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Sarcoidosis and Other Noninfectious Granulomatous Processes

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Diagnostic problems presented by granulomatous lesions are relatively frequent in the practice of pathology. A retrospective analysis of approximately 30,000 surgical pathology reports at Duke University disclosed granulomatous lesions in 3% of specimens.[1] Of these, one third were considered to be primary and pertinent to clinical diagnosis and management, and two thirds were considered to be secondary or incidental to another condition, such as cancer or a foreign body. Of the primary granulomatous lesions, approximately one third each were attributable to infection and sarcoidosis; 18% could not be classified as to etiology. Therefore, infectious diseases and sarcoidosis account for the majority of granulomatous lesions encountered in the lungs (Display 66-1).

The incidence of the various categories of granulomatous lesions seen in surgical pathology material may vary significantly in relation to geographic location and patient population makeup. In a study of 86 solitary necrotizing pulmonary granulomas, mycobacterial or fungal etiology was established for 70%; 26% remained unclassified following appropriate diagnostic workup.[2] A variety of nongranulomatous pulmonary lesions unfortunately have names that give the false impression that they are granulomatous, such as eosinophilic granuloma, pulmonary hyalinizing granuloma, plasma cell granuloma, lymphomatoid granulomatosis, and pulmonary angiitis and granulomatosis.

DEFINITION AND FUNCTION OF GRANULOMAS

A granuloma is "a compact (organized) collection of mature mononuclear phagocytes (macrophages and/or epithelioid cells) which may or may not be accompanied by accessory features such as necrosis or the infiltration of inflammatory leukocytes."[3] Mononuclear phagocytes and lymphocytes are the principal cellular

constituents of granulomas. A granuloma is a nonspecific inflammatory lesion that may represent the host's response to a variety of infectious and noninfectious agents. Its etiology is usually not disclosed by its microscopic appearance.

Adams discussed the origin and function of the granuloma.

> [T]he granuloma appears to be the host's response to a high local concentration of a foreign substance which was not destroyed by the acute inflammatory response and which is being contained and destroyed by mononuclear phagocytes in various stages of maturation or activation. . . . [G]ranulomas ultimately serve to protect the host from high local concentrations of foreign or 'non-self' materials of both endogenous and exogenous origin . . . by degradation, detoxification, and containment of unwanted material.[3,4]

Apart from foreign-body reactions, most granulomas seen by the pathologist contain predominantly epithelioid cells and are termed epithelioid granulomas. Epithelioid cells are derived from the maturation of macrophages, which in turn arise from maturation of bone marrow–derived monocytes.[4] Epithelioid cells and epithelioid granulomas develop under conditions that promote extreme maturation of mononuclear phagocytes; they are larger than macrophages and have greater secretory and bactericidal capability and less phagocytic capability. Foreign-body or Langhans giant cells are often present and arise from fusion of epithelioid cells.[4]

MECHANISM OF GRANULOMA FORMATION

Activation of the cellular immune system with the development of delayed hypersensitivity appears to play a crucial role in initiating and modulating the formation of epithelioid granulomas in sar-

DISPLAY 66-1. CLASSIFICATION OF PULMONARY GRANULOMATOUS DISEASES

Infections
   Mycobacteria
   Fungi
   Helminths
   Pneumocystis carinii
   Syphilis
   Actinomyces
   Nocardia
Sarcoidosis
Necrotizing sarcoid granulomatosis
Hypersensitivity pneumonitis
Beryllium disease
Hard metal lung disease
Wegener granulomatosis
Bronchocentric granulomatosis
Rheumatoid nodules
Foreign-body granulomas
   Lipid aspiration
   Food particles
   Inhalational (*i.e.*, substance abuse)
   Vascular or perivascular (*i.e.*, substance abuse)
Allergic granulomatosis and angiitis (*i.e.*, Churg-Strauss syndrome)
Chronic granulomatous disease of childhood
Unclassified

coidosis and other granulomatous disorders.[5] Formation of epithelioid granulomas is usually triggered by antigenic stimulation and is preceded by an accumulation of activated T lymphocytes and mononuclear phagocytes at sites of disease activity (Fig. 66-1). These immune effector cells produce chemical mediators that promote and modulate granuloma formation. Soluble macrophage factors activate T lymphocytes and their secretion of lymphokines, which have a major role in the recruitment, activation, and maturation of mononuclear phagocytes. The ability of activated macrophages to ingest and destroy granuloma-inciting material is thereby enhanced.

Immunohistochemical studies of the localization of lymphocyte subsets in granulomas have shown that in the epithelioid granulomas of sarcoidosis, tuberculosis, and tuberculoid leprosy, the T-helper/inducer lymphocytes are found throughout the granuloma, whereas the T-suppressor/cytotoxic lymphocytes are found only in the peripheral cellular mantle.[6-8] In lepromatous leprosy and rhinoscleroma, lesions in which macrophages are the predominant cell type and epithelioid cells and granulomas are not formed, the helper and suppressor subtypes are diffusely distributed throughout the lesions without any apparent zonal localization.[7] Although the significance of T-lymphocyte subset localization in epithelioid granulomas is not known, circumstantial evidence indicates that it may be related to the effectiveness of the epithelioid granulomatous response in eliminating the granuloma-inciting agent.[7,8]

Necrosis in Granulomas

Granulomas are classified as either necrotizing or non-necrotizing granulomas. Necrosis in granulomas may occur when the granuloma-inciting agent is highly toxic to the macrophages or when a vigorous delayed hypersensitivity response is evoked.[9] The term

caseous necrosis refers to the cheeselike gross appearance[10] and not to microscopic features of a type of necrosis. It has proved to be a source of substantial confusion for both pathologists and clinicians. Although caseous necrosis is usually associated with tuberculosis, it may be seen in other diseases, including fungal infections, pulmonary angiitis and granulomatosis, malignant neoplasms, parasitic infections, aspiration of cod liver oil, syphilis, tularemia, and typhoid fever.[11] The caseous appearance results from incomplete digestion of necrotic tissue.[11] To state that a lesion is a caseating granuloma based on its microscopic appearance is incorrect. Because the modifiers "caseous," "caseating," and "noncaseating" have no diagnostic relevance and may be misleading because of their association with tuberculosis, it is recommended that they not be used in pathology reports except possibly as gross descriptive terms only. Granulomas may appropriately be reported as necrotizing, non-necrotizing, or exhibiting minimal necrosis.

SARCOIDOSIS

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology and worldwide occurrence. Its etiology has eluded investigators since its initial description at the beginning of the twentieth century. Massive research efforts have significantly increased the understanding of the immunologic events that result in granuloma formation, but little insight has been gained into what triggers these events.

The high incidence of lung and mediastinal lymph node involvement and the distribution pattern of lesions within the lungs provide circumstantial evidence strongly suggesting that the agent or agents that produce sarcoidosis are tiny airborne particles that initially enter the body by way of the lungs and are then transported to the hilar lymph nodes. A number of monographs, review articles, and textbook chapters present comprehensive coverage of the immunology, epidemiology, clinical and radiographic features, pathology, and treatment of sarcoidosis.[12-23]

Clinical Aspects

Sarcoidosis may occur at any age, but young adults are most frequently affected. The majority of patients are asymptomatic at the time of diagnosis and present with radiographic changes of bilateral hilar lymphadenopathy or lung infiltrates. Clinical staging is based on the radiographic appearances as follows: stage I, mediastinal lymphadenopathy only; stage II, mediastinal lymphadenopathy and lung infiltrates; stage III, lung infiltrates only; stage IV, cystic lung lesions.[16]

The lungs are involved in virtually all patients with sarcoidosis.[24] The radiographic finding of bilateral hilar lymphadenopathy in a patient who is asymptomatic and without any abnormality detectable on physical examination is virtually diagnostic of sarcoidosis.[25] Approximately 70% of patients exhibit clinical evidence of extrathoracic lesions at some time during the course of their disease.[26] Extrathoracic manifestations occur predominantly in patients with chronic intrathoracic sarcoidosis and refer to, in descending order of frequency, involvement of peripheral lymph nodes, eye, liver, skin, spleen, bone, salivary glands, heart, and kidneys.[27,28]

The majority of patients with sarcoidosis exhibit elevation of serum angiotensin-converting enzyme (SACE), intrathoracic up-
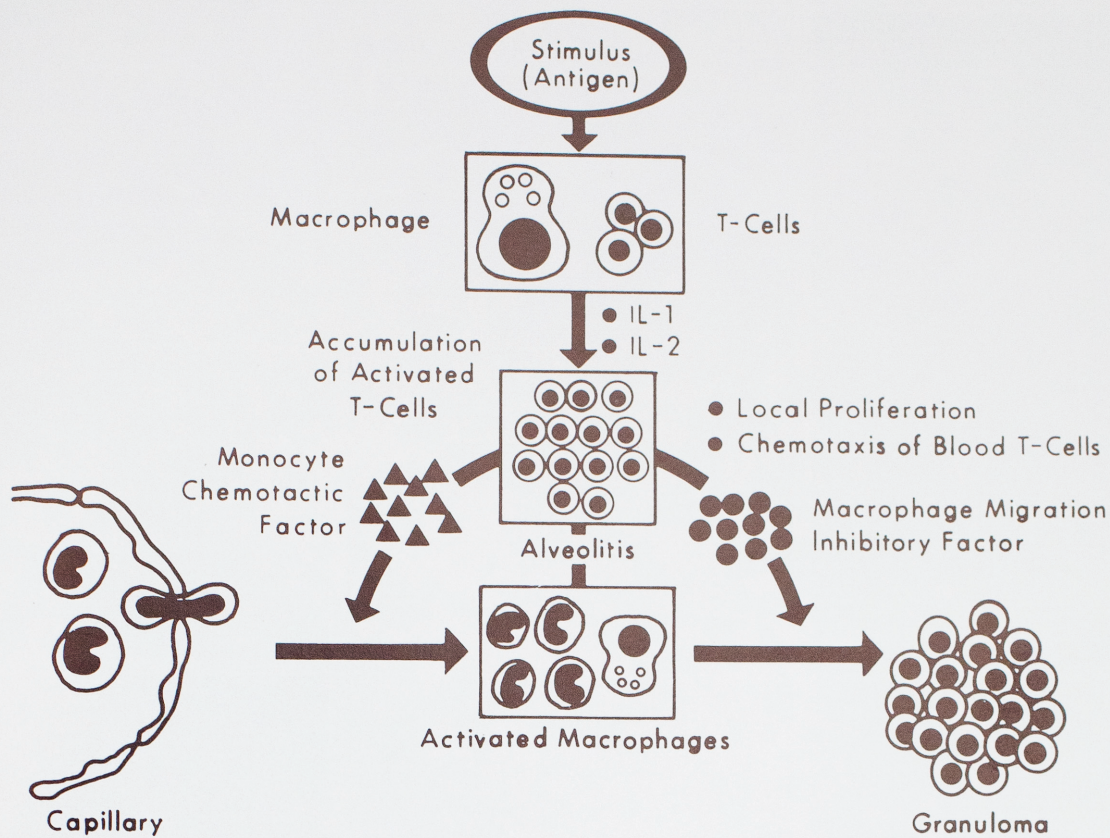
FIGURE 66-1. Pathogenesis of granuloma formation. A stimulus—usually an antigen—activates alveolar macrophages to release interleukin-1 and activates lung T cells to release interleukin-2. The release of these mediators results in an accumulation of activated T cells in the lung, both by stimulating lung T cells to proliferate locally and by functioning as chemoattractants that recruit additional blood T cells to the lung. The activated T cells that are present in the lung regulate granuloma formation by secreting other lymphokines, such as monocyte chemotactic factor, which attracts blood monocytes to the lung. Once monocytes are present in the lung, they differentiate into macrophages that are, in turn, influenced by other T cell–derived lymphokines, such as macrophage migration inhibitory factor and macrophage activating factor. A portion of these macrophages form the compact structure ultimately recognized as a granuloma. (From Garrett KC, Richerson HB, Hunninghake GW. Mechanisms of granuloma formation. Am Rev Respir Dis 1984;130:477.)

take of gallium, and bronchoalveolar lavage fluid T-helper lymphocytosis.[27] These findings are without diagnostic specificity but are regarded as indicators of disease activity. Those with active disease exhibit anergy to a variety of intradermally injected antigens. Stimulation of B lymphocytes by T-helper lymphocytes may produce elevation of serum immunoglobulins. The Kveim-Siltzbach skin test is the only test that, if positive, is considered to be diagnostic of sarcoidosis.[18,27]

The overall prognosis for patients with sarcoidosis is excellent. Approximately 65% recover completely or have minimal residual disease.[28] The chest radiographic abnormalities completely resolve in 54% of all patients.[28,29] The course and prognosis correlate with the mode of onset and with the radiographic stage at diagnosis. An acute onset, particularly if accompanied by fever and erythema nodosum, is associated with spontaneous resolution. An insidious onset may be associated with chronicity and progressive pulmonary fibrosis. Complete resolution of chest radiographic abnormalities has been reported in 61%, 39%, and 38% of patients with stage I, II, and III disease, respectively.[30] Approximately 20% to 25% of patients will remain with some degree of permanent disability, usually from pulmonary fibrosis.[28]

Corticosteroid therapy suppresses inflammation and granuloma formation and provides relief of symptoms. However, the long-term effect of corticosteroids on progression and outcome of the disease is uncertain and controversial. Mortality in sarcoidosis is low, with death attributable to sarcoidosis seen in approximately 2% of patients.[29] Pulmonary fibrosis with respiratory failure and cor pulmonale are the leading causes of death in Western nations. Cardiac involvement is the leading cause of death in Japan.[29] Autopsy studies indicate that the diagnosis of sarcoidosis is not made prior to death in approximately two thirds of patients.[31,32]

Pathology

GRANULOMA

The characteristic lesions of sarcoidosis are discrete, well-formed, compact, non-necrotizing epithelioid granulomas that exhibit uniformity in their size and stage of development (Fig. 66-2A–C). They may exhibit focal necrosis of mild degree (Fig. 66-2D) and may contain a variety of inclusions. Granulomas may undergo fibrosis usually beginning at the periphery and progressing centrally to complete fibrous obliteration (Fig. 66-2E, F). There is no morphologic feature of the granuloma that is either specific for or diagnostic of sarcoidosis.
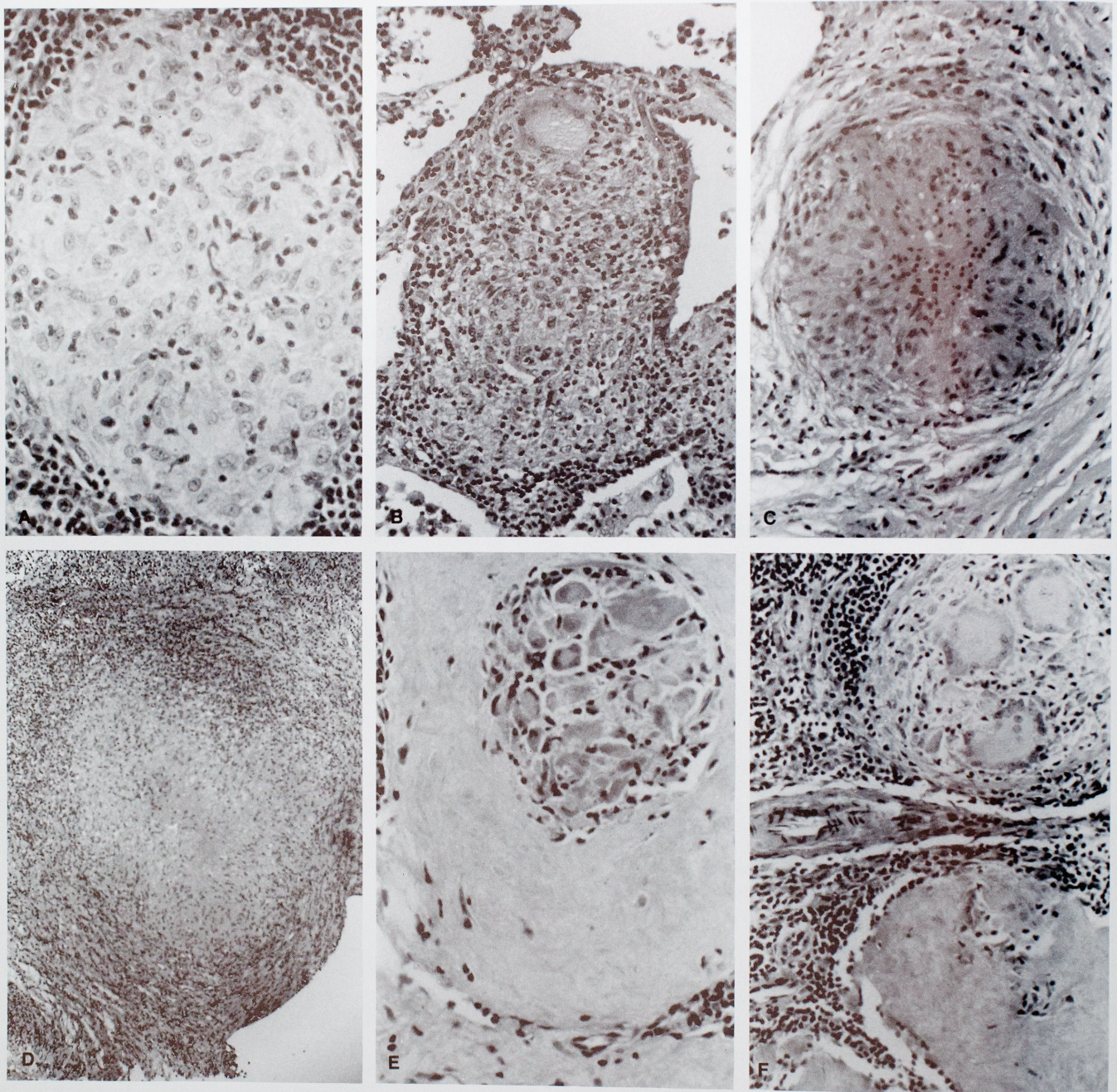
FIGURE 66-2. Granulomas in sarcoidosis. (**A**) Non-necrotizing epithelioid granuloma. (H & E stain; intermediate magnification.) (**B**) Non-necrotizing granuloma with giant cell. (**C**) Hyperchromatic apoptotic bodies (*i.e.,* necrotic epithelioid cells). (**D**) Minimal central necrosis. (**E**) Peripheral fibrosis with partial obliteration. (**F**) Early peripheral fibrosis (*top*) and complete fibrous obliteration (*bottom*). (**B–F**: H & E stain; low magnifications.)

NECROSIS

Although the granulomas in sarcoidosis are generally regarded as being non-necrotizing, the presence of necrosis has been reported in 6% to 39% of the cases.[19,20] The foci of necrosis are usually minute, spotty, and inconspicuous, involving the central portions of only a small proportion of the granulomas. Necrosis has been variously described as fibrinoid, granular, eosinophilic granular, and coagulative, and its resemblance to caseous necrosis has been noted. The necrosis that occurs in tuberculosis and other infectious diseases may appear identical to that seen in sarcoidosis.

Rarely, the granulomas in sarcoidosis may exhibit larger and even confluent areas of necrosis. In sarcoidosis and other granulomatous diseases, individual and isolated necrotic epithelioid cells are often seen in the central portion of the granulomas. They appear as ovoid cells with condensed, hyperchromatic, and fragmented nuclei and acidophilic cytoplasm and have been referred to as "apoptotic bodies" (see Fig. 66-2C).[33]

SCHAUMANN BODIES AND BIREFRINGENT CRYSTALS

Schaumann bodies, also called conchoidal bodies, are large (*i.e.*, 25–200 μm), concentrically lamellated calcified structures with a mucopolysaccharide matrix[34] that are often present within giant cells in sarcoidosis and other granulomatous diseases (Fig. 66-3*A*). They may be extruded into the extracellular space as they enlarge and cause cell rupture. Colorless, birefringent crystals composed predominantly of calcium oxalate, which range in size from 1 μm to 20 μm, are frequently seen within the cytoplasm of giant cells either alone or in combination with Schaumann bodies (Fig. 66-3*B, C*).[35–37]

As many as 70% of Schaumann bodies have crystals associated with them. It has been suggested that the calcium oxalate crystals act as a nidus for the formation of the conchoidal body.[37] Schaumann bodies and crystalline inclusions are, however, diagnostically nonspecific findings. They have been reported in 88% of cases of sarcoidosis, 62% of cases of chronic beryllium disease, and 6% of cases of tuberculosis.[35] Schaumann bodies alone may be seen in approximately 50% of cases of sarcoidosis.[20] Crystalline bodies unaccompanied by Schaumann bodies have been reported in 41% of cases of sarcoidosis, 15% of cases of chronic beryllium disease, and 3% of cases of tuberculosis.[35] Polarized light examination discloses crystalline inclusions in approximately two thirds of biopsy specimens containing non-necrotizing granulomas.[36]

ASTEROID BODIES

Asteroid bodies, 5-μm to 30-μm stellate inclusions with 30 or more rays radiating from a central core, are seen within giant cells in 2% to 9% of tissues from patients with sarcoidosis (Fig. 66-3*D*).[19,20] They may be seen within granulomas of other etiologies and therefore have no diagnostic specificity.[19] Ultrastructural examination reveals a structure containing microfilaments, microtubules, mature centrioles, paracentrioles, and an intervening amorphous matrix.[38] Asteroid bodies probably represent functionally obsolescent cell organelles.

HAMAZAKI-WESENBERG BODIES

Hamazaki-Wesenberg bodies are giant intracellular and extracellular lysosomes that may often be visualized by light microscopy in granulomatous and nongranulomatous lymph nodes from patients with sarcoidosis and a variety of other disorders.[20,39–42] They may be seen either intracellularly or extracellularly, predominantly at or near the peripheral sinus of the lymph node, and almost invariably outside of granulomas. They are oval or spindle-shaped, range in size from 0.5 μm to 0.8 μm, and frequently exhibit a yellow-brown color in hematoxylin and eosin–stained sections (Color Fig. 66-1). They have also been called yellow bodies, yellow-brown bodies, curious bodies, spiral bodies, and spindle bodies. The yellow-brown pigment has the histochemical characteristics of lipofuscin. Positive staining reactions are obtained with the following stains: Gomori methenamine silver, Ziehl-Neelsen, Fontana-Masson, oil red O, Sudan black B, and periodic acid-Schiff with and without diastase.

Because Hamazaki-Wesenberg bodies stain well with methenamine silver and often exhibit an appearance that is similar to yeastlike budding, they may easily be mistaken for fungi.[42] Their pleomorphism, their acid-fastness, and the absence of an associated host inflammatory response are features that aid in facilitating their recognition.

Lung Involvement

Although the granulomas in sarcoidosis may involve all organ systems, the lungs are unique in that their involvement is invariably demonstrable by open lung biopsy even in the absence of radiographic abnormality.[24] Granulomas occur bilaterally and exhibit a tendency to preferentially involve the upper two thirds of
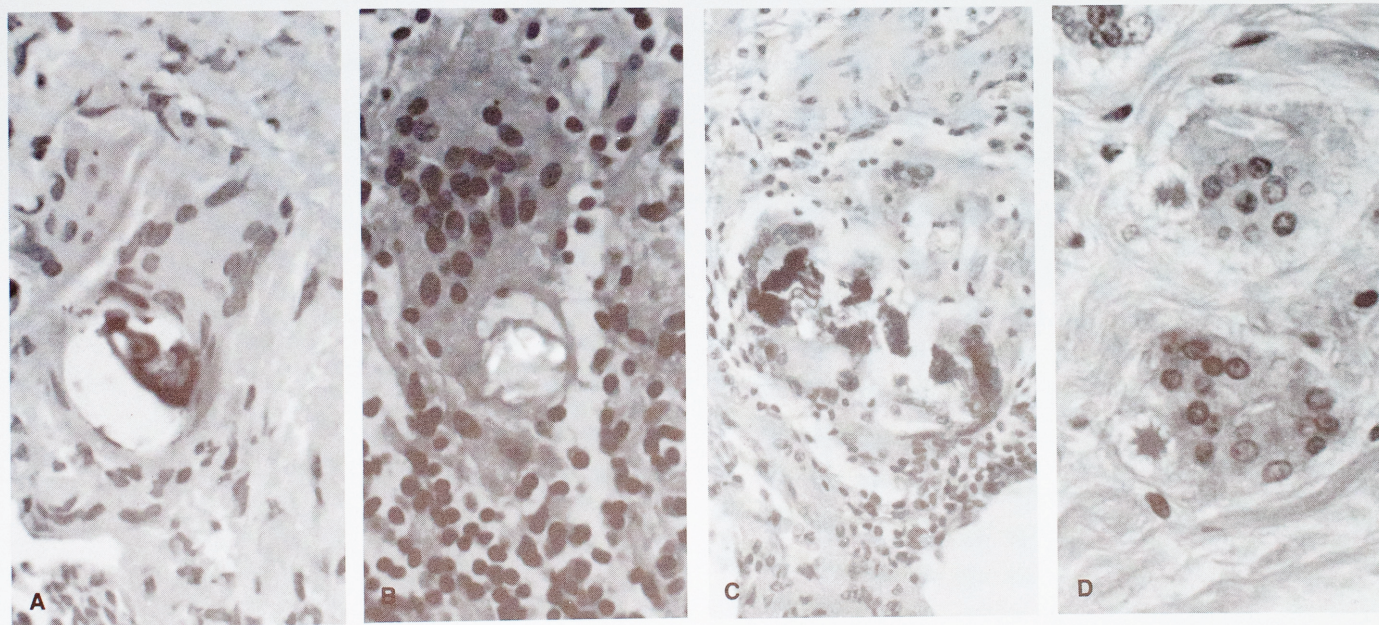

FIGURE 66-3. Inclusions in sarcoidosis. (**A**) Schaumann (*i.e.*, conchoidal) body within giant cell. (**B**) Calcium oxalate crystal within polarized giant cell. (**C**) Schaumann body and polarized calcium oxalate crystals. (**D**) Asteroid bodies within giant cells. (H & E stain; intermediate magnifications.)
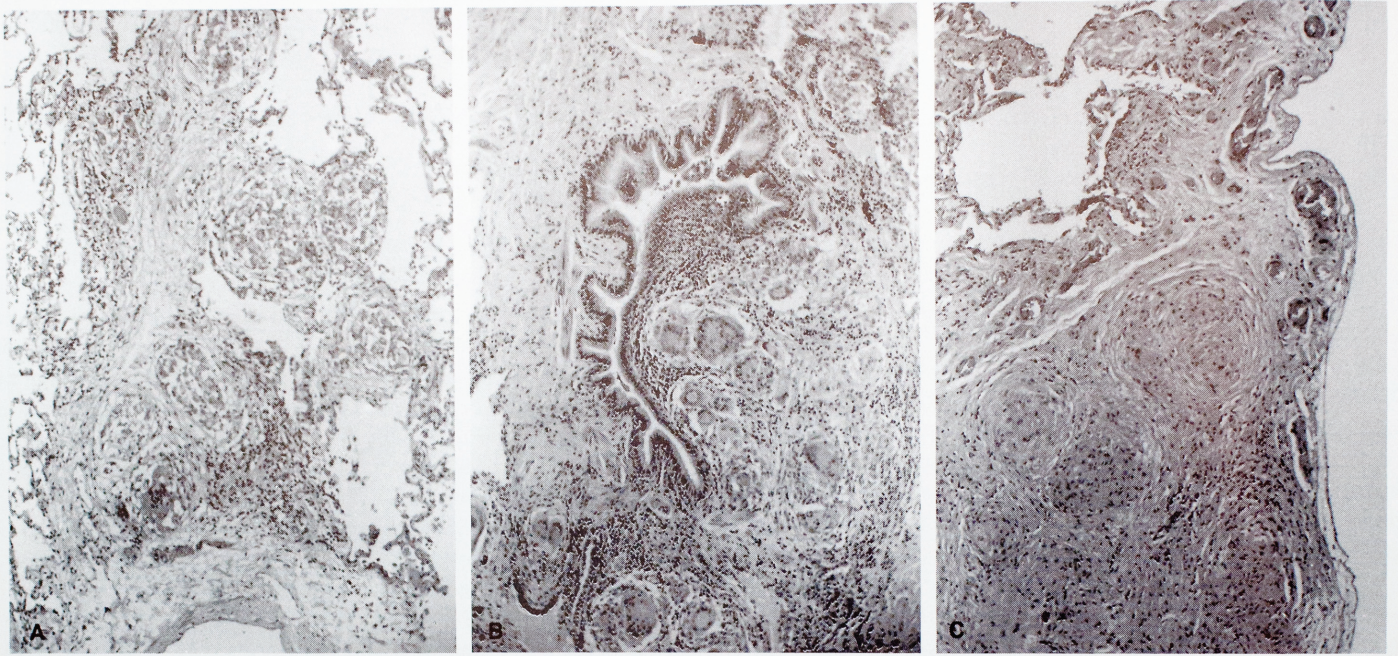
FIGURE 66-4. Lung involvement in sarcoidosis. (**A**) Granulomatous septal and paraseptal localization. (**B**) Granulomatous involvement of bronchiole. (**C**) Pleural involvement. (H & E stains; low magnifications.)

the lungs. As many as 75% of granulomas may be localized in alveolar walls and connective tissue around blood vessels, bronchioles, pleura, and fibrous septae (Fig. 66-4A–C).[43] Poorly defined granulomas are often seen within alveoli.

Although the granulomas are usually discrete, they may be confluent and form nodular masses in approximately 25% of cases. Large nodular lesions, either solitary or multiple (*i.e.*, nodular sarcoidosis), are the presenting radiographic finding in somewhat less than 5% of patients with sarcoidosis (Fig. 66-5).[17] Their radiographic appearance may simulate a primary or metastatic neoplasm.

ALVEOLITIS

Alveolitis (*i.e.*, nongranulomatous interstitial pneumonitis) is characterized by an interstitial cellular infiltrate in which lymphocytes constitute approximately 90% of the cells. This is the earliest pulmonary lesion in sarcoidosis and precedes granuloma formation (Fig. 66-6).[22,43–48] Alveolitis has been identified as the predominating or a prominent microscopic finding in 62% of open lung biopsy specimens from patients with sarcoidosis[45] but is rarely identifiable in transbronchial biopsy specimens. The alveolitis in sarcoidosis is the morphologic representation of the activation of the cellular immune system with proliferation of T lymphocytes that precedes granuloma formation. Bronchoalveolar lavage has demonstrated a marked increase in the number of T lymphocytes, almost all of which are T-helper cells.[50–52]

In active sarcoidosis, the T-helper/T-suppressor ratio is 10 : 1,

FIGURE 66-5. Nodular sarcoidosis is seen in this segmental resection specimen. The white nodule is composed of confluent granulomas with central pigmentation simulating lung cancer.
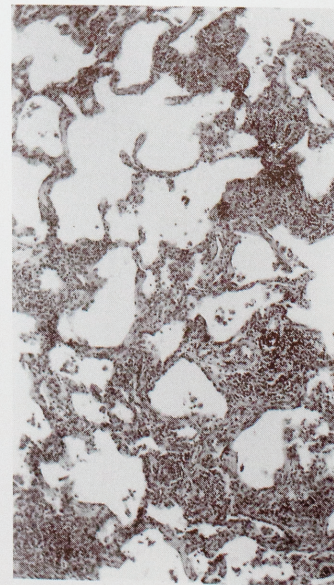

FIGURE 66-6. In early sarcoidosis, there is a significant lymphocytic interstitial infiltrate with indistinct granuloma formation (alveolitis). This histologic appearance must be distinguished from hypersensitivity pneumonitis. (H & E stain; low magnification.)

compared with 1.8 : 1 in the normal lung.[49–51] The alveolitis tends to diminish in intensity and resolve as the disease resolves or becomes chronic. Alveolitis is considered to be critical in influencing the evolution and ultimate outcome of sarcoidosis; there is also evidence that the intensity and duration of the alveolitis and the magnitude of the helper/suppressor ratio of T lymphocytes are inversely related to a good prognosis.[52–54]

GRANULOMATOUS PULMONARY ANGIITIS

Granulomatous involvement of pulmonary blood vessels in sarcoidosis is a frequent finding in open lung biopsy[55] and autopsy material and is only occasionally seen in transbronchial lung biopsy specimens (Fig. 66-7). In geographic locations where sarcoidosis is prevalent, it is probably the most common cause of granulomatous pulmonary angiitis. However, granulomatous pulmonary angiitis is a nonspecific lesion that may also be seen in tuberculosis, Wegener granulomatosis (WG), necrotizing sarcoid granulomatosis (NSG), schistosomiasis, and foreign-body embolization in a drug abuser, and following cardiac catheterization. Granulomas are also seen in association with mineralization and fragmentation of blood vessel elastic laminae accompanying extensive pulmonary hemorrhage and pulmonary venoocclusive disease. Granulomatous pulmonary angiitis is not a feature of hypersensitivity pneumonitis.

The presence and extent of granulomatous angiitis in sarcoidosis vary directly with the number of granulomas present in the lung tissue, and granulomatous angiitis has been identified in approximately two thirds of open lung biopsy specimens.[56] Veins are far more frequently involved than arteries, and elastic tissue stains facilitate the identification of these vascular lesions, particularly when located in the midst of confluent granulomas. Marked destructive medial changes as well as stenosis or complete obliteration of the lumen may be seen; thrombosis, aneurysm formation, and infarction are not usually present. Granulomatous involvement of lymphatic vessels may also occur but is rare. Involvement of large proximal pulmonary blood vessels in patients with sarcoidosis has been reported but is unusual.[56]

Pulmonary hypertension appears to be a rare complication of granulomatous pulmonary angiitis in sarcoidosis.[57–61] A granulomatous condition simulating pulmonary venoocclusive disease has been reported as a result of selective and severe venous involvement.[60,61]

BRONCHIAL AND BRONCHIOLAR INVOLVEMENT

Airway lesions are frequent in sarcoidosis (see Fig. 66-4B) and can be detected by bronchial wall biopsy in 15% to 55% of patients with sarcoidosis[62] and by open lung biopsy in up to 37%.[20] The likelihood of detecting granulomas in abnormal-appearing bronchial mucosa is about twice as great as in normal-appearing mucosa.[63] Pulmonary function studies have shown that airway obstruction is frequent in all stages of sarcoidosis[64] and may be detectable in as many as 75% of patients having radiographic evidence of pulmonary fibrosis.[65]

Bronchostenosis is an unusual complication of granulomatous airway involvement and is detectable by bronchoscopy in approximately 8% of patients.[66,67] Such patients may have expiratory wheezing, dyspnea, and cough. The stenotic lesions are usually multiple and invariably occur in association with radiographic evidence of pulmonary fibrosis.

PLEURAL INVOLVEMENT

Although visceral pleural granulomas are demonstrable in as many as 35% of open lung biopsies from patients with sarcoidosis (see Fig. 66-4C), radiographic evidence of pleural involvement (*i.e.*, pleural effusion or thickening) is present in only 10% of patients.[68,69]

PULMONARY FIBROSIS

Fibrosis of granulomas and lung parenchyma (Fig. 66-8A) may occur in the later stages of disease, but the factors that influence the development of fibrosis are not well understood. Destruction of alveolar wall epithelial basement membranes may lead to fibrosis, because repopulation of alveolar epithelium fol-
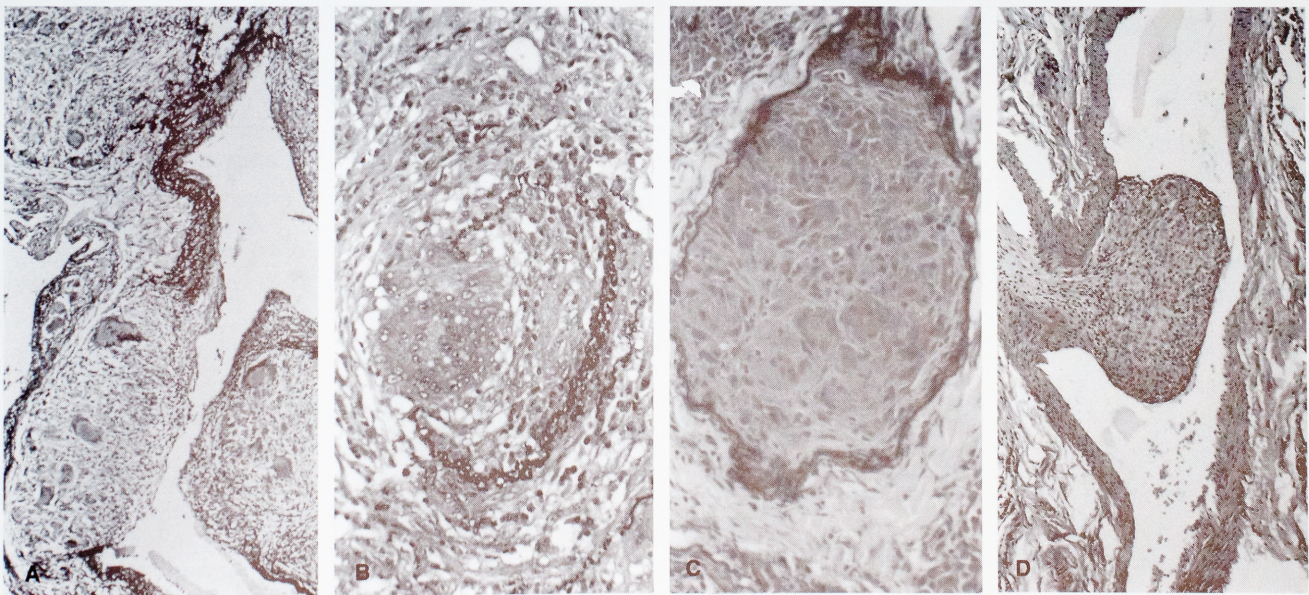

FIGURE 66-7. Granulomatous venulitis of progressive severity (**A** and **B**), terminating in luminal occlusion (**C**). (**A**, **B**) elastic tissue stain; low magnifications. **C:** elastic tissue stain; intermediate magnification. (**D**) Intimal granuloma at a site of arterial branching growing in a polypoid fashion. (H & E stain; low magnification.)
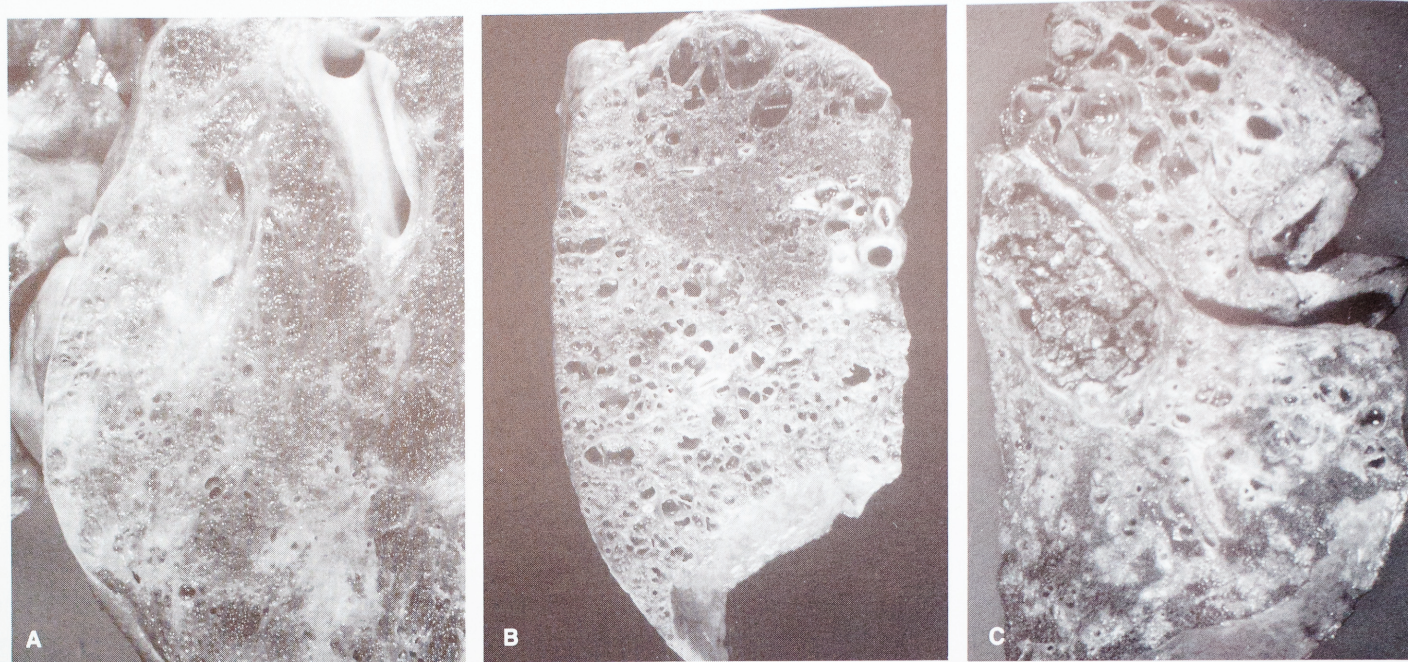
FIGURE 66-8. End stages and complications of lung involvement in sarcoidosis. (**A**) Extensive parenchymal fibrosis. (**B**) Honeycomb lung. (**C**) Bronchiectasis with aspergilloma in the apex of the lower lobe.

lowing injury appears to depend on the presence of an intact basement membrane.[70] Mononuclear phagocytes also appear to have an important role by modulating the local accumulation and replication of fibroblasts through release of mediators such as fibronectin and alveolar macrophage-derived growth factor.[71,72]

End-Stage Sarcoidosis and Other Complications

Honeycombing is the end stage of pulmonary sarcoidosis and other interstitial diseases, and it is characterized by parenchymal fibrosis and bronchiolectasis resulting in abnormal nonfunctional air- and fluid-filled spaces (Fig. 66-8*B*). Honeycombing tends to be most pronounced in the upper portions of the lungs and subpleurally. Relatively few granulomas may be present at this stage. Pulmonary hypertensive arteriopathy may be evident. Bronchiectasis (Fig. 66-8*C*) or bronchostenosis may result from granulomatous airway involvement or superimposed infection. Emphysema may also be seen in end-stage sarcoidosis and in some patients may be a complication of bronchostenosis. The pathogenesis of emphysema in sarcoidosis in the absence of bronchostenosis is obscure. The radiographic cystic lung changes that occur in some patients with advanced disease are produced by foci of saccular bronchiectasis or bullous emphysema. True cavitation rarely, if ever, occurs in sarcoidosis, but it is seen in some cases of NSG. If a patient with sarcoidosis develops a cavitary lung lesion, an etiology other than sarcoidosis must be sought.

Aspergillomas (see Fig. 66-8*C*) may occur in patients with marked cystic parenchymal disease. They often produce hemoptysis, which may be life-threatening.[73] Fungal colonization tends to occur in foci of saccular bronchiectasis. Major or massive hemoptysis in patients with chronic sarcoidosis is almost always due to an aspergilloma. Systemic amyloidosis complicating sarcoidosis is extremely rare.[74–76] There is no definite statistical evidence to

support the suggestion that patients with sarcoidosis are at increased risk for the development of lung carcinoma or malignant lymphomas.[77]

Diagnosis

Establishing the diagnosis of sarcoidosis is a complex matter involving a synthesis of clinical, radiographic, and pathologic findings, each of which is nonspecific. The identification of granulomas and the performance of appropriate examinations to exclude an infectious or other known etiology are the responsibilities of the pathologist. The synthesis of all pertinent information and the ultimate diagnostic decision are the responsibility of the clinician who has undertaken the diagnostic workup and management of the patient.

A diagnosis of sarcoidosis indicates that the patient has a systemic granulomatous disease of undetermined etiology and that known causes of systemic granulomatous diseases have, insofar as possible, been excluded. Because there are no morphologic features of granulomas specific for sarcoidosis, it is not appropriate for the pathologist ever to make a diagnosis of sarcoidosis that is based solely on examination of biopsy specimens. The diagnosis of sarcoidosis requires periodic review, especially in those patients with atypical clinical features.

BIOPSY

Obtaining a tissue specimen to establish that the patient has a granulomatous disease is essential, in most cases, to secure the diagnosis of sarcoidosis. Although the primary purposes of biopsy are to document a granulomatous disease and to exclude, insofar as possible with the use of special stains, an infectious etiology, there are other important purposes: to obtain tissue to culture for microorganisms and to obtain tissue for additional diagnostic and investigative procedures, including electron microscopy, immu-

nohistochemical studies, enzyme determinations, and chemical analysis. The scope of studies that can be accomplished is largely dependent on the size of the biopsy specimen. Small transbronchial biopsy specimens are adequate for demonstration of granulomas and for culture of microorganisms. However, larger specimens are usually required for more extensive morphologic and biochemical studies. Because the lungs and hilar lymph nodes are the sites most frequently involved, most biopsy efforts are directed toward either or both of these tissues. Biopsy specimens may also be obtained from any accessible extrathoracic sites where involvement is suspected.

Procedures. Although the diagnostic yield of granulomas with open lung biopsy is close to 100%,[24] this procedure has virtually disappeared as a primary modality for the diagnosis of sarcoidosis because of the success and popularity of transbronchial lung biopsy. Open lung biopsy is used only in those cases where diagnosis by other means is not possible. Mediastinal lymph node biopsy performed with the mediastinoscope has a diagnostic yield almost as high as open lung biopsy and entails a much lower degree of risk to the patient. It is frequently performed as a second-line procedure in patients with mediastinal lymphadenopathy who have had a negative transbronchial biopsy.

Transthoracic or transbronchial fine needle aspiration biopsy may be used in the presence of nodular lesions.[78] Demonstration of granulomas in extrathoracic sites with fine needle aspiration has been reported.[79,80]

Because of its relative ease of performance, high diagnostic yield, and low morbidity, transbronchial lung biopsy performed with the flexible fiberoptic bronchoscope has become the procedure of choice in patients suspected of having intrathoracic sarcoidosis. The incidence of major complications is 2%, and the mortality is 0.2%.[81] The yield of granulomas in patients suspected of having sarcoidosis is 78% in all stages combined, 69% in stage I, 82% in stage II, and 86% in stage III.[82-86] Its main disadvantage is the potential for sampling error due to the small size of the tissue samples. However, obtaining multiple specimens has been shown to significantly increase the diagnostic yield from 46% with a single biopsy fragment to 90% with four specimens.[87] The diagnostic accuracy of transbronchial lung biopsy in sarcoidosis approaches 100% when 10 biopsy specimens are obtained in stage I disease and when 5 to 6 specimens are obtained in stages II and III.[87,88]

The Kveim-Siltzbach Test. The Kveim-Siltzbach test involves the intradermal injection of a suspension of granuloma-containing spleen or lymph node from a patient with sarcoidosis. It is the only laboratory test that, if positive, is generally regarded as diagnostic of sarcoidosis.[89-94] The test is positive if a papule develops at the injection site within 4 to 6 weeks and if biopsy of the papule discloses the presence of non-necrotizing granulomas not due to foreign bodies. Appropriately validated and satisfactory Kveim testing materials identify at least 60% of patients with active sarcoidosis and exhibit no more than 1% false-positive results in individuals without sarcoidosis. The incidence of positive reactions decreases with increasing duration of sarcoidosis and following corticosteroid therapy. The mechanism of the Kveim-Siltzbach test is under active investigation.

Despite the widely acknowledged value of this test in the diagnosis of sarcoidosis, its use has actually decreased, in large part because of the relative ease of performance and high diagnostic yield of transbronchial lung biopsy. Other significant impediments include the following:

There are difficulties in the preparation, standardization, and validation of the test material.

Four to six weeks are required to obtain results, for which a biopsy procedure is necessary.

Test suspensions are not commercially available.

OTHER MODALITIES FOR PATIENT EVALUATION

Serum Angiotensin-Converting Enzyme. SACE levels are elevated in 50% to 60% of all patients with sarcoidosis and in as many as 85% of patients with active sarcoidosis.[95] SACE levels in sarcoidosis tend to decrease with increasing duration of disease and following corticosteroid therapy.[96,97] Markedly elevated angiotensin-converting enzyme (ACE) levels have been found in virtually all granulomatous lymph nodes in sarcoidosis,[98] and ACE and its cleavage product, angiotensin II, have been identified by immunohistochemical techniques in the cytoplasm of epithelioid cells in more than 90% of granuloma-containing tissues from patients with sarcoidosis.[99,100] These studies failed to demonstrate ACE in tissue containing nonsarcoid granulomas or in tissue without granulomas. It appears likely that ACE is manufactured by cells of the mononuclear phagocytic system in the sarcoid granulomas.[100]

Measurement of SACE levels initially appeared to have the potential for becoming a specific and reliable diagnostic test for sarcoidosis; however, further experience has shown that elevation of SACE is a nonspecific finding. Nevertheless, it may be extremely helpful in the diagnosis of sarcoidosis when considered with other findings. SACE appears to be a marker of disease activity and has its greatest value in monitoring the progression of the disease and its response to corticosteroid therapy, as well as in following treated patients for evidence of relapse.[95,96]

Gallium Scanning. Intravenously administered ^{67}Ga citrate localizes in areas of acute or chronic inflammation and may be demonstrated in various body sites with a scanning technique.[102,103] The isotope has been shown to reside primarily within mononuclear phagocytes, and *in vitro* uptake of ^{67}Ga by macrophages is enhanced when they are activated. The primary application of this technique is to demonstrate inflammation and to follow its course. In approximately 16% of sarcoidosis patients, it is the only noninvasive method capable of detecting clinical activity, and it is more sensitive than radiography in documenting improvement and predicting relapses. It may also be useful in selecting sites for biopsy bronchoalveolar lavage.

Bronchoalveolar Lavage. Bronchoalveolar lavage has been a major factor in the acquisition of data pertaining to the alveolitis of sarcoidosis and other interstitial lung diseases. Although the technique does not have a significant role in the diagnosis of sarcoidosis, it may provide useful information relating to disease activity, prognosis, and response to therapy.[104]

Differential Diagnosis

The following are the major disease categories that may enter into the differential diagnosis of sarcoidosis:

- infectious diseases, especially mycobacterial and fungal infection
- hypersensitivity pneumonitis (*i.e.*, extrinsic allergic alveolitis)
- chronic beryllium disease
- NSG
- WG.

INFECTIOUS GRANULOMAS

Because approximately one third of granulomas seen in routine surgical pathology practice are due to infection,[1] a diligent search for infectious agents should be conducted whenever granulomas are identified, regardless of whether or not necrosis is present. Mycobacterial, fungal, and parasitic infection account for 64%, 30%, and 6%, respectively, of infectious granulomas.[1] As many as one third of biopsy specimens obtained from patients with proven *Mycobacterium tuberculosis* infection exhibit nonnecrotizing granulomas exclusively. The presence of numerous neutrophils within granulomas should suggest the likelihood of a fungal infection.[1] Microscopic sections stained appropriately for acid-fast bacilli and fungi should be examined in all cases.

When the differential diagnosis includes infection and sarcoidosis, tissue, if available, should be submitted for cultures directly from the operating room or bronchoscopy suite. The sensitivity of tissue stains for acid-fast bacilli is low, and the failure to identify acid-fast bacilli does not exclude the possibility of mycobacterial infection. The significance of a negative acid-fast stain also depends on the number of granulomas present. A negative acid-fast stain in a section of a 2-cm lymph node completely replaced by granulomas is obviously of far greater significance than the same result in a transbronchial biopsy specimen containing three granulomas. The possibility of the pathologist identifying a causative fungal or parasitic organism in tissue examination is significantly greater than the possibility of identifying mycobacterial organisms. The differential diagnosis of infectious granulomatous disease is discussed elsewhere in this book (see Chaps. 40, 41, 43, and 44).

HYPERSENSITIVITY PNEUMONITIS AND CHRONIC BERYLLIUM DISEASE

The pulmonary lesions seen in hypersensitivity pneumonitis and chronic beryllium disease may closely resemble each other and the lesions of sarcoidosis. Their differences from sarcoidosis tend to be quantitative. Alveolitis and nongranulomatous inflammation of peripheral airways are generally more prominent, and granulomas less prominent, than in sarcoidosis. Granulomatous pulmonary angiitis, a frequent manifestation of sarcoidosis, is not a known feature of hypersensitivity pneumonitis and is rarely a manifestation of chronic beryllium disease. Hilar lymph nodes are usually not enlarged, but they may contain granulomas.

When biopsy findings suggest the possibility of hypersensitivity pneumonitis, confirmation of the diagnosis requires a history of exposure to aerosolized organic antigen, the observation of clinical improvement when the source of exposure is removed, and, if possible, appropriate serologic tests (see Chap. 65).

An occupational history of exposure is important for the diagnosis of chronic beryllium disease, which may then be confirmed by the demonstration of beryllium in tissue or body fluids, or sensitization of the patient's lymphocytes to beryllium (see Chap. 37).

NECROTIZING SARCOID GRANULOMATOSIS

In 1973, Liebow first described a condition characterized by confluent masses of granulomas in lung tissue, necrosis within the granulomatous masses, and destructive granulomatous vasculitis, which he termed "necrotizing sarcoid granulomatosis."[105] Liebow stated that "the problem is whether the disease represents necrotizing angiitis with sarcoid reaction, or sarcoidosis with necrosis of the granulomas and of the vessels."[105] The answer to this question is still unknown, despite several major studies of this entity.[105a–105c]

Based on present knowledge of NSG and sarcoidosis, it is probable, but unproved, that NSG is part of the spectrum of sarcoidosis. Confluent granulomas, necrosis within granulomas, and granulomatous angiitis occur frequently in sarcoidosis. The extent of the necrosis reported in some cases of NSG is, however, unusual for sarcoidosis. The characteristic nodularity of the lung lesions in NSG, though not typical of sarcoidosis, is seen in 1.5% to 4% of patients with sarcoidosis (see Fig. 66-5).[106–117] Nodular sarcoidosis, although well recognized, has not been well studied. Somewhat less than one half of the patients have hilar lymphadenopathy, and biopsy studies show confluent granulomas that occasionally exhibit necrosis and cavitation. It has been postulated that NSG actually represents nodular sarcoidosis. Yet, the precise nature of NSG remains to be determined. Factors that suggest that NSG may be unrelated to sarcoidosis include the low incidence of hilar lymphadenopathy, the absence of other clinical features of sarcoidosis, the characteristic multinodular radiographic appearance, and the apparent rarity of extrathoracic involvement. This disease is discussed in more detail in Chapter 69.

WEGENER GRANULOMATOSIS

In contrast to sarcoidosis, epithelioid granulomas in WG, if present, tend to be few in number and poorly formed. Angiitis, a prominent feature of both sarcoidosis and NSG, is predominantly nongranulomatous in WG. Large geographic areas of necrosis, a characteristic feature of WG, are not seen in sarcoidosis. The diagnosis of WG is unlikely in a biopsy specimen that exhibits large numbers of well-formed epithelioid granulomas (see Chap. 68).

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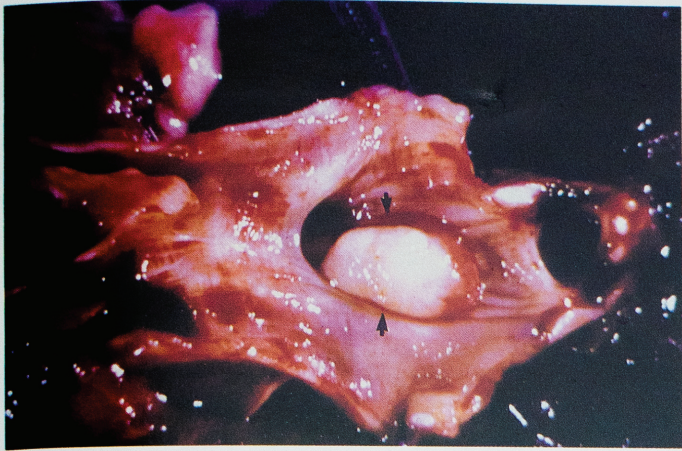
**COLOR FIGURE 56-1.** Endobronchial lipoma presents as a soft yellowish mass (*arrows*).

COLOR FIGURE 56-2. In a gross specimen of intrapulmonary localized fibrous tumor, the mass is white, rubbery-to-firm, and well demarcated (see Fig. 56-3).
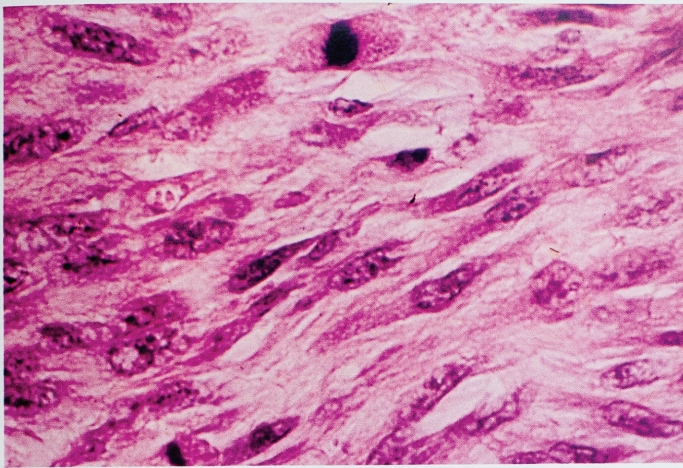

COLOR FIGURE 56-3. Spindle cell proliferation, nuclear pleomorphism, and mitosis are present in this leiomyosarcoma, which was confirmed by vementin and muscle-specific antigen by immunohistochemistry (see Fig. 56-4). (H & E stain; high magnification; contributed by the editor.)
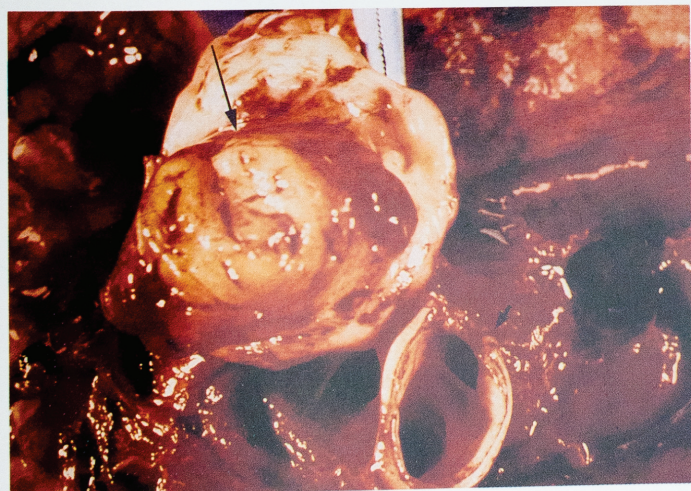
COLOR FIGURE 56-4. A resected lung specimen shows a polypoid mass occupying the lumen of the left pulmonary artery (*long arrow*); this mass is a pulmonary artery sarcoma. The main bronchus underneath is uninvolved (*short arrow*; see Fig. 56-5).
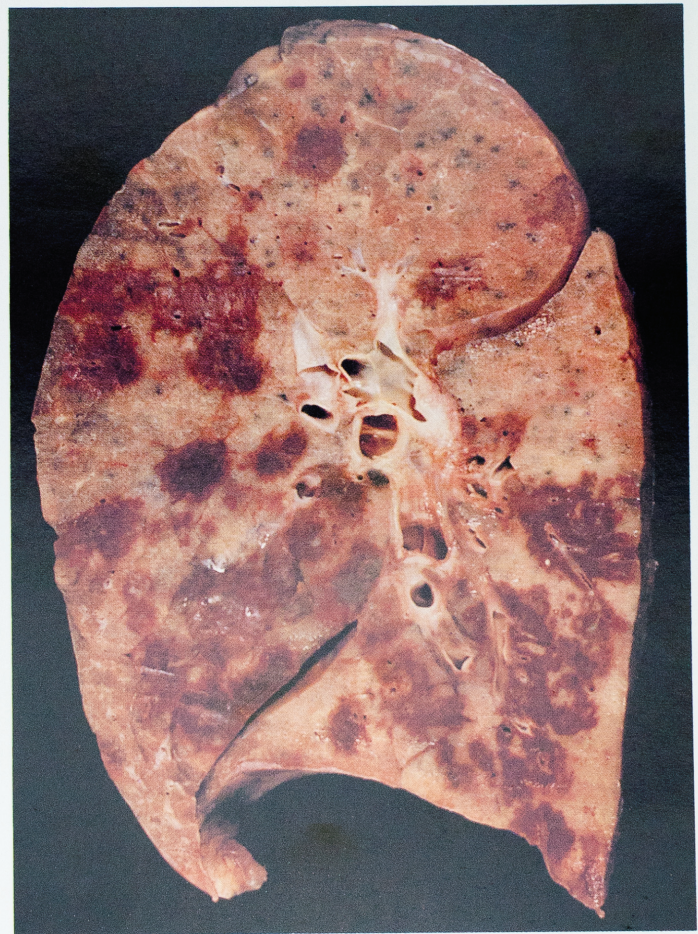
COLOR FIGURE 56-5. Gross appearance of the lung in an adult patient with acquired immunodeficiency syndrome and Kaposi sarcoma (see Fig. 56-7). (Contributed by the editor.)
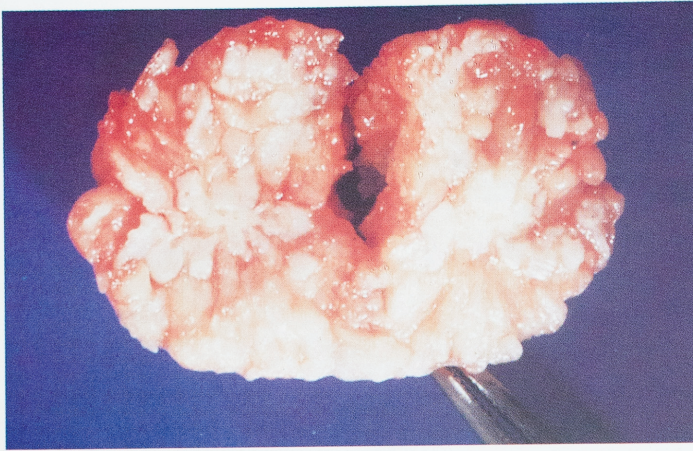
COLOR FIGURE 56-6. A gross specimen of fibrochondrolipoma shows a hard mass that is circumscribed and finely lobulated. (Contributed by the editor.)

COLOR FIGURE 57-1. Asbestos in its natural state has hairlike mineral fibers protruding from crocidolite rock.

COLOR FIGURE 57-2. This man had a history of asbestos exposure and developed mesothelioma of the pleura. The bulging masses are tumors growing through the chest wall. (Contributed by the editor.)
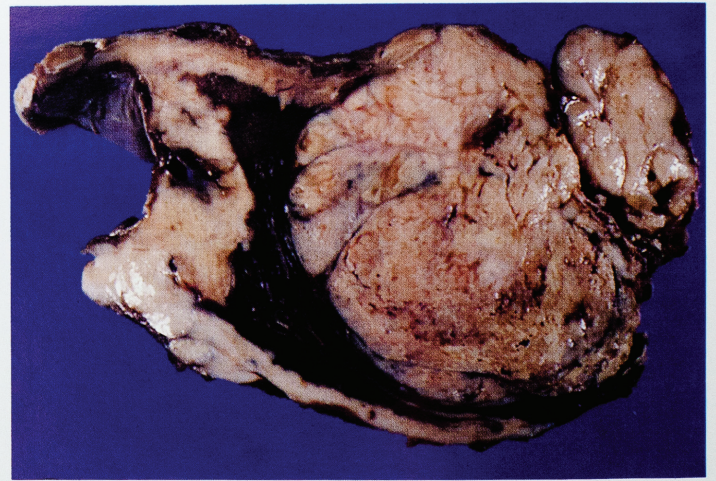
COLOR FIGURE 57-3. Gross appearance of left lung in the patient shown in Color Figure 57-2. The mesothelioma encases the lung and produces large masses within the lung and through the chest wall. (Contributed by the editor.)
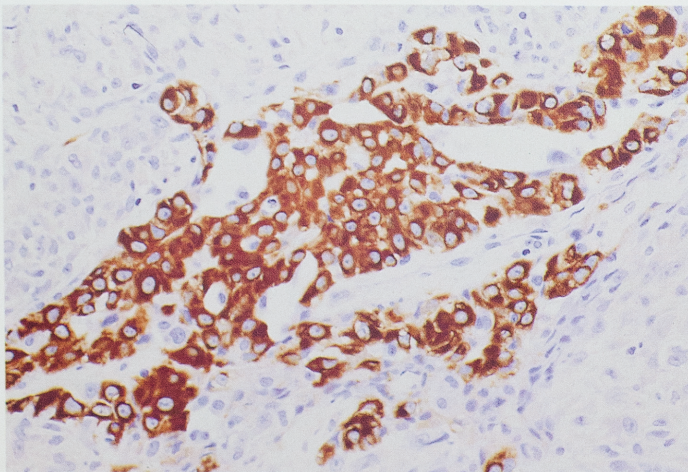
COLOR FIGURE 57-4. Immunopositivity defines the architecture of a neoplastic grouping of tubulopapillary mesothelioma. Only the epithelial element stains positively for keratin. (Intermediate magnification; courtesy of Victor Roggli, M.D., Durham, NC.)
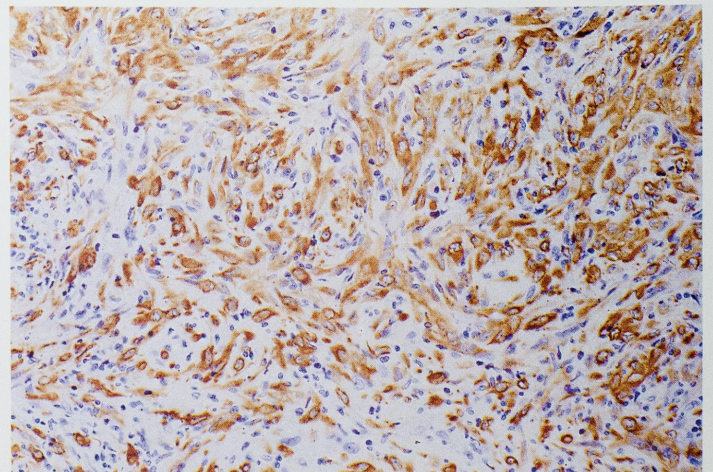
COLOR FIGURE 57-5. Keratin immunostaining of sarcomatoid mesothelioma reveals immunopositivity along the cytoplasm of spindle cells. (Intermediate magnification; courtesy of V. Roggli, M.D., Durham, NC.)
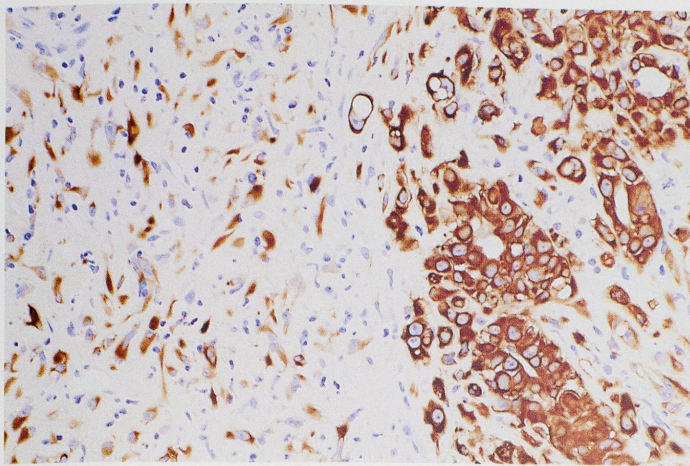
COLOR FIGURE 57-6. Keratin immunostaining in biphasic meso-
thelioma reveals the strong positivity of the epithelial component. Many of
the spindle cells are also positive. (Intermediate magnification; courtesy of
V. Roggli, M.D., Durham, NC.)
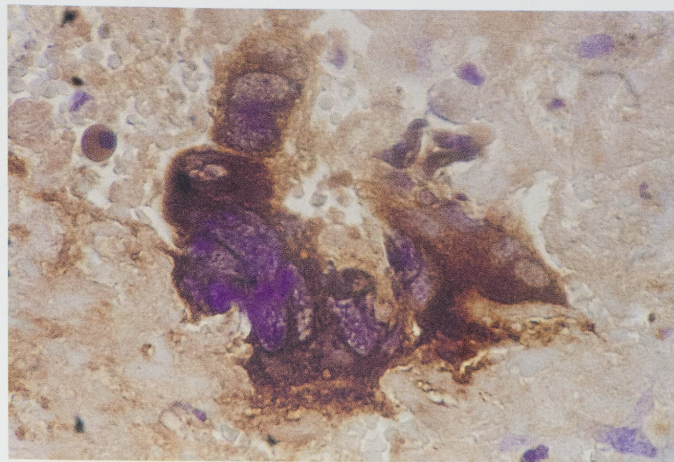
COLOR FIGURE 58-1. Positivity for human chorionic gonadotropin
in the distinctive, malignant trophoblastic cells from the same tumor as in
Figure 58-26 identifies it as choriocarcinoma. (Immunoperoxidase stain;
low magnification; contributed by the editor.)
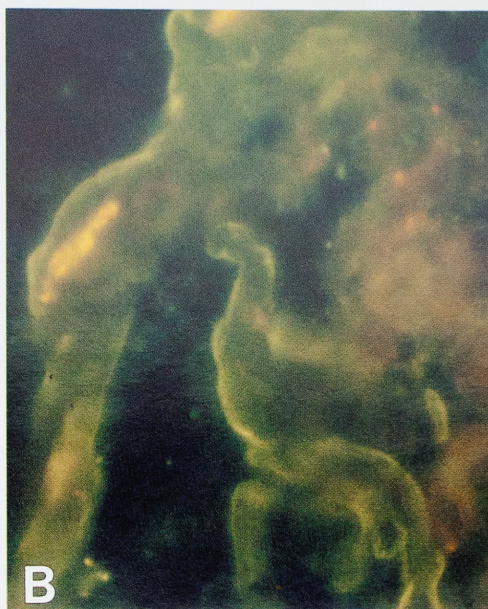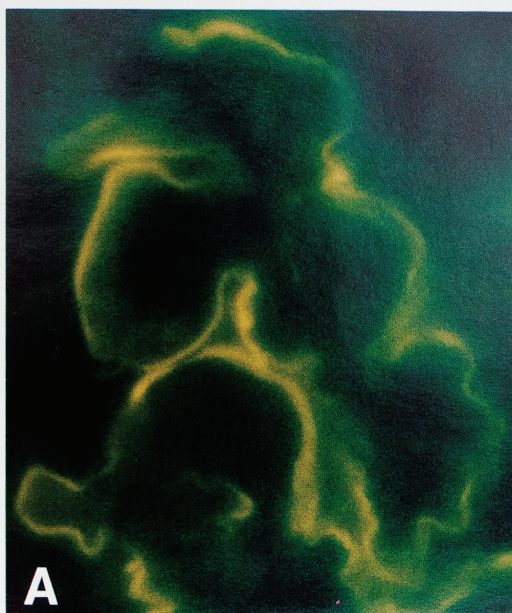
COLOR FIGURE 62-1. Direct immunofluorescence in patients with Goodpasture syndrome shows a delicate
linear basement membrane reaction along both (**A**) glomerular capillaries and (**B**) alveoli septae. (High mag-
nifications; courtesy of J. Goeken, M.D., Iowa City, IA.)
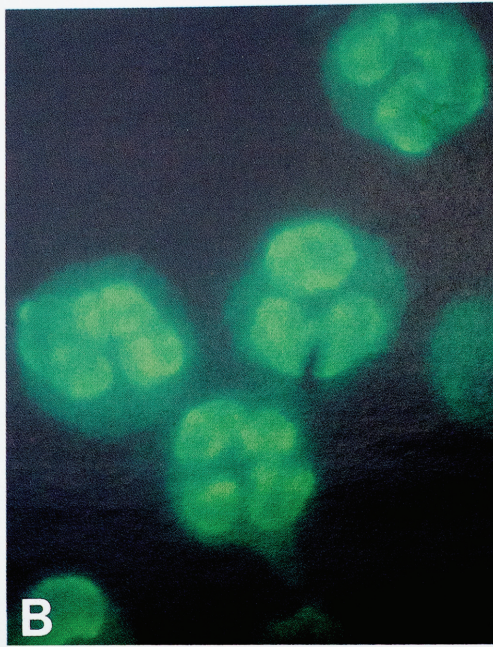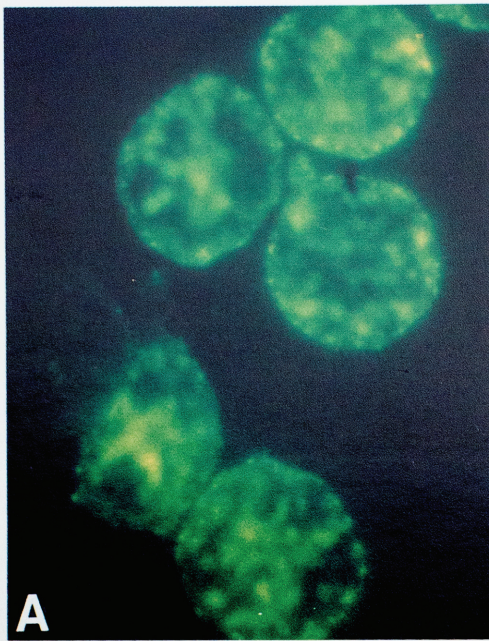
COLOR FIGURE 62-2. Indirect immunofluorescence in ethanol-fixed neutrophils shows (**A**) coarse, granular cytoplasmic reaction of C-ANCA and (**B**) perinuclear or nuclear reaction of P-ANCA. (Oil immersions; courtesy of S. Hardarson, M.D., Reykjavik, Iceland.)
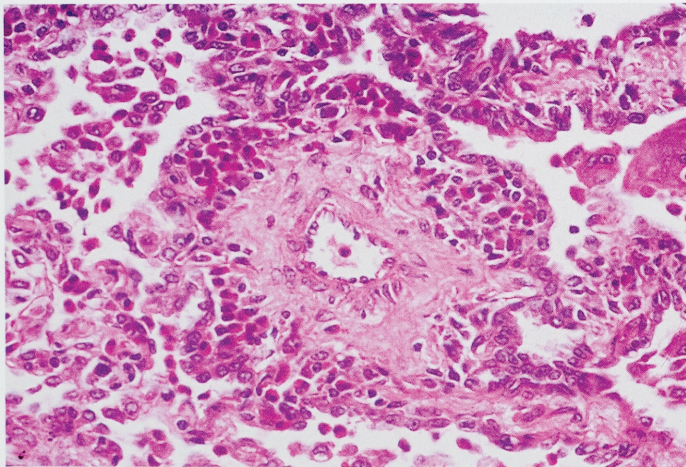
COLOR FIGURE 64-1. Histologic features of chronic eosinophilic pneumonia include perivascular accumulation of inflammatory cells, predominantly eosinophils. The adjacent alveoli contain numerous large histiocytes (see Fig. 64-5). (H & E stain; intermediate magnification.)
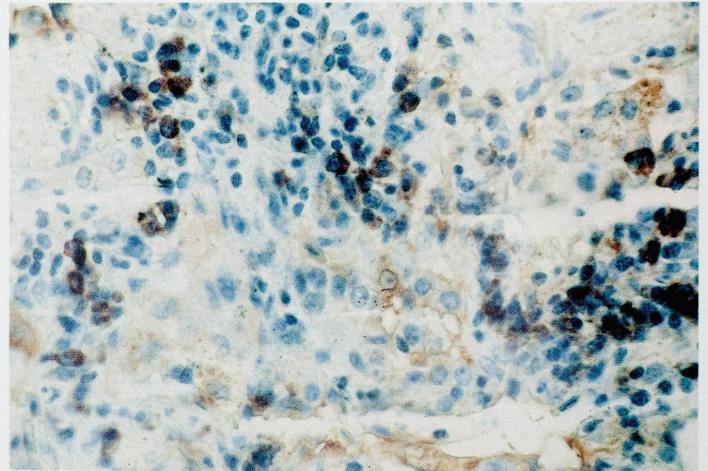
COLOR FIGURE 65-1. In immunoperoxidase reaction for IgG, positive cells are found in the peribronchiolar region in a patient with hypersensitivity pneumomitis. (Peroxidase antiperoxidase stain; dimethylaminoazobenzene chromogen; intermediate magnification.)
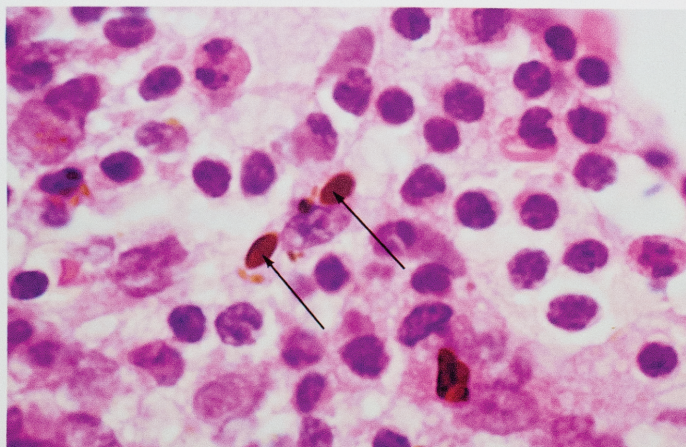
COLOR FIGURE 66-1. Hamazaki-Wesenberg bodies (*arrows*) are seen in a lymph node in a patient with sarcoidosis. (H & E stain; oil immersion.)
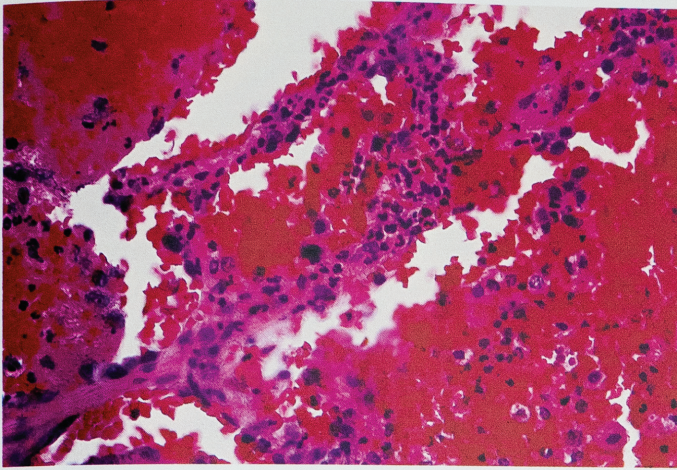
COLOR FIGURE 68-1. A lung biopsy specimen from the same patient as in Figure 68-2 shows neutrophilic capillaritis in Wegener granulomatosis associated with alveolar hemorrhage. (H & E stain; low magnification.)
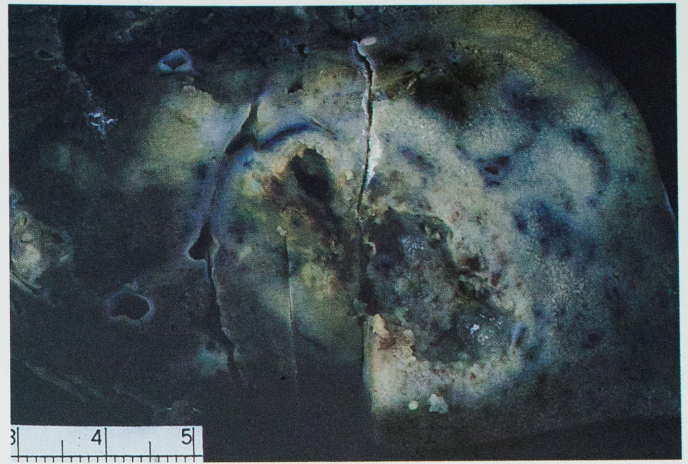

COLOR FIGURE 68-2. A gross specimen of lung demonstrates the characteristic cavitary nodule in a patient with Wegener granulomatosis (see Fig. 68-6). (Courtesy of T. Colby, M.D., Rochester, MN.)
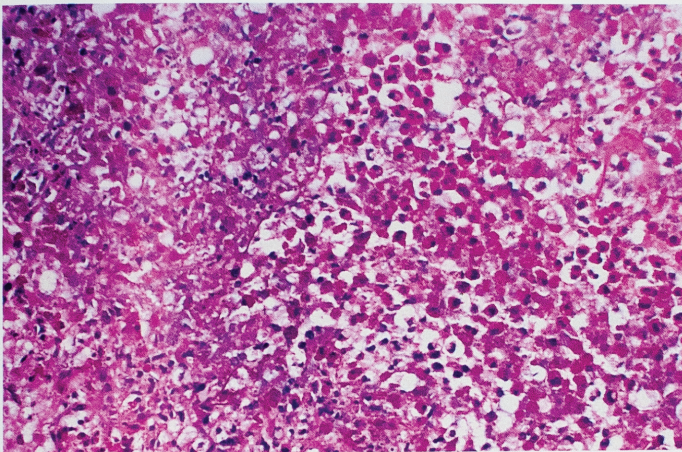

COLOR FIGURE 68-3. In an eosinophilic variant of Wegener granulomatosis, an area of necrosis shows large numbers of eosinophils (see Fig. 68-8).
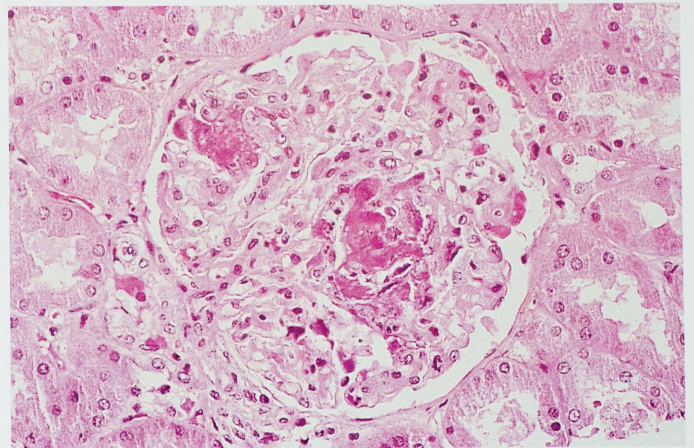
COLOR FIGURE 68-4. Bronchocentric Wegener granulomatosis has produced focal glomerulitis in this patient (see Fig. 68-9). (H & E stain; low magnification.)
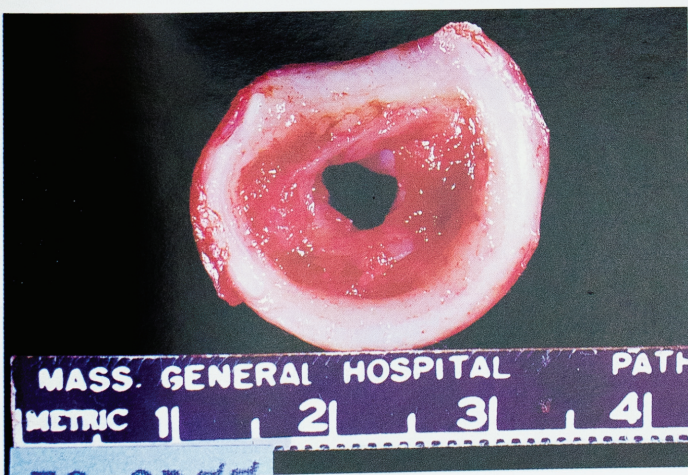

COLOR FIGURE 73-1. Diaphragmlike fibrotic narrowing of the trachea was produced by a tracheostomy inflation cuff. (Courtesy of Hermes Grillo, M.D., Boston, MA.)
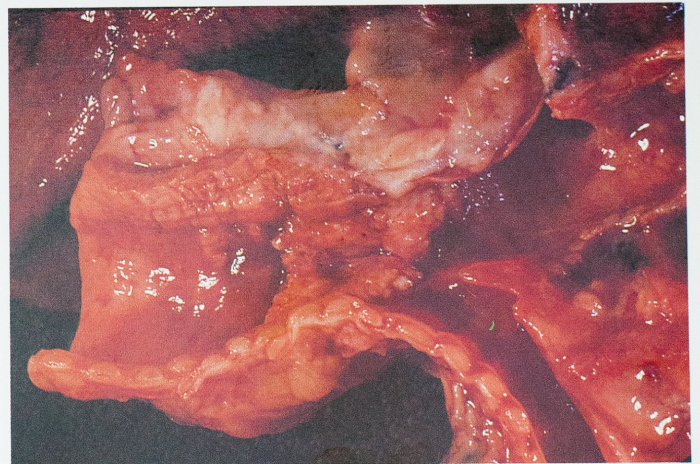

COLOR FIGURE 73-2. This squamous cell carcinoma produced marked narrowing of the lower one third of the trachea (see Fig. 73-7). (Courtesy of Bolivar Kunhardt, M.D., Miami, FL.)
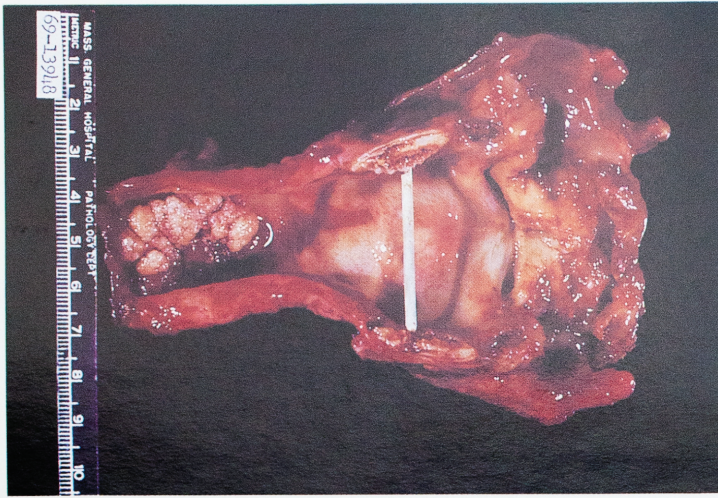
COLOR FIGURE 73-3. Adenoid cystic carcinoma of trachea appears as a sessile, multinodular mass arising from the anterior wall of the trachea (see Fig. 73-9). (Courtesy of Massachusetts General Hospital, Boston, MA; autopsy 69-13948.)
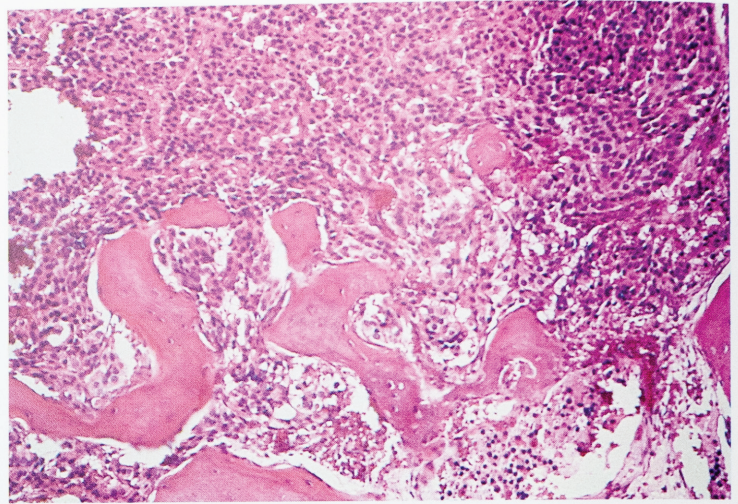

COLOR FIGURE 73-4. Histologic view of an ossifying carcinoid of the trachea shows bone production by carcinoid cells (see Fig. 73-10). (H & E stain; low magnification.)
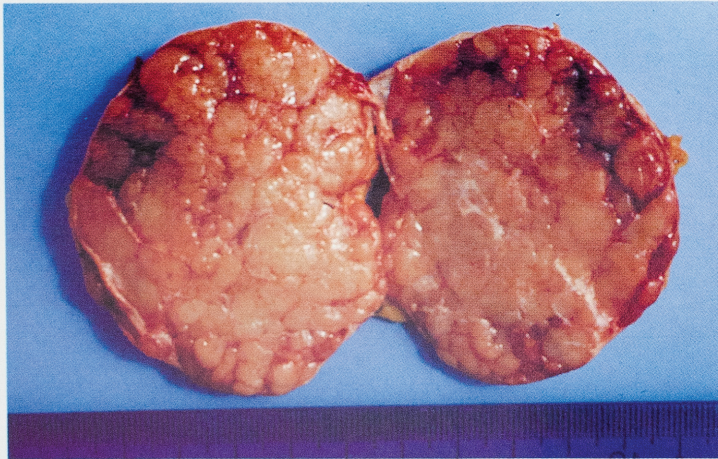

COLOR FIGURE 74-1. Lobularity and encapsulation of the thymoma is characteristic of the tumor. (Contributed by Paulina Ojeda, M.D., Bogotá, Colombia.)
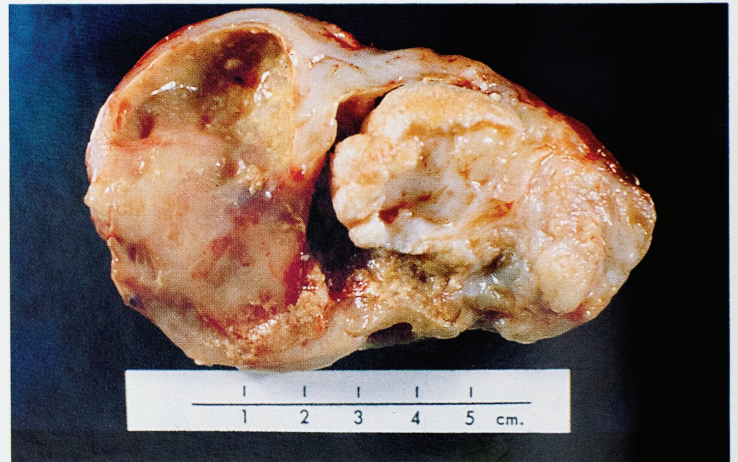
COLOR FIGURE 74-2. In a gross specimen of benign cystic teratoma, solid type, there were foci of cystic degeneration and abundant brain tissue and teeth. (Contributed by the editor.)
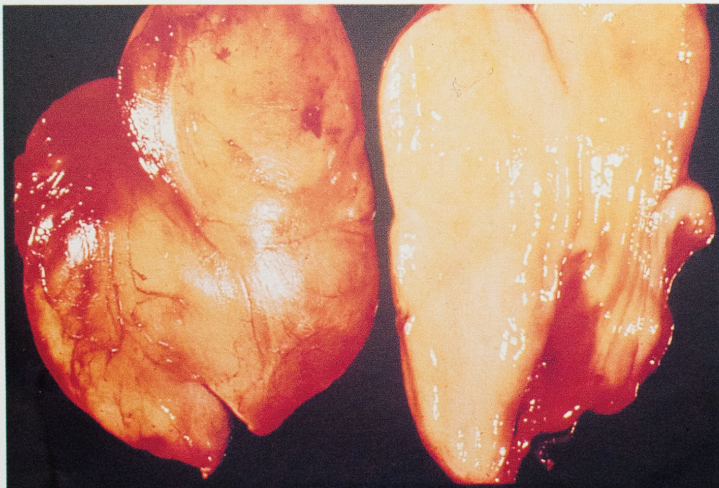

COLOR FIGURE 74-3. Bisected ganglioneuroma of the mediastinum. (Courtesy of Luis Alvarez, M.D., Miami, FL.)
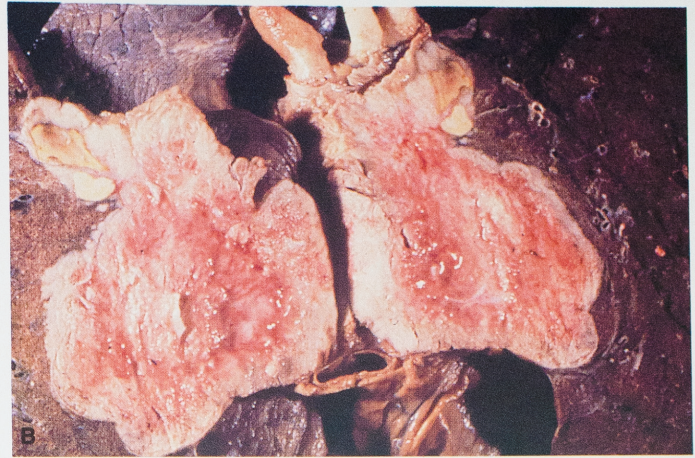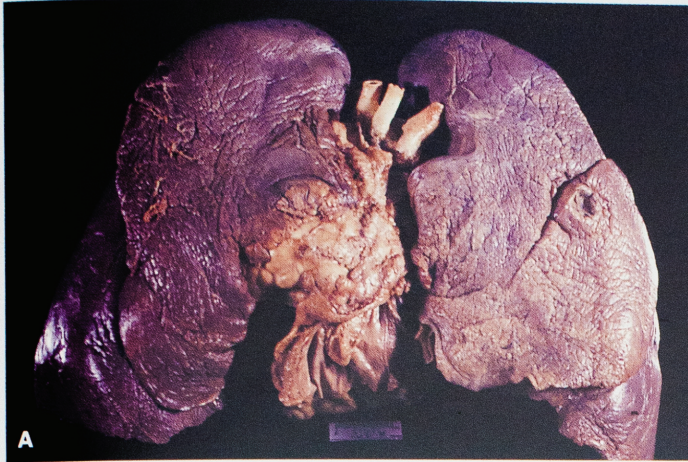
COLOR FIGURE 74-4. (**A**) Gross appearance of an invasive thymoma. (**B**) The tumor is bisected to show infiltration of the pulmonary parenchyma (see Fig. 74-6). (Contributed by the editor.)

COLOR FIGURE 74-5. Teratocarcinoma of the mediastinum shows focal areas of cystic degeneration. (Contributed by the editor.)
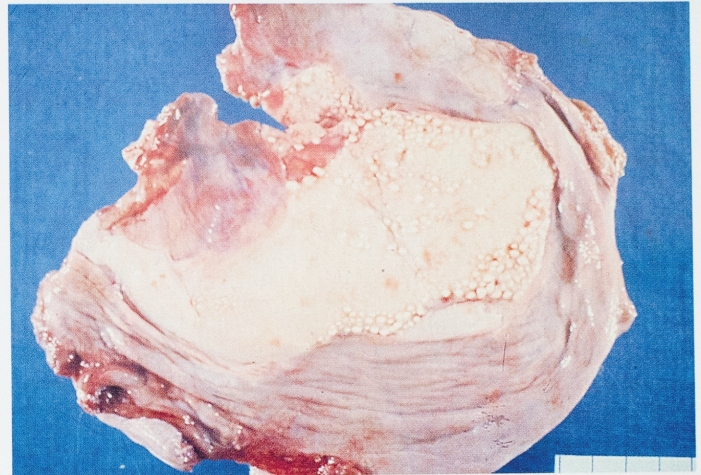

COLOR FIGURE 75-1. The hemidiaphragm in an asbestos-exposed person shows a characteristic fibrous plaque with a candle-wax–drippings appearance. (Contributed by Victor Roggli, M.D., Durham, NC.)

COLOR FIGURE 75-2. In this patient with a history of asbestos exposure, the parietal pleural plaques are elongated and follow the distribution of the ribs. Radiologically, the lesion projected as a peripheral nodule, and the patient underwent thoracotomy because of the suspicion of carcinoma. (Contributed by the editor.)

COLOR FIGURE 76-1. Fragment of a large, grayish-white-and-brown malignant peripheral neuroectodermal tumor (MPNT, Askin tumor) that arose in the thoracopulmonary region of a young boy. (Contributed by the editor.)
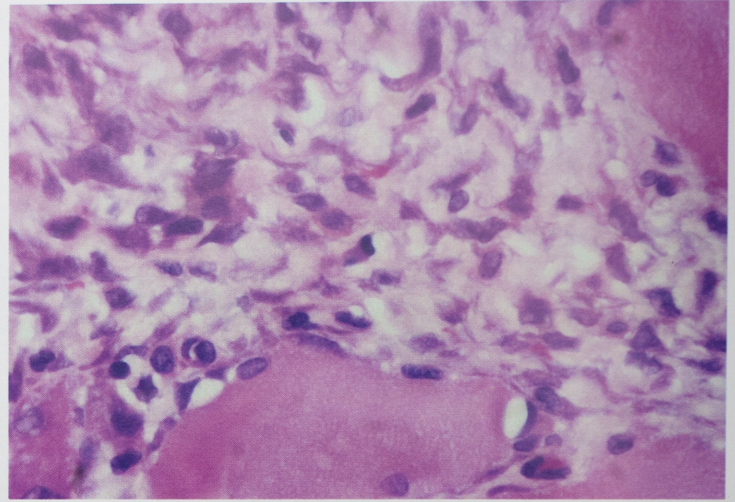
COLOR FIGURE 76-2. Nodular fasciitis of thoracic wall infiltrates the skeletal muscle of diaphragm (see Fig. 76-5). (H & E stain; intermediate magnification; contributed by the editor.)

COLOR FIGURE 77-1. The devastating recent effects of acid rain and air pollution are evident in this otherwise well-preserved statue placed circa 1607–1611 in the gardens of the mansion of the Marquis of Salisbury, known as Hatfield House, in Herefordshire, England.

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