. Some patients with splenic infarction have an associated friction rub over the infarcted area. (See 'Splenectomy' above and "Differential diagnosis of abdominal pain in adults".)
SPLENIC SIZE AND PALPABILITY — The median splenic weight in adults is about 150 grams [3,65]. It is not usually palpable, but may be felt in children, adolescents, and some adults, especially those of asthenic build [66]. A spleen becomes palpable not only as a result of its size, but also its texture. Ordinarily, the spleen is a soft organ, but a spleen infiltrated with lymphoma or one with extramedullary hematopoiesis (eg, a myeloproliferative disorder) is much firmer and thus easier to feel. (See 'Normal splenic function' above.)

Physical examination — A number of studies have shown wide interobserver variability in the ability to appreciate an enlarged spleen, which is generally not associated with the level of clinical experience [67]. There are at least six different palpation and percussion maneuvers available. Only two of these will be discussed here: abdominal palpation and percussion of Traube's semilunar space. The interested reader is referred to the literature and textbooks of physical examination techniques for further information on this subject [37,67-69].

Palpation method — The most frequent errors made in examination of the spleen involve incomplete relaxation of the abdominal musculature of the patient and the musculature of the examiner's hand(s). Effectiveness in palpating the spleen can be maximized by remembering that the major error in splenic palpation is due to pressing too hard on the patient's abdomen, and by paying attention to the following:

- With the patient supine, allow the patient to feel the examining hand on the abdomen before pressing down, and to become adjusted to its presence. Do not suddenly increase pressure during palpation, as an enlarged spleen may be quite tender (particularly if it has enlarged quickly) and the patient may be reluctant to allow the examination to continue.
- Make sure that the patient is relaxed, with arms at the sides of the abdomen. If the arms are raised, this may stiffen the abdominal musculature and make examination more difficult.
- Relaxation of the patient can be improved if the legs and neck are slightly flexed. Relaxation of the examiner can be improved by being comfortably seated in a chair alongside the patient's bed or examining table, with the examiner on the patient's right side, the right hand doing the palpation and the left hand underneath and supporting the patient's left lower posterior rib cage.

A spleen that is only minimally enlarged will be quite movable with respiration, and may be palpable only at the end of inspiration. Using a light touch, with the skin depressed under the left costal margin, a minimally enlarged spleen can be felt as a rounded edge with the consistency of normal liver, which slips under the examiner's fingers at the end of inspiration and back on expiration.

Since the spleen is normally a posterior structure, increased sensitivity can occasionally be obtained by placing the patient in the right lateral decubitus position, with knees and neck flexed. This maneuver also increases relaxation of the abdominal musculature and rotates the spleen to a more anterior position. One study suggested that this additional maneuver was not useful when it followed examination of the patient in the supine position [37]. However, it is this authors' experience that some spleens not palpable with the patient in the supine position are felt with the patient in the right lateral decubitus position.

With greater degrees of enlargement, the spleen rotates to a more anterior and rightward position, and may extend downward into the pelvis. Under these circumstances, the lower pole of the spleen may not be easily felt (since it is well below the left costal margin), and splenomegaly is appreciated either by palpating at successively lower levels on the left side of the abdomen or by palpating the medial edge of the spleen. The presence of a notch or indentation on the medial splenic edge is a further indication that the mass is spleen and not the left kidney or a pancreatic pseudocyst.

In more extreme cases, the enlarged spleen extends across the midline, and may even be palpable
in the right upper quadrant. The presence of exquisite splenic tenderness suggests the presence of infarction or perisplenitis in such massively enlarged spleens.

**Percussion of Traube's semilunar space** — The tympanitic area overlying the gastric stomach bubble in the left lateral hemithorax has been called Traube's semilunar space [70]. The size and location of this space depends upon the contents and position of the stomach. The space will be obliterated in the presence of left pleural or pericardial effusion, and will be displaced downward following enlargement of the left lobe of the liver or, more commonly, the spleen. False-positive and false-negative results may be obtained, however, in patients examined too soon after a meal and in obese subjects, respectively [71].

**Accuracy** — The ability to palpate an enlarged spleen depends upon several variables, including:

- The size of the spleen. Minimally enlarged spleens may not be felt under any circumstance. In one study, all spleens with an estimated weight (from scanning studies) exceeding 300 grams were palpable, with the average estimated weight of a palpable spleen being 285 grams [72]. However, some spleens weighing as much as 900 grams are not palpable [73].

- The body habitus of the patient. The spleen is easier to feel in thin individuals and in those who do not have an increased anterior-posterior thoracic diameter.

- The skill of the examiner coupled with the ability of the patient to cooperate during the examination.

- The method(s) employed (see below).

Using ultrasound examination of the spleen as a gold standard (criteria described above), a number of studies have compared the various palpation and percussion techniques for evaluating splenic size. Major conclusions from all of these studies are the insensitivity of available techniques, wide interobserver variability, and the complementary value of combinations of techniques (ie, palpation plus percussion). Specific observations in individual studies can be summarized:

- Palpation of the spleen was significantly more accurate in lean versus obese individuals [37].

- Sensitivity and specificity of percussion of Traube's semilunar space were 62 and 72 percent, respectively [71].

- The specificity of direct splenic palpation was 92 percent, with a positive predictive value of 92 percent [69].

- The combination of positive results on percussion of Traube's space (ie, dullness to percussion) and positive palpation had a sensitivity and specificity of 46 and 97 percent, respectively [37].

If palpation maneuvers convince the examiner that the spleen is enlarged, this high degree of specificity suggests that follow-up scanning to confirm the finding is not necessary. However, scanning may still be useful to document baseline splenic involvement and size in preparation for treatment, or to document the presence of other abnormalities (eg, infiltrative disease of other abdominal organs, intraabdominal lymphadenopathy).

**Splenic imaging for size estimation** — There is a reasonably close correlation between splenic weight and splenic size on external scanning. This was illustrated in a retrospective study of 81 patients who had undergone a total of 101 abdominal ultrasound examinations within four months of death and whose spleens were weighed during autopsy; the splenic weight in grams was equal to (0.43 x length x width x thickness) for measurements in centimeters [74].

A number of criteria have been proposed to define the size of the normal spleen using these
procedures:

- Ultrasound — The spleen is considered to be normal in size if its length is <13 cm [67] or its thickness is ≤5 cm on ultrasound examination [75]. In one study of healthy stem cell donors, mean values for splenic length and width were 10.8 and 3.6 cm, respectively [76]. The mean predictive errors for repeated ultrasound measurements of splenic length and width were 1.5 and 1.9 mm, respectively.

- Plain film — The spleen is normal in size if it is not seen on the abdominal plain film, if it is <5 cm in width, or if it is less than 85 percent of the size of the normal kidney [72]. It is considered enlarged if it is >6 cm wide or >13.6 cm long, or if (length x width) is >75 cm².

- Liver-spleen colloid scanning — The spleen is normal in size if its length on the posterior view of the liver-spleen scan is ≤13 cm [77]. It is considered enlarged if the posterior length is >14 cm, or if the lateral scan area exceeds 80 cm² [72]. In one study, 98 of 100 spleens with a posterior length ≤13 cm on colloid scanning weighed less than 250 grams and were normal at postmortem examination [77].

- CT scanning — The spleen is enlarged if its length is >10 cm [78]. In one study this value had a sensitivity, specificity, and accuracy of 81, 90, and 88 percent, respectively.

A study of spleen size by CT scanning was done in adults 17 to 88 years of age to determine if a single measurement, as opposed to a volume determination, could be used to define splenomegaly [78]. The authors evaluated splenic length, width, and thickness in 249 CT scans and assessed the spleen’s relationship to the left lobe of the liver and the inferior third of the left kidney. Based upon an upper limit of 314 cubic cm for the volume of a normal spleen, they found a maximum normal spleen length of 9.8 cm, similar to the above-noted value of 10 cm [78]. If the spleen extended below the lower third of the kidney, this was also evidence for splenomegaly.

Using the above criteria as "gold standards" for normal and abnormal splenic size, studies concerning the ability to palpate a normal or enlarged spleen have concluded that not all palpable spleens are abnormal; this is especially true in asthenic individuals. In one study, for example, no splenic pathology was clinically evident in 19 of 21 patients with palpable splenomegaly (at least two observers) and a posterior splenic length ≤13 cm on liver-spleen scan [77].

Nevertheless, a palpable spleen usually means the presence of significant splenomegaly. As a general rule, a spleen has to be increased in size by at least 40 percent before it becomes palpable [79]. However, it has been estimated that 20 percent of spleens with an estimated weight of more than 900 grams are not palpable [73].

CAUSES OF SPLENOMEGALY

General conditions — The causes of an enlarged spleen are multiple; most reflect the presence of hepatic or hematologic disease, infection, or inflammation (table 2). Such causes include the following:

- Splenic engorgement due to sequestration of red blood cells, as in congenital spherocytosis or other congenital or acquired hemolytic anemias. A significantly enlarged spleen is routinely seen in normal subjects serving as hematopoietic cell donors following treatment with granulocyte colony-stimulating factor [76,80].

Other causes for splenic engorgement include splenic trauma with intracapsular hematoma formation, sequestration crisis in sickle cell disease, chronic congestive failure, or portal hypertension. (See "Extrahepatic portal vein obstruction (portal vein thrombosis)", section on 'Splenomegaly'.)

- Chronic inflammation or infection, as in systemic lupus erythematosus, rheumatoid arthritis, infective endocarditis, or chronic malaria. (See "Clinical manifestations and diagnosis of
Felty's syndrome", section on 'Splenomegaly'.

- Lipid deposition disorders such as Gaucher disease (see "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis")
- Congenital causes for splenomegaly include splenic hemangioma, hamartoma, or cysts.
- Splenic invasion with granulomatous or malignant hematologic disease.
- Primary vascular neoplasms (eg, angiosarcoma) [81]

**Splenic metastases** — Non-hematologic malignancies rarely metastasize to the spleen. The most common primary sites include breast, lung, colorectal, ovarian carcinomas and melanoma in cases of cancer involving multiple visceral sites and colorectal and ovarian carcinomas in cases in which there is a solitary splenic lesion [82].

**Common causes** — The relative frequency of the different causes of splenomegaly was evaluated in a series of 449 patients who were studied retrospectively and categorized; the most common cause in each category is shown in parentheses [83]:

- **Liver disease** — 33 percent (cirrhosis)
- **Hematologic malignancy** — 27 percent (lymphoma)
- **Infection** — 23 percent (AIDS, endocarditis)
- **Congestion or inflammation** — 8 percent (congestive failure)
- **Primary splenic disease** — 4 percent (splenic vein thrombosis)
- **Other or unknown** — 5 percent

**Massively enlarged spleen** — A spleen enlarged such that its lower pole is within the pelvis, or which has crossed the midline into the right lower or right upper abdominal quadrants is considered to be massively enlarged. There are only a few conditions that cause this degree of splenic enlargement, each of which discussed elsewhere on the appropriate topic reviews:

- Chronic myeloid leukemia
- Myelofibrosis, idiopathic or post-polycythemic
- Gaucher disease
- Lymphoma, usually indolent, including hairy cell leukemia
- Kala-azar (visceral leishmaniasis)
- Hyperreactive malarial splenomegaly syndrome, also called tropical splenomegaly syndrome [84]
- Thalassemia major
- AIDS with Mycobacterium avium complex [83]

**EVALUATION OF THE PATIENT**

**Initial approach** — The history may provide valuable clues as to the cause of splenomegaly. As examples:

- A patient with chronic alcoholism or hepatitis and ascites probably has splenomegaly secondary to cirrhosis and portal hypertension. (See "Diagnostic approach to the patient with cirrhosis".)
- A young adult with fatigue, fever, sore throat, and splenomegaly is likely to have infectious mononucleosis or other viral infection. (See "Infectious mononucleosis in adults and adolescents", section on 'Classic IM'.)
- An older adult complaining of post-bath pruritus with a ruddy complexion and splenomegaly is likely to have polycythemia vera. (See "Diagnostic approach to the patient with suspected polycythemia vera".)

In the patient with systemic complaints such as fever, night sweats, malaise, and/or weight loss,
an enlarged spleen may reflect activity of a systemic disease that may have already been diagnosed, such as AIDS, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, malaria, tuberculosis, viral infection (infectious mononucleosis, cytomegalovirus, hepatitis), or hematologic disorders (chronic myeloid leukemia, chronic lymphocytic leukemia, hairy cell leukemia). In such cases, the spleen may revert to normal size when the underlying disease is brought under control with appropriate therapy.

Unexplained splenomegaly — A problem often confronting the examining clinician is when the patient presents with splenomegaly for which no prior diagnosed or evident condition can be considered responsible. A reasonable and standard approach to such patients begins with an accurate history (including recent travel information), physical examination, complete blood count with white blood cell differential and platelet count and examination of the peripheral blood smear, liver function studies, urinalysis, and chest x-ray. Testing for the presence of antibodies to HIV should be considered when no other causes for splenomegaly are apparent. Abnormalities found at this time should help guide the physician to an appropriate diagnosis. (See 'Additional approaches' below.)

Imaging studies — A variety of imaging techniques are available for assessment of splenic lesions (eg, splenic cysts, other space-occupying lesions), including CT scanning, magnetic resonance imaging, ultrasound, Tc-99m sulfur colloid scintigraphy, and 18F-FDG PET. The age of the patient, clinical symptomatology, and imaging characteristics may help the radiologist arrive at the correct diagnosis [54,85-87].

CBC and peripheral smear — The complete blood count, examination of the peripheral smear, and white blood cell differential are often of utmost importance in determining the cause of an enlarged spleen:

- Neutropenia, anemia, and/or thrombocytopenia may be present, as these formed elements can be trapped in an enlarged spleen, giving the nonspecific picture termed "hypersplenism." (See "Extrinsic nonimmune hemolytic anemia due to mechanical damage: Fragmentation hemolysis and hypersplenism", section on 'Extravascular nonimmune hemolysis due to hypersplenism'.)

- There is no predictable relationship between the degree of splenomegaly and the presence or degree of these cytopenias or of possible associated symptoms such as colicky abdominal or left upper quadrant pain, pain while lying on one's side, or early satiety [3].

The cytopenias seen with hypersplenism are not associated with abnormal white blood cell or red blood cell forms. However, cytopenias are nonspecific, as multiple other causes, including certain infections, can provoke these changes in a patient with splenomegaly.

- Neutrophilia (ie, absolute neutrophil count >7700/microL) with or without increased numbers of band and metamyelocyte forms ("left shift"), suggest the presence of infection. (See "Approach to the patient with neutrophilia".)

- On occasion, invading organisms may be seen on the peripheral smear, either free in the plasma as in overwhelming sepsis, or within neutrophils or monocytes (bacteria, ehrlichiae) or red blood cells as occurs with bartonellosis, babesiosis (picture 3), and malaria (picture 4A-B). (See "Extrinsic nonimmune hemolytic anemia due to systemic disease", section on 'Direct parasitization'.)

- Patients with overwhelming bacterial sepsis may show other abnormalities on smear, including microangiopathic changes in red blood cells (picture 5) and toxic granulation, vacuoles, and Dohle bodies in neutrophils (picture 6). (See "Approach to the patient with neutrophilia", section on 'Evaluation of the complete blood count'.)

- Certain infectious organisms are associated with relatively specific changes, such as red
blood cell agglutination due to the presence of cold agglutinins (picture 7) in infections with Mycoplasma pneumoniae or in infectious mononucleosis, and the atypical lymphocytes seen in the latter infection (picture 8). (See "Pathogenesis of autoimmune hemolytic anemia: Cold agglutinin disease" and "Infectious mononucleosis in adults and adolescents").

- The combination of sepsis and profound anemia along with hemoglobinemia, hemoglobinuria, and the presence of microspherocytes and red cell ghosts on the peripheral blood smear (ie, massive intravascular hemolysis) suggests infection with a phospholipase-producing Clostridial organism. (See "Clostridial myonecrosis", section on 'Clinical manifestations' and "Extrinsic nonimmune hemolytic anemia due to systemic disease", section on 'Clostridium perfringens'.)

- The presence of white blood cells less mature than band forms and nucleated red cells on the peripheral smear, along with teardrop-shaped red cells (ie, a leukoerythroblastic blood picture) (picture 9), suggests the presence of widespread bone marrow invasion with malignancy. (See "Anemias due to decreased red cell production", section on 'Leukoerythroblastic anemia'.)

This picture may also be seen in tuberculosis and chronic myeloid leukemia and is quite typical for primary and secondary forms of myelofibrosis. These three diagnoses can be established through culture and staining techniques, the presence of the bcr-abl construct or Ph1 chromosome, and bone marrow biopsy, respectively.

- In systemic lupus erythematosus, circulating LE cells (picture 10) can be seen on rare occasions, while patients with neutropenia and rheumatoid arthritis may have an increased percentage of circulating large granular lymphocytes (picture 11). (See "Large granular lymphocyte leukemia in rheumatoid arthritis".)

- The presence of increased numbers of abnormal cells in the peripheral blood suggests the presence of a hematologic malignancy. Morphologic evaluation, coupled with special staining and immunocytochemical techniques, can help to establish the correct diagnosis [88]. (See "Evaluation of the peripheral blood smear", section on 'Worrisome findings'.)

**Additional approaches**

**General considerations** — If no abnormalities are suggested by the above workup, CT examination of the chest and abdomen should be performed to evaluate the patient for disseminated or intra-abdominal malignancy, such as hepatoma or lymphoma, advanced liver disease, or portal hypertension. Consultation with a hematologist would be appropriate at this time, especially if examination of the peripheral blood smear has not been performed, or if changes are present which cannot be adequately assessed by the patient's primary clinician.

An alternative approach is to biopsy tissue depending upon the clinical suspicion. Thus, if infection is suspected, a lymph node or bone marrow aspiration and biopsy may be indicated, a liver biopsy if liver disease is suspected, and a bone marrow biopsy if a hematologic disorder is suspected [83]. Without a specific organ or tissue to biopsy, a reasonable approach would be performance of a bone marrow aspiration with biopsy with culture. Conditions such as lipid storage diseases, disseminated mycobacterial or granulomatous disease, and lymphoid or myeloid disorders may be diagnosed in this way (picture 12 and picture 13). (See "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis".)

**Diagnostic splenectomy** — If the above procedures have not led to a diagnosis (eg, abdominal sonography, whole body CT examination, bone marrow aspiration and biopsy, examination of the peripheral smear, tests of liver and kidney function [89]), splenectomy may be considered, with the value of making a diagnosis balanced by considerations of surgical morbidity and mortality. (See "Hereditary spherocytosis: Clinical features; diagnosis; and treatment", section on 'Splenectomy' and "Treatment and prognosis of immune (idiopathic) thrombocytopenic purpura..."
The resected spleen may reveal a localized splenic tumor, cyst(s), inflammatory pseudotumor, hamartoma, amyloid, vascular anomaly, infection, sarcoidosis, or other rare condition [90,91]. In some cases, a satisfactory answer may not be available even after pathologic examination. In a series of 122 "diagnostic" splenectomies performed for unexplained splenomegaly, splenic mass lesion, or to accurately classify a lymphoproliferative disorder detected but not further characterizable on bone marrow or peripheral blood examination, the most common pathologic diagnoses were [92]:

- Lymphoma/leukemia — 57 percent
- Metastatic carcinoma/sarcoma — 11 percent
- Cyst/pseudocyst — 9 percent
- Benign/malignant vascular neoplasm — 7 percent

In the subgroup of 41 patients undergoing splenectomy for splenomegaly without a splenic mass lesion or evidence of a lymphoproliferative disorder, lymphoma/leukemia was still the most common pathologic diagnosis (58 percent). Of interest, no distinct histologic abnormality was found in 5 percent of the 122 resected spleens. Similar results were reported in two series of patients undergoing diagnostic splenectomy, in which a lymphoma was found in 37 and 39 percent of the resected spleens [93,94].

**Splenic aspiration/biopsy** — Splenic aspiration/biopsy is not widely practiced in the United States because of the risk of bleeding. As an example, a 1985 study reported a major complication rate of 13 percent for percutaneous biopsy of the spleen performed with a 14 gauge needle [95]. However, subsequent reports of fine needle aspiration/biopsy of the spleen under radiologic or ultrasound guidance have indicated much lower complication rates using smaller diameter needles (ie, 18 gauge or smaller), allowing for a safer procedure along with avoidance of the need for major surgical intervention (ie, open splenic biopsy or splenectomy) [96-100].

In a meta-analysis that included four studies meeting inclusion criteria for diagnostic accuracy (639 patients) and nine studies meeting inclusion criteria for complication rates (741 patients), it was concluded that image-guided percutaneous biopsy of the spleen demonstrated high diagnostic accuracy, with a sensitivity and specificity of 87 and 96 percent, respectively [101]. The pooled overall complication rate was 4.2 percent (core needle biopsy: 5.8 percent, fine needle aspiration biopsy: 4.3 percent). However, sensitivity analysis with the removal of biopsies performed with needles larger than 18 gauge showed overall and major complication rates of 3.9 and 1.3 percent, respectively, similar to those reported for biopsies of the liver and kidney.

While splenic aspiration/biopsy is safer than it was in the past, we believe that this procedure is of minimal clinical utility and does not provide information that could not be obtained by other means.

**SUMMARY**

**Splenic function** — The spleen has the following major functions. (See 'Introduction' above and 'Normal splenic function' above.)

- Participates in cellular and humoral immunity
- Removes senescent and/or poorly deformable red cells, bacteria, and other particulates from the circulation
- Under abnormal circumstances the spleen may become the site of extramedullary hematopoiesis
- Approximately one-third of circulating platelets are sequestered in the spleen, where they are in equilibrium with circulating platelets

**Normal splenic size** — The median splenic weight in adults is about 150 grams and the organ is not usually palpable on physical examination. In one study the average estimated weight of a
palpable spleen was 285 grams. On ultrasound the spleen is considered to be normal in size if its length is <13 cm. (See 'Splenic size and palpability' above.)

**Splenic abnormalities** — Symptoms of an enlarged or abnormal spleen include one or all of the following. (See 'Symptoms' above.)

- Pain, fullness, or discomfort in the left upper quadrant of the abdomen
- Pain referred to the left shoulder
- Early fullness after meals, due to pressure on the adjacent stomach

Splenic abnormalities can include the following. (See 'Splenic disorders' above.)

- Increased function (hypersplenism). (See 'Hypersplenism' above.)
- Decreased to absent function (hyposplenism, asplenia). (See 'Hyposplenism and asplenia' above.)
- Abscess, infarction, calcification, cysts. (See 'Splenic abscess' above and 'Splenic infarction' above and 'Splenic calcification and cysts' above.)
- Traumatic or atraumatic rupture. (See 'Splenic rupture' above.)

**Causes for an enlarged spleen** — The major causes for an enlarged spleen are shown in the table (table 2). Only a few disorders are associated with a massively enlarged spleen (ie, lower pole within the pelvis or the splenic edge has crossed the midline). (See 'Causes of splenomegaly' above and 'Massively enlarged spleen' above.)

**REFERENCES**


Jama AH, Salem AH, Dabbous IA. Massive splenic infarction in Saudi patients with sickle cell


92. Kraus MD, Fleming MD, Vonderheide RH. The spleen as a diagnostic specimen: a review of 10


Topic 7134 Version 16.0
This figure shows the two-hour recovery in the general circulation of radioactively-labeled platelets transfused to asplenic (red), normal (green), and splenomegalic (orange) patients. The vast majority of the splenomegalic patients had congestive splenomegaly secondary to cirrhosis with portal hypertension. Adapted from: Aster, RH. Pooling of platelets in the spleen: role in the pathogenesis of 'hypersplenic' thrombocytopenia. J Clin Invest 1966; 45:645.
## Major causes of reactive thrombocytosis

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<tr>
<th>Nonmalignant hematologic conditions</th>
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<tbody>
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<td>Acute blood loss</td>
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<td>Acute hemolytic anemia</td>
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<td>Iron deficiency anemia</td>
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<td>Treatment of vitamin B12 deficiency</td>
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<td>Rebound effect after treatment of ITP</td>
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<td>Rebound effect after ethanol-induced thrombocytopenia</td>
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<td>Metastatic cancer</td>
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<td>Lymphoma</td>
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<td>Rebound effect following use of myelosuppressive agents</td>
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<td>Inflammatory bowel disease</td>
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<td>Celiac disease</td>
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<td>Functional and surgical asplenia</td>
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<td>POEMS syndrome (osteosclerotic myeloma)</td>
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<td>Acute pancreatitis</td>
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<td>Post-surgical period, especially post-splenectomy</td>
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<td>Interleukin-1B</td>
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<td>All-trans retinoic acid</td>
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<td>Thrombopoietin, thrombopoietin mimetics</td>
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<td>Low molecular weight heparins (enoxaparin)</td>
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Howell-Jolly bodies

This peripheral blood smear shows Howell-Jolly bodies in two red cells (black arrows), nuclear remnants that are normally removed by the spleen. Thus, they are seen in patients who have undergone splenectomy (as in this case) or have functional asplenia (eg, sickle disease disease). Target cells are also seen (blue arrows), another consequence of splenectomy. *Courtesy of Carola von Kapff, SH (ASCP).*
Normal peripheral blood smear

High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter. Courtesy of Carola von Kapff, SH (ASCP).
Sickle cell anemia

Peripheral smear from a patient with sickle cell anemia shows multiple spindly sickle cells (blue arrows), a nucleated red blood cell in the upper left, and a Howell-Jolly body (black arrow), which is a nuclear fragment normally removed by the spleen. Target cells are also present (red arrow). This patient has functional asplenia because of repeated splenic infarctions.

*Courtesy of Carola von Kapff, SH (ASCP).*
Normal peripheral blood smear

High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter. *Courtesy of Carola von Kapff, SH (ASCP).*
Major causes of splenomegaly

**Congestive**
- Cirrhosis
- Heart failure
- Thrombosis of portal, hepatic, or splenic veins

**Malignancy**
- Lymphoma, usually indolent variants
- Acute and chronic leukemias
- Polycythemia vera
- Multiple myeloma and its variants
- Essential thrombocythemia
- Agnogenic myeloid metaplasia
- Primary splenic tumors
- Metastatic solid tumors

**Infection**
- Viral - hepatitis, infectious mononucleosis, cytomegalovirus
- Bacterial - salmonella, brucella, tuberculosis
- Parasitic - malaria, schistosomiasis, toxoplasmosis, leishmaniasis
- Infective endocarditis
- Fungal

**Inflammation**
- Sarcoïd
- Serum sickness
- Systemic lupus erythematosus
- Rheumatoid arthritis (Felty syndrome)

**Infiltrative, nonmalignant**
- Gaucher’s disease
- Niemann-Pick disease
- Amyloid
- Glycogen storage disease
- Langerhans cell histiocytosis
- Hemophagocytic lymphohistiocytosis
- Rosai-Dorfman disease

**Hematologic (hypersplenic) states**
- Acute and chronic hemolytic anemias, all etiologies
- Sickle cell disease (children)
Following use of recombinant human granulocyte colony-stimulating factor
**Babesia microti**

**Panel A)** Babesia microti[1]. This thin peripheral blood smear (Giemsa stain; x1000) shows Babesia microti. Several erythrocytes contain multiple parasites, including a diagnostic tetrad form (arrow). **Panel B)** Malaria (for comparison)[2]. Peripheral smear from a patient with malaria shows intraerythrocytic ring forms (trophozoites) (arrows). **Panel C)** Normal[2]. High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter. *Courtesy of:*

1. Harriet Provine
2. Carola von Kapff, SH (ASCP).
Plasmodium vivax

Giemsa-stained thin smear of blood (x1000) shows a ring trophozoite of Plasmodium vivax. Red blood cells infected by P. vivax are enlarged and contain Schüffner’s dots. Courtesy of Harriet Provine.
Blood smear of falciparum malaria

Giemsa- stained thin smear of blood showing the characteristic banana-shaped gametocyte of Plasmodium falciparum (arrow).

Courtesy of Stephen B Calderwood, MD.
Microangiopathic smear

Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (small black arrows), other fragmented red cells (large black arrow); microspherocytes are also seen (blue arrows). The platelet number is reduced; the large platelet in the center (red arrow) suggests that the thrombocytopenia is due to enhanced destruction. *Courtesy of Carola von Kapff, SH (ASCP).*
Normal peripheral blood smear

High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter. Courtesy of Carola von Kapff, SH (ASCP).
Toxic granulations and Döhle bodies

Left panel: Peripheral blood smear shows neutrophils with toxic granulations, which are dark coarse granules. A Döhle body is also seen (arrow). Right panel: A neutrophil with toxic granulations, vacuoles (another toxic change), and a Döhle body (arrow). These abnormalities are characteristic of toxic systemic illnesses. *Courtesy of Carola von Kapff, SH (ASCP).*
High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter. Courtesy of Carola von Kapff, SH (ASCP).
Cold agglutin

Peripheral blood smear from a patient with cold agglutinin hemolytic anemia shows marked red blood cell agglutination into irregular clumps. Courtesy of Carola von Kapff, SH (ASCP).
Normal peripheral blood smear

High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter. *Courtesy of Carola von Kapff, SH (ASCP).*
Atypical lymphocytes

Peripheral smear from a patient with infectious mononucleosis shows three atypical lymphocytes with generous cytoplasm.

*Courtesy of Carola von Kapff, SH (ASCP).*
Leukoerythroblastic smear

Leukoerythroblastic peripheral blood smear showing the presence of nucleated red cells and immature white cells. This pattern occurs with marrow replacement, usually due to fibrosis that may be idiopathic (eg, myelofibrosis with agnogenic myeloid metaplasia) or reactive to conditions such as metastatic cancer. 

*Courtesy of Carola von Kapff, SH (ASCP).*
Normal peripheral blood smear

High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter. Courtesy of Carola von Kapff, SH (ASCP).
LE cell

Blood smear from a patient with systemic lupus erythematosus showing a classical LE cell in which a viable neutrophil has ingested nuclear material. Note the nuclear debris and an adjacent normal neutrophil and the nuclear debris. *Courtesy of the American College of Rheumatology.*
Small and large granular lymphocytes

Distinction between small lymphocytes (A) and large granular lymphocytes (B) on blood smears. The large granular lymphocyte is about twice the size of the red cells and has abundant cytoplasm containing azurophilic granules. Micrographs were viewed with a Leica Leitz DMRB microscope using a 100x/1.30 oil immersion objective. Images were captured with a Sony Exwave HAD camera and manipulated using Tribyn Version 1.3 software. This research was originally published in Blood. Lamy T, Loughran TP Jr. How I treat LGL leukemia. Blood 2011; 117:2764. Copyright © 2011 American Society of Hematology.
Niemann Pick Cells

Bone marrow aspirate from a patient with Niemann Pick disease, showing two large macrophages laden with sphingomyelin, giving the cytoplasm a "foamy" appearance (arrows). *Courtesy of David S Rosenthal, MD and William C Moloney, MD.*
Gaucher cells

Bone marrow aspirate showing a number of large macrophages laden with cerebrosides (Gaucher cells, arrows) in a patient with Gaucher disease and concomitant multiple myeloma. The cytoplasm has a pattern which has been likened to wrinkled silk or crumpled newspaper. *Courtesy of David S Rosenthal, MD and William C Moloney, MD.*