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70 Enlargement of Lymph Nodes and Spleen

Measures of Platelet Function The bleeding time was used in the past to assess platelet function but is nonspecific and it is not recommended for use for this indication. The PFA-100 and similar instruments that measure platelet-dependent coagulation under flow conditions are generally more sensitive and specific for plate let disorders and VWD than the bleeding time; however, data are insufficient to support their use to predict bleeding risk or monitor response to therapy, and they will be normal in some patients with platelet disorders or mild VWD. When they are used in the evalua tion of a patient with bleeding symptoms, abnormal results require specific testing, such as VWF assays and/or platelet aggregation studies. Because all of these “screening” assays may miss patients with mild bleeding disorders, further studies are needed to define their role in hemostasis testing. PART 2 Cardinal Manifestations and Presentation of Diseases For classic platelet aggregometry, various agonists are added to the patient’s platelet-rich plasma or whole blood, and platelet aggregation is measured. Tests of platelet secretion in response to agonists can also be measured. These remain the gold standard for diagnosis of platelet function disorders. However, they are affected by many factors, including numerous medications, and the associa tion between minor defects in these assays and bleeding risk is not clearly established. ■ ■FURTHER READING Baker P et al: Guidelines on the laboratory aspects of assays used in haemostasis and thrombosis. Br J Haematol 191:347, 2020. Connors JM: Thrombophilia testing and venous thrombosis. N Engl J Med 377:12, 2017. Darzi AJ et al: Prognostic factors for VTE and bleeding in hospitalized medical patients: A systematic review and meta-analysis. Blood 135:1788, 2020. Devreese KMJ et al: Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis update of the guidelines for lupus anticoagulant detection and interpretation. J Thromb Haemost 18:2828, 2020. Elbaz C, Sholzberg M: An illustrated review of bleeding assessment tools and common coagulation tests. Res Pract Thromb Haemost 4:761, 2020. Hatfield et al: Dietary supplements and bleeding. Proc (Bayl Univ Med Cent) 35:802, 2022. James PD et al: ASH ISTH NHF WFH 2021 guidelines on the diagno sis of von Willebrand disease. Blood Adv 5:280, 2021. Moran J, Bauer KA: Managing thromboembolic risk in patients with hereditary and acquired thrombophilias. Blood 135:344, 2020. Risman RA et al: Fibrinolysis: an illustrated review. Res Pract Thromb Haemost 7:e100081, 2023. Yau JW et al: Endothelial cell control of thrombosis. BMC Cardiovasc Disord 15:130, 2015. Dan L. Longo

Enlargement of Lymph

Nodes and Spleen This chapter is intended to serve as a guide to the evaluation of patients who present with enlargement of the lymph nodes (lymphadenopathy) or the spleen (splenomegaly). Lymphadenopathy is a rather common clinical finding in primary care settings, whereas palpable spleno megaly is less so.

LYMPHADENOPATHY Lymphadenopathy may be an incidental finding in patients being examined for various reasons, or it may be a presenting sign or symp tom of the patient's illness. The physician must eventually decide whether the lymphadenopathy is a normal finding or one that requires further study, up to and including biopsy. Soft, flat, submandibular nodes (<1 cm) are often palpable in healthy children and young adults; healthy adults may have palpable inguinal nodes of up to 2 cm, which are considered normal. Further evaluation of these normal nodes is not warranted. In contrast, if the physician believes the node(s) to be abnormal, then pursuit of a more precise diagnosis is needed. APPROACH TO THE PATIENT Lymphadenopathy Lymphadenopathy may be a primary or secondary manifesta tion of numerous disorders, as shown in Table 70-1. Many of these disorders are infrequent causes of lymphadenopathy. In primary care practice, more than two-thirds of patients with lymphadenopathy have nonspecific causes or upper respiratory illnesses (viral or bacterial) and <1% have a malignancy. In one study, 84% of patients referred for evaluation of lymphadenopathy had a "benign" diagnosis. The remaining 16% had a malignancy (lymphoma or metastatic adenocarcinoma). Of the patients with benign lymphadenopathy, 63% had a nonspecific or reactive etiol ogy (no causative agent found), and the remainder had a specific cause demonstrated, most commonly infectious mononucleosis, toxoplasmosis, or tuberculosis. Thus, the vast majority of patients with lymphadenopathy will have a nonspecific etiology requiring few diagnostic tests. CLINICAL ASSESSMENT The physician will be aided in the pursuit of an explanation for the lymphadenopathy by a careful medical history, physical examina tion, selected laboratory tests, and perhaps an excisional lymph node biopsy. The medical history should reveal the setting in which lymphade nopathy is occurring. Symptoms such as sore throat, cough, fever, night sweats, fatigue, weight loss, or pain in the nodes should be sought. The patient's age, sex, occupation, exposure to pets, sexual behavior, and use of drugs such as diphenylhydantoin are other important historic points. For example, children and young adults usually have benign (i.e., nonmalignant) disorders that account for the observed lymphadenopathy such as viral or bacterial upper respiratory infections; infectious mononucleosis; toxoplasmosis; and, in some countries, tuberculosis. In contrast, after age 50, the incidence of malignant disorders increases and that of benign dis orders decreases. The physical examination can provide useful clues such as the extent of lymphadenopathy (localized or generalized), size of nodes, texture, presence or absence of nodal tenderness, signs of inflamma tion over the node, skin lesions, and splenomegaly. A thorough ear, nose, and throat (ENT) examination is indicated in adult patients with cervical adenopathy and a history of tobacco use. Localized or regional adenopathy implies involvement of a single anatomic area. Generalized adenopathy has been defined as involvement of three or more noncontiguous lymph node areas. Many of the causes of lymphadenopathy (Table 70-1) can produce localized or generalized adenopathy, so this distinction is of limited utility in the differential diagnosis. Nevertheless, generalized lymphadenopathy is frequently associated with nonmalignant disorders such as infectious mono nucleosis (Epstein-Barr virus [EBV] or cytomegalovirus [CMV]), toxoplasmosis, AIDS, other viral infections, systemic lupus ery thematosus (SLE), and mixed connective tissue disease. Acute and chronic lymphocytic leukemias and

malignant lymphomas also produce generalized adenopathy in adults. The site of localized or regional adenopathy may provide a use ful clue about the cause. Occipital adenopathy often reflects an

TABLE 70-1 Diseases Associated with Lymphadenopathy

1. Infectious diseases a. Viral—infectious mononucleosis syndromes (EBV, CMV), infectious hepatitis, herpes simplex, herpesvirus-6, varicella-zoster virus, rubella, measles, adenovirus, HIV, epidemic keratoconjunctivitis, vaccinia, herpesvirus-8 b. Bacterial—streptococci, staphylococci, cat-scratch disease, brucellosis, tularemia, plague, chancroid, melioidosis, glanders, tuberculosis, atypical mycobacterial infection, primary and secondary syphilis, diphtheria, leprosy, bartonella c. Fungal—histoplasmosis, coccidioidomycosis, paracoccidioidomycosis d. Chlamydial—lymphogranuloma venereum, trachoma e. Parasitic—toxoplasmosis, leishmaniasis, trypanosomiasis, filariasis f. Rickettsial—scrub typhus, rickettsialpox, Q fever
2. Immunologic diseases a. Rheumatoid arthritis b. Juvenile rheumatoid arthritis c. Mixed connective tissue disease d. Systemic lupus erythematosus e. Dermatomyositis f. Sjögren’s syndrome g. Serum sickness h. Drug hypersensitivity—diphenylhydantoin, hydralazine, allopurinol, primidone, gold, carbamazepine, etc. i. Angioimmunoblastic lymphadenopathy j. Primary biliary cirrhosis k. Graft-versus-host disease l. Silicone-associated m. Autoimmune lymphoproliferative syndrome n. IgG4-related disease o. Immune reconstitution inflammatory syndrome (IRIS)
3. Malignant diseases a. Hematologic—Hodgkin’s disease, non-Hodgkin’s lymphomas, acute or chronic lymphocytic leukemia, hairy cell leukemia, malignant histiocytosis, amyloidosis b. Metastatic—from numerous primary sites
4. Lipid storage diseases—Gaucher’s, Niemann-Pick, Fabry, Tangier
5. Endocrine diseases—hyperthyroidism
6. Passive congestion
7. Other disorders a. Castleman’s disease (giant lymph node hyperplasia) b. Sarcoidosis c. Dermatopathic lymphadenitis d. Lymphomatoid granulomatosis e. Histiocytic necrotizing lymphadenitis (Kikuchi’s disease) f. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) g. Mucocutaneous lymph node syndrome (Kawasaki’s disease) h. Histiocytosis X i. Familial Mediterranean fever j. Severe hypertriglyceridemia k. Vascular transformation of sinuses l. Inflammatory pseudotumor of lymph node m. Congestive heart failure Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus. infection of the scalp, and preauricular adenopathy accompanies conjunctival infections and cat-scratch disease. The most frequent site of regional adenopathy is the neck, and most of the causes are benign—upper respiratory infections, oral and dental lesions, infec tious mononucleosis, or other viral illnesses. The chief malignant causes include metastatic cancer from head and neck, breast, lung, and thyroid primaries. Enlargement of supraclavicular and scalene nodes is always abnormal. Because these nodes drain regions of

the lung and retroperitoneal space, they can reflect lymphomas, other cancers, or infectious processes arising in these areas. Vir chow’s node is an enlarged left supraclavicular node infiltrated with metastatic cancer from a gastrointestinal primary. Metastases to supraclavicular nodes also

occur from lung, breast, testis, or ovarian cancers. Tuberculosis, sarcoidosis, and toxoplasmosis are nonneo plastic causes of supraclavicular adenopathy. Axillary adenopathy is usually due to injuries or localized infections of the ipsilateral upper extremity. Malignant causes include melanoma or lymphoma and, in women, breast cancer. Inguinal lymphadenopathy is usually secondary to infections or trauma of the lower extremities and may accompany sexually transmitted diseases such as lymphogranuloma venereum, primary syphilis, genital herpes, or chancroid. These nodes may also be involved by lymphomas and metastatic cancer from primary lesions of the rectum, genitalia, or lower extremities (melanoma). Enlargement of Lymph Nodes and Spleen CHAPTER 70 The size and texture of the lymph node(s) and the presence of pain are useful parameters in evaluating a patient with lymph adenopathy. Nodes <1.0 cm2 in area (1.0 cm × 1.0 cm or less) are almost always secondary to benign, nonspecific reactive causes. In one retrospective analysis of younger patients (9–25 years) who had a lymph node biopsy, a maximum diameter of >2 cm served as one discriminant for predicting that the biopsy would reveal malignant or granulomatous disease. Another study showed that a lymph node size of 2.25 cm2 (1.5 cm × 1.5 cm) was the best size limit for distinguishing malignant or granulomatous lymphadenopathy from other causes of lymphadenopathy. Patients with node(s) ≤1.0 cm2 should be observed after excluding infectious mononucleosis and/ or toxoplasmosis unless there are symptoms and signs of an under lying systemic illness. The texture of lymph nodes may be described as soft, firm, rub bery, hard, discrete, matted, tender, movable, or fixed. Tenderness is found when the capsule is stretched during rapid enlargement, usually secondary to an inflammatory process. Some malignant diseases such as acute leukemia may produce rapid enlargement and pain in the nodes. Nodes involved by lymphoma tend to be large, discrete, symmetric, rubbery, firm, mobile, and nontender. Nodes containing metastatic cancer are often hard, nontender, and nonmovable because of fixation to surrounding tissues. The coexistence of splenomegaly in the patient with lymphadenopathy implies a systemic illness such as infectious mononucleosis, lym phoma, acute or chronic leukemia, SLE, sarcoidosis, toxoplasmosis, cat-scratch disease, or other less common hematologic disorders. The patient’s story should provide helpful clues about the underly ing systemic illness. Nonsuperficial presentations (thoracic or abdominal) of adenop athy are usually detected as the result of a symptom-directed diag nostic workup. Thoracic adenopathy may be detected by routine chest radiography or during the workup for superficial adenopathy. It may also be found because the patient complains of a cough or wheezing from airway compression; hoarseness from recurrent laryngeal nerve involvement; dysphagia from esophageal compres sion; or swelling of the neck, face, or arms secondary to compres sion of the superior vena cava or subclavian vein. The differential diagnosis of mediastinal and hilar adenopathy includes primary lung disorders and systemic illnesses that characteristically involve mediastinal or hilar nodes. In the young, mediastinal adenopathy is associated with infectious mononucleosis and sarcoidosis. In endemic regions, histoplasmosis can cause unilateral paratracheal lymph node involvement that mimics lymphoma. Tuberculosis can also cause unilateral adenopathy. In older patients, the differential diagnosis includes primary lung cancer (especially among smok ers), lymphomas, metastatic carcinoma (usually lung), tuberculosis, fungal infection, and sarcoidosis. Enlarged intraabdominal or retroperitoneal nodes are usu ally malignant. Although tuberculosis may present as mesenteric lymphadenitis, these masses usually contain lymphomas or, in young men, germ cell tumors.

LABORATORY INVESTIGATION The laboratory investigation of patients with lymphadenopathy must be tailored to elucidate the etiology suspected from the patient’s history and physical findings. One study from a family practice clinic evaluated 249 younger patients with “enlarged lymph nodes, not

infected” or “lymphadenitis.” No laboratory studies were obtained in 51%. When studies were performed, the most common were a complete blood count (CBC) (33%), throat culture (16%), chest x-ray (12%), or monospot test (10%). Only eight patients (3%) had a node biopsy, and half of those were normal or reactive. The CBC can provide useful data for the diagnosis of acute or chronic leukemias, EBV or CMV mononucleosis, lymphoma with a leu kemic component, pyogenic infections, or immune cytopenias in illnesses such as SLE. Serologic studies may demonstrate antibod ies specific to components of EBV, CMV, HIV, and other viruses; Toxoplasma gondii; Brucella; etc. If SLE is suspected, antinuclear and anti-DNA antibody studies are warranted. PART 2 Cardinal Manifestations and Presentation of Diseases The chest x-ray is usually negative, but the presence of a pul monary infiltrate or mediastinal lymphadenopathy would suggest tuberculosis, histoplasmosis, sarcoidosis, lymphoma, primary lung cancer, or metastatic cancer and demands further investigation. A variety of imaging techniques (CT, MRI, ultrasound, color Doppler ultrasonography) have been employed to differentiate benign from malignant lymph nodes, especially in patients with head and neck cancer. CT and MRI are comparably accurate (65– 90%) in the diagnosis of metastases to cervical lymph nodes. Ultra sonography has been used to determine the long (L) axis, short (S) axis, and a ratio of long to short axis in cervical nodes. An L/S ratio of <2.0 has a sensitivity and a specificity of 95% for distinguishing benign and malignant nodes in patients with head and neck cancer. This ratio has greater specificity and sensitivity than palpation or measurement of either the long or the short axis alone. The indications for lymph node biopsy are imprecise, yet it is a valuable diagnostic tool. The decision to biopsy may be made early in a patient’s evaluation or delayed for up to two weeks. Prompt biopsy should occur if the patient’s history and physical findings suggest a malignancy; examples include a solitary, hard, nontender cervical node in an older patient who is a chronic user of tobacco; supraclavicular adenopathy; and solitary or generalized adenopathy that is firm, movable, and suggestive of lymphoma. If a primary head and neck cancer is suspected as the basis of a solitary, hard cer vical node, then a careful ENT examination should be performed. Any mucosal lesion that is suspicious for a primary neoplastic process should be biopsied first. If no mucosal lesion is detected, an excisional biopsy of the largest node should be performed. Fineneedle aspiration should not be performed as the first diagnostic procedure. Most diagnoses require more tissue than such aspiration can provide, and it often delays a definitive diagnosis. Fine-needle aspiration should be reserved for thyroid nodules and for confirma tion of relapse in patients whose primary diagnosis is known. If the primary physician is uncertain about whether to proceed to biopsy, consultation with a hematologist or medical oncologist should be helpful. In primary care practices, <5% of lymphadenopathy patients will require a biopsy. That percentage will be considerably larger in referral practices, i.e., hematology, oncology, or ENT. Two groups have reported algorithms that they claim will identify more precisely those lymphadenopathy patients who should have a biopsy. Both reports were retrospective analyses in referral practices. The first study involved patients 9–25 years of age who had a node biopsy performed. Three variables were identified that predicted those young patients with peripheral lymphadenopathy who should undergo biopsy; lymph node size >2 cm in diameter and abnormal chest x-ray had positive predictive values, whereas recent ENT symp toms had negative predictive values. The second study evaluated 220 lymphadenopathy patients in a hematology unit and identified five variables (lymph node size, location [supraclavicular or nonsupra clavicular], age [>40 years or <40 years], texture [nonhard or hard], and tenderness) that were used in a mathematical model to identify

those patients requiring a biopsy. Positive predictive value was found for age >40 years, supraclavicular location, node size >2.25 cm2, hard texture, and lack of pain or tenderness. Negative predictive value was evident for age <40 years, node size <1.0 cm2, nonhard texture, and tender or painful nodes. Ninety-one percent of those who required biopsy were correctly classified by this model. Because both of these studies were retrospective analyses and one was limited to young patients, it is not known how useful these models would be if applied prospectively in a primary care setting. Most lymphadenopathy patients do not require a biopsy, and at least half require no laboratory studies. If the patient's history and physical findings point to a benign cause for lymphadenopathy, careful follow-up at a 2- to 4-week interval can be employed. The patient should be instructed to return for reevaluation if there is an increase in the size of the nodes. Antibiotics are not indicated for lymphadenopathy unless strong evidence of a bacterial infection is present. Glucocorticoids should not be used to treat lymphade nopathy because their lympholytic effect obscures some diagnoses (lymphoma, leukemia, Castleman's disease) and they contribute to delayed healing or activation of underlying infections. An excep tion to this statement is the life-threatening pharyngeal obstruction by enlarged lymphoid tissue in Waldeyer's ring that is occasionally seen in infectious mononucleosis. SPLENOMEGALY ■ ■STRUCTURE AND FUNCTION OF THE SPLEEN The spleen is a reticuloendothelial organ that has its embryologic origin in the dorsal mesogastrium at about 5 weeks' gestation. It arises in a series of hillocks, migrates to its normal adult location in the left upper quadrant (LUQ), and is attached to the stomach via the gastroli enal ligament and to the kidney via the lienorenal ligament. When the hillocks fail to unify into a single tissue mass, accessory spleens may develop in around 20% of persons. The function of the spleen has been elusive. Galen believed it was the source of "black bile" or melancholia, and the word hypochondria (literally, beneath the ribs) and the idiom "to vent one's spleen" attest to the beliefs that the spleen had an impor tant influence on the psyche and emotions.* In humans, its normal physiologic roles seem to be the following:

1. Maintenance of quality control over erythrocytes in the red pulp by removal of senescent and defective red blood cells. The spleen accomplishes this function through a unique organization of its parenchyma and vasculature (Fig. 70-1).
2. Synthesis of antibodies in the white pulp.
3. The removal of antibody-coated bacteria and antibody-coated blood cells from the circulation. An increase in these normal functions may result in splenomegaly. The spleen is composed of red pulp and white pulp, which are Malpighi's terms for the red blood–filled sinuses and reticuloen dothelial cell–lined cords and the white lymphoid follicles arrayed within the red pulp matrix. The spleen is in the portal circulation. The reason for this is unknown but may relate to the fact that lower blood pressure allows less rapid flow and minimizes damage to normal erythrocytes. Blood flows into the spleen at a rate of about 150 mL/min through the splenic artery, which ultimately ramifies into central arterioles. Some blood goes from the arterioles to capillar ies and then to splenic veins and out of the spleen, but the majority of blood from central arterioles flows into the macrophage-lined sinuses and cords. The blood entering the sinuses reenters the circu lation through the splenic venules, but the blood entering the cords is subjected to an inspection of sorts. To return to the circulation, the blood cells in the cords must squeeze through slits in the cord lining to enter the sinuses that lead to the venules. Old and damaged erythrocytes are less deformable and are retained in the cords, where *Reproduced with permission from RS Hillman, KA Ault: Hematology in Clinical Practice, 4th ed. New York, McGraw-Hill;

2005.

Central artery Primary follicle (B-cell area) Secondary follicle with germinal center (B-cell area) Lymphoid T-cell area Marginal lymphoid zone Arterial capillaries Pulp sinus Pulp cord Pulp sinus Pulp cord
Splenic venous system Arterioles Sinusoidal pores Pulp cord Sinusoids Pulp sinuses RE cells To splenic venous system FIGURE 70-1 Schematic spleen structure. The spleen comprises many units of red and white pulp centered around small branches of the splenic artery, called central arteries. White pulp is lymphoid in nature and contains B-cell follicles, a marginal zone around the follicles, and T-cell–rich areas sheathing arterioles. The red pulp areas include pulp sinuses and pulp cords. The cords are dead ends. In order to regain access to the circulation, red blood cells must traverse tiny openings in the sinusoidal lining. Stiff, damaged, or old red cells cannot enter the sinuses. RE, reticuloendothelial. (Bottom portion of figure reproduced with permission from RS Hillman, KA Ault: Hematology in Clinical Practice, 4th ed. New York, McGraw-Hill, 2005.) they are destroyed and their components recycled. Red cell–inclu sion bodies such as parasites (Chaps. 231, 232, and A2), nuclear residua (Howell-Jolly bodies, see Fig. 66-6), or denatured hemoglo bin (Heinz bodies) are pinched off in the process of passing through the slits, a process called pitting. The culling of dead and damaged cells and the pitting of cells with inclusions appear to occur without significant delay because the blood transit time through the spleen is only slightly slower than in other organs. The spleen is also capable of assisting the host in adapting to its hos tile environment. It has at least three adaptive functions: (1) clearance of bacteria and particulates from the blood, (2) the generation of immune responses to certain pathogens, and (3) the generation of cellular components of the blood under circumstances in which the marrow is unable to meet the needs (i.e., extramedullary hematopoiesis). The latter adaptation is a recapitulation of the blood-forming function the spleen plays during gestation. In some animals, the spleen also serves a role in the vascular adaptation to stress because it stores red blood cells (often hemoconcentrated to higher hematocrits than normal) under normal

circumstances and contracts under the influence of β-adrenergic stimu lation to provide the animal with an autotransfusion and improved oxygen-carrying capacity. However, the normal human spleen does not sequester or store red blood cells and does not contract in response to sympathetic stimuli. The normal human spleen contains approximately one-third of the total body platelets and a significant number of margin ated neutrophils. These sequestered cells are available when needed to respond to bleeding or infection.

APPROACH TO THE PATIENT Splenomegaly Enlargement of Lymph Nodes and Spleen CHAPTER 70 CLINICAL ASSESSMENT The most common symptoms produced by diseases involving the spleen are pain and a heavy sensation in the LUQ. Massive sple nomegaly may cause early satiety. Pain may result from acute swelling of the spleen with stretching of the capsule, infarction, or inflammation of the capsule. For many years, it was believed that splenic infarction was clinically silent, which, at times, is true. However, Soma Weiss, in his classic 1942 report of the self-

observations by a Harvard medical student on the clinical course of subacute bacterial endocarditis, documented that severe LUQ and pleuritic chest pain may accompany thromboembolic occlusion of splenic blood flow. Vascular occlusion, with infarction and pain, is commonly seen in children with sickle cell crises. Rupture of the spleen, from either trauma or

infiltrative disease that breaks the capsule, may result in intraperitoneal bleeding, shock, and death. The rupture itself may be painless. A palpable spleen is the major physical sign produced by diseases affecting the spleen and suggests enlargement of the organ. The normal spleen weighs <250 g, decreases in size with age, normally lies entirely within the rib cage, has a maximum cephalocaudad diameter of 13 cm by ultrasonography or maximum length of 12 cm and/or width of 7 cm by radionuclide scan, and is usually not palpa ble. However, a palpable spleen was found in 3% of 2200 asymptom atic, male, freshman college students. Follow-up at 3 years revealed that 30% of those students still had a palpable spleen without any increase in disease prevalence. Ten-year follow-up found no evi dence for lymphoid malignancies. Furthermore, in some tropical countries (e.g., New Guinea), the incidence of splenomegaly may reach 60%. Thus, the presence of a palpable spleen does not always equate with presence of disease. Even when disease is present, splenomegaly may not reflect the primary disease but rather a reac tion to it. For example, in patients with Hodgkin's lymphoma, only two-thirds of the palpable spleens show involvement by the cancer. Physical examination of the spleen uses primarily the techniques of palpation and percussion. Inspection may reveal fullness in the LUQ that descends on inspiration, a finding associated with a mas sively enlarged spleen. Auscultation may reveal a venous hum or friction rub. Palpation can be accomplished by bimanual palpation, bal lotment, and palpation from above (Middleton maneuver). For bimanual palpation, which is at least as reliable as the other tech niques, the patient is supine with flexed knees. The examiner's left hand is placed on the lower rib cage and pulls the skin toward the costal margin, allowing the fingertips of the right hand to feel the tip of the spleen as it descends while the patient inspires slowly, smoothly, and deeply. Palpation is begun with the right hand in the left lower quadrant with gradual movement toward the left costal margin, thereby identifying the lower edge of a massively enlarged spleen. When the spleen tip is felt, the finding is recorded as cen timeters below the left costal margin at some arbitrary point, i.e., 10–15 cm, from the midpoint of the umbilicus or the xiphisternal junction. This allows other examiners to compare findings or the initial examiner to determine changes in size over time. Bimanual palpation in the right lateral decubitus position adds nothing to the supine examination.

Percussion for splenic dullness is accomplished with any of three techniques described by Nixon, Castell, or Barkun:

1. Nixon's method: The patient is placed on the right side so that the spleen lies above the colon and stomach. Percussion begins at the lower level of pulmonary resonance in the posterior axillary line and proceeds diagonally along a perpendicular line toward the lower midanterior costal margin. The upper border of dull ness is normally 6–8 cm above the costal margin. Dullness >8 cm in an adult is presumed to indicate splenic enlargement.
2. Castell's method: With the patient supine, percussion in the lowest intercostal space in the anterior axillary line (8th or 9th) produces a resonant note if the spleen is normal in size. This is true during expiration or full inspiration. A dull percussion note on full inspiration suggests splenomegaly.
3. Percussion of Traube's semilunar space: The borders of Traube's PART 2 Cardinal Manifestations and Presentation of Diseases space are the sixth rib superiorly, the left midaxillary line later ally, and the left costal margin inferiorly. The patient is supine with the left arm slightly abducted. During normal breathing, this space is percussed from medial to lateral margins, yield ing a normal resonant sound. A dull percussion note

suggests splenomegaly. Studies comparing methods of percussion and palpation with a standard of ultrasonography or scintigraphy have revealed sensitiv ity of 56–71% for palpation and 59–82% for percussion. Reproduc ibility among examiners is better for palpation than percussion. Both techniques are less reliable in obese patients or patients who have just eaten. Thus, the physical examination techniques of palpa tion and percussion are imprecise at best. It has been suggested that the examiner perform percussion first and, if positive, proceed to palpation; if the spleen is palpable, then one can be reasonably con fident that splenomegaly exists. However, not all LUQ masses are enlarged spleens; gastric or colon tumors and pancreatic or renal cysts or tumors can mimic splenomegaly. The presence of an enlarged spleen can be more precisely deter mined, if necessary, by liver-spleen radionuclide scan, CT, MRI, or ultrasonography. The latter technique is the current procedure of choice for routine assessment of spleen size (normal = a maximum cephalocaudad diameter of 13 cm) because it has high sensitivity and specificity and is safe, noninvasive, quick, mobile, and less costly. Equipment advances allow ultrasonography to be performed at the bedside with excellent sensitivity and specificity. Nuclear medicine scans are accurate, sensitive, and reliable but are costly, require greater time to generate data, and use immobile equipment. They have the advantage of demonstrating accessory splenic tissue. CT and MRI provide accurate determination of spleen size, but the equipment is immobile and the procedures are expensive. MRI appears to offer no advantage over CT. Changes in spleen structure such as mass lesions, infarcts, inhomogeneous infiltrates, and cysts are more readily assessed by CT, MRI, or ultrasonography. None of these techniques is very reliable in the detection of patchy infiltra tion (e.g., Hodgkin’s lymphoma). DIFFERENTIAL DIAGNOSIS Many of the diseases associated with splenomegaly are listed in Table 70-2. They are grouped according to the presumed basic mechanisms responsible for organ enlargement:

4. Hyperplasia or hypertrophy related to a particular splenic func tion such as reticuloendothelial hyperplasia (work hypertrophy) in diseases such as hereditary spherocytosis or thalassemia syn dromes that require removal of large numbers of defective red blood cells; immune hyperplasia in response to systemic infec tion (infectious mononucleosis, subacute bacterial endocarditis) or to immunologic diseases (immune thrombocytopenia, SLE, Felty’s syndrome).
5. Passive congestion due to decreased blood flow from the spleen in conditions that produce portal hypertension (cirrhosis, BuddChiari syndrome, congestive heart failure).
6. Infiltrative diseases of the spleen (lymphomas, metastatic cancer, amyloidosis, Gaucher’s disease, myeloproliferative disorders with extramedullary hematopoiesis). The differential diagnostic possibilities are much fewer when the spleen is “massively enlarged,” palpable >8 cm below the left costal margin, or its drained weight is ≥1000 g (Table 70-3). The vast majority of such patients will have non-Hodgkin’s lym phoma, chronic lymphocytic leukemia, hairy cell leukemia, chronic myeloid leukemia, myelofibrosis with myeloid metaplasia, or poly cythemia vera. LABORATORY ASSESSMENT The major laboratory abnormalities accompanying splenomegaly are determined by the underlying systemic illness. Erythrocyte counts may be normal, decreased (thalassemia major syndromes, SLE, cirrhosis with portal hypertension), or increased (polycythemia vera). Granulocyte counts may be normal, decreased (Felty’s syndrome, congestive splenomegaly, leukemias), or increased (infections or inflammatory disease, myeloproliferative disorders). Similarly, the platelet count may be normal, decreased when there is enhanced sequestration or

destruction of platelets in an enlarged spleen (congestive splenomegaly, Gaucher's disease, immune thrombocy topenia), or increased in the myeloproliferative disorders such as polycythemia vera. The CBC may reveal cytopenia of one or more blood cell types, which should suggest hypersplenism. This condition is character ized by splenomegaly, cytopenia(s), normal or hyperplastic bone marrow, and a response to splenectomy. The latter characteristic is less precise because reversal of cytopenia, particularly granulocyto penia, is sometimes not sustained after splenectomy. The cytopenias result from increased destruction of the cellular elements secondary to reduced flow of blood through enlarged and congested cords (congestive splenomegaly) or to immune-mediated mechanisms. In hypersplenism, various cell types usually have normal morphol ogy on the peripheral blood smear, although the red cells may be spherocytic due to loss of surface area during their longer transit through the enlarged spleen. The increased marrow production of red cells should be reflected as an increased reticulocyte produc tion index, although the value may be less than expected due to increased sequestration of reticulocytes in the spleen. The need for additional laboratory studies is dictated by the dif ferential diagnosis of the underlying illness of which splenomegaly is a manifestation. SPLENECTOMY Splenectomy is infrequently performed for diagnostic purposes, espe cially in the absence of clinical illness or other diagnostic tests that suggest underlying disease. More often, splenectomy is performed for symptom control in patients with massive splenomegaly, for disease control in patients with traumatic splenic rupture, or for correction of cytopenias in patients with hypersplenism or immune-mediated destruction of one or more cellular blood elements. Splenectomy is necessary for staging of patients with Hodgkin's lymphoma only in those with clinical stage I or II disease in whom radiation therapy alone is contemplated as the treatment. Noninvasive staging of the spleen in Hodgkin's lymphoma is not a sufficiently reliable basis for treatment decisions because one-third of normal-sized spleens will be involved with Hodgkin's lymphoma and one-third of enlarged spleens will be tumor-free. The widespread use of systemic therapy to test all stages of Hodgkin's lymphoma has made staging laparotomy with splenectomy unnecessary. Although splenectomy in chronic myeloid leukemia (CML) does not affect the natural history of disease, removal of the massive spleen usually makes patients significantly more comfortable and simplifies their management by significantly reducing transfusion requirements. The improvements in therapy of CML have reduced the need for splenectomy for symptom control. Splenectomy is an effec tive secondary or tertiary treatment for two chronic B-cell leukemias,

TABLE 70-2 Diseases Associated with Splenomegaly Grouped by Pathogenic Mechanism Enlargement Due to Increased Demand for Splenic Function Reticuloendothelial system hyperplasia (for removal of defective erythrocytes) Malaria Spherocytosis Leishmaniasis Early sickle cell anemia Trypanosomiasis Ovalocytosis Ehrlichiosis Thalassemia major Disordered immunoregulation Hemoglobinopathies Rheumatoid arthritis (Felty's syndrome) Paroxysmal nocturnal hemoglobinuria Systemic lupus erythematosus Pernicious anemia Collagen vascular diseases Immune hyperplasia Serum sickness Response to infection (viral, bacterial, fungal, parasitic) Immune hemolytic anemias Infectious mononucleosis Immune thrombocytopenias AIDS Immune neutropenias Viral hepatitis Drug reactions Cytomegalovirus Angioimmunoblastic lymphadenopathy Subacute bacterial endocarditis Sarcoidosis Bacterial septicemia Thyrotoxicosis (benign lymphoid hypertrophy)

Congenital syphilis Interleukin 2 therapy Splenic abscess Extramedullary hematopoiesis Tuberculosis Myelofibrosis Histoplasmosis Marrow damage by toxins, radiation, strontium Marrow infiltration by tumors, leukemias, Gaucher's disease Enlargement Due to Abnormal Splenic or Portal Blood Flow Cirrhosis Splenic artery aneurysm Hepatic vein obstruction Hepatic schistosomiasis Portal vein obstruction, intrahepatic or extrahepatic Congestive heart failure Cavernous transformation of the portal vein Hepatic echinococcosis Splenic vein obstruction Portal hypertension (any cause including the above): "Banti's disease" Infiltration of the Spleen Intracellular or extracellular depositions Hodgkin's lymphoma Amyloidosis Myeloproliferative syndromes (e.g., polycythemia vera, essential thrombocytosis) Gaucher's disease Angiosarcomas Niemann-Pick disease Metastatic tumors (melanoma is most common) Tangier disease Eosinophilic granuloma Hurler's syndrome and other mucopolysaccharidoses Histiocytosis X Hyperlipidemias Hamartomas Benign and malignant cellular infiltrations Hemangiomas, fibromas, lymphangiomas Leukemias (acute, chronic, lymphoid, myeloid, monocytic) Splenic cysts Lymphomas Hemophagocytic lymphohistiocytosis Unknown Etiology Idiopathic splenomegaly Iron-deficiency anemia Berylliosis hairy cell leukemia and prolymphocytic leukemia, and for the very rare splenic mantle cell or marginal zone lymphoma. Splenectomy in these diseases may be associated with significant tumor regres sion in bone marrow and other sites of disease. Similar regressions of systemic disease have been noted after splenic irradiation in some types of lymphoid tumors, especially chronic lymphocytic leukemia TABLE 70-3 Diseases Associated with Massive Splenomegalya Chronic myeloid leukemia Gaucher's disease Lymphomas Chronic lymphocytic leukemia Hairy cell leukemia Sarcoidosis Myelofibrosis with myeloid metaplasia Autoimmune hemolytic anemia Polycythemia vera Diffuse splenic hemangiomatosis aThe spleen extends >8 cm below left costal margin and/or weighs >1000 g.

 and prolymphocytic leukemia. This has been termed the abscopal effect. Such systemic tumor responses to local therapy directed at the spleen suggest that some hormone or growth factor produced by the spleen may affect tumor cell proliferation, but this conjecture is not yet substantiated. A common therapeutic indication for splenectomy is traumatic or iatrogenic splenic rupture. In a fraction of patients with splenic rupture, peritoneal seeding of splenic fragments can lead to splenosis—the presence of multiple rests of spleen tissue not connected to the portal circulation. This ectopic spleen tissue may cause pain or gastrointestinal obstruction, as in endometriosis. A large number of hematologic, immunologic, and congestive causes of splenomegaly can lead to destruction of one or more cellular blood elements. In the majority of such cases, splenectomy can correct the cytopenias, par ticularly anemia and thrombocytopenia. In a large series of patients seen in two tertiary care centers, the indication for splenectomy was diagnostic in 10% of patients, therapeutic in 44%, staging for Hodgkin's

disease in 20%, and incidental to another procedure in 26%. Perhaps the only contraindication to splenectomy is the presence of marrow failure, in which the enlarged spleen is the only source of hematopoietic tissue.

Often the splenectomy is done by laparoscopy, which is associated with shorter hospital stays and faster recovery than the open proce dure; however, concern has emerged that the laparoscopic approach is associated with a higher risk of postoperative portal venous system thrombosis and Budd-Chiari syndrome. The absence of the spleen has minimal long-term effects on the

hematologic profile. In the immediate postsplenectomy period, leu kocytosis (up to 25,000/μL) and thrombocytosis (up to 1 × 106/μL) may develop, but within 2–3 weeks, blood cell counts and survival of each cell lineage are usually normal. The chronic manifestations of splenectomy are marked variation in size and shape of erythrocytes (anisocytosis, poikilocytosis) and the presence of Howell-Jolly bodies (nuclear remnants), Heinz bodies (denatured hemoglobin), basophilic stippling, and an occasional nucleated erythrocyte in the peripheral blood. When such erythrocyte abnormalities appear in a patient whose spleen has not been removed, one should suspect splenic infiltration by tumor that has interfered with its normal culling and pitting function. PART 2 Cardinal Manifestations and Presentation of Diseases The most serious consequence of splenectomy is increased sus ceptibility to bacterial infections, particularly those with capsules such as Streptococcus pneumoniae, Haemophilus influenzae, and some gram-negative enteric organisms. Patients aged <20 years are particu larly susceptible to overwhelming sepsis with S. pneumoniae, and the overall actuarial risk of sepsis in patients who have had their spleens removed is about 7% in 10 years. The case-fatality rate for pneumococ cal sepsis in splenectomized patients is 50–80%. About 25% of patients without spleens will develop a serious infection at some time in their life. The frequency is highest within the first 3 years after splenectomy. About 15% of the infections are polymicrobial, and lung, skin, and blood are the most common sites. No increased risk of viral infection has been noted in patients who have no spleen. The susceptibility to bacterial infections relates to the inability to remove opsonized bac teria from the bloodstream and a defect in making antibodies to

T cell–independent antigens such as the polysaccharide components of bacterial capsules. Pneumococcal vaccine should be administered to all patients 2 weeks before elective splenectomy. The Advisory Committee on Immunization Practices recommends that these patients receive repeat vaccination 5 years after splenectomy. Efficacy has not been proven for this group, and the recommendation discounts the pos sibility that administration of the vaccine may actually lower the titer of specific pneumococcal antibodies. A more effective pneumococcal conjugate vaccine that involves T cells in the response is now available (PCV13). The vaccine to Neisseria meningitidis should also be given to patients in whom elective splenectomy is planned. Although efficacy data for H. influenzae type b vaccine are not available for older children or adults, it may be given to patients who have had a splenectomy. Splenectomized patients should be educated to consider any unex plained fever as a medical emergency. Prompt medical attention with

evaluation and treatment of suspected bacteremia may be lifesaving. Routine chemoprophylaxis with oral penicillin can result in the emer gence of drug-resistant strains and is not recommended. In addition to an increased susceptibility to bacterial infections, splenectomized patients are also more susceptible to the parasitic dis ease babesiosis. The splenectomized patient should avoid areas where the parasite Babesia is endemic (e.g., Cape Cod, Massachusetts). Surgical removal of the spleen is an obvious cause of hyposplenism. Patients with sickle cell disease often suffer from autosplenectomy as a result of splenic destruction by the numerous infarcts associated with sickle cell crises during childhood. Indeed, the presence of a palpable spleen in a patient with sickle cell disease after age 5 suggests a coexist ing hemoglobinopathy, e.g., thalassemia or hemoglobin C. In addition, patients who receive splenic irradiation for a neoplastic or autoimmune disease are also functionally hyposplenic. The term hyposplenism is preferred to asplenism in referring to the physiologic consequences of splenectomy because asplenia is a rare, specific, and fatal congenital abnormality in which there is a failure of the left side of the coelo mic cavity (which includes the splenic anlagen) to develop normally. Infants with asplenia have no spleens, but that is the least of

their prob lems. The right side of the developing embryo is duplicated on the left so there is liver where the spleen should be, there are two right lungs, and the heart comprises two right atria and two right ventricles. Acknowledgment Patrick H. Henry, MD, friend and mentor now deceased, contributed significantly to the chapter in past editions and much of his work remains in this chapter. ■ ■FURTHER READING Barkun AN et al: The bedside assessment of splenic enlargement. Am J Med 91:512, 1991. Cessford T et al: Comparing physical examination with sono graphic versions of the same examination techniques for splenomegaly. J Ultrasound Med 37:1621, 2018. Facchetti F: Tumors of the spleen. Int J Surg Pathol 18:136S, 2010. Girard E et al: Management of splenic and pancreatic trauma. J Visc Surg 153(suppl 4):45, 2016. Kim DK et al: Advisory committee on immunization practices recom mended immunization schedule for adults aged 19 years or older— United States, 2017. MMWR 66:136, 2017. Kraus MD et al: The spleen as a diagnostic specimen: A review of ten years' experience at two tertiary care institutions. Cancer 91:2001, 2001. McIntyre OR, Ebaugh FG Jr: Palpable spleens: Ten-year follow-up. Ann Intern Med 90:130, 1979. Pangalis GA et al: Clinical approach to lymphadenopathy. Semin Oncol 20:570, 1993. Sjoberg BP et al: Splenomegaly: A combined clinical and radiologic approach to the differential diagnosis. Gastroenterol Clin North Am 47:643, 2018.

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