30
Nonneoplastic Pleural Disease

Samuel P. Hammar

This chapter discusses the etiology, epidemiology, and laboratory features of pleural effusions, and the pathologic features of selected pleural diseases.

Histology of the Normal Pleura

The visceral pleura can be divided into five layers: (1) outermost mesothelial cell layer, (2) submesothelial interstitial connective tissue layer, (3) outer thick elastic fiber layer, (4) inner interstitial connective tissue layer, and (5) inner thin elastic fiber layer (see Fig. 2.35A in Chapter 2).[1] In the resting condition, the different layers of the pleura may be inconspicuous and the mesothelial cells are only about 1 μm thick (Fig. 30.1). However, these cells are extremely reactive to any type of injury and frequently undergo hypertrophy and hyperplasia to produce a much thicker mesothelial cell layer with a significantly increased number of mesothelial cells (Fig. 30.2). The layers of parietal pleura are not as distinct as in the visceral pleura. The landmark that may be used to identify the parietal pleura is the fatty tissue between the skeletal muscle of the chest wall and the connective-elastic tissue of the parietal pleura (see Fig. 2.35B in Chapter 2).

Ultrastructure of the Pleura

The surface mesothelial layer is best appreciated by scanning electron microscopy, which shows the numerous microvilli that arise from mesothelial cells and project into the pleural space (Fig. 30.3).[2] In normal conditions, the microvilli measure about 0.1 μm in diameter and up to about 3 μm in length. When the pleura is injured and there is hypertrophy and hyperplasia of mesothelial cells, the number and length of the microvilli increase. The exact function of the microvilli is not entirely understood. At one time it was thought that they increased the absorptive

surface of the visceral pleura, but later studies showed that the visceral pleura did not absorb pleural fluid to any significant degree.[3] Current thought is that microvilli serve as an increased surface area to release hyaluronic acid, which serves as a lubricant between the visceral and parietal layers of the pleura during movement of the lung in respiration.[3] The density of the microvilli is greater on the visceral mesothelial cells than on the parietal mesothelial cells. The mesothelial cytoplasm is rich in pinocytotic vesicles, mitochondria, and other organelles, as well as prekeratin fibrils (Fig. 30.4). The visceral and parietal pleura have an extensive lymphatic network, although in the normal resting state, these lymphatic channels are inconspicuous. Openings between the mesothelial cells, "called stomata," occur on the parietal surface and range between 2 and 12 μm in diameter (Fig. 30.5).[4–6] These stomata communicate directly with lymphatic lacunae. The stomata are thought to represent exit points for pleural fluid, protein, and cells that come from the pleural space.[5,7]

Pleural Fluid Formation

Pleural fluid formation has been discussed in detail by Sahn[3,8] and Pistolesi et al.[9] Most of the pleural fluid is produced by the parietal pleura, and there is a dynamic interaction between production and resorption. As described by Sahn,[3] six mechanisms have been postulated for the accumulation of abnormal volumes of pleural fluid: (1) increase in hydrostatic pressure in the microvascular circulation, (2) decrease in oncotic pressure in the microvascular circulation, (3) decrease in pressure in the pleural space, (4) increased permeability of the microvascular circulation, (5) impaired lymphatic drainage from the pleural space, and (6) movement of fluid from the peritoneal space.

The diagnostic techniques used in examining pleural fluid and the significance of the findings have been discussed in detail by Sahn[3,10] and by Light.[11]
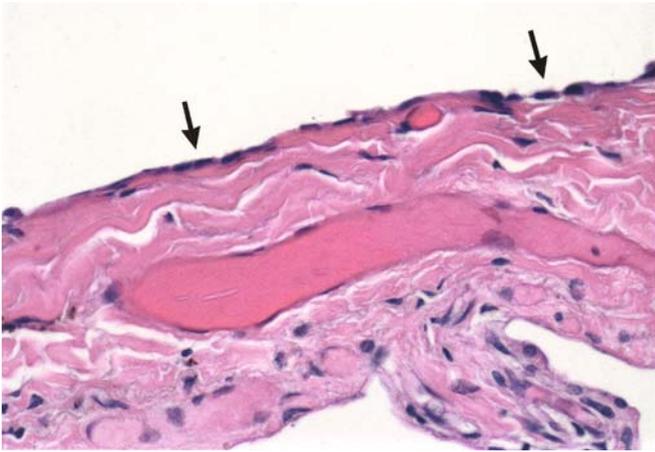
FIGURE 30.1. In resting state, layers of pleura are rather inconspicuous. Note flattened appearance of mesothelial lining cells (arrows).
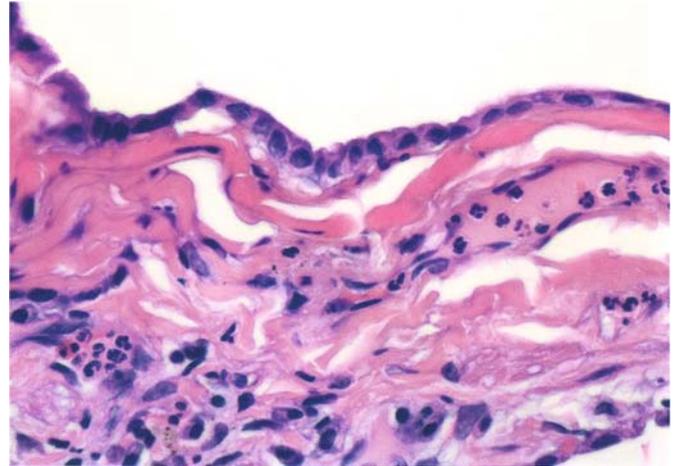

FIGURE 30.2. Very slight irritation causes mesothelial cells to undergo hypertrophy and hyperplasia. Cuboidal cells with enlarged nuclei produce a thickened serosal layer.

Diagnostic Techniques to Evaluate Pleural Disease

Besides examining the characteristics of pleural fluid, closed and open pleural biopsies may be performed to diagnose pleural diseases. What type of biopsy, if any, depends on the clinical situation and the information needed. Open pleural biopsy is the standard against which closed pleural biopsy and thoracoscopic pleural biopsy are compared. As one might expect, open pleural biopsies have a higher diagnostic yield than closed pleural biopsies or thoracoscopic pleural biopsies. As discussed later, in my opinion thoracoscopic pleural biopsies are often adequate for diagnosing nonneoplastic and neoplastic conditions. As long as an adequate tissue sample containing diagnostic material is obtained that can be studied by a variety of methods, a fairly accurate diagnosis is possible in most cases.

The correct way of handling pleural tissue samples is determined to some degree by the clinical history of the patient being biopsied. It is important for the pathologist to communicate with the pulmonologist or surgeon who is performing the biopsy in order to gain insight into the reason for doing the biopsy. For example, if the patient is thought to have an infectious pleuritis, a portion of the biopsy should be sent for culture. If the clinical diagnosis is cancer, then a portion of the specimen should be sent for cytologic evaluation, including potential evaluation by immunohistochemistry and electron microscopy (see Chapter 43 on pleural neoplasms).
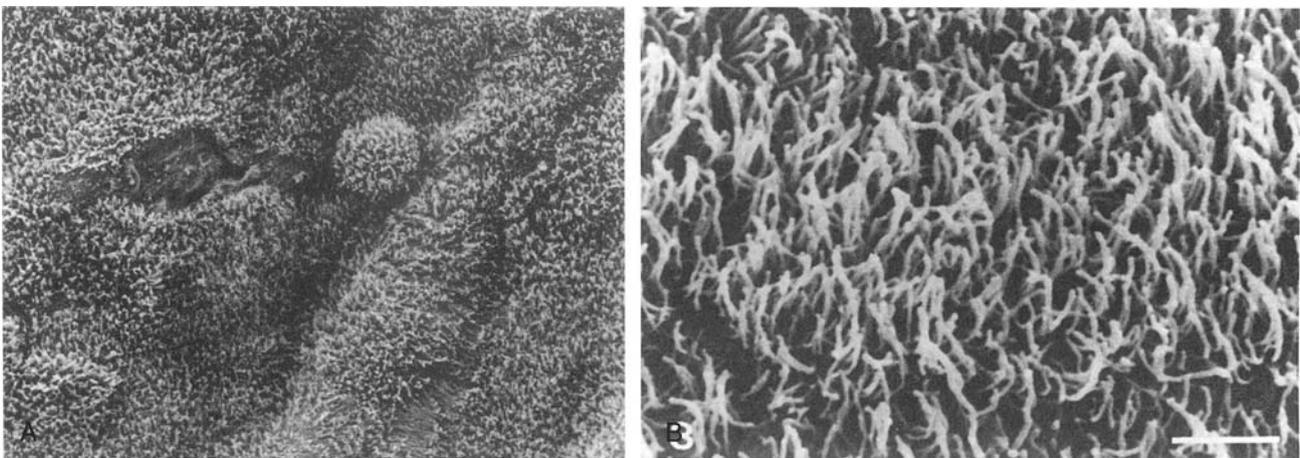

FIGURE 30.3. **A,B.** Scanning electron micrographs of mesothelial lining of pleura show extensive microvillous surface. (From Gaudio et al.,[2] with permission.)
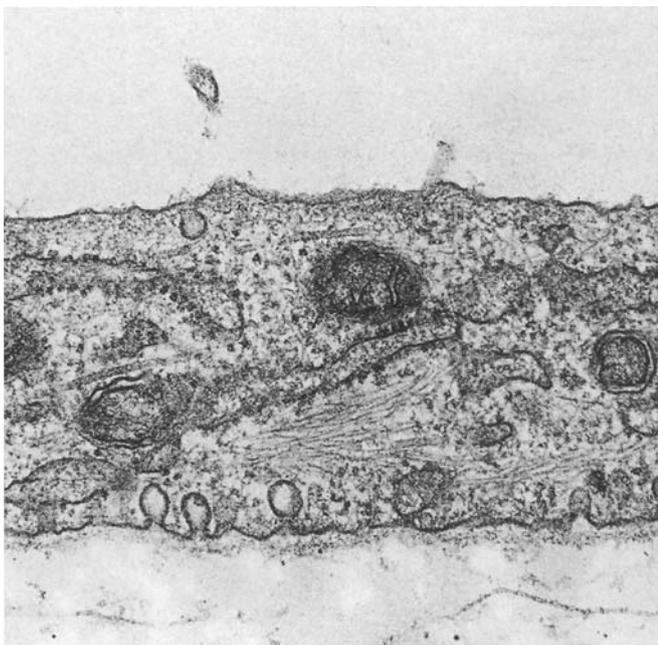
FIGURE 30.4. Cytoplasm of mesothelial cells is rich in mito-chondria, prekeratain fibrils, and other organelles in addition to elongated bushy microvilli. Rabbit. (Transmission electron microscopy [TEM], ×12,600.) (From Wang N-S. The regional difference of pleural mesothelial cells in rabbits. Am Rev Respir Dis 1974;110:623–633, with permission. Copyright © 1974, American Thoracic Society.)

FIGURE 30.5. Openings in mesothelium, called stomata. Arrows point to red blood cells. (From Whitaker D, et al. The pathobiol-ogy of the mesothelium. In: DW Henderson, et al. Malignant mesothelioma. New York: Hemisphere, 1992, with permission of Taylor & Francis Group. Copyright © 1992, via Copyright Clearance Center.)

Fine-needle aspiration biopsy specimens usually provide a small amount of tissue, which can provide a great deal of information if appropriately handled.[12–21] Most fine-needle aspiration biopsies are performed on masses thought to represent neoplasms. Small pieces of tissue obtained from such biopsies can be directly processed for electron micro-scopic examination or prepared as a cell block on which immunohistochemical analyses can be done. Rinses from the needle and the syringe can be directly put into fixative, centrifuged, and processed in a "beam" capsule for elec-tron microscopy (see Chapter 43).

Immunobiology of Pleural Disease

Antony[22] reviewed the immunologic mechanisms involved in pleural disease, and reported that the pleura is a dynamic, metabolically active membrane that is involved in main-taining homeostasis as well as responding to various inflammatory and neoplastic insults. Antony described the importance of mesothelial cells in maintaining homeostatic balance and the changes that occurred in mesothelial cells and other cells in infectious and neoplastic pleural disease. Pleural fluid cytokines observed in infectious disease and malignant disease are shown in Table 30.1.
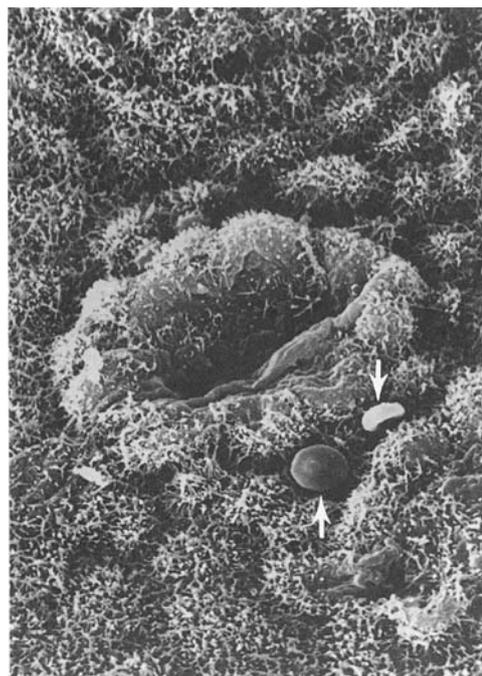
TABLE 30.1. Pleural fluid cytokines

Infectious disease
  Interleukin-1 (IL-8)
  Epithelial neutrophil activating protein-78 (ENA-78)
  Monocyte chemotactic protein-1 (MCP-1)
  Macrophage inflammatory protein-1α (MIP-1α)
  Interleukin-1α (IL-1α)
  Interleukin-1β (IL-1β)
  IL-1 receptor antagonist protein
  Interleukin-6 (IL-6)
  Transforming growth factor-β (TGF-β)
  Fibroblast growth factor (FGF)
  Granulocyte-monocyte colony-stimulating factor (GM-CSF)
  Insulin-like growth factor-1 (IGF-1)
  Endothelin-1 (ET-1)

Malignant disease
  Plasminogen activator inhibitor-1 (PAI-1)
  Endothelin-1 (ET-1)
  Soluble intercellular adhesion molecule-1 (ICAM-1)
  Platelet-derived growth factor (PDGF)
  Fibroblast growth factor-β (FGF-β)
  Vascular endothelial growth factor (VEGF)
  Insulin-like growth factor-I (IGF-I)
  Epidermal growth factor (EGF)
  Hyaluronic acid
  Metalloproteinases (MMP)
  Tissue inhibitor of metalloproteinases (TIMP)
  Interleukin-6 (IL-6)
  Interleukin-8 (IL-8)
  Macrophage inflammatory protein-1α (MIP-1α)

Source: Antony,[22] with permission from ERS Journals Ltd.

TABLE 30.2. Basic causes, proinflammatory stimuli, and pathology of pleural inflammation

Etiology	Inflammatory agents	Pathology	Disease
Bacterial invasion	Lipopolysaccharide, other bacterial pathogens	Neutrophil infiltration, fibrin deposition, fibrosis	Parapneumonic pleurisy, empyema
Immunologic disorder	Immune complexes, activated lymphocytes	Vasculitis, immune complex deposition, inflammatory cell infiltration	Lupus erythematosus, rheumatoid pleurisy
Primary and secondary pleural cancer	Tumor-associated antigens, antitumor immune response	Tumor cell infiltration and growth	Malignant mesothelioma, bronchogenic carcinoma, metastatic cancer
Fiber-associated nonmalignant disease	Fibers	Benign effusion, pleural fibrosis, plaques, neutrophil accumulation	Asbestos-related pleurisy

Source: Kroegel and Antony,[23] with permission from ERS Journals Ltd.

Pleural disease, in general, is associated with an infiltration of a number of inflammatory cells, including neutrophils, eosinophils, lymphocytes, and plasma cells in various proportions depending on the course and etiology of the underlying disease.[23] Mesothelial cells have been demonstrated to actively participate in pleural inflammation via release of various mediators and proteins, including platelet-derived growth factor, interleukin-8, monocyte chemotactic peptide, nitric oxide, collagen, antioxidant enzymes, and plasminogen activation inhibitor. As discussed by Kroegel and Antony,[23] several inflammatory mediators have been detected in increased concentrations within pleural fluid, including lipid mediators, cytokines, and proteins such as adenosine deaminase, lysozyme, eosinophil-derived cationic proteins, and products of the coagulation cascade. The presence of these mediators underlies the concept of pleural inflammation, and certain cytokines seem to be characteristic of specific etiologies of pleuritis (Table 30.2).

Types and Causes of Pleural Effusions (Transudates Versus Exudates)

Pleural effusions are frequently separated clinically into transudates and exudates.[24,25] Transudative pleural effusions are usually clear and straw colored, have a low protein concentration, and contain relatively few cells. In contrast, exudative pleural effusions have higher protein concentrations and usually numerous cells.

The three criteria most frequently used for distinguishing transudates and exudates are referred to as *Light's*

criteria: pleural fluid lactate dehydrogenase (LDH), ratio of pleural fluid to serum LDH, and ratio of pleural fluid to serum protein (Table 30.3).[11,24] The characteristics of pleural fluid transudates and exudates are listed in Table 30.4.[25]

In 2003 Badrinath et al.[26] asked this question: "Do we need all three [of Light's] criteria for the diagnostic separation of pleural fluid into transudates and exudates?" The authors concluded the diagnostic separation of pleural effusions could be done cost-effectively by utilizing pleural fluid absolute lactic dehydrogenase (FLDH) and total protein (TPR) alone with the elimination of serum LDH.

Heffner et al.[27] studied patients with diagnoses of exudative or transudative pleural effusions who underwent thoracentesis and laboratory analysis. Data were obtained on 1448 patients from seven primary investigators or extracted from dot plots in published reports. Likelihood ratios were calculated from extracted data stratified across ranges of test result values. The authors reported there were sufficient data available to calculate multilevel likelihood ratios for the elements of Light's criteria, pleural fluid protein, ratio of pleural fluid to serum cholesterol, pleural fluid cholesterol, and gradient of pleural fluid to serum albumin. Each test provided levels of likelihood ratios through the most clinically relevant range (0 to 10). The authors published the use of likelihood ratios to categorize a pleural effusion (Table 30.5) and concluded that multilevel likelihood ratios combined with the clinician's estimation of the pretest probability of an exudative effusion improved the diagnostic accuracy of discriminating between exudative and transudative pleural effusions. Likelihood ratios were used to

TABLE 30.3. Light's criteria for distinguishing transudates and exudates

Pleural effusion is an exudate if it meets one or more of the following criteria:

- Pleural fluid protein to serum protein ratio >0.5
- Pleural fluid LDH to serum LDH ratio >0.6
- Pleural fluid LDH more than two-thirds the upper limit of normal serum LDH

LDH, lactate dehydrogenase.
Source: Chapman and Davies,[24] with permission. Copyright © 2004 Royal College of Physicians.

TABLE 30.4. Characteristics of pleural fluid (PF) transudates and exudates

PF characteristic	Transudate	Exudate
Protein, g/dL	<3	
LD, U/L	<200	>200
Glucose, mg/dL	>60	
WBC count/mm³	<1000	
Cholesterol, mg/dL	<45	>45
[Protein]$_{pleural fluid}$/[Protein]$_{serum}$	<0.5	>0.5
[LD]$_{pleural fluid}$/[LD]$_{serum}$	<0.6	>0.6
[Glucose]$_{pleural fluid}$/[Glucose]$_{serum}$	1.0	
Associated diseases	Biventricular heart failure with venous hypertension Nephrotic syndrome Peritoneal dialysis Atelectasis Urinothorax	Pneumonia Lung abscess Pancreatitis Pancreatic pseudocyst Tuberculosis Actinomycosis Pleurisy Asbestosis Malignant mesothelioma Lymphoma Meigs syndrome* Lung cancer Pneumothorax

*Triad of benign fibroma (or other ovarian tumors) with ascites and large pleural effusions.
LD, lactate dehydrogenase; WBC, white blood count.
Source: Hussey and Wians,[25] with permission from the American Society for Clinical Pathology.

avoid the confusing terms such as *pseudoexudates* that were derived from the use of a single cutoff point for pleural fluid tests.

Others have looked at different methods for differentiating transudates from exudates. Guleria et al.[28] evaluated pleural fluid cholesterol in differentiating transudative from exudative pleural effusions. They studied the lipid profile of pleural fluid in 50 patients with exudative (25 tuberculous and 25 nontuberculous) and 25 with transudative effusions. The criteria that best identified an exudative pleural effusion was a pleural fluid cholesterol ≥60 mg/dL, pleural fluid to serum cholesterol ratio ≥0.4, pleural fluid triglyceride ≥40 mg/dL, and a pleural fluid to serum triglyceride ratio ≥0.3 mg/dL. The pleural fluid cholesterol had a sensitivity of 88% and a specificity of 100% for exudates with an accuracy of 92%. The pleural fluid to serum cholesterol ratio had a sensitivity of 98% and a

specificity of 84%. The authors concluded these results were superior to the criteria proposed by Light et al.[11,24] The authors further concluded that the pleural fluid cholesterol estimation was an effective and cost-efficient method of differentiating exudative from transudative effusions, but that the lipid profile did not help in diagnosing a tuberculous effusion.

Yilmaz-Turay et al.[29] reported the use of pleural fluid C-reactive protein (CRP) in diagnosing pleural effusions. The aim of the study was to determine whether CRP was a sensitive marker for discriminating between transudative and exudative pleural effusions and to evaluate whether it could be used to distinguish inflammatory pleural effusions from other types of effusions. The authors compared CRP levels among transudates and exudates, inflammatory effusions, and other types of effusions. According to the criteria used, 16 patients were

TABLE 30.5. Likelihood ratios for pleural fluid to serum albumin gradient

Albumin gradients, g/dL	No. of exudates	No. of transudates	Likelihood ratio
≤0.8	146	1	74.86
0.9–1.0	23	1	11.79
1.1–1.2	36	3	6.15
1.3–1.4	14	20	0.36
1.5–1.6	7	13	0.28
1.7–1.8	3	19	0.08
1.9–2.0	3	13	0.12
>2.0	4	51	0.04

Source: Heffner et al.,[27] with permission.

TABLE 30.6. Unusual causes of pleural effusion

Reference	Brief description
Judson et al.[32]	Pleural effusion following lung transplantation
Judson et al.[33]	Pleural effusion due to acute lung rejection
Areno et al.[34]	Persistent pleural effusions following coronary artery bypass surgery
Bourantas et al.[35]	Pleural effusion in association with chronic myelomonocytic leukemia
Diot et al.[36]	Wegener's disease mimicking acute infectious pleurisy
Uchikov et al.[37]	Pleural effusions in acute pancreatitis
Goldsby et al.[38]	Pleural effusions in pediatric patients treated with STI-571 (Gleevec)
Ray et al.[39]	Pleural effusion caused by urinothorax in a patient with metastatic bladder cancer
Assouad et al.[40]	Pleural effusion complicating cirrhosis
Karachalios et al.[41]	Pleural effusion associated with temporal arteritis
Valstar et al.[42]	Pleural effusion in giant cell arteritis
Toh et al.[43]	Malignant pleural effusion in association with breast edema
Breccia et al.[44]	Pleural effusion complicating treatment with Imatinib in patients with CML
Patel et al.[45]	Cerebrospinal fluid–pleural fistula causing recurrent pleural effusion
Berk[46]	Pleural effusion in systemic amyloidosis caused by infiltration of pleura by amyloid

included in the transudate group and 81 in the exudate group. Pleural fluid CRP levels were significantly lower in the transudate group. The ratio of pleural fluid to serum CRP was significantly lower in the transudate group. In the exudate group, 35 patients had neoplastic effusions, 10 chronic nonspecific pleurisy, 19 tuberculous pleurisy, 16 parapneumonic effusions, and 1 postmyocardial injury (Dressler) syndrome (see below). When these subgroups were compared, the ratio between the fluid and serum CRP was significantly higher in the parapneumonic effusion subgroup than in the neoplastic subgroup. The authors concluded that in the differential diagnosis of pleural effusions, higher CRP levels could prove to be a rapid, practical, and accurate method of differentiating parapneumonic effusion from other exudative-type effusions and could be helpful in discriminating exudative from transudative effusions.

Chierakul et al.[30] published a study to determine the validity of pleural fluid CRP concentrations or pleural fluid to serum CRP ratio for differentiating tuberculous pleuritis from malignant pleural effusion in patients presenting with lymphocytic exudative pleural effusions. The authors found the pleural fluid and serum CRP levels were significantly higher in the tuberculous pleuritis group than in the malignant pleural effusion group, and concluded that in patients presenting with lymphocytic exudative pleural effusion, a simple marker of raised pleural fluid CRP could be helpful in discriminating between tuberculous pleuritis and malignant pleural effusion (see Chapter 9).

Ryu et al.[31] evaluated the false-positive rate for pleural fluid carcinoembryonic antigen (CEA) level in nonmalignant pleural effusions and whether the falsely elevated CEA level had any relation to other biochemical param-

eters of pleural effusions. The authors found that elevated pleural fluid CEA level was most commonly observed in patients with empyema and parapneumonic effusion, and the CEA level showed a significant correlation to the indices of pleural inflammation. The authors reported that serial measurement of pleural fluid CEA level could be helpful as a means of monitoring resolution of pleural inflammation, including the possibility of a malignant pleural effusion.

Unusual Causes of Pleural Effusions

Since the publication of the previous edition of this book, a number of papers have been published that describe very unique or unusual causes of pleural effusion.[32–46] These are listed in Table 30.6.

Massive/Large Pleural Effusions

Effusions are sometimes referred to as non-large, large, or massive. The etiology of pleural effusions characterized as large or massive were reported by Porcel and Vives.[47] In this study, pleural effusions were deemed to be non-large (slight or moderate) if they occupied less than two-thirds of the hemithorax; large if they affected two-thirds or more of the hemithorax without reaching its complete length; or massive if they opacified the entire hemithorax. The causes of these pleural effusions were reported to have been determined by well-established clinical criteria. The authors evaluated chest radiographs from 766 patients during the study. Large effusions were identified in 70 patients (9%) and massive pleural effusions were identified in 93 patients

(12%). A similar etiologic spectrum was observed in patients with either large or massive pleural effusions. The most frequent cause of large/massive pleural effusions was malignancy (89 patients; 55%), followed by complicated parapneumonic effusion or empyema (36 patients; 22%), and tuberculosis (19 patients; 12%). The authors found that in patients with large or massive pleural effusions those with malignant effusions were more likely to have higher pleural fluid red blood cell counts and lower adenosine deaminase levels, which were the two parameters that were selected by the logistic-regression model as being independent predictors of malignancy. The authors concluded that the presence of large or massive pleural effusion enabled the clinician to narrow the differential diagnosis of pleurisy since most effusions were secondary to malignancy or infection, either bacterial or mycobacterial. Bloody pleural fluid with a low adenosine deaminase level favored a malignant condition.

Light et al.[48] reported large pleural effusions occurring after coronary artery bypass grafting. They graded the size of the pleural effusion differently than did Porcel and Vives.[47] In their scheme they defined a grade 2 effusion as "more than blunting of the costophrenic angle but less than 25% of the hemithorax occupied by pleural fluid," a grade 3 effusion as "pleural fluid occupying 25–50% of the hemithorax," a grade 4 effusion as "pleural fluid occupying 50–75% of the hemithorax," and a grade 5 effusion as "pleural fluid occupying more than 75% of the hemithorax." They concluded that large pleural effusions could develop in a small proportion of patients who underwent coronary artery bypass grafting, but the cause of the effusions was unclear.

Lazicka-Frelek et al.[49] reported an unusual case of a massive pleural cavity effusion as a manifestation of a pancreaticopleural fistula.

Eosinophilic Pleural Effusion

Several reports of eosinophilic pleural effusions or eosinophilic pleuritis have been reported in the last several years. In 2004, Kalomenidis and Light[50] reviewed the pathogenesis of eosinophilic pleural effusions. These authors defined eosinophilic pleural effusions as those that contained at least 10% eosinophils. They found that eosinophilic pleural effusions accounted for 5% to 16% of exudative pleural effusions and that the pathogenesis was poorly understood. They reviewed the mechanisms that potentially lead to pleural effusions, reporting that they were caused by air or blood or both in the pleural space, infections or other inflammatory diseases, malignancy, pulmonary emboli, asbestos exposure, and drug reactions. The difference in the clinical features suggested that a variety of mechanisms were

operative to induce eosinophilic pleural effusion. Both human and animal studies have suggested that interleukin-5 is important in the pathogenesis of eosinophilic pleural effusions.

Matthai and Kini[51] performed a prospective study on 26 eosinophilic pleural effusions found in 444 consecutive effusions investigated at a tertiary health care center over a 30-month period. Of the 26 eosinophilic pleural effusions studied, five were associated with tuberculosis and three with metastatic disease. Nineteen patients had significant associated lymphocytosis. Twenty-four patients with extended follow-up were in good health with no recurrence of the effusion. The eosinophilic pleural effusion was possibly associated with inflammatory, benign, or malignant conditions, and that a closer search for a definite etiologic agent was warranted in a setting of such an effusion, especially in populations endemic for tuberculosis, such as India, and in populations where there was a high prevalence of malignancy.

Martinez Garcia et al.[52] investigated the potential relationship among the number of eosinophils in the pleural fluid samples, the type (with or without pleural biopsy), and the time elapsed between repeated thoracenteses. The authors did not observe any significant change in the percentage of eosinophils in relation to the number of thoracenteses performed per patient. They also observed this lack of relationship in a subgroup of patients who required one or more pleural biopsies. The authors concluded that their results suggested that repeated thoracenteses were not an important risk factor for the development of eosinophilic pleural effusions regardless of the time elapsed between consecutive thoracenteses. The authors also concluded that multiple punctures should no longer be considered a prevalent cause of pleural eosinophilia.

Moufarrege et al.[53] reported an eosinophilic exudative pleural effusion after treatment of chronic low back pain (as a result of a work-related injury) with tizanidine (Zanaflex). Six weeks after starting tizanidine, a large pleural effusion was noted incidentally on a computed tomography (CT) scan of the thorax. Further evaluation showed no other potential cause of the effusion, and 4 weeks after tizanidine was discontinued, the pleural effusion resolved.

Ashwath et al.[54] reported a case of eosinophilic pleural effusion associated with human toxocariasis. The authors pointed out that human toxocariasis, a helminthozoonosis caused by *Toxocara* species in which the larval migration of organisms through the tissues could cause an eosinophilia associated with a broad spectrum of clinical manifestations (see Chapter 14). In this case, the patient developed an eosinophilic pleural effusion and had a CD8 cell deficiency associated with the *Toxocara* infection. The patient's symptoms were reported to have

promptly responded to a nonsteroidal antiinflammatory medication (naproxen). The report stated this was only the fourth reported case of pleural effusion associated with *Toxocara.*

Killen et al.[55] described a 50-year-old woman who presented with increased breathlessness and a sensation different from her mild asthma, which was controlled with inhaled beclomethasone dipropionate and occasional salbutamol. On physical examination, the patient was found to have small bilateral pleural effusions and inspiratory crackles at the left base. She had a normocytic anemia with blood eosinophilia and an elevated CRP of 95 mg/L, with the normal range being less than 10 mg/L. A chest radiograph confirmed the small bilateral pleural effusions and showed patchy parenchymal shadowing in both lower lobes. A high-resolution CT scan of the chest showed pronounced interlobular and peribronchovascular nodular interstitial thickening and bilateral pleural effusions, but no distortion of the lung architecture. Nerve conduction studies were normal. The patient developed nodular skin lesions, and a fascial biopsy from the right forearm showed subcutaneous infiltration by eosinophils, predominantly in a perivascular distribution. The patient was started on enteric-coated prednisone 30 mg daily and improved sufficiently for discharge from the hospital. Six months later she was well, with no induration, no chest symptoms, and normal chest radiograph, and she was currently taking prednisone at a dose of 5 mg/daily and inhaled beclomethasone dipropionate. This case report is of some interest in that fluticasone dipropionate present in the inhaled drug Advair has been reported to cause an eosinophilic pleural effusion and eosinophilic pleuritis. I have personally encountered such a case recently.

Pleural Effusions in the Medical Intensive Care Unit

As reported by Mattison et al.,[56] pleural effusions occur frequently in the medical intensive care unit (ICU). These authors reported on 100 patients whose length of stay in the medical ICU at the Medical University of South Carolina exceeded 24 hours. The prevalence of pleural effusions in 100 consecutive patients was 62%, with 41% of the effusions detected at admission. Fifty-seven (92%) of 62 pleural effusions were small. Causes of the pleural effusions included heart failure, atelectasis, uncomplicated parapneumonic effusions, hepatic hydrothorax, hypoalbuminemia, malignancy, pancreatitis, uremic pleurisy, and empyema. When compared to patients who never had effusions during their ICU stay, patients with pleural effusions were typically older, and had lower serum albumin concentrations, higher acute physiology

TABLE 30.7. Common causes of pleural effusions in the pediatric population

Cause	Incidence, %
Pneumonia (parapneumonic effusion)	50–70
Renal disease	9
Trauma	7
Viral disease	7
Malignancy	5–10
Congenital heart disease	5–10
Others (liver failure, sickle cell anemia, meningitis)	3

Reprinted from Efrati and Barak,[57] with permission from the American Academy of Pediatrics.

assessment and chronic health evaluation scores, and longer mechanical ventilation. The authors concluded that pleural effusions in medical ICU patients were common, and that most were detected by careful review of chest radiographs taken with the patient in an erect or semi-erect position.

Pleural Effusions in the Pediatric Population

Pleural effusions occur less frequently in children than in adults, and can be caused by a variety of infectious and noninfectious agents. Among adults, the most frequent cause of a transudate is congestive heart failure, and the most frequent causes of an exudative effusion are bacterial pneumonia and malignancy. In children, pleural effusions are most commonly caused by infectious agents (50% to 70%), whereas congestive heart failure causes only 5% to 15%, and malignancy is a rare cause of effusion (Table 30.7).[57] Childhood parapneumonic effusions are further discussed below (see Other Infectious Causes of Pleural Effusion and Pleuritis).

Resolution of Pleural Effusion

A great deal of information has been published on pleural effusions and their etiology. Relatively few articles have been published on the natural history of pleural effusions. In 2001, Cohen and Sahn[58] pointed out that most of the literature on pleural effusions concerned their etiology and characteristics. Cohen and Sahn reviewed the published information regarding the time course of resolution for nonmalignant pleural effusions in the most commonly encountered pleural diseases. This article not only gives information concerning resolution, but also provides an excellent overview of information on various parapneumonic effusions and effusions caused by other conditions. This information is listed in Tables 30.8 to 30.10.

TABLE 30.8. Resolution of pleural effusions

Diseases	Incidence, %	Therapy	Resolution time (range)
Parapneumonic effusion			
Non-HIV	9–66	Antibiotics	2–8 weeks
HIV positive	21	Antibiotics	2–3 weeks
Tuberculosis			
Non-HIV	3–23	No therapy	2–4 months
		Isoniazid, rifampin	2 months
		Isoniazid, pyrazinamide	1–2 months
		Addition of prednisone	1–2 months
HIV positive	3–40	INH, rifampin, PZA	1–2 months
Congestive heart failure	40–60	Diuretics, ACE-I, digoxin	<1 month
Dressler syndrome			
Postmyocardial infarction	40–68	NSAIDS; prednisone	1–5 wk (1 wk–4 mo)
Postpericardiotomy	41–85	NSAIDS; prednisone	1–3 wk (1 wk–4 mo)
Postcoronary artery bypass	40–90	Self-limited	8 wk (6 wk–20 mo)
Rheumatoid arthritis	4–7	Nonsteroidals; prednisone	3–4 mo (1 mo–5 yr)
SLE	16–37	Corticosteroids	2 wk (1–6 wk)
Sarcoidosis	0–7.5	Self-limited; prednisone	1–3 mo (2 wk–6 mo)
Pulmonary embolism	10–50	Heparin, LMWH	<1 wk (3–7 days)
Benign asbestos effusion	1–9	Self-limited	3–4 mo (1–17 mo)
After organ transplantation			
Lung and heart-lung	100	Self-limited	1–2 wk (1–3 wk)
Liver	50–100	Self-limited	2–3 wk (3 d–7 mo)
Uremia	2–3	Hemodialysis	4–6 wk
Pancreatitis			
Acute	4–20	Treat acute pancreatitis	2 wk (1–8 wk)
Chronic	5	NPO; TPN; thoracentesis	2–3 wk (1–8 wk)*

ACE-I, angiotensin-converting enzyme inhibitor; INH, isoniazid; LMWH, low molecular weight heparin; NSAID, nonsteroidal antiinflammatory drug; PZA, pyrazinamide; SLE, systemic lupus erythematosus; TPN, total parenteral nutrition; unc, uncomplicated; NPO, nothing by mouth.
*In 50% of cases.
Source: Cohen and Sahn,[58] with permission.

TABLE 30.9. Resolution of parapneumonic effusions

Organisms	Incidence, %	Therapy	Resolution time (range)
S. pneumoniae	30–60	β-Lactams; macrolides	4–8 wk (2–20 wk)
M. pneumoniae	4–20	Macrolides; tetracyclines	2–3 wk (5 d–8 wk)
L. pneumophila	12–35	Macrolides	4 wk (5 d–4 mo)
F. tularensis	13–64	Streptomycin	6–7 wk
C. immitis	6–19	Self-limited	1–8 wk
H. capsulatum	2–6	Self-limited	2–4 wk
Adenovirus	2–18	Self-limited	2 wk

Source: Cohen and Sahn,[58] with permission.

TABLE 30.10. Pleural effusion resolution by time interval

<2 months	2 to 6 months	>6 months to 1 year	Benign persistent
Congestive heart failure	Tuberculous pleurisy	Rheumatoid arthritis	YNS
Parapneumonic effusion	PCIS	BAPE	Trapped lung
Acute pancreatitis	Postcoronary artery bypass		Lymphangiectasis
PCIS	Rheumatoid pleurisy		Noonan's syndrome (chylothorax)
Postcoronary artery bypass	Sarcoidosis		Lymphangioleiomyomatosis (chylothorax)
After lung/heart/liver transplant	BAPE		
Pulmonary embolism	Chronic pancreatic effusion		
SLE			
Sarcoidosis			
Traumatic chylothorax			
Uremic pleural effusion			

BAPE, benign asbestos pleural effusion; PCIS, postcardiac injury syndrome; YNS, yellow nail syndrome.
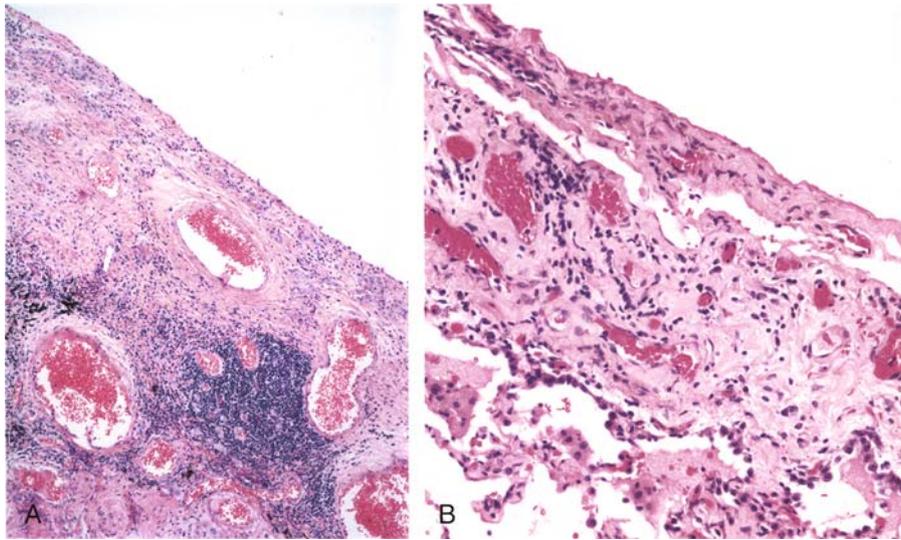*Source:* Cohen and Sahn,[58] with permission.

FIGURE 30.6. **A,B.** Sections of visceral pleura show nonspecific increase in vascularity with mild inflammation and focal fibrin deposition.

Nonspecific Pleural Changes

The pleura is an extremely reactive tissue, and it is perhaps not surprising that it undergoes a variety of nonspecific changes. Pleural inflammation, increased vascularity, and mild fibrosis are often associated with an underlying pneumonia or pulmonary infarct (Fig. 30.6). Following a pulmonary infarct, there may be a relatively well-localized area of pleural reaction characterized by an increased vascularity, inflammation, and a layer of fibrin on the outer surface of the visceral pleura (Fig. 30.7). Mesothelial cell hypertrophy and hyperplasia (Fig. 30.8) are associated with numerous conditions that involve the lung parenchyma, such as idiopathic pulmonary fibrosis, asbestosis, and peripheral lung cancers, when pulmonary involvement is close to the pleural surface. Yokoi and Mark[59] reported seven cases of primary carcinoma of the lung close to the pleural surface that were associated with atypical mesothelial cell hypertrophy and hyperplasia. In my experience, not only is hypertrophy and hyperplasia of epithelial surface mesothelial cells a frequent finding in this setting, but often a proliferation of multipotential subserosal spindle cells may be seen as well.[60] By immunohistochemistry, these subserosal cells express keratin, vimentin, and muscle-specific actin, and by elec-
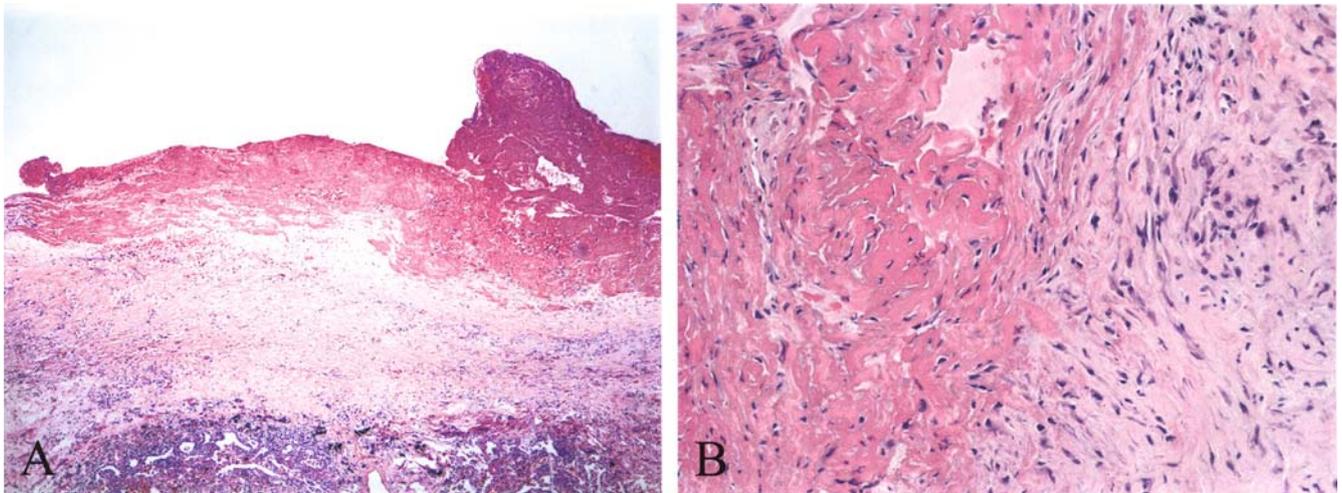

FIGURE 30.7. **A.** Pleura overlying pulmonary infarct shows nonspecific increased vascularity, inflammation, fibrosis, and fibrin on outer surface, change referred to as fibrinous pleuritis. **B.** Organizing fibrinous exudate.
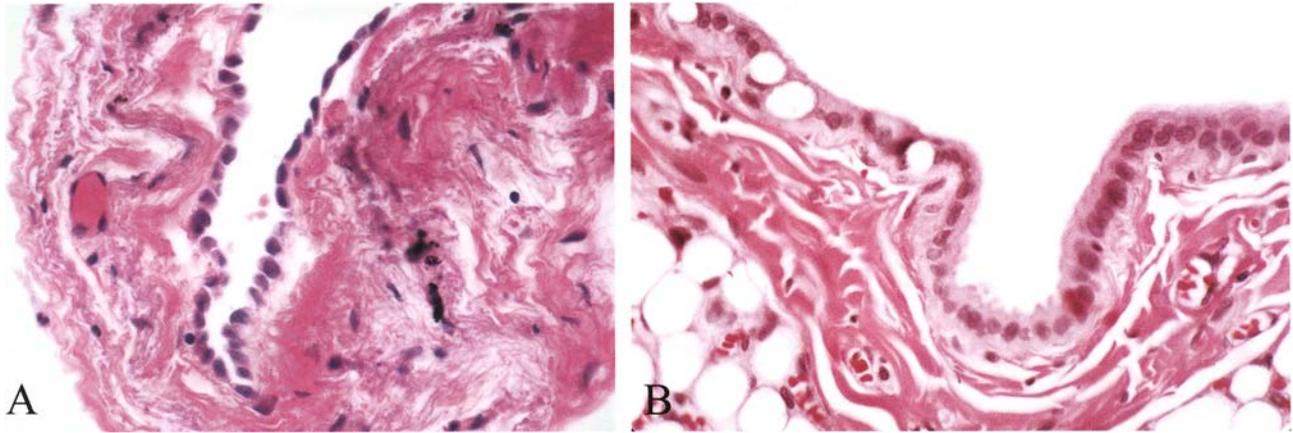
FIGURE 30.8. Mesothelial cell hypertrophy and hyperplasia are nonspecific reactions seen in various conditions affecting underlying lung parenchyma. Sometimes cells show mild atypia. **A.** Mesothelial hyperplasia in apical fibrobullous disease. **B.** Columnar appearance of hyperplastic mesothelial cells in patient with cystic fibrosis.

tron microscopy have the ultrastructural features of myofibroblasts.

Another nonspecific feature is fibrous thickening of the visceral pleura, usually associated with varying degrees of inflammation, which can be seen in a wide variety of pleural injuries of known cause or in idiopathic pleural fibrosis (Fig. 30.9).[61] Reactive eosinophilic pleuritis, a condition that may be confused with pulmonary eosinophilic granuloma, is an inflammatory process described in 1977 by Askin et al.[62] In their report, it was seen primarily in persons who had spontaneous pneumothoraces—specifically, in 22 of 57 cases. None of the patients had clinical or radiographic evidence of interstitial lung disease, and a follow-up of 20 patients from 6 months to 5 years

showed no evidence of other conditions. Their paper distinguished reactive eosinophilic pleuritis from pulmonary eosinophilic granuloma (pulmonary Langerhans' cell histiocytosis; see Chapter 16) because the macrophages associated with the eosinophils often had convoluted nuclei and mimicked the appearance of Langerhans' cells. In my experience reactive eosinophilic pleuritis may be seen in all types of conditions as it is a relatively common, nonspecific reaction to injury (see Figs. 16.48 and 16.49 in Chapter 16). For reasons discussed previously, eosinophils are common inflammatory cells in pleural disease and are seen in a variety of conditions.

Idiopathic Pleuritis

Venekamp et al.[63] attempted to answer the question as to whether idiopathic pleuritis exists. They pointed out that even after a complete workup, including thoracoscopic biopsies, a significant number of patients with pleural exudates were diagnosed with nonspecific pleuritis, and the natural evolution of these patients was poorly understood. The objective of their study was to determine the natural evolution of patients with nonspecific pleuritis diagnosed after thoracoscopy and to evaluate whether the histologic diagnosis of nonspecific pleuritis corresponded with a clinical diagnosis of idiopathic pleuritis. The authors studied the evolution of pleuritis in 75 patients (49 men and 26 women) who underwent diagnostic thoracoscopy for evaluation of an unexplained exudative pleural effusion and in whom the histologic diagnosis of nonspecific pleuritis was made. Follow-up data were obtained through medical files or telephone contacts with the patients' family doctors; 8.3% of the 75 patients eventually developed a malignancy during the

FIGURE 30.9. Diffuse pleural fibrosis seen macroscopically as a thick rind of fibrous tissue encasing lung.

follow-up period, and in the remaining 91.7% the clinical evolution followed a benign course. A probable cause was established on clinical grounds in 40 patients. True idiopathic pleuritis was observed in 25 patients with a histologic diagnosis of nonspecific pleuritis. The authors found recurrence of the effusion in 10 out of 60 (16.7%) patients after a mean period of 26.2 months. The authors concluded the majority of patients with nonspecific pleuritis followed a benign course with a spontaneous resolution of the effusion in 81.8% of cases. In the majority of patients, a probable cause of pleuritis was identified, and idiopathic benign pleuritis occurred in only a minority (25%) of patients.

Apical Pleural Fibrosis

Apical pleural fibrosis is seen in most cases of moderate to severe centrilobular emphysema, and is a relatively nonspecific form of fibrosis, except that the fibrous tissue often has a more granular or less organized appearance than well-formed collagenous fibrosis (Fig. 30.10). Blebs and bullae that occur in the apical portion of the upper lobes as a result of emphysema also show nonspecific types of pleural reactions, with mesothelial hypertrophy and hyperplasia, submesothelial fibrosis, and varying degrees of inflammation (Figs. 30.8A and 30.11).

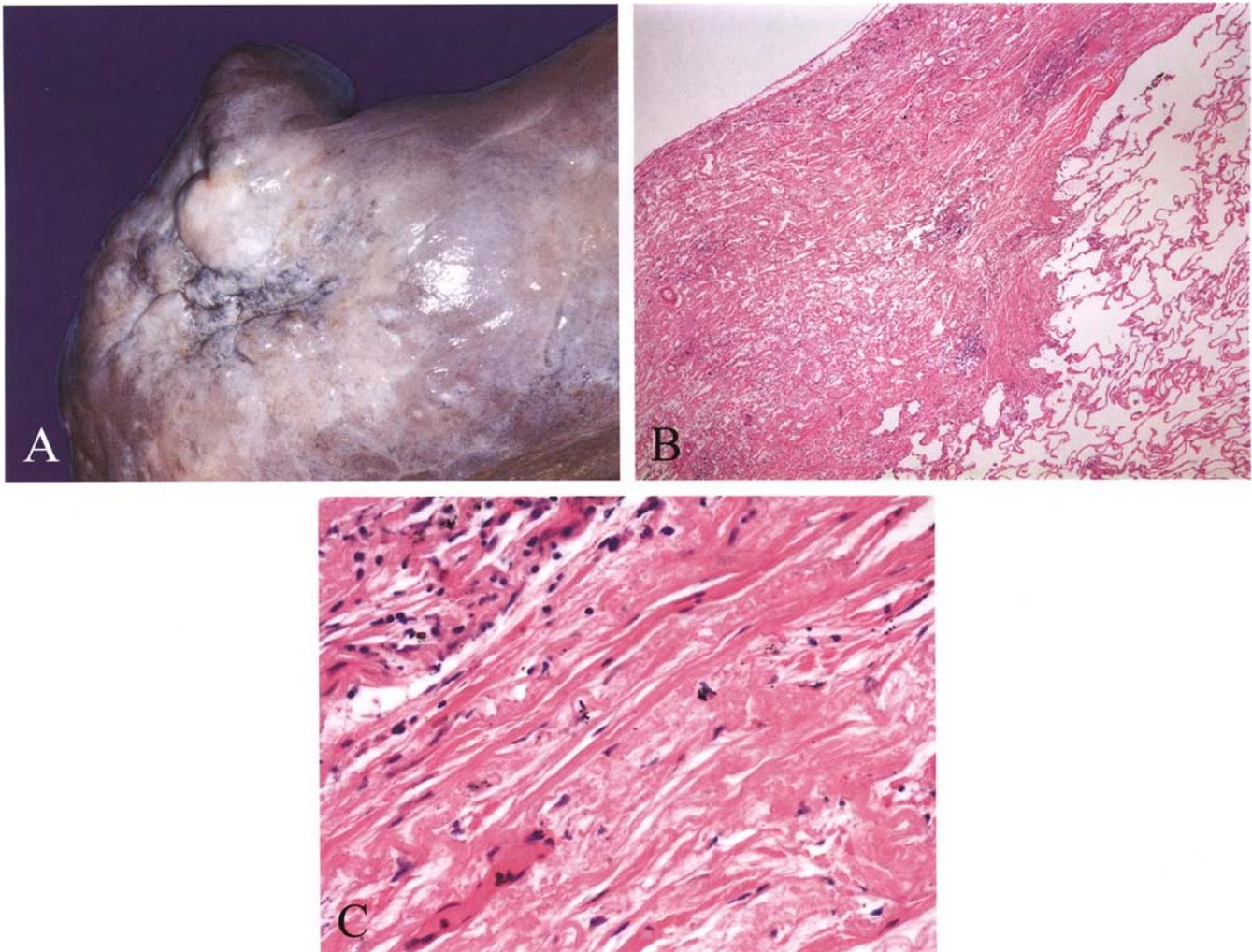FIGURE 30.10. **A.** View of lung apex in apical pleural fibrosis, sometimes referred to as apical pleural cap. The visceral pleura appears grossly as a gray nodular area due in part due to underlying blebs and bullae. **B.** Microscopically a band of fibrosis extends into the underlying lung associated with paracicatricial emphysema. **C.** Fibrosis typically consists of collagen and entangled grayish elastic fibers.
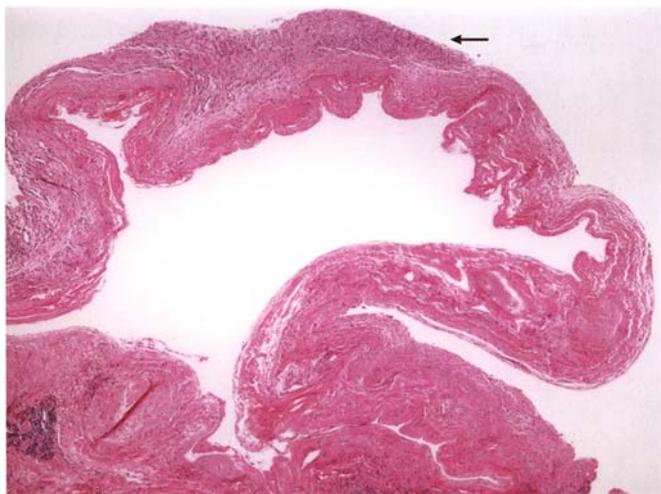
FIGURE 30.11. Apical pleural blebs and bullae resected from patient with centrilobular emphysema and pneumothorax are composed of fibroinflammatory-type tissue. Area of talc pleurodesis seen at arrow is shown in more detail in Figure 30.21.

Apical Cap Lesion

Apical cap lesions are usually identified radiographically as areas of increased opacity in the apex of one or both hemithoraces.[64,65] In most instances, the cause of apical cap lesions is unknown. Morphologically, they usually measure no more than 5mm in thickness and have a sharply marginated, smooth, or undulating lower surface. The prevalence increases with age, being identified in 6% of patients younger than 45 years and in 16% of patients older than 45 years.[64,65] The prevalence is similar in men and women.[64] Pathologically, apical pleural cap lesions consist of the combination of pleural and pulmonary parenchymal fibrous tissue, the latter usually having high concentrations of grayish elastin in hematoxylin and eosin (H&E)-stained sections or blackish-gray color in Movat pentachrome–stained sections (Fig. 30.10). Occasional areas of calcification and ossification are seen in apical cap lesions. The pathogenesis of the fibrosis is uncertain. In one autopsy study, histologic evidence of chronic bronchitis and pulmonary artery narrowing were identified, and the investigators suggested that intermittent or continuing low-grade infection combined with relative apical ischemia might be responsible for the fibrosis.[66] Apical cap lesions have been reported to be more common in patients who have upper lobe fibrosis secondary to tuberculosis.[67]

Yousem[68] reported on 13 cases of apical cap lesions resected for exclusion of a diagnosis of lung cancer. In this study lesions occurred in older individuals, particularly in the apices of the upper lobes, and by radiographic examination appeared as spiculated masses ranging from 0.7 to 5.2cm in diameter. Microscopically, subpleural scars were pyramidal-shaped with overlying pleural adhesions and hyaline-type pleural plaques. They were composed of dense pulmonary fibrous tissue with old, mature collagen and an underlying elastic skeleton contracted in an accordion-like fashion with reduplicated curls of elastic fibers. Scar emphysema was observed at the periphery of the fibrous nodules. Yousem urged that pulmonary apical caps should be recognized for their unique histology because their appearance in the surgical pathology laboratory would likely increase in incidence with the evolution of more sensitive pulmonary radiographic studies. A chronic ischemic etiology was favored.

Pleural Space Infections

Pleural space infections are potentially serious disease processes that show a spectrum ranging from bacterial pneumonia associated with a small pleural effusion to the other end of the spectrum, that is, empyema, in which pus accumulates in the pleural space that may result in visceral and parietal pleural fibrosis, trapped lung, systemic sepsis, respiratory infection, or respiratory failure. At least 50% of all pneumonias are associated with an exudative effusion, which can be divided into three entities: (1) simple parapneumonic effusion, characterized by uninfected pleural fluid with clear appearance, normal pH, glucose and LDH, with most of these resolving with antibiotic treatment alone (drainage usually not required); (2) complicated parapneumonic effusion, characterized by fluid that is infected but not purulent, appearing either clear or turbid, with a pH of <7.3, a low glucose, an elevated LDH, a pleural fluid Gram stain that may or may not be positive, and the effusion usually requires drainage for resolution; and (3) empyema, in which there is pus in the pleural space with pleural fluid Gram stain or culture frequently being positive, and definitely requiring drainage for resolution. A classification scheme of pleural infections is shown in Table 30.11.

Two excellent review articles appeared in the literature in 1999 concerning definitions and epidemiology of pleural space infections, and the pathophysiology of pleural space infections.[69,70] The review article by Antony and Mohammed[69] addressed the pathobiology of the pleural space, and reported that the pleural space is in equilibrium, with a minute quantity of transudative pleural fluid, and with a protein content of less than 1.5g/dL. The normal volume of pleural fluid in a 70-kg adult varies between 3 and 7mL, with a predominance of lymphocytes, macrophages, and mesothelial cells. The authors reported that the pleura is functionally a dynamic layer that covers the chest wall and lung and is composed of a monolayer of mesothelial cells on the surface of the

TABLE 30.11. Classification schemes for pleural space infections

	Less severe ←--→ More severe					
Andrews et al., 1962	Exudative		Fibropurulent			Organizing
Potts et al., 1976	Nonloculated pH ≥ 7.3		Loculated pH < 7.3			Empyema: pus
Potts et al., 1978	Uncomplicated or nonloculated pH ≥7.3 and glu > 60 mg/dL		Complicated or loculated pH < 7.3 and glu < 60 mg/dl			Empyema: pus
Light et al., 1980	Uncomplicated pH > 7.2, glu > 40 mg/dl, and LDH < 1000 IU/L		Complicated pH ≤ 7.2, glu ≤ 40 mg/dl, and LDH ≥ 1000 IU/L			Empyema: pus
Light, 1995	Nonsignificant parapneumonic effusion	Typical parapneumonic effusion	Borderline complicated parapneumonic effusion	Simple complicated parapneumonic effusion	Complex complicated parapneumonic effusion	Simple empyema	Complex empyema
	<10 mm layering on decubitus radiograph	pH > 7.2, glu > 40 mg/dL	pH 7–7.2 and/or LDH > 1000 IU/L, glu > 40 mg/dL	pH < 7 or glu < 40 mg/dL or Gram's stain or culture positive	Simple complicated parapneumonic effusions with multiple loculations	Frank pus with single loculum or free-flowing fluid	Frank pus with multiple loculations

LDH, lactate dehydrogenase.
Source: Strange and Sahn,[70] with permission from Elsevier. Copyright © 1999.

pleura. The authors stated that the pleural mesothelium, which was originally considered to be a simple membrane, has emerged as a dynamic cellular organ with multiple key functions, including its ability to phagocytose structures such as asbestos fibers, bacteria, and other particulate matter. The pleural mesothelial cells also release nitrous oxide, which has a number of effects on bacterial and mycobacterial organisms and has been implicated in their demise. In addition, the pleural mesothelial cells are stimulated by tumor necrosis factor-α, interleukin-1β, interferon-γ, and lipopolysaccharide (LPS) that can produce large amounts of nitrous oxide. The release of oxidant intermediates by mesothelial cells is thought to play a role in killing bacteria. The authors conceptualized the participation of the mesothelial cell as having a primary and secondary response in the pathogenesis of parapneumonic effusions and empyema. This is shown in Figure 30.12.

The sentinel role of the mesothelial cell in orchestrating the recruitment and facilitating the transmigration of neutrophils and mononuclear phagocytes into the pleural space is a critically important event that is responsible for the development of the pleural effusion after infections in the pleural space. The mesothelial cells express adhesion molecules, which cause adherence of neutrophils and monocytes to the mesothelium. Pleural mesothelial cells also release several cytokines that are capable of recruiting phagocytic cells from the vascular compartment into the pleural space (Fig. 30.13).

Interleukin-8 (IL-8) is a member of the supergene family of C-X-C chemotactic cytokines. It has been found in significant quantities in pleural fluid obtained from patients who developed parapneumonic effusions. It is considered to contribute between 30% and 60% of the chemotactic bioactivity of empyema pleural fluids. A significant correlation has been noted between IL-8 levels and the number of neutrophils in empyema fluid. Inter-
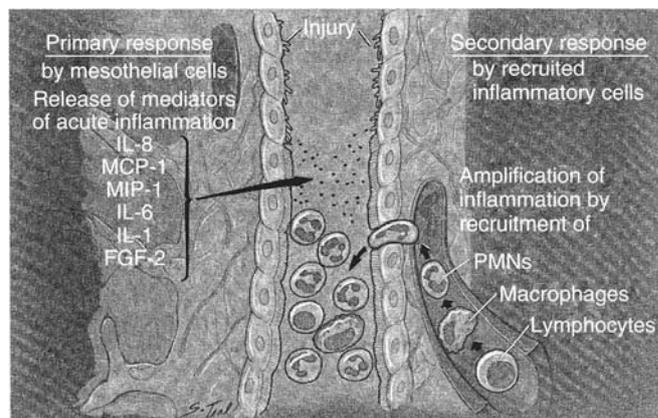

FIGURE 30.12. Primary and secondary responses to injury in the pleural space. FGF, fibroblast growth factor; IL, interleukin; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; PMN, polymorphonuclear neutrophil. (From Antony and Mohammed,[69] with permission.)

leukin-8 is relatively resistant to proteolytic degradation, which could explain why IL-8 remains active in empyema pleural fluid. In vitro studies have shown that IL-1β, tumor necrosis factor-α, and LPS cause mesothelial cells to release IL-8.

Pleural space infections may be caused by penetrating chest wounds with direct bacterial contamination of the pleural space, or by iatrogenic infections that occur when preexisting pleural fluid becomes infected by thoracentesis or some other type of invasive procedure.

The most common cause of pleural space infections or parapneumonic effusions is an underlying pneumonia. Uncomplicated parapneumonic effusions do not require drainage and respond to antibiotic therapy alone for the underlying pneumonia. Complicated parapneumonic effusions do not respond to antibiotic therapy alone and require drainage to prevent the formation of a frank empyema.

Strange and Sahn[70] evaluated epidemiologic factors of patients with parapneumonic effusions. They found that comorbid conditions increased the risk of pleural space infections in patients with pneumonia. Contributing conditions included preexisting pulmonary diseases such as bronchiectasis, chronic obstructive pulmonary disease, and lung cancer. Diabetes was reported as a comorbid factor in 23% of patients in one series.[71]

The coexistence of malignancy increased the risk of death in patients with an empyema. The clinical factors that predicted the presence of an anaerobic pneumonia included poor dentition, sedative drug use, alcohol use, seizures, mental retardation, and gastroesophageal reflux (see Chapters 5 and 8).[72] The causes of bacterial pleural space infections are listed in Table 30.12.

TABLE 30.12. Causes of bacterial pleural space infections

Parapneumonic
  Bacterial pneumonia
Iatrogenic
  Postoperative
    Pulmonary resections
    Esophageal surgery
  Thoracentesis
  Chest tubes
  Indwelling pleural catheters
    Ventriculopleural shunts
    Pleuroperitoneal shunts
Traumatic
  Blunt and penetrating trauma
Mediastinitis
  Esophageal perforation
  Dental abscess
  Epiglottitis
Abdominal infection
  Subphrenic abscess
  Pericolic abscess
  Splenic infarction and abscess
  Hepatic abscess
  Bowel perforation
  Penetrating peptic ulcer disease
Miscellaneous
  Xanthogranulomatous pyelonephritis
  Septic pulmonary emboli
  Pleural rupture of rheumatoid nodules
  Intravenous drug abuse (contaminated needles)
  Spontaneous bacterial peritonitis
  Bacteremic seeding of pre-existing effusion

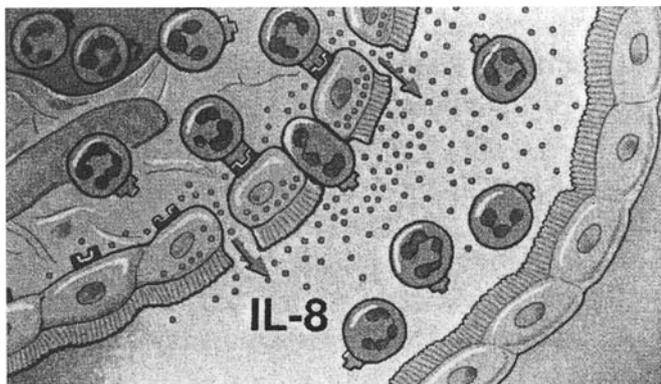Source: Strange and Sahn,[70] with permission from Elsevier. Copyright © 1999.

FIGURE 30.13. Neutrophil transmigration across the pleural mesothelium in response to polar production of IL-8. Neutrophil adherence to the mesothelial cells is mediated via CD11/CD18 integrins expressed on neutrophils and intercellular adhesions molecule-1 on mesothelial cells. (From Antony and Mohammed,[69] with permission.)

Bacterial Infections

Bacterial-induced pneumonia often involves the peripheral portion of the lung and is characterized by a significant pleural neutrophil inflammatory infiltrate that initially may be associated with a sterile pleural effusion.[3] Approximately 60% of cases of pneumococcal pneumonia and 40% of all bacterial-caused pneumonias are associated with an exudative pleural effusion.[73,74] If the condition is not treated, the bacteria invade into and through the pleura resulting in exudative pleural effusion and empyema (Fig. 30.14). The bacteria frequently activate the clotting system, causing a somewhat gelatinous pleural fluid that can serve as a lattice for organization and proliferation of fibroblasts. The most common causes of empyema in North America are anaerobic bacteria, either alone or in concert with aerobic bacteria.[75,76] Gram-negative aerobes and *Staphylococcus aureus* are the next most frequent cause of empyema. The diagnosis of empyema should be made as rapidly as possible so that it can be adequately treated by drainage and antibiotic therapy as well as the instillation of streptokinase into the
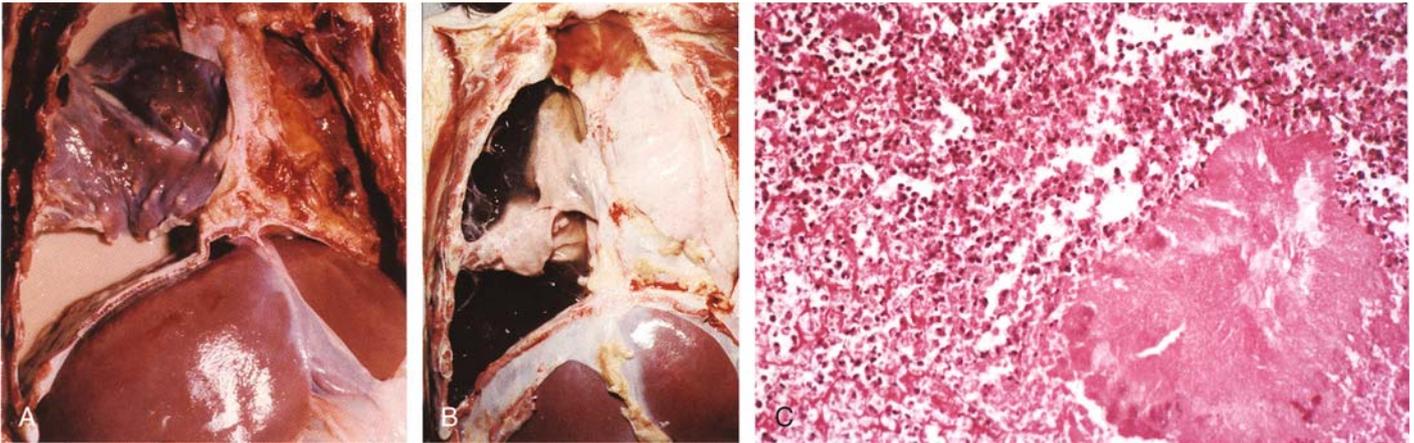
FIGURE 30.14. Suppurative pleuritis with empyema is relatively rarely seen. **A.** Note pus in right pleural cavity surrounding atelectatic lung. Cultures were positive for *Staphylococcus aureus.* **B.** Fibrinopurulent coagulum completely covers left lung, and produces loculations in the right pleural space. **C.** Purulent exudates with bacterial colonies typical of empyema.

pleural fluid. Decortication of an organized empyema (Fig. 30.15) is sometimes necessary to control the pleural infection.

Tuberculous Pleuritis

Tuberculous pleuritis is a relatively infrequent condition in North America, with an incidence of about 1100 cases per year.[77] Pleural effusion is commonly associated with this infection, and usually is serous or serosanguineous in nature, with a protein content greater than 4 g/dL. Tuberculous pleuritis occurs when a focus of tuberculosis below the visceral pleura ruptures into the pleural space.[78,79] These infections may be accompanied by a granulomatous inflammatory reaction, which occasionally can be identified by a closed pleural biopsy (see Chapter 9 for an extended discussion of tuberculous pleuritis, and see Fig. 9.14).

Fungal Pleuritis

Primary fungal pleuritis is an uncommon condition, and in my experience is seen predominantly in people with a variety of malignant neoplasms (often lymphoma or leukemia) treated with chemotherapeutic agents. It has also been described following lobectomy or pneumonectomy for tuberculosis or lung cancer, usually in association with a bronchopleural fistula.[3] Pathologically, there are varying

FIGURE 30.15. Organized empyema produced 5- to 10-mm rind of moderately firm, grayish-white fibroinflammatory tissue. **A.** Flat surface of specimen. **B.** Cross section of decortication specimen showing thickness of pleural fibrotic rind. (Scale equals 1 cm.)

degrees of necrosis and inflammation, and the organisms are usually fairly easy to see, especially if they are large, like aspergillus (see Fig. 10.39A and B in Chapter 10). Most of the common fungi can be associated with pleuritis, and sometimes uncommon fungal organisms cause infection.[80]

Other Infectious Causes of Pleural Effusion and Pleuritis

A variety of other organisms occasionally infect the pleural fluid and cause pleuritis.[3] These include infections with *Entamoeba histolytica, Echinococcus granulosus, Mycoplasma pneumoniae, Coxiella burnetii, Legionella pneumophila, Actinomyces israelii, Nocardia asteroides, Pneumocystis jiroveci,* and viruses such as adenovirus.[81] These infections are rare and usually are not seen by pathologists in pleural biopsy specimens. As listed in Table 30.13, some of these infections produce changes in the pleural fluid that assist in their diagnosis.

Soubani et al.[82] evaluated the spectrum of conditions associated with pleural effusions in patients with acquired immune deficiency syndrome (AIDS). Evaluation of thoracentesis fluid from 24 men and six women showed an infectious cause in 21 (70%) cases and a noninfectious cause in nine (30%) cases. Bacterial pneumonia was the most common cause of pleural effusion (57%). *Streptococcus pneumoniae* and *Staphylococcus aureus* were the major organisms recovered. Mycobacterial infections were identified in three patients and *Nocardia* species in one patient. Non-Hodgkin's lymphoma was the leading noninfectious cause of pleural effusion, followed by Kaposi's sarcoma and adenocarcinoma of the lung. The authors concluded that pleural effusion was an important problem in patients with advanced HIV infections and was most commonly associated with bacterial pneumonia.

Trejo et al.[83] evaluated pleural effusions in patients infected with the HIV virus and found that infection caused the majority of pleural effusions. Parapneumonic effusion was diagnosed in 59 patients and tuberculous pleuritis in 15 patients. *Staphylococcus aureus* was the most frequently isolated bacteria. There was no significant difference detected in the outcome of HIV-positive and HIV-negative patients with pleural disease. Neither the biochemical parameters in pleural fluid nor the outcome differed significantly between HIV-positive and HIV-negative patients.

Childhood Parapneumonic Effusion

Utine et al.[84] evaluated 28 patients who were admitted to the Hacettepe University Children's Hospital over a 2-year period. The patients were grouped according to the stage of the effusion. Thirteen patients had empyema, 12 had complicated parapneumonic effusions, and five had uncomplicated parapneumonic effusions. Protein and glucose levels decreased, and the leukocyte count, neutrophil ratio, tumor necrosis factor-α levels, nitrite levels, and IL-8 levels increased progressively as the stage of the disease progressed. The IL-8 levels, but not the tumor necrosis factor-α and nitrite levels, were statistically different among the groups. The IL-8, tumor necrosis factor-α, and nitrite levels all correlated positively with each other and pH correlated negatively with these markers. At a cutoff value of 701.6 pg/mL, IL-8 differentiated complicated parapneumonic effusions from uncomplicated parapneumonic effusions with a sensitivity of 80%, a specificity of 80%, and an accuracy of 86%. The authors concluded that biochemical markers were interrelated during stages of pleural inflammation and that IL-8 may be used as an alternative marker for discriminating between complicated pleural effusions and uncomplicated pleural effusions in pediatric patients with parapneumonic effusions.

Empyema

Several review articles have been published on empyema.[85–87] According to the article by Bryant and Salmon,[85] the formation of empyema is arbitrarily divided into an exudative phase, during which pus accumulates; a purulent phase, during which fibrin deposition and loculation of pleural exudates occur; and an organization phase, during which fibroblast proliferation and scar formation cause lung entrapment. Pleural effusions are nutritionally rich culture media in which white blood cell defenses are severely impaired. This may be due to the fact that effective phagocytosis of bacteria by neutrophils requires a structure upon which white blood cells can move and ingest bacteria prior to the development of specific antibodies. Bacteria in pleural fluid enlist a complex series of host defense responses that are incompletely understood, despite significant recent advancements in our knowledge. Empyema fluid is relatively deficient in opsonins and complement, and becomes progressively more acidic, hypoxic, and depleted of glucose as infection proceeds. During the inflammatory process, leukocytes release certain substances such as bactericidal permeability-increasing proteins, defensins, lysozyme, cationic proteins, lactoferrin, and zinc-binding proteins. Bacteria within empyemas are relatively unresponsive to antibiotics and may release β-lactamase enzymes capable of degrading β-lactamase–susceptible β-lactam antibiotics. The conditions and causes that

TABLE 30.13. Causes and characteristics of pleural exudates

Disease	Clinical findings	Chest radiograph	Appearance	Cells/µL	Protein (g/dL)	LDH (1 U/L)	Glucose (mg/dL)	pH	Other tests	Diagnosis	Comments
Parapneumonic effusion-uncomplicated	Pneumonia	Small–moderate ipsilateral, free-flowing Pl Eff	Turbid	10,000 PMNs	1.4–6.1	<700	=S	≥7.30	Blood culture	Presumptive	Pl Eff resolves without sequelae on appropriate antibiotics
Parapneumonic effusion-complicated	Pneumonia	Moderate–large ipsilateral Pl Eff with tendency to loculation	Turbid or purulent	>20,000 (200–100,000) PMNs	>4.5	>1000	<40	<7.10	Blood culture, CIE	Pus, + bacteriology ↓pH, ↓glucose and LDH	Requires chest tube drainage for resolution
Tuberculosis	Acute or insidious cough, pleurisy, fever	Small–moderate unilateral Pl Eff pulmonary infiltrate (30%)	Serous	<5000 lymphocytes	>4.0	<700	=S <60 (20%)	Always <7.40 <7.30 (20%)	ADA, lysozyme promising	Presumptive-granuloma on pleural biopsy diagnostic-isolation of organism from Pl Eff or pleural tissue	Culture of pleural biopsy best diagnostic test with yield up to 80%
Actinomycosis	Chronic pneumonia, fever, cough	Consolidation unilateral Pl Eff and thickening, rib involvement	Serous or purulent	Moderate PMNs or lymphocytes	Exudate	Exudate	—	—	—	Culture anaerobically from Pl Eff or sinus tracts	Sulfur granules can be identified in purulent fluid
Nocardiosis	Chronic pneumonia, fever, cough	Consolidation with cavitation, small–moderate Pl Eff	Serous or purulent	Moderate PMNs	Exudate	Exudate	—	—	Sputum	Culture aerobically from Pl Eff, BAL or sputum	Steroids and alveolar proteinosis are predisposing factors
Aspergillosis	Remote pneumothorax therapy—cough, fever, weight loss, postop fever, purulent expectoration	Nodular pleural thickening, small–moderate Pl Eff, density lying free in pleural space postop-persistent air fluid level	Serous, serosanguinous, purulent, or black	Moderate lymphocytes mesothelials	Exudate	Exudate	—	—	Serum precipitins, antigens in Pl Eff	Culture from Pl Eff	Brown clumps of fungal hyphae suggest diagnosis, Ca oxalate crystals in Pl Eff suggest A. niger infection
Blastomycosis	Chronic pneumonia, cough, fever, chest pain	Alveolar and interstitial infiltrates, pleural thickening, unilateral Pl Eff	Serous	180–3990 mononuclears or PMNs	4.2–6.6	>225	=S	≥7.30	Sputum	+PE smear, culture from Pl Eff, organism seen on pleural biopsy	Major pleural disease a poor prognostic sign
Cryptococcosis	Chest pain, cough, fever; pneumonia vs. infarction	Peripheral alveolar infiltrate, small–massive unilateral Pl Eff	Serous or serosanguinous	Small–moderate lymphocytes	2.5–5.7	Exudate	=S	≥7.30	Antigen in Pl Eff	Culture from Pl Eff or pleural tissue, histology of pleural tissue	Normal host with localized pleuropulmonary disease can be observed

Coccidioidomycosis	Primary-fever pleurisy, cough; rupture of cavity—acute systemic toxicity or subacute chest pain, dyspnea	Unilateral moderate–large Pl Eff with infiltrate Hydropneumothorax	Serous, turbid	1000–8000 lymphocytes PMNs	3.5–6.5	Exudate	=S	≥7.30	CF titers	Culture from Pl Eff and pleural tissue, spherules in pleural tissue	Culture of pleural tissue has highest diagnostic yield; culture of Pl Eff usually positive
Histoplasmosis	Cough, fever, malaise, pleurisy	Subpleural infiltrate or nodule with small–moderate Pl Eff	Serous	Small–moderate lymphocytes eosinophilia	4.1–5.7	200–425	=S	≥7.30	CF titers	Culture from Pl Eff or pleural tissue, organism seen in pleural tissue	Treatment not necessary for acute histoplasma Pl Eff
Paragonimiasis	Orientals—cough, fever, hemoptysis, isolated pleural disease; chronic asymptomatic Pl Eff	Diffuse infiltrates with unilateral small–massive Pl Eff	Turbid, white, yellow, or brown	<2000, eosinophilia	6.0–8.0	>1000	<10	<7.10	CF titers, ova in sputum or stool	Ova in Pl Eff	With isolated pleural disease ova in Pl Eff only
Amebiasis	Sympathetic effusion—insidious pleurisy, cough; rupture into pleural space—sudden chest pain, dyspnea, fever, cough	Small-moderate right Pl Eff elevated hemidiaphragm, plate-like atelectasis; large-massive right Pl Eff with contralateral mediastinal shift	Serous, brown pus	Moderate PMNs Moderate–large PMNs		Exudate	—	—	Serology, CT scan	Presumptive organism in Pl Eff, typical brownish pleural aspirate	Uncomplicated amebic empyema responds to early tube thoracostomy
Echinococcosis	Acute chest pain, cough, fever, respiratory distress, shock	Moderate right Pl Eff, hydropneumothorax, elevated hemidiaphragm, RLL pneumonitis	Turbid	Moderate PMNs, eosinophils	Exudate	Exudate	—	—	Casoni skin test, CF titers	Identification of scolices in Pl Eff or in pleural tissue	Requires emergency thoracotomy
Viral	Acute chest pain following viral syndrome	Small unilateral Pl Eff with or without infiltrate, hilar adenopathy may be present	Serous	To 6000 mononuclears	3.2–4.9	Exudate	=S	≥7.30	Serology	Presumptive	May not have parenchymal infiltrates
Mycoplasma	Cough, headache, myalgias	Small–moderate unilateral Pl Eff, lower lobe infiltrate	Serous	600–6000 mononuclears	1.8–4.9	Exudate	=S	≥7.30	Culture of sputum or pharyngeal secretions, serology	Presumptive	Pl Eff resolves in days to weeks
Legionellosis	Older, smoker, high fever, cough, CNS and GI symptoms	Unilobe alveolar infiltrate with progression, small–moderate unilateral Pl Eff	Turbid	Moderate PMNs	Exudate	Exudate	=S	≥7.30	Serology DFA and culture from sputum	Culture from Pl Eff	Pl Eff resolves with infiltrate on erythromycin

(Continued)

TABLE 30.13. Causes and characteristics of pleural exudates (*Continued*)

Disease	Clinical findings	Chest radiograph	Appearance	Cells/μL	Protein (g/dL)	LDH (1 U/L)	Glucose (mg/dL)	pH	Other tests	Diagnosis	Comments
Upper abdominal abscess	Fever, ↑WBC, upper abdominal pain, pleurisy in patient, postabdominal surgery	Elevated hemidiaphragm, small Pl Eff, gas within abscess cavity	Turbid	Moderate PMNs	Exudate	Exudate	>60	>7.20	CT scan, aspiration and culture of abscess	Presumptive	Drainage is definitive treatment, sterile Pl Eff resolves as abscess treated
Hepatic abscess	Fever, chills, constitutional symptoms, RUQ pain in elderly with biliary tract disease or postop	Elevated hemidiaphragm, basilar infiltrates, abscess formation, small right Pl Eff	Turbid	Moderate PMNs	Exudate	Exudate	>60	>7.20	CT scan, aspiration and culture of abscess	Presumptive	Drainage is definitive treatment, sterile Pl Eff resolves with drainage of abscess
Hepatitis	Hepatitis	Small right Pl Eff can be large and bilateral, no pulmonary infiltrates	Dark yellow	Few lymphocytes	3.0–5.0	Exudate	=S	≥7.30	HBeAg, HBsAg, HBV	Presumptive	Pl Eff potentially infectious, resolves prior to resolution of hepatitis
Splenic abscess	Fever, abdominal pain, splenomegaly in patient with endocarditis	Small left Pl Eff, basilar infiltrates and atelectasis, contralateral mediastinal shift, elevated hemidiaphragm	Serous	Moderate PMNs	T/E	T/E	=S	≥7.30	CT scan	Presumptive	Treatment is antibiotics and splenectomy
Esophageal perforation (spontaneous)	Severe retching or vomiting followed by chest pain and fever, subcutaneous air	Subcutaneous and mediastinal air, left pneumothorax early, left Pl Eff later	Early-serous, late-turbid, purulent	Moderate PMNs, Many PMNs	Exudate	Exudate	=S	≥7.30 <7.30	Esophagram	pH 6.00, ↑ amylase	With early diagnosis, prognosis good with primary closure
Carcinoma	Dyspnea with exertion, cough, weight loss, appear chronically ill	Lung-unilateral moderate–large Pl Eff, primary lesion may be seen; extrathoracic primary-unilateral or bilateral moderate–large Pl Eff without other evidence of metastases	Serous- lymphatic obstruction; bloody- pleural invasion	2500–4000 lymphocytes, macrophages, mesothelials	4.0 (1.5–8.0)	300, exudates by LDH only suggests malignancy	=S <60 (30%)	≥7.30 6.95–7.29 (30%)	CT scan, bronchoscopy, other biopsies	Cytology, pleural biopsy	Lung and breast most common, primaries, pleural fluid pH has prognostic and therapeutic implications
Lymphoma	Dyspnea with exertion, cough	Unilateral moderate– large Pl Eff without other findings	Serous	Few lymphocytes	Exudate	Exudate	=S <60 (20%)	≥7.30 <7.30 (20%)	CT scan, lymph node biopsy	Cytology, pleural biopsy	Diagnosis more readily made by cytology or pleural biopsy in NHL than Hodgkin's; presence of Pl Eff poor prognostic sign

Mesothelioma	Males 6th–9th decade, asbestos exposure, chest pain, dyspnea with exertion	Large unilateral Pl Eff, absence of contralateral mediastinal shift, nodularity of pleura	Serous, bloody, viscous	<5000 (few 100–20,000) mononuclears	3.5–5.5	36– >600	<60 (70%)	<7.30 (70%)	High levels of hyaluronic acid in Pl Eff supports Dx	Examination of tissue obtained at thoracoscopy or thoracotomy	Prognosis related to stage of disease at diagnosis and histologic variant
Rheumatoid pleurisy	Males 6th decade, moderate–severe arthritis, subcutaneous nodules, develop Pl Eff within 5yr of onset of disease, chest pain or asymptomatic	Small–moderate unilateral Pl Eff, other evidence of rheumatoid lung (30%)	Turbid, yellow-green, debris	Few 100–15,000 acute-PMNs chronic-lymphocytes	Exudate to 7.3	Frequently >1000	Initially <30 (67%) <50 (80%)	7.00 (80%)	Low complement; ↑immune complexes in Pl Eff	Glucose, <30, pH 7.00, LDH >1000, RF ≥1:320	Pl Eff resolves over several months but may be recurrent and lead to trapped lung
Lupus pleuritis	Known lupus, pleuritic pain, pleural rub, fever, cough, dyspnea	Small–moderate bilateral Pl Eff may have cardiomegaly, alveolar infiltrates or atelectasis	Serous, bloody	5000 (few 100–20,000) PMNs or mononuclears	Exudate	Exudate	=S <60 (20%)	≥7.30 <7.30 (20%)	Low complement; ↑immune complexes and ANA ≥1:160 in Pl Eff	LE cells in Pl Eff	Good response to steroids with resolution by 2 wk
Postcardiac injury syndrome	Pleuritic pain, pericardial rub, fever, dyspnea, rales 3 weeks following pericardial injury	Left sided or bilateral small–moderate Pl Eff, left lower lobe pulmonary infiltrates	Serosanguinous, bloody	9500 (500–39,000) PMNs or mononuclears	3.7 (3.0–4.5)	202	>60	≥7.30	—	Presumptive	Pl Eff resolves in 1–3 wk spontaneously or with steroids
Sarcoidosis	Stage 2 or 3 disease, chest pain or asymptomatic	Hilar adenopathy, interstitial disease, small–moderate unilateral Pl Eff	Serous, turbid, serosanguinous	100–7000 >90% lymphocytes	Exudate	Exudate	=S	≥7.30	↑T lymphocytes with predominance of helper cells	Dx of exclusion; noncaseating granulomas on pleural biopsy, negative for fungi and AFB	Pl Eff resolves spontaneously or with steroids
Immunoblastic lymphadenopathy	Constitutional symptoms, diffuse lymphadenopathy, hepatosplenomegaly	Bilateral interstitial infiltrates and mediastinal or hilar adenopathy, bilateral small–moderate Pl Eff	Serous	Few lymphocytes	Exudate	Exudate	=S	≥7.30	Lymph node biopsy	Presumptive	Impaired lymphatic drainage or lymphocytic pleural infiltration most likely mechanisms
Pulmonary embolism	Pleuritic chest pain, tachypnea, rales, fever	Unilateral small–moderate Pl Eff, pulmonary infiltrate	Bloody or serous	100–50,000 PMNs or lymphocytes	Exudate, transudate (20%)	Exudate, transudate (20%)	=S	≥7.30	Lung scan, angiogram	Presumptive	Pl Eff apparent on admission, reaches maximum volume by 72h
Pancreatitis	Acute abdominal pain, nausea, vomiting, fever	Unilateral, left-sided small Pl Eff (60%), right (30%), bilateral (10%), atelectasis	Turbid	1000–50,000 PMNs	Exudate	Exudate	=S	7.30–7.35	↑Serum amylase	PF/S amylase >1.0	Pl Eff resolves as pancreatitis resolves

(Continued)

TABLE 30.13. Causes and characteristics of pleural exudates (*Continued*)

Disease	Clinical findings	Chest radiograph	Appearance	Cells/μL	Protein (g/dL)	LDH (1 U/L)	Glucose (mg/dL)	pH	Other tests	Diagnosis	Comments
Pancreatic pseudocyst	Dyspnea, chest pain, cough, history of pancreatitis or alcoholism	Large–massive left Pl Eff without parenchymal infiltrates, may be right or bilateral	Serous, serosanguinous	Few to moderate mononuclears	Exudate	Exudate	=S	≥7.30	Ultrasound, CT may show pseudocyst and fistula	Amylase in Pl Eff, may be >100,000	Recurs rapidly following thoracentesis, surgery necessary for Pl Eff refractory to conservative Rx
Asbestos pleural effusion	Asbestos exposure, asymptomatic (70%) chest pain	Small unilateral Pl Eff, pleural plaques (10%)	Serosanguinous	500–6000, PMNs mononuclears eosinophilia	4.7–7.5	Exudate	=S		—	Presumptive	Pl Eff resolves in 3–4 months, frequently is recurrent, diffuse pleural thickening may occur years after initial Pl Eff
Uremic pleural effusion	Uremia >1 year, fever, chestpain, cough, pleural rub	Unilateral moderate Pl Eff	Serosanguinous, bloody	80–3700 lymphocytes	2.1–6.7	102–770	=S	≥7.30	PF/S creatinine <1.0	Presumptive	Pl Eff usually resolves over weeks with continued dialysis
Trapped lung	Remote history of pneumonia, hemo- or pneumothorax asymptomatic	Unilateral small–moderate Pl Eff	Serous	Few mononuclears	T/E	T/E	=S	≥7.30	Pleural liquid pressure measurement	Presumptive	Pl Eff reaccumulates rapidly after thoracentesis, asymptomatic patient requires no RX
Meigs' syndrome	Postmenopausal, ascites and Pl Eff, chronic illness, dyspnea	Small–massive right Pl Eff	Serous	Few mononuclears	Exudate	Exudate	=S	=7.30	CT scan, laparoscopy	Presumptive	Removal of ovarian neoplasm results in resolution of Pl Eff
Chylothorax	Dyspnea with exertion symptoms of underlying disease, most commonly lymphoma	Large unilateral Pl Eff without parenchymal disease	Milky, may be bloody, turbid or serous	2000–20,000 lymphocytes	Exudate	Exudate	=S	>7.40	CT scan	Chylomicrons, triglycerides >110mg/dL	Major complications: malnutrition, immunologic compromise, radiation effective in lymphoma
Lymphangio-leiomyomatosis	Women of reproductive age, dyspnea, pneumothorax, chylothorax, hemoptysis	Interstitial lung disease with normal or increased lung volumes, chylothorax (75%), pneumothorax (40%)	Milky	2000–20,000 lymphocytes	Exudate	Exudate	=S	>7.40	PFTs, lung biopsy	Chylothorax in women of childbearing age with ILD and normal lung volumes	Treatment symptomatic anecdotes with successful hormonal manipulation

Yellow nail syndrome	40-year-old with yellow nails, lymphedema and respiratory tract involvement	Small–massive unilateral or bilateral Pl Eff	Serous	<1000 lymphocytes	>4.0	>200	=S	7.40	—	Presumptive	Triad seldom appears simultaneously, chemical pleurodesis effective
Radiation pleuritis	Pleuritic pain or asymptomatic Pl Eff from 2–6 months following >4000 rads, radiation pneumonitis	Small unilateral Pl Eff with loculations, radiation pneumonitis	Serosanguinous	Reactive mesothelials	Exudate	Exudate	=S	7.40	—	Presumptive	Pl Eff persists for at least 4 months, may remain constant for years
Endoscopic esophageal sclerotherapy	Chest pain following sclerotherapy, large sclerosant volume	Small unilateral (R or L) or bilateral Pl Eff within 48–72h of procedure	Serosanguinous	100–38,000 PMNs, mononuclears	1.10–4.80	77–1368	>100	≥7.30	—	Presumptive	Requires no specific therapy, resolves over days to weeks
Dantrolene	Pleuritic pain and fever 2 months to 3yr after beginning drug	Unilateral small Pl Eff without pulmonary infiltrates	Serosanguinous	Moderate eosinophils (36–66%)	Exudate	Exudate	=S	≥7.30	Blood eosinophilia	Presumptive	Symptoms abate within days of stopping drug, CXR lags
Methysergide	Recurrent chest pain, dyspnea, fever, pleural rub 1 month to 6yr after drug started	Bilateral loculated Pl Eff	Serous, serosanguinous	<1000 mononuclears	Exudate	Exudate	51 (one case)	—	—	Presumptive	Symptoms resolve quickly when drug stopped. CXR takes months to resolve and may not clear
Amiodarone	Dyspnea, cough, constitutional symptoms, pleuritic pain, pleural rub after ingesting >100g	Peripheral alveolar or interstitial infiltrates, pleural thickening, unilateral or bilateral small–massive Pl Eff	Serous, serosanguinous	<1000 macrophages, lymphocytes	2.8–3.7	128 (one case)	=S	7.43 (one case)	—	Presumptive	Pleural fluid macrophages containing foamy cytoplasm may be diagnostic

ADA, adenosine deaminase; AFB, acid-fast bacillus; ANA, antinuclear antibody; BAL, bronchoalveolar lavage; CF, complement fixation; CIE, counter immuno-electropheresis; CT, computed tomography; CXR, chest x-ray; DFA, direct fluorescence antibody; HB$_e$Ag, hepatitis B early antigen; HB$_s$Ag, hepatitis B surface antigen; HBV, hepatitis B virus; ILD, interstitial lung disease; NHL, non-Hodgkin's lymphoma; PF/S, pleural fluid/serum; Pl Eff, pleural effusion; PMN, polymorphonuclear neutrophil; RF, rheumatoid factor; RLL, right lower lobe; RUQ, right upper quadrant; T/E, transudate or exudate; TWBC, total white blood count; =S, equals serum value; PFT, pulmonary function test.
Source: Sahn,[3] with permission. Copyright © 1988, American Thoracic Society.

TABLE 30.14. Conditions associated with nontuberculous bacterial empyema

Cause	No. (%) of patients
Pulmonary infection	301 (56)
Surgery	119 (22)
Trauma	20 (4)
Esophageal perforation	21 (4)
Complication of thoracentesis/chest tube placement	21 (4)
Subdiaphragmatic infection	15 (3)
Spontaneous pneumothorax	7 (1)
Septicemia	8 (1)
Other or unknown	30 (5)
Total	542 (100)

Source: Bryant and Salmon,[85] with permission of the University of Chicago Press. Copyright ©1996.

contribute to bacterial empyema are shown in Table 30.14.

Immunocompromised patients are susceptible to pleural involvement with fungal or aerobic gram-negative bacillary organisms, whereas in patients with malignancy, fungal or tuberculous foci may become reactivated and empyema may develop. Fungal or mycobacterial empyema may develop in transplant recipients and AIDS patients. The bacteria that have been isolated from nontuberculous pleural empyema fluid in various studies are shown in Table 30.15.

Tuberculous empyema has been reviewed by Sahn and Iseman.[88] Tuberculous empyema represents a chronic, active infection of the pleural space and is relatively rare compared to tuberculous pleural effusion. According to Sahn and Iseman, the inflammatory process may be present for years with a paucity of clinical symptoms. The clinical diagnosis of tuberculous empyema is somewhat characteristic by CT scan, showing a thick, calcified pleural rind and rib thickening surrounding loculated pleural fluid (see also Chapter 9).

An eosinophilic empyema was associated with crack cocaine, which is a known cause of eosinophilic pneumonia. Strong et al.[89] suggested that a pleural effusion that appears to be grossly purulent in the setting of cocaine abuse should not be drained until an eosinophil predominant effusion is ruled out. If infection is excluded, an eosinophilic empyema in the setting of crack cocaine should be treated with corticosteroids.

Drug-Induced Pleural Disease

Pharmaceutical drugs continue to be a potential cause of pleural disease.[90–92] As reviewed by Huggins and Sahn,[92] the pathogenetic mechanisms for most drug-induced pleural diseases remain speculative. Possible mechanisms include (1) hypersensitivity or allergic reaction, (2) direct toxic effect, (3) increased oxygen free radical production,

TABLE 30.15. Bacteria isolated from nontuberculous pleural empyema fluid in various studies

Bacteria isolated	Percentage of patients with empyema	
	In combined series	Following trauma
Aerobic		
Streptococcus species	26	8
Streptococcus pneumoniae	8	
Staphylococcus aureus	18	37
Staphylococcus epidermidis	8	
Escherichia coli	9	5
Enterobacter species	5	5
Proteus species	5	
Klebsiella species	6	5
Pseudomonas aeruginosa	12	16
Other gram-negative bacilli		16
Aerobic organisms only	27	
Anaerobic		
Bacteroides species	30	
Clostridium species	5	
Actinomyces species	2	
Eubacterium species	4	
Proprionibacterium species	3	
Veillonella species	4	
Fusobacterium species	13	
Microaerophilic streptococci	10	
Peptostreptococcus species	13	
Anaerobic organisms only	23	8
No organisms	~18	

Source: Bryant and Salmon,[85] with permission of the University of Chicago Press. Copyright © 1996.

TABLE 30.16. Drugs associated with pleural fluid eosinophilia

Drug	Pleural fluid eosinophilia (%)	Peripheral blood eosinophilia (%)	Parenchymal infiltrate
Valproic acid	62–84%	26%	Not reported
Propylthiouracil	16–45%	No	No
Isotretinoin	>20%	No	No
Nitrofurantoin	17%	9–83%	Interstitial
Bromocriptine	12–30%	Not reported	No
Dantrolene	33–66%	7–18%	No
Gliclazide	80%	20%	Interstitial
Mesalamine	Not reported	7%	Interstitial

Source: Huggins and Sahn,[92] with permission from Elsevier. Copyright © 2004.

(4) suppression of the antioxidant defenses, and (5) chemical-induced inflammation. The presentation of patients with drug-induced pleural disease varies from an asymptomatic pleural effusion to acute pleuritis with chest pain and exertional dyspnea. According to Huggins and Sahn, approximately 30 drugs are thought to cause pleural disease. These include cardiovascular agents, ergoline drugs, sclerotherapy agents (see below), and chemotherapeutic agents. To date, eight drugs have been reported to be associated with pleural fluid eosinophilia (Table 30.16). I have seen one case of Advair-induced pleuritis and eosinophilic pneumonia, an infrequent but recognized complication (see above).[93] In any unusual case of pleuritis where a cause is not obviously determined, it is worthwhile checking on what medications the patient may be taking (see also Chapter 22 on drug-induced lung disease, and Table 22.12). A number of drugs are capable of inducing lupus pleuritis.[92] These are listed in Table 30.17.

Immunologic-Associated Pleural Disease

Collagen Vascular-Induced Pleural Disease

Rheumatoid arthritis is associated with the highest incidence of pleural involvement of all the collagen vascular diseases.[94–96] Rheumatoid pleuritis occurs in approximately 5% of patients with rheumatoid disease,[96,97] and may be associated with visceral pleural fibrosis, rheumatoid nodules involving the visceral pleura (Fig. 30.16), or, occasionally, fibrosis and inflammation of the visceral and parietal layers of the pleura with adhesions. Autopsy studies suggest pleural involvement in rheumatoid disease approaches 50%, although most patients are apparently asymptomatic. In contrast to the overall incidence of rheumatoid arthritis, symptomatic rheumatoid lung disease is more common in men than in women, and that

TABLE 30.17. Medications associated with drug-induced lupus

Strongly associated with lupus pleuritis
  Chlorpromazine
  Hydralazine
  Isoniazid
  Methyldopa
  Penicillamine
  Quinidine
Anticonvulsants
  Carbamazepine
  Ethosuximide
  Primidone
Antiinflammatory agents
  Diclofenac
  Ibuprofen
  Para-aminosalicyclic acid
  Sulindac
  Tolmetin
Antimicrobials
  Griseofulvin
  Nalidixic acid
  Nitrofurantoin
  Penicillin
  Streptomycin
Cardiovascular agents
  Acebutolol
  Amiodarone
  Atenolol
  Captopril
  Clonidine
  Disopyramide
  Labetalol
  Lovastatin
  Minoxidil
  Practolol
  Prinolol
  Spironolactone
Endocrine agents
  Aminoglutethimide
  Methimazole
  Propylthiouracil
Gastrointestinal agents
  Promethazine
  Sulfasalazine
Gynecologic agents
  Danazol
  Oral contraceptives
Immune modulators
  Gold salts
  Interferon (α, γ)
Neurologic agents
  Levo-dopa
  Methylsergide
Oncologic agents
  Leuprolide acetate
Ophthalmologic agent
  Timolol eye drops
Psychiatric agents
  Lithium carbonate

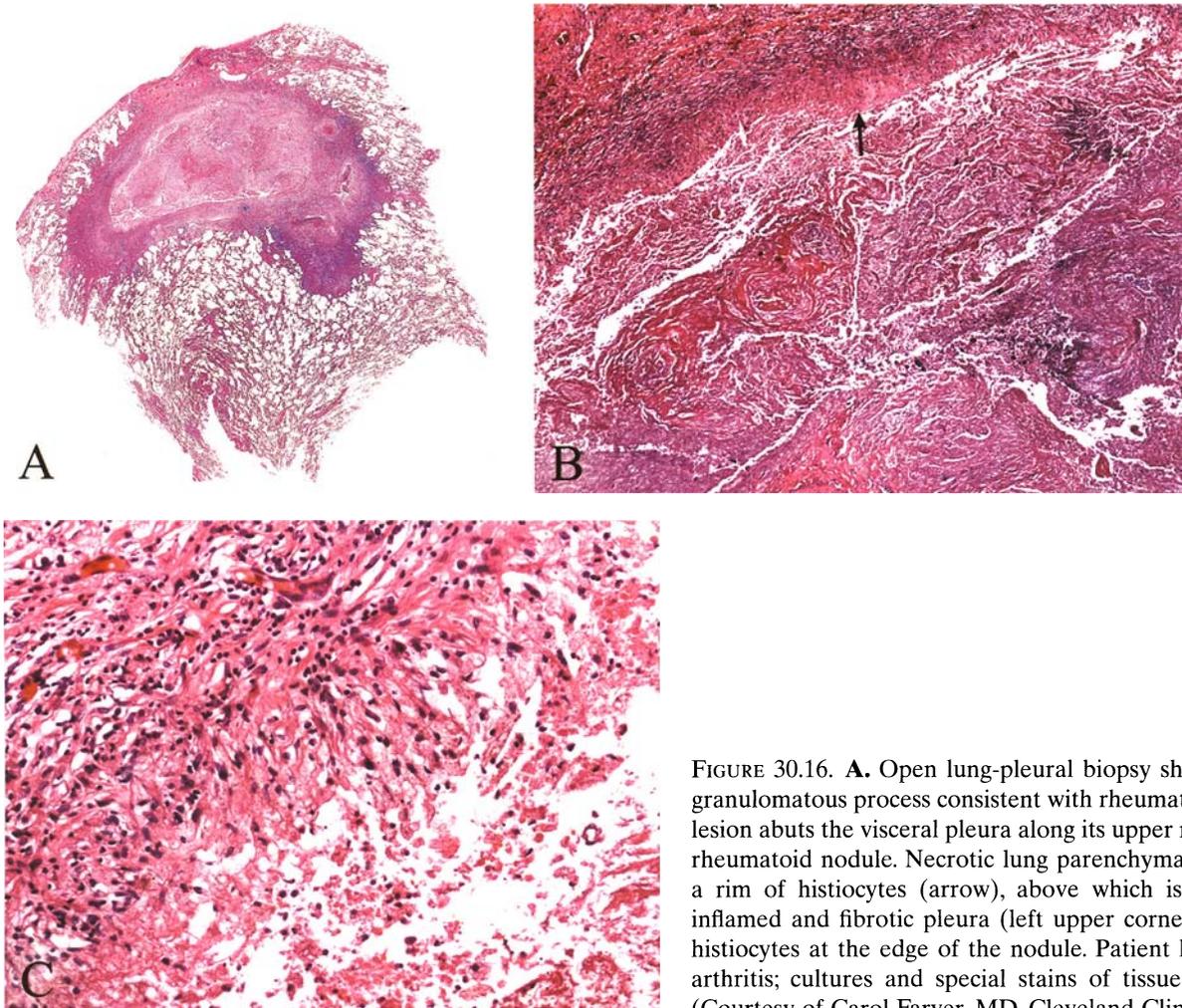*Source:* Huggins and Sahn,[92] with permission from Elsevier. Copyright © 2004.

FIGURE 30.16. **A.** Open lung-pleural biopsy shows necrotizing granulomatous process consistent with rheumatoid nodule. The lesion abuts the visceral pleura along its upper rim. **B.** Detail of rheumatoid nodule. Necrotic lung parenchyma is bordered by a rim of histiocytes (arrow), above which is the thickened, inflamed and fibrotic pleura (left upper corner). **C.** Palisaded histiocytes at the edge of the nodule. Patient had rheumatoid arthritis; cultures and special stains of tissue were negative. (Courtesy of Carol Farver, MD, Cleveland Clinic Foundation.)

holds true for rheumatoid pleuritis. The typical patient who develops rheumatoid pleuritis is a man in the sixth decade with a pleural effusion within 5 years after the onset of rheumatoid disease. In most instances, patients with rheumatoid pleuritis have a high rheumatoid factor titer, and this antibody is also found in the pleural fluid. The most striking consistent features of rheumatoid pleural effusions are low pleural fluid glucose, low pH, and high LDH (see Chapter 20 on collagen vascular diseases).

Involvement of the pleura in patients with systemic lupus erythematosus occurs to some degree in 50% to 75% of patients diagnosed with lupus, and may be the presenting manifestation in up to 5% of patients.[3] The changes in the pleura are nonspecific and can consist of acute and chronic inflammation and fibrosis (Fig. 30.17). In most instances, the pleuritis is associated with an exacerbation of the basic disease. In contrast to the pleural fluid in rheumatoid pleuritis, in lupus pleuritis the pleural fluid glucose and pH are usually within normal limits. One can identify LE cells in the pleural fluid, although other serologic studies, such as DNA binding and extract-

able nuclear antigen (ENA) titers, help clarify or prove the diagnosis of systemic lupus erythematosus. Medications associated with drug-induced lupus are listed in Table 30.17.
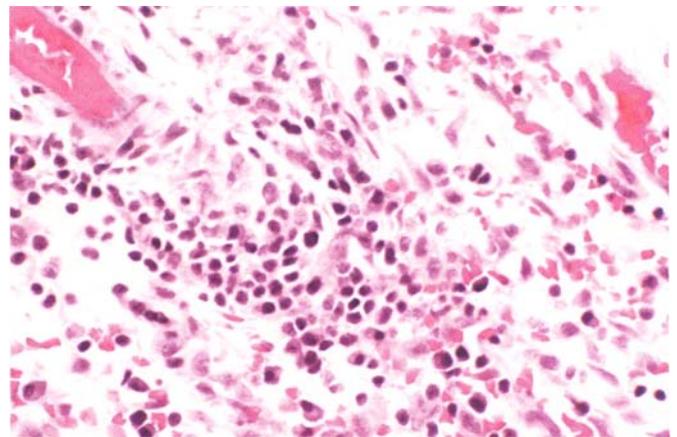

FIGURE 30.17. Nonspecific chronic pleuritis in 35-year-old woman with systemic lupus erythematosus.

Sarcoidosis

Sarcoidosis is a nonnecrotizing granulomatous disease involving lymph nodes, pulmonary parenchyma, and other tissues and organs. Not infrequently, sarcoid involves the pleura (see Fig. 18.11 in Chapter 18), and in one retrospective study of more than 200 patients with biopsy-proven sarcoidosis, 10% had radiographic evidence of pleural thickening or effusion and 7% had evidence of pleural effusion.[98] Most patients with pleural involvement by sarcoid have at least radiographic stage II disease (see Chapter 18). The pleural fluid may be a transudate or an exudate, and often has an increased number of lymphocytes, specifically helper-inducer (CD4-positive) lymphocytes.

Wegener's Granulomatosis

As discussed in Chapter 29, Wegener's granulomatosis is characterized by a necrotizing granulomatous inflammatory process typically involving the lungs and not infrequently involving the kidneys and other tissues and organs. As described by Mark et al.,[99] the basic lesion is necrobiosis of collagen that incites the inflammatory reaction. If these areas of necrosis and inflammation occur close to or involve the pleural surface, one would expect an inflammatory reaction to be located in that region (Fig. 30.18). In some series,[100] pleural effusion has been observed in as many as 55% of cases, although in most instances the incidence of pleural effusion is much less than that. The characteristic features of pleural fluid in Wegener's granulomatosis have not been fully defined. A case of pleural effusion associated with Wegener's granulomatosis is described by Diot and colleagues.[36]

Postcardiac Injury Syndrome—Dressler Syndrome

The occurrence of pleuropericarditis and parenchymal pulmonary infiltrates, usually occurring approximately 3 weeks following injury to the myocardium or pericardium, is referred to as postcardiac injury syndrome and is
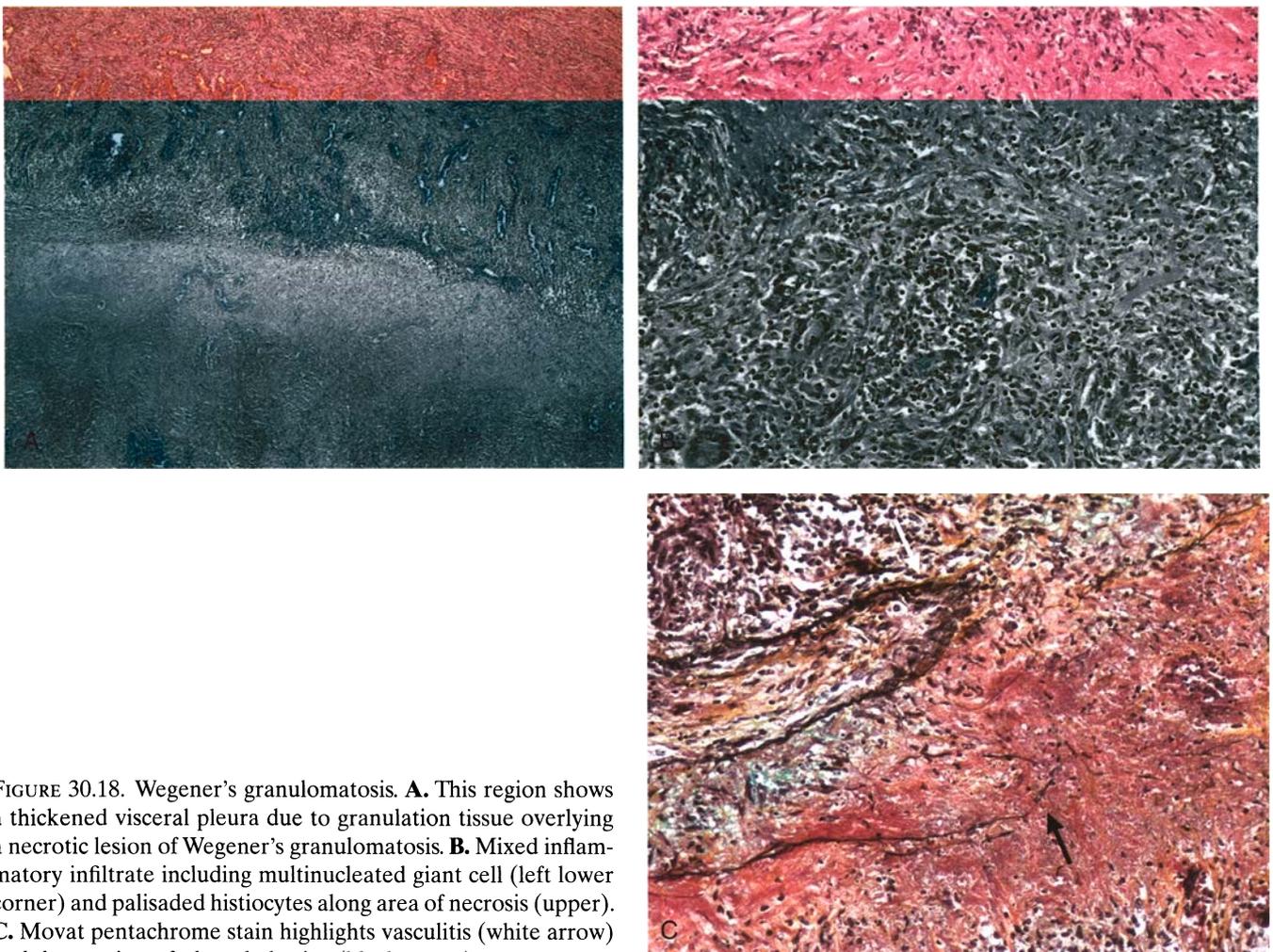

FIGURE 30.18. Wegener's granulomatosis. **A.** This region shows a thickened visceral pleura due to granulation tissue overlying a necrotic lesion of Wegener's granulomatosis. **B.** Mixed inflammatory infiltrate including multinucleated giant cell (left lower corner) and palisaded histiocytes along area of necrosis (upper). **C.** Movat pentachrome stain highlights vasculitis (white arrow) and destruction of pleural elastica (black arrow).
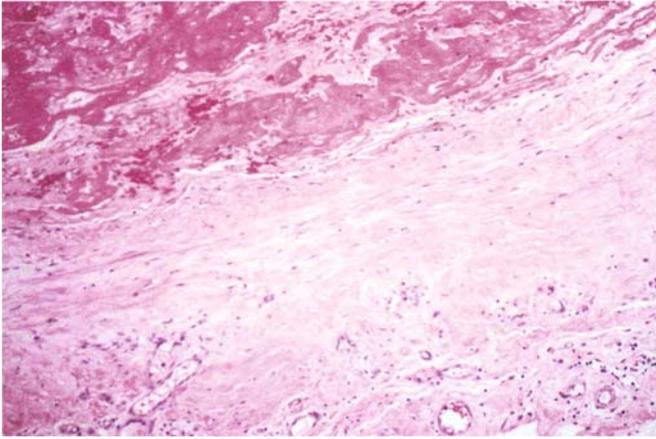
FIGURE 30.19. Nonspecific organizing chronic fibrinous pleuritis in patient with postcardiac injury syndrome. Most inflammatory cells are plasma cells.

characterized by the onset of fever with the pleuropericarditis. The incidence of this syndrome varies from approximately less than 1% to 15%,[101,102] and is thought to be related to an immunologic reaction characterized by antibodies to myocardial tissue.[103,104] The pleuropulmonary manifestations are the most significant in this syndrome, and most patients present with pleuritic chest pain. Pleural fluid is characteristically a serosanguineous or bloody exudate, and may result in chronic pleural thickening with varying degrees of inflammation (Fig. 30.19).

Kim and Sahn[105] described in 1996 an immunologic assessment of pleural fluid in a patient with postcardiac injury syndrome. They identified antimyocardial antibodies in the pleural fluid. A publication in 2004 by Bendjelid and Pugin[106] suggested that the incidence of postacute myocardial infarction syndrome had decreased in the reperfusion era, most likely due to the extensive use of therapies that significantly decreased the size of myocardial necrosis.

Other Conditions

Pleural Fibrosis

Huggins and Sahn[107] reviewed the conditions that resulted in pleural fibrosis. They pointed out that a variety of inflammatory processes, including dust exposure, immunologic diseases, infection, medications, malignancy, post–coronary bypass surgery, and uremic pleurisy, could result in pleural fibrosis. Those that were reported to cause a trapped lung are shown in Table 30.18. The authors concluded that pleural fibrosis could result from diverse inflammatory conditions, and the development of pleural fibrosis followed severe pleural inflammation, which was typically associated with an exudative effusion. Another critical factor stated to be important in pleural fibrosis

was the formation of fibrinous intrapleural neomatrix. The neomatrix was stated to result from a disorder of fibrin turnover whereby fibrin formation was upregulated and fibrin dissolution was downregulated. The authors reported that transforming growth factor-β (TGF-β) and tumor necrosis factor-α (TNF-α) facilitated the disordered fibrin turnover, and that clinically significant pleural fibrosis required involvement of the visceral pleura.

Hemothorax

Hemothorax refers to the presence of blood within the pleural cavity. It is occasionally seen as an almost invariably fatal complication of a ruptured thoracic aortic aneurysm or a traumatic rupture of the aorta. A moderate amount of blood causing a bloody pleural effusion can be seen in other conditions, such as asbestos-induced pleural disease, tuberculosis, and a variety of neoplasms such as mesothelioma and primary lung cancers invading the pleura. The pathologic features of these conditions depend on the specific etiology.

Chylothorax

Chylothorax refers to accumulation of lymphatic fluid within the pleural cavity that has the features of lymph fluid, containing a high concentration of emulsified neutral fats and fatty acids with a low concentration of cholesterol. A chyliform effusion results from degeneration of malignant and other cells in pleural fluid, and a pseudochylous effusion results from the presence of cholesterol crystals and occurs most commonly in tuberculosis, rheumatoid disease, and nephrotic syndrome. Chylothorax may be bilateral, although it is more commonly seen on the left side. There are numerous causes of chylothorax.[108] These are listed in Table 30.19.

A definitive diagnosis of chylothorax is made by laboratory analysis of pleural fluid. The presence of chylomicrons on lipoprotein electrophoresis is confirmatory. Staats et al.[109] performed a study in which triglyceride values were determined for 142 effusions defined as chylous or nonchylous by the gold standard test of lipoprotein electrophoresis. Using the Gaussian distribution method, it was estimated that fluid with a triglyceride value of more than

TABLE 30.18. Causes of trapped lung

Conditions
Coronary artery bypass surgery
Complicated parapneumonic effusion/empyema
Tuberculous pleurisy
Rheumatoid pleurisy
Hemothorax
Uremic pleuritis
Pneumothorax therapy for tuberculosis

Source: Huggins and Sahn,[107] with permission.

TABLE 30.19. Etiologies of chylothorax

Congenital
  Congenital lymphatic malformations
  Birth trauma (normal or difficult labor)
Traumatic
  Iatrogenic
    Thoracic surgery
    Radical neck dissection
    Abdominal lymph node dissection
    Subclavian or internal jugular vein cannulation
  Noniatrogenic
    Penetrating
    Blunt (less common)
Nontraumatic
  Malignancy
    Lymphoma
    Metastatic carcinoma
    Kaposi sarcoma
  Infectious
    Tuberculosis
    Filariasis
  Subclavian vein thrombosis
  Mediastinal radiation therapy
  Pancreatitis and pancreatic pseudocysts
  Hypothyroidism
  Nephrotic syndrome
Pseudochylothorax
  Tuberculosis
  Rheumatoid arthritis

Source: Chinnock,[108] with permission.

110 mg/dL had less than a 1% chance of not being chylous, and fluid with a triglyceride value of less than 50 mg/dL had no more than a 5% chance of being chylous.

Chylothorax rarely occurs as a complication of coronary artery bypass surgery as a result of injury to the left internal mammary lymphatics during dissection of the vessel or from injury to the parasternal nodes.[110] Tuberculosis is also an unusual cause of chylothorax.[111]

Another rare condition in which chylothorax may occur is lymphangioleiomyomatosis.[112] The mechanism of chylothorax in lymphangioleiomyomatosis includes (1) chyle leak secondary to proximal lymphatic obstruction or direct involvement of the thoracic duct or its tributaries, (2) general oozing from pleural lymphatics or collateral vessels, and (3) transdiaphragmatic flow of chylous ascites (see Chapter 39).

Pneumothorax

Pneumothorax refers to air or gas in pleural cavities and may be spontaneous, traumatic, or therapeutic. Spontaneous pneumothoraces are caused by abnormalities of the parenchyma that allow the escape of air into the pleural cavity. These may be caused by blebs and bullae associated with emphysema, by an abscess cavity that communicates with the pleural space, or occasionally by asthma, which results in areas of overexpansion of the lung paren-

chyma that then ruptures. Therapeutic pneumothorax was once commonly used to treat tuberculosis. Pneumothoraces occasionally occur during fine-needle aspiration biopsy attempts, and when inserting various catheters into the subclavian vein. Primary spontaneous idiopathic pneumothorax characteristically affects young persons (predominantly young males of asthenic body habitus), is associated with cigarette smoking, and in most cases is due to ruptured apical blebs and bullae.[113,114] Recurrent attacks are frequent and disabling, and often require surgical intervention to "roughen" the pleural surface with the hope of causing scarring and preventing further air leaks. Histologically, resected apical lung tissue in patients with primary spontaneous pneumothorax shows, in addition to pleural chronic inflammation and reactive eosinophilic pleuritis, parenchymal changes of band-like subpleural fibrosis, blebs, and paracicatricial emphysema.[113,115] Increased pigment-laden macrophages in distal air spaces are consistent with a cigarette smoking history. Parenchymal blood vessels in the vicinity of the pleura may exhibit medial hypertrophy and intimal fibrosis, but these changes should not be interpreted as indicative of pulmonary hypertension.[116] Rarely, eosinophils may infiltrate the underlying lung parenchyma and prominently infiltrate blood vessels, mimicking the changes in Churg-Strauss syndrome or Langerhans' cell histiocytosis (Fig. 30.20) (see also Chapters 16 and 29).[117]

Air leak in the absence of trauma or iatrogenic causes within the pleural cavity is referred to as *spontaneous pneumothorax* and can be either primary, in which there is no obvious clinical or radiographic evidence of significant pulmonary disease, or secondary, in which a disease is present. Primary spontaneous pneumothorax is caused by rupture of air-containing spaces in the visceral pleura or immediately below the visceral pleura. The most common causes are bullae, which are defined as sharply
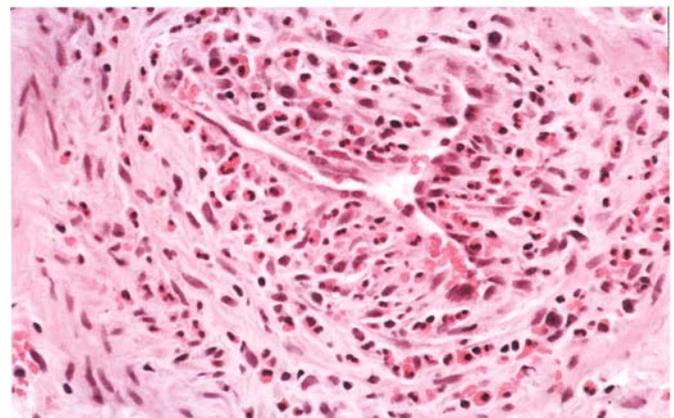

FIGURE 30.20. Eosinophilic vascular infiltration in spontaneous pneumothorax. A muscular pulmonary artery is densely infiltrated by eosinophils.

demarcated regions of emphysema greater than 1 cm in diameter.[113] A bleb is defined as a gas-containing space situated entirely within the pleura (see Chapter 24 on emphysema). It is thought that most air-containing spaces associated with pneumothorax are bullae. Computed tomography scans demonstrate areas of emphysema in more than 80% of patients who have spontaneous pneumothorax, even in lifelong nonsmokers.[118,119]

Spontaneous pneumothoraces are multifactorial in causation.[120] The common causes are listed in Table 30.20. Iatrogenic causes of pneumothorax are listed in Table 30.21.

TABLE 30.20. Causes of secondary spontaneous pneumothorax

Chronic obstructive pulmonary disease
  Asthma
  Emphysema
  Cystic fibrosis
Immunologic disease
  Wegener's granulomatosis
  Idiopathic pulmonary hemorrhage
  Idiopathic pulmonary fibrosis
  Langerhans' cell histiocytosis
  Sarcoidosis
Drugs and toxins
  Chemotherapy for malignancy
  Paraquat poisoning
  Hyperbaric oxygen therapy
  Radiation therapy
  Aerosolized pentamidine therapy in patients with AIDS
Connective tissue disease
  Lymphangioleiomyomatosis
  Tuberous sclerosis
  Neurofibromatosis
  Marfan's syndrome
  Ehlers-Danlos syndrome
  Mitral valve prolapse
Neoplasms
  Primary pulmonary carcinoma
  Carcinoid tumor
  Mesothelioma
  Metastatic carcinoma
  Metastatic sarcoma
  Metastatic germ cell tumors
Pneumoconiosis
  Silicoproteinosis
  Berylliosis
  Bauxite pneumoconiosis
Vascular disease
  Pulmonary infarction
Metabolic disease
  Pulmonary alveolar proteinosis
Developmental disease
  Congenital cystic adenomatoid malformation
Intraabdominal disease
  Gastropleural fistula
  Colopleural fistula
Infection
  Fungal pneumonia (particularly *Pneumocystis jiroveci* pneumonia
    in patients with AIDS)
  Hydatid disease
  Bacterial pneumonia

TABLE 30.21. Causes of iatrogenic pneumothorax

Biopsy procedures
  Transthoracic needle aspiration
  Transbronchial biopsy
  Transtracheal biopsy
  Colonoscopy
  Liver biopsy
  Fine-needle aspiration of breast

Therapeutic procedures
  Thoracentesis
  Central venous catheterization
  Feeding tube insertion
  Positive-pressure ventilation
  Tracheal intubation
  Pacemaker insertion
  Electromyographic electrode insertion
  Acupuncture
  Percutaneous nephrolithotomy
  Use of a voice box prosthesis

Butnor and Guinee[121] recently reported on the pathologic features of the Birt-Hogg-Dubé syndrome, a rare inherited genodermatosis characterized by distinct cutaneous lesions with an increased risk of renal and colonic cancer and the development of pleuropulmonary blebs and cysts. Histologically, the lung shows basilar cysts composed of intraparenchymal collections of air surrounded by normal parenchymal or thin fibrous walls, and blebs consisting of collections of air within the pleura. The authors point out that these histologic findings are nonspecific, although their predominantly basilar location contrasts with the apical distribution of well-recognized causes of spontaneous pneumothorax, such as emphysematous bullae and idiopathic blebs. As suggested by the authors, it is important for pathologists to be aware of this rare cause of spontaneous pneumothorax because Birt-Hogg-Dubé syndrome can radiographically simulate other causes of pulmonary cysts, and the lung and pleura may be the initial site of involvement of this condition.

Pleural Endometriosis

Pleuropulmonary endometriosis is a rare condition and it is discussed in Chapter 41. It can be an uncommon cause of pneumothorax and can present as a bloody pleural effusion. Deciduosis can also occur in areas of pleural endometriosis and occasionally may be confused with deciduoid mesothelioma.[122-128]

Other Uncommon Causes of Pleural Effusion

As reported by Jarratt and Sahn,[129] pleural effusions have been seen in hospitalized patients receiving long-term hemodialysis. Although heart failure was the most

common cause, other diseases were responsible for most of the effusions, and a unilateral effusion suggested a diagnosis other than heart failure, most commonly parapneumonic effusion or atelectasis, which warranted prompt thoracentesis.

Pleurodesis

Patients with recurrent pneumothorax or uncontrolled recurrent pleural effusions may require iatrogenic symphysis of the parietal and visceral pleura in order to maintain lung inflation and prevent recurrent episodes.[130] Relatively common indications include spontaneous idiopathic pneumothorax in young adults, pneumothoraces in patients with cystic fibrosis or bullous emphysema, and recurrent malignant pleural effusions. Techniques for inducing pleural adhesions include mechanical pleural abrasion, chemical pleurodesis with sclerosing agents like tetracycline derivatives or bleomycin, or instillation of talc into the pleural space.[131–133] The fibroinflammatory response following chemical pleurodesis is a nonspecific organizing fibrinous pleuritis leading to pleural fibrosis.[134,135] Experimentally, a neutrophil-rich exudative pleural effusion is followed by an increase in mononuclear cells.[135] The mechanism of tetracycline pleurodesis includes production of a fibroblast growth factor by stimulated mesothelial cells.[136]

Talc, instilled into the pleural space by poudrage or slurry, is the most frequent agent currently used for pleurodesis.[130] Mixed talc, with a mean particle size of $15\,\mu m$, is typically utilized.[137] Talc induces a histiocytic and granulomatous foreign body reaction followed by pleural fibrosis, surrounding brightly birefringent talc particles (Fig. 30.21). Occasionally the talc accumulates in the dependent regions of the pleural space producing macroscopic friable chalky yellow-tan pleural deposits (Fig. 30.21C). Intrapleural talc instillation has been associated with hypoxemia and rare instances of acute respiratory
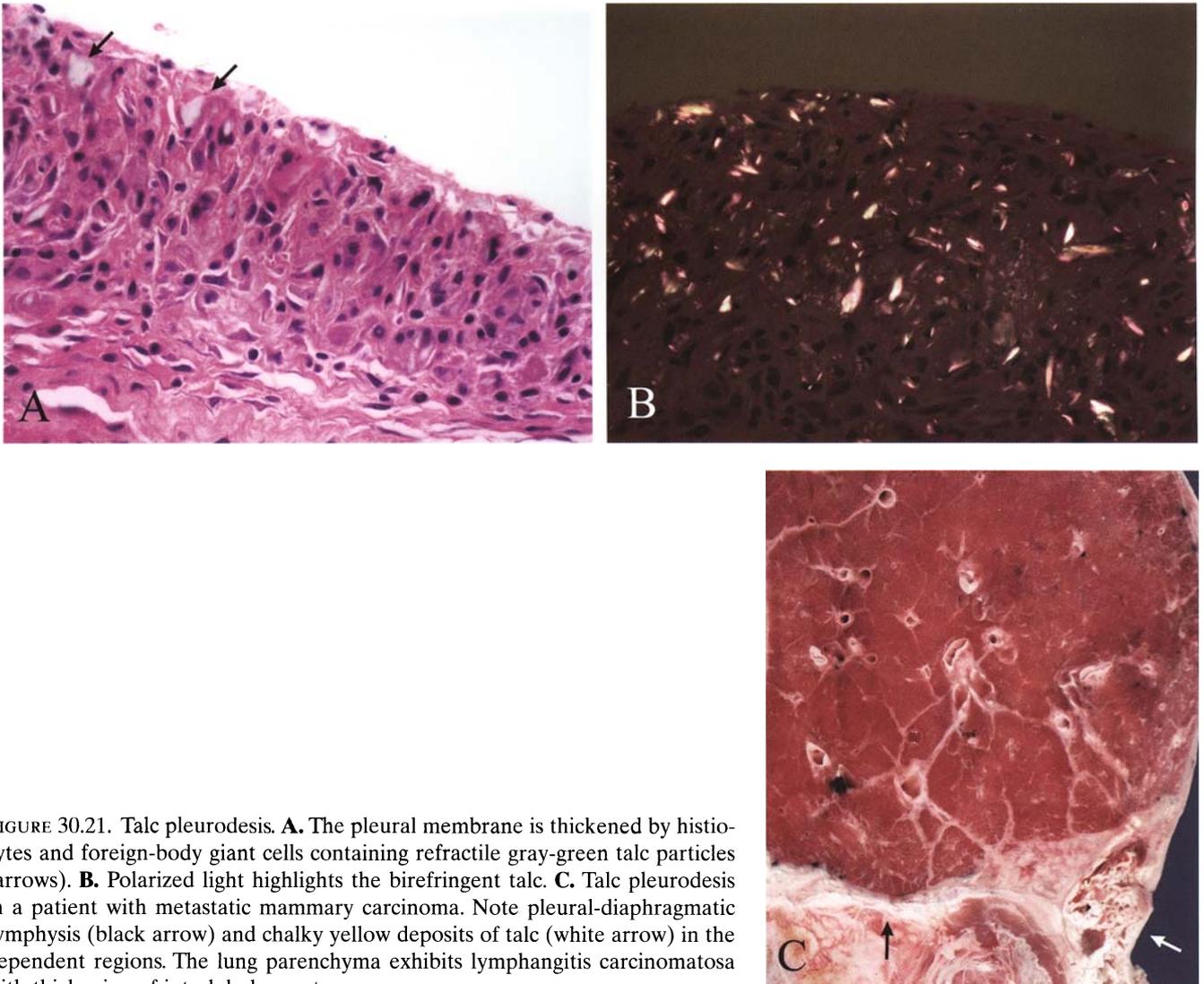
FIGURE 30.21. Talc pleurodesis. **A.** The pleural membrane is thickened by histiocytes and foreign-body giant cells containing refractile gray-green talc particles (arrows). **B.** Polarized light highlights the birefringent talc. **C.** Talc pleurodesis in a patient with metastatic mammary carcinoma. Note pleural-diaphragmatic symphysis (black arrow) and chalky yellow deposits of talc (white arrow) in the dependent regions. The lung parenchyma exhibits lymphangitis carcinomatosa with thickening of interlobular septa.

distress syndrome (ARDS), including fatal ARDS.[137–141] This systemic response has been especially associated with small (≤10 μm) particles which probably gain access to the systemic circulation.[137,142]

References

1. Antony VB, Sahn SA, Mossman B, Gail DB, Kalica A. Pleural cell biology in health and disease. Am Rev Respir Dis 1992;145:1236–1239.
2. Gaudio E, Rendina E, Pannarale L, Ricci C, Marinozzi G. Surface morphology of the human pleura: a scanning electron microscopic study. Chest 1988;92:149–153.
3. Sahn SA. The pleura. Am Rev Respir Dis 1988;138:184–234.
4. Minot C. The mesoderm and the coelom of vertebrates. Am Nat 1890;24:877–898.
5. Wang NS. The preformed stomas connecting the pleural cavity and lymphatics in the parietal pleura. Am Rev Respir Dis 1975;111:12–20.
6. Leak LV, Rahil L. Permeability of the diaphragmatic mesothelium: The ultrastructural basis for "stomata." Am J Anat 1978;151:557–594.
7. Courtice FC, Simmonds SJ. Physiological significance of lymph drainage of the serous cavities and lungs. Physiol Rev 1954;34:419–448.
8. Sahn SA. The differential diagnosis of pleural effusions. West J Med 1982;137:99–108.
9. Pistolesi M, Miniati M, Giontini C. Pleural liquid and solute exchange. Am Rev Respir Dis 1989;140:825–847.
10. Sahn SA, Heffner JE. Pleural fluid analysis. In: Light RW, Lee CY, eds. Textbook of pleural diseases. London: Arnold 2003:191–209.
11. Light RW. Clinical manifestations and useful tests. Pleural diseases, 2nd ed. Philadelphia: Lea & Febiger, 1990:39–73.
12. Patel T, Bansal R, Trivedi P, et al. Subcutaneous metastases of sarcomatoid mesothelioma with its differential diagnosis on fine needle aspiration—a case report. Indian J Pathol Microbiol 2005;48:482–484.
13. Cimbaluk D, Kasuganti D, Kluskens L, et al. Malignant biphasic pleural mesothelioma metastatic to the liver diagnosed by fine needle aspiration. Diagn Cytopathol 2006;34:33–36.
14. Gong Y, Ren R, Ordonez NG, et al. Fine needle aspiration cytology of well-differentiated papillary mesothelioma: a case report. Acta Cytol 2005;49:537–542.
15. Turbat-Herrera EA, Herrera GA. Electron microscopy renders the diagnostic capabilities of cytopathology more precise: an approach to everyday practice. Ultrastruct Pathol 2005;29:475–482.
16. Tafazzoli A, Raza A, Martin SE. Primary diagnosis of malignant mesothelioma by fine-needle aspiration of a supraclavicular lymph node. Diagn Cytopathol 2005;33:122–125.
17. Nguyen GK, Akin MR, Villanueva RR, Slatnik J. Cytopathology of malignant mesothelioma of the pleura in fine-needle aspiration biopsy. Diagn Cytopathol 1999;21:253–259.
18. Craig FE, Fishback NF, Schwartz JG, Powers CN. Occult metastatic mesothelioma—diagnosis by fine-needle aspiration. A case report. Am J Clin Pathol 1992;97:493–497.
19. Tao LC. Aspiration biopsy cytology of mesothelioma. Diagn Cytopathol 1989;5:14–21.
20. Wills EJ, Carr S, Philips J. Electron microscopy in the diagnosis of percutaneous fine needle aspiration specimens. Ultrastruct Pathol 1987;11:361–387.
21. Reuter K, Raptopoulos V, Reale F, et al. Diagnosis of peritoneal mesothelioma: computed tomography, sonography, and fine-needle aspiration biopsy. Am J Roentgenol 1983;140:1189–1194.
22. Antony VB. Immunologic mechanisms in pleural disease. Eur Respir J 2003;21:539–544.
23. Kroegel C, Antony VB. Immunobiology of pleural inflammation: potential implications for pathogenesis, diagnosis and therapy. Eur Respir J 1997;10:2411–2418.
24. Chapman SJ, Davies RJO. Pleural effusions. Respir Med 2004;4:207–210.
25. Hussey SM, Wians FH Jr. Shortness of breath in a 74-year-old woman. Case study. Lab Med 2004;35:408–412.
26. Badrinath JJ, Basran GS, Sahn SA. Do we need all three criteria for the diagnostic separation of pleural fluid into transudates and exudates? An appraisal of the traditional criteria. Med Sci Monit 2003;9:CR474–476.
27. Heffner JE, Sahn SA, Brown LK. Multilevel likelihood ratios for identifying exudative pleural effusions. Chest 2002;121:1916–1920.
28. Guleria R, Agarwal SR, Sinha S, et al. Role of pleural fluid cholesterol in differentiating transudative from exudative pleural effusion. Natl Med J India 2003;16:64–69.
29. Yilmaz-Turay U, Yildirim Z, Turkoz Y, et al. Use of pleural fluid C-reactive protein in diagnosis of pleural effusions. Respir Med 2000;94:432–435.
30. Chierakul N, Kanitsap A, Chaiprasert A, Viriyataveekul R. A simple C-reactive protein measurement for the differentiation between tuberculous and malignant pleural effusion. Respirology 2004;9:66–69.
31. Ryu JS, Lee HJ, Cho JH, Han HS, Lee HL. The implication of elevated carcinoembryonic antigen level in pleural fluid of patients with non-malignant pleural effusion. Respirology 2003;8:487–491.
32. Judson MA, Handy JR, Sahn SA. Pleural effusions following lung transplantation. Time course, characteristics, and clinical implications. Chest 1996;109:1190–1194.
33. Judson MA, Handy JR, Sahn SA. Pleural effusion from acute lung rejection. Chest 1997;111:1128–1130.
34. Areno JP, McCartney JP, Eggerstedt J, Grafton W, George RB. Persistent pleural effusions following coronary bypass surgery. Chest 1998;114:311–314.
35. Bourantas KL, Tsiara S, Panteli A, Milionis C, Christou L. Pleural effusion in chronic myelomonocytic leukemia. Acta Haematol 1998;99:34–37.
36. Diot E, Lavigne C, Renjard L, et al. Wegener's disease mimicking acute infectious pleurisy. Rev Pneumol Clin 2000;56:265–268.
37. Uchikov AP, Shipkov HD, Markova DI. Pleural effusions in acute pancreatitis. Folia Med 2000;42:34–36.

38. Goldsby R, Pulsipher M, Adams R, et al. Unexpected pleural effusions in 3 pediatric patients treated with STI-571. J Pediatr Hematol Oncol 2002;24:694–695.

39. Ray K, Rattan S, Yohannes T. Urinothorax: unexpected cause of a pleural effusion. Mayo Clin Proc 2003;78:1433–1434.

40. Assouad J, Barthes-Fle P, Shaker W, Souilamas R, Riquet M. Recurrent pleural effusion complicating liver cirrhosis. Ann Thorac Surg 2003;75:986–989.

41. Karachalios G, Charalabopoulos A, Charalabopoulos K. Pleural effusion in temporal arteritis. In Vivo 2003;17:151–152.

42. Valstar MH, Terpstra WF, de Jong RS. Pericardial and pleural effusion in giant cell arteritis. Am J Med 2003;114:708–709.

43. Toh CK, Leong SS, Thng CH, Tan EH. Unilateral breast edema in two patients with malignant pleural effusion. Tumori 2004;90:501–503.

44. Breccia M, D'Elia GM, D'Andrea M, Latagliata R, Alimena G. Pleural-pericardic effusion as uncommon complication in CML patients treated with Imatinib. Eur J Haematol 2005;74:89–90.

45. Patel MR, Wehner JH, Soule WC, Meter JJ. Intracranial hypotension and recurrent pleural effusion after snow-boarding injury: a manifestation of cerebrospinal fluid-pleural fistula. Spine J 2005;5:336–338.

46. Berk JL. Pleural effusions in systemic amyloidosis. Curr Opin Pulm Med 2005;11:324–328.

47. Porcel JM, Vives M. Etiology and pleural fluid characteristics of large and massive effusions. Chest 2003;124:978–983.

48. Light RW, Rogers JT, Chent D, Rodriguez M. Large pleural effusions occurring after coronary artery bypass grafting. Ann Intern Med 1999;130:891–896.

49. Lazicka-Frelek M, Pogorzelska J, Bogolowska-Stieblich A, Marcinowska-Suchowierska E. Massive pleural cavity effusion as the manifestation for the pancreatico-pleural fistula. Pol Arch Med Wewn 2002;1079–1083.

50. Kalomenidis I, Light RW. Pathogenesis of the eosinophilic pleural effusions. Curr Opin Pulmon Med 2004;10:289–293.

51. Matthai SM, Kini U. Diagnostic value of eosinophils in pleural effusion: a prospective study of 26 cases. Diagn Cytopathol 2003;28:96–99.

52. Martinez Garcia MA, Cases Viedma E, Perpina Tordera M, Sanchis-Aldas JL. Repeated thoracentesis: an important risk factor for eosinophilic pleural effusion? Respiration 2003;70:82–86.

53. Moufarrege G, Frank E, Carstens DD. Eosinophilic exudative pleural effusion after initiation of tizanidine treatment: a case report. Pain Med 2003;4:85–90.

54. Ashwath ML, Robinson DR, Katner HP. A presumptive case of toxocariasis associated with eosinophilic pleural effusion: case report and literature review. Am J Trop Med Hyg 2004;71:764.

55. Killen JWW, Swift GL, White RJ. Eosinophilic fasciitis with pulmonary and pleural involvement. Postgrad Med J 2000;76:36–37.

56. Mattison LE, Coppage L, Alderman DF, Herlong JO, Sahn SA. Pleural effusions in the medical ICU: Prevalence, causes and clinical implications. Chest 1997;111:1018–1023.

57. Efrati O, Barak A. Pleural effusions in the pediatric population. Pediatr Rev 2002;23:417–426.

58. Cohen M, Sahn SA. Resolution of pleural effusions. Chest 2001;119:1547–1562.

59. Yokoi T, Mark EJ. Atypical mesothelial hyperplasia associated with bronchogenic carcinoma. Hum Pathol 1991;22:695–699.

60. Bolen JW, Hammar SP, McNutt MA. Reactive and neoplastic serosal tissue. A light microscopic, ultrastructural and immunocytochemical study. Am J Surg Pathol 1986;10:34–47.

61. Buchanan DR, Johnston IP, Ken IH, et al. Cryptogenic bilateral fibrosing pleuritis. Br J Dis Chest 1988;82:186–193.

62. Askin FB, McCann BC, Kuhn C. Reactive eosinophilic pleuritis: a lesion to be distinguished from pulmonary eosinophilic granuloma. Arch Pathol Lab Med 1977;101:187–191.

63. Venekamp LN, Velkeniers B, Noppen M. Does "idiopathic pleuritis" exist? Natural history of non-specific pleuritis diagnosed after thoracoscopy. Respiration 2005;72:74–78.

64. Renner RR, Markarian B, Pernice NJ, Heitzman ER. The apical cap. Radiology 1974;110:569–573.

65. McLoud TC, Isler RJ, Novelline RA et al. The apical cap. Am J Roentgenol 1981;137:299–306.

66. Butler C 2nd, Kleinerman J. The pulmonary apical cap. Am J Pathol 1970;60:205–216.

67. Im JG, Webb WR, Han MC, Park JH. Apical opacity associated with pulmonary tuberculosis: high-resolution CT findings. Radiology 1991;78:727–731.

68. Yousem SA. Pulmonary apical cap: a distinctive but poorly recognized lesion in pulmonary surgical pathology. Am J Surg Pathol 2001;25:679–683.

69. Antony VB, Mohammed KA. Pathophysiology of pleural space infections. Sem Respir Infect 1999;14:9–17.

70. Strange C, Sahn SA. The definitions and epidemiology of pleural space infection. Sem Respir Infect 1999;14:3–8.

71. Chin LK, Lim TK. Treatment of complicated parapneumonic effusions and pleural empyema: a four-year prospective study. Singapore Med J 1996;37:631–635.

72. Ferguson AD, Prescott RJ, Selkon JB, et al. The clinical course and management of thoracic empyema. Q J Med 1996;89:285–289.

73. Light RW, Girard WM, Jenkinson SG, George RB. Parapneumonic effusions. Am J Med 1980;985–986.

74. Taryle DA, Potts DE, Sahn SA. The incidence and clinical correlates of parapneumonic effusions in pneumococcal pneumonia. Chest 1978;74:170–173.

75. Bartlett JG, Gorbach SL, Thadepalli H, Finegold SM. Bacteriology of empyema. Lancet 1974;1:338–340.

76. Varkey B, Rose HD, Kutty CPK, Politis J. Empyema thoracis during a ten-year period. Arch Intern Med 1981;141:1771–1776.

77. United States Department of Health, Education, and Welfare, Public Health Service. Center for Disease Control. Extrapulmonary tuberculosis in the United States. DHEW Publication (CDC) 78-8360. Washington, DC: DHEW, 1978.

78. Stead WW, Eichenholz A, Stauss HK. Operative and pathologic findings in twenty-four patients with syndrome of idiopathic pleurisy with effusion, presumably tuberculosis. Am Rev Tuberc 1955;71:473–502.

79. Abrams WB, Small MJ. Current concepts of tuberculous pleurisy with effusion as derived from pleural biopsy studies. Scand J Respir Dis 1960;38:60–65.

80. Green WR, Bouchette D. Pleural mucormycosis (zygomycosis). Arch Pathol Lab Med 1986;110:441–442.

81. Mariuz P, Raviglione MC, Gould IA, Molten MP. Pleural pneumocystis carinii infection. Chest 1991;99:774–776.

82. Soubani AO, Michelson MK, Karnik A. Pleural fluid findings in patients with the acquired immunodeficiency syndrome: correlation with concomitant pulmonary disease. South Med J 1999;92:400–403.

83. Trejo O, Giron JA, Perez-Guzman E, et al. Pleural effusion in patients infected with the human immunodeficiency virus. Eur J Clin Microbiol Infect Dis 1997;16:807–815.

84. Utine GE, Ozcelik U, Yalcin E, et al. Childhood parapneumonic effusions: Biochemical and inflammatory markers. Chest 2005;128:1436–1441.

85. Bryant RE, Salmon CJ. Pleural empyema. Clin Infect Dis 1996;22:747–762.

86. Vikram HR, Quagliarello VJ. Diagnosis and management of empyema. Curr Clin Top Infect Dis 2002;22:196–213.

87. LeMense GP, Strange C, Sahn SA. Empyema thoracis: Therapeutic management and outcome. Chest 1995;107:1532–1537.

88. Sahn SA, Iseman MD. Tuberculous empyema. Sem Respir Infec 1999;14:82–87.

89. Strong DH, Westcott JY, Biller JA, et al. Eosinophilic "empyema" associated with crack cocaine use. Thorax 2003;58:823–824.

90. Antony VB. Drug-induced pleural disease. Clin Chest Med 1998;19:331–340.

91. Morelock SY, Sahn SA. Drugs and the pleura. Chest 1999;116:212–221.

92. Huggins JT, Sahn SA. Drug-induced pleural disease. Clin Chest Med 2004;25:141–153.

93. Physicians' Desk Reference. Montvale, NJ: Thompson, 2006.

94. Rubin EH. Pulmonary lesions in "rheumatoid disease" with remarks on diffuse interstitial fibrosis. Am J Med 1955;19:569–582.

95. Sievers K, Aho K, Hurri L, Perttala Y. Studies of rheumatoid pulmonary disease: A comparison of roentgenographic findings among patients with high rheumatoid factor titers and with completely negative reactions. Acta Tuberc Scand 1964;45:21–34.

96. Walker WC, Wright V. Pulmonary lesions and rheumatoid arthritis. Medicine (Baltimore) 1968;47:501–519.

97. Horler AR, Thompson M. The pleural and pulmonary complications of rheumatoid arthritis. Ann Intern Med 1959;51:1179–1203.

98. Wilen SB, Rabinowitz JG, Ulrich S, Lyons HA. Pleural involvement in sarcoidosis. Am J Med 1974;57:200–209.

99. Mark EJ, Matsubara O, Jan-Liu NS, Fineberg R. The pulmonary biopsy in the early diagnosis of Wegener's (pathergic) granulomatosis: a study based on 35 open lung biopsies. Hum Pathol 1988;19:1065–1071.

100. Gonzalez L, VanOrdstrand HS. Wegener's granulomatosis. Radiology 1973;107:295–300.

101. Liem K, ten Veen JH, Lie KI, Feltkamp TEW, Durrer D. Incidence and significance of heart muscle antibodies in patients with acute myocardial infarction and unstable angina. Acta Med Scand 1979;206:473–475.

102. Toole JC, Silverman ME. Pericarditis of acute myocardial infarction. Chest 1975;67:647–653.

103. Engle MA, McCabe JC, Ebert PA, Zabriskie J. The postcardiotomy syndrome and anti-heart antibodies. Circulation 1974;49:401–406.

104. Van Der Geld H. Anti-heart antibodies in the postpericardiotomy and post-myocardial infarction syndromes. Lancet 1964;2:617–621.

105. Kim S, Sahn SA. Postcardiac injury syndrome: an immunologic pleural fluid analysis. Chest 1996;109:570–572.

106. Bendjelid K, Pugin J. Is Dressler syndrome dead? Chest 2004;126:1680–1682.

107. Huggins JT, Sahn SA. Causes and management of pleural fibrosis. Respirology 2004;9:441–447.

108. Chinnock BF. Chylothorax: case report and review of the literature. J Emerg Med 2003;24:259–262.

109. Staats BA, Ellefson RD, Budahn LL, et al. The lipoprotein profile of chylous and nonchylous pleural effusion. Mayo Clin Proc 1980;55:700–704.

110. Kayacan O, Karnak D, Beder S, Koksal D. Left pleural effusion in a woman with coronary artery by-pass grafting. Postgrad Med J 2004;80:368.

111. Saumoy M, Miron M, Oltra C, Vidal F, Richart C. Tuberculous chylothorax: case report and review of the literature. An Med Interna 2005;22:238–240.

112. Ryu JH, Doerr CH, Fisher SD, Olson EJ, Sahn SA. Chylothorax in lymphangioleiomyomatosis. Chest 2003;123:623–627.

113. Lichter I, Gwynne JF. Spontaneous pneumothorax in young subjects. A clinical and pathological study. Thorax 1971;26:409–417.

114. Sahn SA, Heffner JE. Spontaneous pneumothorax. N Engl J Med 2000;342:868–873.

115. Tomashefski JF Jr, Dahms B, Bruce M. Pleura in pneumothorax—comparison of patients with cystic fibrosis and "idiopathic" spontaneous pneumothorax. Arch Pathol Lab Med 1985;109:910–916.

116. Cyr PV, Vincic L, Kay M. Pulmonary vasculopathy in idiopathic spontaneous pneumothorax in young subjects. Arch Pathol Lab Med 2000;124:717–720.

117. Luna E, Tomashefski JF Jr, Brown D, et al. Reactive eosinophilic pulmonary vascular infiltration in patients with spontaneous pneumothorax. Am J Surg Pathol 1994;18:195–199.

118. Lesur O, Delorme N, Fromaget JM, et al. Computed tomography and the etiologic assessment of idiopathic spontaneous pneumothorax. Chest 1990;98:341–347.

119. Bense L, Lewander R, Eklund G, et al. Nonsmoking, non-alpha 1–antitrypsin deficiency-induced emphysema in nonsmokers with healed spontaneous pneumothorax, identified by computed tomography of lung. Chest 1993;103:433–438.

120. Fraser RS, Müller NL, Colman N, Paré PD. Pneumothorax. In: Fraser RS, Paré PD, eds. Diagnosis of diseases of the

chest. 4th ed. Philadelphia: WB Saunders, 1999:2781–2794.

121. Butnor KJ, Guinee DG Jr. Pleuropulmonary pathology of Birt-Hogg-Dubé Syndrome. Am J Surg Pathol 2006;30:395–399.

122. Joseph J, Sahn SA. Thoracic endometriosis syndrome: new observations from an analysis of 110 cases. Am J Med 1996;100:164–170.

123. Ziedalski TM, Sankaranarayanan V, Chitkara RK. Thoracic endometriosis: a case report and literature review. J Thorac Cardiovasc Surg 2004;127:1513–1514.

124. Alifano M, Roth T, Broet SC, et al. Catamenial pneumothorax: a prospective study. Chest 2003;124:1004–1008.

125. Sakamoto K, Ohmori T, Takei H. Catamenial pneumothorax caused by endometriosis in the visceral pleura. Ann Thorac Surg 2003;76:290–291.

126. Byanyima RK. Endometriosis presenting as bloody pleural effusion and ascites—report of a case and review of the literature. Arch Gynecol Obstet 2000;264:39–41.

127. Honore GM. Extrapelvic endometriosis. Clin Obstet Gynecol 1999;42:699–711.

128. Flieder DB, Moran CA, Travis WD, Koss MN, Mark EJ. Pleuro-pulmonary endometriosis and pulmonary ectopic deciduosis: a clinicopathologic and immunohistochemical study of 10 cases with emphasis on diagnostic pitfalls. Hum Pathol 1998;29:1495–1503.

129. Jarratt MJ, Sahn SA. Pleural effusions in hospitalized patients receiving long-term hemodialysis. Chest 1995;108:470–474.

130. Rodriquez-Panadero F, Antony VB. State of the art: pleurodesis. Eur Respir J 1997;10:1648–1654.

131. Walker-Renard PB, Vaughan LM, Sahn SA. Chemical pleurodesis for malignant pleural effusions. Ann Intern Med 1994;120:56–64.

132. Wallach HW. Intrapleural tetracycline for malignant pleural effusions. Chest 1975;68:510–512.

133. Kennedy L, Sahn SA. Talc pleurodesis for the treatment of pneumothorax and pleural effusion. Chest 1994;106:1215–1222.

134. Sassoon CSH, Light RW, Vargas FS, et al. Temporal evolution of pleural fibrosis induced by intrapleural minocycline injection. Am J Respir Crit Care Med 1995;151:791–794.

135. Sahn SA, Potts DE. The effect of tetracycline on rabbit pleura. Am Rev Respir Dis 1978;117:493–498.

136. Antony VB, Rothfuss KJ, Godbey SW, et al. Mechanism of tetracycline-hydrochloride-induced pleurodesis. Tetracycline-hydrochloride-stimulated mesothelial cells produce a growth-factor-like activity for fibroblasts. Am Rev Respir Dis 1992;146:1009–1013.

137. Maskell NA, Lee YCG, Gleeson FV, et al. Randomized trials describing lung inflammation after pleurodesis with talc of varying particle size. Am J Respir Crit Care Med 2004;170:377–382.

138. Rinaldo JE, Owens GR, Rogers RM. Adult respiratory distress syndrome following intrapleural instillation of talc. J Thorac Cardiovasc Surg 1983;85:523–526.

139. Bouchama A, Chastre J, Gaudichet A, et al. Acute pneumonitis with bilateral pleural effusion after talc pleurodesis. Chest 1984;86:795–797.

140. Rehse DH, Aye RW, Florence MG. Respiratory failure following talc pleurodesis. Am J Surg 1999;177:437–440.

141. Campos JR, Werebe EC, Vargas FS, et al. Respiratory failure due to insufflated talc. Lancet 1997;349:251–252.

142. Sahn SA, Light RW. Pro/Con Editorials. Talc should/should not be used for pleurodesis. Am J Respir Crit Care Med 2000;162:2023–2026.