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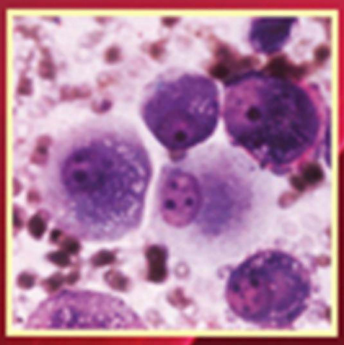
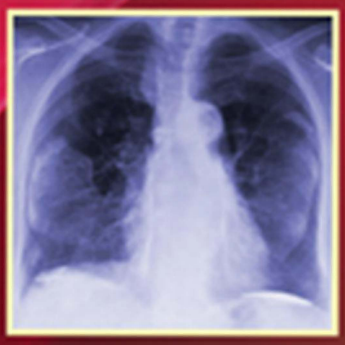
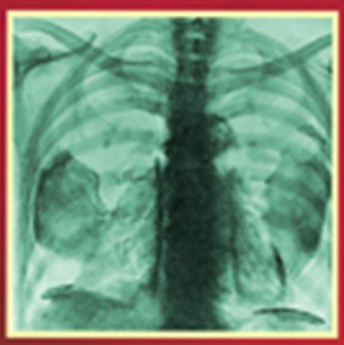
SIXTH EDITION

PLEURAL DISEASES

Richard W. Light

Wolters Kluwer Health | Lippincott Williams & Wilkins

PLEURAL DISEASES

SIXTH EDITION

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This book is dedicated to my wife and best friend, Judi Light.

Preface

The first five editions of Pleural Diseases were well received. Since the fifth edition was published in 2007, there has been a rapid advancement in the knowledge concerning pleural diseases. Accordingly, the publishers have requested that I prepare a sixth edition.

Some of the important advances in the knowledge about pleural disease that has become available since 2007 include the following. It has become apparent that right heart failure such as occurs with pulmonary hypertension at times leads to pleural effusions. The use of N terminal-probrain natriuretic factor in the diagnosis of pleural effusions due to heart failure has assumed a more prominent role. There have been many articles on the use of biomarkers for the diagnosis of mesothelioma. The recommendations for the surgical treatment of mesothelioma have been revised. A new definition for the post cardiac injury syndrome has been proposed. It has been demonstrated that the administration of colchicine will diminish the incidence of the post cardiac injury syndrome and the incidence of pleural effusion after coronary artery bypass surgery. The combination of DNase and tissue plasminogen activator has been shown to significantly improve the rate of improvement of complicated parapneumonic effusions compared to either agent alone or to placebo. The use of the indwelling catheter for the management of malignant pleural effusions has become much more common. Several articles have demonstrated that small chest tubes (9-12 F) are as effective as larger chest tubes (>20 F) in most patients who require chest tubes.

However, if the small chest tubes are used for the treatment of parapneumonic effusions, they should be irrigated every six hours with saline. The importance of adequate training and the use of ultrasound when thoracenteses are performed has been demonstrated. The blood patch technique has been shown to be an inexpensive, simple and effective technique for the management of prolonged airleaks associated with pneumothorax or after thoracic surgery. The pleural effusions that occur commonly when the anti-leukemic drug dasatinib is administered are discussed. Image guided needle biopsy of the pleural (CT scan or ultrasound) is more efficient than blind needle biopsy. Thoracentesis in patients on mechanical ventilation improves oxygenation and decreases the time on the ventilator. Thoracoliths and pleuroparenchymal fibroelastosis are described for the first time.

Details concerning all the above advances are included in this new edition. Overall, about 10-15% new references have been added.

It is my hope that the sixth edition of this book will continue to provide a practical, updated reference book for physicians who take care of patients with pleural disease.

Richard W. Light, MD
Nashville, Tennessee

Preface to the First Edition

Approximately 1 million patients develop a pleural effusion each year. Pleural effusions may occur with many different infections or as a complication of pulmonary disease. Additionally, pleural effusions frequently complicate malignant disease, heart disease, liver disease, gastrointestinal disease, kidney disease, and collagen vascular disease. Yet there are no recent books on pleural disease to guide the practicing physician in determining the origin of a pleural effusion or in managing a patient with pleural disease. Moreover, diseases of the pleura receive only superficial treatment in books on pulmonary disease or internal medicine.

This book is intended primarily as a reference book for physicians who take care of patients with pleural diseases. Recent advances in the knowledge of pleural disease make publication of this volume timely. In this one volume, the practicing physician will have a comprehensive discussion of all aspects of pleural disease.

The first three chapters discuss the anatomy, physiology, and radiology of the pleura. The next chapter describes the clinical manifestations of pleural disease and discusses in depth the various diagnostic tests that might be used to establish the etiology of a pleural effusion. In Chapter 5, I present my recommended approach to the patient with an undiagnosed pleural effusion. The following 13 chapters contain discussions of the various disease states that can be associated with a pleural effusion. For each disease, the pathophysiology, clinical manifestations, diagnosis, and management of pleural effusion are outlined. In Chapters 19 through 21, pneumothorax, hemothorax, and chylothorax are presented, respectively. Pleural thickening not associated with pleural fluid is covered in Chapter 22. The next two chapters are devoted to those procedures used most often in managing patients with pleural disease, namely, diagnostic and therapeutic thoracentesis, pleural biopsy, and tube thoracostomy. The final chapter includes a description of the various drainage systems used with chest tubes.

It is my hope that publication of this book will result in better and more cost-effective management of patients with pleural disease.

Richard W. Light, MD

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There are several people that I would like to acknowledge who helped with the preparation of this edition. The people that I would like to acknowledge at Wolters Kluwer Health – Lippincott Williams & Wilkins include Sonya Seigafuse, Senior Acquisitions Editor, Kerry B. Barrett and Kristina Oberle, Senior Product Managers, and Jeff Gunning, Developmental Editor. Lastly, I would like to acknowledge Subrahmanyam Katakam of S4Carlisle Publishing Services, who did a fantastic job preparing the page proofs.

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chapter 1

Anatomy of the Pleura

The pleura is the serous membrane that covers the lung parenchyma, the mediastinum, the diaphragm, and the rib cage. This structure is divided into the visceral pleura and the parietal pleura. The visceral pleura covers the lung parenchyma, not only at its points of contact with the chest wall, diaphragm, and mediastinum but also in the interlobar fissures. The parietal pleura lines the inside of the thoracic cavities. In accordance with the intrathoracic surfaces that it lines, it is subdivided into the costal, mediastinal, and diaphragmatic parietal pleura. The visceral and the parietal pleura meet at the lung root. At the pulmonary hilus, the mediastinal pleura is swept laterally onto the root of the lung. Posterior to the lung root, the pleura is carried downward as a thin double fold called the *pulmonary ligament*.

A film of fluid (pleural fluid) is normally present between the parietal and the visceral pleura. This thin layer of fluid acts as a lubricant and allows the visceral pleura covering the lung to slide along the parietal pleura lining the thoracic cavity during respiratory movements. The space, or potential space, between the two layers of pleura is designated as the *pleural space*. The mediastinum completely separates the right pleural space from the left in humans. As previously mentioned, only a thin layer of fluid is normally present in this space, so it is a potential space rather than an actual one. Many diseases are associated with increased amounts of pleural fluid, however, and a large segment of this book is directed toward an understanding of these diseases.

EMBRYOLOGY OF THE PLEURA AND PLEURAL SPACE

The body cavity in the embryo, the coelomic cavity, is a U-shaped system with the thick bend cephalad. The cephalad portion becomes the pericardium and communicates bilaterally with the pleural canals, which, in turn, communicate with the peritoneal canals. With development, the coelomic cavity becomes divided into the pericardium, the pleural cavities, and the peritoneal cavity through the development of three sets of partitions: (a) the septum transversum, which serves as an early, partial diaphragm; (b) the pleuropericardial membranes, which divide the pericardial and pleural cavities; and (c) the pleuroperitoneal membranes, which unite with the septum transversum to complete the partition between each pleural cavity and the peritoneal cavity. This newly formed pleural cavity is fully lined by a mesothelial membrane, the pleura (1).

When the primordial bronchial buds first appear, they and the trachea lie in a median mass of mesenchyme, cranial and dorsal to the peritoneal cavity. This mass of mesenchymal tissue is the future mediastinum, and it separates the two pleural cavities. In humans, no communication normally exists between the two pleural cavities. As the growing primordial lung buds bulge into the right and left pleural cavities, they carry with them a covering of the lining mesothelium, which becomes the visceral pleura. As the separate lobes evolve, they retain their mesothelial covering. This covering becomes the visceral pleura in the fissures. The lining mesothelium of the pleural cavity becomes the parietal pleura (2).

HISTOLOGY OF THE PLEURA

The parietal pleura over the ribs and intercostal spaces is composed of loose, irregular connective tissue covered by a single layer of mesothelial cells. Within the pleura are blood vessels, mainly capillaries, and lymphatic lacunas. The lacunas are specialized initial

lymphatics shaped like flat cisterns and are located over the intercostal spaces, at least in sheep (3). The mean thickness of the parietal pleura in sheep is 20 to 25 μm, whereas the distance from the microvessels to the pleural space is 10 to 12 μm. Deeper to the parietal pleura is the endothoracic fascia. This continuous band of dense irregular connective tissue, composed mainly of collagen and elastin, covers the ribs and intercostal spaces and varies in thickness from 75 to 150 μm (3).

The anatomy of the visceral pleura differs markedly from that of the parietal pleura and also varies among species, primarily in its thickness. Dogs, cats, and monkeys have a thin visceral pleura, whereas humans, sheep, cows, pigs, and horses have a thick visceral pleura (4). The distinction between lungs with a thick or thin visceral pleura is important physiologically because the blood supply is dependent on the thickness of the pleura. In animals with a thick visceral pleura, the predominant source of blood is the systemic circulation; in those with a thin pleura, the predominant source of blood is the pulmonary circulation (4).

Histologically, a thick visceral pleura is composed of two layers: the mesothelium and connective tissue. Blood, lymph vessels and nerves are located in the connective tissue. Animals with a thick visceral pleura have a layer of dense connective tissue of varying thickness interposed between the mesothelium and the blood vessels (4). In sheep, the visceral pleura ranges in thickness from 25 to 83 μm (as compared with 10 to 25 μm for the parietal pleura) and the distance from the microvessels to the pleural space ranges from 18 to 56 μm (as compared with 10 to 12 μm for the parietal space) (3).

The connective tissue layer in the visceral pleura has two important functions: (a) it contributes to the elastic recoil of the lung, which is important in expelling air from the lung, and (b) it restricts the volume to which the lung can be inflated, thereby protecting it (5). In the visceral pleura, fibers of the elastic and collagenous systems are clearly interdependent elements. Collagenous fibers are interwoven in a pleated structure that closely resembles the osiers of a wicker basket, suggesting that collagen fibers allow the lung volume to increase up to a point of maximal stretching of the system (5). The pleural contribution to the elastic recoil pressure of the lung originates from the elastic network, which returns to its resting position when inspiratory pressures are negligible (5).

Both the visceral and the parietal pleura are lined with a single layer of flat mesothelial cells. These mesothelial cells range in size from 6 to 12 μm in diameter (6). With scanning electron microscopy (7), the pleural surface is found to be either flattened or bumpy (Fig. 1.1). The bumpy areas include most of the visceral pleura and portions of the parietal pleura, including the subcostal regions and the pleural recesses. These areas appear to result from a lack of rigidity of the underlying structures (6).

Scanning electron microscopy also demonstrates that microvilli are present diffusely over the entire pleural surface (Fig. 1.1), but the distribution of the microvilli is irregular. The density of the microvilli

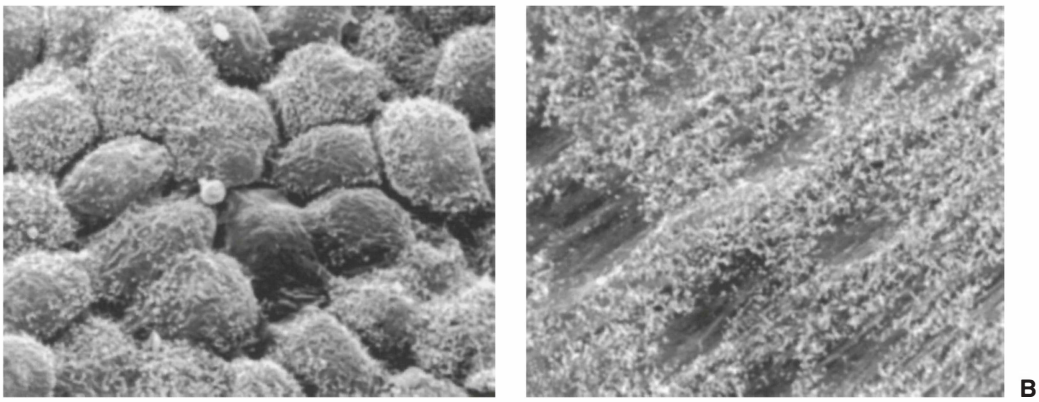

FIGURE 1.1 ■ Scanning electron microscopic studies of the pleura. **A**: Bumpy pleural surface with cellular borders irregularly depressed. Note that the number of microvilli present on each cell is variable (original magnification: 1,300×). **B**: Flattened pleural surface with indistinct cell boundaries and sparse microvilli (original magnification: 1,250×). *(From Wang NS. The regional difference of pleural mesothelial cells in rabbits.* Am Rev Respir Dis. *1974;110:623–633, with permission.)*

ranges from a few to more than 600/100 μm^2, with a mean of approximately 300 (1). The microvilli are most numerous on the inferior parts of the visceral pleura and the anterior and inferior mediastinum on the parietal pleura (1). At corresponding regions in the thoracic cavity, more microvilli are present on the visceral pleura than on the parietal pleura. The microvilli are approximately 0.1 μm in diameter, and their length varies from 0.5 to 3.0 μm (1).

The exact function of these numerous microvilli is yet to be defined. At one time, it was believed that their presence increased the capacity of the visceral pleura to absorb pleural fluid. This is probably incorrect because recent observations have indicated that the visceral pleura plays a limited role in the absorption of pleural fluid. It is now thought that the most important function of the microvilli is to enmesh glycoproteins that are rich in hyaluronic acid, especially in the lower thorax, to lessen the friction between the lung and the chest wall (7). Moreover, as mentioned earlier, a thin rim of fluid normally separates the visceral and parietal pleura. Impingement of the microvilli from one pleural surface into the opposing pleural surface could possibly help maintain this thin rim of fluid (8), but this is controversial (9).

The mesothelial layer is very fragile. At thoracotomy in patients without clinical pleural disease, focal denudation of mesothelial cells is common (10). When the normal layer of mesothelial cells lining the pleura is disrupted, the defect is repaired through mitosis and migration of the mesothelial cells (11). When irritated, they retract but retain continuity with adjacent cells by projections called *cellular bridges*. Mesothelial cells are frequently dislodged from the pleural surfaces and are thereby free in the pleural fluid. When free in the pleural space, the cells become round or oval (11). Their cytoplasm is rich in organelles. From this state, they may be transformed into macrophages capable of phagocytosis and erythrophagocytosis (11). Such transformed cells frequently have vacuoles in their cytoplasm. Not all the macrophages in pleural fluid evolve from mesothelial cells; some definitely evolve from peripheral blood mononuclear cells, and some may evolve from alveolar macrophages (12). An immunologic role has been suggested for the macrophages derived from the mesothelial cells (12).

MESOTHELIAL CELLS

Mesothelial cells form a monolayer of specialized pavement-like cells that line the pleural surfaces. The mesothelial cells are active cells, and they are sensitive and responsive to various stimuli. The mesothelial cells that line the pleural cavity and those that line the other body cavities have no recognizable cytologic difference (13). The cytoplasm always contains a moderate to abundant amount of organelles, including mitochondria, rough and smooth endoplasmic reticulum, polyribosomes, intermediate fibrils, Golgi apparatus, and some glycogen granules, suggesting that the mesothelial cell is a metabolically active cell (14).

The mesothelium is now recognized as a dynamic cellular membrane with many important functions. These include transport and movement of fluid and particulate matter across the pleural surfaces; leukocyte migration in response to inflammatory mediators; synthesis of cytokines, growth factors, and extracellular matrix proteins; release of factors to promote both the deposition and clearance of fibrin; and antigen presentation (15). Mesothelial regeneration involves migration of cells from the wound edge and attachment and incorporation of free-floating mesothelial cells from the pleural fluid onto the denuded pleural surface (16). There is strong evidence that mesothelial cells can convert to myofibroblasts. Yang et al. (17) assessed the effects of incubating peritoneal mesothelial cells with transforming growth factor beta (TGF-β) and reported that the mesothelial cells took on the characteristic myofibroblastic phenotype. We have observed that the incubation of human mesothelial cells with TGF-β results in their morphologic transformation to cells that look like fibroblasts. It has been shown that the intrapleural administration of TGF-β results in an excellent pleurodesis (18) and the morphologic changes induced by TGF-β referred to here may be important in producing the pleurodesis.

In cell culture, mesothelial cells have been shown to produce type I, type II, and type IV collagens, elastin, fibronectin, and laminin, and to express intermediate filaments typical of both epithelial cells and fibroblasts (19). Mesothelial cells also express procoagulant activity because of a tissue factor that binds factor VII at the cell surface (20). Mesothelial cells have also been demonstrated to produce nitric oxide (21) and TGF-β_1 as well as many other cytokines (see Chapter 5) (18).

PLEURAL FLUID

Major considerations in the understanding of pleural fluid are volume, thickness, cellular components, and physicochemical factors.

Volume

Normally, a small amount of pleural fluid is present in the pleural space. The mechanisms responsible for this small amount of residual fluid are discussed in Chapter 2. Noppen et al. (22) have demonstrated that the mean amount of fluid in the right pleural space in normal individuals is 8.4 ± 4.3 mL. Normally, the volume of fluid in the right and left pleural spaces is quite similar (22). Expressed per kilogram of body mass, the total pleural fluid volume in normal, nonsmoking humans is 0.26 ± 0.1 mL/kg (22). The mean total volume of pleural fluid in animal studies has been found to vary from 0.04 to 0.2 mL/kg (23).

Thickness

The small amount of residual pleural fluid appears to be distributed relatively evenly throughout the pleural space. Therefore, the pleural fluid behaves as a continuous system. Albertine et al. studied the thickness of pleural fluid in rabbits by four different methods (9). They found that the average arithmetic mean width of the pleural space was slightly more narrow near the top (18.5 μm) than at the bottom (20.3 μm). Pleural space width in the most dependent recesses, such as the costodiaphragmatic recess, reached 1 to 2 mm. They were unable to find any contacts between the visceral and parietal pleura. Because the microvilli of the mesothelial cells in the visceral and parietal pleura do not interdigitate, the frictional forces between the lungs and chest wall are low (9).

Cells

Noppen et al. (22) analyzed the cellular contents of pleural fluid from patients with normal pleura who were undergoing thoracoscopy for hyperhidrosis. They reported that the mean white blood cell count was 1,716 cells/mm^3 and the mean red cell count was approximately 700 cells/mm^3 (22). These numbers are similar to those recorded in animals (23). Miserocchi and Agostoni reported that pleural fluid in rabbits and dogs contains approximately 2,450 and 2,200 white blood cells/mm^3, respectively (24).

In humans, approximately 75% of the cells in the pleural fluid are macrophages and 25% are lymphocytes, with mesothelial cells, neutrophils, and eosinophils accounting for less than 2% each (22). In rabbits, 32% of the cells are mesothelial cells, whereas 61% are mononuclear cells and 7% are lymphocytes. In dogs, 70% of the cells are mesothelial cells, 28% are mononuclear cells, and 2% are lymphocytes. The variance in the differential count in these series may be related to the stains used and the definition of mesothelial cells and macrophages.

Physicochemical Factors

A small amount of protein is normally present in the pleural fluid. In rabbits, the protein concentration averages 1.33 g/dL, whereas in dogs, it averages 1.06 g/dL (24). The mean oncotic pressure in the pleural fluid is 4.8 cm H_2O in rabbits and 3.2 cm H_2O in dogs (24). Protein electrophoresis demonstrates that the electrophoretic pattern for pleural fluid is similar to that of the corresponding serum, except that low-molecular-weight proteins such as albumin are present in relatively greater quantities in the pleural fluid.

Interestingly, the ionic concentrations in pleural fluid differ significantly from those in serum. The pleural fluid bicarbonate concentration is increased by 20% to 25% relative to that in plasma, whereas the major cation (Na^+) is reduced by 3% to 5%, and the major anion (Cl^-) is reduced by 6% to 9%. The concentration of K^+ and glucose in the pleural fluid and plasma appears to be nearly identical (25). The gradient for bicarbonate persists when the animals are given a carbonic anhydrase inhibitor. When unilateral artificial pleural effusions of distilled water were produced in rats, electrolyte equilibrium between pleural fluid and venous plasma was reached in approximately 40 minutes, but the foregoing gradients persisted. The pleural fluid PCO_2 is approximately the same as the plasma PCO_2. Accordingly, in view of the elevated pleural fluid bicarbonate, the pleural fluid is alkaline with respect to the plasma pH (25). These gradients for electrolytes suggest that an active process is involved in pleural fluid formation. The significance of such an active process remains to be defined.

BLOOD SUPPLY TO THE PLEURA

The parietal pleura receives its blood supply from the systemic capillaries. Small branches of the intercostal arteries supply the costal pleura, whereas the mediastinal pleura is supplied principally by the pericardiacophrenic artery. The diaphragmatic pleura is supplied by the superior phrenic and musculophrenic arteries. The venous drainage of the parietal pleura is primarily by the intercostal veins, which empty into the inferior vena cava or the brachiocephalic trunk. The venous drainage of the diaphragm is either caudally into the inferior vena cava through the inferior phrenic veins, or cranially into the superior vena cava through the superior phrenic veins (14).

The blood supply to the visceral pleura is dependent on whether the animal has a thick or thin pleura. In general, the blood supply to the visceral pleura in animals with a thin pleura originates from the pulmonary circulation, whereas the blood supply in animals with a thick pleura originates from the systemic circulation through the bronchial arteries. Albertine et al. have demonstrated in sheep, an animal with a thick pleura, that the bronchial artery supplies the visceral pleura completely and exclusively (4). Humans have a thick visceral pleura, which is probably why it is also supplied by the bronchial artery, but there is still controversy (26) concerning this statement. All investigators agree that the bronchial artery supplies most of the visceral pleura facing the mediastinum, the pleura covering the interlobular surfaces, and a part of the diaphragmatic surface (14). The blood supply for the remaining portions of the visceral pleura is less understood and is thought by some to be through the pulmonary artery (14). The venous drainage of the visceral pleura is through the pulmonary veins.

PLEURAL LYMPHATICS

The lymphatic plexuses in the costal pleura are mainly confined to the intercostal spaces and are absent or minimal over the ribs (14). The lymphatic vessels of the costal pleura drain ventrally toward nodes along the internal thoracic artery and dorsally toward the internal intercostal lymph nodes near the heads of the ribs. The lymphatic vessels of the mediastinal pleura pass to the tracheobronchial and mediastinal nodes, whereas the lymphatic vessels of the diaphragmatic pleura pass to the parasternal, middle phrenic, and posterior mediastinal nodes. When quantum dots with a diameter of 15 μm are injected into the pleural space of pigs, they are first visualized in the superior mediastinal nodes (27).

The lymphatic vessels in the parietal pleura are in communication with the pleural space by means of stomas that range in diameter from 2 to 6 μm (Fig. 1.2) (28,29). When nitric oxide concentrations are increased, the stomas enlarge (30). In one study, in rabbits the average density of the stomas was 121/mm^3 (29). These stomas have a round or slit-like shape and are found mostly on the mediastinal pleura and on the intercostal surface, especially in the depressed areas just inferior to the ribs in the lower thorax. There are more stomas in areas where the mesothelial cells are cuboidal rather than flat (29). Few stomas are present in other portions of the parietal pleura (3,28). The distribution of stomas is similar to the distribution of particulate matter injected into the pleural space (Chapter 2).

The lymphatic vessels in the parietal pleura have many branches. Some submesothelial branches have dilated lymphatic spaces called lacunas (Fig. 1.2B) (28). Stomas are found only over the lacunas. At the stoma, the mesothelial cells with their microvilli are in continuity with the endothelial cells of the lymphatic

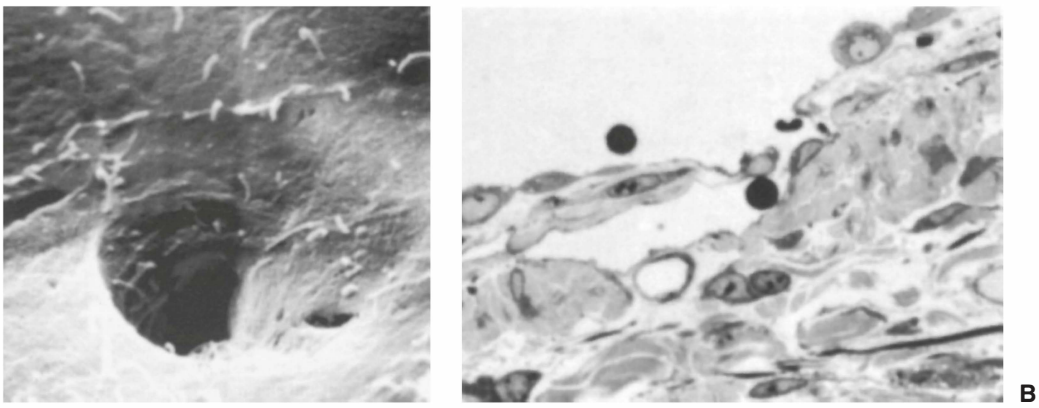

FIGURE 1.2 ■ Lymphatics of the parietal pleura. **A**: Scanning electron microscopic study of the parietal pleura in the rabbit, demonstrating a lymphatic stoma. Microvilli and micropinocytic openings on the mesothelial surface are both much smaller than the stoma (original magnification: 6,500×). **B**: Toluidine blue stain demonstrating a red blood cell at the stoma of a lacuna (original magnification: 1,000×). *(From Wang NS. The preformed stomas connecting the pleural cavity and the lymphatics in the parietal pleura.* Am Rev Respir Dis. *1975;111:12–20, with permission.)*

vessels. When red blood cells or carbon particles are injected into the pleural space, they collect around the stomas and in the lacunas and lymphatic vessels (Fig. 1.2B) (3,28). Therefore, these stomas with their associated lacunas and lymphatic vessels are thought to be the main pathway for the elimination of particulate matter from the pleural space (3,28). Occasionally macrophages can be visible emerging from lymphatic stoma and entering the pleural cavity (29).

The existence of such stomas has been difficult to demonstrate in humans. Gaudio et al. (6) were unable to demonstrate any such stomas in specimens from 30 patients undergoing thoracic surgical procedures. Peng et al. (10) were able to demonstrate stomas in only two of their nine human specimens. However, subsequently Li (31) was able to demonstrate pleural stoma in the diaphragmatic pleura in human specimens. The stoma were usually round or oval in shape and approximately 6.2 μm in diameter. The stoma were not present in the visceral pleura or the parietal pleura on the chest wall. Most stoma were quite deep, forming channels that seemed to connect the pleural cavity with the underlying lymphatic lacunae. Interestingly, in the golden hamster, there are many stoma but none in the diaphragmatic pleura (32).

The visceral pleura is abundantly endowed with lymphatic vessels. These lymphatics form a plexus of intercommunicating vessels that run over the surface of the lung toward the hilum and also penetrate the lung to join the bronchial lymph vessels by passing through the interlobular septa. Although lymph may flow in either direction, all lymph from the visceral pleura eventually reaches the lung root either by penetrating the lung or by flowing on the surface of the lung. The larger lymphatic vessels in the visceral pleura are equipped with one-way valves directing flow toward the hilum of the lung (14). No stomas are seen in the visceral pleura, and the lymphatic vessels of the visceral pleura are separated from the mesothelial cells by a layer of connective tissue. The lack of stomas in the visceral pleura explains the observation that particulate matter injected in the pleural space is removed through the parietal pleura (see Chapter 2). Fluid from the pleural space does not enter the lymphatics in the visceral pleura in humans.

Kampmeier Foci

Kampmeier (33) in 1928 described small milky spots in the dorsal and caudal portions of the mediastinum in rats and humans. Microscopically, the foci are an aggregate of lymphocytes, histiocytes, plasma cells, and other mononuclear cells around central lymphatic or vascular vessels. It has been suggested that the black spots in patients with parietal anthracosis correspond to the Kampmeier foci and that the distribution of asbestos fibers in the pleura is also concentrated in these foci (34). It has been hypothesized that the high concentrations of asbestos in these foci leads to the development of pleural plaques and mesothelioma (34). However, the occurrence of pleural plaques is not related to the location of the black spots (35).

INNERVATION OF THE PLEURA

Sensory nerve endings are present in the costal and diaphragmatic parietal pleura. The intercostal nerves supply the costal pleura and the peripheral part of the diaphragmatic pleura. When either of these areas is stimulated, pain is perceived in the adjacent chest wall. In contrast, the central portion of the diaphragm is innervated by the phrenic nerve, and stimulation of this pleura causes the pain to be perceived in the ipsilateral shoulder. The visceral pleura contains no pain fibers and may be manipulated without causing unpleasant sensation. Therefore, the presence of pleuritic chest pain indicates inflammation or irritation of the parietal pleura. However, the visceral pleura does have sensory receptors closely related to elastic fibers (36). The functional role of these receptors remains to be defined (36).

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chapter 2

Physiology of the Pleural Space

The pleural space is the coupling system between the lung and the chest wall, and, accordingly, it is a crucial feature of the breathing apparatus. The pressure within the pleural space (the pleural pressure) is important in cardiopulmonary physiology because it is the pressure at the outer surface of the lung and the heart and the inner surface of the thoracic cavity. Because the lung, the heart, and the thoracic cavity are all distensible, and because the volume of a distensible object depends on the pressure difference between the inside and the outside of the object and its compliance, pleural pressure plays an important role in determining the volume of these three important structures.

PLEURAL PRESSURE

If the thorax is opened to atmospheric pressure, the lungs decrease in volume because of their elastic recoil, while at the same time, the thorax enlarges. With the thorax open, the volume of the thoracic cavity is approximately 55% of the vital capacity, whereas the volume of the lung is below its residual volume. With the chest closed and the patient relaxed, the respiratory system is at its functional residual capacity (FRC), which is approximately 35% of the total lung capacity (1). Thus, at FRC, the opposing elastic forces of the chest wall and lung produce a negative pressure between the visceral and the parietal pleura. This pressure, the pleural pressure, surrounds the lung and is the primary determinant of the volume of the lung. The pleural pressure represents the balance between the outward pull of the thoracic cavity and the inward pull of the lung (1).

Pleural Liquid Pressure versus Pleural Surface Pressure

There has been a controversy for many years as to whether there are two pleural pressures or one (2). The two different pressures had been proposed to explain a discrepancy obtained when the pleural pressure was measured in two different ways. If the pressure was measured using fluid-filled catheters, the vertical gradient obtained was approximately 1.0 cm H_2O/cm vertical height. This pressure was designated the *pleural liquid pressure* and was believed to represent the pressure that influenced the absorption of fluid. If the pressure was measured using surface balloons or suction cups, then a gradient of 0.3 cm H_2O/cm vertical height was obtained. This pressure was designated the *pleural surface pressure* and represented the balance between the outward pull of the thoracic cavity and the inward pull of the lung. It now appears that there is only one pressure, the pleural surface pressure, and that the discrepancies in the pressures arose because of the distortion from the catheters (3). It should be noted, however, that there is still a school of researchers who believe in the presence of two different pressures (4,5).

Measurement

Pleural pressure can be measured directly by inserting needles, trocars, catheters, or balloons into the pleural space. Direct measurement of the pleural pressure is not usually made because of the danger of producing a pneumothorax or of introducing infection into the pleural space. Rather, the pleural pressure is measured indirectly by a balloon positioned in the esophagus (6,7). Because the esophagus is a compliant structure

situated between the two pleural spaces, esophageal pressure measurements provide a close approximation of the pleural pressure at the level of the balloon in the thorax (7,8). Estimation of pleural pressure by means of an esophageal balloon is not without difficulties (8). The volume of air within the balloon must be small so that the balloon is not stretched and the esophageal walls are not displaced; otherwise, pleural pressure estimates are falsely elevated. Moreover, the balloon must be short and must be placed in the lower part of the esophagus. It has been demonstrated that reliable measurements of esophageal pressures can be made with micromanometers (9). The use of the micromanometer should circumvent some of the problems associated with esophageal balloons.

Gradients

Only one value for the pleural pressure is obtained when it is estimated by an esophageal catheter or balloon. It should be emphasized, however, that the pleural pressure is not uniform throughout the pleural space. A gradient in pleural pressure is seen between the superior and the inferior portions of the lung, with the pleural pressure being lowest or most negative in the superior portion and highest or least negative in the inferior portion (3). The main factors responsible for this pleural pressure gradient are probably gravity, mismatching of the shapes of the chest wall and lung, and the weight of the lungs and other intrathoracic structures (1).

The magnitude of the pleural pressure gradient appears to be approximately 0.30 cm H_2O/cm vertical distance (3). It should be noted that over the last 30 years, there have been many studies directed at measuring the pleural pressure gradient and the resulting values have ranged from 0.20 to 0.93 cm H_2O/cm vertical distance (3). The results have been largely dependent on the method used (3). It appears that the higher values were obtained with catheters that were large relative to the narrow pleural space and accordingly produced distortion of the pleura with subsequent alterations in the measured pressures (3).

In the upright position, the difference in the pleural pressure between the apex and the base of the lungs may be 8 cm H_2O or more. Because the alveolar pressure is constant throughout the lungs, the end result of the gradient in the pleural pressure is that different parts of the lungs have different distending pressures. The pressure–volume curve is thought to be the same for all regions of the lungs; therefore, the pleural pressure gradient causes the alveoli in the superior parts of the lung to be larger than those in the inferior parts. The higher pressure gradient at the apex of the lung is thought to be responsible for the formation of pleural blebs almost exclusively at the apex of the lung. The pleural pressure gradients also account for some unevenness in the distribution of ventilation.

PLEURAL FLUID FORMATION

Fluid that enters the pleural space can originate in the pleural capillaries, the interstitial spaces of the lung, the intrathoracic lymphatics, the intrathoracic blood vessels, or the peritoneal cavity.

Pleural Capillaries

The movement of fluid between the pleural capillaries and the pleural space is believed to be governed by Starling's law of transcapillary exchange (10). When this law is applied to the pleura as shown in Equation 2.1,

$$\dot{Q}_r = L_p \cdot A\left[\left(P_{cap} - P_{pl}\right) - \sigma_d\left(\pi_{cap} - \pi_{pl}\right)\right] \quad (2.1)$$

where $\dot{Q}_r$ is the liquid movement; L_p is the filtration coefficient/unit area or the hydraulic water conductivity of the membrane; A is the surface area of the membrane; P and π are the hydrostatic and oncotic pressures, respectively, of the capillary (cap) and pleural (pl) space; and σ_d is the solute reflection coefficient for protein, a measure of the membrane's ability to restrict the passage of large molecules (3). Widely varying values for σ_d have been reported. For example, the σ_d of the canine visceral pleura combined with the endothelium has been reported to exceed 0.80 (3), indicating a marked restriction in the movement of large molecules such as albumin. In contrast, the σ_d of the mediastinal pleura in the pig was reported to be between 0.02 and 0.05, indicating little restriction in the movement of large molecules (3). It appears that the restriction of protein by the pleural capillary endothelial–interstitial barrier is largely associated with the endothelium (3).

Estimates for the magnitude of the pressures affecting fluid movement from the capillaries to the pleural space in humans are shown in Figure 2.1. In the parietal pleura, a gradient for fluid formation is normally present. The hydrostatic pressure in the parietal pleura is approximately 30 cm H_2O, whereas the pleural

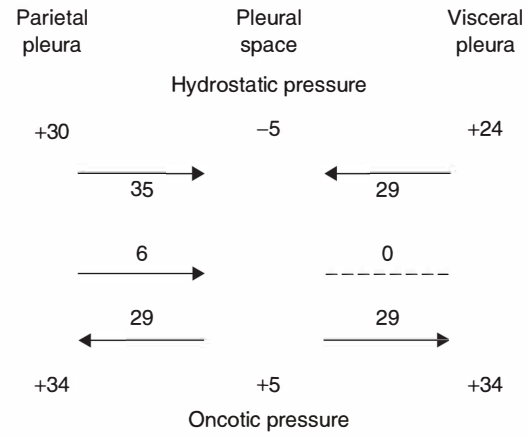

FIGURE 2.1 ■ Various pressures that normally influence the movement of fluid in and out of the pleural space in species with a thick visceral pleura, such as humans.

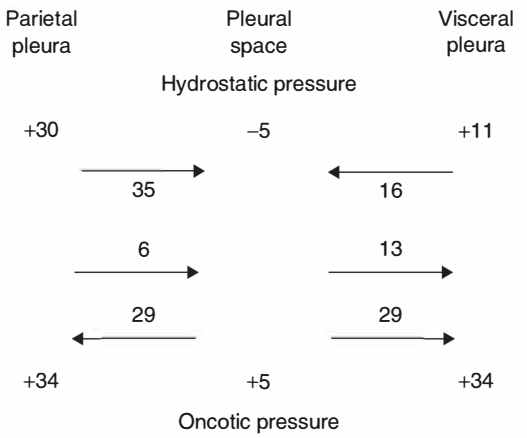

FIGURE 2.2 ■ Various pressures that normally influence the movement of fluid in and out of the pleural space in species with a thin visceral pleura, such as the dog. See text for explanation.

pressure is approximately −5 cm H_2O. The net hydrostatic pressure is therefore 30 − (−5) = 35 cm H_2O, and this favors the movement of fluid from the capillaries in the parietal pleura to the pleural space. Opposing this hydrostatic pressure gradient is the oncotic pressure gradient. The oncotic pressure in the plasma is approximately 34 cm H_2O. Normally, the small amount of pleural fluid contains a small amount of protein and has an oncotic pressure of approximately 5 cm H_2O (11), yielding a net oncotic pressure gradient of 34 − 5 = 29 cm H_2O. Thus, the net gradient is 35 − 29 = 6 cm H_2O, favoring the movement of fluid from the capillaries in the parietal pleura to the pleural space.

The net gradient for fluid movement across the visceral pleura in humans is probably close to zero, but this has not been demonstrated (Fig. 2.1). The pressure in the visceral pleural capillaries is approximately 6 cm H_2O less than that in the parietal pleural capillaries because the visceral pleural capillaries drain into the pulmonary veins. Because this is the only pressure that differs from those affecting fluid movement across the parietal pleura and because the net gradient for the parietal pleura is 6 cm H_2O, it follows that the net gradient for fluid movement across the visceral pleura is approximately zero. It is also likely that the filtration coefficient (L_p) for the visceral pleura is substantially less than that for the parietal pleura because the capillaries in the visceral pleura are much farther from the pleural space than those in the parietal pleura (12).

The movement of pleural fluid is not the same across all the parietal pleura. Wang and Lai-Fook (13) used Evans blue–dyed albumin to study regional pleural filtration of prone anesthetized rabbits. They reported that there appeared to be more fluid formation across the parietal pleura over the ribs compared with the intercostal spaces. In contrast, pleural liquid absorption was primarily in the parietal pleura adjacent to the intercostal space rather than in the parietal pleura overlying the ribs. There was also more fluid formation over the caudal ribs than over the cranial ribs (13). If the breathing frequency was increased, more fluid was formed (13).

The transpleural exchange of fluid is species dependent. Humans and sheep have a thick visceral pleura and its blood supply is from the bronchial artery rather than from the pulmonary artery (14). However, many species, such as the rabbit and the dog, have a thin visceral pleura that receives its blood supply from the pulmonary circulation. In such a situation, as shown in Figure 2.2, the net gradients favor pleural fluid formation across the parietal pleura and pleural fluid absorption through the visceral pleura.

Interstitial Origin

The origin of much of the fluid that enters the pleural space in disease states is the interstitial spaces of the lungs. Either high-pressure or high-permeability pulmonary edema can lead to the accumulation of pleural fluid. When sheep are volume overloaded to

produce high-pressure pulmonary edema, approximately 25% of all the fluid that enters the interstitial spaces of the lungs is cleared from the lung through the pleural space (15). Within 2 hours of starting the volume overloading, the amount of fluid entering the pleural space increases, and within 3 hours, the protein concentration in the pleural fluid is the same as that in the interstitial spaces of the lungs (15). The amount of pleural fluid formed is directly related to the elevation in the wedge pressure. Increases in pleural fluid accumulation occur only after the development of pulmonary edema (16).

The pulmonary interstitial space is the predominant origin of pleural fluid in patients with congestive heart failure. The likelihood of a pleural effusion increases as the severity of pulmonary edema increases (17). In addition, the presence of pleural effusions is more closely correlated with the pulmonary venous pressure than with the systemic venous pressure (17). However, patients with right heart failure due to pulmonary hypertension may have pleural effusions although their wedge pressures are normal (18). The origin of the pleural fluid in this situation is probably the capillaries in the parietal pleura (18). The amount of fluid that enters the pleural space is also increased when there is increased interstitial fluid due to high-permeability pulmonary edema. When increased-permeability edema was induced in sheep by the infusion of oleic acid, again, pleural fluid accumulated only after pulmonary edema developed (19). In this study, there was no morphologic evidence of pleural injury. When pulmonary edema is induced by xylazine (20) or hyperoxia (21) in rats, or by ethchlorvynol in sheep (22), the high-protein pleural fluid appears to originate in the interstitial spaces of the lungs. The pleural fluid associated with experimental Pseudomonas pneumonia in rabbits originates in the lung (23). It is likely that the origin of the pleural fluid with many conditions associated with lung injury, such as pulmonary embolization and lung transplantation, is also the interstitial spaces of the lung (2). In experimental studies of hydrostatic and increased-permeability edema, a pleural effusion develops when the extravascular lung water has reached a critical level in a certain amount of time (24). The necessary level of edema appears to be between 5 and 8 g of fluid/gram of dry lung, depending on whether the edema is secondary to hydrostatic edema, oleic acid lung injury, or α-naphthyl thiourea lung injury (24). With increasing levels of interstitial fluid, it has been shown that the subpleural interstitial pressure increases (25). The barrier to the movement of fluid across the visceral pleura appears to be weak, even though the visceral pleura is thick (26). Therefore, once the subpleural interstitial pressure increases, it follows that fluid will traverse the visceral pleura to the pleural space.

Peritoneal Cavity

Pleural fluid accumulation can occur if there is free fluid in the peritoneal cavity and if there are openings in the diaphragm. Under these conditions, the fluid will flow from the peritoneal space to the pleural space because the pressure in the pleural cavity is less than the pressure in the peritoneal cavity. The peritoneal cavity is the origin of the pleural fluid in hepatic hydrothorax (Chapter 9), Meigs' syndrome (Chapter 20), and peritoneal dialysis (Chapter 9) (27). There are no direct lymphatic connections between the peritoneal and pleural cavities (28).

Thoracic Duct or Blood Vessel Disruption

If the thoracic duct is disrupted, lymph will accumulate in the pleural space, producing a chylothorax (see Chapter 26). The rate of fluid accumulation with chylothorax can be more than 1,000 mL/day. When the thoracic duct is lacerated in dogs, sizeable pleural effusions begin to develop almost immediately (29). In a like manner, when a large blood vessel in the thorax is disrupted owing to trauma or disease, blood can accumulate rapidly in the pleural space, producing a hemothorax (see Chapter 25).

Origin of Normal Pleural Fluid

It is believed that the fluid that normally enters the pleural space originates in the capillaries in the parietal pleura (30). The normal pleural fluid production is approximately 0.01 mL/kg/hour in awake sheep and 0.02 mL/kg/hour in rabbits (30). If these rates are extrapolated to human beings, the amount of pleural fluid formed daily in a 50-kg individual would be approximately 15 mL (30). The origin of the fluid does not appear to be the interstitial spaces of the lung because the protein level in the interstitial spaces is normally approximately 4.5 g/dL, whereas the protein level in normal pleural fluid is only approximately 1 to 1.5 g/dL. From Figure 2.1, it appears unlikely that the fluid originates from the visceral pleura. Likewise, both a lymphatic origin and a peritoneal cavity origin appear unlikely. Supporting evidence for this theory has been provided by Broaddus et al. (31).

These workers measured the vascular pressures and the pleural fluid protein levels in sheep of different ages. They found that the systemic vascular pressures progressively increased with age, whereas the pleural fluid protein levels progressively decreased with age. These findings support a parietal pleural origin for normal pleural fluid because higher vascular pressures should produce pleural fluid with lower protein levels (31). Studies in rabbits with Evans blue–dyed albumin have demonstrated that most fluid originates in the parietal pleura over the ribs (13).

PLEURAL FLUID ABSORPTION

Lymphatic Clearance

From Figure 2.1, one might have the impression that pleural fluid should continuously accumulate because Starling's equation favors fluid formation through the parietal pleura and there is no gradient for fluid absorption through the visceral pleura. Fluid clearance through the pleural lymphatics is thought to explain the lack of fluid accumulation in normal individuals. The pleural space is in communication with the lymphatic vessels in the parietal pleura by means of stomas in the parietal pleura. No such stomas are present in the visceral pleura. Proteins, cells, and all other particulate matter are removed from the pleural space by these lymphatics in the parietal pleura (32–35). When carbon particles are injected into the pleural space of anesthetized monkeys, thoracoscopy demonstrates that the carbon particles go directly to the costal, mediastinal, and diaphragmatic pleura within 15 minutes of injection (36). The stomas through which the carbon particles exit the pleural space are in areas where the mesothelial cells are small and not flattened (36). Increased levels of nitric oxide in the pleura will cause these stomas to increase in diameter (37).

The amount of fluid that can be cleared through these lymphatics is substantial. Stewart (38) found that the mean lymphatic flow from one pleural space in seven patients was 0.40 mL/kg/hour, whereas Leckie and Tothill (39) found that the mean lymphatic flow was 0.22 mL/kg/hour in seven patients with congestive heart failure. In both these studies, marked variability was noted from one patient to another. If these results in patients with congestive heart failure are extrapolated to the normal person, a 60-kg individual should have a lymphatic drainage from each pleural space on the order of 20 mL/hr or 500 mL/day.

Experimental work with sheep, a species with a thick visceral pleura similar to that of humans, suggests that most of the fluid that enters the pleural space in sheep is removed through the lymphatics. Broaddus et al. (40) produced artificial hydrothoraces in awake sheep by injecting an autologous protein solution at a volume of 10 mL/kg, with a protein level of 1.0 g/dL. These investigators found that the hydrothorax was removed almost completely by the lymphatics in a linear manner at a rate of 0.28 mL/kg/hour. The linearity suggests that the lymphatics operate at maximum capacity once the volume of the pleural liquid exceeds a certain threshold. Note that the capacity for lymphatic clearance is 28 times as high as the normal rate of pleural fluid formation.

In the experiments of Broaddus et al. discussed in the preceding text (40), the fluid introduced into the pleural space had an oncotic pressure of approximately 5 cm H_2O, and from Figure 2.1, one might speculate that if fluids with oncotic pressures other than 5 cm had been introduced, the equilibrium would have been altered such that fluid would enter the pleural space from the visceral pleura in animals with high pleural fluid oncotic pressures and would leave the pleural space through the visceral pleura in animals with low oncotic pressures. This does not appear to be the case. Aiba et al. produced artificial pleural effusions in dogs with protein levels ranging from 0.1 to 9.0 g/dL (41). Even when the induced pleural effusion had a protein level of 0.1 g/dL, there was no increase in the concentration of protein with time, indicating that the low oncotic pressure did not induce a rapid efflux of fluid out of the pleural space. When the protein concentration of the induced effusions was above 4 g/dL, the concentration of protein in the pleural fluid did gradually decrease with time, indicating a net transfer of protein-free fluid into the pleural space. However, the net amount of fluid entering the pleural space even with a protein level of 9.0 g/dL was only 0.22 mL/kg/hour. This degree of fluid flux is similar to the lymphatic clearance of 0.22 mL/kg/hour reported in the same studies. These observations strongly suggest that most pleural fluid is removed through the lymphatics in the parietal pleura in species with thick visceral pleura, such as humans.

Clearance through Capillaries in Visceral Pleura

Until the mid-1980s, it was thought that the primary route for the exit of fluid from the pleural space was through the capillaries in the visceral pleura (42).

This conclusion was based primarily on experiments in animals with thin pleura. It is easily seen from Figure 2.2 that in animals with thin pleura, there is a sizable gradient for the movement of fluid from the pleural space into the capillaries in the visceral pleura. In addition, fluid probably moves across a thin visceral pleura more easily than it does across a thick pleural membrane. However, on the basis of the observations cited, it appears that in humans, almost all the pleural fluid is removed through the lymphatics in the parietal pleura. Nevertheless, it should be noted that this view is not accepted by all (43).

The observations mentioned earlier should not be interpreted as indicating that small molecules do not move across the pleural surfaces. Indeed, water and small-sized molecules exchange easily across both pleural surfaces (44). When hydrothoraces are induced in dogs, the clearance rate for para-aminohippurate (PAH) (molecular weight 216) is approximately 2 mL/kg/hour (41). When urea is injected intrapleurally into patients with pleural effusions, its concentration decreases much more rapidly than does that of radiolabeled protein (45). Indeed, the urea clearance rate is several hundred milliliters/hour (45). Because urea and water have comparable molecular weights, one can assume that the rates of exchange for urea and water across the pleural membranes are similar. Therefore, several hundred milliliters of water probably traverse the pleural membranes each day, but the net movement is of only a few milliliters because the osmolarity is nearly identical on each side of the membrane.

Alternative Mechanisms for Pleural Fluid Removal

Although the assumption that all pleural fluid is removed from the pleural space via bulk flow through the lymphatics is attractive and has a lot of supporting evidence, there are some questions about the validity of this theory. There is some evidence that transcytosis contributes to the removal of protein from the pleural space. Agostoni et al. (46) studied the removal of albumin and dextran from the pleural space of anesthetized rabbits with and without the administration of nocodazole, a transcytosis inhibitor. They reported that the removal of both the albumin and dextran was significantly greater in the control group (46). They concluded that 0.05 mL/hour of liquid was removed by transcytosis (46). These same researchers subsequently conducted a study (47) in which they assessed the removal of labeled albumin and labeled dextran from the pleural space of rabbits. Assuming that the 2,000 kDa dextran left the pleural space only through stoma, they concluded that only 29% of the overall removal of albumin occurred through the stoma with small hydrothoraces, while 64% of the albumin from large hydrothoraces was removed through the stoma (47).

Shinto et al. (48) reported that when the volume of pleural fluid decreased with diuresis in patients with congestive heart failure, the concentration of the protein and LDH only increased slightly. They took this as evidence that all pleural fluid was removed by bulk flow through the lymphatics. However, Romero et al. (49) reported quite different results in 15 patients who had their pleural fluid chemistries measured before and at a mean of 115 hours after diuresis was started. They reported that the mean protein level increased from 2.3 g/dL to 3.5 g/dL while the LDH increased from 176 IU/L to 262 IU/L (49). Similar percentage increases were seen in the albumin, cholesterol, and cholinesterase concentrations. Their results suggest that not all fluid is removed by bulk flow through the lymphatics.

If large molecules are removed through lymphatics and smaller molecules are removed by a different mechanism, then there should be a level at which larger molecules are all removed at one rate and below which molecules are removed at a different rate. However, Stashenko et al. (50) have shown that when dextran molecules of varying sizes are placed in the pleural space of rabbits, there was a continuous spectrum in the rate of absorption of the dextran molecules with the larger molecules being absorbed more slowly (50). This latter observation is consistent with multiple pore sizes or pores that allow particles through with a probability dependent on the size of the particle (50).

PATHOGENESIS OF PLEURAL EFFUSIONS

Pleural fluid accumulates when the rate of pleural fluid formation exceeds the rate of pleural fluid absorption. The main factors that lead to increased pleural fluid formation or decreased pleural fluid absorption are tabulated in Table 2.1. Normally, a small amount (0.01 mL/kg/hour) of fluid constantly enters the pleural space from the capillaries in the parietal pleura. Almost all of this fluid is removed by the lymphatics in the parietal pleura, which have a capacity to remove at least 0.20 mL/kg/hour. Note that the capacity of the lymphatics to remove fluid exceeds the normal rate of fluid formation by a factor of 20.

TABLE 2.1 ■ General Causes of Pleural Effusions

Increased pleural fluid formation
Increased interstitial fluid in the lung
Left ventricular failure, pneumonia, and pulmonary embolus
Increased intravascular pressure in pleura
Right or left ventricular failure, superior vena caval syndrome
Increased permeability of the capillaries in the pleura
Pleural inflammation
Increased levels of vascular endothelial growth factor
Increased pleural fluid protein level
Decreased pleural pressure
Lung atelectasis or increased elastic recoil of the lung
Increased fluid in peritoneal cavity
Ascites or peritoneal dialysis
Disruption of the thoracic duct
Disruption of blood vessels in the thorax
Decreased pleural fluid absorption
Obstruction of the lymphatics draining the parietal pleura
Elevation of systemic vascular pressures
Superior vena caval syndrome or right ventricular failure
Disruption of the aquaporin system in the pleura

INCREASED PLEURAL FLUID FORMATION

Increased pleural fluid formation can occur when there is increased pulmonary interstitial fluid or when one of the terms in Starling's equation (Equation 2.1) is changed such that more fluid is formed.

Increased Interstitial Fluid

The most common cause of increased pleural fluid formation is increased interstitial fluid in the lung. As mentioned earlier, whenever the amount of edema in the lung exceeds 5 g/gram of dry lung weight, pleural fluid accumulates, irrespective of whether the edema is due to high-protein or low-protein fluid (24). This appears to be the predominant mechanism for the formation of pleural effusions in patients with congestive heart failure, parapneumonic effusions, pulmonary embolism, acute respiratory distress syndrome, and in those who have undergone lung transplantation.

Increased Hydrostatic Pressure Gradient

If there is an increase in the gradient between the intravascular pressure and the pleural pressure, there will be an increase in the rate of pleural fluid formation through Starling's equation (Equation 2.1). Increases in the intravascular pressure can occur with right ventricular failure, left ventricular failure, pericardial effusions, or the superior vena cava syndrome. The most common situation producing a decrease in the pleural pressure is bronchial obstruction leading to atelectasis of the lower lobe or complete lung. A decrease in the pleural pressure also occurs when the visceral pleura becomes coated with a collagenous peel and the lung becomes trapped. In these instances, the pleural pressure can become very negative (below -50 cm H_2O) (51). Decreased pleural pressures can also contribute to pleural fluid accumulation in diseases in which the elastic recoil of the lung is increased.

Increased Capillary Permeability

It can also be seen from Equation 2.1 that increased permeability of the pleura can also lead to increased pleural fluid formation. In Equation 2.1, a generalized increase in the pleural permeability is reflected by an increase in L_p (hydraulic conductivity). It is thought that increased levels of vascular endothelial growth factor (VEGF) increase the permeability of the capillaries and may be at least partially responsible for the accumulation of pleural fluid in certain instances (52,53). VEGF receptors have been demonstrated on mesothelial cells (53), and the levels of VEGF are higher in exudative effusions than in transudative pleural effusions (52,53). Of course, if the pleural surfaces become inflamed, the permeability of the capillaries may be increased.

Decreased Oncotic Pressure Gradient

A decrease in the oncotic pressure gradient can also lead to increased pleural fluid formation through its influence on Starling's equation (Fig. 2.1). For example, if the protein level in the serum and pleural fluid are identical, then there should be gradients of 35 and 29 cm H_2O favoring pleural fluid formation from the parietal and visceral pleura, respectively (instead of the normal 6 and 0 cm H_2O). Increased pleural fluid protein levels occur with increased-permeability pulmonary edema, hemothorax, and with conditions in which the permeability of the pleural capillaries is increased. This mechanism, however, is probably

not too important because when a pleural effusion is induced in sheep with a protein level of 9.0 g/dL, the rate of fluid entry into the pleural space is only 0.22 mL/kg/hour (41). This rate of fluid formation is approximately equal to the capacity of the lymphatics to remove pleural fluid. Moreover, hypoproteinemia is thought to be a very uncommon cause of pleural effusion (54).

Presence of Free Peritoneal Fluid, or Disruption of the Thoracic Duct or an Intrathoracic Blood Vessel

If there is free fluid in the peritoneal cavity, it will lead to pleural fluid accumulation if there is a hole in the diaphragm (27). In a similar manner, chyle will accumulate in the pleural space if there is a disruption in the thoracic duct, and blood will accumulate in the pleural space if there is a disruption of a blood vessel in the thorax.

Decreased Pleural Fluid Absorption

Obstruction of Lymphatics

The most common cause of a decrease in pleural fluid absorption is obstruction of the lymphatics draining the parietal pleura. Normally, the lymphatic flow from the pleural space is approximately 0.01 mL/kg/hour or 15 mL/day because this is the amount of pleural fluid formed. However, the capacity of the lymphatics is approximately 0.20 mL/kg/hour or 300 mL/day. Lymphatic blockade is an important factor that contributes to the development of a malignant pleural effusion. Leckie and Tothill (39) studied the lymphatic flow in eight patients with lung carcinoma and six patients with metastatic breast carcinoma and found that the mean lymphatic flow was only 0.08 mL/kg/hour. Obviously, pleural effusions would not have developed in these patients unless excess fluid had also been entering the pleural space. Unless the lymphatic flow is markedly impaired, another factor must be present in addition to lymphatic disease to produce a pleural effusion given the excess reserve capacity of the lymphatics.

Elevation of Systemic Venous Pressures

There is high incidence of pleural effusions in patients with pulmonary hypertension (18). Most of the patients with pulmonary hypertension who have pleural effusions also have right heart failure (18). It is thought that pleural fluid accumulates because the elevated systemic venous pressure leads to more pleural fluid formation (18). Pleural effusions also develop in sheep when the pressure in the superior vena cava is increased. Allen et al. (55) found that pleural fluid accumulated over a 24-hour period when the pressure in the superior vena cava exceeded 15 mm Hg. The amount of pleural fluid that accumulated increased exponentially as the pressure was increased. These workers reported that the larger the pleural effusion, the higher the protein level. They concluded that the pleural effusions developed because of (a) lymph leakage out of the lymphatics that pass through the chest (these include the thoracic duct and the diaphragmatic and pulmonary lymphatics) or (b) obstruction of lung or chest wall lymphatics with subsequent leakage of interstitial fluid into the pleural space (55).

Role of Aquaporins in Pleural Fluid Exchange

The aquaporins (AQPs) are a family of proteins that transport water across membranes (56). A deficiency of an AQP in certain organs has produced significant abnormalities. For example, deletion of AQP1 in mice results in a severe defect in the ability to concentrate urine and the mice become profoundly dehydrated when deprived of water (56).

There are at least four AQPs present in the lung (57). Transgenic mouse models with AQP deletion have provided information about their physiologic role. In the lung, AQP1 and AQP5 provide the principal route for osmotically driven water transport; however, neither alveolar fluid clearance in the neonatal and adult lungs nor fluid accumulation in experimental models of lung injury is affected by AQP deletion (57).

Immunostaining of the pleura has revealed the presence of AQP1 in microvascular endothelia near the visceral and parietal pleura and in mesothelial cells in the visceral pleura (58). In AQP1 knockout mice, osmotic equilibration of either hypertonic or hypotonic pleural fluid was slowed by a factor of four compared with wild-type mice (58).

However, in a fluid overload model produced by intraperitoneal saline administration and renal artery ligation, the accumulation of pleural fluid was not affected by AQP1 deletion (58). Moreover, in a thiourea toxicity model of acute endothelial injury causing pleural effusions and lung interstitial edema, AQP1 deletion did not affect pleural fluid accumulation (58). These results suggest that AQP1 does not play a role in clinically relevant mechanisms of pleural fluid accumulation or clearance.

WHY IS THERE NO AIR IN THE PLEURAL SPACE?

Although the pleural pressure is negative at FRC and throughout most of the respiratory cycle, why is there normally no air in the pleural space? Gases move in and out of the pleural space from the capillaries in the visceral and parietal pleura (59). The movement of each gas is dependent on its partial pressure in the pleural space, as compared with that in the capillary blood. The sum of all the partial pressures in the capillary blood averages 706 mm Hg (PH_2O = 47, PCO_2 = 46, PN_2 = 573, and PO_2 = 40 mm Hg). Therefore, a net movement of gas into the pleural space should occur only if the pleural pressure is below 706 mm Hg or below −54 mm Hg relative to atmospheric pressure. Because mean pleural pressures this low hardly ever occur, the pleural space normally remains gas free.

If air is discovered in the pleural space, it means that one of the three things has occurred: (a) a communication exists or has recently existed between the alveoli and the pleural space; (b) a communication exists or has recently existed between the atmosphere and the pleural space; or (c) gas-producing organisms are present in the pleural space.

When air does enter the pleural space and thereby produces a pneumothorax, its rate of absorption depends on the difference between the sum of the partial pressures in the pleural space and in the capillary blood. The sum of the partial pressures in the pleural space is close to atmospheric pressure. Because the sum of the partial pressures in the capillary blood is most dependent on the PN_2, this sum can be rapidly reduced by having the patient breathe supplemental oxygen, which reduces the PN_2 of the capillary blood without substantially changing the other partial pressures. In patients who have pneumothoraces, administration of supplemental oxygen facilitates the reabsorption of the pneumothorax (60). The higher the inspired concentration of oxygen, the faster the reabsorption of pleural air.

HOW IMPORTANT IS THE PLEURAL SPACE?

The pleural space serves as the coupling system between the lung and the chest wall. The thin rim of fluid that normally separates the parietal pleura from the visceral pleura is thought to facilitate the movements of the lung within the thoracic cavity. Therefore, what are the consequences of obliterating the pleural space? Surprisingly, patients with obliterated pleural spaces appear to suffer no significant ill effects. Gaensler (61) studied the pulmonary function of four patients before and 6 to 17 months after they had been subjected to pleurectomy. The mean vital capacity and maximal breathing capacity were virtually identical preoperatively and postoperatively. Moreover, the ventilation and oxygen uptake on the operated side, as compared with the intact side, were unchanged postoperatively.

Fleetham et al. (62) studied regional lung function in four men who had undergone thoracotomy for pleurodesis 2 to 9 years earlier. They found that in all subjects, boluses of xenon inhaled slowly at FRC were distributed more to the apex and less to the base of the lung on the operated side than on the intact side. These researchers believed, however, that these minor differences were probably not clinically significant.

Further evidence for the lack of importance of the pleural space is provided by studies of elephants. The pleural space of both Asian and African elephants has been found to be obliterated by connective tissue (63). It has been hypothesized that the reason that elephants have an obliterated pleural space is to allow them to snorkel at depth (63). The fact that many of these large mammals function without a pleural space indicates the relative lack of importance of this structure for normal function. However, the pleural space does play a major role in many disease states.

The pleural space may be important in clearing fluid from the interstitium of the lung. When noncardiogenic pulmonary edema is produced in sheep through the intravenous injection of oleic acid, approximately 20% of the fluid that enters the interstitium of the lung crosses the visceral pleura to the pleural space (19). The relevance of this observation to disease in humans is yet to be proved. The infrequency of unilateral pulmonary edema in patients with a previous pleurodesis makes one skeptical about the clinical significance of these findings.

Therapeutic Uses of the Pleural Space

The pleural space is an attractive site for administering gene products to the lung parenchyma, other thoracic structures, and the systemic circulation. The advantages of using the pleural space for gene therapy include (a) easy accessibility, (b) large surface area, (c) ability to provide high concentrations of secreted gene products to chest structures, and (d) low risk of detrimental effects of possible vector-induced inflammation compared with intravascular delivery (64). Our group has shown that when liposomes

containing the plasmid for placental alkaline phosphatase are injected into the pleural space of rabbits, the levels of placental alkaline phosphatase increase in both the pleural fluid and the serum (65). Another group (66) administered adenoviruses containing an antiangiogenesis vector expressing a soluble, secreted, extracellular portion of the Flt-1 receptor for VEGF intrapleurally in mice that had lung tumors. Treatment of mice with established lung metastases significantly improved survival as compared with control animals (66). This group also demonstrated in mice that unilateral intrapleural administration was sufficient to transfer genes bilaterally to the pleura (66). There are a few other studies that have demonstrated the feasibility of using the pleural space for gene transfer in animals, but the utility of this approach in humans with disease is yet to be demonstrated.

A second therapeutic use of the pleural space is to warm individuals with accidental hypothermia. Kjaergaard and Bach (67) reported that they had successfully warmed five patients with accidental hypothermia, who were unconscious but who had a stable heart rhythm with pleural lavage. They inserted bilateral chest tubes and then injected 500 mL isotonic saline at 40°C in one pleural space followed by clamping of the chest tube for approximately 2 minutes. After the tube was unclamped, the procedure was repeated on the other side. The pleural lavage was continued until the bladder temperature was above 40°C. All five patients survived and were discharged. The amount of lavage varied between 32 and 102 L (67).

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chapter 3

Physiological Effects of Pneumothorax and Pleural Effusion

In this chapter, the effects of pleural air or pleural fluid on pleural pressures, pulmonary function and gas exchange, the diaphragm, the heart, and exercise tolerance will be discussed.

EFFECTS OF PNEUMOTHORAX ON PLEURAL PRESSURE

Normally, the pressure in the pleural space is negative with reference to the atmospheric pressure during the entire respiratory cycle. The negative pressure is due to the inherent tendency of the lungs to collapse and of the chest wall to expand. The resting volume of the lung, the functional residual capacity (FRC), is the volume at which the outward pull of the chest wall is equal, but opposite in direction, to the inward pull of the lung with the respiratory muscles relaxed. In Figure. 3.1, the FRC is at 36% of the vital capacity.

The pleural pressure is always less than the alveolar pressure and the atmospheric pressure owing to the elastic recoil of the lung. Therefore, if a communication develops between the pleural space and an alveolus or between the pleural space and the atmosphere, air will flow into the pleural space until a pressure gradient no longer exists or until the communication is sealed. Because the thoracic cavity is below its resting volume and the lung is above its resting volume, with a pneumothorax, the thoracic cavity enlarges and the lung becomes smaller.

When a pneumothorax is present, the pleural pressure increases as it does with the presence of a pleural effusion. However, with a pneumothorax the pressure is the same throughout the entire pleural space if it is not loculated. In contrast, with a pleural effusion there is a gradient in the pleural pressure due to the hydrostatic column of fluid. Accordingly, the pleural pressure with a pleural effusion in the dependent part of the hemithorax is much greater than it is in the superior part of the hemithorax. The net result is that with a pneumothorax, the upper lobe is affected more than the lower lobe whereas with a pleural effusion the lower lobe is affected more than the upper lobes. The upper lobes are affected more with pneumothorax because the pressure in the apices is normally much more negative than that at the bases. With a pneumothorax the pleural pressures are only slightly negative so there are much greater changes in pleural pressure at the apex of the lung. One way to conceptualize the difference between air and liquid is to understand that with a pneumothorax the lung sinks to the bottom of the hemithorax because it is heavier than air, whereas with a pleural effusion, the lung rises to the top of the hemithorax because it is lighter than the fluid and is floating in the fluid (1).

EFFECTS OF PNEUMOTHORAX ON PULMONARY FUNCTION

When there is a communication between the alveoli and the pleural space or between the ambient air and the pleural space, air will enter the pleural space because the pleural pressure is normally negative. As air enters the pleural space, the pleural pressure gradually increases. Air will continue to enter the pleural space until the pleural pressure becomes zero or the communication is closed.

The influence of a pneumothorax on the volumes of the hemithorax and lung is illustrated in Figure 3.1. In the example, enough air entered the pleural space to increase the pleural pressure from −5 to −2.5 cm

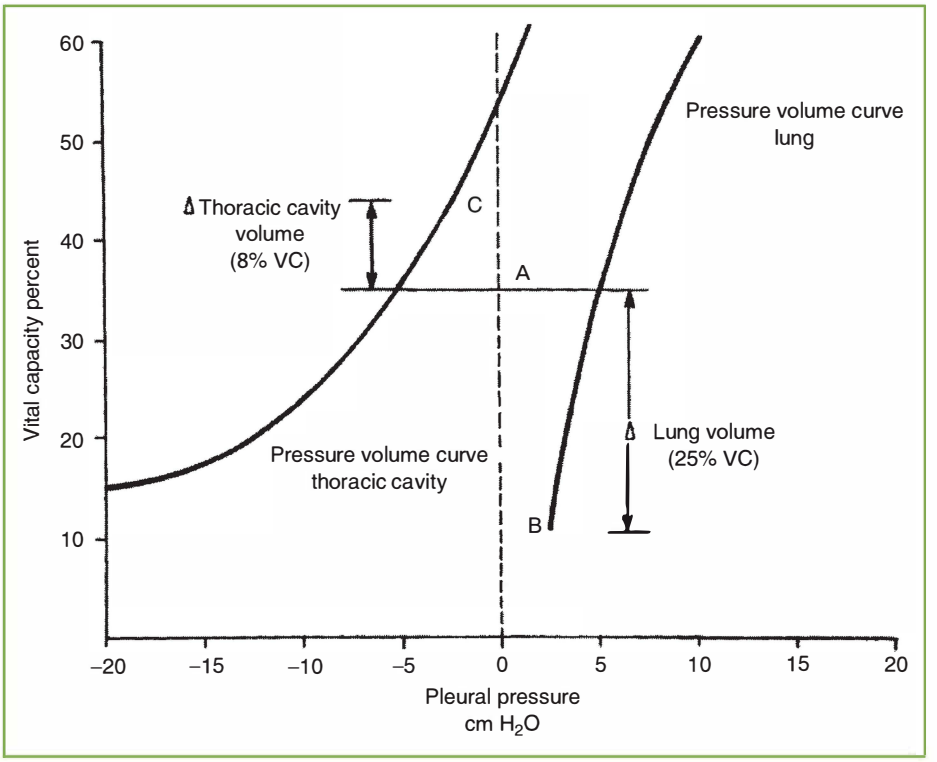

FIGURE 3.1 ■ Influence of a pneumothorax on the volumes of the lung and hemithorax. VC, vital capacity.

H_2O at end expiration. The end-expiratory volume of the lung (point B) decreased from 36% to 11% of the vital capacity, whereas the end-expiratory volume of the hemithorax (point C) increased from 36% to 44% of the vital capacity. The total volume of the pneumothorax is equal to 33% of the vital capacity, of which 25% represents a decrease in lung volume and 8% represents an increase in the volume of the hemithorax. There is essentially no information available on the results of the pulmonary function tests of patients with pneumothorax since they rarely undergo pulmonary function testing while the pneumothorax is present.

EFFECTS OF PNEUMOTHORAX ON BLOOD GASES

The main physiologic consequences of a pneumothorax are a decrease in the vital capacity and a decrease in PaO_2. In the otherwise healthy individual, the decrease in the vital capacity is well tolerated. If the patient's lung function is compromised before the pneumothorax, however, the decrease in the vital capacity may lead to respiratory insufficiency with alveolar hypoventilation and respiratory acidosis.

Most patients with a pneumothorax have a reduced PaO_2 and an increased alveolar–arterial oxygen difference [$P(A-a)O_2$]. In one series of 12 patients, the PaO_2 was below 80 mm Hg in 9 patients (75%) and was below 55 mm Hg in 2 patients (2). In the same series, 10 of the 12 patients (83%) had an increased $P(A-a)O_2$. As one would expect, patients with secondary spontaneous pneumothorax and those with larger pneumothoraces tended to have a greater decrease in the PaO_2 (2). In the Veteran's Administration (VA) cooperative pneumothorax study, blood gases were obtained in 118 patients with spontaneous pneumothorax; the mean PaO_2 was below 55 mm Hg in 20 (17%) and below 45 in 5 (4%), and the mean $PaCO_2$ exceeded 50 mm Hg in 19 (16%) and 60 mm Hg in 5 (4%) (3). Of course, the abnormalities in the blood gases may have been due at least in part to the underlying lung disease in this study (3). Similar findings are present in animals with pneumothoraces.

When a pneumothorax was induced in awake, standing dogs by the intrapleural injection of 50 mL/kg N_2, the mean PaO_2 fell from 86 to 51 mm Hg (4).

The reduction in PaO_2 appears to be due to both anatomic shunts and areas of low ventilation–perfusion ratios in the partially atelectatic lung. When Norris et al. (2) gave 100% oxygen to their 12 patients, the average anatomic shunt was more than 10%. The larger pneumothoraces were associated with greater shunts (2). Pneumothoraces occupying less than 25% of the hemithorax are not associated with increased shunts.

In the study on dogs conducted by Moran et al. (4), the relative perfusion of the lungs was not altered when pneumothorax was induced, but the ventilation to the ipsilateral lung was reduced, resulting in low ventilation–perfusion ratios on the side with the pneumothorax. Anthonisen (5) reported that lungs with pneumothorax demonstrated uniform airway closure at low lung volumes, and he suggested that airway closure is the chief cause of ventilation maldistribution in spontaneous pneumothorax.

The PaO_2 usually improves with treatment of the pneumothorax. In the animal study of Moran et al. (4) in which the mean PaO_2 dropped from 86 to 51 mm Hg with the introduction of a pneumothorax, the PaO_2 returned to baseline immediately after reexpansion. In humans treated for pneumothorax, the normalization of the PaO_2 takes longer. Three patients with an initial anatomic shunt above 20% had a reduction of at least 10% in their shunt 30 to 90 minutes after the removal of intrapleural air, but it still remained above 5% in all patients (2). Three additional patients with anatomic shunts of 10% to 20% had no change in their shunts when the air was removed (2). The delay in improvement in humans as compared with animals may be related to the duration of the pneumothorax.

When a tension pneumothorax is produced in animals spontaneously breathing room air , there is a profound deterioration in the oxygenation status. In one study in goats, the mean PaO_2 fell from 85 to 28 mm Hg, whereas in monkeys the PaO_2 fell from 90 to 22 mm Hg before the animals became apneic (6). There was a linear reduction in the PaO_2 as the volume of pleural air was increased (6). The reduction in the PaO_2 appeared to be due to the continued perfusion of the side with the pneumothorax despite decreased ventilation (6). The cardiac output was relatively well preserved in the animals with a tension pneumothorax (6). When the air is evacuated from the pleural space in experimental animals with tension pneumothorax, the oxygenation status returns to normal almost immediately (6).

EFFECTS OF PNEUMOTHORAX ON DIAPHRAGMATIC FUNCTION

To my knowledge there have been no studies evaluating the effects of a pneumothorax on diaphragmatic function. I would anticipate that the presence of a pneumothorax would have less effect on the diaphragmatic function than would a pleural effusion of comparable volume, since the pleural pressure would increase much more with the pleural fluid. The diaphragmatic inversion that is seen relatively frequently with a pleural effusion is not seen with pneumothorax. With a tension pneumothorax, the diaphragm may be displaced inferiorly because of the increased pleural pressure but the functional significance of this displacement is not known.

EFFECTS OF PNEUMOTHORAX ON EXERCISE TOLERANCE

There have been no studies on the effects of a pneumothorax on the exercise tolerance of either animals or man. However, it would be anticipated that the exercise tolerance would be markedly impaired since many patients are dyspneic at rest.

EFFECTS OF PNEUMOTHORAX ON CARDIAC FUNCTION

The presence of a small-to-moderate pneumothorax has very little influence on cardiac function. When Moran et al. (4) introduced 50 mL/kg N_2 into the pleural spaces of dogs, the cardiac output was not significantly affected. However, the presence of a tension pneumothorax in an animal can cause a marked reduction in cardiac output. Carvalho et al. (7) produced right-sided tension pneumothoraces with mean pleural pressures of +10 and +25 cm H_2O in 10 mechanically ventilated adult sheep. In these animals, the mean cardiac output fell from 3.5 L/minute to approximately 1.2 L/minute and the mean blood pressure fell from 80 mm Hg to less than 40 mm Hg with a pleural pressure of +25 cm H_2O.

The development of a tension pneumothorax in humans is also associated with impaired hemodynamics. Beards and Lipman (8) recorded the hemodynamics of three patients who developed a tension pneumothorax while on mechanical ventilation. With the development of the tension pneumothorax, the mean cardiac

outputs that were 7.3, 4.8, and 3.6 L/minute/m^2 at baseline fell to 3.0, 3.1, and 1.4 L/minute/m^2, respectively. The mean arterial pressures that were 97, 96, and 68 mm Hg fell to 33, 68, and 57 mm Hg, respectively. The probable mechanism for the decreased cardiac output is decreased venous return due to the increased pleural pressures. Moderate increases in the pleural pressure with a pneumothorax in conjunction with thoracoscopy have little influence on the cardiac output. Ohtsuka et al. (9) studied the hemodynamics while the lung was hemicollapsed and CO_2 was infused at a pressure of 8 to 10 mm Hg. The mean cardiac index was virtually the same before and after 30 minutes of CO_2 infusion (1.98 vs. 1.95 L/minute/m^2) (9).

EFFECTS OF EFFUSION ON THE PLEURAL PRESSURE

When pleural fluid is present, its volume must be compensated for by an increase in the size of the thoracic cavity, a decrease in the size of the lung, a decrease in the size of the heart, or a combination of these changes (1). Since the thoracic cavity, lungs, and heart are all distensible objects, the volume of each is dependent on the pressure inside minus the pressure outside. The presence of pleural fluid increases the pleural pressure. Since the distending pressure of the thoracic wall is the atmospheric pressure minus the pleural pressure, an increase in the pleural pressure will lead to an increase in the distending pressure of the thoracic cavity and an increase in the volume of the thoracic cavity. The distending pressure of the lungs is the alveolar pressure minus the pleural pressure. Therefore, an increase in the pleural pressure will lead to a decreased lung volume. Since the distending pressure of the heart is the intracardiac pressure minus the pleural pressure, an increase in the pleural pressure will lead to a decrease in the size of the heart.

The pleural pressure is normally negative. However, when more than minimal pleural fluid accumulates, the pleural pressure becomes positive. When there is sufficient pleural fluid such that the lung is separated from the chest wall, there is a vertical gradient of 1 cm H_2O/cm vertical height due to the weight of the fluid (10). If there is a hydrostatic column 40 cm high in a hemithorax, then the pressure at the bottom of the column would be expected to be approximately 40 cm H_2O. When pleural pressures are measured in patients with pleural effusions, the mean pressure is not particularly high. We measured the pleural pressure in 52 patients with significant pleural effusions (median amount of fluid greater than 1,000 mL). Overall, the mean pleural pressure was approximately zero, but there was a wide range in the pleural pressures from −21 to +8 cm H_2O (Fig. 3.2) (11). Pleural pressures of −5 cm H_2O and less were seen only with a trapped lung or with malignancy. Villena et al. (12) measured the pleural pressure in 61 patients and reported that the initial pleural pressure ranged from −12 to +25 cm H_2O. The mean pressure in the patients was approximately +5 cm H_2O (12). The probable reason that the pleural pressures were not more positive in the two studies is that the thoracentesis needle was inserted closer to the superior than the inferior aspect of the hydrostatic column produced by the pleural effusion. With a pleural effusion, pleural pressures can at

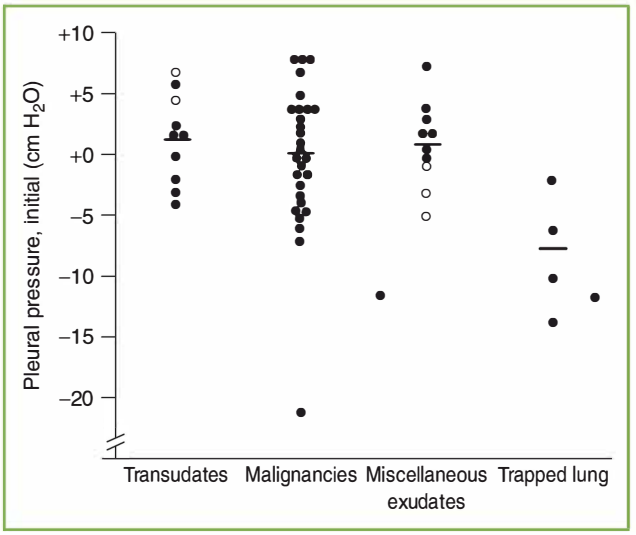

FIGURE 3.2 ■ Initial pleural pressures for 52 patients at the time of thoracentesis. Each patient is represented by a single point. The open circles in the category of transudates represent the patients with hepatic hydrothorax. The closed circles in the category of miscellaneous exudates represent patients with pleural infection. *(Reprinted with permission from Light RW, Jenkinson SG, Minh VD, et al. Observations on pleural fluid pressures as fluid is withdrawn during thoracentesis.* Am Rev Respir Dis. *1980;121:799–804.)*

times be quite positive. Neff and Buchanan (13) reported that the initial pleural pressure was 76 cm H_2O in a patient with a pleural effusion secondary to pneumothorax therapy for tuberculosis many years earlier.

When pleural fluid is removed with thoracentesis, the volume removed is compensated for by an increase in the volume of the lung, an increase in the volume of the heart, and/or a decrease in the volume of the hemithorax. When the volume of these organs changes in this manner, the pleural pressure must decrease. When the pleural pressure is monitored during pleural fluid removal, there is tremendous variability in its changes from patient to patient (11,12).

The elastance of the pleural space has been defined as the change in pleural pressure (cm H_2O) divided by the amount of fluid removed (liters) (11). The larger this number the greater the pleural pressure change per unit volume change. In our original series of 52 patients, the pleural space elastance varied from 2 to more than 150 cm H_2O/L with a mean elastance of approximately 15 cm H_2O/L (11). Patients with trapped lungs due to malignancy or benign disease had pleural space elastances that exceeded 25 cm H_2O/L. Villena et al. (12) reported similar values for pleural space elastances. If one looks at the plot of the pleural pressure versus the volume of fluid removed (Fig. 3.3), the elastance tends to be higher during the latter part of the thoracentesis (11,12).

Clinically, it is useful to measure the pleural pressure and calculate the pleural elastance during a thoracentesis. The demonstration that the pleural elastance is greater than 25 cm H_2O/L establishes the diagnosis of trapped lung (11,12). Thoracentesis can be continued safely as long as the pleural pressure remains above -20 cm H_2O and the patient does not develop chest tightness or pernicious coughing (11,12). Indeed, on several occasions I have removed more than 5,000 mL pleural fluid from patients when the pleural pressure remained above -20 cm H_2O and the patients suffered no ill consequences.

Measurements of the pleural space elastance appear to be useful in predicting whether a pleurodesis will be successful (14). The theory is that if the pleural pressure falls rapidly when fluid is removed from the pleural space, then the negative pleural pressure will make it difficult to create a pleurodesis because the two pleural surfaces will be difficult to be kept together (which is necessary to create a pleurodesis). Lan et al.

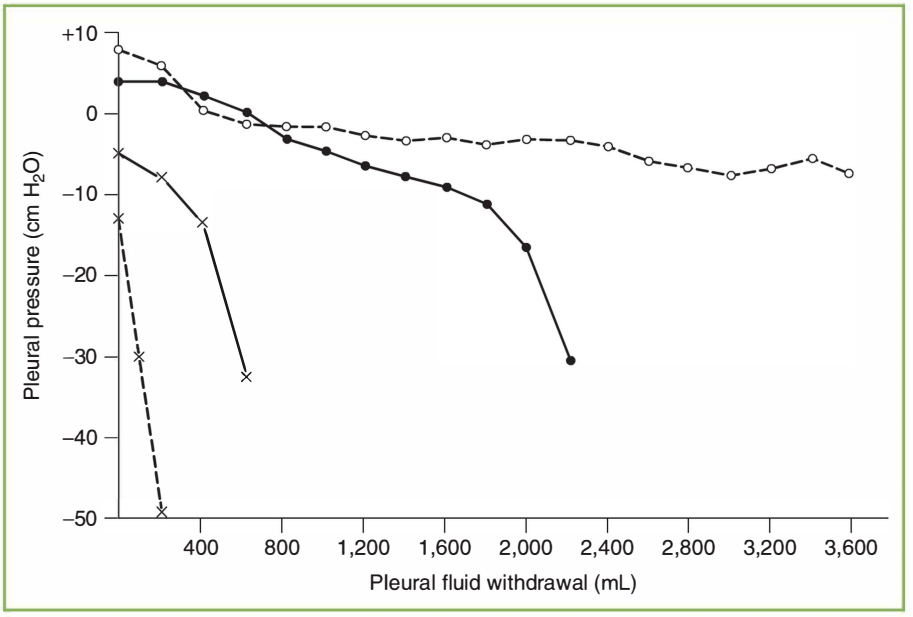

FIGURE 3.3 ■ The relationship between the pleural pressure and the amount of pleural fluid withdrawn in two patients with malignancy (*circles*) and two patients with trapped lung (*x's*). *(Reprinted with permission from Light RW, Jenkinson SG, Minh VD, et al. Observations on pleural fluid pressures as fluid is withdrawn during thoracentesis.* Am Rev Respir Dis. *1980;121:799–804.)*

(14) measured the change in pleural pressure after 500 mL of pleural fluid had been withdrawn in 65 patients with a pleural malignancy. They then inserted a chest tube and continued to drain the pleural space until (a) the drainage was less than 150 mL/day, (b) the drainage was less than 250 mL/day for four consecutive days, or (c) the drainage had continued for 10 days. After one of the three criteria was met, they attempted pleurodesis if the lung had expanded. They reported that the lung did not reexpand (trapped lung) in 11 of the 14 patients who had a pleural elastance greater than 19 cm H_2O/L (14). Pleurodesis was attempted in the other three patients with a high pleural elastance and it failed in all three. In contrast, only 3 of 51 patients with pleural elastance less than 19 cm H_2O/L had a trapped lung, and pleurodesis was successful in 42 of 43 patients (98%) who returned for evaluation (14).

EFFECTS OF EFFUSION ON PULMONARY FUNCTION

The effects of a pleural effusion on pulmonary function are difficult to determine. Many diseases that cause pleural effusions, such as congestive heart failure, malignancy, pneumonia and pulmonary embolism, also affect the pulmonary parenchyma. Therefore, it is frequently difficult to determine what part of the pulmonary dysfunction is due to the pleural effusion and what part is due to the underlying disease.

There have been a few studies on the effects of a pleural effusion on the pulmonary function of animals. Krell and Rodarte (15) studied the volume changes in the lung and thorax of dogs after 200 to 1,200 mL fluid was added to the right hemithorax. They found that the decrease in lung volume at FRC was approximately one third of the added saline volume, whereas the decrease in the lung volume at total lung capacity (TLC) was one fifth of the added saline volume. Consequently, the chest wall volume increased by two thirds of the added saline volume at FRC and by four fifths of the added saline volume at TLC (15). The decrease in the upper lobe volume was less than that of the lower lobe volume (15).

There have been several studies concerning the pulmonary function of patients with pleural effusions. We measured the pulmonary function in 15 patients with moderate to large pleural effusions and found that the mean forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) were only 43% ± 17% and 49% ± 17% of the predicted values respectively (16). Seven of the 15 patients had obstructive lung disease as reflected by an FEV_1/FVC ratio less than 0.70. Estenne et al. (17) reported that the FVC was less than 50% of the predicted value in all nine patients with a large pleural effusion.

TABLE 3.1 ■ Results of Maximal Exercise Tests Before and After a Therapeutic Thoracentesis in 15 Patients from Whom a Mean of 1,612 mL Pleural Fluid was Removed

Parameter	Preprocedure	Postprocedure	Change	Probability
FEV_1, L (% predicted)	1.56 + 0.63 (43)	1.74 + 0.69 (47)	0.18 + 0.23	0.007
FVC, L (% predicted)	2.32 + 0.76 (49)	2.63 + 0.81 (56)	0.31 + 0.43	0.013
Maxwork, watts (% predicted)	77.7 + 44.5 (43)	79.0 + 40.7 (44)	1.3 + 19.4	0.794
$\dot{V}o_2$max, mL/minute (% predicted)	992 + 431 (41)	1,038 + 395 (43)	46 + 226	0.449
$\dot{V}_E$max,L/min (% predicted)	45.1 + 20.2 (79)	48.2 + 18.8 (77)	3.1 + 11.8	0.321
$\dot{V}_E/\dot{V}o_2$max (% predicted)	46.1 + 9.9 (158)	47.3 + 12.0 (162)	1.2 + 5.2	0.394
$\dot{V}_E/\dot{V}co_2$max (% predicted)	45.6 + 7.4 (172)	44.7 + 8.1 (1.68)	−0.9 + 4.7	0.454
HR rest, bpm	93.4 + 16.6	93.6 + 17.2	0.2 + 12.9	0.953
HR max, bpm (% predicted)	120.7 + 15.6 (78)	114.6 + 17.3 (74)	−6.1 + 10.6	0.049
O_2 pulse rest, mL/beat	3.28 + 0.72	3.38 + 0.53	0.11 + 0.67	0.547
O_2 pulse SW, mL/beat	8.02 + 2.94	8.59 + 2.68	0.58 + 1.14	0.083
O_2 pulse max, mL/beat (% predicted)	8.21 + 2.99 (61)	9.04 + 3.00 (67)	0.83 + 1.57	0.070

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; $\dot{V}o_2$max, maximum oxygen consumption; $\dot{V}_E$max, maximum expired volume per unit time; Vco_2, carbon dioxide consumption per unit time; HR, heart rate; SW, same workload.

The pulmonary function abnormalities are not completely corrected by performing a therapeutic thoracentesis. We performed pulmonary function tests before and 24 hours after thoracentesis in 15 patients from whom a mean of 1,612 mL pleural fluid was withdrawn (Table 3.1) (16). In this study, the mean FEV_1 and FVC, expressed as a percent of predicted value, increased from 43% to 47% and from 49% to 56%, respectively (15). In a second study, we measured the pulmonary function in 26 patients before and 24 hours after thoracentesis during which a mean of 1,740 mL pleural fluid was removed. In this study, the FVC and the FEV_1 each increased by approximately 400 mL while the TLC improved by approximately 700 ml (18). In other words, for every 1,000 mL pleural fluid removed, FVC and FEV_1 improved by approximately 200 mL and the TLC improved more than the FVC or FEV_1. Our results are in contrast to the dog study outlined here, where the TLC was impacted less than the FRC. A possible explanation for the varying results in humans and in dogs is that in humans, the lower lobe is frequently completely atelectatic when a large pleural effusion is present. When fluid is then removed, the lower lobe reexpands and the residual volume in the reexpanded lobe increases the TLC more than just the vital capacity of the lobe.

Although on the average there is a 20-mL increase in the FVC for every 100 mL of pleural fluid withdrawn, much interindividual variability exists (Fig. 3.4). Changes in the FVC are related to pressure measurements during thoracentesis (18). Patients with higher initial pleural pressures and patients with smaller changes in the pleural pressure as fluid was removed tended to have larger improvements in their vital capacity. Nevertheless, when multiple regression was performed with the change in the FVC as the dependent variable and the initial pleural pressure, the pleural elastance, and the amount of fluid removed as the independent variables, the multiple regression coefficient (r) never exceeded 0.60 (18). This indicates that less than 40% of the variance in the change in the FVC was related to the amount of fluid removed and the measures of pleural pressure. Possible explanations for the poor correlation are that (a) the pulmonary function testing was not performed until 24 hours after the thoracentesis and the fluid might have returned to a variable degree at this time, and (b) the pleural pressure changes recorded reflected the elastance of the pleural space during the thoracentesis. If the lung had been atelectatic for a prolonged period, it may take several hours or days for the lung to reexpand, and (c) in some patients with large effusions, there is mediastinal shift to the

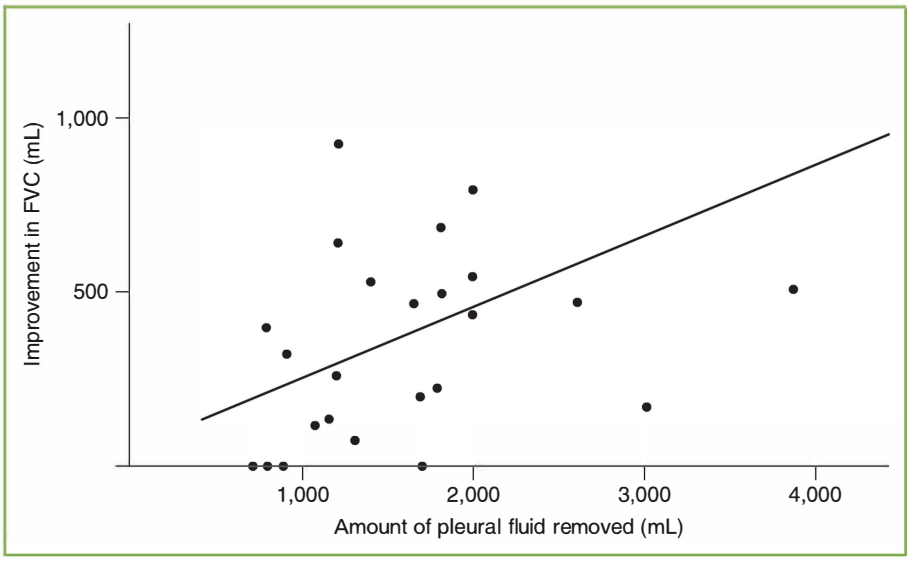

FIGURE 3.4 ■ Relationship between the amount of pleural fluid removed during thoracentesis and the improvement in the forced vital capacity (FVC) 24 hours after thoracentesis. *(Reprinted with permission from Light RW, Stansbury DW, Brown SE. The relationship between pleural pressures and changes in pulmonary function following therapeutic thoracentesis.* Am Rev Respir Dis. *1986;133:658–661.)*

opposite side, but this does not always occur with malignancy because of fixation of the mediastinum by the malignant process (18).

Estenne et al. (17) measured the changes in respiratory mechanics in nine patients 2 hours after the removal of a mean 1,818 mL pleural fluid. They reported a mean increase of 300 mL in the vital capacity, which was similar to what we have reported. They also found that the TLC increased approximately twice as much as did the FVC (17). In addition, they studied the maximal pressures generated by the inspiratory muscles and found that postthoracentesis the pressures generated were much greater at a given lung volume. The greater inspiratory pressures were attributed to a decrease in the thoracic cage volume (17). Although a mean of 1,818 mL pleural fluid was removed, the mean TLC increased by only 640 mL, indicating that the thoracic cage volume decreased by 1,818 − 640 = 1,178 mL. The changes in the inspiratory pressures were significant. For example, the maximal inspiratory pressure (MIP) at TLC was −16 cm H_2O before thoracentesis and increased to −25 cm H_2O after thoracentesis, whereas the highest MIP went from −41 cm H_2O before thoracentesis to −52 cm H_2O postthoracentesis (17). I believe that one factor that allows the patient to generate more pressure postthoracentesis is that the thoracentesis can relieve the downward displacement of the diaphragm by the pleural fluid.

Wang and coworkers (19) have provided support for the last hypothesis. These researchers compared the changes in pulmonary function before and 24 hours after a therapeutic thoracentesis in 21 patients with pleural effusion and paradoxical movement of a diaphragm and 41 patients without paradoxical movement of a diaphragm. Although the amount of pleural fluid removed did not differ in the two groups, post thoracentesis the paradoxical movement group had significant improvements in the FEV_1, the FVC, the A–a O_2 gradient, and the Borg score while the group without paradoxical movement did not have a significant change in any parameter. They found that the mean FVC increased by 260 mL, whereas the mean FEV_1 increased by 210 mL in the paradoxical movement group, which were changes similar to those observed by Estenne et al. (17) and our group (16,18). Interestingly, the patients in this study with paradoxical diaphragmatic movement were very dyspneic before thoracentesis and their dyspnea improved markedly following the thoracentesis. They attributed the decreased dyspnea to the fact that the diaphragm was no longer inverted.

A therapeutic thoracentesis has essentially no effect on the diffusion capacity of the lung (DLCO) (18) or the specific airway conductance (17,18).

EFFECTS OF EFFUSION ON BLOOD GASES

Although patients with pleural effusions frequently have abnormal arterial blood gas results, the performance of a therapeutic thoracentesis has relatively little effect on the arterial blood gas results.

In animals, the experimental induction of a pleural effusion can have a profound effect on the blood gases if the effusion is large enough. Nishida et al. (20) induced bilateral pleural effusions in pigs and reported that there was a mild decrease in PaO_2 (525 to 375 mm Hg on 100% O_2), while the $PaCO_2$ remained stable as the total amount of pleural fluid was increased to 30 mL/kg. However, when additional fluid was added, PaO_2 dropped precipitously and $PaCO_2$ started to increase (20). When the amount of pleural fluid reached 80 mL/kg, the PaO_2 (on 100% oxygen) was less than 80 mm Hg, whereas the $PaCO_2$ had increased from 34 to 51 mm Hg. When the pleural fluid was removed in these normal pigs, PaO_2 and $PaCO_2$ rapidly returned to normal (20).

Things seem more complicated in humans probably because of disease in the underlying lung and the fact that the pleural effusion has been present for much longer. Brandstetter and Cohen (21) obtained blood gases on 16 patients before, and then 20 minutes, 2 hours, and 24 hours after a thoracentesis in which 150 to 1,600 mL pleural fluid was removed. They reported that the mean PaO_2 at baseline was 70.4 mm Hg, and this decreased significantly to 61.2 mm Hg 20 minutes following thoracentesis. In every patient there was a decrease in PaO_2 over this 20-minute period. PaO_2 remained significantly reduced at 2 hours (64.4 mm Hg) but returned to baseline 24 hours later (21). In this study there were no significant changes in the pH or the $PaCO_2$ (21). Conflicting results were reported in a study (22) of 19 patients with adult respiratory distress syndrome (ARDS) on mechanical ventilation who had pleural effusions and refractory hypoxemia. When chest tubes were inserted to drain the fluid, PaO_2/FiO_2 improved from 151 ± 13 to 245 ± 29 mm Hg (22). In addition, the dynamic compliance of the lung increased from 27.1 to 35.7 mL/cm H_2O immediately after the insertion of the chest tubes (22). However, in another study on eight patients with pleural effusions of various etiologies receiving mechanical

TABLE 3.2 ■ Effects of Position on Oxygenation Status of Patients with Pleural Effusion

Study	n	PO_2 Effusion Down (%)	PO_2 Effusion Up (%)
Sonnenblick et al. (25)	8	66.7 ± 8.7	71.9 ± 9.3
Neagley et al. (26)	10	93.4 ± 2.1 (Sao_2)	94.7 ± 2.1 (Sao_2)
Chang et al. (27)	21	66.0 ± 66.0	69.6 ± 14.6
Romero et al. (28)	33	78.0 ± 12.5	81.4 ± 8.5

ventilation, there was no improvement in the alveolar–arterial oxygen gradient [$P(A\text{-}a)O_2$] after a therapeutic thoracentesis (23).

Why do patients with pleural effusions have hypoxemia? Agusti et al. (24) used the multiple inert gas technique in an attempt to determine the mechanisms for hypoxemia with pleural effusions. They studied the nine patients before and immediately after a thoracentesis (mean 693 ± 424 mL) (24). They reported that the mean $P(A\text{-}a)O_2$ was 29 mm Hg before thoracentesis and remained at 29 mm Hg post-thoracentesis (24). These investigators also showed that the main mechanism underlying arterial hypoxemia in patients with pleural effusion is an intrapulmonary shunt, which does not change significantly after thoracentesis. It is likely that the intrapulmonary shunt results from blood flowing through an atelectatic lung.

There have been four studies that examined the effects of position on the oxygenation status of patients with pleural effusions (25–28). In each study, the oxygenation status was slightly better when the patients were positioned with the side of the effusion superior (Table 3.2). The improvement was thought to be due to the effect of gravity distributing more blood to the lung that was not partially compressed by the pleural effusion. However, the differences in the mean levels of the oxygenation were not statistically significant in any of the studies and are probably not clinically significant either.

EFFECTS OF EFFUSION ON THE DIAPHRAGM

The presence of fluid in the pleural space can profoundly affect the function of the ipsilateral diaphragm because of the weight of the fluid on the diaphragm. The changes in the diaphragm have been classified into three categories by Mulvey (29) on the basis of the findings on the plain film and fluoroscopy. In the first or least severe category, the hemidiaphragm is domed and it functions normally. Patients in this category are usually asymptomatic although the effusion may be large. In the second category, the diaphragm is flattened and does not move with respiration. Patients in this category frequently complain of dyspnea, which is likely to be relieved with a therapeutic thoracentesis. In the third category, the diaphragm is inverted, and there may be paradoxical movements on respiration. Patients in this category usually have severe dyspnea that is markedly relieved with a therapeutic thoracentesis.

The percentage of patients in each of the three categories has not been studied carefully. Inversion of the diaphragm may be more common than is generally realized. Wang and coworkers (19) were able to document diaphragmatic inversion in 21 patients over a 3-year period. Interestingly, when these patients underwent therapeutic thoracentesis, they experienced marked relief of their dyspnea.

EFFECTS OF EFFUSION ON THE HEART

The presence of pleural fluid may also adversely influence cardiac function. Vaska et al. (30) studied seven spontaneously breathing dogs with a two-dimensional echocardiograph during the infusion of saline into both pleural spaces. In this study, right ventricular diastolic collapse began when the mean pleural pressure increased by 5 mm Hg. By the time the mean pleural pressure increased by 15 mm Hg, the stroke volume had fallen by nearly 50%, and the cardiac output had fallen by 33% (30). In contrast, Nishida et al. reported that the infusion of 20 mL/kg saline into each pleural space had no effect on the cardiac output in anesthetized pigs (20). In the Nishida study, the pleural pressure increased only by 3 mm Hg (20) as compared with 15 mm Hg in the Vaska study (30). It should be noted that Vaska et al. infused more than 50 mL/kg saline into the pleural spaces of their dogs (30).

The frequency with which large pleural effusions adversely affect cardiac function is not clear. Traylor et al. (31) studied 27 patients who had more than a

hemithorax occupied by pleural fluid. Before thoracentesis, some of the patients had clinical or echocardiographic signs of cardiac tamponade. Eight subjects had elevated jugular venous pressure, 8 had pulsus paradoxus, 6 had right ventricular diastolic collapse and 23 had flow velocity paradoxus. After thoracentesis, these abnormalities resolved in all but one of the patients (31). In most instances, however, the presence of a moderate or large pleural effusion occupying less than an entire hemithorax does not adversely affect the cardiac output. Sadaniantz et al. (32) reviewed the echocardiograms of 116 patients with pleural effusion and reported that 21 (18%) had right atrial collapse. Of those with right atrial collapse, one had concomitant right ventricular collapse, four had left atrial collapse and none had left ventricular collapse (32). Of the 21 patients with chamber collapse, 13 had large, 3 had moderate and 2 had small left pleural effusions. Chamber collapse was unusual with right-sided pleural effusion (32). It was not clear whether the chamber collapse compromised the hemodynamics in any of these patients (32). Ahmed et al. (33) studied the hemodynamics and the oxygen delivery in 22 mechanically ventilated patients who had moderate or large pleural effusions before and after they underwent drainage (mean 1,262 mL) of the effusions with a pigtail catheter. They reported that the mean cardiac output increased from 7.7 to 8.4 L/minute, but this change was not statistically significant (33). The pulmonary capillary wedge pressure and the central venous pressure both decreased significantly after the pleural fluid was drained (33).

There have been three reports of patients with life-threatening compromised cardiac output attributed to large pleural effusions (34–36). Negus et al. (34) reported a 60-year-old woman who presented with a large left-sided pleural effusion with marked mediastinal shift to the right. Shortly after presentation, her blood pressure became unobtainable, and her carotid and femoral pulses were very weak. When a chest tube was placed and 1,125 mL of pleural fluid was withdrawn, the blood pressure rose to 140/86 mm Hg and the pulses became bounding (34). Kisanuki et al. (35) reported a 68-year-old man who presented with a blood pressure of 90/60 and a large left encapsulated pleural effusion. A two-dimensional echocardiogram revealed that the pleural effusion compressed the lateral wall of the left ventricle. With M-mode echocardiogram, the left ventricular collapse was observed throughout diastole. After drainage of 500 mL of pleural fluid, the blood pressure rose from 90/60 to 120/80 mm Hg and the left ventricular collapse during diastole resolved (35). Kopterides et al. (36) reported two patients who had hemodynamic compromise with large left-sided effusions in whom transthoracic echocardiography demonstrated left ventricular diastolic collapse. It is probable that the increased pleural pressure resulting from the pleural fluid is responsible for the ventricular collapse and the decreased cardiac output.

EFFECTS OF EFFUSION ON EXERCISE TOLERANCE

There has been limited research on the effects of a pleural effusion on the exercise tolerance of patients. We obtained maximum exercise tests on 15 patients with moderate to large pleural effusions before and after they underwent a therapeutic thoracentesis. The symptom-limited exercise tests were conducted on a bicycle ergometer with 15-watt increments every minute (16). The mean age of the patients was 64.7 and most of them had malignant pleural effusions.

The exercise tolerance of these elderly patients was significantly reduced before the thoracentesis. The mean maximum workload was only 79 watts (43% of predicted) while the mean maximum $\dot{V}O_2$ was only 907 mL/minute (37% of predicted) (Table 3.1). When the individual exercise tests were examined, the explanation for the reduced exercise tolerance was not obvious. Eight of the patients appeared to be ventilatory limited ($\dot{V}E$max greater than 80% of predicted maximum at exhaustion), and four of these also appeared to be cardiac limited (maximum heart rate greater than 80% of predicted at exhaustion). There were two additional patients who appeared to be only cardiac limited. At the maximum tolerated workload (Emax) the remaining five patients appeared to be neither ventilatory nor cardiac limited. In general, the patients' ventilation was inefficient as evidenced by the high ventilatory equivalents for oxygen ($\dot{V}E/\dot{V}O_2$) and carbon dioxide ($\dot{V}E/\dot{V}CO_2$) (Table 3.1). In addition, the patients' cardiac function appeared to be impaired as evidenced by the high resting pulse (Table 3.1) and the reduced oxygen pulse (O_2 pulse), which is a reflection of the stroke volume.

The exercise tolerance of these 15 patients did not increase impressively after the performance of therapeutic thoracentesis (mean, 1,612 mL) (Table 3.1). Although the mean FEV_1 and FVC both improved significantly (Table 3.1), there was no significant change in the maximum workload or the $\dot{V}O_2$max. Overall, after thoracentesis five patients had an improvement in their workload, five patients had a decrease in the workload, and five patients had no change in the

workload. The change in exercise capacity was not significantly correlated with the amount of fluid removed or with the changes in pleural pressure. However, there was a significant correlation with changes in the FEV_1 ($r = 0.576$, $p < 0.05$), changes in the FVC ($r = 0.610$, $p < 0.05$), and changes in the maximum O_2 pulse ($r = 0.78$, $p < 0.05$).

In summary, based on this series, elderly patients with moderate to large pleural effusions have a marked reduction in their exercise capacity. Lung function, as reflected by the FEV_1 and the FVC, and cardiac function, as reflected by the O_2 pulse, are both reduced and contribute to the exercise limitation. However, the performance of a therapeutic thoracentesis results in no significant improvement in the mean exercise tolerance of the patients.

In a second study, Cartaxo and coworkers (37) measured the 6-minute walking distance before and 48 hours following a thoracentesis in 25 patients from whom a mean of 1,564 ml pleural fluid was removed. The 6-minute walking distance increased from 432 m to 495 m ($p < 0.001$) after the thoracentesis. The mean Borg score at the end of the walk decreased from 5.1 to 2.4. The fluid removal had no significant effect on the Spo_2 (37).

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chapter 4

Animal Models in Pleural Investigation

The pleural space is involved in many different disease processes. Animal models of pleural disease offer the opportunity to answer many questions regarding the pathophysiology and treatment of pleural diseases. There are several advantages to studying animal models rather than human disease. Animals are certainly easier to recruit. Variables can be more closely controlled in animal models than in humans. This reduces variance in the results and allows conclusions to be made with a smaller number of study participants. Investigational agents can be instilled in animals with much less bureaucracy than when they are instilled in humans.

When performing experiments in animals, it is important to select the appropriate species. Investigators should be aware of two important anatomical characteristics of the species they use. First, many animals, such as mice, have incomplete mediastinal separations with the left and right pleural spaces being in free communication (1). This eliminates the possibility of using the contralateral pleural space as a control. Second, some animals such as sheep have a thick visceral pleura resembling that of humans, whereas other animals such as dogs, rabbits, and mice have a thin visceral pleura. This difference in the thickness of the pleura has large influences on the formation and reabsorption of pleural fluid. Another important factor to consider is the availability of commercial enzyme-linked immunosorbent assays (ELISAs) for the proposed species. These kits are usually available only for humans and mice and one must determine if there is sufficient cross-reactivity with other species such as rabbits, guinea pigs, and sheep (1).

A large number of animal models have been developed to study diseases of the pleura. In this chapter, an attempt is made to outline the more common models that have been developed and to give examples of the type of information that has been obtained with their use.

MALIGNANCY

In general, there are three types of experimental models of malignant pleural effusion. In the first type, cells derived from spontaneously occurring tumors are injected into the species from which they are derived in an attempt to produce a malignant pleural effusion. The animals are immunocompetent. In the second type, tumor cells from different species are injected intravenously or intrapleurally. Most animals in which malignancies have been induced have some type of immunologic deficiency. In the third type, malignant pleural mesothelioma develops after animals are exposed to asbestos particles (intrapleurally, inhalationally, intratracheally, or intraperitoneally) (2).

Adenocarcinoma

In Mice. The best model malignant pleural effusion in mice has been developed by Stathopoulos et al. (3). In this model, 1.5×10^5 Lewis lung cancer cells, derived from a spontaneously arising lung adenocarcinoma in C57B/6 mice, are injected directly into the pleural space of C57B/6 mice. This results in multiple discrete pleural tumors and a malignant pleural effusion with a mean volume of 667 μL by day 14 and a 100% mortality by day 17 (3). The unique aspect of this model is that the animals are immunocompetent.

This model has been used to study several aspects of malignant pleural effusion including the following.

(a) Nuclear factor (NF)-κB is important for the progression of the tumor. If Lewis lung cancer cells expressing a dominant NF-κB inhibitor are injected, there is decreased tumor burden and decreased pleural effusion volume (3). (b) Administration of a vascular endothelial growth factor (VEGF) inhibitor decreases the bulk of the tumor and the amount of pleural fluid (4). (c) The administration of recombinant adenovirus-mediated delivery of human endostatin resulted in significant reduction in pleural effusion volume, the number of pleural tumor foci, microvessel density, and vascular permeability, while it significantly prolonged the survival time (5). (d) Host-derived IL-5 promotes experimental MPE and may be involved in the pathogenesis of human MPE (6). (e) A sundilac derivative with antiangiogenic capabilities halted experimental pleural effusion formation and intrapleural tumor dissemination, through down-regulation of pleural vascular permeability (7). (f) Angiopoietin/Tie2 axis blockade significantly reduced pleural fluid volume and pleural tumor foci (8). (g) Zoledronic acid, an aminobiphosphonate, treatment resulted in significant reductions in pleural fluid accumulation and tumor dissemination, while it significantly prolonged survival (9). (h) The knockout of osteopontin in the lung cancer cells significantly reduces the formation of MPE, but does not inhibit in vivo tumor growth of the cancer cells in mice (10). (i) Elevated expressions of aquaporin-1 and VEGF-protein are associated with increased volume of malignant effusion (11). Studies such as those outlined above can provide insights into possible treatment for malignant effusions in humans.

In another model of malignant pleural effusion in mice, male thymic BALL/c nude mice (Animal Production Area of the National Cancer Institute, Frederick Cancer Research Facility, Frederick, Maryland) are used (12). The tumor cells (1×10^6/300 μL of HBSS lung adenocarcinoma cell line PC14PE6 or the squamous cell line H226) are injected into the lateral tail vein of unanesthetized nude mice. The mice develop colonies of the adenocarcinoma in the lungs as early as 4 weeks after tumor inoculation and all recipients of the adenocarcinoma line, but not the squamous cell line, develop bloody pleural effusions (13).

The role of VEGF in the production of malignant pleural effusion has been investigated using the model in the above paragraph (13). Yano et al. (14) found that the intravenous injection of PC14, the adenocarcinoma cell line, resulted in multiple lung lesions with invasion of the pleura, and produced a pleural effusion containing high levels of VEGF. The level of expression of VEGF messenger ribonucleic acid (mRNA) and protein by the cell lines directly correlated with the amount of pleural effusion. When the PC14 cells were transfected with the antisense VEGF-165 gene, the tumor invasion of the pleura was not altered, but the amount of pleural effusion was decreased. When the H226 cells were transfected with either sense VEGF-165 or sense VEGF-121 genes, their direct implantation, but not their intravenous injection, led to localized vascular hyperpermeability and pleural effusion. This study suggested that in order for a metastatic malignancy to produce a pleural effusion, the tumor must both invade the pleura and express high levels of VEGF (14).

These same researchers then attempted to block the formation of malignant pleural effusion in their model by administering VEGF inhibitors (13). The inhibitor studied, PTK 787, is a specific inhibitor of VEGF receptor tyrosine kinase phosphorylation. The administration of PTK 787 at a dose of 100 mg/kg nearly eliminated the formation of pleural effusions, but doses of 10 and 50 mg/kg had no significant effect. PTK 787 appeared to decrease the formation of pleural fluid by reducing vascular permeability rather than by inhibiting tumor growth or pleural invasion. This experiment suggested that PTK 787 or other inhibitors of VEGF could be useful for the treatment of malignant pleural effusions.

Nagamachi et al. (15) assessed the effects of injecting various human non-small cell lung carcinoma (NSCLC) cell lines into nude mice. They injected 2×10^6 cells from eight different cell lines into the left pleural space. Seven of the eight cell lines were tumorigenic and growth rates were relatively high in four of the cell lines (PC14, Lu65, Lu99A, and H157) (15). Pleural effusions were not mentioned with these cell types. However, when mice were injected with the PC9 cells, they developed malignant pleural effusions (15). It was concluded that the PC9 cells could be used for a model of malignant pleural effusion (15).

In Rats. Ohta et al. (16) have developed a model of malignant pleural effusion in immune deficient rats that also uses the PC-14 adenocarcinoma cell line. These researchers reported that the injection of 1×10^7 cells into the subpleural space of the parietal pleura or into the pneumonectomy space resulted in disseminated malignancy in 8/8 animals and the development of a pleural effusion in 5/8 animals with a positive pleural fluid cytology in two (16). Interestingly, these workers showed that the intraperitoneal injection of monoclonal antihuman VEGF antibody

at a dose of 250 μg twice weekly prevented the development of the pleural effusion but did not affect the dissemination of the tumor (16).

Ebright et al. (17) injected 1×10^7 A549 cells of the human lung adenocarcinoma into nude male rats and reported that by 5 weeks, three of nine rats had developed pleural effusions. All the rats had tumor nodules on the lung and pericardium (17). In this model the intrapleural administration of NV1020, which is a novel, multimutated, replication-restricted herpes simplex virus, significantly inhibited the growth of the tumor (17).

Prosst et al. (18) used a similar model to assess the usefulness of thoracoscopic fluorescence in the diagnosis of pleural malignancies. These workers injected human lung cancer cells (adenocarcinoma 82/5) into the right pleural cavity through the lateral diaphragm and found that after 5 to 7 weeks the entire pleural cavity was affected with the malignancy (18). They did not mention whether the animals developed pleural effusions. They used this model to demonstrate that fluorescence enhanced the diagnostic capabilities of thoracoscopy (18).

In Rabbits. The intravenous injection of VX2 tumor cells in rabbits can lead to the development of a pleural effusion (19,20). The VX2 is rabbit papilloma tumor. Tumors are created in rabbits by the intravenous injection of approximately 25,000 VX2 cells obtained from an alive donor rabbit (19,20). When the rabbits are sacrificed 28 days after the injection, approximately 15% have a pleural effusion (20). The problem with this model is that the production of each pleural effusion is expensive because pleural effusions develop in only 15% of the animals. We have tried to create malignant effusions in rabbits by injecting the VX2 cells directly into the pleural space but were unsuccessful.

Melanoma

Melanoma metastatic to the lung can be produced by injecting murine melanoma cell lines into the lateral tail vein of syngeneic mice (21). In this model, syngeneic mice receive 5×10^4 B16-BL6 or B16-F10 melanoma cells in a total volume of 0.2 mL. At sacrifice 21 days after the cells were injected, Wang et al. (21) reported that all 20 mice injected with the two different cell lines developed lung metastases. The injection of B16-BL6 cells resulted in a pleural effusion in 8/10 with a median volume of 250 μL whereas the injection of the B16-F10 cells resulted in a pleural effusion in 9/10 mice with a mean volume of 320 μL. If the melanoma cells were administered to syngeneic mice lacking the gene for nitric oxide synthase (NOS) II, only approximately 50% of the animals developed pleural effusions and those that did had a lower volume (21). Immunohistochemical analyses indicated that absence of NOS II expression was correlated with decreased VEGF expression and tumor-associated vascular formation.

Fibrosarcoma

The intrapleural injection of fibrosarcoma can lead to a pleural fibrosarcoma with pleural effusion. Yasutake et al. (22) injected 1×10^5 Meth A fibrosarcoma cells intrapleurally in syngeneic BALB/c mice. All the injected mice in this model developed pleural fibrosarcoma and all developed pleural effusions with a mean volume of 733 μL. The mean survival of the injected mice was only 8.7 days after injection. Interestingly, when heat-killed cells of *Lactobacillus casei* were injected on day 3 or day 6, the mean survival was increased beyond 40 days and the amount of pleural fluid was only 14 μL (22). Intrapleural injection of antibodies against tumor necrosis factor alpha (TNF-α) completely eliminated the antitumor effect of the heat-killed cells of *L. casei* (22). The results of this study suggest that TNF-α can act as an antitumor drug in this model.

ASBESTOS AND MESOTHELIOMA

There have been many papers published on the relationship between asbestos and mesothelioma. Wagner (23) first reported in 1962 that in rats the intrapleural administration of chrysotile and crocidolite led to the production of mesothelioma. Then in 1965, Smith et al. (24) demonstrated that the intrapleural injection of amosite in hamsters led to the development of mesothelioma. Subsequently, there have been many papers written on the induction of mesotheliomas in animals. Asbestos has been administered intrapleurally, intratracheally, intraperitoneally, and by inhalation. In the following section, the results will be briefly described when asbestos is administered through these different routes.

Intrapleural Injections

The intrapleural injection of asbestos leads to the development of mesothelioma of the pleural space. Most studies have been performed in rats (23, 25–30), although there has been at least one report in hamsters

(24). When asbestos fibers are injected intrapleurally, approximately 30% to 60% of the animals develop a pleural mesothelioma (26,30). The tumors develop approximately 18 months after the intrapleural injection (26). There is a dose response, with larger doses being associated with higher incidence of tumor (30). When different types of asbestos are compared, the intrapleural injection of 25 mg chrysotile or crocidolite produce mesotheliomas in approximately 60% whereas the same dose of amosite produces tumors in 35% (31). The main difference in these types of asbestos is that mesotheliomas occur approximately 200 days later for amosite than for the other two types (31).

The propensity of a fiber type to produce a mesothelioma is dependent to a large extent on its geometric configuration. Long, thin fibers appear particularly likely to produce mesothelioma in man (27). The chemical composition of the asbestos fiber also influences whether its intrapleural injection will induce mesothelioma. If more than 80% of the magnesium is leached from chrysotile fibers, the proportion of animals developing mesotheliomas is dramatically lower than with untreated chrysotile (28). The rate of pleural mesothelioma will be more than doubled if pleural inflammation is induced by the intrapleural injection of carrageenan several months after the initial injection of asbestos (31).

Of all fibers tested, the most potent inducer of pleural mesothelioma is erionite (25,32). Wagner et al. (32) injected 20 mg of Oregon erionite, Karain Rock fiber, chrysotile, or nonfibrous zeolite intrapleurally to rats, and the incidence of mesothelioma was as follows: erionite 40/40 (100%), Karain Rock fiber 38/40 (95%), chrysotile 19/40 (48%), and nonfibrous zeolite 2/40 (5%) (32). Erionite in the air has been implicated in the epidemic of mesotheliomas in Turkey (33).

If normal rat mesothelial cells are treated *in vitro* with chrysotile fibers, mesotheliomas will develop rapidly when these cells are injected subcutaneously into nude mice. Fleury-Feith et al. (34) demonstrated that when untreated cells were injected, tumors developed in 3/5 animals at a median of 22 weeks after injection. However, if the cells were treated repeatedly with chrysotile, tumors developed in 5/5 animals at a median of only 1 week after injection (34).

Inhaled Asbestos

It is more difficult in general to produce tumors by the inhalation of asbestos than by intrapleural administration. There have been numerous reports of the effects of inhaled asbestos on rats (35–41), and one on baboons (42). Wagner et al. (40) exposed rats to asbestos clouds 7 hours/day, 5 days/week for 1 year. Even when asbestos is administered with such intensive regimens, the incidence of mesothelioma is less than it is after one intrapleural (41) or one intraperitoneal injection (38) of asbestos. When rats are given inhaled asbestos for 1 year, less than 10% develop mesothelioma, but approximately 30% develop lung tumors (40). Multivariate fibers analysis of multiple inhalational experiments has shown that the measure most highly correlated with tumor incidence is the concentration of structures 20 μm or more in length (35). Potency appears to increase with increasing length, with fibers longer than 40 μm being approximately 500 times more potent than fibers between 5 and 40 μm (35). When different types of asbestos are compared, chrysotile is less potent than amphiboles in inducing mesothelioma, but comparable in producing lung tumors (35). The most efficient agent at inducing mesothelioma after inhalation is erionite (32). Wagner et al. (32) demonstrated that the inhalation of Oregon erionite induced mesotheliomas in 27 of 28 (96%) rats and decreased their mean survival time from 738 days to 504 days.

It has also been demonstrated that inhaled asbestos can induce mesotheliomas in primates. Webster et al. (42) exposed baboons 6 hours daily for 5 days a week to amosite asbestos, except for 3 weeks of the year when the chamber had to be serviced. The animals were exposed for up to 900 days. Five of 10 animals developed malignant mesothelioma between 6 and 10 years after the initial exposure, and the remaining animals all developed asbestosis (42).

Intratracheal Injections

There have also been a few reports on the effects of asbestos administered intratracheally in hamsters (43,44), dogs (45), and monkeys (45). It is less burdensome to administer the asbestos intratracheally than to do inhalational treatments nearly daily for a year or more. However, in general it is difficult to induce mesotheliomas with intratracheal asbestos. Pylev (43) administered 10 mg of chrysotile twice a month to hamsters and reported that only 1 of 41 animals developed a malignant mesothelioma, although 25% of the animals developed a malignant lung tumor. The same researcher also tried to induce tumors in three monkeys with the intratracheal administration of 400 to 600 mg asbestos and reported that no tumors developed during 17 to 22 months of follow-up (43).

However, mesotheliomas were easier to induce in rats as the intratracheal injection of commercial chrysotile and commercial anthophyllite induced mesothelioma in 65.5% and 41.4%, respectively. Adachi et al. (44) administered amosite and crocidolite asbestos (2 mg/dose) intratracheally once a week for 5 weeks to Syrian hamsters and observed them for the following 2 years. Only 1 of the 40 animals that were exposed developed a mesothelioma. The study with the highest incidence of mesothelioma after intratracheal asbestos was reported by Humphrey et al. (45). In this study crocidolite, 4.75 mg/kg/week, was administered for 3 weeks every year for 4 years to 10 dogs. Seven of the dogs also smoked nine cigarettes per day, 5 days/week. They reported that pleural mesotheliomas developed in 6 of the 10 animals (60%), including 2 of the 3 that did not smoke (45). The animals with the mesotheliomas died between 6.5 and 9 years after the initial exposure. Four of the animals with mesothelioma had concomitant adenocarcinomas.

Intraperitoneal Injections

In general, it takes a smaller amount of asbestos administered intraperitoneally compared with that administered intrapleurally to produce a mesothelioma in the cavity where the asbestos was injected (25). The tumors after intraperitoneal injections usually occur in the peritoneal cavity. There have been many studies on the induction of mesothelioma by the intraperitoneal injection of asbestos, primarily because it is the easiest way to administer asbestos. The intraperitoneal injection of asbestos produces tumors sooner (~9 to 10 months) compared with intrapleural injections (~18 months) (26). Moreover, the order in which fibers induce mesotheliomas is the same after intrapleural and intraperitoneal injection. Erionite is the most potent, followed by chrysotile, crocidolite, and then amosite (25). Interestingly, silicon carbide is more potent at inducing peritoneal mesotheliomas than are any of the asbestos types (46).

The length of the fiber appears to be important in producing mesothelioma after intraperitoneal injections as well as intrapleural injections (47). Fibers longer than 20 μm and thinner than 0.95 μm were most likely to induce peritoneal mesotheliomas. When animals develop malignant peritoneal mesotheliomas after the intraperitoneal injection of asbestos, the first manifestation is the development of ascites (48). The ascitic fluid can then be injected into other animals so that the antitumor effects of different chemotherapeutic agents can be assessed (49).

ASBESTOS PLEURAL EFFUSIONS

Clinically, pleural effusions develop in patients who have been exposed to asbestos. The time between the initial exposure and the appearance of the pleural effusion is usually several decades. Attempts have been made to duplicate this asbestos pleural effusion in animals. When animals are observed for prolonged periods after asbestos is administered intrapleurally or inhaled, no benign effusions are observed. The intrapleural administration of 5 mL of 1% crocidolite asbestos suspension (50) into the pleural spaces of rabbits does result in a pleural effusion of 1.5 mL at 4 hours. The pleural fluid white blood cell (WBC) count and the chemotactic activity were higher in the animals given asbestos than in animals given saline (50). It was subsequently shown that interleukin 8 (IL-8) was responsible for much of the chemotactic activity (51). The relationship of this model to the asbestos effusion in man is not clear because the time course is so different.

Sahn and Antony (52) demonstrated that the intrapleural injection of 150 mg of UICC chrysotile B asbestos into rabbits resulted in a pleural effusion that reached its maximal volume of 3.8 $\pm$ 0.5 mL at 7 days and gradually decreased after that time. At 3, 6, and 8 months there was generally less than 1.5 mL pleural fluid present (52). The peak cellular influx (WBCs = 27,000 cells/mm^3) occurred at 24 hours when there were predominantly neutrophils in the pleural fluid. By 72 hours, macrophages were the predominant cells, whereas at 120 hours, lymphocytes were the predominant cells. The animals developed pleural plaques by 7 days and the pleural plaques were fully developed by 28 days. If the animals were made neutropenic before the asbestos was injected, there was never a macrophage influx. Moreover, the neutropenic animals did not develop pleural plaques, but rather developed marked fibrosis of the pleural space (52).

EMPYEMA

In general, there are only a limited number of good human studies on the treatment of parapneumonic effusion and empyema (53). One reason for this is that there is tremendous diversity in patients who have parapneumonic effusions and empyema. To compensate for this diversity, patients should be stratified according to the severity of their illness and their comorbidities (54). However, once stratification is accomplished, a given medical center sees only a few patients in each category per year. Therefore, good studies take a long time or they need to be

multicentered. Unfortunately, multicentered studies are expensive and difficult.

In view of these factors, one would think that there would be many studies in animals to help answer questions such as the following: (a) What is the role of therapeutic thoracentesis in the management of parapneumonic effusions? (b) What is the role of fibrinolytics in the management of loculated parapneumonic effusions? (c) Is the penetration of all antibiotics into the pleural space similar? (d) Is there a role for intrapleural antibiotics in the management of pleural infections?

Surprisingly, there has been little work done with experimental empyema. This may be related to the fact that it is difficult to produce an empyema in an animal without killing it. For example, if *Staphylococcus aureus, Escherichia coli*, or *Bacteroides fragilis* is injected into the pleural space of guinea pigs, the animals either survive without developing empyema or die of overwhelming sepsis (55).

At least six different models of experimental empyema have been developed.

Direct Injection into Dogs. This model was the first model developed to help study the empyema epidemic that occurred in United States servicemen during World War I. Graham and Bell (56) in 1918 injected 30 mL of pure broth cultures of a virulent strain of hemolytic streptococci into the pleural cavity of dogs. The first dog injected with this amount of broth died within 12 hours, but had 200 mL of serofibrinous fluid with a myriad of streptococci and a few necrotic leukocytes. This exudate was quite similar to that which was recovered from early human cases of streptococcus empyema. When these investigators subsequently injected smaller amounts of the broth into the animals, the survival improved. In their primary experiment, 20 dogs were injected with 1 to 3 mL of the pure broth. Then 4 to 24 hours after the injection, open drainage of the pleural space was established with a chest tube in 10 of the dogs, whereas the remaining dogs did not receive a chest tube. The dogs were paired and the stronger dog of the pair was selected for the open drainage. Nine of the 10 dogs that received the open drainage died, whereas only 7 of the 10 dogs without the drainage died. The only dog with the open drainage that survived pulled its chest tube out the day following the operation. In each pair, the dog that received the chest tube died sooner than the control dog (56). This experiment demonstrated that open drainage was detrimental to the dog. The results from this experiment were extrapolated to man and the practice of early open tube drainage of empyemas was discontinued.

Rabbits with Turpentine-Induced Pleural Effusions. This second model was developed by Sahn and Potts (57) in the late 1970s. In this model a sterile exudative pleural effusion was induced in rabbits by intrapleural injection of 0.3 mL turpentine. An empyema was produced when 1×10^9 *Streptococcus pneumoniae* organisms were injected into the pleural fluid 96 hours after the turpentine was injected (58). Within 3 hours of injecting the bacteria, the pleural fluid pH fell to a mean of 7.05 and the pleural fluid glucose fell to below 46 mg/dL. By 6 hours postinjection, the mean pleural fluid WBCs exceeded 75,000/mm^3. Subsequently, Shohet et al. (59) used this model to study empyemas due to *Klebsiella pneumoniae*. They injected 1×10^9 *K. pneumoniae* 96 hours after the turpentine was injected and demonstrated that at 1, 3, and 5 days postinoculation, the pleural fluid glucose was below 10 mg/dL and the pleural fluid pH was below 7.00 (59). It has also been demonstrated with this model that clarithromycin, moxifloxacin, and levofloxacin diffuse rapidly into the pleural fluid after they are administered intravenously. The area under the curve for all three of these antibiotics in the pleural fluid is higher than their area under the curve in simultaneously obtained serum (60,61).

One must question how closely this model mirrors empyema in humans because without antibiotic therapy or tube thoracostomy the pleural effusions resolve within 10 days, and at autopsy there are no significant findings in the pleural cavity or lungs (58). In addition, although this model has been used to study the penetration of antibiotics into the pleural space (59–61), the pleural thickening induced by the turpentine probably influenced the results.

Guinea Pigs with Umbilical Tape. The third model was developed in the mid-1980s to assess the factors that influence the development of an empyema when bacteria are injected into the pleural space (55). In this model, bacteria are injected into the pleural space after umbilical tape is placed in the pleural space to act as a foreign body to promote infection. If umbilical tape is not placed, the animals die of sepsis and do not develop an empyema (55). After the guinea pigs are anesthetized with an intramuscular injection of ketamine hydrochloride, 55 mg/kg, and acepromazine maleate, 0.5 mg/kg, a small skin incision is made at the level of the sixth to ninth intercostal space and the pleural space is bluntly entered. Then a piece of cotton umbilical tape 1 cm long and 1/8 in. wide is placed in the pleural space.

Using this model, Mavroudis et al. (55) demonstrated that the development of an empyema is

dependent upon the organisms injected. None of the animals injected with *B. fragilis* developed empyema, whereas empyema developed in 33% of those injected with *B. fragilis* plus *S. aureus* and 31% of those injected with *E. coli* plus *B. fragilis* (62). These investigators also used this model to demonstrate that the more organisms injected into the pleural space, the more likely the animal was to develop an empyema. For example, if 1×10^8 *E. coli* plus *B. fragilis* were injected, 10/10 animals developed an empyema, whereas if 1×10^6 of these organisms were injected, only 5/10 animals developed an empyema (55). If blood were injected in conjunction with the bacteria, the likelihood of developing an empyema was not increased. Lastly, guinea pigs that developed pneumonia were more likely to have an empyema.

The primary problem with this model is that it requires a foreign body in the pleural space that does not mimic the clinical situation in humans.

Rabbits with Bacteria in Agar. The fourth model was developed in the late 1990s by Sasse et al. (63). In this rabbit model, 1×10^9 *Pasteurella multocida* cultured in agar (rather than broth) were injected into the pleural space of rabbits. Agar, rather than broth, was used so that the mixture would remain in the pleural space longer. Procaine penicillin G was administered once per day starting 24 hours after the initial injection to prevent death from sepsis. With this model, the rabbits developed an empyema; 24 hours postinjection, the mean pleural fluid pH was 7.01, the mean glucose was 10 mg/dL, the mean lactic acid dehydrogenase (LDH) was 70 times higher than the upper normal limit for serum, and the Gram's stain and culture of the pleural fluid were positive (63). At 96 hours postinjection, the Gram's stain and culture of the pleural fluid were usually negative, but gross pus remained in the pleural space. Ten days postinjection, at least 50% of the animals had gross pus in their pleural space. Approximately 60% of the rabbits survived for 14 days and at autopsy most animals had pus in their pleural space. The typical rabbit at autopsy at 14 days would have its entire right chest filled with thick pus. In addition, the right lung would be completely collapsed with a thick peel of collagenous material covering the visceral pleura. Adhesions between the visceral and parietal pleura were uncommon.

This model closely mimics the empyema that occurs in humans. The process is not cured with antibiotics alone. The pleural fluid becomes infected, then loculated, and a rind is formed over the visceral pleura. The loculation in this model is less than that seen in human empyema.

This model has been used in an attempt to answer several questions concerning the management of empyema. One question that was investigated was whether therapeutic thoracentesis was a reasonable alternative to tube thoracostomy in the management of rabbits with empyema (64). Rabbits were randomized to receive daily therapeutic thoracentesis starting at 48 hours, chest tubes at 48 hours, or neither therapeutic thoracentesis nor tube thoracostomy (controls). The animals in the chest tube group had their chest tubes attached to a Heimlich valve and had their chest tubes aspirated at 12-hour intervals. In this study, the mortality rate in the therapeutic thoracentesis group (0/16) was significantly less ($p = 0.02$) than the mortality rate in the other two groups combined (9/33). When the surviving animals were sacrificed at 10 days, the gross empyema score in the therapeutic thoracentesis group was significantly lower ($p < 0.05$) than that in the chest tube group or the control group (64). This study suggests that therapeutic thoracentesis possibly has a role in the management of patients with empyema.

A second question addressed was whether the timing of the chest tube insertion is important in the treatment of empyema. Rabbits were randomized to receive no chest tube or a chest tube 24, 48, or 72 hours after receiving the *P. multocida* intrapleurally (Fig. 4.1) (65). The rabbits that received the chest tube at 24 or 48 hours had significantly better results

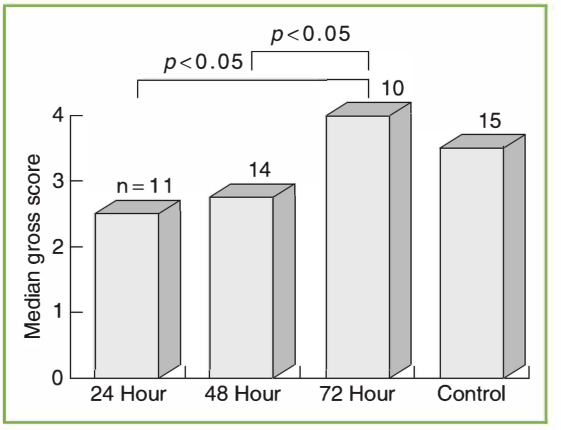

FIGURE 4.1 ■ Relationship between gross anatomical score and time of placement of chest tube. A score of 4 indicates pus in the pleural space, 3 = moderate pleural peel without gross pus, 2 = minimal pleural peel, 1 = adhesions between the visceral and parietal pleura, and 0 = normal pleural space. *(Reprinted with permission from Sasse S, Nguyen T, Teixeira LR, et al. The utility of daily therapeutic thoracentesis for the treatment of early empyema. Chest. 1999;116:1703–1708.)*

than did the rabbits that received the chest tube at 72 hours or those that did not receive a chest tube at all (65). This study demonstrates that a relatively short delay in initiating tube thoracostomy adversely affects the outcome in these animals with an empyema.

The third question addressed with this model was whether all antibiotics penetrate empyemic pleural fluid similarly (66). Twenty-four hours after the intrapleural injection of *P. multocida*, Teixeira et al. (66) injected either penicillin 24,000 units/kg, clindamycin 9 mg/kg, gentamicin 1 mg/kg, metronidazole 37 mg/kg, vancomycin 15 mg/kg, or ceftriaxone 30 mg/kg intravenously. Antibiotic levels in samples of pleural fluid and serum, collected serially for up to 480 minutes, were determined using a bioassay. In this study, the degree to which antibiotics penetrated the pleural fluid was highly variable (Figure 12.2) (66). Metronidazole penetrated most easily, followed by penicillin, clindamycin, vancomycin, ceftriaxone, and gentamicin. This variance in the penetration of antibiotics into empyemic pleural fluid should be taken into consideration when antibiotic therapy is chosen in patients with empyema.

Sasse et al. (67) investigated the role of transforming growth factor beta 1 (TGF-β_1) in the production of pleural fibrosis that sometimes occurs in this experimental model. These investigators reported that the levels of TGF-β_1 closely correlated with microscopic pleural thickness ($r = 0.7$, $p < 0.001$) and number of fibroblasts present in the visceral pleura ($r = 0.68$, $p < 0.001$). The level of TGF-β_1 increased during the 8 days of observation (67). This study suggests that inhibition of TGF-β_1 in patients with empyema might decrease the amount of residual fibrosis. These workers subsequently administered monoclonal antibodies to TGF-β_1 to determine if the antibodies would decrease the degree of fibrosis associated with the empyema (68). When the animals were sacrificed on day 6, immunohistochemistry revealed that the TGF-β_1 was localized to the macrophages in the exudative material and the visceral pleura. The animals that received antibody to TGF-β_1 had markedly decreased amounts of exudative material in the pleural space relative to control animals. All markers of empyema and pleural fibrosis were also significantly decreased in the rabbits receiving intrapleural anti–TGF-β_1 (68).

The technique reported by Sasse was modified so that chest tubes were implanted and drawn out between the scapulae to facilitate the intrapleural administration of therapeutic agents and the aspiration of pleural fluid (69). With this modification we have recently evaluated the usefulness of tissue plasminogen activator (tPA), or human recombinant DNase (rhDNase), or their combination in facilitating the drainage in this rabbit model of empyema (69). The combination of tPA (4 mg) and rhDNase (1 mg) administered intrapleurally twice a day for a total of six doses led to significantly lower empyema scores when the rabbits were sacrificed on day 10 (69). Neither agent by itself significantly reduced the empyema score (69). However, the mean amount of fluid aspirated from the rabbits that received tPA either alone or in combination with rhDNase (186 mL) was much greater than that in the rabbits that received rhDNase alone (0.7 mL) or saline (5.8 mL) (69). These results demonstrate that the administration of a combination of a fibrinolytic agent and a DNAase may be more effective than the administration of either agent by itself. These results also demonstrate that the administration of tPA leads to the production of large amounts of pleural fluid, but does not improve the empyema score. A possible explanation for the lack of benefit in this model with tPA alone is the observation that at autopsy, the animals have very few adhesions between the visceral and parietal pleura and the pleural fluid is not loculated in any group. Our group has also shown that in this model the intrapleural administration of 1,000 IU heparin alone or in combination with 1 mg of rhDNase every 12 hours for 3 days is no more effective than saline in the treatment of empyema in rabbits (70).

Na et al. (71) have subsequently shown that the excess fluid induced by the tPA is very inflammatory. The pleural fluid WBC count is above 100,000, the pH is below 7.10, and the LDH is more than 20 times the upper limit of normal. The characteristics of the fluid change little with time. This study (71) suggests that the intrapleural administration of tPA creates a large inflammatory process in the pleural space associated with the production of large amounts of pleural fluid.

Rats with Bacteria in Agar or Broth. Empyema can also be induced in rats by the intrapleural instillation of bacteria in agar (72) or broth (73). An empyema was induced in 25 rats by the intrapleural instillation of 1×10^{10} *S. aureus* in agar and 5 died of sepsis within the first 24 hours. Nine rats were sacrificed on the third day and all had pleural fluid (volume 0.5 to 3.8 mL) and bacteria in the pleural fluid. Eight rats were sacrificed on the fifth day and only three had pleural fluid (72). The amount of pus with this rat model appears to be less than when rabbits are injected with *P. multocida* in agar. Luo and associates

evaluated the effect of LP17, a synthetic inhibitor of triggering receptor expressed on myeloid cells-1 (TREM-1) on empyemas induced by the intrapleural injection of *Pseudomonas aeroginosa* or *Staphylococcus aureus* (73). They reported that there was a marked reduction in neutrophil numbers in the LP17 treated rats due to the reduction of both pleural effusion volume and total cell numbers. The LP17 treated rats also had a significantly higher survival rate.

Mice with Pneumonia Induced by Intranasal Inoculation of Bacteria. None of the above models mimic parapneumonic effusions because none of the animals have pneumonia as the primary cause of the effusion. Wilkosz et al (74) developed a model of empyema in mice via the intranasal inoculation of 0.5 to 1.0 $\times$ 10^7 *Streptococcus pneumonia*. The animals developed pneumonia. By 48 hours, all the mice had developed macroscopic pus in their pleural spaces. By 4 hours after inoculation, bacteria were detected in the pleural space of 33% of animals and by 48 hours all animals had large numbers of bacteria in their pleural spaces.

TUBERCULOSIS

Three types of animal models have been developed that relate to tuberculosis and pleural disease. In the hypersensitivity model, an animal is sensitized to tuberculous protein. Subsequently when tuberculous protein is injected into the pleural space, a pleural effusion develops. In the Bacillus Calmette-Guérinrin (BCG) model, BCG is injected directly into the pleural space and a pleural effusion develops. In the direct inoculation model, M. tuberculosis is injected directly into the pleural space in either sensitized or nonsensitized animals.

Hypersensitivity Model. With this model, which was first developed by Allen and Apicella (75), guinea pigs are immunized with a footpad injection of 0.2 mL of complete Freund's adjuvant containing 1 mg killed tubercle bacilli/mL, emulsified with an equal volume of isotonic saline. Three to 5 weeks after immunization, tuberculin purified protein derivative (PPD) in a total volume of 0.5 mL is injected intrapleurally. A pleural effusion then develops with a maximal volume of 4 mL at 24 hours and a protein concentration of 3.8 g/dL. In nonimmunized animals, the intrapleural injection of PPD leads to effusions with much lower volumes. There is no clear relationship between the amount of PPD injected and the size of the effusion once a threshold amount of PPD is given. This hypersensitivity and the capacity to form pleural effusions can be transferred passively with cells from a sensitized animal (75). This experiment was the first conclusive evidence that the pleural effusion with tuberculosis could be due to hypersensitivity.

Leibowitz et al. (76) subsequently used this same model to demonstrate that neutrophils were the predominant cells in the early stages of the effusion (<6 hours), whereas at 24 hours, lymphocytes and macrophages were the predominant cells. They also demonstrated that antilymphocyte serum (ALS) could completely suppress the reaction (76). Moreover, after treatment with ALS, the ability to produce a pleural effusion with the intrapleural injection of PPD paralleled the return of the positive skin reaction. These studies provided additional evidence that delayed hypersensitivity is responsible for the effusion.

BCG Model. Widstrom and Nilson (77) first described this model in which guinea pigs are immunized by the intracutaneous injection of 0.4 mg BCG into the left thigh that causes a small necrotizing skin reaction. Within 3 weeks of the injection, the animals have a positive skin test to PPD. Then if 2 mg of BCG is injected into the pleural space, a pleural effusion develops. The effusion is larger (mean 8 mL) than with the hypersensitivity model, reaches its maximal size at approximately 14 days and has, for the most part, disappeared by 21 days (77). Again in this model neutrophils were the predominant cells in the first 24 hours, but lymphocytes were the predominant cell after 5 days (77). When the lymphocytes first appear in the pleural fluid on approximately day 3, they do not respond to PPD. From day 5 onward, however, reactivity to PPD is found in most cases (78). The reactivity of the lymphocytes in the peripheral blood parallels that of the pleural lymphocytes (78). A similar model in which guinea pigs were immunized with a low-virulent strain of *Mycobacterium tuberculosis* was described by Paterson in 1917 (79).

A rabbit model using BCG has been described by Antony et al. (80). The rabbits are sensitized by the injection of BCG (1 $\times$ 10^6 organisms) intradermally on the leg. Three weeks later the rabbits have a positive skin test to PPD. Then BCG (4 $\times$ 10^6 organisms) is instilled into the pleural space (80). This results in a pleural effusion with a maximal volume of 5.9 $\pm$ 0.6 mL at 24 hours that decreases to 1.8 $\pm$ 0.4 mL by 120 hours (80). Neutrophils are the predominant cells in the first 24 hours, whereas macrophages are the predominant cells after 48 hours (80). If the

animals are made neutropenic, then the accumulation of pleural fluid and inflammatory cells is decreased (80). The intrapleural injection of neutrophils in the neutropenic animals restores the response to control levels. The neutrophils in the pleural space appear to secrete a monocyte chemotaxin that recruits monocytes to the pleural space and thereby contributes to the formation of granulomas (80).

Direct Inoculation Model. If nonsensitized guinea pigs are given *M. tuberculosis* intrapleurally, they die of generalized tuberculosis within 4 to 6 weeks (79). Ly and associated studied the role of TNF alpha in guinea pig tuberculous pleuritis in guinea pigs sensitized to BCG (81). In this study, *M. tuberculosis* was directly injected into the pleural space. They reported that the neutralization of TNF alpha hastened the transition to an anti-inflammatory cytokine response in guinea pig pleural granulomas and exudate cells (81). Du and coworkers injected *M. tuberculosis* intrapleurally to rats sensitized to BCG (82). They reported that all injected rats developed bilateral pleural effusions within 5 days. The pleural fluid had predominantly neutrophils at day 1 but lymphocytes by day 5. When an adenovirus carrying the vector for aquaporin-1 was injected intrapleurally 7 days prior to the injection of *M. tuberculosis*, the volume of pleural fluid was significantly increased (82).

PLEURAL INFLAMMATION

Inflammation of the pleural space has been studied by means of the intrapleural injection of several different inflammation-producing agents. Advantages of the pleural space for the study of inflammation in comparison to the paw edema and cutaneous models include the following (a) inflammatory exudates can be harvested relatively simply from the pleural cavity and (b) inflammatory irritants can be directly injected into the pleural cavity (83). Although pleural inflammation following the injection of carrageenan has been studied most intensively, the inflammatory reaction following the injection of other agents such as zymosan (84,85); endotoxin, or lipopolysaccharide (LPS) (86,87); monosodium urate (89); and miconazole (90), and following antigen–antibody reactions (88) has also been studied.

Carrageenan

Carrageenan-induced pleurisy in rats or mice has been widely used for many years for the study of inflammation in general and pleural inflammation in particular. When 1.2 mL of 0.25% carrageenan is injected into the pleural space of rats, the initial inflammatory response is in the immediate subpleural tissue that contains the blood vessels (91). Then there is a rapid release of WBCs into the pleural space along with the development of an exudative pleural effusion (91). The peak amount of exudative pleural fluid (1.75 mL) and the peak number of WBCs occur approximately 16 hours after injection (91). Initially, most of the WBCs are neutrophils. The number of mononuclear cells peaks at 24 hours when the numbers of mononuclear cells and neutrophils are comparable. By 72 hours postinjection, mononuclear cells account for 90% of the cells. By 96 hours, negligible numbers of neutrophils and pleural fluid remain (92). Pleural inflammation has also been studied in mice after the intrapleural administration of carrageenan. They develop inflammatory exudates 4 hours postinjection (93).

This model has been used to investigate the influence of many compounds on this inflammatory reaction. The following are a few examples of the many investigations carried out. The early (<48 hours) inflammatory response is depressed by cyclooxygenase inhibitors (aspirin and indomethacin) (91), but the response at 72 hours is influenced much less (92). Corticosteroids decrease the inflammatory response throughout the entire period (91). The selective cyclooxygenase inhibitors celecoxib and rofecoxib inhibit the inflammatory process less than aspirin or indomethacin (94).

There have also been studies at a more basic level. D'Acquisto et al. (95) demonstrated that there was NF-κB deoxyribonucleic acid (DNA) binding activity in the inflammatory cells that migrated into the pleural cavity at 3 and 6 hours. This activity was markedly increased at 24 hours and then decreased at 48 hours (95). Frode et al. (96) demonstrated that the intraperitoneal administration of NF-κB inhibitors before the intrapleural injection of carrageenan inhibited the inflammatory response. Sautebin et al. (97) demonstrated that there was a close correlation between the levels of nitric oxide and prostaglandin E_2 4 hours after the intrapleural injection of carrageenan (97). Scavengers of nitric oxide such as hemoglobin reduced the inflammation and the amount of prostaglandin E_2 in the pleural fluid (97).

The intrapleural injection of IL-6 5 minutes before the injection of carrageenan reduced in a dose-dependent and significant manner the exudation and total and differential leukocyte migration in both the early and late phases of the inflammatory response (98). The intrapleural injection of IL-10 resulted in

a significant inhibition of the early but not the late response (98). The administration of anti–IL-6 antibodies caused a significant decrease in both total and differential leukocyte influx, but significantly increased the exudation at 4 hours. The administration of anti–IL-10 antibodies caused graded and marked increases of both total and differential leukocyte influx and fluid exudation (98).

This model has also been used in experiments with knockout mice (mice deficient in certain genes). When IL-6 knockout mice are injected with carrageenan, both the amount of pleural fluid and the pleural fluid WBCs fall by 50%, as compared with wild-type mice (99). The same reduction in the inflammatory response is obtained if the mice are given anti–IL-6 before the carrageenan treatment (99). There is a marked reduction in the inflammatory response to carrageenan intrapleurally in mice deficient for the inducible NOS gene, as compared with mice that are not deficient in this gene (93).

Yuhki et al. (100) induced pleurisy with intrapleural carrageenan in knockout mice for the prostaglandin receptors (IP, EP1, EP2, EP3, or EP4) and demonstrated that the pleural exudation at 1 to 5 hours was significantly reduced in the IP, EP2, and EP3 knockout mice, but not in the EP1 or EP4 knockout mice. Leukocyte migration into the pleural cavity was not influenced by any of the receptor deficiencies (100). This study demonstrated that fluid exudation and leukocyte migration are not coupled. Knockout mice for 5-lipoxygenase have a significantly reduced inflammatory reaction to the intrapleural injection of carrageenan (101).

Zymosan

The intrapleural injection of zymosan in rats also produces an inflammatory exudate. When 0.1 mL of 2% zymosan is injected into the pleural space, the reaction is similar to that induced by carrageenan, with an early neutrophil influx and the maximal accumulation of pleural fluid at 24 hours. The maximal amount of fluid following zymosan and carrageenan in the rat are comparable (~1.5 mL) (85,91,102). The levels of TNF-α, IL-1, IL-6, and cytokine-induced neutrophil chemoattractant (CINC) in the pleural fluid all begin to increase after 1 to 2 hours, preceding the influx of neutrophils, and peak after 4 to 5 hours (85). The inflammatory response to carrageenan and zymosan are very similar. However, after the intrapleural administration of zymosan in the mouse, more Evans blue dye (a marker of vascular permeability) accumulates in the pleural cavity than when carrageenan is administered (103). Kikuchi et al. (102) have demonstrated that 5-lipoxygenase inhibitors, but not cyclooxygenase inhibitors (e.g., indomethacin), inhibit the infiltration of leukocytes into the pleural fluid 3 hours after the intrapleural injection of zymosan in rats. However, another study in mice (104) demonstrated that the administration of indomethacin reduced exudate formation to almost the extent that it was reduced in knockout mice for prostaglandin I_2. The degree of exudation was similar in the wild type mice and in the knockout mice for the prostaglandin E_2.

Lipopolysaccharide or Endotoxin

The injection of endotoxin into the pleural space of mice (88), rats (105), guinea pigs (105), and rabbits (87,106,107) leads to the accumulation of neutrophils in the pleural space at 4 hours and the accumulation of eosinophils and mononuclear cells at 24 hours, which persist for at least 96 hours (105). This model has been used to study pleural fluid eosinophilia (105).

Although the intrapleural injection of platelet activating factor (PAF) (108), leukotriene B_4 (108) or bradykinin (108) all induce delayed and long-lasting eosinophil infiltration in the rat pleural cavity, none of these appears to be involved in the eosinophil accumulation resulting from endotoxin. Treatment with inhibitors of any of these three cytokines does not prevent the eosinophil accumulation after endotoxin intrapleurally (105). In contrast, dexamethasone and the protein synthesis inhibitor, cycloheximide, abolish endotoxin-induced eosinophil accumulation (109). It has also been shown that the blockade of nitric oxide biosynthesis prevents endotoxin-induced eosinophil accumulation (110). Inhibitors of IL-5 do not prevent eosinophil accumulation after endotoxin is given intrapleurally (105), but they do prevent eosinophil accumulation after antigen-induced inflammation (111).

In rabbits, the intrapleural injection of endotoxin leads to neutrophil influx into the pleural space that peaks at 6 hours (87,106). There is also a biphasic increase in the vascular permeability with the first increase 15 minutes after the injection and the second increase 2 hours after the injection (87,106). Broaddus et al. (107) have demonstrated that the neutrophil influx is profoundly inhibited by neutralization of IL-8. Edamitsu et al. (87) have demonstrated that the early neutrophil influx is partly inhibited by anti–TNF-α

but not IL-1 receptor antagonists. In contrast, the late phase is inhibited by both anti–TNF-α and IL-1 receptor antagonists (87). These latter investigators also demonstrated that the immediate increase in permeability was inhibited by antihistamines but not by anti–TNF-α or IL-1 receptor antagonists (87). The late increase in vascular permeability was completely inhibited by either the depletion of neutrophils or by anti–TNF-α but not by IL-1 receptor antagonists (87). Fukumoto et al. (106) confirmed these results and also demonstrated that the delayed increase in vascular permeability was due to TNF-α-induced increases in IL-8.

Miconazole

There has been one study that reported that the intrapleural injection of 1, 2, or 4 mg of the synthetic antifungal imidazole, miconazole, resulted in an exudative pleural effusion in rats (90). The peak amount of fluid (~3 mL) occurs at 9 hours and is dose dependent. The peak cellular influx is at 7 hours and tends to persist for at least 24 hours. At 7 hours, most of the cells are neutrophils, whereas at 24 hours there are approximately 40% neutrophils, 40% mononuclear cells, and 20% eosinophils. Dexamethasone, and to a lesser degree phenylbutazone, but not chlorpheniramine or methysergide, markedly attenuate the fluid formation and leukocyte accumulation.

HYPERSENSITIVITY REACTIONS

The pleural space has also been used to study hypersensitivity reactions. In one model, rats are sensitized to ovalbumin with a subcutaneous injection of a mixture containing 50 μg of ovalbumin and 5 mg of aluminum hydroxide (112). Then 14 days after sensitization, 12 μg of ovalbumin are injected into the pleural space (112). After this intrapleural injection, there is an intense and early leakage of plasma proteins (as shown by Evans blue dye leakage) that peaks at 10 minutes and decays precipitously thereafter. Over a 4-hour period, approximately 1 mL of pleural fluid accumulates. The total pleural leukocyte count peaks at 24 hours and then declines over the following day. Neutrophils account for most of the cells in the first 24 hours, but thereafter eosinophils and mononuclear cells predominate (112). This model has been used to study the mechanisms of this allergic hypersensitivity reaction. The administration of systemic corticosteroids blocks the neutrophilic and eosinophilic influx in this model (88). The blockade of endothelin receptor A, but not endothelin receptor B, inhibits the antigen-induced eosinophil and mononuclear cell migration (113). The administration of a bradykinin receptor antagonist blocks the entire response in a dose-dependent manner (114). This model has also been used to show that lipoxin A4 and aspirin-triggered 15-epi-LXA dramatically block the influx of eosinophils into the pleural fluid, while concurrently inhibiting the earlier edema and neutrophil influx (115). The intrapleural injection of CCL22 by itself induces a dose- and time-dependent recruitment of eosinophils into the pleural cavity of mice (116). However, the administration of anti-CCL22 polyclonal antibodies during sensitization or before challenge had no significant effect on eosinophil recruitment (116).

A model of allergic pleurisy has also been developed in mice. In this model, mice are injected subcutaneously on days 1 and 8 with 100 μg of ovalbumin and 70 μg of aluminum hydroxide. Then 0.1 to 10 μg of ovalbumin are injected into the pleural space 7 to 10 days after the last subcutaneous injection. In this model, there is a dose-dependent recruitment of eosinophils after 48 hours (117). As in the rat model, leukocytes also accumulate early in the pleural cavity. This model has been used to show that both stem cell factor (SCF) (117) and eotaxin (118) play a major role in the recruitment of eosinophils in allergic pleurisy. In addition, this model has been used to show that the administration of IL-5 monoclonal antibodies prevents the accumulation of eosinophils in the pleural space (119).

PLEURODESIS

In patients with pneumothoraces or pleural effusions, one frequently wants to fuse the visceral and parietal pleura (pleurodesis) to prevent collapse of the lung with pneumothorax or accumulation of pleural fluid with pleural effusions. Animal models have been used to test the effectiveness of various agents for producing a pleurodesis.

Rabbit Model. The rabbit has been used more extensively than any other animal in the study of experimental pleurodesis. The primary problem with using the rabbit for a model of pleurodesis is that the rabbit has a thin visceral pleura whereas humans have a thick visceral pleura. Therefore, it is not obvious that the results of pleurodesis in rabbits can be extrapolated to humans.

Sahn and Good (120) performed the first comprehensive study of pleurodesis when they intrapleurally injected tetracycline (7 mg/kg, 20 mg/kg, 35 mg/kg),

hydrochloric acid (0.01 N), quinacrine (10 mg/kg), nitrogen mustard (0.2 mg/kg), bleomycin (1.5 mg/kg), and NaOH (5%) each in a total volume of 2 mL. These animals did not have chest tubes but did undergo five diagnostic thoracenteses over the first 6 days so the pleural fluid could be sampled. The intrapleural injection of any of these agents led to an exudative pleural effusion with very similar characteristics. However, when the animals were sacrificed at 30 days, the pleural space was essentially normal in all the animals except those that received 35 mg/kg tetracycline (120). Pleural symphysis involving more than 75% of the pleural space occurred in 9 of the 10 animals that received this dose of tetracycline. On the basis of this study, tetracycline became the most popular agent for pleurodesis in the 1980s.

In the early 1990s, the company that manufactured parenteral tetracycline in the United States ceased to produce the product because of more stringent manufacturing requirements. Accordingly, animal studies were performed to evaluate possible alternative agents. Light et al. (121) demonstrated that minocycline at doses of 7 mg/kg and doxycycline at doses of 20 mg/kg and above produced pleurodesis comparable to tetracycline 35 mg/kg. These investigators did not aspirate the pleural fluid. They noted that hemothorax occurred with doses that produced effective pleurodesis (121). Subsequently, Wu et al. (122) demonstrated that if small chest tubes were implanted in the rabbits at the time that they received the minocycline intrapleurally and if the chest tubes were aspirated on a daily basis, the hemothoraces did not develop and the excess mortality was prevented. In their initial publication concerning chest tubes, the chest tubes were kept in place with thoracic vests. Later investigators demonstrated that a better way to keep the chest tubes in place was to tunnel the tubing under the skin and draw the proximal end out through the skin posteriorly and superiorly between the two scapulae (123). The exterior end of the catheter is plugged with a stub adaptor fitted with a Luer lock. Air or liquid can be aspirated through a self-sealing injection site fitting with a Luer lock (123). The site of the exit wound posteriorly between the scapulae is very important. If the rabbit can reach up to this site, it will destroy the chest tube and the animal will end up with a pneumothorax.

There have been several studies that attempted to answer simple questions concerning pleurodesis with the tetracycline derivatives. Bilaceroglu et al. (124) have demonstrated that solutions of *oral* tetracycline and doxycycline preparations that are passed through a sterile membrane filter are as effective as the parenteral preparations in producing pleurodesis in rabbits. Ors Kaya et al. (125) have shown that administration of systemic diclofenac sodium, an antiinflammatory agent, decreases the effectiveness of tetracycline 35 mg/kg in producing pleurodesis. Zhu et al. (126) have shown that the pleurodesis score at autopsy correlates very well with the gliding sign on ultrasound. They concluded that ultrasound was the best way to noninvasively assess pleurodesis (126).

Komissarov et al. (127) showed that the loculations that occur after the intrapleural administration of tetracycline are better broken down with the proenzyme single chain urokinase plasminogen activator (scuPA) than with urokinase or alteplase. The profibrinolytic activity in the pleural fluid is greater after scuPA administration than after the other two agents (127). Lastly, these researchers concluded that scuPA promotes durable intrapleural fibrinolysis via formation of alphaM/uPA complexes. These complexes promote uPA-mediated plasminogen activation in scuPA-treated rabbits with TCN-induced pleural injury (127).

There have been multiple studies evaluating the effectiveness of talc for producing a pleurodesis in rabbits. The intrapleural administration of talc slurry produces a pleurodesis in rabbits, but the dose necessary to produce a satisfactory pleurodesis in rabbits (~400 mg/kg) is much larger than the dose that is normally recommended for humans (~100 mg/kg) (128). The pleurodesis that results from talc develops slowly and the pleurodesis at 28 days is much better than the pleurodesis at 14 days (129). The pleurodesis that results from this large dose of talc is less complete than the pleurodesis that results from tetracycline derivatives (128) or silver nitrate (130). The addition of thymol iodide to the talc does not lead to a better pleurodesis (131). If the rabbits are given systemic corticosteroids concomitantly, the effectiveness of the pleurodesis is decreased (132).

When humans are given talc intrapleurally in an attempt to create a pleurodesis, a small percentage develop the acute respiratory distress syndrome (133). There have been several studies in rabbits that have investigated the pathogenesis of this syndrome. Ferrer et al. (134) investigated the influence of talc particle size on extra pleural talc dissemination after talc slurry. They reported that although normal talc and large talc were both effective in producing a pleurodesis, the intrapleural injection of normal talc elicited a greater pulmonary and systemic talc particle

deposition than did the large size talc (134). A second study by the same group attempted to determine if the dose of the talc had any effect on its systemic distribution (135). They found that pleurodesis with the high talc dose (200 mg/kg) was associated with an increased risk of extra pleural talc deposition compared with the low talc dose (50 mg/kg) (135). Kennedy et al. (136) demonstrated talc in the mediastinal lymph nodes, kidney, and spleen in some of the animals that received 70 mg/kg talc intrapleurally. Marchi et al. (137) have shown that the intrapleural injection of 400 mg/kg talc produces a significant increase in the blood WBC count and percentage of neutrophils and an increase in the blood VEGF levels. Montes et al. (138) have demonstrated nerves in adhesions between the visceral and parietal pleural seven days after the intrapleural administration of talc slurry.

Recent studies have demonstrated that the intrapleural administration of 2 mL of 0.5% silver nitrate produces an excellent pleurodesis in rabbits (139). The pleurodesis resulting from this dose of silver nitrate is equivalent to that resulting from 35 mg/kg of tetracycline (130) and better than that resulting from 400 mg/kg of talc (139,140). The pleurodesis following silver nitrate intrapleurally persists for at least 1 year (140). Marchi et al. (137) have shown that there is a systemic inflammatory reaction after silver nitrate is given intrapleurally manifested by an increase in the serum LDH and IL-8 levels along with an increase in the VEGF level in the serum. This same group has demonstrated that if 0.1% silver nitrate is given three times rather than 0.5% silver nitrate once, the systemic inflammatory is markedly reduced, but the degree of pleurodesis is not altered. (141). Tremblay (142) and associates have demonstrated that the administration of 2 ml of 0.05% silver nitrate daily for 14 days results in an adequate pleurodesis.

Guo and associates (143) have shown that the intrapleural instillation of 2 ml of 2% or 4% iodopovidone (Betadine) produces a pleurodesis equivalent to that produced by 10 mg/kg doxycycline. If 0.8 mg/kg triamcinolone was administered weekly intramuscularly to the rabbits that received 4% iodopovidone, the degree of pleurodesis was markedly reduced (143).

The efficacy of various antineoplastic agents to induce a pleurodesis has also been investigated. Although bleomycin is used in humans with malignant pleural effusions to produce a pleurodesis, it is ineffective in rabbits at doses up to 3.0 IU/kg (120,144). In rabbits, the best antineoplastic agent for producing a pleurodesis appears to be nitrogen mustard (0.8 mg/kg) (145). Mitoxantrone is also effective in producing a pleurodesis, but at the doses necessary to produce a pleurodesis, cardiac toxicity develops and the animals develop congestive heart failure (146,147). Interestingly, the intrapleural injection of mitoxantrone leads to much more pleural inflammation than does the intrapleural injection of the tetracycline derivatives or talc (146). The intrapleural injection of dacarbazine or cytarabine does not produce a pleurodesis (145).

The mechanism of pleurodesis is not definitely known and it may vary from agent to agent (148). It has been thought that the initial event in the production of a pleurodesis is an injury to the pleura because the intrapleural injection of all the agents listed in the preceding text produces an acute exudative pleural effusion. However, the factors that dictate whether the inflammatory response will resolve or proceed to pleural fibrosis are not known. It has been shown that the intrapleural administration of tetracycline results in the local elaboration of IL-8 and monocyte chemotactic protein 1 (MCP-1) (149). The pleurodesis resulting from talc slurry but not that resulting from tetracycline derivatives is partially inhibited by blocking antibodies to TNF-α (123) and corticosteroids (150).

Cytokines are without a doubt involved in the production of a pleurodesis. In our first experiment to assess this assertion, we injected IL-8 alone or with talc to see if it would facilitate the creation of a pleurodesis. We found that IL-8 had no effect on the production of the pleurodesis in either circumstance (unpublished data). We next turned our attention to TGF-β. We demonstrated that the intrapleural injection of one dose of TGF-β_2 could produce a pleurodesis in a dose-dependent manner with a dose of 1.67 μg/kg producing an excellent pleurodesis (151). The intrapleural injection of TGF-β_2 also led to the production of large amounts of exudative pleural fluid, but the WBC count and the LDH level in the fluid were much lower than in the fluid resulting from the intrapleural administration of either talc slurry or tetracycline derivatives (151). These observations suggested that TGF-β_2 stimulated the mesothelial cells to produce collagen even in the absence of injury to the pleura. We subsequently demonstrated that the pleurodesis that resulted from TGF-β_2 occurred much faster than that which occurred following talc administration (152) and that the pleurodesis that occurs following intrapleural TGF-β_2 is not inhibited by corticosteroids (153). We have also shown that TGF-β_3 produces a pleurodesis comparable to that

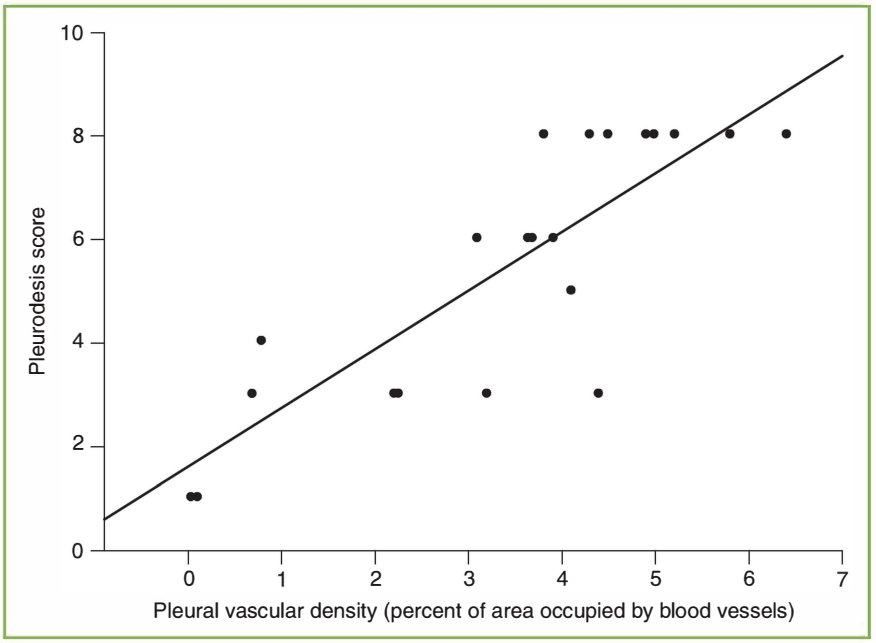

FIGURE 4.2 ■ Relationship between pleural vascular density and pleurodesis score ($r = 0.835$, $p < 0.01$). *(Reprinted with permission from Guo YB, Kalomenidis I, Hawthorne M, et al. Pleurodesis is inhibited by anti vascular endothelial growth factor antibody.* Chest. *2005;128:1790–1797.)*

produced by TGF-β_2 (154). I feel confident that the future for pleurodesis lies in its production by the intrapleural injection of cytokines.

This rabbit model has been used to investigate the mechanisms involved in the production of a pleurodesis. Idell et al. (155) have demonstrated that the intrapleural administration of single-chain urokinase plasminogen activator 24 and 48 hours after intrapleural tetracycline prevents the formation of adhesions at 72 hours indicating that fibrinogenesis is important in producing a pleurodesis. Marchi et al (156) measured the pleural fluid levels of IL-8, VEGF and TGF-β_1 in rabbits 6. 24 and 48 hour after they received 200 mg/kg talc. They found that the pleural fluid IL-8 concentration peaked at 6 hours whereas the VEGF and TGF-β_1 concentrations increased steadily over 24 hours. Guo et al. (157) administered anti-VEGF antibodies before rabbits were given TGF-β_2 intrapleurally with the hypothesis that the TGF-β_2 was inducing VEGF that was responsible for the large amounts of pleural fluid seen with intrapleural TGF-β_2. They were surprised when they observed that the rabbits that received the anti-VEGF antibodies had much less effective pleurodesis (157). When all the rabbits were analyzed, there was a close relationship between the angiogenesis in the pleural tissue and the pleurodesis score (157) (Fig. 4.2).

Teixeira et al (158) have shown that anti-VEGF antibodies also reduce the pleurodesis that occurs after the intrapleural administration of talc or silver nitrate. These studies demonstrate that pleural angiogenesis is very important in producing a pleurodesis.

Dog Model. There have been several studies of pleurodesis that utilized dogs. However, dogs, as do rabbits, have a thin visceral pleura, so extrapolating results in dogs to humans may not be possible. Bresticker et al. (159) performed bilateral thoracotomies on mongrel dogs and subjected the animals to mechanical dry gauze abrasion, chemical sclerosis with 500 mg of tetracycline, talc poudrage with 1 g, Nd:yttrium aluminium garnet (YAG) laser photocoagulation, or argon beam electrocoagulation of the parietal pleura (159). When the animals were sacrificed at 30 days, the mechanical abrasion and the talc were found to produce the best pleurodesis and were virtually equivalent. Jerram et al. (160) reported that mechanical abrasion was significantly better than 1 g talc slurry at producing a pleurodesis (160). Colt et al. (161) compared the pleurodesis resulting from

dry gauze abrasion, thoracoscopic mechanical abrasion using a commercially available stainless-steel grooved burr abrader, thoracoscopic talc insufflation (4 g), and instillation of talc slurry (5 g) at 30 days. They reported that the talc insufflation was the best, followed by mechanical abrasion (161). The differing results in the studies mentioned in the preceding text may be related to the vigor with which mechanical abrasion was performed or the amount of talc used.

Pig Model. There have also been several articles in which pleurodesis has been studied in pigs, a species which has a thick pleura similar to humans. Whitlow et al. compared the pleurodesis that results from 3 g of insufflated talc and 300 mg of minocycline administered during thoracoscopy and reported that the insufflated talc produced superior pleurodesis (162). Cohen et al. reported that the pleurodesis resulting from the insufflation of 5 g of talc or the instillation of 5 g of talc as a slurry was virtually identical (163). Lardinois et al. (164) reported that the systemic administration of diclofenac (2 mg/kg) orally for 3 weeks after surgery significantly reduced the pleurodesis scores in pigs.

Sheep Model. There has been one pleurodesis study in sheep, another species with a thick pleura like that in humans. Lee et al. (165) demonstrated that the intrapleural administration of TGF-β_2 produced an excellent pleurodesis in sheep as it had in rabbits (151). There were two significant differences in the results with sheep and those with rabbits. First, the dose of TGF-β_2 necessary for pleurodesis in the rabbits (1.67 μg/kg) was much larger than the dose necessary for pleurodesis in sheep (0.25 μg/kg). One possible explanation for this observation is that the dose is more dependent on the body surface area than on the weight. This is a reasonable supposition because the surface of the lung is more directly correlated with the body surface area than it is with the body weight. Indeed, if the dose of the TGF-β_2 is adjusted for body surface area, the dose in each species is approximately the same, 9.2 μg/m^2 in rabbits and 6.3 μg/m^2 in sheep. This relationship of dose to body surface area should be considered when results in animals are extrapolated to humans. Secondly, in sheep, the pleurodesis could be accomplished without the side effect of producing large amounts of pleural fluid. These studies demonstrate that the species used has a significant influence on the results for pleurodesis.

Rat Model. Pleurodesis has also been investigated in the rat. Sugarmann et al. (166) studied the effectiveness of pleural abrasion with or without absorbable polyglactin (Vicryl) or nonabsorbable polypropylene (Marlex) meshes in rats. Marlex alone incited an extensive and dense pleural reaction not suitable for clinical use because it induces a fibrothorax (1). However, the use of Vicryl in conjunction with pleural abrasion produced a better pleurodesis than the pleural abrasion alone 3 to 4 months after the procedure (166). Cetin et al. (167) demonstrated that the intrapleural administration of 2.5 mg of 0.5% polidocanol, a sclerosing agent used in the treatment of extremity and esophageal varices, was more effective than 35 mg/kg of tetracycline in producing a pleurodesis. The same group (168) subsequently demonstrated that fibrin tissue adhesive with fibrinogen and thrombin concentrations of 30 mg/mL and 10 U/mL was more effective for pleurodesis than tetracycline 35 mg/kg. Werebe et al. (169) administered 10 or 20 mg of talc intrapleurally to 40 rats and found talc crystals in every organ examined 24 to 48 hours after the intrapleural injection. Fraticelli et al. (170) came to the opposite conclusion after they injected 33 rats with 40 mg of talc slurry. They reported that a few talc particles were found in the liver of two rats, in the spleen of one rat, and on the brain surface of another rat (170). Unfortunately, there were no control animals in either of these studies.

Mouse model. It would be very useful to have a mouse model of pleurodesis. Mice are inexpensive and the availability of knockout mice would allow one to study the mechanisms of pleurodesis. However, it is difficult to produce pleurodesis in mice. Kalomenidis et al. (171) attempted to produce pleurodesis in mice by the injection of up to 1,360 μg/kg of TGF-β_2, 100 mg/kg of doxycycline or 4 g/kg of talc, and none of the mice had a pleurodesis in which there was more than 25% symphysis between the visceral and parietal pleura.

Pleural Fibrosis. Animal models have also been used to study pleural fibrosis. Decologne and associates (172) used adenoviral gene transfer of TGF-beta$_1$ in rats to demonstrate that local and transient TGF-beta$_1$ overexpression induces homogenous, prolonged, and progressive pleural fibrosis without pleurodesis. They further demonstrated that pleural fibrosis can expand into the lung parenchyma from the visceral layer, but not into the muscle from the parietal layer (172). This same group (173) also showed that carbon particles administered to the pleural cavity caused severe pleural fibrosis in the presence of bleomycin, whereas bleomycin alone had no fibrogenic effect. The pleural response was associated with

progressive fibrosis in subpleural regions, similar to human interstitial pulmonary fibrosis. Matrix accumulation within this area evolved through "mesothelial-fibroblastoid transformation" where mesothelial cells acquire myofibroblast characteristics. In contrast, carbon did not exaggerate bleomycin-induced pulmonary fibrosis after combined intratracheal administration (173). These studies suggest that the mesothelium might be important in the production of interstitial pulmonary fibrosis.

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chapter 5

Cytokines and the Pleura

Cytokines are soluble peptides secreted by cells that affect the behavior of either the same or nearby cells through nonenzymatic means. Often they are glycopeptides and typically exert their effects at very low concentrations in the picomolar to nanomolar range. Within this broad class are a number of subclasses, including polypeptide growth factors, interleukins (ILs), interferons, and colony-stimulating factors.

In recent years, much research has been devoted toward understanding the role of these peptides. It is not surprising, therefore, that there have been numerous reports assessing the diagnostic utility of the levels of different cytokines in the pleural fluid. In general, with the exception of interferon-gamma, the diagnostic usefulness of cytokine levels in pleural fluid remains to be demonstrated. Nevertheless, I have elected to include a chapter on cytokines and the pleura because their study has provided clues about the pathogenesis and resolution of pleural injury.

INTERLEUKIN 1

IL-1 has an essential role in T-cell activation and is considered a proinflammatory cytokine (1). It is a strong immune adjuvant and contributes to the stimulation of nonspecific host responses besides promoting wound healing (2). It enhances blood flow and the induction of chemoattractants, which bring to the injury sites the key inflammatory cells. The administration of high doses of IL-1 to animals produces a clinical picture of systemic inflammation that mimics septic shock (2). IL-1 is composed of two separate cytokines, IL-1α and IL-1β (3). IL-1α is an immunoregulatory cytokine with an essential role in T-cell activation (3). IL-1β is the predominant form of IL-1 released upon stimulation of human monocytes and macrophages (3). IL-1β induces mesothelial cells to release plasminogen activator inhibitor type 1 (PAI-1) and transforming growth factor beta (TGF-β) (4).

The highest levels of pleural fluid IL-1 (5) and IL-1β (6) are seen with empyema, which is the pleural disease with the most inflammation. Pleural fluid IL-1 and tissue necrosis factor alpha (TNF-α) are significantly correlated (1). The mean levels of IL-1 are significantly higher in tuberculous than in malignant effusions (1,7), but there is sufficient overlap that IL-1 levels are not useful diagnostically. In one paper, the pleural fluid levels of IL-1 were higher than the simultaneous serum levels, suggesting local production (1). In another paper (3) the pleural fluid levels of both IL-1α and IL-1β were lower than the simultaneously obtained serum levels in patients with both malignant and benign pleural effusions. The pleural fluid levels of IL-1β are higher in exudates than in transudates.

Pleural fluid levels of IL-1 appear to be associated with loculated pleural effusions and the development of pleural fibrosis. Patients with tuberculous pleuritis who develop chronic pleural thickening have significantly higher IL-1 levels than those who do not (1). Patients with loculated pleural effusions have much higher pleural fluid levels of IL-1β than patients with nonloculated pleural effusions irrespective of whether the effusions are due to malignancy, pneumonia, or tuberculosis (4). The levels of IL-1β correlate positively with the levels of TGF-β and PAI-1 in the pleural fluid, but negatively with the levels of tissue type plasminogen activator (tPA) (4).

There is a naturally occurring interleukin-1 receptor antagonist (IL-1RA). Marie et al. (8) measured the IL-1RA levels in the pleural fluid and serum of 24 patients. They found that the mean plasma level of

IL-1RA was significantly higher than the mean pleural fluid level and patients with infections did not have higher levels than those without infections (8).

INTERLEUKIN 2

IL-2 plays a crucial role in the mediation of the immune response. The interaction of IL-2 with the IL-2 receptor stimulates a cytokine cascade that includes various interleukins, interferons, and TNF-α (2). IL-2 also induces and maintains the proliferation of T lymphocytes following mitogen or antigen activation and it also induces production of cytotoxic lymphocytes, natural killer (NK) cells, and lymphokine-activated killer cells (2).

The ability of IL-2 to induce the production of these lymphocytes has led to the evaluation of its antitumor effects. Intrapleural IL-2 has been used to treat malignant pleural effusions because of its ability to induce the production of the various lymphocytes (9). When IL-2 is administered intrapleurally, there are increases in the pleural fluid levels of IL-6, but not of TNF-α or IL-1 (9). When IL-2 is injected intrapleurally in patients with positive pleural fluid cytology, the cytology becomes negative within approximately 1 week (10). When mesothelial cells are incubated with IL-2, there is a significant increase in their proliferative response and cytolytic activity against autologous tumors (11). In one study, the intrapleural administration of low-dose IL-2, as an initial treatment, resulted in an objective clinical response in 72 of 100 patients (72%) with a median duration of 5 months (12).

There is one other situation in which IL-2 is relevant to the pleural space. When high-dose intravenous IL-2 is used to treat metastatic disease, a capillary leak syndrome develops in some patients (see Chapter 22) (2). This syndrome is characterized by an increase in vascular permeability which frequently results in pleural effusions (13). In mice, this capillary leak syndrome can be prevented by the oral administration of a nitric oxide inhibitor (14).

As with IL-1, the pleural fluid levels of IL-2 are higher with exudates than with transudates and with tuberculous pleuritis than with malignant pleural effusion, but there is much overlap (7,15). IL-2 levels tend to be lower in the pleural fluid than in the simultaneously obtained serum (3). The pleural fluid levels of IL-2 are significantly correlated with the pleural fluid levels of IL-4, IL-5, IL-10, and TNF-α (16). One of the first events with T-cell activation is the synthesis and surface expression of an interleukin 2 receptor (IL-2R) along with the release of a shorter soluble form of IL-2R. The median levels of the soluble IL-2R are higher in exudates than in transudates and are higher in tuberculous effusions than in malignant pleural effusions, and parapneumonic pleural effusions, but again there is substantial overlap (15,17). The highest pleural fluid IL-2R levels are seen with rheumatoid pleuritis (18).

INTERLEUKIN 3

IL-3 induces the proliferation of eosinophils *in vitro* and also prolongs their survival. In patients with eosinophilic pleural effusions, IL-3 appears to help promote the eosinophil proliferation and also prolongs the survival of eosinophils. It appears, however, that IL-3 is less important than IL-5 in promoting these two activities in patients with eosinophilic pleural effusions. Blocking antibodies to IL-5 neutralize more of these activities than do blocking antibodies to IL-3 (19). IL-3 is not detectable by enzyme-linked immunosorbent assay (ELISA) in eosinophilic pleural effusions (20,21).

INTERLEUKIN 4

Human immunity has two major components—cellular and humoral. The T-helper type 1 (Th1) pathway favors cellular immunity, whereas the Th2 pathway favors humoral immunity (22). Early determination toward Th1 and Th2 cells in the immune response is dependent on the balance between IL-12, which favors the Th1 response, and IL-4, which favors the Th2 response. In a murine model of delayed hypersensitivity, the subcutaneous administration of recombinant murine IL-4 significantly blocked cell trafficking into the pleural space (23).

In one study on 21 patients with malignant pleural effusions, IL-4 levels in the pleural fluid were below minimal detectable concentrations (22). In another paper, the IL-4 pleural fluid levels were measurable in at least some patients, but there was no significant difference in the levels in patients with tuberculosis or malignancy (24). However, in a subsequent study, IL-4 levels were detectable by cytometric bead array in almost all the pleural fluids that were tested (16).

INTERLEUKIN 5

IL-5 is a T-helper 2 cytokine, which is important in the trafficking of eosinophils. IL-5 induces the proliferation of eosinophils *in vitro* and prolongs their survival. Pleural fluid IL-5 levels are elevated in patients with

posttraumatic eosinophilic pleural effusions (20). The pleural fluid from such individuals acts as a stimulus for eosinophil colony formation, and this stimulatory capability is largely blocked by specific antibodies toward IL-5. In like manner, eosinophilic pleural fluid enhances the survival of eosinophils, and this capability is largely blocked by specific antibodies toward IL-5.

When air is introduced into the pleural space of mice, there is a brisk eosinophilic response with a 100-fold increase in pleural eosinophils by 12 hours, which peaks at 48 hours (25). When IL-5 knockout mice are injected with air, the number of eosinophils in the pleural lavage increases, but only approximately 10% as much as they did in the wild-type mice (25).

In 40 patients with pleural fluid eosinophilia, including 30 with more than 10% eosinophils, there was a significant relationship between the number of eosinophils in the pleural fluid and the pleural fluid IL-5 level ($r = 0.55$) (21). In a subsequent paper, the pleural fluid and serum IL-5 levels were measured in 38 patients with pleural effusions occurring after coronary artery bypass graft surgery including 13 with eosinophilic pleural effusions (26). In this study, the pleural fluid IL-5 levels significantly correlated with the pleural fluid eosinophil counts and the serum IL-5 levels significantly correlated with the number of blood eosinophils (26). The pleural fluid IL-5 levels were significantly higher than the serum IL-5 levels (26). In patients with paragonimiasis, the pleural fluid IL-5 levels are markedly elevated and correlate with the number of eosinophils in the pleural fluid (27). Therefore, it appears that IL-5 is one of the primary factors responsible for eosinophilic pleural effusions.

It appears that pleural fluid IL-5 is important in the pathogenesis of malignant pleural effusions at least in mice. When Lewis Lung Cancer cells or adenocarcinoma cells are injected directly into the pleural space of mice, host derived IL-5 promotes the formation of malignant pleural fluid (28). Knockout mice for IL-5 produce much less pleural fluid and have less tumor growth than wild type mice (28).

INTERLEUKIN 6

IL-6, also called *B-cell stimulatory factor*-2 or *hepatocyte-stimulating growth factor*, is a multifunctional cytokine produced by several different cell types such as monocytes, fibroblasts, and endothelial cells (29). IL-6 has a pivotal role in many regulatory functions including maturation of B-cells to antibody-producing cells and induction of the synthesis of acute phase proteins. When IL-6 is injected 5 minutes before the intrapleural injection of carrageenan in the mouse, the exudation and total and differential leukocyte migration in both the early and late response are reduced in a dose-dependent and significant manner (30). The intrapleural injection of IL-6 antibodies 30 minutes before the intrapleural injection of carrageenan decreases both the total and differential leukocyte influx, but significantly increases the exudation (30).

The levels of IL-6 are much higher in the pleural fluid than they are in the serum (3,29,31) and the mean IL-6 levels are much higher in exudates than in transudates (6,29,32). Tuberculous effusions contain a significantly higher level of IL-6 than do malignant pleural effusions (32) or parapneumonic effusions (6). The pleural fluid from patients with mesothelioma has a significantly higher mean IL-6 level than does the pleural fluid from patients with adenocarcinoma (33). It has been postulated that the thrombocytosis seen in patients with mesothelioma is due to the intrapleural production of large amounts of IL-6 (33). The intrapleural administration of IL-2 results in increased pleural fluid levels of IL-6 in malignant pleural effusions (9). One study reported that the levels of soluble IL-6 receptor in the pleural fluid were lower than those in the serum and were comparable in different diagnostic categories (34).

INTERLEUKIN 7

IL-7 was originally discovered as a pre–B-cell growth factor (35). Soon thereafter, it was found to be a critical cytokine for normal T and B lymphopoiesis and a mobilizer of pluripotent stem cells and myeloid progenitors. It has also been found to enhance T-cell functioning and induce cytokine expression in monocytes (35). In cell culture, the proliferative response of lymphocytes from malignant pleural effusions is increased significantly more with IL-7 plus IL-2 than with IL-12 plus IL-2. Chen et al (35) concluded that IL-7 in the presence of IL-2 could restore the immunosuppressed cytolytic activity of the lymphocytes of malignant pleural effusion against autologous tumor. To my knowledge, there have been no studies in which the pleural fluid levels of IL-7 have been measured.

INTERLEUKIN 8

IL-8 is a powerful neutrophil chemotaxin that contributes to the influx of neutrophils into the pleural space (36–38). IL-8 is a downstream cytokine to IL-1 and TNF-α. Cultured mesothelial cells produce IL-8 in response to IL-1, TNF-α, or endotoxin (35). In

contrast, antibodies to IL-1 or TNF-α inhibit IL-8 release from mesothelial cells (2). Mesothelial cells produce IL-8 in basal conditions and the production is increased if the mesothelial cells are stimulated with inflammatory stimuli, asbestos fibers, or infective agents (2). The pleural fluid IL-8 levels are higher than the serum IL-8 levels in exudative pleural effusions suggesting that *in vivo* IL-8 is produced in the pleural space (3). IL-8 can also stimulate the growth of certain tumors. In mesothelioma cell lines, IL-8 causes a dose-dependent increase in proliferating activity. Lastly IL-8 has angiogenic properties (3).

Pleural fluid IL-8 levels are higher in exudates than in transudates (6). Pleural fluid IL-8 levels are most elevated in patients with empyema (37–40). There are also relatively high levels of IL-8 in the pleural fluid from patients with cancer or tuberculosis, but the levels of IL-8 in the pleural fluid from patients with congestive heart failure are low (41,42). There is a significant correlation between the number of neutrophils in empyema fluid and the level of IL-8 in the fluid (36,37). Neutrophil chemotactic activity is correlated with IL-8 activity, and most of the neutrophil chemotactic activity in pleural fluid is neutralized with anti–IL-8 antibodies (36).

IL-8 may also induce lymphocyte chemotaxis for the pleural space (41). Pace et al. (41) demonstrated that in patients with malignant and tuberculous pleural effusions, the lymphocyte count was more closely correlated with the IL-8 level than was the neutrophil count. Moreover, these workers reported that the pleural fluid was chemotactic for lymphocytes and that the chemotactic activity could be eliminated with antibodies to IL-8 (41).

INTERLEUKIN 10

IL-10 is the most important antiinflammatory cytokine found within the human immune response (42). An antiinflammatory cytokine, by definition, is one that can inhibit the synthesis of IL-1, TNF-α, or other major proinflammatory cytokines (42). IL-10 is a potent inhibitor of Th1 cell cytokines, including IL-2 and interferon-gamma (42). In humans, the main sources of IL-10 are the lymphocytes and monocytes, but macrophages, mast cells, and eosinophils also synthesize IL-10 (2). In a mouse model of hypersensitivity pleuritis, the administration of recombinant murine IL-10 before challenge significantly blocked cell trafficking to the pleural cavity (23). IL-4 was more potent than IL-10 in blocking this trafficking in this model (23). In the mouse model of carrageenan pleurisy, the intrapleural injection of IL-10 5 minutes before the injection of carrageenan led to a significant inhibition of the early phase (4 hours) but had no significant effect on the late phase (48 hours) of the response to carrageenan (30). In the same model, the administration of anti–IL-10 antibody caused a graded and marked increase of both total and differential leukocyte influx and also increased fluid leakage in the early phase, but had no effect on the late phase (30).

Chen et al. (22) measured the pleural fluid and serum IL-10 in 21 patients with a malignant pleural effusion. They reported that IL-10 was detectable in 19 of the 21 pleural fluids (90%) and that the levels of IL-10 were higher in the pleural fluid than in the serum (22). However, a second study reported that the IL-10 levels were comparable in the pleural fluid and in the serum (31). Chen et al (22) found no correlation between IL-10 levels and lymphocyte subpopulations. Aoe et al. (16) measured the pleural fluid levels of IL-10 in 93 pleural fluids and found detectable levels in 92. The levels were similar in patients with malignant effusions, tuberculous pleuritis, and other miscellaneous effusions (16). In this study, the pleural fluid IL-10 levels were significantly correlated with the levels of IL-2 and IL-4 (16).

INTERLEUKIN 12

IL-12 is a heterodimeric cytokine composed of two subunits of molecular masses of 40 kd (p40) and 35 kd (p35) (43). IL-12 is capable of enhancing cell-mediated and cytotoxic immune responses to intracellular pathogens and tumors. It is produced primarily by antigen-presenting cells and is considered crucial in promoting Th1 responses and subsequent cell-mediated immunity (2). Knockout mice with deficient IL-12 genes have defective cell-mediated immunity, fail to develop granulomatous reactions, and are prone to develop tuberculosis (2). When pleural cells are incubated with heat-killed *Mycobacterium tuberculosis*, IL-12 is detectable in the supernatants (43). The addition of anti–IL-12 antibodies suppressed proliferative responses of pleural fluid cells to *M. tuberculosis* by 36% (43).

The mean pleural fluid level of IL-12 was approximately 10 times higher (585 pg/mL) than that in the simultaneously obtained serum when an ELISA was used that detects both the IL-12 and p40 (43). When an ELISA was used that detects only heterodimeric IL-12, the mean IL-12 concentration in the pleural fluid in patients with tuberculous pleuritis was 165 $\pm$ 28 pg/mL with undetectable levels in serum

of the same patients or in pleural fluid of patients with malignancy (43). Although pleural fluid levels of IL-12p40 are higher in tuberculous than in malignant effusions (44), they are less efficient at identifying tuberculous pleural effusions than are pleural fluid levels of adenosine deaminase (45). In another study on 21 patients with malignant pleural effusion, pleural fluid IL-12 was below the minimal detectable concentration for all serum and pleural fluid samples (22). It is interesting to note that the intralesional injection of IL-12 into mesotheliomas in the mouse model of mesothelioma leads to tumor regression (46).

INTERLEUKIN 13

IL-13 plays a major role in Th2-dependent eosinophilic inflammation. It induces the expression of eotaxin, a potent eosinophil chemoattractant and vascular cell adhesion molecule-1, which mediates tissue migration of eosinophils (25). The injection of IL-13 into the rat's pleural space leads to eotaxin generation and a dose-dependent accumulation of eosinophils following immunoglobulin E (IgE)-passive sensitization and challenge 7 days later (47). The injection of IL-13 into the pleural space of naive rats induces a significant increase in the number of eosinophils recovered from the pleural effluent 24 hours after stimulation, returning to the baseline within 72 hours (47). However, when air is introduced intrapleurally in IL-13 knockout mice, the eosinophil response is not significantly different than when air is introduced in wild-type mice (25).

INTERLEUKIN 16

IL-16 is a T-cell chemoattractant that is generated from mitogen- or antigen-stimulated human peripheral blood mononuclear cells (48). It can stimulate the synthesis of proinflammatory cytokines including IL-1, IL-6, and TNF-α (48). It has been shown that the levels of IL-16 are significantly higher in the pleural fluid from tuberculous when compared with malignant pleural effusions, but there was too much overlap for the differences to be diagnostically useful (48). The pleural fluid levels of IL-16 were approximately four times higher than those in the simultaneously obtained serum (48). The IL-16 levels were positively correlated with the number of $CD4^+$ T cells (48).

MONOCYTE CHEMOTACTIC PEPTIDE

Monocyte chemotactic peptide 1 (MCP-1) is a cytokine that is chemotactic for monocytes. Cultured mesothelial cells in response to IL-1, TNF-α, or endotoxin produce MCP-1 (39). Antony et al. (37) have shown that the pleural fluid levels of MCP-1 are higher in patients with malignant pleural effusions and tuberculous pleural effusions than they are in patients with parapneumonic effusions or congestive heart failure. There is a correlation between the number of monocytes and the pleural fluid MCP-1 levels in patients with malignant pleural effusions. Specific neutralizing antibodies to MCP-1 eliminate approximately 70% of the monocyte chemotactic activity in pleural fluid (37).

TUMOR NECROSIS FACTOR α

TNF-α is a proinflammatory cytokine. In the inflammatory process, TNF-α is one of the first cytokines to appear along with IL-1. Incubation of mesothelial cells in the presence of TNF-α leads to the release of a wide variety of cytokines including IL-8, monocyte chemotactic peptide, and vascular endothelial growth factor (VEGF) (2,37). Mesothelial cells produce TNF-α and IL-8 to a variety of stimuli (2). The addition of TNF-α to mesothelial cell cultures results in the mesothelial cells producing PAI-1 and tPA. In human mesothelial cells, interferon-gamma inhibits basal and TNF-α–induced IL-8 release (2). In rabbits, the administration of polyclonal anti–TNF-α Fab fragments diminishes the pleurodesis induced by talc but not that resulting from doxycycline (49), indicating the important role of pleural inflammation in producing a pleurodesis.

The level of TNF-α in the pleural fluid is a marker of the degree of inflammation. Exudative pleural fluids have higher levels of TNF-α than do transudative fluids (29). Patients with complicated parapneumonic effusions have higher pleural fluid levels of TNF-α than do patients with uncomplicated parapneumonic effusions (50). The pleural fluid TNF-α levels in patients with tuberculosis are significantly greater than those in patients with pleural malignancy (1,51). Moreover, the TNF-α levels are higher in the pleural fluid than in the serum of the patients with tuberculosis but not in those with malignancy (1). In pleural fluids from patients with tuberculosis, the TNF-α levels are significantly correlated with the IL-1 levels (1). Patients with loculated pleural effusions whether they are due to malignancy, tuberculosis, or pneumonia have higher TNF-α levels than patients with free flowing pleural effusions (4). Patients with tuberculous pleuritis who go on to develop pleural thickening have higher levels of TNF-α in their pleural fluid than do those who do not develop thickening (1).

TRANSFORMING GROWTH FACTOR β

TGF-β is a family of multifunctional growth-modulating cytokines notable for their prodigious capacity to modulate a wide range of cellular behaviors (2). In mammals, there are three forms of TGF-β: TGF-β_1, TGF-β_2, and TGF-β_3 (52). All TGF-β isoforms can induce the production of each other. TGF-β is produced by and can act on mesothelial cells as well as most inflammatory and malignant cells that infiltrate the pleura (2). TGF-β is one of the most potent fibrogenic agents ever discovered. Accordingly, TGF-β is an important agent when one considers the response of the pleura to injury. The incubation of human pleural mesothelial cells with TGF-β results in a morphologic transition such that the mesothelial cells take on the morphologic characteristics of fibroblasts (53). This transformation is dependent on SMAD-2 signaling (53). The incubation of human mesothelial cells with TGF-β results in the synthesis of collagen (54), matrix proteins, matrix metalloproteinases (MMPs), and tissue inhibitors of MMPs (2). TGF-β suppresses fibrinolysis by reducing tissue plasminogen activators as well as by increasing the mesothelial cell production of PAI-1 (55).

The fibrogenic and autoinduction capabilities of TGF-β suggest that it could be a useful agent for pleurodesis. Indeed the intrapleural injection of small amounts of TGF-β_2 produces a pleurodesis in both rabbits (56) and sheep (57), which is at least as good as that resulting from tetracycline derivatives or talc and is faster than that resulting from talc (58). The intrapleural injection of TGF-β_3 can also produce an excellent pleurodesis in rabbits (59). The pleural fluid that results from the intrapleural injection of TGF-β_2 is much more voluminous and much less inflammatory than that which results from the intrapleural injection of a tetracycline derivative or talc (56). The large amounts of fluid may be related to the observations that TGF-β stimulates the mesothelial cells to produce VEGF (60).

TGF-β also appears to be important in the production of loculations and fibrosis in patients with pleural infections. In one study in rabbits with empyema, the median levels of pleural fluid TGF-β_1 increased from 8,100 pg/mL (days 1 and 2) to 39,600 pg/mL (day 8) (61). The levels of TGF-β_1 in the pleural fluid in this study were closely correlated with microscopic pleural thickness ($r = 0.70$) and number of fibroblasts present in the visceral pleura ($r = 0.68$). The same research group subsequently demonstrated that the intrapleural administration of a panspecific monoclonal antibody to TGF-β for 2 successive days after the pleural infection was initiated resulted in a marked decrease in the amount of purulent, exudative material in the pleural space at autopsy on day 6 (62). All markers of empyema and pleural fibrosis were also significantly decreased in the rabbits receiving intrapleural anti–TGF-β (62). Immunohistochemistry revealed localization of TGF-β to macrophages in the exudative material and the visceral pleura (62).

Both TGF-β_1 and TGF-β_2 are present in pleural fluids from patients (63). The mean levels of TGF-β_1 and TGF-β_2 are higher in exudates than in transudates (63,64). The levels of TGF-β_1 and TGF-β_2 correlate with the pleural fluid lactate dehydrogenase (LDH) level (63). In general, the levels of TGF-β_1 are approximately 10 times higher than the levels of TGF-β_2 (63). The pleural fluid levels of TGF-β_1 are significantly higher in loculated effusions than in nonloculated effusions and in patients with tuberculous pleurisy who develop pleural thickening than in those who do not (4). The pleural fluid from patients with mesothelioma tends to have higher levels of TGF-β than does the pleural fluid from patients with metastatic adenocarcinoma (64).

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

VEGF, also known as *vascular permeability factor* or *vasculotropin*, is a multifunctional cytokine that has two primary functions: (a) it increases the permeability of the vasculature, and (b) it is an important angiogenic and lymphogenic factor (65). VEGF is crucial to life. The loss of a single VEGF allele is lethal *in utero* (65). In some assays, VEGF is more potent than histamine in increasing vascular permeability (66). The permeability-enhancing capabilities of VEGF are probably very important in regard to pulmonary disease. It has been hypothesized that VEGF is important in increasing the permeability of the capillaries of the pleura and increasing the rate of pleural fluid formation (67). If this hypothesis proves to be true, pleural effusions in the future may be controlled with inhibitors of VEGF (68).

There is some evidence that anti-VEGF antibodies or VEGF receptor blockers may be efficacious in controlling malignant pleural effusions (2). When cancer cells are injected into mice, the VEGF expression by the tumor correlates directly with the volume of the effusion formed (69). If the cancer cells are transfected with antisense VEGF genes, the volume of the effusion is markedly decreased (69). If the cancer cells are transfected with sense VEGF genes, the VEGF production is increased and there is more pleural fluid formation (69). When pleural effusions are induced

in mice by the intrapleural injection of Lewis Lung cancer cells, mice that are given SU11248, a VEGF inhibitor, have less pleural fluid and less tumor burden (70). It is unclear as to whether the reduction in the fluid volume is due to lessened permeability or a reduction in the size of the tumor (70). The addition of VEGF to mesothelioma cell cultures increases their proliferation (71).

It appears that VEGF is important in the production of a pleurodesis. The intrapleural injection of TGF-β in rabbits results in an excellent pleurodesis (72). However, when anti-VEGF antibodies are administered before the TGF-β is given, the degree of pleurodesis is markedly diminished (72). When the pleurodesis scores are correlated with the angiogenesis score in all the rabbits that received either TGF-β alone or TGF-β plus anti–VEGF antibodies, there is a close correlation between the angiogenesis score in the visceral pleura and the pleurodesis scores (72).

In a second study, anti-VEGF antibodies were administered intravenously 30 minutes before animals received talc or silver nitrate intrapleurally (73). Animals pretreated with anti-VEGF antibody showed significant reductions in pleural fluid volumes after talc or silver nitrate injection. IL-8 levels, vascular permeability and macroscopic pleural adhesion scores were also reduced in the groups that received the anti-VEGF antibody (73). These studies demonstrate the importance of angiogenesis, as promoted by VEGF, in the production of a pleurodesis.

Most VEGF in pleural effusions is believed to originate from local production (2). VEGF is produced by most cell types, but mesothelial cells are thought to represent the principal source of pleural fluid VEGF, although infiltrating inflammatory cells and malignant cells also contribute (2). VEGF production can be stimulated by various cytokines among which TGF-β is the most consistent. *In vitro* many other cytokines including IL-1, IL-6, TNF-α, platelet derived growth factor (PDGF) and platelet-activating factor (PAF) can also stimulate VEGF synthesis (2).

There are detectable levels of VEGF in all pleural effusions (66,70,74). In patients with exudative pleural effusions, the pleural fluid levels are several times higher than the serum values suggesting local production (74). The levels of VEGF are higher in exudates than in transudates, but there is significant overlap (66,74). The VEGF levels tend to be higher in malignant effusions than in tuberculous or parapneumonic effusions (75), but there is too much overlap for the differences to be useful diagnostically. The levels of pleural fluid VEGF are correlated significantly with both the levels of TGF-β_1 and TGF-β_2 (63). In one study of 83 patients, the levels of VEGF and MMP-9 were highly correlated ($r = 0.88$) (76). The levels of VEGF and LDH in the pleural fluid were significantly correlated in one study (66) but not in another (75). It has also been shown that both VEGF mRNA and endostatin mRNA are higher in malignant effusions than in benign effusions and it has been suggested that their measurement might assist in the diagnosis of malignant effusions (77).

TUMOR NECROSIS FACTOR-α

Tumor necrosis factor-α (TNF-α) plays a predominant role in inflammatory processes. It increases neutrophil margination and activates neutrophils, monocytes, macrophages, and eosinophils. It often elicits acute-phase reactions characterized by fever and anorexia (2). Mesothelial cells produce TNF-α in response to a variety of stimuli. TNF-α is present in pleural effusions and levels are significantly higher in exudative than in transudative effusions. Pleural fluid TNF-α levels are higher in malignant than in benign effusions but there is considerable overlap (2). Anti-TNF-α antibodies inhibit talc pleurodesis (78).

BASIC FIBROBLAST GROWTH FACTOR

Mesothelial cells synthesize and release considerable amounts of basic fibroblastic growth factor (b-FGF) (2). Most b-FGF is intracellular and the remainder is associated with the extracellular matrix components on the mesothelial cell surface (2). b-FGF stimulates mesothelial cell proliferation *in vitro* and *in vivo* (2). Like VEGF, b-FGF is a potent angiogenic factor and is implicated in cancer growth and metastasis (2).

Ruiz et al. (79) found that the b-FGF levels were below detectable levels (3 pg/mL) in most uncomplicated parapneumonic, tuberculous, malignant, and transudative pleural effusions. In contrast, b-FGF was detectable in most empyemas or complicated parapneumonic effusions (79). In an earlier study, Strizzi et al. (80) reported that the mean pleural fluid b-FGF level in malignant effusions (8.5 $\pm$ 6.1 pg/mL) was significantly lower than the mean level in nonmalignant effusions (23.0 $\pm$ 19.8 pg/mL). The explanation for the contrasting results in the above two studies is not clear. Economidou et al. (81) reported that the levels of b-FGF were comparable in patients with transudates and exudates.

ANGIOPOIETINS

Angiopoietin (Ang)-1 and Ang-2 are receptor tyrosine kinase ligands that act in conjunction with VEGF I promoting angiogenesis (82). In addition Ang-1 has anti-inflammatory and antipermeability properties and inhibits vascular permeability caused by VEGF and inflammatory agents. It is thought that Ang-2 promotes vascular permeability. It has been shown that the levels of Ang-2 but not Ang-1 are significantly higher in exudates than in transudates (82). The pleural fluid levels of Ang-2 are significantly correlated with the pleural fluid levels of VEGF (82). These observations suggest that Ang-2 possibly has a role in the pathogenesis of exudative pleural effusions.

ENDOSTATIN

Endostatin, in contradistinction to VEGF or b-FGF, is an angiogenesis inhibitor. It is an endogenously produced fragment of XVIII collagen. Sumi et al. (83) measured pleural fluid endostatin levels in 67 patients and reported that the free form of endostatin was measurable (>11.2 pg/mL) in 26 of 38 malignant and 13 of 29 nonmalignant effusions and the levels of endostatin in the malignant and nonmalignant effusions did not differ significantly. Ruiz et al. (79) found that the mean pleural fluid endostatin levels did not differ significantly between patients with complicated or uncomplicated parapneumonic effusions or effusions secondary to malignancy, tuberculosis, or parapneumonic effusions.

It is possible that endostatin might have a role in treating malignant pleural effusions. Fang et al injected viruses containing the gene for endostatin in mice with pleural effusions due to the intrapleural injection of Lewis lung cancer cells. They reported that this treatment resulted in significant reduction in pleural effusion volume, the number of pleural tumor foci, microvessel density, and vascular permeability, while it significantly prolonged the survival time (84).

PLATELET-ACTIVATING FACTOR

PAF is a potent lipid mediator that activates platelets, neutrophils, eosinophils, and macrophages, and increases vascular permeability (85). Mesothelial cells synthesize PAF in response to thrombin (85). When PAF is injected intrapleurally, inflammation of the pleura develops in association with neutrophils and eosinophils (85). The relationship between pleural fluid eosinophilia and pleural fluid levels of PAF is unclear. In one recent report analyzing eosinophilic pleural fluid associated with pneumothorax, there was no correlation between the PAF levels and the number of eosinophils (86). However, in a previous report eosinophilic pleural fluids with high levels of eosinophils tended to have high pleural fluid PAF levels (87).

MATRIX METALLOPROTEINASES AND TISSUE INHIBITORS OF MATRIX METALLOPROTEINASES

MMPs are not cytokines, but I will discuss them briefly in this chapter because there have been several papers in the past few years discussing their relationship to pleural disease. MMPs are a large group of zinc-containing proteolytic enzymes with a central role in the degradation of all types of extracellular matrix components (88). The MMP family consists of more than 25 members (88). These enzymes are known to play an important role in pathologic conditions such as tumor invasion (76). MMP-9 is the member of the MMP family that is thought to play a role in chronic inflammation. This enzyme induces migration of inflammatory cells such as eosinophils, neutrophils, and lymphocytes across the basement membrane (76). MMP-9 activity is down regulated by tissue inhibitors of matrix metalloproteinase 1 (TIMP-1). TIMP-1 is secreted by mononuclear phagocytes (89). The balance between local MMP-9 and TIMP-1 concentrations critically determines the net proteolytic activity (89).

In one report, the mean pleural fluid levels of MMP-9 in patients with lung cancer were higher than those in patients with tuberculosis, which in turn were higher than those in patients with cirrhosis of the liver (80). A different paper reported that the levels of MMP-9 were higher in tuberculous than in malignant pleural effusions (89). The levels of MMP-9 are significantly correlated with the number of lymphocytes in the pleural fluid and the levels of VEGF in the pleural fluid (76). Pleural fluid concentrations of TIMP-1 were significantly higher in lung cancer and tuberculosis than in transudates (87), but there were no significant differences in the levels of TIMP-1 if the levels were normalized to the levels of protein in the pleural fluid (89). The intrapleural administration of talc leads to a decrease in the levels of MMP-1 and TIMP-1 in the pleural fluid (90).

There have been studies assessing the levels of other MMPs in the pleural fluid including MMP-1 (90,91), MMP-2 (91,92), MMP-3 (92), MMP-8 (91,92), and TIMP-2 (91,92). In general, the levels of the MMPs are higher in exudates than in transudates.

Levels of MMP-1, MMP-2, TIMP-1 and TIMP-2 in tuberculous pleural fluid are higher than in the simultaneously obtained serum (92).

FIBRINOGENESIS AND FIBRINOLYSIS IN THE PLEURAL SPACE

Pleural fibrin deposition is a characteristic of many diseases of the pleura, and fibrin membranes are responsible for the loculations that make the drainage of complicated parapneumonic effusions and empyema difficult. Fibrin membranes can also produce a loculated pleural effusion in other situations such as tuberculosis or malignancy, and the progress of fibrin deposition followed by collagen deposition can lead to chronic pleural thickening.

When the pleura is inflamed, the amount of fibrin that is laid down is the result of the balance between fibrinogenesis and fibrinolysis. Thrombin acts on fibrinogen to produce fibrin. Fibrogenesis occurs when the factors that favor fibrogenesis such as TNF-α, TGF-β, and plasminogen activation inhibitor-1 (PAI-1) are dominant. Fibrinolysis occurs when more fibrin is being broken down than is being created. Plasminogen breaks down fibrin and is activated by tPA (55). Human mesothelial cells express tPA, but no detectable fibrinolytic activity is found in a fibrin plate assay. The explanation for the lack of fibrinolytic activity appears to be the production of the PAI-1. In mesothelial cell cultures, PAI-1 increases in response to both TNF-α and TGF-β (55).

In pleural fluids from humans, patients with tuberculosis have higher levels of PAI-1 than do patients with pleural malignancy, and the levels in the pleural fluid are approximately four times higher than those in the blood (1). In contrast, the pleural fluid levels of tPA are approximately three times higher in patients with malignancy than in patients with tuberculosis (1). This factor possibly explains why there is so much more fibrin deposition in patients with tuberculosis than in patients with pleural malignancy. Patients with pleural TB who develop residual pleural thickening have significantly greater pleural fluid levels of TNF-α and PAI-1 (1).

One might hypothesize that the development of the loculations would depend on the balance between the procoagulant and the fibrinolytic activity in the pleural space. Idell et al. (93) measured the procoagulant and fibrinolytic activity in 36 pleural fluids, including 21 due to malignancy, 3 due to empyema, 8 due to congestive heart failure, and 4 due to pneumonia. They found that procoagulant activity was present in some of the exudates, but its presence did not necessarily correlate with loculation and its level did not serve to differentiate the different exudates. The transudates had no active procoagulant. Fibrinolytic activity was absent in all the exudates, whereas five of the eight transudates had fibrinolytic activity (93). In view of the above-mentioned observations measurement of the procoagulant activity in pleural fluids does not appear to be useful either diagnostically or prognostically.

Since the publication of this study more than 20 years ago, there have been several more publications regarding fibrogenesis and fibrinolysis in the pleural space. Lin et al. (94) demonstrated that the pleural fluid levels of PAI-1 and the PAI-1/tPA ratio were approximately four times higher in patients with parapneumonic effusions or empyema than in patients with tuberculous pleuritis. Their tuberculosis patients with residual pleural thickening had significantly higher PAI-1/tPA levels (94). Chung et al. (95) compared the PAI-1 and the tPA levels in the pleural fluid from patients with loculated and nonloculated pleural effusions due to malignancy, tuberculosis, and pneumonia. As expected, the patients with loculated pleural effusion had higher levels of pleural fluid PAI-1 than did the patients with nonloculated pleural effusions. However, the pleural fluid levels of tPA did not differ significantly between the two groups (95). In addition, the PAI-1/tPA ratio correlated positively with the levels of TNF-α, IL-1β and TGF-β_1 (95).

The performance of serial thoracenteses leads to loculation of the pleural fluid in some patients. Chung et al. (95) performed thoracentesis daily for 3 days in 26 patients with malignant pleural effusions. They noted, through ultrasound, that on day 6 after the initial thoracentesis, 11 of the patients had fibrous strands in their pleural fluid. (95). When the PAI-1 was measured in the pleural fluid, it had increased significantly in the patients who developed the fibrous strands but not in those who did not (95).

All the above facts suggest that the balance between fibrinogenesis and fibrinolysis, as reflected by the PAI-1/tPA ratio, is very important in determining whether a patient will get a loculated pleural effusion or develop residual pleural thickening. Possibly, therapeutic interventions aimed at decreasing this ratio will decrease the amount of pleural loculation and residual pleural thickening.

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chapter 6

Radiographic Examinations

PLEURAL EFFUSIONS

Typical Arrangement of Free Pleural Fluid

Two main factors influence the distribution of free fluid in the pleural space. First, the pleural fluid accumulates in the most dependent part of the thoracic cavity because the lung is less dense than pleural fluid. In essence, the lung floats in the pleural fluid. Second, the lobes of the lung maintain their traditional shape at all stages of collapse owing to their elastic recoil (1). The shape of a lobe when it is partially or completely collapsed is a miniature replica of its shape when fully distended.

Bearing in mind that the distribution of fluid within the free pleural space obeys the law of gravity and that the lung maintains its shape when compressed, it is easy to predict the distribution of excess pleural fluid. The fluid first gravitates to the base of the hemithorax and comes to rest between the inferior surface of the lung and the diaphragm, particularly posteriorly, where the pleural sinus is the most inferior. As more fluid accumulates, the fluid spills out into the costophrenic sinuses posteriorly, laterally, and anteriorly. Additional fluid spreads upward in a mantle-like manner around the convexity of the lung and gradually tapers as it assumes a higher position in the thorax.

On the basis of this pattern of fluid accumulation, the typical radiographic appearance of a pleural effusion of moderate size (1,000 mL) is as follows. In the posteroanterior projection (Fig. 6.1A), the lateral costophrenic angle is obliterated. The density of the fluid is high laterally and curves gently downward and medially with a smooth, meniscus-shaped upper border to terminate at the mediastinum. The layer of fluid is narrower at the mediastinal border than at the costal border; the reason for this difference is that the mediastinal surface of the lower lobe of the lung possesses less elastic recoil because it is fixed at the hilum and pulmonary ligament (1). In the lateral projection (Fig. 6.1B), the upper surface of the fluid density is semicircular, high anteriorly and posteriorly, and curving smoothly downward to its lowest point approximately midway between the sternum and the posterior chest wall.

Frequently, a "middle lobe step" is observed on the lateral radiograph (Fig. 6.1B). The explanation for the middle lobe step is that as pleural fluid accumulates, the first affected lobe is the lower lobe because it is the most dependent. Therefore, it starts to shrink and float but maintains its shape. The middle lobe is unaffected and maintains its full volume. Accordingly, the result is a shrunken lower lobe with a middle lobe that retains its usual size. Radiographically, the fluid is mostly in the posterior part of the chest (Fig. 6.1B).

On the basis of the radiologic appearance, one might surmise that the height of the pleural fluid is greater laterally. The true upper limit of pleural fluid, however, is usually the same throughout the hemithorax (2). The meniscus shape is seen because the layer of fluid is of insufficient depth to cast a discernible shadow when viewed *en face* (Fig. 6.2).

Radiologic Signs

With the patient in the upright position, fluid first accumulates between the inferior surface of the lower lobe and the diaphragm. If the amount of fluid is small (approximately 75 mL), it may occupy only this position without spilling into the costophrenic sinuses. With this small amount of fluid, the normal configuration of the diaphragm is maintained, and the

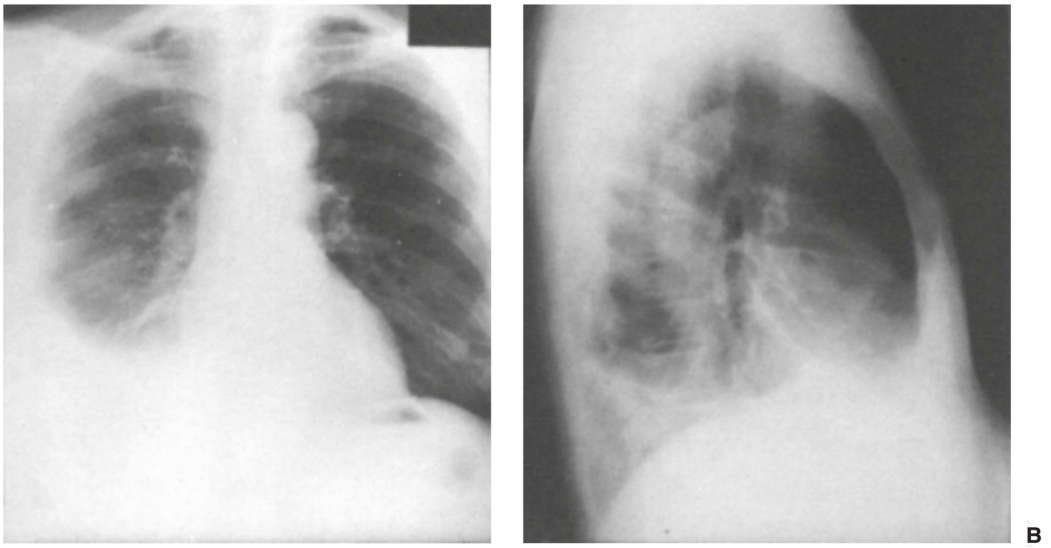

FIGURE 6.1 ■ Typical arrangement of free pleural fluid. **A**: Posteroanterior view revealing obliteration of the lateral costophrenic angle. Note that in this figure, a small amount of fluid appears in the lateral aspect of the minor fissure. **B**: Lateral view revealing obliteration of the diaphragmatic outline. Note that fluid is present in both major and minor fissures such that the right middle lobe is well outlined.

chest radiograph does not indicate that pleural fluid is present. When more fluid accumulates, it spills over into the posterior costophrenic angle and obliterates that sinus as viewed in the lateral projection (Fig. 6.1B). The normally sharp posterior costophrenic angle is obliterated by a shallow, homogeneous shadow whose upper surface is meniscus shaped. The pleural line up the posterior thoracic wall is also widened. Anytime the posterior costophrenic angle is obliterated or the posterior part of one or both diaphragms is obscured, the presence of pleural fluid is suggested and further diagnostic efforts should be made. Moreover, if both posterior costophrenic angles are clear and sharp, the presence of clinically significant amounts of free pleural fluid can be nearly excluded.

Increasing amounts of fluid blunt the lateral costophrenic angle of the posteroanterior (PA) radiograph. Collins et al. (3) injected fluid into the pleural spaces of upright cadavers. They demonstrated that at least 175 mL pleural fluid had to be injected before the lateral costophrenic angle was blunted and, in some cases, more than 500 mL pleural fluid could be present without blunting the lateral costophrenic angle. As more fluid accumulates, the entire outline of the diaphragm on the affected side is lost, and the fluid extends upward around the anterior, lateral, and posterior thoracic walls. This fluid produces opacification of the lung base and the typical meniscus shape of the fluid, as demonstrated in Figure 6.1.

Subpulmonic or Infrapulmonary Effusions

At times, for unknown reasons, substantial amounts of pleural fluid (more than 1,000 mL) can be present and may remain in an infrapulmonary location without spilling into the costophrenic sulci or extending up the chest wall. Such pleural fluid accumulations are called *subpulmonic* or *infrapulmonary pleural effusions* (Fig. 6.3). Although the posterior costophrenic angle is usually blunted, at times it is perfectly clear (1).

The following radiologic characteristics are common to most cases of subpulmonic effusions (1), and the presence of one or more of these characteristics should serve as an indication for decubitus examinations to rule out the possibility of a subpulmonic pleural effusion: (a) apparent elevation of one or both diaphragms; (b) in the posteroanterior projection with subpulmonic effusions, the apex of the apparent diaphragm is more lateral than usual, near the junction of the middle third and the lateral third of the diaphragm, rather than at the center of the diaphragm; (c) the apparent diaphragm slopes much more sharply toward the lateral costophrenic angle (Fig. 6.4); (d) if the subpulmonic effusion is on the left side, the lower border of the lung is separated farther

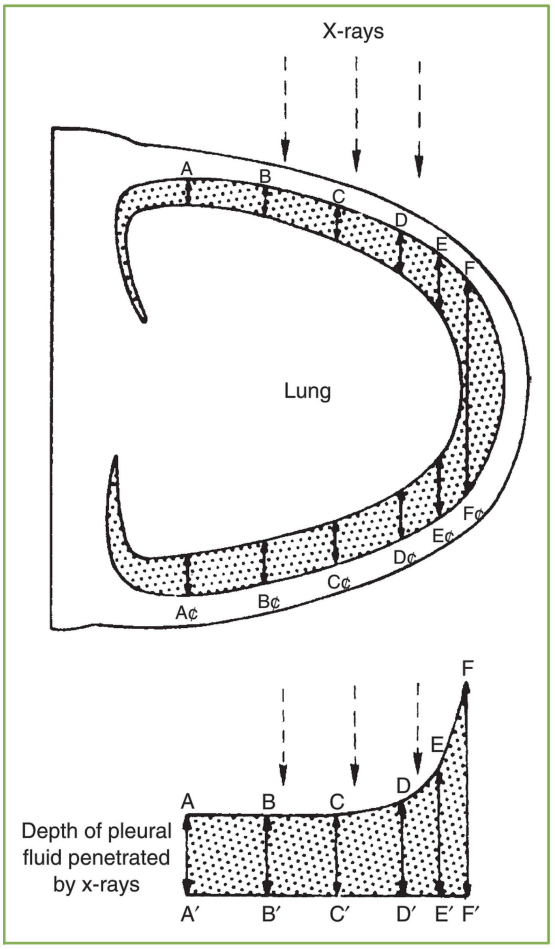

FIGURE 6.2 ■ Diagrammatic explanation for the meniscus shape of pleural fluid. The distance between the lung and the chest wall is the same around the entire lung. The depth of the fluid when viewed *en face* AA′ to CC′ is not sufficient to increase the radiodensity. More laterally at DD′ to FF′, however, the x-ray beam passes through more and more pleural fluid, so that an increase in density is radiologically evident.

from the gastric air bubble than usual; normally, the top of the left diaphragm on the posteroanterior view is less than 2 cm above the stomach air bubble (4); a separation greater than 2 cm suggests a subpulmonic effusion, but, of course, it can also be due to subdiaphragmatic fluid accumulation; if no gastric air bubble is present, the ingestion of a carbonated beverage by the patient will allow evaluation of this sign; (e) in the lateral projection, the major fissure often bows anteriorly where it meets the convex upper margin of the fluid; a small amount of fluid is usually apparent in the lower end of the major fissure at its junction with the infrapulmonary effusion; and (f) the lower lobe vessels may not be seen below the apparent diaphragmatic border.

Diaphragmatic Inversion

At times, the weight of the fluid may cause the diaphragm to become inverted such that its normally convex superior border becomes concave. This inversion occurs much more commonly with effusions on the left, but it can occur with effusions on the right (5). Radiologically, the gastric air bubble is pushed inferiorly, and the superior border of the diaphragm is concave upward rather than convex. When viewed under fluoroscopy, such inverted diaphragms move paradoxically with respiration, rising on inspiration and descending on expiration (6). At times, patients with large left pleural effusions suddenly become dyspneic coincidentally with the development of inversion of the left diaphragm. In such instances, therapeutic thoracentesis is indicated (see Chapter 28). The removal of some of the pleural fluid restores the normal configuration to the diaphragm and rapidly relieves the patient's symptoms (6).

Supine Position

Until this time, I have only discussed the radiologic characteristics of pleural effusions with the patient in the upright position. Many chest radiographs, however, particularly those in acutely ill patients, are obtained with the patient in the supine position. When the patient is in this position, pleural fluid gravitates to the posterior parts of the thoracic cavity. Because the pleural fluid is spread over a large area, considerable quantities must be present before any radiographic changes are seen. In one study of 117 pleural effusions documented by CT scan, the portable anteroposterior radiograph demonstrated only 66% of the effusions including 57% of small, 71% of moderate, and 91% of large-sized effusions (7). However, in a recent study (8) of 61 patients with parapneumonic effusions, the portable chest radiograph identified 76% of the effusions correctly while the later radiograph identified 87% and the PA identified 81% correctly compared with the CT scan. Most of the patients in whom the pleural effusions were missed had lower lobe infiltrates (8).

The presence of free pleural fluid elicits several signs on the supine radiograph. These signs include blunting of the costophrenic angle, increased homogeneous density superimposed over the lung, loss of the hemidiaphragm silhouette, apical capping, elevation of the hemidiaphragm, decreased visibility of lower lobe vasculature, and accentuation of the minor fissure

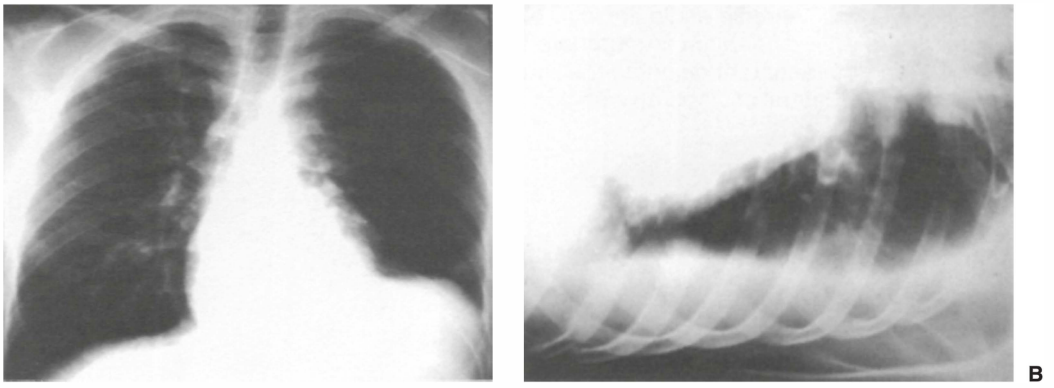

FIGURE 6.3 ■ Subpulmonic pleural effusion. **A**: Posteroanterior chest radiograph showing apparent elevation of the left diaphragm with the apex of the apparent diaphragm more lateral than usual. **B**: Lateral decubitus film of this patient showing free pleural fluid. *(Courtesy of Dr. Harry Sassoon.)*

(9,10). Some patients with a small-to-moderate-sized pleural effusion have none of these signs. In one study (9), none of these radiologic signs were present in 9 of 16 patients with small effusions (defined as measuring <1.5 cm on the decubitus radiograph) and in 3 of 13 patients with moderate effusions (defined as measuring 1.5–4.5 cm on the decubitus radiograph). In a second study, the supine chest radiograph suggested the presence of pleural fluid in 29 of 30 patients (97%) who had more than 300 mL pleural fluid (11). In this study, increased homogeneous density, blunted costophrenic angle, and loss of a diaphragm silhouette were the most accurate signs in diagnosing a pleural effusion with an accuracy of approximately 80% (11). The increased homogeneous density in most cases with a pleural effusion was limited to the lower one- or two-thirds of the lung field or was more pronounced there (11).

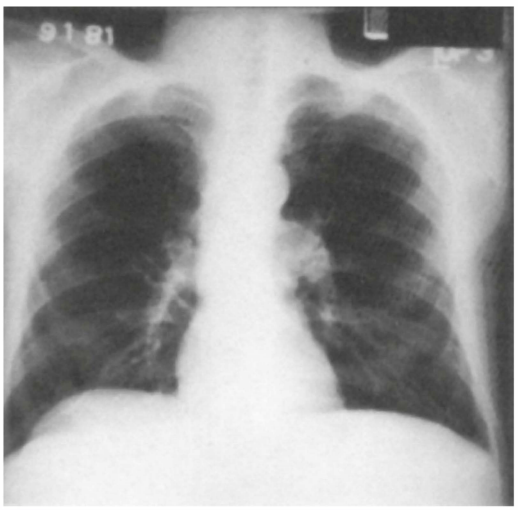

FIGURE 6.4 ■ Subpulmonic pleural effusion. Note that the right lateral costophrenic angle is clear, but the apex of the right diaphragm is more lateral than usual, and the apparent diaphragm slopes sharply toward the lateral costophrenic angle.

The earliest sign is blunting of the costophrenic angle (9). Subsequently, increased density of the hemithorax, loss of the hemidiaphragm, and decreased visibility of the lower lobe vasculature occur. Apical capping does occur with pleural effusion, but it does not appear to be related to the size of the pleural effusion (9). Elevation of the hemidiaphragm and accentuation of the minor fissure are insensitive signs in that they occur in a minority of patients and are not related to the size of the effusion (9).

Three characteristics serve to differentiate the increased density due to pleural fluid from that due to a parenchymal infiltrate. First, if the density is caused by pleural fluid, the vascular structures of the lung will be readily visible through the density in a properly exposed film. Any intrapulmonary process that produces a similar density, however, obliterates the vascular structure by the "silhouette effect." Second, if the density is due to pleural fluid, it is usually completely homogeneous. In contrast, infiltrates caused by intrapulmonary processes are usually less homogeneous. Third, air bronchograms are present only if the increased density is due to a parenchymal infiltrate.

Atypical Effusion

The typical arrangement of fluid in the pleural space depends on an underlying lung free of disease and thereby having uniform elastic recoil. If the lung

underlying the effusion is diseased, the elastic recoil of the diseased portion is frequently different from that of the remainder of the lung, and fluid accumulates most where the elastic recoil is greatest. Therefore, an atypical collection of pleural fluid is an indication of underlying parenchymal as well as pleural disease. For example, if disease in a lower lobe increases its elastic recoil, fluid will collect posteromedially. Accordingly, in the posteroanterior projection, the opacity is higher on the mediastinal than on the axillary border, in contrast to the typical appearance in which the opacity is higher at the axillary border. Moreover, the upper surface curves downward and laterally toward the lateral costophrenic sulcus and thereby simulates atelectasis and consolidation of the middle and lower lobes. In the lateral projection, the upper border of the density roughly parallels the major fissure, beginning high in the thorax posteriorly and running downward and anteriorly to the anterior costophrenic sulcus. For the interested reader, Fleischner (12) has detailed the radiographic appearance of atypical pleural fluid accumulation in disease affecting all the individual lobes.

Loculated Effusion

Pleural fluid may become encapsulated by adhesions anywhere between the parietal and the visceral pleura or in the interlobar fissures. Because the encapsulation is caused by adhesions between contiguous pleural surfaces, it occurs most frequently in association with conditions that cause intense pleural inflammation, such as empyema, hemothorax, or tuberculous pleuritis. Loculations occurring between the lung and the chest wall produce a characteristic radiographic picture. When viewed in profile (Fig. 6.5), the loculation is D-shaped, with the base of the D against the chest wall and the smooth convexity protruding inward toward the lung because of the compressibility of the lung parenchyma. If the loculation is in the lower part of the thoracic cavity, its lower border may not be visible. Loculation may be differentiated from parenchymal infiltrates by the absence of air bronchograms. A definitive diagnosis of loculated pleural effusion is best established by ultrasound (see the discussion on ultrasound). Because multiple locules are common, the demonstration of one locule should serve as an indication to search for additional locules.

Loculation in the Fissures

The plane of the lung fissures is such that fluid encapsulated in the fissure is usually seen in profile in the lateral view. Fluid encapsulated in a fissure has a profile similar to a biconvex lens. Its margins are sharply defined and blend imperceptibly into interlobar fissures (Fig. 6.6). In some situations, the loculated effusion may simulate a mass on the posteroanterior radiograph. This situation is most frequently seen in patients with congestive heart failure, and because the fluid absorbs spontaneously when the congestive heart failure is treated, these fluid collections have been termed *vanishing tumors* or *pseudotumors*. The most common location of these "tumors" is in the right horizontal fissure (13). These pseudotumors are usually less than 4 cm in diameter, but pseudotumors as large as 10 cm in their largest diameter have been reported (14). The distinctive configuration of the loculated interlobar effusion should establish the diagnosis. The disappearance of the apparent mass as the effusion resolves definitely establishes the diagnosis.

At times, it is difficult to differentiate encapsulated fluid in the lower half of a major fissure from atelectasis or combined atelectasis and consolidation of the right middle lobe. The following three points help make the distinction (1). First, if the minor fissure is visible as a separate shadow, the diagnosis of encapsulated fluid is certain. Second, encapsulated fluid does not usually obscure the border of the right side of the heart; in contrast, middle lobe atelectasis almost invariably does. Third, in the lateral projection, loculated effusions usually have a convex border on one or both sides. When the right middle lobe is diseased, the borders of the shadow are either straight or slightly concave.

RADIOLOGIC DOCUMENTATION

Most of the changes discussed in the previous sections are suggestive rather than diagnostic of the presence of pleural fluid. For example, blunting of the posterior or lateral costophrenic angles can be due to pleural effusion, but it can also be caused by pleural thickening or hyperinflation of the lung. Pleural effusion can obliterate one or both diaphragms on the lateral radiograph, but so can atelectasis or parenchymal infiltrates. Therefore, when the posteroanterior or the lateral chest radiograph suggests a pleural effusion, further radiographic studies are usually needed to document the presence of pleural fluid. Currently, ultrasound is used most frequently to document the presence of a pleural effusion, but lateral decubitus radiographs and computed tomography (CT) scans are useful in this situation.

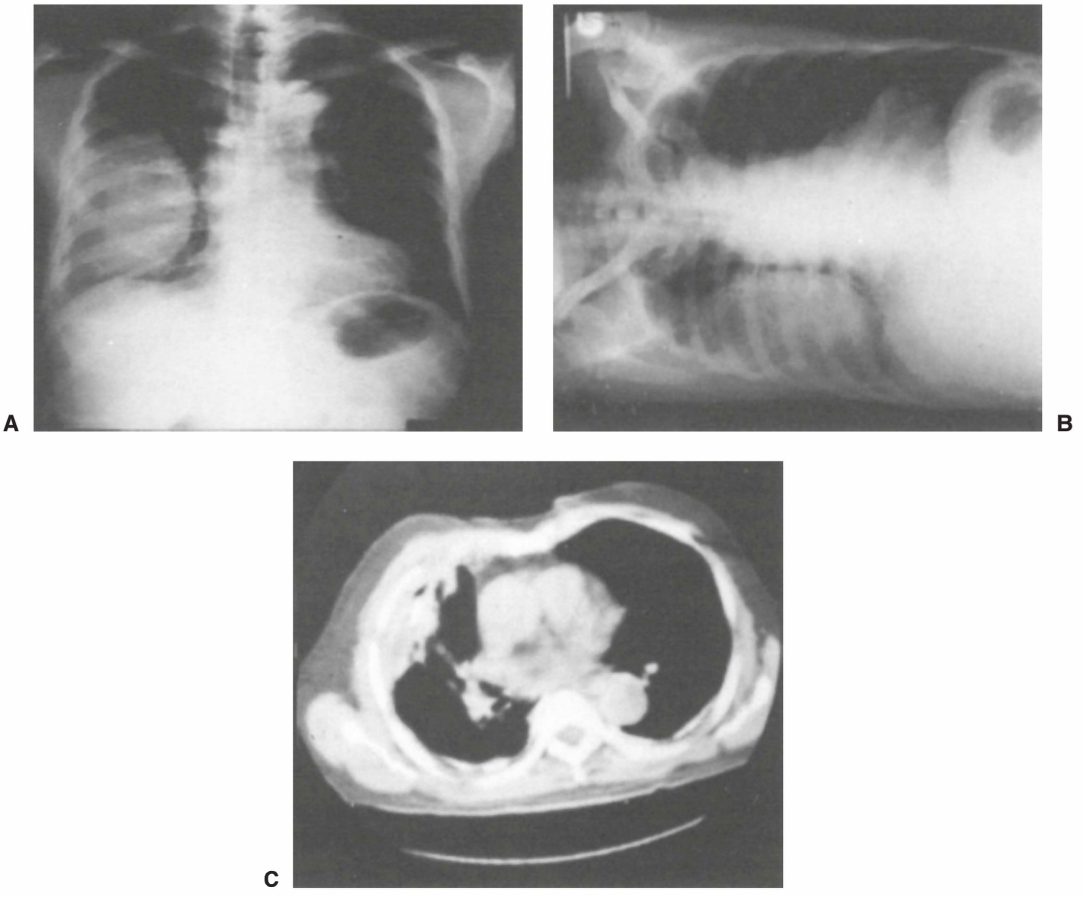

FIGURE 6.5 ■ Loculated pleural effusion. **A**: Posteroanterior radiograph demonstrating a D-shaped density, with base of the D against the right lateral chest wall. **B**: Right lateral decubitus radiograph demonstrating the absence of free pleural fluid in the same patient. **C**: Computed tomography (CT) scan demonstrating parenchymal involvement adjacent to loculated pleural effusion. This patient has an anaerobic infection of the lung and pleural space.

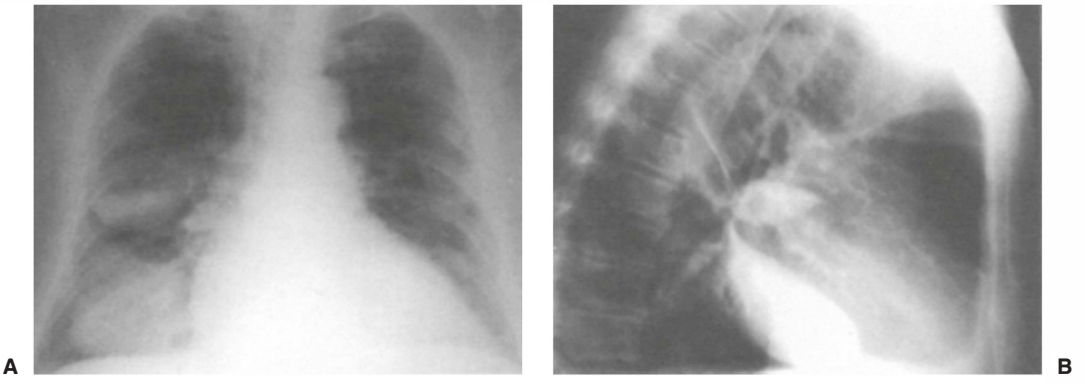

FIGURE 6.6 ■ Posteroanterior **(A)** and lateral **(B)** radiographs of a patient with congestive heart failure. **A**: Two mass-like lesions are visible in the lower right lung field. **B**: The biconvex configuration of loculated fluid in both the major and the minor fissures is evident. With treatment of the patient's heart failure, the lung fields cleared, and the apparent masses disappeared. *(Courtesy of Dr. Harry Sassoon.)*

Lateral Decubitus Radiographs

The basis for the use of the lateral decubitus view is that free fluid gravitates to the most dependent part of the pleural space. The patient is placed in the lateral recumbent position, with the suspect side dependent. Sufficient radiolucent padding should be placed between the tabletop and the patient such that an unobstructed tangential view of the dependent chest wall can be obtained. The x-ray film should be exposed with a high voltage to ensure that the interface between the fluid and the lung can be identified.

In the decubitus view, free pleural fluid is evidenced by a homogeneous density with a straight horizontal superior border between the dependent chest wall and the lower border of the lung (Fig. 6.7). This appearance is due to the lung floating in the fluid. By injecting fluid into the pleural space of cadavers, Moskowitz et al. have demonstrated that as little as 5 mL pleural fluid can be seen on properly exposed decubitus radiographs (15). Fluid is more easily demonstrated if the decubitus radiographs are obtained at full expiration rather than at full inspiration (16). The amount of free pleural fluid can be semiquantitated by measuring the distance between the inner border of the chest wall and the outer border of the lung (Fig. 6.7); the greater this distance, the more free pleural fluid. Empirically, I have found that when this distance is less than 10 mm, diagnostic thoracentesis is difficult because the amount of pleural fluid is small. Accordingly, I rarely attempt a diagnostic thoracentesis when the thickness of the pleural fluid on the decubitus radiograph is less than 10 mm.

Many patients suspected of having pleural effusions have apparent pleural thickening on the posteroanterior chest radiograph. When decubitus views are obtained in such patients, one must compare the distance between the lung and chest wall on the decubitus view to that on the posteroanterior view. If the distance between the lung and the chest wall is not at least 10 mm greater on the decubitus view, the patient does not have a significant amount of free pleural fluid.

In general, bilateral decubitus chest radiographs should be ordered. The film with the suspect side superior is informative because, in this view, the fluid gravitates toward the mediastinum. With the fluid shifted away from the chest wall and the lung, one can more readily assess the underlying lung for infiltrates or atelectasis (Fig. 6.7C). In addition, if the lateral costophrenic angle is blunted on the posteroanterior view and is clear on the decubitus view with the suspect side superior, one can be certain that the blunting is caused by free pleural fluid.

Frequently, when decubitus radiographs are obtained, confusion exists as to which side is down. An arrow is usually seen on the x-ray film, but whether the arrow is pointing up or down in relation to the patient's position is the question. Four radiologic characteristics allow the interpreter to ascertain the position of the patient when the radiograph is obtained. First, the dependent lung receives a greater percentage of the perfusion and is therefore more radiodense. Second, with the patient in the decubitus position, the abdominal pressure is greater on the dependent side; therefore, the diaphragm on the dependent side is pushed higher in the thoracic cavity than the contralateral diaphragm. Third, the radiolucent padding or the examination table is often evident outside the thoracic cavity on the dependent side (Fig. 6.7). Fourth, if air–fluid levels are present in the stomach or the intestines, the air will always be on the superior side.

ULTRASOUND

Ultrasound is very useful in the study of pleural disease (17–19). Koh et al. (19) and Koenig et al. (20) have produced excellent reviews with several different movies demonstrating various ultrasound findings with pleural disease. Ultrasound can be used in several different situations, including the following: (a) determining whether pleural fluid is present; (b) identification of the appropriate location for an attempted thoracentesis, pleural biopsy, or chest tube placement; (c) identification of pleural fluid loculations; (d) distinction of pleural fluid from pleural thickening; (e) semiquantitation of the amount of pleural fluid; (f) differentiation of a pyopneumothorax from a lung abscess; (g) assessment as to whether a pleurodesis is present; and (h) evaluation of the trauma patient for the presence of a hemothorax or a pneumothorax. The advantages of ultrasound over CT are the ease and speed with which the examination can be performed, the availability of portable units that can be brought to the bedside of seriously ill patients, the lack of ionizing radiation, the relatively low cost, and the capacity to diagnose and distinguish an associated subphrenic process (18,21). With ultrasound, one can also assess the thickness of the parietal pleura and identify pleural nodules and focal pleural thickening (22). Given these advantages, there is no doubt that ultrasound has been underused in the assessment of pleural disease in the United States, but its use has increased dramatically in the past few years. Pulmonologist are utilizing ultrasound themselves more and more extensively (23).

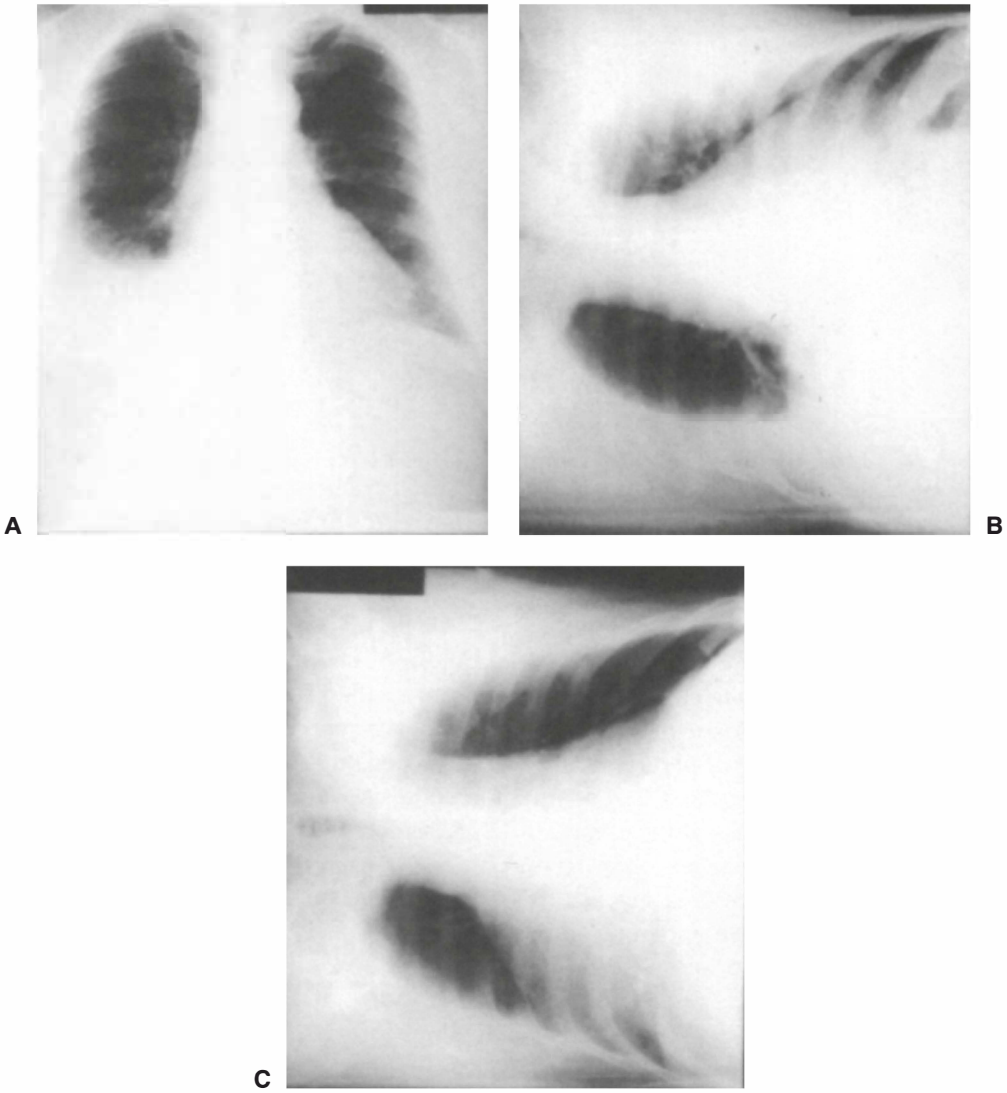

FIGURE 6.7 ■ A: Posteroanterior radiograph demonstrating blunting of the right costophrenic angle. **B**: Right lateral decubitus radiograph of the same patient demonstrating a large amount of free pleural fluid. **C**: Left lateral decubitus radiograph demonstrating that the lower right lung field is clear of parenchymal infiltrates.

Pleural fluid on ultrasound appears echo free (anechoic), or hypoechoic (reduced echogenicity relative to the liver) (20). For simplicity, pleural fluid collections with ultrasound can be characterized as echo free (anechoic), complex septated if there are fibrin strands or septa floating inside the hypoechoic pleural effusions, complex nonseptated if heterogeneous echogenic material is inside the hypoechoic pleural effusion, and homogeneously echogenic if homogeneously echogenic spaces are present between the visceral and parietal pleura. In one series of 320 patients with pleural effusions, 172 (54%) were anechoic, 50 (16%) were complex nonseptated, 76 (24%) were complex septated, and 22 (7%) were homogeneously echogenic (22). Interestingly, all the patients who had complex-nonseptated, complex-septated, or homogeneously echogenic results had exudative pleural effusions. Patients who had anechoic effusions could have either transudative or exudative pleural effusions (22). However, in a more

recent study 70 of 127 patients (55%) with transudative effusions had a complex nonseptated pattern (24).

Transthoracic chest ultrasonography can be performed with any modern ultrasound unit. A 3.5 to 5.0 MHz with a small footprint allows visualization of the deeper structures, and the sector scan field allows a wider field of view through a small acoustic window. Once an abnormality has been identified, a high-resolution 7.5 to 10 MHz linear probe can be used to provide detailed depiction of any chest wall, pleural, or peripheral lung abnormality (19,20). The high-frequency transducer improves resolution in the near field so that internal echoes in a solid lesion are easier to image, which helps the examiner distinguish solid lesions from cystic lesions. In addition, near-field reverberation artifacts, which might otherwise obscure fluid close to the skin, are reduced. Real-time scanning is preferred to conventional static scanning because it allows one to assess the changing configuration of pleural fluid with respiration, is easier to use in the intercostal spaces, and requires less time to scan large areas (21). The best distinguishing characteristic of a pleural fluid collection on ultrasound is that it changes its shape with respiration (25).

The posterior chest is best imaged with the patient sitting upright, whereas the anterior and lateral chest are best assessed in the lateral decubitus position. If the patient's arm is raised above his head, the distance between the rib spaces is increased and this facilitates scanning the patient in the erect or recumbent position (19).

Identifying the Presence of Pleural Fluid

Ultrasound is accurate in identifying the presence of pleural fluid. In one recent study of 60 patients with congestive heart failure, CT scans demonstrated pleural effusions in 52 of the 60 (87%) (26). Ultrasound demonstrated pleural fluid in more than 90% of the patients in whom the fluid was identified by CT scans (26). In another study, lateral decubitus radiographs were able to identify the presence of pleural fluid in 92% of 52 patients who had small amounts of pleural fluid demonstrated by ultrasound (27). Moreover, there was a close correlation between the thickness of the fluid on the ultrasound examination and the decubitus radiograph (27). In a recent study, pulmonologists were able to correctly identify the presence or absence of pleural fluid in 951 of 955 patients (99.6%) (23).

It has been suggested that color Doppler ultrasound is superior to real-time gray-scale ultrasound in the identification of pleural fluid (28). With the color Doppler ultrasound, pleural fluid is identified because it provides a color signal. In one report of 51 patients with minimal pleural effusions, color Doppler ultrasound correctly demonstrated color in 33 of 35 (94%) patients with pleural fluid but was negative in the 16 patients without pleural fluid. In contrast, real-time gray-scale ultrasound identified fluid in all 35 patients with fluid but also in 5 of 16 patients without fluid (28). Another study recently confirmed that color Doppler ultrasound was superior to gray-scale ultrasound in demonstrating the presence of pleural effusion (29).

Ultrasound can demonstrate pleural fluid in normal individuals. Kocijancic et al. (30) performed ultrasonography on a group of 106 healthy volunteers in the lateral decubitus position and then leaning on the elbow. They reported that a layer of pleural fluid greater than 2 mm in thickness was found in 28 of the 106 volunteers (26%). The effusion was bilateral in 17 volunteers and unilateral in 11 (30). When the ultrasonography was repeated 2 to 4 months later, 21 of the original volunteers with fluid still had it, whereas an additional 11 patients had fluid which was not present initially (30).

Identifying the Site for Thoracentesis or Thoracoscopy

Ultrasonic techniques are useful in identifying the appropriate site for thoracentesis (21,22,31) and ultrasound guidance is being used more and more frequently to identify the site for thoracentesis. The appropriate site can be identified both in patients with loculated pleural effusions and in those with small amounts of pleural fluid. In addition to identifying the site for aspiration, the appropriate depth for aspiration can also be ascertained, thereby increasing the safety of the procedure. It is important to perform the thoracentesis at the time the fluid is identified by ultrasound. When the skin is only marked at the time of the ultrasonic examination and the patient is sent back to the ward, the patient is frequently in a different position when the thoracentesis is attempted. In such instances, the relationship between the skin and the pleural fluid is altered, and the thoracentesis attempt may occur at the wrong location (31). The safety of this method was documented in one retrospective review of 941 thoracenteses performed during a 3-year period at a single institution. Of these, only 24 patients (2.5%) developed a pneumothorax and only 8 (0.8%) required a chest tube (32). It is probably safer to perform thoracentesis with ultrasound

guidance. Barnes et al. (33), in a retrospective study, reported that the incidence of pneumothorax and chest tube requirement was 4.9% and 0.7% in 305 ultrasonically guided procedures and 10.3% and 4.1% in 145 thoracenteses done without ultrasound. When ultrasound is used to guide thoracentesis, the lung gliding sign should be assessed pre- and post-procedure to ascertain whether the procedure resulted in a pneumothorax (20).

In a similar manner, the site for medical thoracoscopy can be evaluated with ultrasound. Feller–Kopman et al. evaluated the use of transthoracic ultrasound to locate a safe entry site for trocar placement during medical thoracoscopy in 20 patients without induction of a preprocedure pneumothorax (34). The ultrasound identified entry sites in all 20 patients including three patients with adhesions (34). These authors felt that the use of ultrasound may replace the practice of pneumothorax induction before medical thoracoscopy. Ultrasound guidance also facilitates the insertion of chest tubes (19) and indwelling pleural catheters such as the Pleurx catheter (35). Lastly, ultrasound guidance facilitates needle biopsy of the pleura with a standard Abrams needle or an automated cutting needle device (19). One study compared the use of ultrasound guided Tru-cut needle biopsy and unaided Abrams needle biopsy in the diagnosis of pleural malignancy and tuberculosis and reported that the ultrasonically guided procedure had higher sensitivity and specificity (36).

Ultrasound in the Intensive Care Unit

The intensive care unit (ICU) is one of the locations where ultrasound has its greatest utility (37,38). Because many chest radiographs are taken with the patient in the supine position, pleural effusions and pneumothorax are often missed. Ultrasound can identify which of the patients in the ICU have pleural effusions or pneumothorax. Identification of the presence of significant amounts of pleural fluid in patients in the ICU is important for at least two reasons. If the patient is on a ventilator, removal of the fluid may facilitate weaning. If the patient is febrile, it is important to ascertain whether the patient has infected pleural fluid. In a prospective study, Tu et al. (39) performed a 1-year study of febrile patients with physical, radiographic and ultrasonographic evidence of pleural effusion. They performed thoracentesis with ultrasound guidance on 94 patients and 15 (16%) of them had empyema (39). All the patients with empyema had a hyperechoic pattern or a complex-septated pattern. They suggested that patients could be selected for thoracentesis based on their ultrasonography findings (39).

Semiquantitating the Amount of Pleural Fluid

It is possible to estimate, with some degree of reliability, the amount of pleural fluid with either ultrasonography or lateral decubitus chest radiographs. Eibenberger et al. (40) studied 51 patients who underwent lateral decubitus chest radiography and ultrasonography while supine. The thickness of the fluid on the lateral decubitus radiograph and on ultrasonography was measured just cranial to the base of the lung. Subsequent to these studies, the patients underwent therapeutic thoracentesis with removal of all of the pleural fluid. The relationship between the measurements and the amount of fluid withdrawn is shown in Figure 6.8. It can be seen in the same figure that the amount of fluid is more closely correlated with the ultrasonic measurement than with the lateral decubitus measurement. Also note that on the lateral decubitus radiograph, a fluid thickness of 30 mm corresponds to a volume of 1,000 mL, whereas on the ultrasound measurement, a fluid thickness of 40 mm corresponds to a volume of 1,000 mL. Roch et al. (41) evaluated the utility of ultrasound in detecting pleural effusions with volumes greater than 500 mL in patients in the ICU. They concluded that if the distance between the lung and the parietal pleura was more than 5 cm at the base of the lung, there was a sensitivity of 83% and a specificity of 90% that the patient had a pleural effusion with more than 500 mL (41). In a recent study, Balik et al. (42) found that the amount of pleural fluid in 81 patients on mechanical ventilation could be predicted by the following formula: volume pleural fluid (mL) = 20 × the separation of the visceral and parietal pleura in mm. The mean prediction error was 158 ± 160 mL in this study (42).

The amount of pleural fluid can also be estimated from the CT scan (43). The volumes estimated from the CT scan correlate well with the volumes estimated by ultrasound (43). The amount of pleural fluid can also be roughly semiquantitated from the posteroanterior and lateral chest radiographs (44). Blackmore et al. (44) have demonstrated that when more than 50 mL pleural fluid is present, it becomes visible on the lateral radiograph as a meniscus posteriorly. When more than 200 mL fluid is present, a meniscus can be identified in the lateral costophrenic angle of the posteroanterior radiograph. When more than 500 mL is present, the meniscus obscures the entire hemidiaphragm.

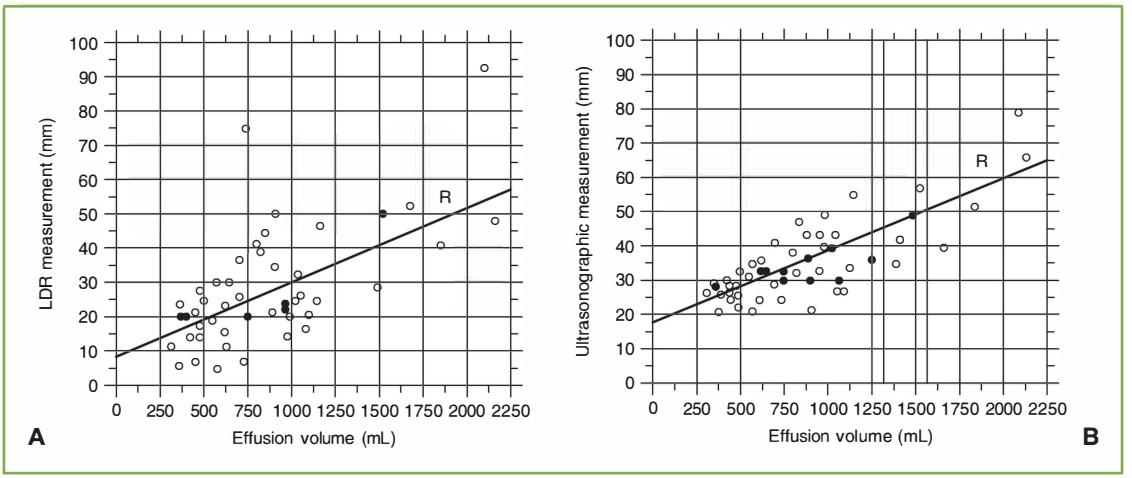

FIGURE 6.8 ■ Correlation of actual volume of pleural effusion with **(A)** thickness of fluid on the lateral decubitus radiograph (LDR) and with **(B)** thickness of fluid on sonography. Values are from 51 patients before thoracentesis. The sonographic measurements were more closely correlated with the volume of the fluid ($r = 0.80$) than were the lateral decubitus measurements ($r = 0.58$). *(From Eibenberger KL, Dock WI, Ammann ME, et al. Quantification of pleural effusions: sonography versus radiography.* Radiology. *1994;191:681–684, with permission.)*

Identifying Whether a Pleurodesis Is Present

It is frequently difficult to tell whether a pleurodesis is present. Both chest radiographs and chest CT will show whether pleural fluid or pleural thickening is present, but neither can show whether a pleurodesis is present. Zhu et al. (45) induced a pleurodesis in rabbits by a single injection of transforming growth factor beta-2 (TGF-β_2) and showed that there was an excellent correlation ($r = 0.81$) between the gliding sign score and the pleurodesis score. The gliding sign is said to be present when one can see the visceral pleura glide over the parietal pleura on ultrasound. Absence of the gliding sign indicates that the two pleural surfaces are fused. These findings were confirmed in another study on rabbits (46). It appears that absence of pleural sliding also identifies pleurodesis in humans. Leo et al. (47) reported that pleural gliding was absent at nine different locations in five of five patients who received complete pleurectomy for spontaneous pneumothorax.

Identifying Pneumothorax and Hemothorax in Trauma Patients

Ultrasound is being used more and more frequently to assess trauma patients for the presence of a hemothorax or a pneumothorax. Ma et al. (48) reported that the ultrasound performed by emergency room physicians correctly identified 24 of 25 hem(r = 0.58) othoraces (96%). In another study of 360 patients, 39 of 40 hemothoraces were detected by ultrasound, whereas 37 were detected by chest radiograph. The performance time for ultrasonography was significantly faster than that for chest radiography (1.3 vs. 14.2 minutes) (49). Not all studies have concluded that ultrasound is good at identifying hemothorax. Abboud and Kendall (50) reviewed the ultrasound results and the CT scan results of 142 patients with blunt trauma who had both these studies. They found that the ultrasound identified only two of 16 (12.5%) patients with hemothorax. However, it should be noted that all the hemothoraces in this study were small or tiny and were probably not clinically significant.

Ultrasound can also identify trauma patients with pneumothorax. Ultrasound appears to be better at diagnosing pneumothorax than the supine radiograph. Rowan et al. (51) obtained CT scans, supine chest radiographs, and thoracic ultrasound on 27 patients with blunt chest trauma. Eleven patients had pneumothoraces, and all were detected with thoracic ultrasound and chest CT, but only four were seen on the chest radiograph (51).

COMPUTED TOMOGRAPHY

The availability of CT has markedly improved our ability to assess pleural abnormalities radiologically.

Pleural abnormalities can be more readily detected and distinguished from lung parenchymal and extra pleural disease by CT than by standard radiographs because these anatomic compartments are distinct on the cross-sectional image with CT (52). Pleural collections or masses tend to conform to the pleural space. As with chest radiographs, the angle of the lesion with the chest wall may help identify whether the lesion is pleural or parenchymal. If the angle of the abnormality with the chest wall is acute, then the lesion probably has a parenchymal origin, whereas if the angle is obtuse, the lesion probably has a pleural origin. Sometimes, however, the CT findings are as ambiguous as the radiographs, particularly when there is atelectasis or pneumonia or when a pleural collection forms acute angles with the chest wall.

Free-flowing pleural fluid produces a sickle-shaped opacity in the most dependent part of the thorax posteriorly (21). Loculated fluid collections are seen as lenticular opacities of fixed position. When free fluid lies in the posterior costophrenic recess adjacent to the diaphragm, it may be difficult to differentiate from ascites. Several CT features have been described that aid in the differentiation of pleural fluid from ascites. These are the displaced crus sign, the interface sign, the diaphragm sign, and the bare-area sign (21). With the displaced crus sign, the displacement of the diaphragmatic crus away from the spine by the fluid indicates that the fluid is in the pleural space. In contrast, ascites lies lateral and anterior to the crus. With the interface sign, a sharp interface can be identified between the fluid and the liver or spleen, and this interface indicates that ascites is present. This line is much less distinct if pleural fluid is present. With the diaphragm sign, fluid that is outside the diaphragm is pleural fluid, whereas that which is inside the diaphragm is ascites. With the bare-area sign, restriction of ascites by the coronary ligaments from the bare area of the liver indicates that the patient has ascites.

CT is effective in demonstrating abnormalities in the lung parenchyma that are obscured on the conventional chest radiograph by the pleural disease. Chest CT is particularly useful in distinguishing empyema with air–fluid levels from lung abscess, as discussed subsequently. In patients with pleural effusions, CT can also identify pleural thickening, which suggests that the patient has an exudative effusion. In one study, 36 of 59 exudative effusions (61%) had associated pleural thickening, whereas only 1 of 27 transudates (4%) had associated pleural thickening (53). However, in another study, pleural thickening was present in 36% of transudates (54). An added bonus with CT is the clear demonstration of bone pathology such as metastases or tuberculosis.

Findings on CT can help distinguish benign and malignant effusions. In one study of 146 patients with pleural disease, the following findings (with their sensitivities and specificities) were suggestive of malignancy: pleural nodularity (37%/97%), pleural rind (22%/97%), mediastinal pleural involvement (31%/85%), and pleural thickening greater than 1 cm (35%/87%) (55). Traill et al. (56) reported that 27 of 32 patients with malignant pleural effusion had pleural nodularity or irregularity or pleural thickness greater than 1 cm whereas none of 8 patients with benign disease met these criteria.

Chest CT is not indicated in all patients with suspected pleural disease. The density coefficients from CT are not specific enough to distinguish among parenchymal lesions, solid pleural masses, or pleural collections of serous fluid, blood, or pus (19). Moreover, the attenuation coefficients from the CT scan do not differ significantly between transudates and exudates (54). Ultrasonic examinations are preferred to CT when the primary question is whether pleural fluid is present.

CT examinations of the chest have also provided additional information concerning the effects of a pleural effusion on the underlying lung. Paling and Griffin (57) reviewed the chest CT, obtained in the supine position, of 46 cases with a moderate or large pleural effusion. The volume of the underlying lung, particularly the lower lobe, was reduced in all patients, and there was atelectasis of the underlying lung in 44 of the 46 (96%) patients. In 19 patients, there was segmental collapse of the lower lobe. In seven patients, the atelectatic segment was so large as to produce an appearance initially suggestive of complete collapse of the lower lobe. In 25 of 46 patients, the lower lobe collapse involved all except the superior segment, which tended to remain aerated. Recognition of a major degree of volume loss in the lower lobe depended on identification of the bronchial anatomy serving the airless lung and on the loss of an identifiable inferior pulmonary vein, which was buried within the collapsed lung.

CT examinations of the chest have also been used to evaluate the major and minor fissures. In one report, 100 CT scans of patients with normal lungs were reviewed to determine the normal characteristics of the major and minor fissures. Each major fissure was imaged most often as a lucent band, less often as a line, and least often as a dense band.

In contrast, the minor fissure was imaged as a lucent area, which was usually triangular with its apex at the hilar region (58).

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) has generated considerable interest as a safe and sensitive technique for imaging human pathologic conditions. The technique basically consists of inducing transitions between energy states by causing certain atoms to absorb and transfer energy. This is accomplished by directing a radio frequency pulse at a substance placed within a large magnetic field. Measures of the time required for the material to return to a baseline energy state (relaxation time) can be translated by a complex computer algorithm to a visual image. There are two time constants associated with relaxation, called T1 and T2. The T1 relaxation time characterizes a time constant with which the nuclei align in a given magnetic field. In contrast, T2 reflects the time constant for loss of phase coherence of excited spins (59,60).

With MRI, the lungs are seen as regions of black signal intensity similar to the black appearance of the lungs on CT. When evaluating the soft tissues, however, several differences are noted. The subcutaneous fat on MRI has bright signal intensity, compared with the low signal intensity of CT. On MRI, the vascular structures including the aorta and main, left, and right pulmonary arteries are seen as regions of signal void (black) that is distinct from the surrounding mediastinal fat. With noncontrast CT, the vessels and masses have a similar attenuation. The bony structures on MRI may be seen as regions of bright signal intensity because of the fat within the marrow or low intensity for cortical bone (60).

Pleural effusions can be identified with MRI. A pleural fluid collection is visualized as an area of abnormally low signal intensity on T1-weighted images that increases in brightness on T2-weighted images. This characteristic is consistent with the relatively long T1 and T2 values of pleural fluid. With MRI, different types of pleural fluid collections such as transudative fluid, chylothorax, hemothorax, or pus may appear somewhat different, but their characteristics are not sufficiently distinct as to be diagnostic. A diagnostic thoracentesis is certainly more definitive and less expensive.

In general, MRI has a limited role in the investigation of pleural disease because of poor spatial resolution and motion artifact (61). For patients with mesothelioma, the CT and MRI provide comparable information in most instances. The MRI is superior to CT in revealing solitary foci of chest wall invasion and endothoracic fascia involvement, and also in showing diaphragmatic muscle invasion (62). However, these findings do not affect surgical treatment (62). It should be noted that many normal individuals have a small amount of fluid on MRI. Nguyen et al. (63) reviewed 200 normal women who had an MRI for breast cancer screening and reported that 174 patients had a pleural effusion of which 124 were bilateral. Most of the effusions were less than 7 mm in maximal thickness (63).

In summary, MRI of the chest is currently less satisfactory than ultrasound or CT in identifying the presence of a pleural effusion. At present, there are no definite clinical indications for MRI of the chest in the management of patients with pleural disease.

POSITRON EMISSION TOMOGRAPH (PET) SCANS

Co-registration of PET and CT using combined scanners has expanded the use of PET imaging throughout the body, although its relatively high cost, limited availability, and length of examination time limits it use (64). Malignant cells concentrate 18-fluorodeoxyglucose (^{18}FDG) more avidly than normal tissue. However, any area with intense inflammation is likely to be PET positive. PET scans appear to be useful in the evaluation of pleural effusions and pleural thickening or nodules. Orki et al. (65) performed PET scans combined with CT in 60 patients with pleural effusion and 23 patients with pleural thickening before thoracoscopy. The PET scans were positive in all 44 cases with malignancy (including 25 cases with malignant mesothelioma) and in two of the 39 benign cases both of whom had tuberculosis (65).

AIR–FLUID LEVELS IN THE PLEURAL SPACE

When both air and fluid are present in the pleural space, an air–fluid level is apparent on radiographs obtained in the erect position (Fig. 6.9). An air–fluid level is manifested as an absolutely straight line parallel to the bottom of the radiograph. Of course, if the radiograph is obtained with the patient in the supine position, no air–fluid level will be present unless it is a cross-table lateral view. The presence of an air–fluid level in the pleural space indicates that

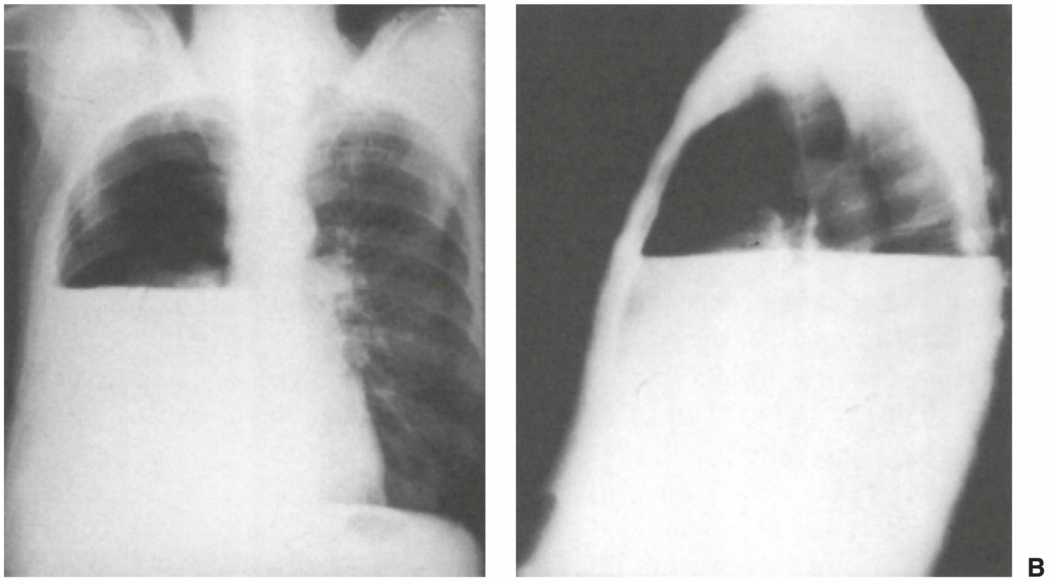

FIGURE 6.9 ■ Posteroanterior **(A)** and lateral **(B)** radiographs of a patient with a hydropneumothorax. Note that the air–fluid level extends throughout the length and width of the hemithorax. This hydropneumothorax followed an attempted thoracentesis in this patient with a massive right pleural effusion.

air has gained entry into the pleural space. The differential diagnosis includes bronchopleural fistula from pulmonary infections, spontaneous pneumothorax with pleural effusion or hemothorax, trauma (iatrogenic or noniatrogenic), the presence of gas-forming organisms in the pleural space, and rupture of the esophagus into the pleural space. Air–fluid levels in the pleural space must be distinguished from air–fluid levels in dilated loops of bowel entering the thoracic cavity through a diaphragmatic hernia. Contrast media studies of the gastrointestinal tract are diagnostic in doubtful cases.

It is frequently difficult to distinguish a loculated pyopneumothorax with a bronchopleural fistula from a peripheral lung abscess. This differentiation is important because pyopneumothorax should be treated on an emergency basis with pleural drainage (see Chapter 12), whereas a lung abscess usually responds to antibiotics and postural drainage alone. One indication that the air-fluid is in the pleural space is whether the length of the air-fluid level varies markedly between the PA and lateral radiographs. A lung abscess is round and the length of the air-fluid level is about the same on both the PA and lateral radiographs.

Both ultrasound and CT are useful in distinguishing between these two conditions. With ultrasonic examination during hyperventilation, asymmetric motion of the proximal (chest wall–parietal pleura) and the distal (visceral pleura–lung) interface occurs when the process is in the pleural space. If the process is within the lung parenchyma, the proximal and distal interfaces (anterior and posterior walls of the cavity) move symmetrically (66). Other characteristics of pyopneumothorax, but not of a lung abscess, are loss of the gliding sign above the air–fluid level and the curtain sign which is movement of the air–fluid level synchronized with respiration (67). In a study of 16 patients with lung abscess and 19 patients with pyopneumothorax, Lin et al. (67) reported that the absence of the gliding sign and the curtain sign were the findings which best separated the two entities (67). Recently, it has been shown that color Doppler effectively distinguishes lung abscess for pyopneumothorax (68). Chen et al. (68) performed a color Doppler study of 34 patients with lung abscess and 30 patient with empyema and demonstrated that if the identification of color Doppler vessel signals in peri-cavitary consolidation was used as an indicator of peripheral lung abscess, the sensitivity, specificity, positive predictive value, and negative predictive value were 94%, 100%, 100%, and 94%, respectively.

Empyema with a bronchopleural fistula can also be distinguished from a lung abscess by chest CT (69). With CT scanning, a pyopneumothorax is

characterized by unequal fluid levels on positional scanning that closely approximate the chest wall. The space characteristically has a smooth, regular margin that is sharply defined without side pockets. The appearance of the cavity often changes with variations in the patient's position. In contrast, a lung abscess is typically round with an irregular, thick wall and has an air–fluid level of equal length in all positions. When the patient's position is changed, the shapes of the cavity and of the mass do not change. Frequently, multiple side pockets are adjacent to the main cavity. An additional distinguishing feature is that the larger empyemas displace the adjacent lung and lung abscesses do not (69).

CT is not infallible in distinguishing empyemas from lung abscesses. Bressler et al. (70) reviewed the CT scans from 71 patients in whom the question was whether the individual had a lung abscess or empyema. In 5 of the 71 patients, the foregoing morphologic criteria were insufficient to make the distinction. The intravenous administration of a bolus of contrast medium in conjunction with CT was diagnostically useful. The demonstration of vessels within a lesion unequivocally identifies the lesion as parenchymal rather than pleural. Moreover, after administration of sufficient amounts of contrast material, pulmonary parenchyma is enhanced, whereas most pleural lesions show minimal or no enhancement (70).

Another condition that must be differentiated from empyema in a patient with air–fluid levels in the chest is fluid-filled bullae or lung cysts in which the CT findings may resemble those of empyema. On CT scan, the fluid-filled cavities have many characteristics of loculated pleural fluid collections including lenticular shape; air–fluid levels of different length on orthogonal views; uniform, smooth inner walls; and mass effect on the adjacent lung. Two features are useful in differentiating fluid-filled cysts from empyema: (a) cysts tend to be located in the upper lobes and the air–fluid levels are limited by fissures, and (b) one notes the absence of preexisting or coexisting large pleural effusion with fluid-filled cysts (71).

MASSIVE EFFUSION

When an entire hemithorax is opacified, one should first examine the position of the mediastinum because its position is influenced by the pleural pressures (Fig. 6.10). If the pleural pressure is lower on the side of the effusion, the mediastinum will be shifted toward the side of the effusion (Fig. 6.10A). Alternately, if the pleural pressure is higher on the side of the effusion, the mediastinum will be shifted toward the contralateral side (Fig. 6.10B). Of course, if the mediastinum is invaded by tumor or other infiltrative processes, it will be fixed, and no shift will be evident on the PA radiograph.

When the patient's mediastinum is shifted toward the side of the effusion, the lung underlying the effusion is usually diseased. In such a case, overexpansion

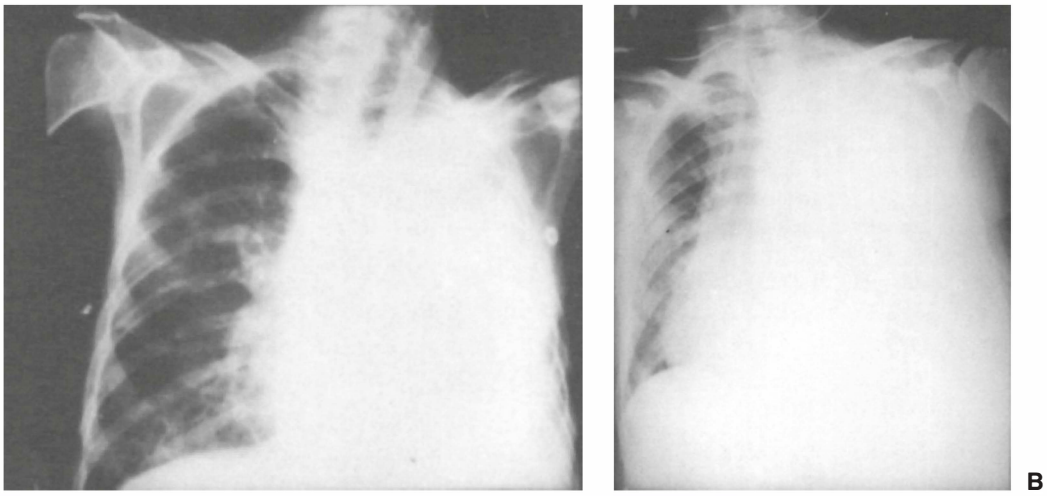

FIGURE 6.10 ■ A: Massive pleural effusion with marked shift of the trachea and mediastinum toward the side of the effusion. This patient had a bronchogenic carcinoma obstructing the left main bronchus. **B**: Massive pleural effusion with marked shift of the trachea and mediastinum away from the side of the effusion.

of the contralateral lung produces an enlarged retrosternal clear space on the lateral view. By far, the most common cause of this radiographic picture is complete obstruction of the ipsilateral main stem bronchus by a neoplasm. Therefore, if the mediastinum is shifted toward the side of the effusion, the initial diagnostic procedure should be bronchoscopy to assess the patency of the bronchial tree. If an obstructing lesion is found, thoracentesis is not recommended because it is unnecessary diagnostically, and it carries an increased risk because of the negative pleural pressure, which can lead to a pneumothorax or reexpansion pulmonary edema. If no obstructing lesion is found, removal of large amounts (greater than 1,000 mL) of pleural fluid should only be attempted if pleural pressures are monitored (72).

When the patient's mediastinum is shifted toward the contralateral side, an active process in the pleural space has led to the accumulation of pleural fluid. In such instances, not only is the ipsilateral lung completely nonfunctional, but the function of the contralateral lung is also compromised (Fig. 6.10B). A therapeutic thoracentesis (see Chapter 28) should be performed immediately to restore the mediastinum to midline. The most common cause of massive pleural effusion with mediastinal shift is metastatic disease of the pleura (73), but tuberculosis, empyema, cirrhosis with hepatothorax, chylothorax, hemothorax, and congestive heart failure may also cause this picture. If the mediastinum is midline in a patient with a massive pleural effusion, the mediastinum is usually invaded by tumor. At times, most of the mediastinum is in the midline, but the tracheal air shadow is shifted. This picture is suggestive of bronchogenic carcinoma (74).

Both CT scan and ultrasound are quite useful in evaluating patients with unilateral hemithorax opacification. Yu et al. (75) evaluated these two diagnostic modalities in 50 patients with unilateral hemithorax opacification. Either procedure can demonstrate whether the opacification is due to fluid, a tissue mass, or a combination. It is interesting that 9 of the 50 patients in the series mentioned in the preceding text (18%) had no fluid in their pleural space. Both procedures are very effective in demonstrating pleural or parenchymal abnormalities, whereas only the CT scan effectively demonstrates mediastinal involvement (75).

PLEURAL THICKENING

The pleura may become thickened over the convexity of the thorax and occasionally in the interlobar fissure.

Radiologic Signs

Normally, no line is visible between the inside of the chest wall and the outer border of the lung, but in response to inflammation of the pleura, the lung may become separated from the chest wall by a pleural line. After an episode of pleuritis, the thickness of the pleural line may be 1 to 10 mm. The pleural thickening that follows pleural inflammation results almost exclusively from fibrosis of the visceral pleural surface. The thickening may be either localized or generalized. If the pleural thickening is localized, it most commonly involves the inferior portions of the thoracic cavity because that is where the pleural fluid containing inflammatory mediators accumulates. Frequently, with localized pleural thickening the costophrenic angles are partially or completely obliterated. In such instances, decubitus radiographs or ultrasound are indicated to rule out free pleural fluid. The main significance of localized pleural thickening is as an index of previous pleural inflammation.

Following intense pleural inflammation, such as occurs with a massive hemothorax, pyothorax, or tuberculous pleuritis, generalized pleural thickening of an entire hemithorax may occur. This thickening is again due to the deposition of fibrous tissue on the visceral pleura. The thickness of the pleura may exceed 2 cm. Frequently, the inner aspect of this "peel" is calcified, providing an accurate measurement of the thickness of the peel. If the patient is symptomatic and if the underlying lung is functional, decortication (see Chapter 27) may provide symptomatic relief.

Apical Thickening

The pleura in the apex of the lungs sometimes becomes thickened. Although in the past, apical pleural thickening was usually attributed to tuberculosis (1), currently tuberculosis is not responsible for most cases. Renner et al. (76) studied the apical pleura at autopsy in 19 patients with radiologically visible pleural thickening and found no evidence of tuberculosis in any of the patients. However, the apical cap is commonly present in patients who have upper lobe fibrosis secondary to tuberculosis. The frequency of apical pleural thickening increases with age, and the authors suggested that the apical pleural thickening might be related to the healing of pulmonary disease in the presence of chronic ischemia (76). Apical pleural thickening is frequently bilateral but can be unilateral (76). Gross asymmetry should raise the suspicion of apical pulmonary carcinoma or Pancoast's tumor.

Asbestos-Induced Thickening

Pleural thickening can also result from asbestos exposure (see Chapter 27). In contrast to other types of pleural thickening, the parietal pleura rather than the visceral pleura is thickened following asbestos exposure. The pleural thickening can either be localized, in which case the thickenings are called *pleural plaques*, or generalized (77). An average of 30 years elapse between the first exposure to asbestos and the appearance of pleural plaques (77). The pleural thickening or plaques associated with asbestos exposure are usually bilateral, more prominent in the lower half of the thorax, and follow the rib contours (78). The pleural thickening due to asbestos exposure eventually becomes calcified. The calcification ranges from small linear or circular shadows, which are usually situated over the diaphragmatic domes, to complete encirclement of the lower portion of the lungs. CT of the chest is more sensitive than other radiologic procedures in identifying both pleural thickening and pleural calcification due to asbestos exposure (79).

In obese patients, subcostal fat may mimic pleural thickening. Typically, it appears as a symmetric, smooth, soft tissue density that parallels the chest wall and is of greatest thickness over the apices. In problem cases, subcostal fat can be distinguished from either diffuse thickening or localized plaques with CT. On CT, subcostal fat can be identified as low-density tissue internal to the ribs and external to the parietal pleura (21).

PNEUMOTHORAX

The radiographic signs of a pneumothorax are influenced by two factors (1). First, air in the pleural space accumulates in the highest part of the thoracic cavity because air is less dense than the lung. Second, the lobes of the lung maintain their traditional shape at all stages of collapse. Note that these are the same factors that influence pleural fluid accumulation. The only difference is that with pneumothorax, air rises to the apex of the hemithorax and causes early collapse of the upper lobes of the lung, whereas with pleural effusion, the pleural fluid falls to the bottom of the hemithorax and collapses the lower lobes.

Radiologic Signs

A definitive radiologic diagnosis of pneumothorax can be made only when a visceral pleural line can be identified (Fig. 6.11). The visceral pleural line is evident as a faint but sharply defined line separating the lung parenchyma from the remainder of the thoracic cavity, which is clear and devoid of lung markings. Although one might suppose that the partially collapsed lung would have increased density radiologically, it does not for the following reasons. First, blood flow through the partially collapsed lung, which contributes substantially to the density radiologically, decreases proportionately to the degree of collapse. Second, the thorax is a cylinder, and with a pneumothorax, the presence of air both anterior and posterior to the partially collapsed lung decreases the overall density of the lung. The radiologic density of the lung does not increase until the lung loses approximately 90% of its volume. Complete atelectasis of a lung due to pneumothorax is characterized ipsilaterally by an enlarged hemithorax, a depressed diaphragm, a shift of the mediastinum to the contralateral side, and a fist-sized mass of increased density at the lower part of the hilum representing the collapsed lung (Fig. 6.12).

The diagnosis of pneumothorax is usually easily established by demonstrating the visceral pleural line on the posteroanterior radiograph. With small pneumothoraces, however, the visceral pleural line may not be visible on the routine radiographs. In such cases, one of the following two procedures can establish

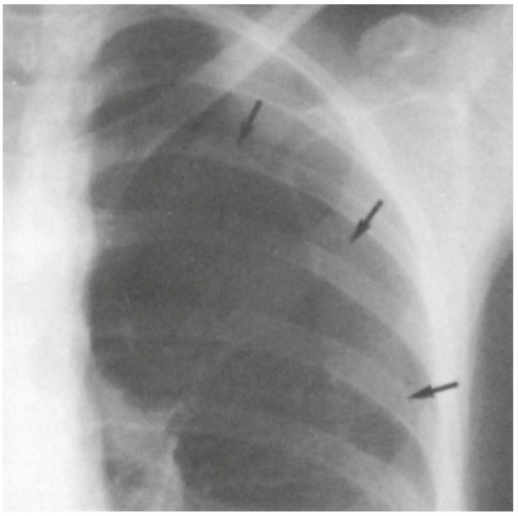

FIGURE 6.11 ■ Posteroanterior radiograph of a patient with a pneumothorax on the left side. Note the obvious pleural line (*arrows*) separating the lung from the air in the pleural space. The density of the radiograph inside and outside the pleural line is similar. Also note that a bleb (*upper arrow*) is present along the surface of the apical pleural line. This bleb was probably responsible for the pneumothorax. *(Courtesy of Dr. Harry Sassoon.)*

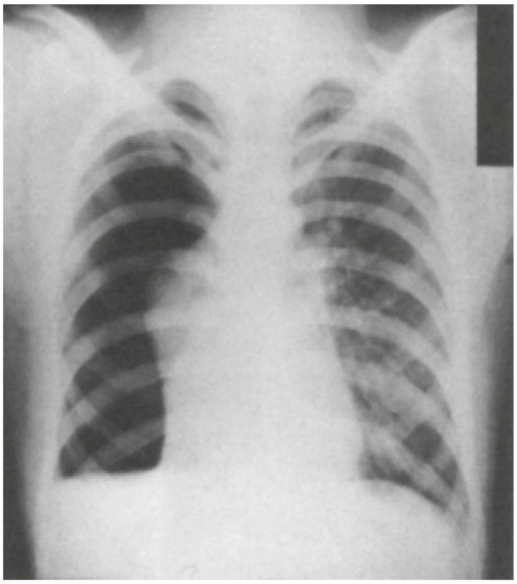

FIGURE 6.12 ■ Posteroanterior radiograph of a patient with a pneumothorax and complete atelectasis of the right lung.

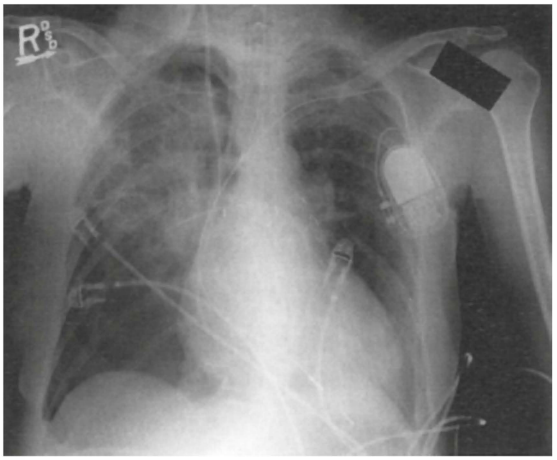

FIGURE 6.13 ■ Anteroposterior radiograph of a patient with a pneumothorax in the right apex and a skin fold in the left apex. On the side with the pneumothorax, note the sharp black–white interface medial to the apparent pleural line. In contrast, note that on the side with the skin fold (left side), there is gradual fading from the white pleural line as one moves medially.

the diagnosis: (a) radiographs can be obtained in the upright position in full expiration; the rationale is that, although the volume of gas in the pleural space is constant, with full expiration, the lung volume is reduced, and therefore, the percentage of the hemithorax occupied by air increases, making identification of the visceral pleural line much easier; and (b) radiographs can be obtained in the lateral decubitus position, with the side of the suspected pneumothorax superior; the free air in the pleural space rises, increasing the distance between the lung and the chest wall; additionally, fewer conflicting shadows are seen over the lateral chest wall than at the apex. It appears that the decubitus position is the most sensitive for detecting a pneumothorax. Carr et al. (80) obtained conventional chest radiographs and CT scans on cadavers in which varying amounts of intrapleural air had been introduced. They found that the lateral decubitus film was most sensitive (88%) for the diagnosis of pneumothorax, followed by the erect (59%) and supine (37%) views. These researchers reported that the pneumothorax was always detected in the lateral decubitus position when there was more than 40 mL of intrapleural air. In addition, they found that a CT scan was no more sensitive than the decubitus views (80).

Pneumothoraces are more difficult to recognize on lateral projections than on posteroanterior projections. In one series, the pneumothorax could not be identified on the lateral projection in 13 of 122 patients (11%) (81). When the pneumothorax is identifiable, the displaced pleural line is usually anteriorly or posteriorly located rather than at the lung apex. In 10% of the patients, an air–fluid level was the only recognizable finding of a pneumothorax on the lateral projection (81).

Skin folds may superficially mimic a pleural line and possibly lead to a misdiagnosis of pneumothorax. A skin fold results in an abnormal edge with a sharp black–white interface laterally, with gradual fading of the density from white to black medially (Fig. 6.13). In contrast, there is no such fading medial to the line with pneumothorax. In addition, lung markings are seen peripheral to the edge of the skin fold, in contrast to absence of lung markings peripheral to the line of a pneumothorax (82).

It is much more difficult to establish the diagnosis of pneumothorax on a supine radiograph. In a review of 88 critically ill patients with 112 cases of pneumothorax, 30% of the cases were not initially detected by the radiologist, and half these patients progressed to tension pneumothorax (82). The most common location for collections of air on the supine film is the anteromedial location because this area is the least dependent pleural recess. The three other locations in which air collects on the supine radiograph are

subpulmonically, apicolaterally, and posteromedially. Depending on the size and location of the gas collection, any of the following features can be signs of a pneumothorax in the supine position: an exceptionally deep radiolucent costophrenic sulcus; a lucency over the right or left upper quadrant; or a much sharper than normal appearance of the hemidiaphragm, with or without the presence of a visible visceral pleural line above the diaphragm (1). The interested reader is referred to the review article by Buckner et al. (82) for details concerning the radiologic appearance of air in these locations.

Ultrasound can be used to establish the diagnosis of pneumothorax (83–85). Normal lung is characterized by having so-called lung sliding and comet tail artifacts on ultrasound. Normally, with real-time sonography, respiratory excursions of the visceral pleura can be discerned from the movement of discrete hypoechoic inhomogeneities within the high-echo band of the pleural reflection (84). This movement has been called *pleural gliding* or *lung sliding* (84). In addition, at the boundary between the pleura and the ventilated lung tissue, intensive band-like reverberation echoes (comet tail artifacts) are normally evoked during breathing movements (85). Lichtenstein et al. (85) performed ultrasound examinations over the anterior chest on 184 hemithoraces, including 41 with pneumothorax. They reported that both lung sliding and comet tail artifacts were absent in all 41 patients with pneumothorax but in only 4 of the other 142 hemithoraces (2.8%). Ultrasound is particularly useful in diagnosing pneumothorax in the critically ill patient. If the right main stem bronchus is intubated, there will be no lung sliding on the left, but this does not indicate that a pneumothorax is present (86).

Atypical Pneumothorax

As with pleural effusions, the radiologic appearance of a pneumothorax can be atypical. If the parenchyma of the lung is diseased such that the lung does not retain its normal shape, the appearance of the partially collapsed lung is altered. The presence of adhesions between the visceral and the parietal pleura also alters the radiologic appearance of pneumothoraces. Such adhesions are frequently manifested as band-like structures tethering the partially collapsed lung to the chest wall. Diffuse adhesions between the visceral and the parietal pleura may prevent collapse of an entire lobe (Fig. 6.14).

Clinically and radiologically, it is important to distinguish giant bullae from pneumothoraces because the treatments for the two conditions are different. This differentiation at times is difficult because a large bulla may mimic a large pneumothorax with adhesions. If doubt exists, a CT scan should be obtained because it can unequivocally establish the diagnosis (87).

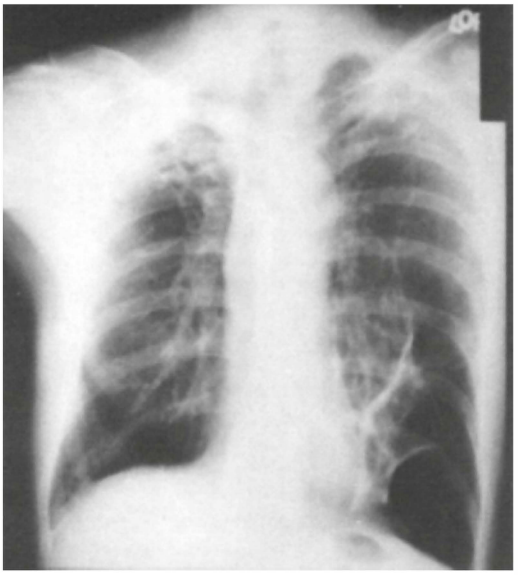

FIGURE 6.14 ■ Atypical pneumothorax. Posteroanterior radiograph of a patient with old pulmonary tuberculosis and a secondary spontaneous pneumothorax on the left side. Note that the pleural air is seen only in the lower part of the hemithorax because the visceral and parietal pleura over the upper lung had become fused by the old tuberculosis.

Tension Pneumothorax

A tension pneumothorax exists when the pressure in the pleural space is positive throughout the respiratory cycle. Because the increased pleural pressure can seriously compromise pulmonary gas exchange and cardiac output (see Chapter 24), it is important to recognize the presence of a tension pneumothorax so that treatment can be undertaken immediately. The radiologic diagnosis of a tension pneumothorax is unreliable from plain radiographic films alone. Although it is frequently stated that enlargement of a hemithorax, flattening of the diaphragm, and contralateral shift of the mediastinum indicate a tension pneumothorax, all three signs occur occasionally with nontension pneumothoraces (1). A definitive diagnosis can be established radiologically only by fluoroscopic examination. With a tension pneumothorax,

the increased pleural pressure prevents the shift of the mediastinum toward the involved side on inspiration, as occurs with a nontension pneumothorax, and the movement of the ipsilateral diaphragm is restricted (1). In general, however, it is better to insert a needle into the pleural space to ascertain the presence of a tension pneumothorax than to waste time with radiologic procedures (see Chapter 24) (88).

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chapter 7

Clinical Manifestations and Useful Tests

Normally, the pleural space contains only a few milliliters of pleural fluid. If fluid in the pleural space is detected on a radiologic examination, it is abnormal. Many conditions can be associated with pleural fluid accumulation (Table 8.1). When pleural fluid is detected, an effort should be made to determine which of the many conditions listed in Table 8.1 is responsible. In this chapter, the clinical manifestations of pleural effusions are first discussed. Then, the various tests used in the differential diagnosis of pleural effusions are reviewed. In Chapter 8, recommendations are given for a systematic approach to the patient with an undiagnosed pleural effusion.

CLINICAL MANIFESTATIONS

The presence of moderate-to-large amounts of pleural fluid produces symptoms and characteristic changes on physical examination.

Symptoms

The symptoms of a patient with a pleural effusion are mainly dictated by the underlying process causing the effusion. Many patients have no symptoms referable to the effusion. When symptoms are related to the effusion, they arise either from inflammation of the pleura, from compromise of pulmonary mechanics, from interference with gas exchange, or, on rare occasions, from decreased cardiac output. A pleural effusion associated with pleuritic chest pain indicates inflammation of the pleura, specifically, the parietal pleura as the visceral pleura does not have pain fibers. Some patients with pleural effusions experience a dull, aching chest pain rather than pleuritic chest pain. This symptom is very suggestive that the patient has pleural malignancy (1). The presence of either pleuritic chest pain or dull, aching chest pain indicates that the parietal pleura is probably involved and that the patient has an exudative pleural effusion.

Ordinarily, the pain associated with pleural disease is well localized and coincides with the affected area of the pleura because the parietal pleura is innervated mostly by the intercostal nerves. At times, however, pleuritic pain is referred to the abdomen because intercostal nerves are also distributed to the abdomen. A notable exception to the localization of the pain occurs when the central portion of the diaphragmatic pleura is involved. The nerve supply to this portion of the parietal pleura is the phrenic nerve; therefore, inflammation of the central portion of the diaphragm is referred to the tip of the ipsilateral shoulder. Pleuritic pain felt simultaneously in the lower chest and ipsilateral shoulder is pathognomonic of diaphragmatic involvement.

A second symptom of pleural effusion is a dry, nonproductive cough. The mechanism producing the cough is not clear, although it may be related to pleural inflammation. Alternately, lung compression by the fluid may bring opposing bronchial walls into contact, stimulating the cough reflex.

The third symptom of pleural effusion is dyspnea. A pleural effusion acts as a space-occupying process in the thoracic cavity and therefore reduces all subdivisions of lung volumes. Small-to-moderate-sized pleural effusions displace rather than compress the lung and have little effect on pulmonary function (2). Larger pleural effusions obviously cause a significant reduction in lung volumes, but the improvement in pulmonary function following therapeutic thoracentesis is much less than what one would anticipate. We obtained spirometry before and 24 hours after thoracentesis in 26 patients from whom a mean of 1,740 mL pleural fluid was withdrawn (3). In these patients, the mean vital capacity improved 410 ± 390 mL. Patients in this

study, with higher pleural pressures after the removal of 800 mL pleural fluid and patients with smaller decreases in the pleural pressure after the removal of 800 mL pleural fluid, had greater improvements in the forced vital capacity (FVC) after thoracentesis.

Associated parenchymal disease probably explains this small increase in pulmonary function following therapeutic thoracentesis. The degree of dyspnea is frequently out of proportion to the size of the pleural effusion. Often, this feature is the result of compromised diaphragmatic function due to the weight of fluid on the diaphragm. At times, the diaphragm becomes inverted and this usually results in disproportionate dyspnea (4). Either pleuritic chest pain, with the resultant splinting, or concomitant parenchymal disease can also be responsible for the disproportionate dyspnea. When the pleural effusion is large, ventricular filling may be impeded, leading to decreased cardiac output and dyspnea (5). Arterial blood gases usually remain at clinically acceptable levels whatever the size of the effusion (6) because of the reflex reduction in perfusion to the lung underlying the effusion.

Physical Examination

When a patient presents with chest symptoms, the physical examination is useful in suggesting whether pleural fluid is present (7). In such an examination, attention should be paid to the relative sizes of the hemithoraces and the intercostal spaces. If the pleural pressure is increased on the side of the effusion, that hemithorax will be larger, and the usual concavity of the intercostal spaces will be blunted or even convex. In contrast, if the pleural pressure on the side of the effusion is decreased, as with obstruction of a major bronchus or a trapped lung, the ipsilateral hemithorax will be smaller, and the normal concavity of the intercostal spaces will be exaggerated. In addition, with inspiratory efforts, the intercostal spaces retract. Enlargement of the hemithorax with bulging of the intercostal spaces is an indication for therapeutic thoracentesis to relieve the increased pleural pressure. Signs of decreased pleural pressure are a relative contraindication to therapeutic thoracentesis because the decreased pleural pressure can lead to reexpansion pulmonary edema (8). Of course, in many patients with pleural effusions, the hemithoraces are equal in size and the intercostal spaces are normal.

Palpation of the chest in patients with pleural effusions is useful in delineating the extent of the effusion. In areas of the chest where pleural fluid separates the lung from the chest wall, tactile fremitus is absent or attenuated because the fluid absorbs the vibrations emanating from the lung. Tactile fremitus is much more reliable than percussion for identifying both the upper border of the pleural fluid and the proper site to attempt a thoracentesis. With a thin rim of fluid, the percussion note may still be resonant, but the tactile fremitus is diminished. Palpation may also reveal that the cardiac point of maximum impulse is shifted to one side or the other. With large left pleural effusions, the cardiac point of maximum impulse may not be palpable. In patients with pleural effusions, the position of the trachea should always be ascertained because it indicates the relationship between the pleural pressures in the two hemithoraces.

The percussion note over a pleural effusion is dull or flat. The dullness is maximum at the lung bases where the thickness of the fluid is the greatest. As mentioned earlier, however, the percussion note may not be duller if only a thin rim of fluid is present. Light percussion is better than heavy percussion for identifying small amounts of pleural fluid. If the dullness to percussion shifts as the position of the patient is changed, one can be almost certain that free pleural fluid is present (9).

Auscultation over the pleural fluid characteristically reveals decreased or absent breath sounds. Near the superior border of the fluid, however, breath sounds may be accentuated and may take on a bronchial characteristic. This phenomenon has been attributed to increased conductance of breath sounds through the partially atelectatic lung compressed by the fluid (10). This accentuation of breath sounds does not mean that an associated parenchymal infiltrate is present. Auscultation may also reveal a pleural rub. Pleural rubs are characterized by coarse, creaking, leathery sounds most commonly heard during the latter part of inspiration and the early part of expiration, producing a to-and-fro pattern of sound. Pleural rubs, caused by the rubbing together of the roughened pleural surfaces during respiration, are often associated with local pain on breathing that subsides with breath-holding. Pleural rubs often appear as pleural effusions diminish in size, either spontaneously or as a result of treatment, because the pleural fluid is no longer present between the roughened pleural surfaces.

It is important to realize that an elevated hemidiaphragm can produce all the classic physical findings associated with a pleural effusion. Obviously, the chest is not the only structure that should be examined when evaluating a patient with a pleural effusion; clues to

the origin of the effusion are often present elsewhere. The effusion is probably due to congestive heart failure (CHF) if the patient has cardiomegaly, neck vein distension, or peripheral edema. Signs of joint disease or subcutaneous nodules suggest that the pleural effusion is due to rheumatoid disease or lupus erythematosus. An enlarged, nontender nodular liver or the presence of hypertrophic osteoarthropathy suggests metastatic disease, as do breast masses or the absence of a breast. Abdominal tenderness suggests a subdiaphragmatic process, whereas tense ascites suggests cirrhosis and a hepatothorax. Lymphadenopathy suggests lymphoma, metastatic disease, or sarcoidosis.

SEPARATION OF TRANSUDATIVE FROM EXUDATIVE EFFUSIONS

The accumulation of clinically detectable quantities of pleural fluid is distinctly abnormal. A diagnostic thoracentesis (see Chapter 28) should be attempted whenever the thickness of pleural fluid on ultrasound or the decubitus radiograph is greater than 10 mm or whenever loculated pleural fluid is demonstrated with ultrasound unless the etiology of the effusion is known. A properly performed diagnostic thoracentesis takes less than 10 minutes and should cause no more morbidity than a venipuncture. The information available from examination of the pleural fluid is invaluable in the management of the patient.

Pleural effusions have classically been divided into transudates and exudates (11). A transudative pleural effusion develops when the systemic factors influencing the formation or absorption of pleural fluid are altered so that pleural fluid accumulates. The pleural fluid is a transudate. The fluid may originate in the lung, the pleura, or the peritoneal cavity (12). The permeability of the capillaries to proteins is normal in the area where the fluid is formed. Examples of conditions producing transudative pleural effusions are left ventricular failure producing increased pulmonary interstitial fluid and a resulting pleural effusion, ascites due to cirrhosis with movement of fluid through the diaphragm, and decreased serum oncotic pressure with hypoproteinemia.

In contrast, an exudative pleural effusion develops when the pleural surfaces or the capillaries in the location where the fluid originates are altered such that fluid accumulates. The pleural fluid is an exudate. The most common causes of exudative pleural effusions are pleural malignancy, parapneumonic effusions, and pulmonary embolism.

The first question to ask in assessing a patient with a pleural effusion is whether that effusion is a transudate or an exudate. If the effusion is a transudate, no further diagnostic pleural procedures are necessary, and therapy is directed to the underlying CHF, cirrhosis, or nephrosis. Alternately, if the effusion proves to be an exudate, a more extensive diagnostic investigation is indicated to delineate the cause of the effusion. It has been shown that pulmonary specialists are not very accurate at doing this on the basis of clinical history, physical examination, and radiographic findings (13).

For many years, a pleural fluid protein level of 3.0 g/dL was used to separate transudates from exudates, with exudative pleural effusions characterized by a protein level above 3.0 g/dL (14,15). Use of this one simple test led to the misclassification of approximately 10% of pleural effusions (14–16). Light et al. subsequently demonstrated that with the use of simultaneously obtained serum and pleural fluid protein and lactic acid dehydrogenase (LDH) values, 99% of pleural effusions could be correctly classified as either transudates or exudates (16). Exudative pleural effusions meet at least one of the following criteria, whereas transudative pleural effusions meet none (Light's criteria):

1. Pleural fluid protein divided by serum protein greater than 0.5
2. Pleural fluid LDH divided by serum LDH greater than 0.6
3. Pleural fluid LDH greater than two thirds of the upper limit of normal serum LDH

Subsequent studies have demonstrated that Light's criteria classify virtually all exudates correctly but misclassify about 25% of transudates as exudates.

In recent years, other tests have been proposed for the separation of transudates from exudates. The tests that have been proposed to indicate a pleural exudate have included a pleural fluid cholesterol greater than 60 mg/dL (17,18), a pleural fluid cholesterol greater than 45 mg/dL (19), a gradient of less than 1.2 g/dL for the difference in the pleural fluid and serum albumin level (20), a pleural fluid-to-serum bilirubin ratio above 0.6 (21), a high pleural fluid viscosity (22), a high level of oxidative stress markers (23), soluble leukocyte selectin (24), cytokines (25), uric acid (26), and a pleural fluid-to-serum cholinesterase ratio above 0.23 (27).

Two subsequent reports (28,29) have compared Light's criteria with some of the other proposed tests and have concluded that Light's criteria best separate exudates and transudates. In the study of Romero et al. (28) of 297 patients including 44 transudates and 253 exudates, Light's criteria were superior to cholesterol measurement in making the distinction. In this study

with Light's criteria, 98% of the exudates and 77% of the transudates were correctly classified (28). In a subsequent study of 393 patients including 123 with transudates and 270 with exudates from South Africa (29), Light's criteria were found to be superior to the serum effusion albumin gradient, the effusion cholesterol concentration, and the pleura fluid-to-serum bilirubin ratio (29). Again in this study, Light's criteria identified 98% of the exudates correctly, but they were less accurate in identifying transudates, misclassifying 19 of 112 (17%) (29). Two additional studies (30,31) have come to similar conclusions. It is unlikely that the pleural fluid cholesterol measurement will provide additional information to the ratio of the pleural fluid to the serum protein because the pleural fluid cholesterol level can be accurately predicted from the serum cholesterol and the ratio of the pleural fluid to the serum protein level (32).

The number of false positives and false negatives with any test depends upon the cutoff level chosen for the identification of an exudate. If a high cutoff level is chosen, all transudates will be identified correctly, whereas if a low level is chosen, all exudates will be identified correctly. Light et al. originally developed Light's criteria with the goal to identify all exudates correctly, and the criteria are remarkably effective in achieving this goal.

An alternative approach is to select the cutoff level that will correctly identify the highest percentage of patients. Using this approach, Heffner et al. (33) analyzed the data from eight studies with a total of 1,448 patients and concluded that the best cutoff levels for the different pleural fluid tests were as follows: protein ratio 0.5, pleural fluid LDH 0.45 of the upper limits of the normal for serum, LDH ratio 0.45.

As demonstrated in the preceding text, Light's criteria identify approximately 25% of transudative effusions as exudates. This mislabeling occurs most commonly when patients with CHF are treated with diuretics before thoracentesis is performed (34). These mislabeled transudates barely meet the exudative criteria. The protein ratio is less than 0.65, the LDH ratio is less than 1.0 and the level of the LDH is less than the upper limit of normal. How can these mislabeled transudates be identified? One possible means is to examine the gradient between the serum and the pleural fluid protein levels. If this gradient is greater than 3.1 g/dL, one can presume that the fluid is actually a transudate (34). In a previous edition of this book, it was recommended that an albumin gradient of 1.2 g/dL (29) rather than the protein gradient of 3.1 g/dL be used. Bielsa et al. (35) reported that the albumin gradient identified more of these effusions correctly than did the protein gradient. It is suggested that the protein gradient first be examined because it is already available from Light's criteria. If the protein gradient is not definitive, then one may use the albumin gradient or the NT-pro-BNP.

In the discussion in the preceding text, pleural effusions have been dichotomized into transudates or exudates on the basis of a single cutoff point. An alternative approach is to use likelihood ratios for identifying whether a pleural fluid is a transudate or an exudate (36,37). The idea behind this approach is that the higher a value, for example, the pleural fluid LDH, the more likely the effusion is to be an exudate and the lower the value, the less likely the effusion is to be an exudate. Heffner et al. have derived multilevel (36) and continuous (37) likelihood ratios for the usual biochemical tests used to differentiate transudates and exudates. When these likelihood ratios are used in conjunction with pretest probabilities using Bayes' theorem, posttest probabilities can be derived (37). Difficulties in using this approach occur because the pretest probabilities vary significantly from physician to physician, and most physicians do not understand the mathematics involved. This approach does emphasize that it is important to take into consideration the absolute value of the measurements. Very high or very low values are almost always indicative of exudates and transudates, respectively, whereas values near the cutoff levels can be associated with either transudates or exudates.

The following approach is recommended for determining whether a pleural effusion is a transudate or an exudate. First assess the fluid with Light's criteria. The higher the value for the protein ratio, the LDH ratio, and the absolute value of the LDH, the more likely the fluid is an exudate. If the fluid meets the criteria for a transudative effusion, it is a transudate. If the fluid meets the criteria for an exudative effusion by only a small margin and the clinical picture is compatible with a transudative effusion, measure the protein gradient between the serum and pleural fluid. If this value is greater than 3.1 g/dL, then the fluid can be relabeled a transudate. An alternative approach is to measure the brain natriuretic peptide (BNP) level in the pleural fluid or the serum. If this is greater than 1,500 pg/mL, the diagnosis of CHF is established (see the discussion on NT-pro-BNP later in this chapter).

Specific Gravity

The specific gravity of the pleural fluid as measured with a hydrometer was used in the past to separate transudates from exudates (38) because it was a simple

and rapid method of estimating the protein content of the fluid. A specific gravity of 1.015 corresponds to a protein content of 3 g/dL, and this value was used to separate transudates from exudates (38). At the present time, the specific gravity of pleural fluid is usually measured with a refractometer rather than a hydrometer. Unfortunately, the scale on the commercially available refractometers is calibrated for the specific gravity of urine rather than for pleural fluid. A reading of 1.020 on the urine specific gravity scale corresponds to a pleural fluid protein level of 3 g/dL. However, there is a scale on the same refractometer for protein levels that is valid for pleural fluid. Because the only reason to measure specific gravity is to estimate the protein level, and because the pleural fluid specific gravity measurement is extraneous and confusing, it should no longer be ordered (39). However, a rapid estimate of the pleural fluid protein content can be obtained at the patient's bedside with the protein scale on the refractometer (39).

Other Characteristics of Transudates

Most transudates are clear, straw colored, nonviscid, and odorless. It takes a pleural fluid RBC count of more than 10,000/mm^3 to give the pleural fluid a pinkish tinge. Approximately 15% have RBC counts above this level. Therefore, the discovery of blood-tinged pleural fluid does not mean that the fluid is not a transudate. Because RBCs contain a large amount of LDH, one might suppose that the LDH level in a blood-tinged or bloody transudative pleural effusion would be so elevated that it would meet the criteria for an exudative pleural effusion. Such does not appear to be the case, however. The LDH isoenzyme present in RBCs is LDH-1, and in one study of 23 patients with bloody pleural effusions (pleural fluid red cell counts greater than 100,000/mm^3), the fraction of LDH-1 in the pleural fluid was only slightly increased (40).

The pleural fluid white blood cell (WBC) count of most transudates is less than 1,000/mm^3, but approximately 20% have WBC counts that exceed 1,000/mm^3 (41). Pleural fluid WBC counts above 10,000/mm^3 are rare with transudative pleural effusions. The differential WBC count in transudative pleural effusions may be dominated by polymorphonuclear leukocytes, small lymphocytes, or other mononuclear cells. In a series of 47 transudative effusions, 6 (13%) had more than 50% polymorphonuclear leukocytes, 16 (34%) had predominantly small lymphocytes, 22 (47%) had predominantly other mononuclear cells, and 3 (6%) had no single predominant cell type (41). The pleural fluid glucose level is similar to the serum glucose level, and the pleural fluid amylase level is low (42). The pleural fluid pH with transudative pleural effusions is higher than the simultaneously obtained blood pH (43), probably because of active transport of bicarbonate from the blood into the pleural space (44).

Probrain Natriuretic Peptide (BNP)

The levels of NT-pro-BNP and BNP in the pleural fluid are useful in establishing that the etiology of the pleural effusion is CHF. When the ventricles are subjected to increased pressure or volume, these peptides are released into the circulation (45). The biologically active BNP and the larger amino terminal part NT-pro-BNP are released in equimolar amounts into the circulation (45). The serum levels of BNP are used to help establish the diagnosis of CHF. In clinical practice, levels above 500 pg/mL are considered diagnostic of CHF whereas levels below 100 pg/mL are thought to make the diagnosis of CHF unlikely (46).

Porcel et al. (47) first demonstrated that the pleural fluid levels of NT-pro-BNP are elevated in patients with heart failure. They measured NT-pro-BNP levels in 117 pleural fluid samples with the following diagnoses: CHF in 44 samples, malignancy in 25, tuberculous pleuritis in 20, hepatic hydrothorax in 10, and miscellaneous in 18. The mean NT-pro-BNP fluid level in the CHF patients (6,931 pg/mL) was significantly higher than the 551 pg/mL in the patients with hepatic hydrothorax and the 292 pg/mL in the patients with exudative pleural effusions (45). When a cutoff level of 1,500 pg/mL was used, the sensitivity was 91% and the specificity was 93% for the diagnosis of CHF. We have compared the pleural fluid NT-pro-BNP levels in 10 patients each with effusions due to CHF, pulmonary embolism, post-coronary artery bypass surgery, and malignancy (48). All the patients with CHF had NT-pro-BNP levels above 1,500 pg/mL, and none of the other patients had NT-pro-BNP levels this high (48).

It should be emphasized that the serum or pleural fluid BNP and NT-pro-BNP cannot be used interchangeably in the diagnosis of pleural effusions due to CHF (49). The BNP levels are only about 10% of the NT-pro-BNP levels. There is not a close correlation between the BNP levels and the NT-pro-BNP levels ($r = 0.78$) (50). Moreover, the diagnostic usefulness of the NT-pro-BNP in making the diagnosis of heart failure is superior to that of the BNP (50,51). The accuracy of NT-pro-BNP in making the diagnosis of pleural effusion due to heart failure was attested to

in a meta-analysis of 10 studies with a total of 1,120 patients in which the pooled sensitivity and specificity were 94% and 94%, respectively (52).

The pleural fluid NT-pro-BNP is also superior to the BNP and the protein gradient in identifying patients with heart failure who meet Light's criteria for exudates (50). In one study of 20 patients with heart failure who met Light's criteria for exudates, 18 had NT-pro-BNP levels above 1,300, 16 had NT-pro-BNP levels above 1,500, but only 10 had serum pleural fluid protein gradient greater than 3.1 g/dL (50).

Other workers have demonstrated that there is a close relationship between the levels of NT-pro-BNP in the pleural fluid and serum. Han et al. (53) measured the NT-pro-BNP levels in 240 patients and reported that the correlation coefficient between the pleural and serum NT-pro BNP was 0.928. In a second study, Kolditz et al. (54) measured the serum and pleural fluid NT-pro-BNP levels in 93 patients including 25 with CHF. They confirmed the results of the above study in that the levels of serum and pleural fluid NT-pro-BNP were again closely correlated ($r^2 = 0.90$). From the latter two studies it appears that measurement of the pleural fluid NT-pro-BNP levels provides no additional information beyond the serum measurements.

GENERAL TESTS FOR DIFFERENTIATING CAUSES OF EXUDATES

Appearance of Fluid

The gross appearance of the pleural fluid frequently yields useful diagnostic information. The color, turbidity, viscosity, and odor should be described. Most transudative and many exudative pleural effusions are clear, straw colored, nonviscid, and odorless. Any deviations should be noted and investigated.

A reddish color indicates that blood is present, and a brownish tinge indicates that the blood has been present for a prolonged period. If the pleural fluid is blood tinged, the pleural fluid RBC count is between 5,000 and 10,000/mm^3. If the pleural fluid appears grossly bloody, a hematocrit should be obtained to determine whether the patient has a hemothorax (see Chapter 25).

On rare occasions, the pleural fluid can be black. Black pleural fluid has been reported with infection due to *Aspergillus niger*, infection due to *Rhizopus oryzae*, pigment laden macrophages following massive bleeding due to metastatic carcinoma (55) and melanoma (56).

Turbid pleural fluid can occur from either increased cellular content or increased lipid content. These two entities can be differentiated if the pleural fluid is centrifuged and the supernatant examined. If turbidity remains after centrifugation, it is in all probability due to increased lipid content, and the fluid should be sent for lipid analysis (see the discussion later in this chapter).

Alternately, if the supernatant is clear, the original turbidity was due to increased numbers of cells or other debris. The discovery of pleural fluid that looks like chocolate sauce or anchovy paste is suggestive of amebiasis with a hepatopleural fistula (57). This appearance is due to the presence of a mixture of blood, cytolyzed liver tissue, and small solid particles of liver parenchyma that have resisted dissolution.

A pleural fluid with a high viscosity is suggestive of malignant mesothelioma; the high viscosity is secondary to an elevated pleural fluid hyaluronic acid level. Of course, the fluid from a pyothorax is also viscid because of the large amounts of cells and debris in the fluid.

The odor of all pleura fluids should be noted. One can immediately establish two diagnoses by smelling the pleural fluid. A feculent odor indicates that the patient has a bacterial infection of the pleural space that is probably anaerobic. If the pleural fluid smells like urine, the patient probably has a urinothorax.

Red Blood Cell Count

Only 5,000 to 10,000 RBCs per mm^3 need be present to impart a red color to pleural fluid. If a pleural effusion has a total volume of 500 mL and the RBC count in the peripheral blood is 5 million/mm^3, a leak of only 1 mL blood into the pleural space will result in a blood-tinged pleural effusion. It is probably for this reason that the presence of blood-tinged or serosanguineous pleural fluid has little diagnostic significance. More than 15% of transudative and more than 40% of all types of exudative pleural fluids are blood tinged (41); that is, they have pleural fluid RBC counts between 5,000 and 100,000/mm^3.

Occasionally, pleural fluid obtained by diagnostic thoracentesis appears grossly bloody. In such cases, one can assume that the RBC count in the pleural fluid is above 100,000/mm^3. One should obtain a hematocrit on such pleural fluids to document the amount of blood in the pleural fluid. If the hematocrit of the pleural fluid is greater than 50% of the peripheral hematocrit, a hemothorax is present, and one should consider inserting a chest tube (see Chapter 25). Usually, the hematocrit of bloody pleural fluid is much lower than

what one would expect from its gross appearance. If a pleural fluid hematocrit is not available, its estimate can be obtained by dividing the pleural fluid RBC count by 100,000.

The presence of bloody pleural fluid suggests one of three diagnoses, namely, malignant disease, trauma, or pulmonary embolization. In a series of 22 bloody pleural effusions that I observed on medical wards, 12 were due to malignant disease, 5 to pulmonary embolization, 2 to trauma, and 2 to pneumonia, and 1 was a transudative effusion secondary to cirrhosis (30). The traumatic origin of the pleural effusion may not be obvious, particularly when the patient is on a medical ward. The patient may have broken a rib while coughing or suffered trauma during an episode of inebriation that is not remembered.

At times, it is unclear whether blood in the pleural fluid resulted from or was present before the thoracentesis. If the blood is a result of the thoracentesis, the degree of red discoloration of the fluid frequently is not uniform throughout the course of aspiration. Examination of the fluid microscopically may also be useful. If the RBCs were present before the thoracentesis, the macrophages in the pleural fluid usually contain hemoglobin inclusions. Although the levels of D-dimer in the cerebrospinal fluid are useful in demonstrating whether blood in the fluid has a traumatic origin, pleural fluid levels of D-dimer are not useful in making this differentiation (58). Crenation of the RBC in the pleural fluid rarely occurs because the osmotic pressure of the pleural fluid is similar to that of serum.

White Blood Cell Count

Although WBC counts on the pleural fluid were traditionally performed manually, we have shown that the automated counters provide accurate pleural fluid WBC counts (59). The pleural fluid for cell counts and differentials should be collected in a test tube with an anticoagulant (59). If the pleural fluid is collected in plastic or glass tubes without an anticoagulant, the fluid may clot or the cells may clump, providing inaccurate cell counts and differentials (59).

The pleural fluid WBC count is of limited diagnostic use. Most transudates have WBC counts below 1,000/mm^3, whereas most exudates have WBC counts above 1,000/mm^3 (16). Pleural fluid WBC counts above 10,000/mm^3 are most commonly seen with parapneumonic effusions, but they are also seen with many other diseases (41), as shown in Table 7.1. I have seen pleural fluid WBC counts above 50,000/mm^3 with both pancreatic disease and pulmonary embolization. With grossly purulent pleural fluid, the pleural fluid WBC count is frequently much lower than what one would anticipate because debris, rather than cells, accounts for much of the turbidity.

Differential White Cell Count

Examination of a Wright's stain of pleural fluid is one of the most informative tests on pleural fluid. Because the pleural fluid WBC count is frequently less than 5,000/mm^3, it is useful to concentrate the cells before staining. This is easily accomplished by centrifuging approximately 10 mL of fluid and then resuspending the button of cells in approximately 0.5 mL of supernatant. After thorough mixing, slides that are similar to those for examining peripheral blood are made and stained in the usual way. Occasionally, large amounts of fibrinogen adhere to the cells. In such cases, resuspension in saline solution, followed by centrifugation, is indicated in order to evaluate cellular morphologic features. Automatic cell counters do not provide sufficiently accurate differential cell counts for clinical use (59,60), presumably because of the high number of mesothelial, lymphoid, and tumors cells in pleural fluid.

TABLE 7.1 ■ Etiology of 25 Effusions Containing More than 10,000 WBCs/mm^3

Diagnosis	Number with >10,000 WBCs/mm^3	Total Number of Effusions	Percentage Having >10,000 WBCs/mm^3
Parapneumonic effusion	13	26	50
Malignant disease	3	43	7
Pulmonary embolization	3	8	37
Tuberculosis	2	14	14
Pancreatitis	2	5	40
Postmyocardial infarction Syndrome	1	3	33
Systemic lupus erythematosus	1	1	100

WBC, white blood cell.

Although most laboratories divide pleural fluid WBCs into polymorphonuclear leukocytes and mononuclear cells, I prefer to divide them into four categories—polymorphonuclear leukocytes, lymphocytes, other mononuclear cells, and eosinophils—because of the diagnostic significance of small lymphocytes (see the discussion on lymphocytes later in this chapter). The mononuclear cells include mesothelial cells, macrophages, plasma cells, and malignant cells. Excellent color plates demonstrating the morphologic and staining characteristics of the different cells in pleural effusions are contained in the monograph by Spriggs and Boddington (61).

Neutrophils

Because neutrophils are the cellular component of the acute inflammatory response, they predominate in pleural fluid resulting from acute inflammation as with pneumonia, pancreatitis, pulmonary embolization, subphrenic abscess, and early tuberculosis. Although more than 10% of transudative pleural effusions contain predominantly neutrophils, pleural fluid neutrophilia in transudates has no clinical significance (41). The significance of neutrophils in an exudative pleural effusion is that they indicate acute inflammation of the pleural surface.

Interleukin 8 (IL-8) appears to be one of the primary chemotaxins for neutrophils in the pleural space (62,63). The number of neutrophils in pleural fluid is correlated with the IL-8 level, and empyemas have the highest levels of IL-8. The addition of IL-8 neutralizing serum decreases the chemotactic activity for neutrophils in empyema fluids (63). The cellular source of IL-8 is unknown (62).

Examination of the pleural fluid neutrophils in patients with parapneumonic effusions is useful in identifying those that are infected. If pleural infection is present, the neutrophils undergo a characteristic degeneration. The nucleus becomes blurred and is no longer stained purple. The cytoplasm shows toxic granulation initially. Subsequently, the neutrophilic granules become indistinct and are then lost. Finally, only a smear cell remains (61).

Eosinophils

Approximately 7% of pleural fluids are characterized by pleural fluid eosinophilia (>10%) (64,65). Most clinicians believe that significant numbers of eosinophils (>10%) in pleural fluid should be a clue to the origin of the pleural effusion. In most instances, the pleural fluid eosinophilia is due to either air or blood in the pleural space and therefore does not contribute any diagnostic information in these situations. Charcot–Leyden crystals (66), as well as Curschmann's spirals (67), are occasionally found in the pleural fluid of patients with pleural eosinophilia. Their presence appears to have no diagnostic significance.

The factors responsible for pleural fluid eosinophilia have been intensively studied, but there is still no unifying concept and it is likely that multiple factors are involved. In animals, it has been shown that the intrapleural injection of stem cell factor (68), platelet-activating factor (PAF) (69), endotoxin (70,71), bradykinin (72), and leukotriene B_4 (69) all result in pleural fluid eosinophilia. The eosinophil influx is inhibited in some but not all situations by monoclonal antibodies (MAb) directed against IL-5.

In humans, pleural fluid from patients with eosinophilic pleural effusions stimulates bone marrow cells to form colonies of eosinophils (73,74). In addition, when eosinophils are incubated in the presence of eosinophilic pleural fluid, their survival is prolonged (73). Peripheral blood from patients with eosinophilic pleural effusions does not stimulate the bone marrow to form eosinophil colonies and does not prolong survival of eosinophils. The factor responsible for the increased colony-forming activity and the increased survival appears to be IL-5 (73,74), although IL-3 and granulocyte or macrophage colony-stimulating factor (GM-CSF) may also play a role (73). In patients with eosinophilic pleural effusions, the pleural fluid level of IL-5 is significantly correlated with the pleural fluid eosinophil count ($r = 0.55$) and the pleural fluid eosinophil percentage ($r = 0.54$) (75). Both bloody and nonbloody eosinophilic effusions have high levels of IL-5 (75). In patients with eosinophilic pleural effusions, the pleural fluid levels of vascular cell adhesion molecule (VCAM)-1 and eotaxin-3 are also significantly correlated with the eosinophil count and percentage of eosinophils in the pleural fluid (76). VCAM-1 is an adhesion molecule that is expressed on the endothelial surface and interacts with the β1-integrins expressed on the eosinophil surface to facilitate eosinophil tissue migration (76).

The source of the IL-5 appears to be the $CD4^+$ lymphocyte in the pleural fluid (74), but the eosinophils in the pleural fluid may themselves also produce IL-5 (73). The source of the eosinophils in eosinophilic pleural effusions appears to be the bone marrow; no progenitor cells are present in the pleural space. It is not known what stimulates the $CD4^+$ lymphocytes to produce the IL-5. However, it probably results

from another cytokine because the intrapleural injection of IL-2 into malignant pleural effusions results in an eosinophilic pleural effusion with a high level of IL-5 (77). There are factors other than IL-5 that recruit eosinophils to the pleural space. Antibodies to IL-5 eliminate the eosinophilic influx to an allergen but not to endotoxin in the mouse (78). However, antibodies to gamma delta lymphocytes eliminate the eosinophilic response to endotoxin (71).

The most common cause of pleural fluid eosinophilia is air in the pleural space. In a series of 127 cases with more than 20% eosinophils in the pleural fluid, 81 (64%) were thought to have pleural fluid eosinophilia secondary to air in the pleural space (61). In a review of 343 pleural effusions with greater than 10% eosinophils, 95 (28%) had air in the pleural space (79). It is likely that the pleural fluid eosinophilia in many other patients in this series was also due to the introduction of air into the pleural space during a prior thoracentesis. On numerous occasions over the past three decades, I have seen patients who had no pleural fluid eosinophilia at the initial thoracentesis but who had many eosinophils at a subsequent thoracentesis. In each case, a small pneumothorax resulted from the initial thoracentesis. When patients with spontaneous pneumothorax undergo thoracotomy, a reactive eosinophilic pleuritis frequently exists in the resected parietal pleura (80). It should be noted, however, that in two recent series (64,81) the prevalence of eosinophilic pleural effusion did not increase after a thoracentesis or a pleural biopsy.

The mechanism responsible for the pleural fluid eosinophilia in response to air in the pleural space is unknown but is probably related to IL-5. Smit et al. (82) measured the percentage of eosinophils and the levels of IL-5 in 23 patients with pneumothorax and pleural fluid. They found that IL-5 level and the eosinophil concentration in the pleural fluid were highly correlated ($r = 0.84$) and that the eosinophil percentage tended to increase with time, with a mean of less than 5% in the first 24 hours, 20% at days 1 to 3, 40% at days 4 to 7, and 50% after day 7 (82). There was no relationship between the PAF level or the monocyte chemotactic protein-1 levels and the eosinophils. In these fluids, IL-8 was not detectable. When air is injected into the pleural space of a mouse, pleural fluid eosinophilia occurs within 30 minutes and peaks at 48 hours (83).

The second most common cause of pleural fluid eosinophilia is blood in the pleural space. Following traumatic hemothorax, pleural fluid eosinophils do not usually become numerous until the second week (61). There is frequently an associated peripheral blood eosinophilia that does not disappear until the pleural effusion is completely resolved (84). The pleural effusions associated with pulmonary embolization are frequently bloody and contain numerous eosinophils (85). Bloody pleural fluids due to malignant disease are not usually characterized by eosinophilia (41,61). In a study conducted by my colleagues and me of bloody pleural effusions, none of the 11 cases of malignant pleural effusions with pleural fluid RBC counts greater than 100,000/mm^3 had more than 10% eosinophils (41). Patients with pleural effusions postcoronary artery bypass graft (CABG) surgery, frequently have bloody pleural effusions in the first few weeks after surgery. In these effusions, the pleural fluid IL-5 level is higher than the corresponding serum level and there is a significant correlation between the pleural fluid and serum IL-5 level (86). Moreover, the pleural fluid IL-5 levels are significantly correlated with the pleural fluid eosinophil counts (86). In addition, the pleural fluid eotaxin-3 levels are significantly higher than the serum levels and the pleural fluid eotaxin-3 levels significantly correlate with the pleural fluid eosinophil count (86).

If the patient has neither blood nor air in their pleural space, what is the significance of an eosinophilic pleural effusion? Kalomenidis and Light (87) reviewed the etiology of 392 cases of eosinophilic pleural effusions when cases associated with pleural air and/or blood were excluded. They reported that the most common diagnosis was idiopathic (39.8%), followed by malignancy (17%), parapneumonic (12.5%), transudates (7.9%), tuberculosis (5.6%), pulmonary embolism (4.3%), and others (12.8%). In a recent study of 135 patients with eosinophilic pleural effusions from a single institution, the following diseases were responsible: malignancy 34.8%, infections 19.2%, unknown 14.1%, posttraumatic 8.9%, and miscellaneous 23.0%. (64). The incidence of malignancy was significantly higher in patients with a lower (<40%) pleural fluid eosinophil percentage (64).

If neither air nor blood is present in the pleural space, several unusual diagnoses should be considered. Pleural eosinophilia is common in patients with asbestos-related pleural effusions. In a review of eosinophilic pleural effusions (79), 15 of 29 (52%) asbestos-related pleural effusions had more than 10% eosinophils in the pleural fluid. Patients with eosinophilic pneumonia frequently have pleural effusions and the mean eosinophil percentage in the pleural fluid was 38% in one study (88). The pleural effusions secondary to drug reactions are frequently eosinophilic.

Offending drugs include dantrolene, bromocriptine, and nitrofurantoin (see Chapter 22). Pleural effusions secondary to parasitic diseases (see Chapter 15) such as paragonimiasis (68), hydatid disease (89), amebiasis (61), or ascariasis (61) frequently contain a large percentage of eosinophils. Lastly, the pleural effusion associated with the Churg-Strauss syndrome (see Chapter 21) is eosinophilic (90).

If none of the foregoing rare diseases is causing the pleural effusion, the following statements are pertinent to patients with eosinophilic pleural effusions. If the patient has pneumonia and pleural effusion, the presence of pleural fluid eosinophilia is a good prognostic sign because such an effusion rarely becomes infected. The origin of approximately 40% of eosinophilic effusions is not established, and these effusions resolve spontaneously.

Basophils

Basophilic pleural effusions are distinctly uncommon. I have not seen a pleural effusion that contained more than 2% basophils. A few basophils are usually present in pleural effusions with eosinophils. Basophil counts greater than 10% are most common with leukemic pleural involvement (61). Basophil counts greater than 5% are most common with pneumothorax, pneumonia, and transudates (91).

Lymphocytes

The discovery that more than 50% of the WBCs in an exudative pleural effusion are small lymphocytes is diagnostically important because it means that the patient probably has a malignant disease, tuberculous pleuritis, or a pleural effusion after CABG surgery. In two series (41,92) studied before the advent of CABG surgery, 96 of 211 exudative pleural effusions had more than 50% small lymphocytes. Of these 96 effusions, 90 (94%) were due to tuberculosis or malignant disease.

When the foregoing series are analyzed, almost all of the effusions secondary to tuberculosis (43 of 46), but only two thirds of the effusions secondary to malignant disease (47 of 70), had predominantly small lymphocytes. In one series of 26 patients with chronic pleural effusions post-CABG, the mean percentage of lymphocytes in the pleural fluid was 61% (93). Approximately one third of transudative pleural effusions contain predominantly small lymphocytes (41), and a lymphocytic transudative effusion is not an indication for pleural biopsy.

Several papers have assessed the diagnostic utility of separating pleural lymphocytes into T and B lymphocytes (94–97). In general, this separation has not been useful diagnostically. With most disease states, the pleural fluid contains a higher percentage of T lymphocytes (70%), a lower percentage of B lymphocytes (10%), and a higher percentage of null cells (20%) than the corresponding peripheral blood (94,95). The partitioning of lymphocytes may be useful, however, when chronic lymphatic leukemia or lymphoma is suspected. In a report of four such patients, all had more than 80% B lymphocytes in their pleural fluid (96).

The development of MAb has permitted a further subdivision of T lymphocytes. In comparison to peripheral blood, in pleural fluid the ratio of the helper and inducer cells ($CD4^+$) to the suppressor and cytotoxic cells ($CD8^+$) is higher, regardless of the etiology of the pleural effusion (98–100). Therefore, this subdivision is not useful diagnostically.

Natural killer (NK) cells are lymphocytes derived from an unimmunized host that lyse certain tumor cell lines and virus-infected cells. In general, the percentage of T lymphocytes in pleural fluid that are identified as NK cells is approximately the same (~15%) as in the peripheral blood (101). There are two types of NK cells, $CD56^{bright}$ and $CD56^{dim}$. In the pleural fluid, there is a much higher percentage of $CD56^{bright}$ cells than $C56^{dull}$ cells (101). The $CD56^{dim}$ subset has cytotoxic activity that is superior to that of the $CD56^{bright}$ subset. However, there is a discrepancy between the number of NK positive cells and the NK activity of the cells when patients with tuberculosis are compared with patients with malignancy. Although the number of NK cells is comparable in the two populations, there is much more NK activity in the tuberculous pleural effusions (102). Differences in the NK subset percentages may explain the variation in the NK activity (103).

Mesothelial Cells

Mesothelial cells line the pleural cavities. They frequently become dislodged from the pleural surfaces and are present in the small amount of normal pleural fluid (104). These cells are usually 12 to 30 μm in diameter, but multinucleated forms may have diameters up to 75 μm. Their cytoplasm is light blue (Fig. 7.1A) and often contains a few vacuoles. The nucleus is large (9–22 μm) and stains purplish with a uniform appearance. The nucleus usually contains one to three bright blue nucleoli (61). Mesothelial cells are discussed in more detail in Chapter 1.

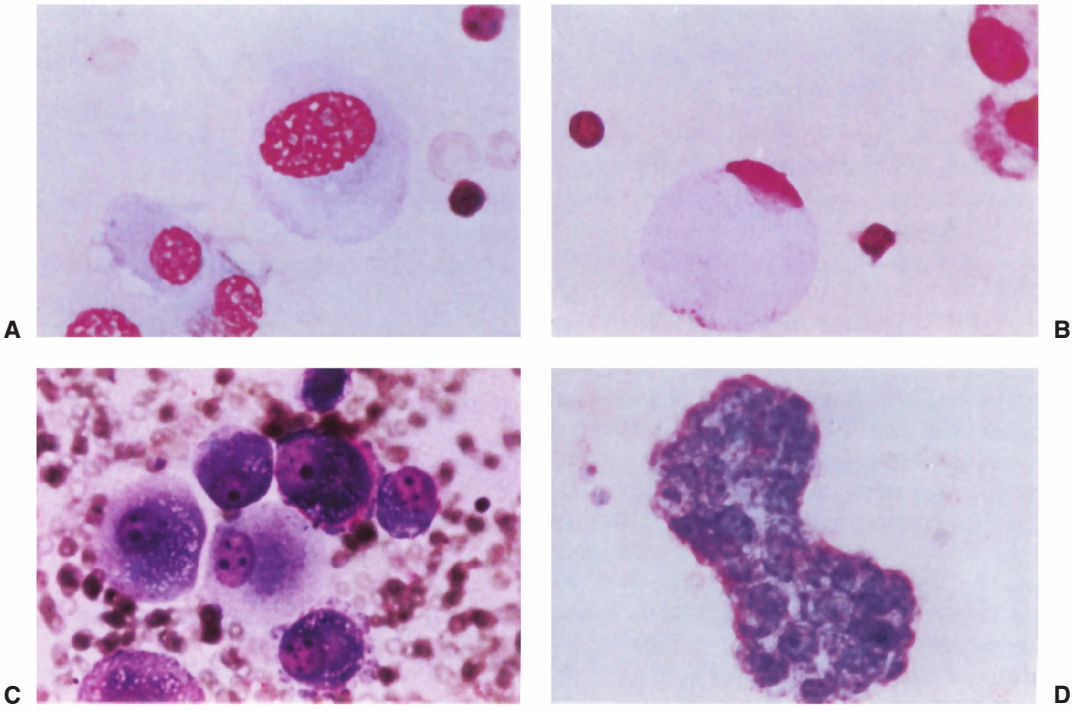

FIGURE 7.1 ■ A: Mesothelial cell. Note that the mesothelial cell is large in comparison to the lymphocyte and has light blue cytoplasm and light blue nucleoli of varying shapes and sizes. **B**: Signet-ring cell. This macrophage, which has engorged itself with pleural debris, is not a malignant cell. **C**: Malignant cells. Several large cells are similar but vary in size. Note the large, dark nucleoli, which are so different from the nucleoli in the mesothelial cell. **D**: Clump of malignant cells from the pleural fluid of a patient with metastatic adenocarcinoma.

Mesothelial cells are significant for two reasons. First, their presence or absence is often useful diagnostically because these cells are uncommon in tuberculous effusions. Spriggs and Boddington (61) analyzed 65 tuberculous effusions and found that only one effusion had more than a single mesothelial cell per 1,000 cells (61). Light et al. have confirmed the paucity of mesothelial cells in tuberculous pleural effusions (41), as have Yam (92) and Hurwitz et al. (105). The exception to this observation is the patient with acquired immunodeficiency syndrome (AIDS). Patients with AIDS having a low $CD4^+$ count who have tuberculous pleuritis may have numerous mesothelial cells in their pleural fluid (106). The lack of mesothelial cells is not diagnostic of tuberculosis, however. It simply indicates that the pleural surfaces have become extensively involved by the disease process so that the mesothelial cells cannot enter the pleural space. The absence of mesothelial cells is common with complicated parapneumonic effusions and with other conditions in which the pleura becomes coated with fibrin. It is also common with malignant effusions after sclerosing agents have been injected to effect a pleurodesis. Second, mesothelial cells, particularly in their activated form, may be confused with malignant cells. Frequently, an experienced pathologist is required to make the differentiation. Immunohistochemistry is useful in making this distinction (see discussion later in this chapter).

Macrophages

In general, the presence of macrophages in pleural fluid is of limited diagnostic use. By definition, macrophages are cells that store vital dyes. It appears that the origin of the pleural fluid macrophages can be either the circulating monocyte or the mesothelial cell (107). Macrophages vary in diameter from 15 to 50 μm and have irregular nuclei. Their cytoplasm is gray, cloudy, and full of vacuoles. At times, the macrophage may become engorged with debris, taking on the appearance of a "signet-ring" cell, with the nucleus flattened

against the side of the cell (Fig. 7.1B). It is important not to confuse these cells with malignant cells. During phagocytosis, macrophages may engulf polymorphonuclear leukocytes or RBCs. These cells may be evident within the macrophage in various stages of digestion. If RBCs have been ingested, the iron pigment is retained as dark blue or brown staining material (61). It is important not to confuse macrophages with mesothelial cells because macrophages are sometimes present in tuberculous pleural effusions (61).

Macrophages in the pleural fluid can definitively be identified using the MAb CD68 (108) or CD14 and using either flow cytometry or immunohistochemistry (109). Most pleural fluids have more than 10% macrophages (109). The macrophages in the pleural fluid, in addition to their phagocytic function, can also release IL-1 and tumor necrosis factor (TNF) (108). The macrophages in the pleural fluid are also efficient accessory cells for T-cell proliferation (108). Mice depleted of macrophages have a dramatic reduction in the neutrophil influx in response to intrapleural carrageenan or *Staphylococcus aureus* (110).

Plasma Cells

The presence of numerous plasma cells in the pleural fluid suggests multiple myeloma. Smaller numbers of plasma cells are not of any particular diagnostic importance. These cells are of the lymphoid series and produce immunoglobulins. Morphologically, they are larger than small lymphocytes and have an eccentric nucleus and deeply staining basophilic cytoplasm with a clear area at the cell center (Golgi zone) (61). Mature forms have well-defined nuclear chromatin blocks. In a series of 18 effusions with more than 5% plasma cells, 4 were due to malignant disease, 3 due to tuberculosis, 3 due to CHF, 3 due to pulmonary embolization, 2 due to pneumonia, 1 due to sepsis, and 2 were of undetermined origin (61).

Dendritic Cells

Dendritic cells are human leukocyte antigen (HLA) DR–positive accessory cells that play a critical role in the development of cell-mediated immune reactions. Dendritic cells have been identified in the pleural fluid (111). It is unknown whether the dendritic cells in pleural fluid are resident in the pleural space or reach the pleural space from the blood. Light microscopy reveals that dendritic cells from pleural fluid are intermediate in size between lymphocytes and macrophages, do not contain intracytoplasmic inclusions, and have an eccentric nucleus (111).

PROTEIN MEASUREMENTS

The pleural fluid protein levels are generally higher in exudative pleural effusions than in transudative pleural effusions, and this observation serves as a basis for separating transudates from exudates (see the foregoing discussion on this differentiation in this chapter). Pleural fluid protein levels are not useful in separating the various types of exudative effusions, however, because the protein level in most exudates is elevated to a comparable degree (Fig. 7.2). At times, a pleural fluid meets the exudative criteria with its LDH, but not with its protein level. Such exudative pleural effusions are almost always parapneumonic effusions or are secondary to malignant pleural disease (16).

Simultaneous electrophoretic studies of serum and pleural fluid demonstrate that the pattern in the pleural fluid is essentially an image of that in the serum, except that proportionately more albumin is present in the pleural fluid (112,113). Along the same lines, the ratio of the pleural fluid to the serum IgG, IgA, and IgM is always below unity and appears to have no diagnostic value (113). The ratio of the concentration of these proteins is inversely related to their molecular weight (113). The immunoglobulin measurement that may be diagnostically useful is that of IgE. Yokogawa et al. (114) measured the pleural fluid and serum IgE levels in five patients with paragonimiasis. In all five patients, the pleural fluid IgE level was above 4,000 IU and exceeded the serum level. A subsequent report, however, measured the pleural fluid and serum IgE levels in seven patients with eosinophilic pleural effusions and seven with noneosinophilic pleural effusions. The pleural fluid levels and the ratio of the pleural fluid and serum IgE concentration were comparable in the two groups, and it was concluded that pleural fluid IgE was the result of passive diffusion from the serum (115). None of the patients in this latter series, however, had paragonimiasis.

GLUCOSE MEASUREMENT

Measurement of the pleural fluid glucose level is useful in the differential diagnosis of exudative pleural effusions because a low pleural fluid glucose level (<60 mg/dL) indicates that the patient probably has one of four disorders, namely, a parapneumonic effusion, malignant disease, rheumatoid disease, or tuberculous pleuritis. Other rare causes of a low glucose pleural effusion include paragonimiasis, hemothorax, Churg-Strauss syndrome, and, occasionally, lupus pleuritis. The pleural fluid glucose level of all transudates and of most exudates parallels that of the serum.

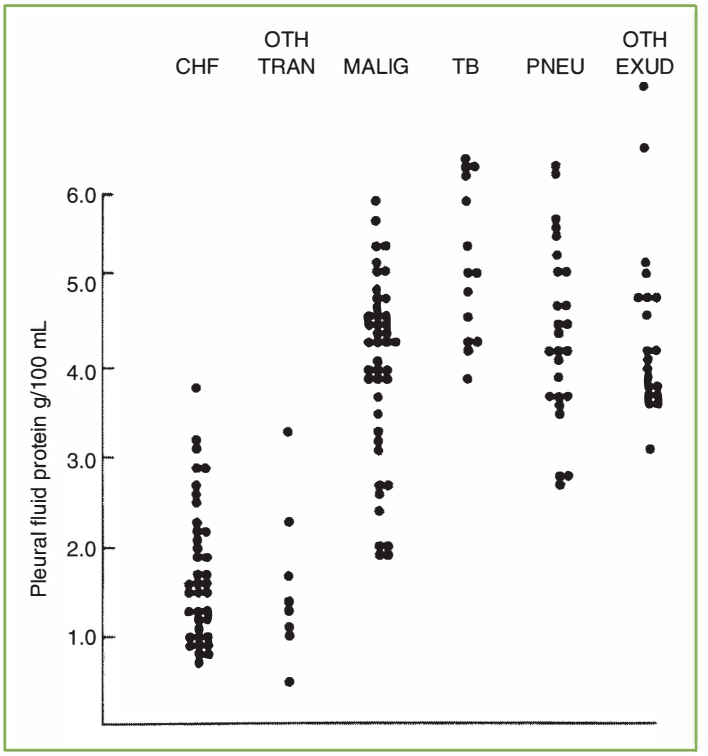

FIGURE 7.2 ■ Pleural fluid protein levels in effusion secondary to congestive heart failure (CHF), other transudates (OTH TRAN), malignant disease (MALIG), tuberculosis (TB), pneumonia (PNEU), and other exudates (OTH EXUD). Each point represents one pleural fluid. Note that the distribution of protein levels for all categories of exudative pleural effusions is similar. *(From Light RW, MacGregor MI, Luchsinger PC, et al. Pleural effusions: the diagnostic separation of transudates and exudates.* Ann Intern Med. *1972;77:507–513, with permission.)*

In my experience, it is not necessary to obtain pleural fluid glucose levels with the patient fasting or to take the serum glucose level into consideration when evaluating the pleural fluid glucose level.

The pleural fluid glucose level is low in some patients with parapneumonic effusions or empyema (116,117). The lower the pleural fluid glucose level, the more likely that one is dealing with a complicated parapneumonic pleural effusion. If the pleural fluid is thick and purulent, the pleural fluid glucose level is frequently close to zero (116). Even in more serous fluid, the glucose level may be reduced. The presence of a low pleural fluid glucose is a poor prognostic sign in patients with parapneumonic effusion and serves as an indicator that more aggressive therapy such as tube thoracostomy or thoracoscopy with the breakdown of loculations is necessary (118).

Approximately 15% to 25% of patients with malignant pleural effusions have pleural fluid glucose levels below 60 mg/dL (42,119,120) and the level may be less than 10 mg/dL. Patients with malignant pleural effusions and a low glucose level have a greater tumor burden in their pleural space than do those with normal pleural fluid glucose levels. In one report of 77 patients with malignant pleural effusion who underwent thoracoscopic examination (120), the extent of the tumor at thoracoscopy was significantly higher in those 16 patients in whom the pleural fluid glucose was less than 60 mg/dL. In addition, patients with a low pleural fluid glucose are more likely to have positive pleural fluid cytology and a positive pleural biopsy (121), are less likely to have a good result from chemical pleurodesis (120,122), and have a shortened life expectancy (122,123).

The pleural fluid glucose level is also reduced in some patients with tuberculous pleuritis. Indeed, early reports indicated that low pleural fluid glucose levels were seen only with tuberculous pleural effusions (124,125). Subsequent studies (41,116,119,126), however, revealed that low pleural fluid glucose levels also occurred with malignant and rheumatoid disease and parapneumonic effusion.

The distribution of pleural fluid glucose levels for tuberculous and malignant pleural effusions is, in fact, similar (42). Most patients with tuberculous pleuritis have a pleural fluid glucose level above 80 mg/dL (42). Accordingly, a low pleural fluid glucose level is compatible with the diagnosis of tuberculous pleuritis, but it is not necessary for the diagnosis.

Pleural effusions due to rheumatoid disease (see Chapter 21) classically have a low pleural fluid glucose level. Carr and Power (126) first reported that

rheumatoid pleural effusions had a low pleural fluid glucose level. In a subsequent review of 76 cases of rheumatoid pleural effusions (127), 42% had pleural fluid glucose levels below 10 mg/dL, and 78% had levels below 30 mg/dL. The explanation for the low pleural fluid glucose level in this condition appears to be a selective block to the entry of glucose into the pleural effusion (128). The pleural fluid glucose level in effusions secondary to LE is usually normal. In one report of nine patients, the pleural fluid glucose; the pleural fluid glucose level was below 50 mg/dL in 2 of 14 (14%) patients with lupus pleuritis.

AMYLASE DETERMINATION

Pleural fluid amylase determinations are useful in the differential diagnosis of exudative pleural effusions because a pleural fluid amylase level above the upper normal limits for serum indicates that the patient has one of three problems: pancreatic disease, malignant tumor, or esophageal rupture (42). However, it is not cost effective to obtain an amylase measurement on every undiagnosed pleural fluid; rather, pleural fluid amylase levels should be determined only when esophageal rupture or pancreatic disease is suspected (131).

Approximately 50% of patients with inflammatory pancreatic disease have an accompanying pleural effusion (132). In such patients, the pleural fluid amylase level is usually raised well above the normal upper limits for serum and is also higher than the simultaneously sampled serum (42,133). On rare occasions, the pleural fluid amylase level is normal at the time of the original thoracentesis, only to become elevated at the time of a subsequent thoracentesis. In some patients with acute pancreatitis with pleural effusion, the chest symptoms of pleuritic chest pain and dyspnea may overshadow the abdominal symptoms. In such instances, an elevated pleural fluid amylase level may be the first hint of a pancreatic problem (42).

Patients with chronic pancreatic disease may also present with a pleural effusion with a high amylase content (134). The effusion results when a sinus tract connects the pancreatic pseudocyst and the pleural space. The patients typically appear chronically ill without abdominal symptoms and appear to have cancer. If a pleural fluid amylase level is not measured, the correct diagnosis may never be established. The key to this diagnosis is a markedly elevated (>1,000 U/L) pleural fluid amylase level (135).

The pleural fluid amylase level is elevated in approximately 10% of malignant pleural effusions (42,135). The serum amylase level is also elevated in approximately 50% of patients with malignant pleural effusions and an elevated pleural fluid amylase. The pleural fluid amylase level in malignant pleural effusions is usually only minimally to moderately elevated, in contrast to the marked elevations with pancreatitis or esophageal rupture. The primary site of the tumor in patients with neoplastic pleural effusions and elevated pleural fluid amylase levels is usually not the pancreas (42,136). Because the amylase in malignant pleural effusions is of the salivary type (137), amylase isoenzyme determinations are useful in distinguishing between malignant and pancreas-related pleural effusions with high amylase levels.

The pleural fluid amylase level is also elevated with esophageal rupture (42,138). The origin of the amylase with esophageal rupture has been shown to be the salivary gland rather than the pancreas (139). With the tear in the esophagus, the swallowed saliva with its high amylase content passes into the pleural space. Because the early diagnosis of esophageal perforation is imperative, owing to the high mortality rate without rapid operative intervention, the pleural fluid amylase determination should be performed promptly when this diagnosis is suspected. In animal experiments, the pleural fluid amylase concentration is elevated within 2 hours of esophageal rupture (140).

LACTIC ACID DEHYDROGENASE MEASUREMENT

The pleural fluid LDH level is used to separate transudates from exudates (see discussion earlier in this chapter). Most patients who meet the criteria for exudative pleural effusions with LDH but not with protein levels have either parapneumonic effusions or malignant pleural disease. Although initial reports suggested that the pleural fluid LDH level was increased only in patients with malignant pleural disease (141), subsequent reports demonstrated that the pleural fluid LDH was elevated in most exudative effusions regardless of origin (Fig. 7.3), and therefore, this determination is of no use in the differential diagnosis of exudative pleural effusions (16).

Nevertheless, every time that I perform a thoracentesis, I obtain a pleural fluid LDH level. This is because the level of the pleural fluid LDH is a reliable indicator of the degree of pleural inflammation; the higher the LDH, the more inflamed the pleural surfaces. Serial measurement of the pleural fluid LDH levels is informative when one is dealing with a patient with an undiagnosed pleural effusion. If with repeated thoracenteses the pleural fluid LDH level becomes progressively

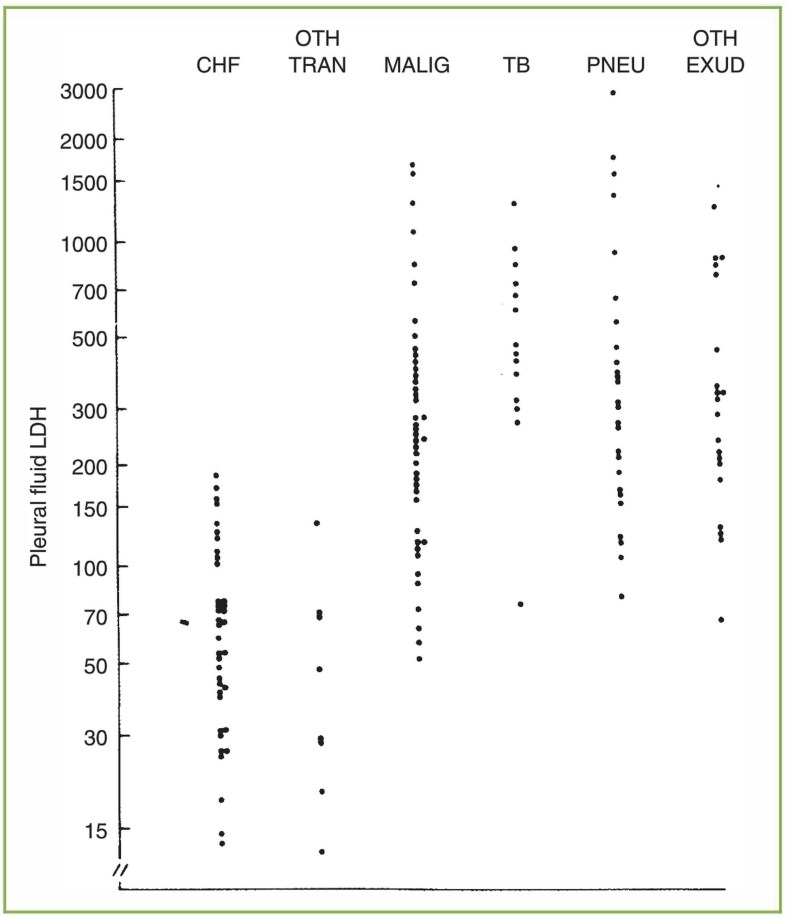

FIGURE 7.3 ■ Pleural fluid lactic dehydrogenase (LDH) levels. Note the similar distributions of the LDH levels for all categories of exudative pleural effusions. CHF, congestive heart failure; OTH TRAN, other transudates; MALIG, malignant disease; TB, tuberculosis; PNEU, pneumonia; OTH EXUD, other exudates. *(From Light RW, MacGregor MI, Luchsinger PC, et al. Pleural effusions: the diagnostic separation of transudates and exudates.* Ann Intern Med. *1972;77:507–513, with permission.)*

higher, the degree of inflammation in the pleural space is increasing and one should be aggressive in pursuing a diagnosis. Alternatively, if the pleural fluid LDH level decreases with time, the process is resolving and one need not be as aggressive in the approach to the patient. It should be noted that needle biopsy of the pleura results in an increase in the pleural fluid LDH level of slightly more than 10% 48 hours after the biopsy (81).

When bloody pleural fluid is obtained, one might wonder whether the LDH measurement would be useful because RBCs contain large amounts of LDH. The presence of blood in the pleural fluid, however, usually does not adversely affect the measurement of the LDH. In one study, LDH isoenzyme analysis was performed on 12 pleural fluids that had contained more than 100,000 erythrocytes/mm^3. In only one effusion was the LDH-1 more than 5% above that in the serum, and the total pleural fluid LDH in that effusion was only 107 IU/L (40).

Although the total pleural fluid LDH level is not useful in distinguishing among various exudative pleural effusions, one might suppose that LDH isoenzymes would be useful in the differentiation. Three studies have shown that LDH isoenzymes have limited value in the differential diagnosis of exudative pleural effusions (40,142,143). All benign effusions with elevated pleural fluid LDH levels and most malignant effusions are characterized by a higher percentage of LDH-4 and LDH-5 in the pleural fluid than in the corresponding serum (40).

The increased amounts of LDH-4 and LDH-5 are thought to arise from the inflammatory WBCs

in the pleural effusion (40). Approximately, one third of malignant pleural effusions have a different pleural fluid LDH isoenzyme pattern that is characterized by large amounts (>35%) of LDH-2 and less LDH-4 and LDH-5. None of the 31 benign exudates in one series had more than 35% LDH-2 (40). No relationship exists between the histologic type of the malignant pleural disease and the pleural fluid LDH isoenzyme pattern (40). At present, the only situation in which we obtain LDH isoenzyme analysis of pleural fluid is when there is a bloody pleural effusion in a patient who is clinically thought to have a transudative pleural effusion. If the LDH is in the exudative range and the protein is in the transudative range, the demonstration that most of the pleural LDH is LDH-1 indicates that the increase in the LDH is due to the blood.

pH AND P_{CO_2} MEASUREMENT

Measurement of the pleural fluid pH and P_{CO_2} is useful in the differential diagnosis of exudative pleural effusions. If the pleural fluid pH is less than 7.2, it means that the patient has 1 of 10 conditions: (a) complicated parapneumonic effusion, (b) esophageal rupture, (c) rheumatoid pleuritis, (d) tuberculous pleuritis, (e) malignant pleural disease, (f) hemothorax, (g) systemic acidosis, (h) paragonimiasis, (i) lupus pleuritis, or (j) urinothorax.

The pleural fluid pH is obviously influenced by the arterial pH. With transudative pleural effusions, the pleural fluid pH is usually higher than the simultaneous blood pH (43), presumably because of active transport of bicarbonate from the blood into the pleural space (44). If a low pleural fluid pH is discovered, the arterial pH should be checked to ensure that the patient does not have systemic acidosis. With certain exudative effusions, the pleural fluid pH falls substantially below that of the arterial pH. The explanation for the relative pleural fluid acidosis is as follows. The relationship between the pleural fluid pH and the blood pH depends on the extent to which the blood and pleural fluid P_{CO_2} and bicarbonate are in equilibrium. In conditions associated with pleural fluid acidosis, lactic acid accumulates in the pleural fluid (144,145), presumably from anaerobic glycolysis in the pleural fluid or tissues.

The hydrogen ions associated with the lactic acid combine with bicarbonate to form water and carbon dioxide. Accordingly, the pleural fluid P_{CO_2} increases and the pH decreases. Because the addition of 1 mEq of fixed acid to 1 L of pleural fluid results in an increase of 33 mm Hg in the P_{CO_2} but in a decrease of only 1 mEq in the bicarbonate concentration (146), pleural fluid acidosis is characterized by a P_{CO_2} that is increased proportionately more than the bicarbonate is reduced (43,144).

The increased pleural fluid P_{CO_2} could result from either an increased production of CO_2 or a decreased diffusion of CO_2 from the pleural fluid to blood or a combination of these factors. It is my belief that limited diffusion of CO_2 out of the pleural space is the predominant mechanism. In Figure 7.4A, it can be seen that changes in the arterial P_{CO_2} of a patient with a malignant pleural effusion and mild pleural fluid acidosis were not associated with changes in the pleural fluid P_{CO_2}.

Similarly, in a second patient, the administration of bicarbonate with an increase in the arterial pH from 7.40 to 7.59 did not change the pleural fluid pH or bicarbonate level (Fig. 7.4B). When pleural fluids are incubated at 37°C *in vitro*, no correlation exists between the rate of acid accumulation *in vitro* and the pleural fluid pH *in vivo* (146,147), with the possible exception of patients with complicated parapneumonic effusions in whom the rate of acid accumulation is high (147).

The pleural fluid pH is frequently not measured correctly (148–150). Chandler et al. (148) surveyed the methods by which pleural fluid pHs were measured at 277 acute care institutions in the southeastern part of the United States in 1998. They reported that the pleural fluid pH was measured with the blood gas machine in only 32% of the institutions, whereas it was measured with dip stick or pH indicator paper in 56% and by a pH meter in 12% (148). A survey of 267 pulmonologists in 2008 from the United States revealed that 39% of the physicians who use the pleural fluid pH in the management of parapneumonic effusions were wrong in their assumption that their laboratory used the blood gas machine to measure pleural fluid pH (150). It has been shown that neither pH indicator strip paper (148,151,152) nor pH meters (151) are sufficiently accurate for clinical use. Bowling et al. (153) recently reported similar results from North Carolina. In this study, only 2 of 11 hospitals measured pleural fluid pH with a blood gas analyzer. In a second study (153), 43% of 221 pulmonologists who use the pleural fluid pH were not aware that only pH's obtained with the blood gas machine are sufficiently accurate. The above studies demonstrate that it is important for physicians who order pleural fluid pH to know how their hospital measures the pleural fluid pH. The pH meter gives a reading that is approximately 0.20 to 0.30 too high because it measures the pH at

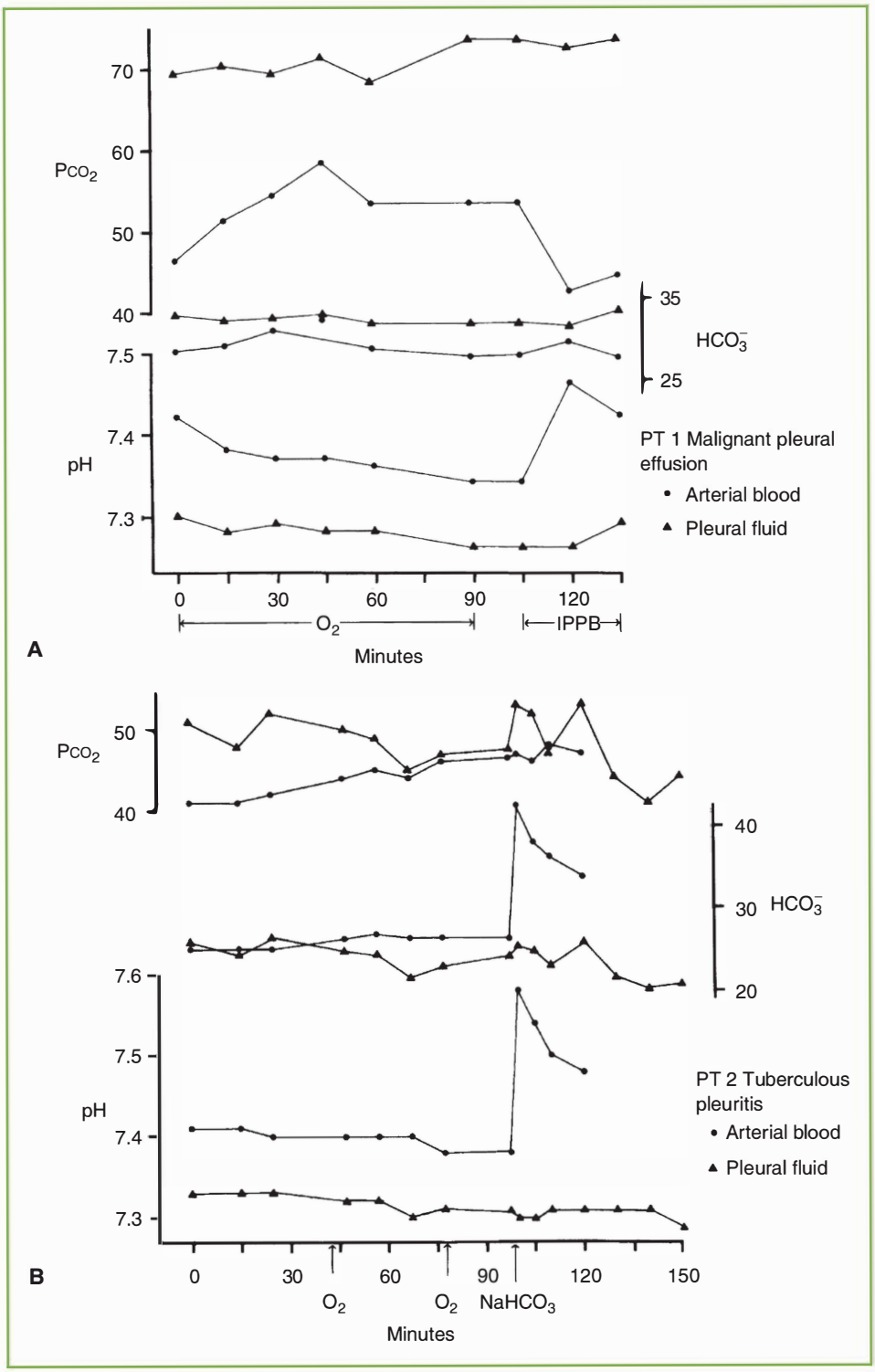

FIGURE 7.4 ■ Relationship between pleural fluid and arterial pH, P_{CO_2}, and HCO_3^-. **A**: Patient with a malignant pleural effusion in whom the administration of supplemental oxygen resulted in an increase in the P_{aCO_2} from 46 to 58. Note that no concomitant change is seen in the pleural fluid P_{CO_2}. **B**: Patient with a slightly acidic pleural fluid. The administration of bicarbonate raised the arterial pH from 7.40 to 7.59 but had no influence on the pleural fluid pH. IPPB, intermittent positive pressure breathing.

room temperature (at which the P_{CO_2} is lower) and the sample comes in contact with room air, which allows the CO_2 to escape again lowering the P_{CO_2} (151). At times, laboratory personnel object to injecting the pleural fluid through blood gas machines for fear of the development of clots. This objection can be overcome if a clot-catching apparatus is inserted between the syringe and blood gas machine (151). The pleural fluid pH can also be measured accurately with a handheld analyzer such as the I-STAT Portable Clinical Analyzer that is used in intensive care units for measuring blood gases (149).

When the pleural fluid pH is used as a diagnostic test, it must be measured with the same care as arterial pH. The fluid should be collected anaerobically in a heparinized syringe (see Chapter 28). If the fluid is opened to room air, carbon dioxide will leave the fluid and the recorded pH will be falsely high (151,154). It appears that it is not necessary to put the fluid on ice if the pH is measured within an hour or so (154,155). Accurate results are also obtained when pleural fluid is transferred from a large syringe to a small heparinized syringe (156). If the effusion is small, injection of a local anesthetic into the pleural fluid may falsely lower the pH (157) as can residual lidocaine in the blood gas syringe (154). If frank pus is obtained at thoracentesis, one should not submit it for pH determination because the thick, purulent fluid may clog the blood gas machine and laboratory personnel may hesitate to analyze subsequent pleural fluids.

In general, pleural fluids with a low pH also have low glucose and high LDH levels (144). If the laboratory reports a low pH with normal glucose and low LDH levels, the pH measurement is probably in error. In a similar manner, a low glucose level with a normal pH and a low LDH is probably a laboratory error.

The only reason to measure the pleural fluid P_{CO_2} is to verify the pleural fluid pH because a low pleural fluid pH is almost always associated with a high P_{CO_2} (43,144). The pleural fluid P_{CO_2} adds no diagnostic value.

The pleural fluid pH is most useful in indicating the prognosis of patients with pneumonic effusions (see Chapter 9). If the pleural fluid pH is below 7.0, the patient invariably has a complicated parapneumonic effusion, and attempts should be made to remove all the pleural fluid with therapeutic thoracentesis or tube thoracostomy (118). If the pleural fluid pH is above 7.2, the prognosis of the patient is excellent and the pleural fluid need not be removed. The American College of Chest Physicians recommends using the pleural fluid pH to determine whether invasive procedures on the pleura are necessary for patients with parapneumonic effusions (158). If the patient has an infection with *Proteus* organisms, the pleural fluid pH may be elevated because these organisms produce ammonia by their urea-splitting ability, which can increase the pH (159). In patients with parapneumonic effusions, the pleural fluid pH may fall before the pleural fluid glucose level becomes depressed (117,160). It should be noted that the pH can vary markedly from locule to locule in patients with parapneumonic effusions (161).

The pleural fluid pH is also decreased with esophageal rupture (138,162). In fact, Dye and Laforet (162) concluded that a pleural fluid pH of less than 6.0 was highly suggestive of esophageal rupture. These workers attributed the low pleural fluid pH to the reflux of gastric acid through the rent in the esophagus into the pleural space. Subsequent studies in rabbits (163), however, have demonstrated that the pleural fluid pH becomes just as acidic after esophageal rupture if the esophagogastric junction is ligated. It appears that the low pleural fluid pH is due to infection in the pleural space rather than to acid reflux. Over the past few years, we have seen several patients with pleural infection without esophageal rupture in whom the pleural fluid pH was below 6.0.

In summary, esophageal rupture is associated with a low pleural fluid pH because of the concomitant pleural infection and not acid reflux. A pleural fluid pH below 6.0 is consistent with but not diagnostic of esophageal rupture.

Patients with pleural effusions secondary to both malignant disease and tuberculosis may have a low pleural fluid pH (43,144,164). When Light et al. wrote their first paper on pleural fluid pH (43), they concluded that the pleural fluid pH was useful in distinguishing tuberculous pleural effusions from malignant pleural effusions; a pleural fluid pH below 7.3 suggested tuberculosis, whereas a pleural fluid pH above 7.4 suggested malignant disease. Subsequent studies by others (145,164,165), however, and my own observations have not supported this conclusion. At present, I consider the pleural fluid pH valueless in distinguishing tuberculous pleural effusions from malignant pleural effusions. The pleural fluid pH does provide information about malignant pleural effusions because patients with a low pleural fluid pH have a shorter life expectancy and are less likely to have a favorable response to pleurodesis (121,165).

The pleural fluid pH is almost always less than 7.2 with rheumatoid pleural effusions (129). The pleural fluid pH with lupus pleuritis is usually above

7.35 (129), but occasionally, it is less than 7.2 (130). The pleural fluid pH tends to be low with both paragonimiasis (166) and Churg-Strauss syndrome (90), and these are the only two conditions in which a low pleural fluid pH is associated with pleural eosinophilia. Another situation in which the pleural fluid pH may be decreased is with a large hemothorax (43). The metabolism of the many RBCs in this condition, in conjunction with the atelectatic underlying lung, is the probable explanation for the decreased pH. Finally, the pleural fluid pH may be reduced with urinothorax (167). This is the only situation in which a transudative pleural fluid has a low pH without concomitant systemic acidosis.

TESTS FOR DIAGNOSING PLEURAL MALIGNANCY

Cytologic Examination of Pleural Fluid

Cytologic examination of pleural fluid is one of the most informative laboratory procedures in the diagnosis of pleural effusions because with it a definitive diagnosis can be made in more than 50% of patients with malignant disease involving the pleura. It is important to process pleural fluid specimens expeditiously when they are submitted for cytology. Specimens maintained at room temperature deteriorate markedly within 48 hours as do refrigerated specimens maintained for 96 hours (168). The optimal amount of pleural fluid to submit for direct smear and cell block preparations appears to be 150 ml although the diagnosis of malignancy can be established in most patients with 10 ml pleural fluid (169).

Malignant cells have several characteristics that differentiate them from other cells in the pleural fluid (61). Malignant cells in a given pleural effusion are recognizably similar to each other and are different from any nonmalignant cells in pleural fluid (Fig. 7.1C). Although the overall appearance of the malignant cells is similar, sometimes there is a marked variation in their sizes and shapes; one cell may have many times the diameter of its twin.

Frequently, malignant cells are large. The nuclei of malignant cells may exceed 50 μm in diameter, in contrast with mesothelial cell nuclei, which rarely exceed 20 μm in diameter. Small lymphocytes, by comparison, have a diameter of approximately 10 μm. The nucleoli of malignant cells are often large, exceeding 5 μm in diameter, whereas the nucleoli of nonmalignant cells in pleural fluid usually do not exceed 3 μm. Malignant cells have a high nucleocytoplasmic ratio. Indeed, the nuclear size of the cells in pleural effusions has been used diagnostically. Marchevsky et al. (170) performed a computer-assisted morphometric study of 48 pleural fluids including 20 benign fluids, eight mesotheliomas, and 20 carcinomas. If the mean nuclear diameter exceeded 10.5 μm or the mean nuclear diameter exceeded 9.3 μm, and the mean nuclear diameter divided by the cytoplasmic diameter exceeded 0.74, the patient had a malignant pleural effusion. This morphologic analysis was not able to separate carcinomas from mesotheliomas.

There are, however, cytologic characteristics that tend to be different for mesothelioma and adenocarcinomas. Stevens et al. (171) compared the cytologic characteristics of 44 cases of malignant mesothelioma and 46 cases of metastatic adenocarcinomas. They concluded that the following five features separate malignant mesothelioma from adenocarcinoma with more than 95% accuracy. Mesotheliomas tend to have true papillary aggregation, multinucleation with atypia, and cell-to-cell apposition, whereas adenocarcinomas tend to have acinus-like structures and balloon-like vacuolation (171).

Malignant cells sometimes aggregate, and large balls or clumps of cells are characteristic of adenocarcinoma (Fig. 7.1D). Although aggregates of 20 or more benign mesothelial cells occasionally occur, the bizarre, large, vacuolated cells with adenocarcinoma allow for a differentiation between these entities. Both malignant cells and macrophages may have vacuolation. Small numbers of mitotic figures frequently occur in benign effusions, and, accordingly, the presence of such figures is not indicative of malignant disease.

The accuracy of the cytologic diagnosis of malignant pleural effusions has been reported to be anywhere between 40% and 87% (172–174). Several factors influence the percentages in the various reports. First, in many patients with proven malignant disease and pleural effusion, the effusion is not related to malignant involvement of the pleura but is rather secondary to other factors such as CHF, pulmonary emboli, pneumonia, lymphatic blockade, or hypoproteinemia. In such patients, one cannot expect the result of the pleural fluid cytologic test to be positive. For example, it is unusual for the results of pleural fluid cytologic tests to be positive in patients with squamous cell carcinoma (41,61,175) because the pleural effusions are usually due to bronchial obstruction or lymphatic blockade. Second, the frequency of positive cytologic results depends on the tumor type. For example, with lymphoma, the cytologic examination was positive in

75% of patients with diffuse histiocytic lymphoma but in only 25% of patients with Hodgkin's disease in one series (176). The cytologic test is more frequently positive with adenocarcinomas than with sarcomas (175). Third, the accuracy of the results depends on the way in which the specimens are examined. If both cell blocks and smears are prepared and examined, the percentage of positive diagnoses will be greater than if only one method is used (177). It is recommended that the standard preparation of an effusion should include the preparation of a cellblock, and cytospins stained with Diff-Quik and Papanicolaou stains (178). Fourth, the more separate specimens submitted for cytologic examination, the higher the percentage of positive reports (41,176). In my own experience in patients with proven malignant disease involving the pleural space, the initial pleural fluid cytologic examination is positive in approximately 60% of patients, and if three separate specimens are submitted, nearly 80% of the patients will have positive results (42). The third specimen frequently contains fresher cells that allow the diagnosis to be made. Fifth, the incidence of positive diagnoses is obviously dependent on the skill of the cytologist. Sixth, the incidence of positive diagnoses is related to the tumor burden in the pleural space. A patient with a large tumor burden is more likely to have a positive pleural fluid cytology than is a patient with a small tumor burden.

Most tumors that are metastatic to the pleura have an epithelial origin whereas the cells that are normally in the pleural space (neutrophils, lymphocytes, mesothelial cells and macrophages) do not have an epithelial origin. Kielhorn et al. (179) reported that the yield with cytology was increased if epithelial cells were selected by immunomagnetic selection of cells binding to EpCAM antibodies. In their study of 59 effusions, the cytology alone was positive in 12 patients, but when the epithelial cells were identified with the EpCAM antibodies, the cytology became positive in 16 patients (179).

In summary, when three separate pleural fluid specimens from a patient with malignant pleural disease are submitted to an experienced cytologist, one should expect a positive diagnosis in approximately 80% of patients. Because it is important to prevent the pleural fluid specimen from clotting, about 0.5 mL heparin should be added to the syringe during a diagnostic thoracentesis (see Chapter 28). If a larger volume of pleural fluid is obtained during a therapeutic thoracentesis for submission to a cytologist, additional heparin should be added. From the examination of the exfoliated cancer cells, it is usually possible to classify the neoplasm accurately into its histologic type such as adenocarcinoma. Only occasionally is it possible to suggest with confidence the primary site of the neoplasm (175).

Nucleolar Organizer Regions

Nucleolar organizer regions (NOR) are loops of DNA in the nucleus that code for ribosomal RNA and are important in the synthesis of protein (180). These regions are associated with acidic nonhistone proteins that can be visualized by argyrophilic staining (AgNOR). In general, malignant cells have more AgNOR staining than benign cells (180). Although several papers have concluded that AgNOR staining is useful in separating benign and malignant effusions (181–184), there has been no standardization of the technique and there is overlap between benign and malignant cells. Until more research is conducted on AgNOR, it cannot be recommended.

Immunohistochemical Studies

With the development of the necessary technology for MAb, numerous papers have been published in the last 25 years that have assessed the diagnostic utility of MAb in the diagnosis of pleural malignancy.

The basis for this approach is the belief that there are antigens that are unique for benign mesothelial cells, adenocarcinoma cells, and malignant mesothelioma cells. If MAb are developed against these specific antigens, then positive identification of these cells can be made when tissue samples or cytologic preparations are incubated with the antibody and then counterstained with immunoalkaline phosphatase or using some similar method.

Many studies have compared the usefulness of the different antibodies in distinguishing the three different cells and these studies are summarized in a recent article by Ordonez (185). At the present time, the best markers for adenocarcinoma appear to be carcinoembryonic antigen (CEA), MOC-31, B72.3, Ber-EP4, BG8, and TTF-1, whereas the best markers for mesothelioma appear to be calretinin, keratin 5/6, podoplanin, and WT1 (185). TTF-1 has high specificity for lung carcinoma (185). It is important to realize that nonmalignant mesothelial cells will also stain positive for calretinin and cytokeratin 5/6 (186). Moreover, the sarcomatous type of mesothelioma is positive with calretinin less than 10% of the time (187). Ordonez concluded that D2-40 and podoplanin are the best immunohistochemical markers for epithelioid mesotheliomas (188).

When immunohistochemistry is used to differentiate adenocarcinoma from mesothelioma, a panel of MAb including two that stain with mesothelioma and two that stain with adenocarcinoma should be used (185). There are some additional points that need to be made about the immunohistochemical tests. For some of the antibodies, the pattern of the staining is very important. Therefore, it is necessary to have an experienced immunohistochemist performing the tests. There are new antibodies being evaluated continuously, and it is hoped that in the near future, antibodies will be developed that are specific for malignant mesothelioma and benign mesothelial cells. One preliminary report suggested that malignant mesotheliomas and benign mesothelial cells could be separated by the use of desmin and epithelial membrane antigen (EMA) (189). In this study 6/60 (10%) mesotheliomas and 34/40 (85%) of the benign mesothelial cells reacted to desmin, whereas 80% of mesotheliomas but only 20% of benign mesothelial cells reacted to EMA (189).

On occasions, one is faced with the situation where the cytology of the pleural fluid is positive but the location of the primary is unknown. Immunohistochemistry can suggest the location of the primary in some instances. For example, in one study of 67 patients with metastatic breast carcinoma, 21 of the patients (31.3%) stained positive with lactoferrin whereas no more than 15% of any other primaries were positive with this antibody (190). For 56 cases of ovarian carcinoma, immunohistochemistry was positive in 30% for CA-125 whereas no more than 12% of any of the other primaries were positive for this antibody (190). Probably the best antibody is thyroid transcription factor-1 (TTF-1). In one study, the pleural tissue stained positive for TTF-1 in 27/34 metastatic lung carcinomas but in none of the 48 other malignancies of the pleura (191). Cell-blocks from pleural effusions from patients with lung primaries also stain positive for TTF-1 (192). Small cell lung carcinoma also stains positive with TTF-1 as it does with chromographin A, a neuroendocrine marker (193). Nevertheless, there are no antibodies that are 100% specific for any primary (with the possible exception of TTF-1) and most antibodies are not very specific (190). In one case report of a patient with prostatic carcinoma metastatic to the pleura, the prostate specific antigen (PSA) was higher in the pleural fluid than it was in the serum (194).

It appears that immunohistochemistry is quite useful in establishing the diagnosis of a lymphomatous pleural effusion. Guzman et al. (195) performed immunocytochemical analysis with the peroxidase–antiperoxidase adhesive slide assay for detection of cell surface antigens using a broad panel of MAb in nine patients with pleural lymphoma. They were able to clearly recognize six cases of B-cell lymphoma, one case of Hodgkin's disease, and one case of hairy cell leukemia (195).

Immunohistochemical tests on cell blocks of pleural fluid or pleural biopsy specimens are available from Propath in Dallas, Texas, 1-800-258-1253 or www.propathlab.com.

Electron Microscopic Examination

The diagnosis of mesothelioma and metastatic carcinoma to the pleura is made in most instances by cytology and immunohistochemical assessment, but electron microscopy (EM) still plays a decisive role in some cases with unusual morphology or anomalous histochemical reactions. Accordingly, when malignant mesothelioma is suspected, a portion of the pleural biopsy specimen should be routinely fixed at the time of biopsy for possible subsequent processing for EM (196). EM has its greatest utility in differentiating metastatic adenocarcinoma from mesothelioma. The ultrastructural features of mesotheliomas are so characteristic as to be almost diagnostic. These characteristics include characteristic microvilli; the absence of microvillus core rootlets, glycocalyceal bodies, and secretory granules; the presence of intracellular desmosomes, junctional complexes, and intracytoplasmic lumina; and characteristic microvilli.

The appearance of the microvilli is the most important diagnostic feature. With adenocarcinoma, they are less abundant and are usually short and stubby, whereas with mesothelioma, they are numerous and are characteristically long and thin (197,198). These long microvilli can be visualized with light microscopy if the pleural fluid specimen is stained with the Ultrafast Papanicolaou stain (199).

Histochemical Studies

Immunohistochemical tests have replaced histochemical tests in distinguishing adenocarcinoma from mesothelioma in many laboratories. However, there are two primary histochemical tests that can be used to differentiate mesotheliomas from adenocarcinomas. The Alcian blue stain detects the acid mucins characteristic of mesothelioma (200). In one study, the Alcian blue stain was positive in 14 of 29 (47%) mesotheliomas (200), but in none of 44 patients with adenocarcinoma. The periodic acid-Schiff stain after diastase digestion (PAS-D) detects neutral

mucins, which are diagnostic of adenocarcinomas. In one study the PAS-D stain was positive in 27 of 44 (61%) patients with adenocarcinoma but in no patients with mesothelioma (200). In summary, if the cells stain positive with PAS-D, the patient in all probability has an adenocarcinoma. If the cells stain positive with Alcian blue, the patient in all probability has a mesothelioma. If the cells stain positive with neither, no conclusion can be made.

Tumor Markers in Pleural Fluid

The possibility of establishing the diagnosis of pleural malignancy by demonstrating an elevated level of a tumor marker in the pleural fluid has been the subject of many publications. The tumor markers that have been evaluated have included (201–212), carbohydrate antigens CA 15-3 (201,205–209,212–214), CA 19-9 (201,205,207,208,215), CA 549 (212), CA 72-4 (201,205,212), cytokeratin 19 fragments (CYFRA 21-1) (201,202,206,207,216), cancer antigen 125 (CA 125) (206,207), sialyl stage-specific antigen (217,218), neuron-specific enolase (201,203,219), squamous cell carcinoma antigen (201,203), HER-2/neu (220) and telomerase (221,222).

In general, I do not recommend that tumor markers be used in the evaluation of patients with undiagnosed pleural effusions (223). Although an elevated level of any of the tumor markers is very suggestive of malignancy, specificity is not high enough to establish the diagnosis. Although there is no doubt that the median levels of the different tumor markers are significantly higher in patients with malignancy than in patients with benign pleural effusions, there is always some overlap in the values. If the cutoff level for a tumor marker is set high enough that the level is exceeded by none of the benign effusions, then the test tends to be very insensitive. The same criticism could be made of tests on the pleural fluid for tuberculosis, such as adenosine deaminase (ADA) or interferon-gamma. Nevertheless, I rely heavily on these tests to establish the diagnosis of tuberculosis. The primary difference in the two situations is that it would be disastrous to wrongly make the diagnosis of malignancy with a tumor marker because the patient is essentially told that he or she has only 90 days to live. If the diagnosis of tuberculosis is wrongly established, the patient is not sentenced to death but rather to taking antituberculous medications for 6 to 9 months.

The best study to date was reported by Porcel et al. (206). They measured the pleural fluid levels of CEA, CA-125, CA 15-3 and cytokeratin 19 fragments in 416 patients including 166 with definite malignant effusion, 77 with probable malignant effusions, and 173 with benign effusions. Cutoff levels were established such that the levels in all 173 benign effusions were below the cutoff level. Using these cutoff levels, 54% of the malignant effusions were classified as malignant and more than one third of the cytology-negative malignant pleural effusions could be identified by at least one marker (206). These authors suggested that the main use of measuring tumor markers in the pleural fluid would be to select patients (those with the higher levels) for more invasive studies (206).

Soluble Mesothelin Related Protein (SMRP)

It has been suggested that elevated pleural fluid levels of SMRP are useful in the diagnosis of malignant mesothelioma (224–226). Creaney et al. (224) measured the SMRP levels in pleural fluids from 192 patients presenting to a respiratory clinic including 52 with malignant mesothelioma, 56 with nonmesotheliomatous malignancies and 84 benign effusions. The pleural effusions from the patients with mesothelioma had significantly higher concentrations of SMRP than did the other patients (224). However, the SMRP in patients with sarcomatoid mesothelioma did not differ significantly from nonmalignant effusions (224). Davies et al. (225) measured pleural fluid SMRP in 24 patients with mesothelioma, 67 patients with pleural metastases and 75 patients with benign conditions. Using ROC curve analysis, pleural fluid SMRP had an AUC of 0.878 in its ability to differentiate between patients with mesothelioma and all other diagnoses at an optimal cutoff value of 20 nM (225). At this cutoff, the diagnostic sensitive and specificity were 0.71 and 0.90, respectively (225). Again, the levels of SMRP were lower in patients who had sarcomatoid mesothelioma (225). Adenocarcinomas accounted for 12 of the 13 false positives. The above two studies demonstrate that pleural fluid SMRP measurement provide additional information to cytology. However, tissue confirmation of mesothelioma is indicated in most situations.

Oncogenes

The development of cancer is a multistep process in which multiple genetic alterations must occur. The transforming genes are collectively called *oncogenes*. The oncogenes may be related to viruses, environmental carcinogens, or spontaneous mutations. Because the oncogenes are associated with the development of malignancy, one might hypothesize that

patients with pleural malignancy would have cells in their pleural fluid containing oncogenes.

There have now been several studies testing this hypothesis. Zoppi et al. (227) attempted to detect the p53 protein in 34 embedded blocks of neoplastic fluids and 30 nonneoplastic effusions. They reported that 11 (34%) of the tumor fluids were positive, whereas all the benign fluids were negative (227). Mayall et al. (228) reported similar findings for p53. Tawfik and Coleman (229) reported that benign and malignant effusions did not differ significantly in their expression of the *CMYC* oncogene. Athanassiadou et al. (230) reported that although 21 of 24 malignant effusions (87%) were positive for the *CHARAS* oncogene, the diagnostic usefulness of the test was limited because 6 of 16 benign effusions (37%) also tested positive.

Hyaluronic Acid

Pleural fluid from patients with mesotheliomas is sometimes abnormally viscid. The increased viscosity in such fluids is due to the presence of increased amounts of hyaluronate, which was previously called *hyaluronic acid*. Rasmussen and Faber (231) examined the diagnostic usefulness of pleural fluid hyaluronic acid levels in 202 exudates including 19 malignant mesotheliomas. These investigators found that 7 of 19 pleural fluids (37%) from patients with malignant mesotheliomas had hyaluronate concentrations above 1 mg/mL, whereas none of the other pleural fluids had hyaluronate levels above 0.8 mg/mL. Nurminen et al. (232) assayed the levels of hyaluronate in 1,039 pleural effusions including 50 from patients with mesothelioma. They reported that when a cutoff level of 75 mg/mL was used, the assay specificity for malignant mesothelioma was 100% and the sensitivity was 56%. Two more recent papers (233,234) have reported that the mean levels of hyaluronate are comparable in patients with mesothelioma and metastatic adenocarcinoma. The explanation for the discrepant results appears to be methodologic (235). The measurements of Nurminen were obtained with high-pressure liquid chromatography (HPLC), whereas those of the latter two groups were by radioimmunoassay. Unfortunately, the only commercially available measurements in the United States of which I am aware use radioimmunoassay (Specialty Laboratories, San Diego, CA, USA, and SmithKline Beecham Clinical Laboratories, Philadelphia, PA, USA). Until the results with this assay are verified, it cannot be recommended on a routine basis.

Lectin Binding

Lectins are a class of glycoproteins of nonimmune origin that bind specifically to carbohydrate groups found ubiquitously in various biologic products. Kawai et al. (236) investigated lectin binding in 23 pleural mesotheliomas, 6 effusions with reactive mesothelial cells, and 28 well-differentiated pulmonary adenocarcinomas. In this study, some of the lectins were much more likely to bind to adenocarcinomas than to reactive mesothelial cells or mesothelioma cells. These workers could not find significant differences in lectin binding between mesotheliomas and reactive mesothelial cells. Additional research in this area may well demonstrate that studies of lectin binding are useful diagnostically. At the present time, such studies should be considered experimental.

Flow Cytometry

Flow cytometry provides a method for the rapid quantitative measurement of nuclear DNA. It has been proposed as a suitable tool for differentiating between benign and malignant cells because most malignant tumor cells possess an abnormal number of chromosomes (aneuploidy), and consequently an abnormal DNA content (DNA aneuploidy) (237). However, a substantial percentage of metastatic adenocarcinomas and most malignant mesotheliomas are diploid, as demonstrated through flow cytometry (180,238–240). Moreover, some benign effusions are aneuploid (239). Accordingly, the routine use of flow cytometry to quantitate nuclear DNA levels for the differentiation of benign and malignant effusions cannot be recommended.

Flow cytometry can also be used to identify the surface markers of lymphocytes rapidly and specifically using immunocytometry (241). Accordingly, the cell lineage (T or B cells) and the clonality of a population of lymphocytes can be determined. These techniques can therefore be used to establish the diagnosis of pleural lymphomas and are recommended in lymphocytic pleural effusions on which the diagnosis of lymphoma is a consideration (241).

Flow cytometry can also be used with the cells labeled with a panel of antibodies such as MOC-31, EMA, CEA, B72.3, keratin, desmin, CA-125, IMP3 and GLUT-1 (242,243). These studies appear to be complementary to studies using only cytology (242,243).

Chromosomal Analysis

Abnormalities undoubtedly exist in the chromosome number and structure in some patients with malignant

pleural effusions (244,245). Malignant cells have more chromosomes and marker chromosomes, which are chromosomes with structural abnormalities (translocation, deletion, acentric, dicentric, inversion, isochromosome, or ring) (244). It remains to be demonstrated that there is a place for chromosomal analysis in the routine examination of pleural fluid. However, there may be a place for fluorescence in situ hybridization (FISH) to demonstrate chromosomal abnormalities.

In the last few years, a new methodology called *FISH* has been introduced (246). With this technique prespecified chromosomal aberrations can be visualized in cytologic smears (246). Fiegl et al. (247) used cytology and FISH techniques on 194 effusions from patients with malignancy. They reported that cytology was positive in 99 (51%) whereas FISH was positive in 116 (60%) (247). One of the two tests was positive in 133 (69%) of the effusions (247). They concluded that the FISH technique was complimentary to cytology in establishing the diagnosis of malignant pleural effusion (247). The FISH technique on the pleural fluid is also useful in distinguishing mesothelioma from benign effusions (248).

Proteomics

Proteomics involves identifying all the proteins present in a given specimen and then identifying those proteins that are unique to a certain condition. There have been a couple of preliminary articles exploring the feasibility of using proteomics for the diagnosis of malignant pleural effusions (249,250). Unique proteins have been identified but it is still too early to determine whether proteomics will turn out to be diagnostically useful. Another preliminary study (251) used proteomics to analyze the proteins from exosomes isolated from pleural effusions and reported that they were able to identify some proteins that were not previously reported.

TESTS FOR DIAGNOSING PLEURAL TUBERCULOSIS

Adenosine Deaminase Measurement (ADA)

Measurement of the ADA level in pleural fluid is diagnostically useful because ADA levels tend to be higher in tuberculous pleural effusions than in other exudates (252–256). ADA is the enzyme that catalyzes the conversion of adenosine to inosine. In general, a cutoff level of between 40 and 45 U/L is used with levels above this being indicative of tuberculosis. The higher the level, the more likely the patient is to have tuberculosis. Liang et al. (255) performed a meta-analysis of 63 articles evaluating the diagnostic usefulness of ADA that included 2,796 patients with tuberculous pleuritis and 5,297 patients with other diseases. They reported that the mean sensitivity was 0.92, the mean specificity was 0.90, the mean positive likelihood ratio was 0.903 and the mean negative likelihood ratio was 0.10 (255). In the largest series from a single institution, Porcel et al. (256) reported measurements of the pleural fluid ADA. In their study of 2,104 pleural effusions including 221 with tuberculous pleuritis, the sensitivity was 0.93, the specificity was 0.90, the positive likelihood ratio was 10.05 and the negative likelihood ratio was 0.07 (245). Valdés et al. (254) reported their results on pleural fluids from 405 patients, including 91 due to tuberculosis, 110 due to malignancy, 58 due to pneumonia, 10 due to empyema, 88 transudates, and 48 miscellaneous. Their results were very similar to those of previous workers with the exception that empyemas also had very high ADA levels (Fig. 7.5). Measurement of the ratio of the pleural fluid to the serum ADA is much less useful diagnostically (254).

The pleural fluid ADA is also elevated in patients with tuberculous pleuritis who are immunosuppressed. The levels of ADA in patients with and without AIDS are comparable (257) and renal transplant patients who develop a tuberculous pleural effusion have an elevated pleural fluid ADA level (258).

Some caution must be used in relying on ADA levels exclusively to establish the diagnosis of tuberculous pleuritis. The two main diseases that cause an elevated ADA in addition to tuberculosis are rheumatoid pleuritis and empyema (254,259). If the diagnostic criteria for tuberculous pleuritis also include a pleural fluid lymphocyte-to-neutrophil ratio greater than 0.75, the specificity of the test is increased (260). High pleural fluid ADA levels have also been reported with a very small percent of other neoplasms (261), with Q fever (262), with brucellosis (263) and with Legionnaire's disease (264).

The pleural fluid ADA level can be used to exclude the diagnosis of tuberculous pleural effusions in patients with undiagnosed lymphocytic pleural effusions. Two series (265,266) measured the pleural fluid ADA levels in 506 patients with lymphocytic pleural effusions not due to tuberculosis. Only 10 patients (2%) had an ADA level above 40 U/L. The diagnoses in these 10 patients included 3 cases of lymphoma, 3 cases of parapneumonic effusions, 2 bronchogenic carcinomas, 1 mesothelioma, and 1 idiopathic pleural effusion (265,266). The pleural effusions that occur

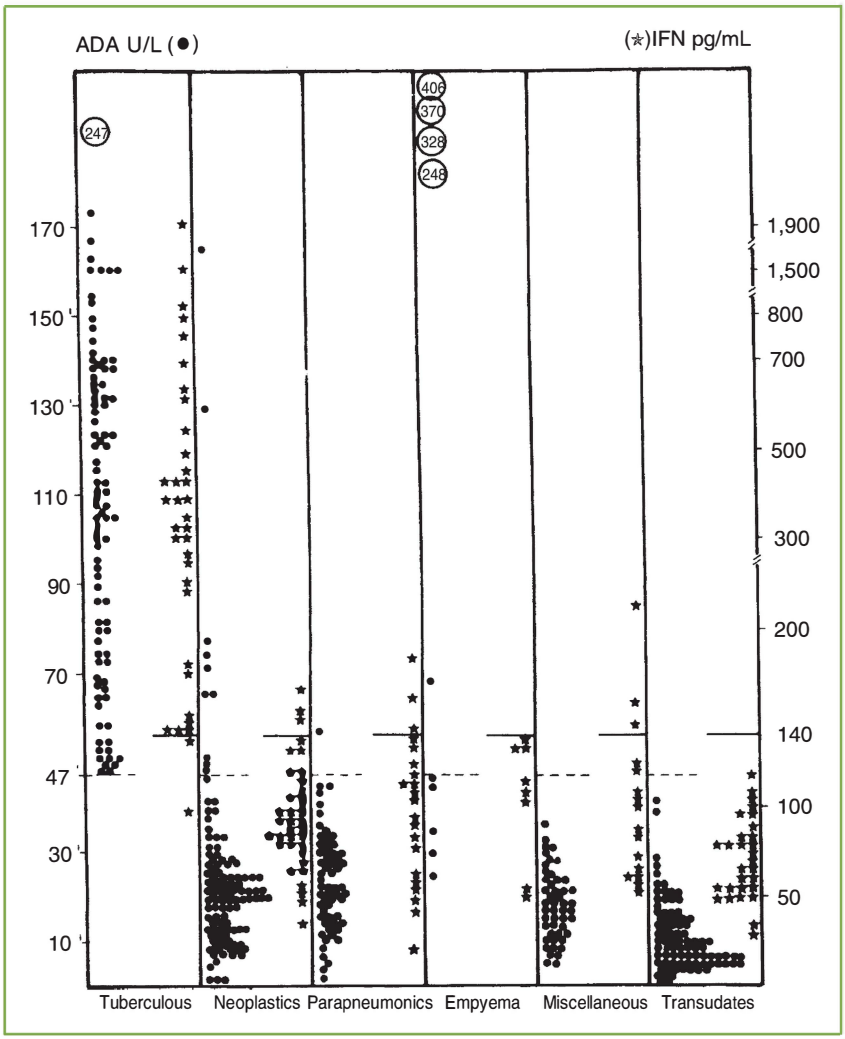

FIGURE 7.5 ■ Pleural fluid adenosine deaminase (ADA) and interferon (IFN)-gamma levels in 430 cases. *(From Valdés L, San Jose E, Alvarez D, et al. Diagnosis of tuberculous pleurisy using the biologic parameters adenosine deaminase, lysozyme, and interferon-gamma.* Chest. *1993;103:458–465, with permission.)*

after CABG surgery are typically lymphocytic, but their ADA levels are below 40 U/L (265).

Several papers have been written on the diagnostic utility of ADA isoenzymes. ADA has two isoenzymes, ADA1 and ADA2 (267–270). ADA1 is ubiquitous and is produced by lymphocytes, neutrophils, monocytes, and macrophages (268). In contrast, ADA2 exists only in monocytes and macrophages. The increase in ADA activity with tuberculous pleuritis is mainly due to ADA2, which is surprising because most of the cells in the pleural fluid are lymphocytes. These observations suggest that the origin of the pleural fluid ADA is probably in the pleural tissues rather than the cells in the pleural fluid. There is one report in which the use of an ADA1-to-ADA total ratio of less than 0.42 increased the accuracy with which the diagnosis of tuberculous pleuritis was established (269). In most cases, ADA isoenzymes are not needed to establish the diagnosis of tuberculosis. However, in certain instances they can be quite useful.

An added advantage of ADA in the diagnosis of pleural effusions is that if 0.9 mL pleural fluid is added to a test tube containing 0.10 mL of a mixture of 50% glycerol and 50% ethylene glycol, the pleural fluid can be mailed by regular mail with no loss of ADA activity (271). If the pleural fluid is stored at

4 degrees C or -20 degrees C, the level of ADA remains stable up to 28 days (272).

In view of the foregoing information, it is recommended that facilities in which a sizable percentage of the cases of pleural effusions are due to tuberculosis develop the faculty to perform ADA assays on pleural fluid. An ADA level above 70 U/L in a patient who does not have an empyema or rheumatoid arthritis (RA) is essentially diagnostic of tuberculous pleuritis. An ADA level above 40 is suggestive of tuberculosis, and the higher the ADA, the more likely the diagnosis of tuberculous pleuritis.

Interferon-Gamma

Measurement of the pleural fluid levels of interferon-gamma is useful in the diagnosis of tuberculous pleuritis because patients with tuberculous pleuritis tend to have higher levels of interferon-gamma than do other types of exudates (273–278). Jiang et al. (278) performed a meta-analysis on the diagnostic usefulness of pleural fluid interferon-gamma levels in 22 studies with 782 patient with tuberculous pleuritis and 1,319 patients with pleural effusions due to other diseases. They reported that the mean sensitivity was 0.89, the mean specificity was 0.97, the mean positive likelihood ratio was 23.45 and the mean negative likelihood ratio was 0.11 (278).

Individual studies have reported similar results. Pleural fluid interferon-gamma levels from the 145 patients reported by Valdés et al. are shown in Figure 7.5. As can be seen from this figure, 26 of 35 patients (74%) with tuberculous pleurisy had interferon-gamma levels above 200 pg/mL, whereas only 1 out of 110 other effusions that were not empyemas had an interferon-gamma level that exceeded this. Villena et al. (277) reported comparable results in the pleural fluids of 595 patients, including 82 with tuberculous effusions. She reported that an interferon-gamma level of 3.7 IU/mL (as measured by radioimmunoassay) had a sensitivity of 0.98 and a specificity of 0.98 (277) for the diagnosis of tuberculous pleuritis.

Interferon-gamma is produced by the $CD4^+$ lymphocytes from patients with tuberculous pleuritis (275). The production of interferon-gamma appears to be a useful defense mechanism. Interferon-gamma enhances polymyristate acetate–induced hydrogen peroxide production in macrophages, facilitating elimination of intracellular parasites. This lymphokine also inhibits mycobacterial growth in human monocytes (275).

In view of the information mentioned in the preceding text, it appears that measurement of the interferon-gamma level is very useful in the diagnosis of tuberculous pleuritis. One must be careful in interpreting the results from a given laboratory, however, as different laboratories report their results in different units. In the United States, pleural fluid interferon-gamma levels can be obtained from Immunoscience Laboratory in Los Angeles, 310-667-1077, www.immuno-sci-lab.com.

Which test should be used to establish the diagnosis of tuberculous pleuritis? Greco et al. (279) reviewed all English language studies from 1978 to November 2000. The studies included 4,738 patients on whom ADA was measured and 1,189 patients on whom interferon-gamma was measured. These researchers reported that the maximum joint sensitivity and specificity for ADA was 93%, whereas it was 96% for interferon-gamma (279). Because there is not much difference in the performance of the two tests and as ADA is much less expensive, ADA appears to be the preferred test.

Interferon-gamma release assays (IGRA)

IGRA on the blood were designed to diagnose latent tuberculosis (280). There are two commercially available assays the QuantiFERON TB Gold (Qtf Gold; Cellestis Ltd., Carnegie, Victoria, Australia) and the T SPOT.TB (Oxford Immunotec Ltd., Abington, UK). These tests incubate whole-blood or isolated peripheral blood mononuclear cells with Mycobacterium tuberculosis specific antigens and assay the amount of interferon-gamma released.

The IGRA are inferior to the pleural fluid interferon-gamma levels (280–281). Zhou et al. (281) performed a meta-analysis of the available reports on IGRA on the pleural fluid for diagnosing tuberculous pleuritis. They analyzed seven reports with a total of 213 patients with tuberculous pleuritis and 153 patients with pleural effusions of other etiologies and reported that the mean sensitivity was 0.75, the mean specificity was 0.82, the mean positive likelihood ratio was 3.49 and the mean negative predictive ratio was 0.24 (281). Since these results are markedly inferior to those with ADA or interferon-gamma, the IGRA should not be used in assessing whether patients have tuberculous pleuritis.

Polymerase Chain Reaction

The role of the polymerase chain reaction (PCR) and other nucleic acid amplification (NAA)–based tests

in the diagnosis of tuberculous pleuritis remains to be established. There are several NAA tests available for the rapid detection of *Mycobacterium tuberculosis* in clinical specimens. At present, the U.S. Food and Drug Administration (FDA) has not given its approval for the use of these tests on extrapulmonary materials (282).

Pai et al. (283) performed a meta-analysis on 14 studies utilizing NAA-based tests for the diagnosis of tuberculous pleuritis using three different commercial kits including 127 patients with tuberculous pleuritis and 1,400 patients with pleural effusions due to other diseases. They reported that the mean sensitivity was only 0.62 while the mean specificity was 0.98 (283). The mean positive likelihood ratio was 25.4 while the mean negative likelihood ratio was 0.40 (283).

In general, PCR on pleural fluid has been less sensitive than the PCR on other specimens, possibly due to the low numbers of tuberculous bacilli present in pleural fluid and possibly due to the manner in which the DNA is extracted (284). PCR has also been tried on pleural biopsy specimens and the results have not been particularly promising (285).

In view of their low sensitivity, the use of the PCR or other NAA-based tests should be considered investigative. Certainly, the expense associated with these tests is much greater than that associated with pleural fluid ADA measurements. In the future, it is possible that these tests will be widely used in the diagnosis of tuberculous pleuritis.

C-Reactive Protein

Patients with tuberculous pleuritis tend to have higher pleural fluid levels of C-reactive protein (CRP) than do patients with other lymphocytic pleural effusions. Garcia-Pachon et al. (286) measured the CRP in 144 patients with lymphocytic pleural effusions including 20 with tuberculosis, 69 with malignancy, 38 with transudates, and 17 with other benign exudates. They found that CRP levels greater than 50 mg/L had a high specificity for tuberculosis (95%) and levels less than 30 mg/L had a high sensitivity (95%) for excluding tuberculosis. In a second study (287) of 148 patients with lymphocytic exudative pleural effusions including 55 with tuberculous pleuritis, a pleural fluid CRP level above 30 mg/L had a sensitivity of 72% with 93% specificity. The advantage of the CRP test is that it is inexpensive and widely available. However, it does not appear to be as accurate as ADA levels in making the diagnosis of tuberculous pleuritis. Moreover, the mean pleural fluid levels in patient with parapneumonic effusions is greater than that in tuberculous pleural effusions (288).

Lysozyme

The level of lysozyme in the pleural fluid tends to be higher in the pleural fluid from patients with tuberculous pleuritis than in other types of exudates (242,243,289,290). Lysozyme is a bacteriolytic protein with a low molecular weight distributed extensively in organic fluids. In general, the lysozyme levels in tuberculous pleural effusions are greater than those in malignant pleural effusions, but there is so much overlap that the pleural fluid levels themselves are not particularly useful diagnostically. There was one report that suggested that the ratio of the pleural fluid to the serum lysozyme level was useful in separating the two diseases (290). Verea Hernando et al. (290) reported the results for 54 patients with tuberculous pleural effusions and 35 patients with malignant pleural effusions. All of the patients with tuberculosis had a ratio above 1.2, whereas only 1 of the 35 patients (3%) with malignant pleural effusions had ratios above 1.2. A recent study by Valdés et al. (254) did not reproduce these good results; nearly one third of the patients with tuberculous pleuritis had a lysozyme ratio less than 1.1, and many other exudates had ratios that exceeded this value. In this latter article, both the interferon-gamma and the ADA were superior to the lysozyme ratio in differentiating tuberculous exudates from nontuberculous exudates (254). At the present time, the routine measurement of pleural fluid lysozyme to help establish the diagnosis of pleural tuberculosis is not recommended.

Procalcitonin

Serum procalcitonin levels are a useful marker of severe systemic bacterial infection (291). Serum levels of procalcitonin are useful in the early diagnosis of systemic bacterial infection and sepsis, assessment of the severity and prognosis of sepsis and multiple organ failure, and the differentiating of bacterial and viral infections (291). For procalcitonin levels in the pleural fluid, it has been shown that the highest mean levels are with empyema followed by parapneumonic effusions and then tuberculous pleurisy and malignant pleural effusion (291,292). However, there is so much overlap that the diagnostic value of procalcitonin is very limited.

Tuberculous Antigens and Their Antibodies

The possibility of establishing the diagnosis of tuberculous pleuritis by the demonstration of tuberculous antigens or specific antibodies against tuberculous proteins in the pleural fluid has also been investigated.

Two reports have evaluated the diagnostic utility of measuring the levels of different tuberculous antigens in the pleural fluid (292,293). Although the mean levels of tuberculous antigens were higher in the pleural fluid of patients with tuberculous pleuritis than in the pleural fluid of other patients, there was so much overlap that the test was of little diagnostic use. In a similar vein, there have been at least eight separate reports (294–301) that have indicated that patients with tuberculous pleural effusions tend to have higher levels of specific antituberculous antibodies in their pleural fluid than do patients with other types of exudative effusions. The source of the antibodies, however, is apparently the serum rather than local antibody production in the pleural space in most instances (296), although in one study, the pleural fluid levels of IgM antibodies against mycobacterial antigen A60 were higher in the pleural fluid than in the serum and were higher in patients with tuberculous pleuritis than in those without tuberculous pleuritis (301). If these results can be confirmed, this test may prove useful in identifying patients with tuberculous pleuritis.

IMMUNOLOGIC STUDIES

Because nearly 5% of patients with RA (302) and 50% of patients with systemic lupus erythematosus (SLE) have pleural effusions sometime during the course of their disease, and because such effusions may be present before the underlying disease is obvious (129,302), it is important to consider these diagnostic possibilities in patients with exudative pleural effusions of undetermined origin. Numerous papers have assessed the diagnostic utility of various immunologic measurements of the pleural fluid in establishing these diagnoses.

Rheumatoid Factor

Berger and Seckler (303) first reported that rheumatoid factor (RF) was elevated in the pleural fluid of patients with rheumatoid pleuritis. Subsequently, Levine et al. (304) studied pleural fluid RF levels in 65 patients with pleural effusions and found that 41% of patients with bacterial pneumonia and 20% of patients with carcinoma had pleural fluid RF titers equal to or greater than 1:160. In seven of the 65 fluids, the pleural fluid RF titers were greater than the serum titers, but the pleural fluid titer was greater than 1:640 in only one of the patients. These workers concluded that the RF titers in pleural fluid were not useful diagnostically. Halla et al. (129), however, found that the pleural fluid RF was elevated in 11 of 11 seropositive patients with rheumatoid pleural effusions. In each patient, the pleural fluid RF titer was equal to or greater than 1:320 and was equal to or greater than that in the serum. In view of the last-mentioned study, I recommend that RF titers be determined in pleural fluid when the diagnosis of rheumatoid pleuritis is considered. The demonstration of a pleural fluid RF titer equal to or greater than 1:320 and equal to or greater than the serum titer is strong evidence that the patient has a rheumatoid pleural effusion.

Antinuclear Antibodies

In the earlier editions of this book, I stated that measurement of the antinuclear antibody (ANA) levels in pleural fluid appeared to be the best test for establishing the diagnosis of lupus pleuritis. Two subsequent studies (305,306) have cast doubt on this statement. Khare et al. (305) measured pleural fluid ANA levels using the Hep-2 cell line on 82 pleural fluids including 8 with SLE. Six of the eight patients (75%) with SLE had high (>1:320) titers of ANA in their pleural fluid with a homogeneous staining pattern. In none did the pleural fluid ANA titer differ by more than one dilution from the serum titer. The other two patients with SLE had alternative explanations for their pleural effusions. However, 8 of the remaining 74 patients (10.8%) had positive pleural fluid ANA titer (>1:40) and 2 had a homogeneous pattern. In the patients with SLE, pleural fluid analysis of anti-ssDNA, anti-dsDNA, anti-Sm, anti-SSA, and anti-SSB antibodies reflected the findings in the serum (305).

A more recent study evaluated the ANA titers in 126 pleural fluids using the HEP-2 cell line as substrate (306). Again all of the pleural fluids from the patients with SLE had a high ANA titer (>1:160), but in this study, the pattern could be either homogeneous or speckled (306). Moreover, pleural fluid ANA titers were greater than 1:160 in 13 other patients, 11 of whom had malignant pleural effusions. The pleural fluid and the serum ANA titers were closely correlated in all patients. The explanation for the discrepancy between these two recent studies and two older studies (130,307), which suggested that the pleural fluid ANA levels were very useful, is not known but it may be related to the cell line used for the assays.

Nevertheless, the two more recent studies suggest that measurement of the pleural fluid ANA titer adds

essentially nothing to measuring the serum ANA titer in the differential diagnosis of pleural effusions.

Lupus Erythematosus Cells

In the past, the demonstration of LE cells in a pleural effusion was thought to be diagnostic of lupus pleuritis (130). LE cells are formed when polymorphonuclear leukocytes ingest extracellular nuclear material to form a polymorphonuclear leukocyte with a large inclusion of nuclear material. Most pleural effusions secondary to SLE contain LE cells (307). Wang et al. (308) reported that LE cells were present in the pleural fluid in 8 of 10 patients (80%) with SLE and polyserositis but in none of 112 pleural fluids with other etiologies (308). Noteworthy was the observation that the LE cell test results were identical in the serum and the pleural fluid. This suggests that the diagnosis of SLE can be established by an LE test on the serum, but an LE test on the pleural fluid adds nothing diagnostically. Moreover, with the development of better immunologic tests for SLE, LE preparations are being performed less and less frequently and laboratories therefore become less proficient in performing this test. Testing for LE cells is not recommended unless the laboratory is proficient in this test. It should also be noted that false-positive LE cell results have been reported (309).

Rheumatoid Arthritis Cells

The cytologic picture with rheumatoid pleuritis can help establish the diagnosis of rheumatoid pleuritis. Nosanchuk and Naylor (310) initially described a unique cytologic picture characterized by large elongated cells, giant round or oval nucleated cells, and a background of amorphous granular material. These elongated cells are sometime called *comet tadpole* or *comet-shaped cells* (Fig. 7.6). This cytologic picture is thought to be highly specific and pathognomonic of rheumatoid pleuritis (311).

Complement Levels

Most patients with pleural effusions secondary to either SLE or RA have reduced pleural fluid complement (Fig. 7.6), irrespective of whether whole complement (CH50) (312,313), C3 (129), or C4 (129,312) is measured. The measurement of pleural fluid complement does not absolutely separate patients with SLE or RA from patients with other exudative pleural effusions, as shown in Figure 7.7,

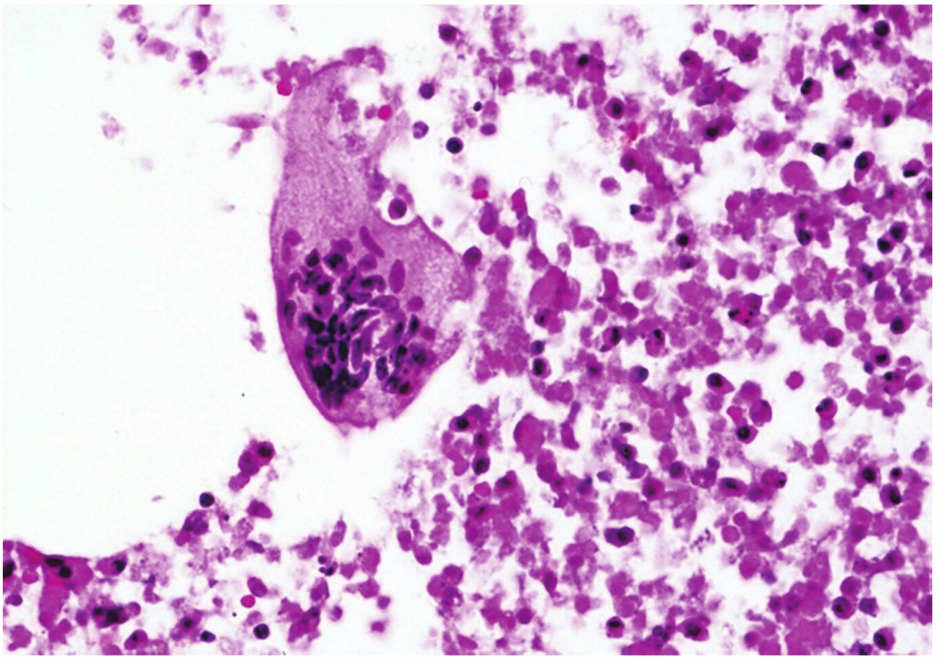

FIGURE 7.6 ■ Multinucleated tear drop–shaped cell from a patient with rheumatoid pleuritis, which is thought to be pathognomonic of this disease.

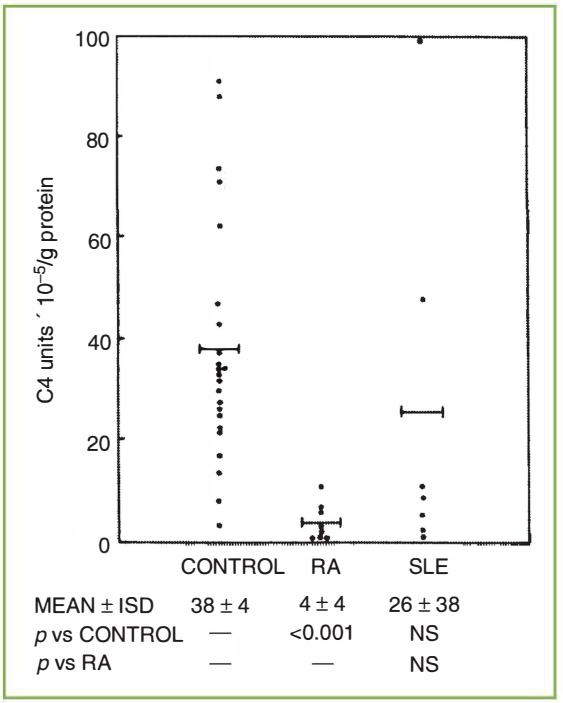

FIGURE 7.7 ■ Levels of hemolytic C4 adjusted for total protein in control, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) pleural fluids. Note that the pleural fluid from the patients with RA and SLE has lower levels of hemolytic C4. NS, not significant. *(From Halla JT, Schrohenloher RE, Volanakis JE. Immune complexes and other laboratory features of pleural effusions.* Ann Intern Med. *1980;92:748–752, with permission.)*

regardless of whether CH50, C3, or C4 is measured. Nevertheless, a CH50 level below 10 U/mL (312) or a C4 level below 10 times 10^{-5} U/g protein (129) is seen with most patients with either RA or SLE and rarely with other diseases. Because the serum ANA levels and the RF titers appear to be more specific and more sensitive at identifying individuals with pleural effusions due to RA or SLE, measurement of pleural fluid complement levels is not routinely recommended.

There have been several articles that have evaluated the diagnostic utility of complement activation products in pleural fluid. Two studies have demonstrated that the pleural fluid levels of SC5b-9, which is a product of C3 activation, are elevated in tuberculous pleural fluid as opposed to malignant pleural effusions or transudates (314,315) and that the SC5b-9 levels are highest in patients with rheumatoid disease (315). Another study (316) demonstrated that the SC5b-9 levels tended to be higher in complicated than uncomplicated parapneumonic effusions. However, the overlap between the various groups limits the diagnostic usefulness of this test.

Immune Complexes

Patients with pleural effusions secondary to RA or SLE also have higher pleural fluid levels of immune complexes than patients with effusions due to other causes (129,317,318). The differentiation of pleural effusions secondary to SLE and RA from other exudative pleural effusions is less distinct when pleural fluid immune complex levels are used than when pleural fluid complement is used because a substantial percentage of other exudative pleural effusions have elevated pleural fluid immune complex levels (129,317). The presence of pleural fluid immune complexes also depends on the assay system (129). Patients with SLE have higher levels of immune complexes when the assay is performed with the Clq component of complement or the Raji cell assay than with monoclonal RF. With RA, the level of immune complexes in the pleural fluid is higher than that in the simultaneously obtained serum, whereas in other disease states, the serum level of immune complexes is higher (129). Because measurement of the immune complex level appears to add no information to that obtained from measuring complement levels, it is recommended that pleural fluid immune complex determinations be performed only in research situations.

LIPID STUDIES

Pleural fluid is occasionally milky or opalescent. This opalescence is sometimes mistakenly attributed to myriad WBCs in the pleural fluid, and the patient is treated for an empyema. This mistake is not made if the supernatant of the centrifuged pleural fluid is examined. In empyema, the supernatant is clear, whereas in a chylous or chyliform effusion, the supernatant remains cloudy or milky. Some pleural fluids with high lipid content also contain numerous RBCs, and their color is accordingly red or brown. The supernatants of all pleural fluids should be examined for turbidity. Lipid studies of the pleural fluid should be ordered whenever the supernatant is turbid.

The persistent cloudiness of these pleural fluids after centrifugation is due to their high lipid content, which can result from one of three mechanisms. First, the lymphatic duct may be disrupted so that chyle accumulates in the pleural space. The patient is then said to have a chylothorax, and the pleural effusion is

called a *chylous pleural effusion.* Second, large amounts of cholesterol or lecithin–globulin complexes can accumulate for unknown reasons in the pleural fluid. The patient is then said to have a pseudochylothorax and a chyliform pleural effusion. Although some authors have separated pseudochylothoraces into chyliform pleural effusions characterized by high lecithin–globulin levels and pseudochylous effusions characterized by the presence of cholesterol crystals (319,320) I see no advantage in making this differentiation. Third, if the patient is receiving parenteral nutrition through a central line and the superior vena cava is perforated, the fat emulsion can collect in the pleural space. It is important to distinguish these three entities because the treatment is different for each one.

When milky pleural fluid is discovered, the first question that should be asked is whether the patient is receiving parenteral nutrition through a central line. If the superior vena cava is perforated in such a setting, the intravenous infusion fluid may accumulate rapidly in the pleural space (321). If the patient is receiving a lipid emulsion, the pleural fluid triglyceride level can be very high. However, the pleural fluid glucose and the potassium levels are usually exceedingly high if the fat emulsion is entering the pleural space (321).

The diagnosis of chylothorax is best made by measuring the triglyceride levels in the pleural fluid. If the pleural fluid triglyceride level exceeds 110 mg/dL, the patient probably has a chylothorax; if the triglyceride level is below 50 mg/dL, the patient does not have a chylothorax (Fig. 7.8). If the triglyceride level is between 50 and 110 mg/dL, the patient may or may not have a chylothorax (322). When the diagnosis is uncertain, lipoprotein analysis of the fluid should be ordered. The demonstration of chylomicrons in the pleural fluid with lipoprotein analysis is diagnostic of chylothorax (322,323). Most patients with chylothoraces and pleural fluid triglyceride levels below 110 mg/dL are malnourished. Except for diagnosing chylothorax, pleural fluid triglyceride levels have no role in the diagnosis of pleural effusions (324).

Romero et al. (325) have suggested that the diagnosis of chylothorax should also require a pleural fluid-to-serum cholesterol ratio lower than 1 and a pleural fluid-to-serum triglyceride ratio less than 1. The first requirement is reasonable because patients

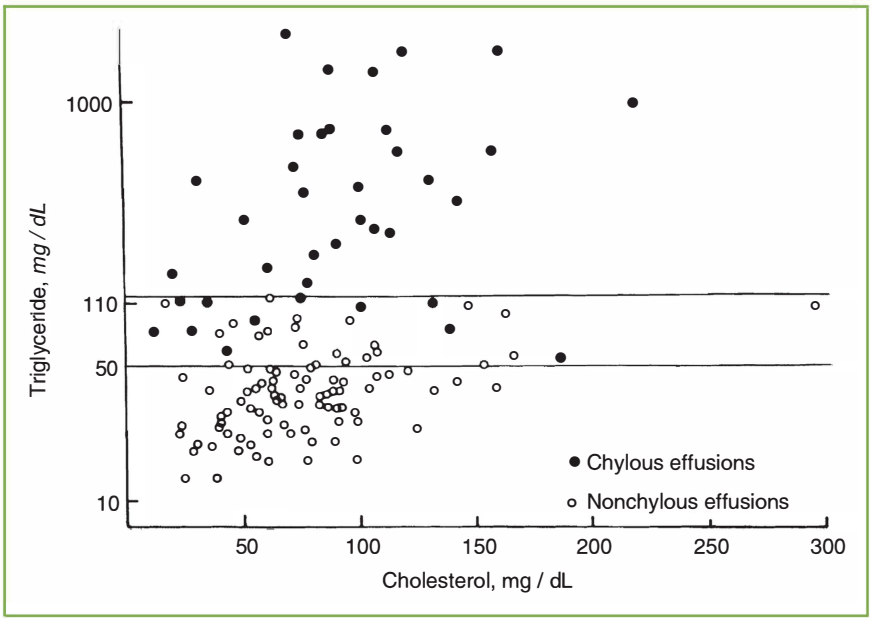

FIGURE 7.8 ■ Scattergram of cholesterol and triglyceride values in pleural fluid. Solid dots represent patients whose effusions contained chylomicrons and were considered chylous. Open circles represent patients without chylomicrons whose effusions were considered nonchylous. All patients with triglyceride levels above 110 mg/dL had chylous effusions, whereas no patient with triglyceride levels below 50 mg/dL had a chylous effusion. *(From Staats BA, Ellefson RD, Budahn LL, et al. The lipoprotein profile of chylous and nonchylous pleural effusions.* Mayo Clin Proc. *1980;55:700–704, with permission.)*

with chyliform pleural effusions often have pleural fluid cholesterol levels above 250 mg/dL (326) and this requirement should eliminate them. It should be noted that the clinical picture with chyliform effusion of a long-standing pleural effusion with thickened pleura should be easy to differentiate from that of an acute pleural effusion with normal pleural surfaces seen with chylous effusion. If any doubt exists, lipoprotein analysis of the pleural fluid should be performed. The second criteria proposed by Romero et al. (325) is probably not necessary because in patients without chylothorax, there is no relationship between the serum and the pleural fluid triglyceride level, and the mean pleural fluid triglyceride level is only approximately 25% of the serum level (32).

Other studies useful for diagnosing turbid pleural fluids are the total lipid content, the cholesterol content, and microscopic examination of the sediment. Most pleural effusions that are cloudy secondary to high lipid levels have a total fat content greater than 400 mg/dL (327). The cholesterol levels in the pleural fluid are elevated in high-lipid pleural effusions because of high numbers of cholesterol crystals or lecithin–globulin complexes (320), but cholesterol levels may also be elevated in chylous pleural effusions (322), as demonstrated in Figure 7.8. When the turbidity is due to high numbers of cholesterol crystals, examination of the pleural fluid sediment reveals the cholesterol crystals, which are large, rhombic, or polyhedric, as illustrated in Figure 26.1.

MICROBIOLOGIC STUDIES ON PLEURAL FLUID

Cultures

Pleural fluid from patients with undiagnosed exudative pleural effusions should be cultured for bacteria (both aerobically and anaerobically), mycobacteria, and fungi. For aerobic and anaerobic bacterial cultures, the pleural fluid should be inoculated directly into blood culture media at the bedside because the number of positive cultures will increase with this method (328,329). In one study (329) of 62 patients with suspected pleural infection, the addition of the blood culture bottle culture to the standard culture increased the proportion of patients with identifiable pathogens from 37.7% to 58.5%. If the fluid is not inoculated at the bedside, it should be sent to the laboratory in an anaerobic transport container at room temperature (330). A Gram's stain of the fluid should also be obtained.

For mycobacterial cultures, use of a BACTEC system with bedside inoculation provides higher yields and faster results than do conventional methods. In one study, the median time for the BACTEC cultures to become positive was 18 days (range 3–40 days), whereas the median time for conventional cultures was 33.5 days (range 21–48 days) (331). Routine smears for mycobacteria are not indicated because they are almost always negative, unless the patient has a tuberculous empyema or unless the patient is HIV positive.

It has been suggested that microbiologic testing of pleural fluid should be ordered more selectively (332). The basis for this recommendation was the observation at the Mayo Clinic that only 15 of 476 patients (3%) had positive cultures (332). The results of the study by Ferrer et al. (333) tend to go against this conclusion. They reviewed the results of 245 pleural fluid specimens inoculated into blood culture vials and found that 15% of the specimens were positive and 60% of the positive specimens occurred in fluid that was nonpurulent (333). Certainly, it is not cost effective to obtain cultures from transudative pleural fluids, but I believe cultures should be obtained from most patients with exudative effusions of unknown etiology.

Culturing pleural fluid from chest tube drainage should be discouraged. Cultures from chest tubes yield inaccurate culture results when compared with direct aspirates (330).

Nucleic Acid Amplification (NAA)

It has been shown that using NAA to amplify and sequence the bacterial ribosomal RNA gene, that the bacteria responsible for a complicated parapneumonic effusion can frequently be identified (334). Maskell et al. (334) performed this procedure on 404 pleural fluid specimens obtained during the First Multicenter Intrapleural Sepsis Trial (335). They reported that the NAA technique identified bacteria in 70 samples which were negative on culture (335). The standard cultures and the nuclear amplification technique were complimentary in identifying different organisms when they were both positive (334).

Countercurrent Immunoelectrophoresis

The goal of countercurrent immunoelectrophoresis (CIE) is to identify bacterial antigens in pleural fluid, and to thereby establish a presumptive bacteriologic diagnosis in patients with parapneumonic pleural effusions. CIE depends on the interaction of an antigen with a negative charge and a specific antibody with a positive charge in an electrical field to form a

distinct precipitin line (336,337). The advantage of CIE over bacterial cultures is that results are available within hours rather than days, so that appropriate antibiotics can be administered sooner. CIE is most useful in the diagnosis of pleural effusions in children, in whom most pleural effusions are due to bacterial infections with *Streptococcus pneumoniae, S. aureus,* or *Hemophilus influenza.* These are the three bacteria for which antigens are available to perform CIE studies. In a series of 87 pediatric patients with pleural effusions (336), pleural fluid cultures were positive for one of these three bacteria in 34 patients, and CIE correctly identified the offending organisms in 33 (97%). In approximately 25% of those patients, the Gram's stain of the pleural fluid was negative. In an additional 23 patients, CIE identified antigens in the pleural fluid when the pleural fluid cultures were negative (336).

Another advantage of CIE is that it remains positive for several days after antibiotic therapy is initiated (332,333). To my knowledge, examination of pleural fluid with CIE has not been performed on a large series of adult patients with pleural effusion. The disadvantage of CIE in the adult patient with a complicated parapneumonic effusion is that many such effusions are due to anaerobic bacteria (117), and antigens for all the anaerobic organisms are not yet available for routine use. Certainly, if CIE is readily available, it should be performed on the pleural fluid from patients with an acute febrile illness and pleural effusion.

Direct Gas–Liquid Chromatography

Most anaerobic bacteria produce volatile fatty acids. Demonstration of such fatty acids by direct gas–liquid chromatography of the pleural fluid has been proposed as a means to establish the diagnosis of anaerobic pleural infections. In one report, pleural fluid from 52 patients, including 14 with anaerobic infections, were analyzed with direct gas–liquid chromatography (338). Multiple volatile fatty acids or succinic acid was present in 13 of the 14 (93%) fluids from patients with anaerobic infections. Succinic acid was the major product in 10 patients, and 9 of them had infections due to *Bacteroides*. In contrast, pleural fluid from other patients did not contain multiple volatile fatty acids or succinic acid (338). Direct gas–liquid chromatography is a difficult and expensive procedure, however, and it requires specially trained technicians. The resources required for gas–liquid chromatography are probably better spent in upgrading anaerobic culture techniques.

Fibrinogen and Fibrin Degradation Products

The fibrinogen levels in pleural fluid are low in comparison to those in plasma (339,340). The levels of fibrinogen tend to be low in patients with CHF and malignancy, and high in patients with tuberculosis and empyema but there is much overlap. The level of D-dimer is comparable in all pleural effusions (340).

MISCELLANEOUS TESTS ON PLEURAL FLUID

Other Proteins

Numerous studies have evaluated the diagnostic usefulness of measuring other proteins in the pleural fluid, including, ferritin (341), mucoproteins (112), fibronectin (342), acid glycosaminoglycans (mucopolysaccharides) (343), β_2-microglobulins (344), and α-fetoprotein (344). The pleural fluid levels of these proteins are not useful in the differential diagnosis of exudative pleural effusions.

Other Enzyme Determinations

Many other enzymes, including aldolase (345), glutamic oxaloacetic transaminase, glutamic pyruvic transaminase (345), phosphohexose isomerase (345), malic dehydrogenase (345), isocitric dehydrogenase (345), glutathione reductase (345), alkaline phosphatase (346), angiotensin-converting enzyme (347), and transketolase, have been measured in the pleural fluid and have been found to give no useful diagnostic information. One report suggested that elevation of the acid phosphatase level in the pleural fluid was diagnostic of metastatic prostatic carcinoma (348), but a second report indicated that approximately 10% of all pleural effusions have acid phosphatase levels above the upper normal limit for serum and higher than those in the corresponding serum (349).

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chapter 8

Approach to the Patient

Whenever a patient with an abnormal chest radiograph is evaluated, the possibility of a pleural effusion should be considered. Increased densities on the chest radiograph are frequently attributed to parenchymal infiltrates when they actually represent pleural fluid. Most patients with pleural effusions have blunting of the posterior costophrenic sulcus on the lateral chest radiograph. If this angle is blunted, the patient should be evaluated with ultrasound, CT scan, or bilateral decubitus chest radiographs to ascertain whether free pleural fluid is present (see Chapter 6). This chapter provides a guide to the approach to a patient with an undiagnosed pleural effusion. The British Thoracic Society has recently published guidelines for the investigation of a unilateral pleural effusion in adults (1). The management of patients with pleural effusions due to specific diseases is discussed in the chapters dealing with those diseases.

FREQUENCIES OF VARIOUS DIAGNOSES

Pleural effusions can occur as complications of many different diseases (Table 8.1). The vigor with which various diagnoses are pursued depends on the likelihood that the individual has that particular disease. Table 8.2 shows the approximate annual incidence for the most common causes of pleural effusions. An epidemiologic study from the Czech Republic found that the four leading causes of pleural effusions in order of incidence were congestive heart failure, malignancy, pneumonia, and pulmonary embolism (2). Congestive heart failure and cirrhosis cause almost all transudative pleural effusions, whereas malignant disease, pneumonia, and pulmonary embolization are the three main causes of exudative pleural effusions. Two other frequent causes of exudative pleural effusions are viral infections and the effusion that occurs after coronary artery bypass graft (CABG) surgery.

SEPARATION OF EXUDATES FROM TRANSUDATES

If free pleural fluid is demonstrated on the decubitus film, with ultrasound or with a CT scan, one should consider performing a diagnostic thoracentesis (Fig. 8.1). It has been my experience that diagnostic thoracentesis is difficult if the thickness of the fluid on the decubitus radiograph, ultrasound, or the CT scan is less than 10 mm. If the thickness of the fluid is greater than 10 mm, however, consideration should be given to performing a diagnostic thoracentesis (see Chapter 28). If the patient has obvious congestive heart failure, I perform a diagnostic thoracentesis if any of the following three conditions are met: (a) the effusions are not bilateral and comparably sized, (b) the patient has pleuritic chest pain, or (c) the patient is febrile. Otherwise, treatment of the congestive heart failure is initiated. If the pleural effusions do not rapidly disappear, I then perform a diagnostic thoracentesis several days later. It must be remembered, however, that the characteristics of the pleural fluid may change from those of a transudate to those of an exudate with diuresis. Romero et al. (3) performed a thoracentesis on 15 patients with congestive heart failure before and every 48 hours after diuretic therapy was initiated. Before diuretics were administered, only one effusion was misclassified as an exudate by Light's criteria, but at the time of the third thoracentesis 10 effusions were misclassified as exudates. Between the first and the third thoracentesis, the mean protein level increased from 2.3 to 3.5 g/dL and the mean lactate dehydrogenase (LDH) level increased from 176 to 262 IU/L (3).

TABLE 8.1 ■ Differential Diagnosis of Pleural Effusion

I. Transudative pleural effusions
- A. Congestive heart failure
- B. Cirrhosis
- C. Nephrotic syndrome
- D. Superior vena caval obstruction
- E. Urinothorax
- F. Peritoneal dialysis
- G. Glomerulonephritis
- H. Myxedema
- I. Cerebrospinal fluid leaks to pleura
- J. Hypoalbuminemia
- K. Sarcoidosis

II. Exudative pleural effusions
- A. Neoplastic diseases
  1. Metastatic disease
  2. Mesothelioma
  3. Body cavity lymphoma
  4. Pyothorax-associated lymphoma
- B. Infectious diseases
  1. Bacterial infections
  2. Tuberculosis
  3. Fungal infections
  4. Parasitic infections
  5. Viral infections
- C. Pulmonary embolization
- D. Gastrointestinal disease
  1. Pancreatic disease
  2. Subphrenic abscess
  3. Intrahepatic abscess
  4. Intrasplenic abscess
  5. Esophageal perforation
  6. Postabdominal surgery
  7. Diaphragmatic hernia
  8. Endoscopic variceal sclerosis
  9. Postliver transplant
- E. Heart diseases
  1. Postcoronary artery bypass graft surgery
  2. Postcardiac injury (Dressler's) syndrome
  3. Pericardial disease
  4. Post-Fontan procedure
  5. Pulmonary vein stenosis postcatheter ablation of atrial fibrillation
- F. Obstetric and gynecologic disease
  1. Ovarian hyperstimulation syndrome
  2. Fetal pleural effusion
  3. Postpartum pleural effusion
  4. Meigs' syndrome
  5. Endometriosis
- G. Collagen vascular diseases
  1. Rheumatoid pleuritis
  2. Systemic lupus erythematosus
  3. Drug-induced lupus
  4. Sjögren's syndrome
  5. Familial Mediterranean fever
  6. Churg-Strauss syndrome
  7. Wegener's granulomatosis
- H. Drug-induced pleural disease
  1. Nitrofurantoin
  2. Dantrolene
  3. Methysergide
  4. Ergot drugs
  5. Dasatinib
  6. Amiodarone
  7. Interleukin 2
  8. Procarbazine
  9. Methotrexate
  10. Clozapine
- I. Miscellaneous diseases and conditions
  1. Asbestos exposure
  2 Postlung transplant
  3. Postbone marrow transplant
  4. Yellow nail syndrome
  5. Sarcoidosis
  6. Uremia
  7. Trapped lung
  8. Therapeutic radiation exposure
  9. Drowning
  10. Amyloidosis
  11. Milk of calcium pleural effusion
  12. Electrical burns
  13. Extramedullary hematopoiesis
  14. Rupture of mediastinal cyst
  15. Acute respiratory distress syndrome
  16. Whipple's disease
  17. Iatrogenic pleural effusions
- J. Hemothorax
- K. Chylothorax

One of the main purposes of the diagnostic thoracentesis is to determine whether the patient has a transudative or an exudative pleural effusion. This distinction is made by analysis of the levels of protein and LDH in the pleural fluid and in the serum (4). If none of the criteria in Figure 8.1 is met, the patient has a transudative pleural effusion. Therefore, the pleural surfaces can be ignored while the congestive heart failure, cirrhosis, or nephrosis, for example, is treated. Alternately, if any of the three criteria in Figure 8.1 is met, the patient probably has an exudative pleural effusion. The exudative nature indicates that the pleural effusion resulted from local disease where the fluid originated, and further investigation should

TABLE 8.2 ■ Approximate Annual Incidence of Various Types of Pleural Effusions in the United States

Congestive heart failure	500,000
Parapneumonic effusion	300,000
Malignant pleural effusion	200,000
Lung	60,000
Breast	50,000
Lymphoma	40,000
Other	50,000
Pulmonary embolization	150,000
Viral disease	100,000
Cirrhosis with ascites	50,000
Postcoronary artery bypass graft surgery	50,000
Gastrointestinal disease	25,000
Tuberculosis	2,500
Mesothelioma	2,300
Asbestos exposure	2,000

be directed toward the genesis of the local disease (5). It should be remembered, however, that 15% to 20% of patients with congestive heart failure or cirrhosis will meet Light's criteria for exudative effusions. This is particularly likely if the patient has been receiving diuretics before the thoracentesis (6). If a patient has congestive heart failure or cirrhosis but the pleural fluid meets exudative criteria, the difference between the serum protein and pleural fluid protein (the pleural fluid protein gradient) should be measured. If this difference exceeds 3.1 g/dL, the patient should be classified as having a transudative pleural effusion and no further diagnostic tests are indicated (3). Alternatively, if the pleural fluid or serum NT-pro-BNP is greater than 1,300 pg/ml, the patient most likely has congestive heart failure (7).

If there is a significant likelihood that the patient has a transudative pleural effusion, the most cost-effective utilization of the laboratory is to only obtain the protein and LDH levels of the pleural fluid at the initial diagnostic thoracentesis. Pleural fluid can be set aside for other tests if the fluid proves to be an exudate. Peterman and Speicher (8) reviewed the charts of 83 patients whose pleural fluid was a transudate by protein and LDH levels during a 1-year period. They found that 725 additional studies were performed on these 83 pleural fluids. Only 9 of the 725 studies yielded a positive result, and the positive result was eventually proved to be false in seven of the nine instances. If no tests other than the protein and LDH had been obtained in these 83 patients, there would have been a mean cost savings of US$185 per patient.

DIFFERENTIATING AMONG VARIOUS EXUDATIVE PLEURAL EFFUSIONS

To differentiate among the various causes of exudative pleural effusions, one should initially examine the gross appearance of the fluid, obtain a pleural fluid differential cell count and cytologic examination, measure the levels of glucose and LDH in the pleural fluid, and obtain a test for a pleural fluid marker for tuberculosis. Other tests can then be ordered on an individual basis.

Appearance of Pleural Fluid

The gross appearance of the pleural fluid should always be noted and evaluated as outlined in Figure 8.2. If the pleural fluid appears bloody, a hematocrit should be obtained on the fluid. The hematocrit is frequently much lower than would be expected from the appearance of the pleural fluid. The blood in the pleural fluid is not significant if the pleural fluid hematocrit is less than 1% (9). If the pleural fluid hematocrit is greater than 1%, the patient most likely has malignant pleural disease, a pulmonary embolus, or a traumatically induced pleural effusion (9). If the hematocrit is greater than 50% of that of the peripheral blood, the patient has a hemothorax, and one should consider performing a tube thoracostomy (see Chapter 25).

Many laboratories are hesitant to perform hematocrits on pleural fluid and rather report a red blood cell (RBC) count. These RBC counts are often inaccurate because the counts are not done with an automated counter and laboratory personnel are not always adept at determining RBC counts in body fluids that are bloody. Nevertheless, if the RBC count is obtained and is accurate, one can get a good estimation of the hematocrit in the pleural fluid by dividing the RBC count by 100,000. For example, a RBC count of 1,000,000 correlates with a hematocrit of 10.

If the pleural fluid is turbid or milky or if it is bloody, the supernatant of the pleural fluid should be examined to see whether it is cloudy. If the pleural fluid was turbid when originally withdrawn, but the turbidity clears with centrifugation, it was due to cells or debris in the pleural fluid. Most patients who have very turbid pleural fluid that clears with centrifugation have a pleural infection. If the turbidity persists after centrifugation, the patient probably has a chylothorax or a pseudochylothorax (see Chapter 26). These two entities can be differentiated by the patient's history, examination of the sediment for cholesterol crystals, and lipid analysis of the supernatant (Fig. 8.2). Pseudochylothoraces

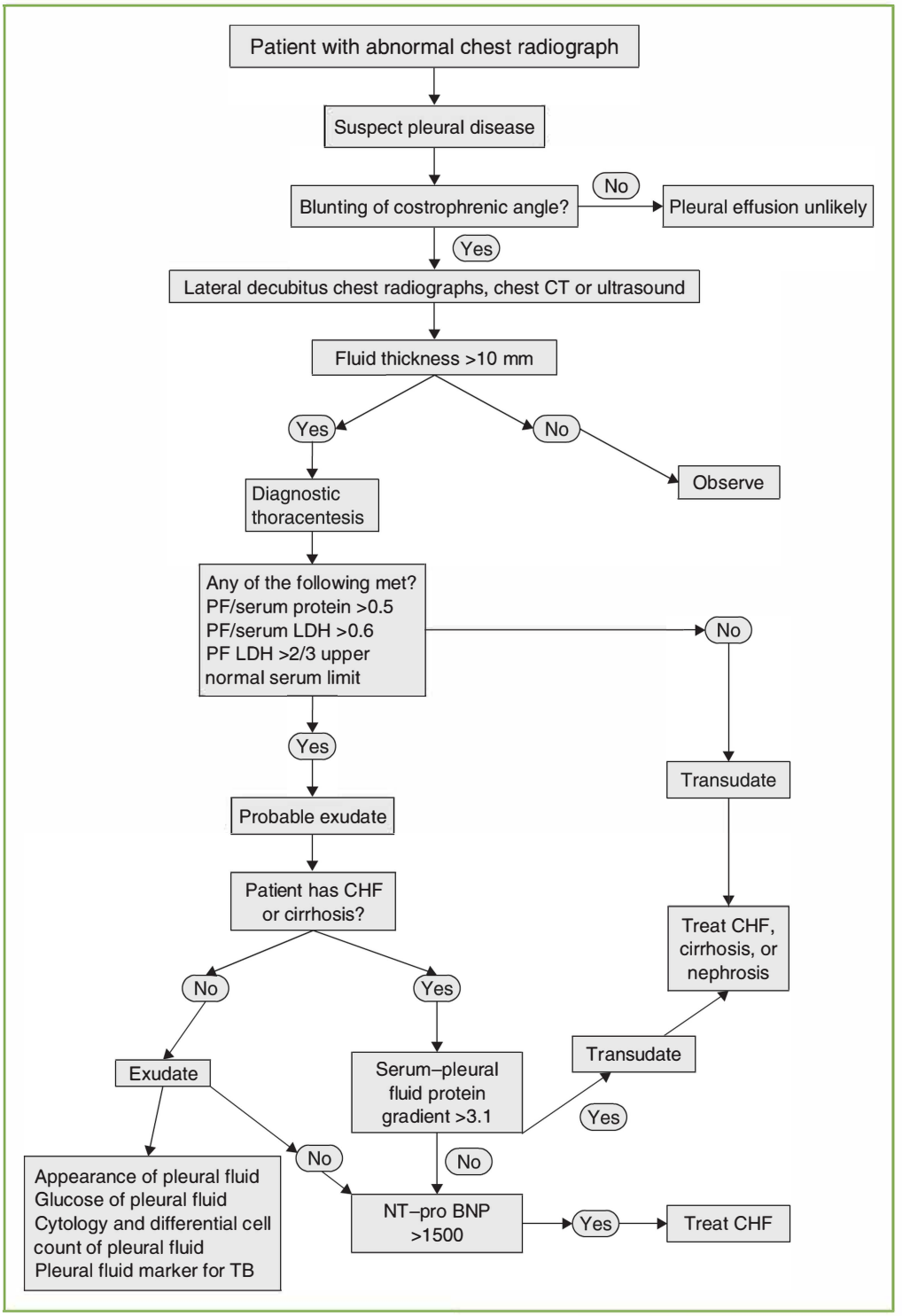

FIGURE 8.1 ■ Algorithm for distinguishing transudative from exudative pleural effusions. CT, computed tomograph; LDH, lactate dehydrogenase; CHF, congestive heart failure.

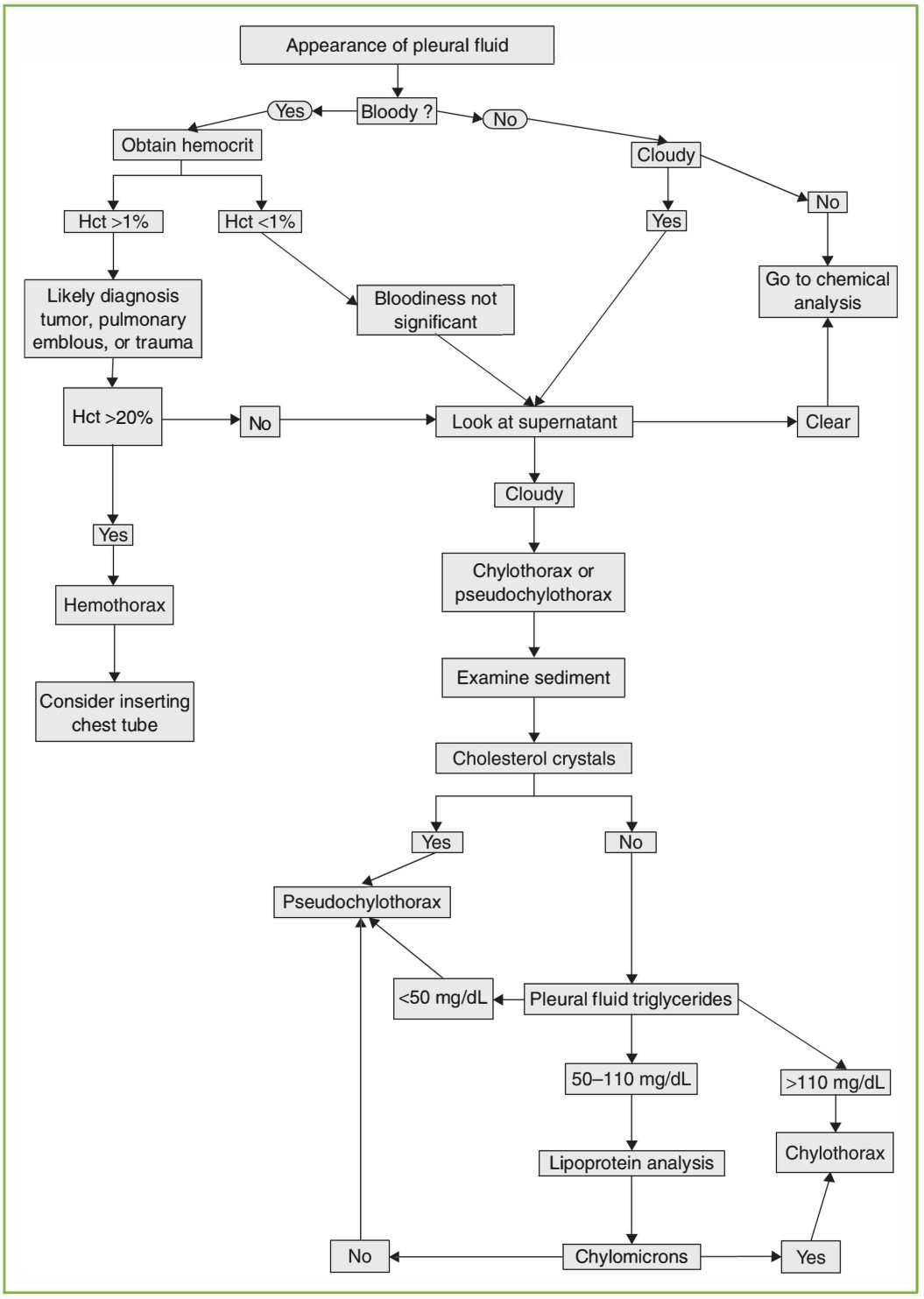

FIGURE 8.2 ■ Algorithm for evalating the appearance of pleural fluid. Hct, hematocrit.

usually occur when the pleural effusion has been present for many years. Cholesterol crystals may be found in the sediment, and high levels of triglycerides are not usually present in the pleural fluid. In contrast, chylothoraces are more acute, do not contain cholesterol crystals, and are characterized by high levels of triglycerides. The management of a patient with a chylothorax or a pseudochylothorax is discussed in Chapter 26.

Routine Measurements on Exudative Pleural Fluids

When a patient has an undiagnosed exudative effusion, there are several tests that should be routinely obtained, namely, a pleural fluid cell count and differential, a pleural fluid glucose and LDH level, examination of the pleural fluid for malignant cells, and a pleural fluid marker for tuberculosis (10). A good starting point for the diagnostic assessment of an unknown exudate is the pleural fluid cytology. An algorithm starting with the pleural cytology is presented in Figure 8.3.

In previous editions of this book, I recommended that a pleural fluid amylase also be obtained. However, the pleural fluid amylase only helps occasionally in making a diagnosis and, therefore, it should not be obtained on a routine basis (11). It should be obtained if acute pancreatitis, esophageal rupture, or chronic pancreatic pleural effusion is suspected (11).

Pleural Fluid Differential Cell Count

In patients with exudative pleural effusions, the cell count and the differential provide clues about the etiology of the pleural effusion. When neutrophils predominate in the pleural fluid, an acute process is affecting the pleural surfaces, and the chest radiograph should be evaluated for parenchymal infiltrates. The presence of an infiltrate indicates that the patient probably has a parapneumonic effusion although pulmonary embolus and bronchogenic carcinoma should also be considered. The diagnosis of a parapneumonic effusion is likely if purulent sputum is present. When purulent sputum or peripheral leukocytosis is not seen, the patient should undergo a CT angiogram scan to rule out pulmonary embolus. In the event of a negative scan result, a bronchoscopy with transbronchial biopsy should be performed to determine the cause of the parenchymal infiltrate. If after all these studies the diagnosis is still not clear, video-assisted thoracoscopy (see Chapter 30) should be performed if the infiltrate is worsening or the effusion is increasing in size.

The patient with an exudative pleural effusion with predominantly polymorphonuclear leukocytes and without parenchymal infiltrates most likely has pulmonary embolus, viral infection, gastrointestinal disease, asbestos pleural effusion, malignant pleural disease, or acute tuberculous pleuritis. Accordingly, the patient should undergo a CT angiogram scan or a lung scan for evaluation of pulmonary embolus. A gastrointestinal etiology of the pleural effusion can be evaluated with an abdominal CT scan or ultrasound. A careful history should be taken for asbestos exposure. The marker for tuberculosis (adenosine deaminase [ADA] or interferon-gamma) will indicate whether the patient has tuberculosis, and the cytology will provide the first evaluation for pleural malignancy.

The patient with an exudative pleural effusion with predominantly mononuclear cells in the pleural fluid has a chronic process involving the pleural space. Malignant disease, pulmonary embolization, pleural effusions following CABG, and tuberculosis are the four most common causes of this picture. Again, the cytology on the pleural fluid is the first step in evaluating the possibility of malignancy. The history will reveal whether the patient underwent CABG surgery the previous year. An elevated level of ADA or interferon-gamma in the pleural fluid essentially establishes the diagnosis of tuberculous pleuritis (see Chapter 13). If none of the tests mentioned in the preceding text is positive, the possibility of pulmonary embolus should be assessed with a CT angiogram or a lung scan.

Pleural Fluid Glucose

The routine measurement of the pleural fluid glucose level is recommended because the presence of a reduced (<60 mg/dL) pleural fluid glucose reduces the spectrum of diagnostic possibilities. Most patients with a reduced pleural fluid glucose level (<60 mg/dL) have one of four conditions: parapneumonic effusion, malignant pleural effusion, tuberculous pleuritis, or rheumatoid pleural effusion (12). Other rare causes of a low glucose pleural effusion include paragonimiasis, hemothorax, Churg-Strauss syndrome, urinothorax, and occasionally lupus pleuritis. Most patients with a reduced pleural fluid glucose level also have a reduced pleural fluid pH and an increased pleural fluid LDH level. Laboratory errors in the performance of one of these three tests should be suspected when these relationships are not maintained.

Patients with either parapneumonic effusions or tuberculous pleuritis may have an acute illness

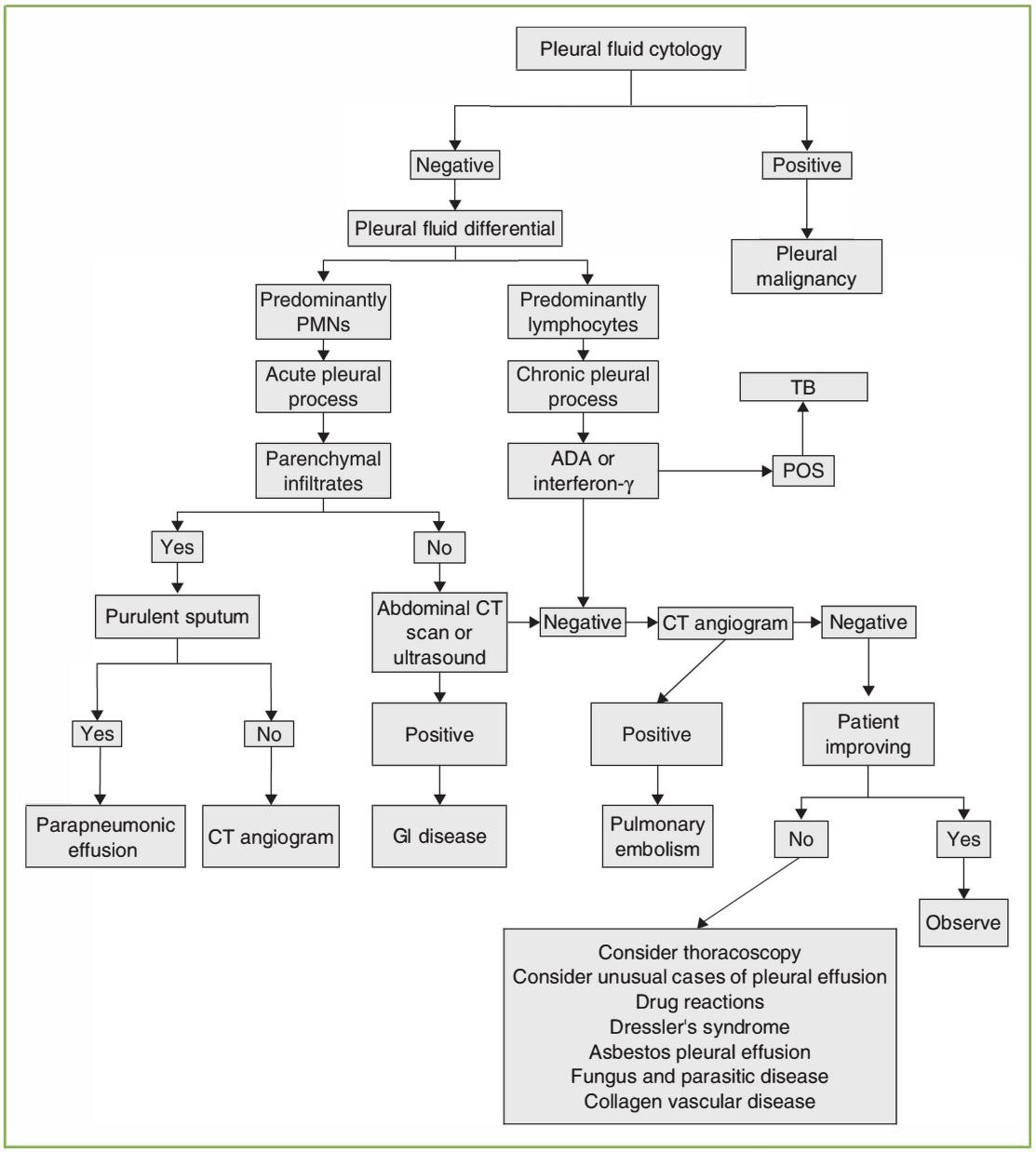

FIGURE 8.3 ■ Algorithm for evaluating exudates with an unknown etiology. PMN, polymorphonuclear neutrophil; TB, tuberculosis; ADA, adenosine deaminase; CT, computed tomography; GI, gastrointestinal; POS, positive.

characterized by fever, cough, and pleuritic chest pain and a low pleural fluid glucose level. Patients with parapneumonic effusions usually have radiologically evident parenchymal infiltrates, whereas most of those with tuberculous pleuritis have no infiltrates. The differential cell count on the pleural fluid is also useful in making the differentiation because most patients with parapneumonic effusions have predominantly neutrophils in their pleural fluid, whereas most patients with tuberculous pleuritis have predominantly lymphocytes.

Patients with subacute or chronic symptoms and a low pleural fluid glucose level may have malignant pleural disease, rheumatoid disease, tuberculosis, or

even a chronic bacterial infection. The diagnosis of rheumatoid pleuritis (see Chapter 21) is usually easy. The differentiation among tuberculosis, malignant disease, and chronic bacterial infection may be more difficult. The pleural fluid cytology is usually positive for malignant cells in patients with a malignant pleural effusion and a low pleural fluid glucose level. The pleural fluid marker for tuberculosis should be positive with tuberculous pleuritis, and neutrophils should predominate in the pleural fluid if a chronic bacterial infection is present.

Pleural Fluid Lactate Dehydrogenase

Although the level of LDH in the pleural fluid is not particularly useful in the differentiation of the various exudative pleural effusions, a pleural fluid LDH should be obtained every time a thoracentesis is performed on a patient with an undiagnosed pleural effusion. The pleural fluid LDH is a reliable indicator of the degree of pleural inflammation. If, with repeated thoracentesis, the pleural fluid LDH level increases, the degree of inflammation in the pleural space is becoming progressively worse and one should be aggressive in pursuing a diagnosis. Alternatively, if the pleural fluid LDH level decreases with repeated thoracentesis, the degree of inflammation in the pleural space is becoming progressively less and one need not be as aggressive in the approach to the patient.

Pleural Fluid Cytology

If a patient has malignancy, cytologic examination of the pleural fluid is a fast, efficient, and minimally invasive means by which to establish the diagnosis. The percentage of malignant pleural effusions that are diagnosed with cytology has been reported to be anywhere between 40% and 87%. There are several factors that influence the diagnostic yield with cytology. Almost all adenocarcinomas are diagnosed with cytology, but the yield is less with squamous cell carcinoma, Hodgkin's disease, and sarcomas. Obviously, the yield will also depend on the skill of the cytologist. It also depends on the extent of the tumor—the greater the tumor burden in the pleural space, the more likely the cytology is to be positive.

Pleural Fluid Markers for Tuberculosis

Over the last 50 years, the diagnosis of tuberculous pleuritis was usually established with needle biopsy of the pleura. However, it is now possible to make the diagnosis of pleural tuberculosis by measuring the level of ADA or the level of interferon-gamma in the pleural fluid.

Pleural Fluid Adenosine Deaminase Level

The diagnosis of tuberculosis is virtually established if the pleural fluid ADA level is more than 40 U/L and the patient has predominantly lymphocytes in the pleural fluid (see Chapter 7). The higher the pleural fluid ADA level, the more likely the patient is to have tuberculous pleuritis. In one study, the ADA was more than 47 U/L in 253 of 254 patients with tuberculous pleuritis (13). In a second report, only 5 of 173 patients (3%) with pleural effusions due to other etiologies, including 46 with malignancy and 30 with pneumonia, had ADA levels that exceeded 45 U/L (14). The two other disease entities that tend to have a high pleural fluid ADA level are empyema and rheumatoid pleuritis (14), and both these conditions are easily distinguished from pleural tuberculosis by the clinical picture.

Pleural Fluid Interferon-Gamma Levels

Pleural fluid interferon-gamma levels are also elevated with tuberculous pleuritis (see Chapter 7). Pleural fluid interferon-gamma levels are very efficient at differentiating tuberculous from nontuberculous pleural effusion. Using a cutoff level of 3.7 U/mL, Villena et al. (15) demonstrated that this test resulted in a sensitivity of 0.98 and a specificity of 0.98 in a series of 595 pleural effusions including 82 tuberculous effusions. These results were better than the same group reported with ADA levels (16).

OPTIONS WHEN NO DIAGNOSIS IS OBTAINED AFTER INITIAL THORACENTESIS

When no diagnosis has been obtained after an initial thoracentesis that includes a pleural fluid marker for tuberculosis and cytology, the options are as follows in the subsequent text. The first thing that we recommend is a CT angiogram. With the CT angiogram, the possibility of pulmonary embolus can be evaluated and the presence of pulmonary infiltrates, pleural masses, or mediastinal lymphadenopathy can also be evaluated (17). If the CT angiogram scan does not demonstrate a pulmonary embolus, then there are five options available to the physician, namely, observation, needle biopsy of the pleura, bronchoscopy, thoracoscopy, or thoracotomy with open biopsy.

Observation

This is probably the best option if the patient is improving and there are no parenchymal infiltrates.

Remember that no diagnosis is ever established in approximately 15% of patients with exudative pleural effusion. If the patient has malignancy, spontaneous improvement is unlikely to occur. If the patient has pulmonary embolism, the diagnosis should have been made by CT angiogram, whereas if the patient has tuberculous pleuritis, one of the pleural fluid markers for tuberculosis should have been positive.

Bronchoscopy

Bronchoscopy is useful in the diagnosis of pleural effusion only if one or more of the following four conditions are present (18): (a) A pulmonary infiltrate is present on the chest radiograph or the chest CT scan; in this situation, particular attention should be paid to the area that contains the infiltrate. (b) Hemoptysis is present; hemoptysis in the presence of a pleural effusion is suggestive of an endobronchial lesion (or pulmonary embolism). (c) The pleural effusion is massive, that is, it occupies more than three fourths of the hemithorax. (d) The mediastinum is shifted toward the side of the effusion; in this situation, an endobronchial lesion is probable. In patients with pleural effusions with positive cytology but no hemoptysis or parenchymal infiltrates, bronchoscopy will not identify the primary tumor (19).

Thoracoscopy

In the diagnosis of pleural disease, thoracoscopic procedures (see Chapter 30) should be used only when the less invasive diagnostic methods such as thoracentesis with cytology and markers for tuberculosis have not yielded a diagnosis. In one series of 620 patients with pleural effusions, only 48 (8%) remained without a diagnosis after less invasive procedures and were subjected to thoracoscopy (20). If the patient has malignancy, thoracoscopy will establish the diagnosis more than 90% of the time and the diagnosis of mesothelioma is probably best made with thoracoscopy. Thoracoscopy can also establish the diagnosis of tuberculosis (21,22). An advantage of thoracoscopy in the diagnosis of pleural disease is that pleurodesis can also be performed at the time of the procedure. It should be emphasized, however, that thoracoscopy rarely establishes the diagnosis of benign disease (23). Thoracoscopy is indicated in the patient with an undiagnosed pleural effusion who is not improving spontaneously and in whom there is a significant likelihood that malignancy or tuberculosis is responsible for the pleural effusion.

Needle Biopsy of the Pleura

The primary use of needle biopsy of the pleura over the last 50 years has been to diagnose tuberculous pleuritis. However, as outlined earlier, markers for tuberculosis obtained from the pleural fluid are very efficient in establishing this diagnosis. In recent years, with the emergence of multidrug-resistant tuberculosis, cultures for *Mycobacteria tuberculosis* have become important in guiding the therapy of tuberculosis. Some have advocated performing a needle biopsy of the pleura so that a specimen of the pleura could be cultured. However, only approximately 33% of patients with tuberculous pleuritis have a positive pleural biopsy culture and a negative pleural fluid culture (24). In addition, to my knowledge, no patient has developed disseminated multidrug-resistant tuberculosis after presenting with a pleural effusion without parenchymal infiltrates and receiving a standard course of antituberculous drugs. In view of the factors mentioned in the preceding text, pleural biopsy is usually not indicated for the diagnosis of tuberculous pleuritis.

Pleural biopsy can also establish the diagnosis of malignant pleural disease. However, in most series, cytology of the pleural fluid is much more sensitive in establishing the diagnosis. If the cytology of the fluid is negative, the pleural biopsy is usually nondiagnostic. In one series, the pleural biopsy was positive in only 20 of 118 (17%) of patients with pleural malignancy and negative cytology (25). Because thoracoscopy is diagnostic in more than 90% of patients with pleural malignancy and negative cytology, it is the preferred diagnostic procedure in the patient with a cytology-negative pleural effusion who is suspected of having malignancy. Needle biopsy of the pleura is indicated if the patient has an undiagnosed pleural effusion that is not improving and thoracoscopy is not available. It is also indicated if pleural tuberculosis is suspected and a pleural fluid marked for tuberculosis is unavailable or equivocal.

Open Pleural Biopsy

Open thoracotomy with direct biopsy of the pleura has been supplanted by thoracoscopy in most institutions. The main indication for open pleural biopsy (or for thoracoscopy) is progressive undiagnosed pleural disease. If both procedures are available, thoracoscopy is usually preferred because it is associated with less morbidity.

It should be emphasized that open pleural biopsy does not always provide a diagnosis in a patient with an undiagnosed pleural effusion. Douglass et al. (26)

reported that thoracotomy failed to provide a specific diagnosis for 7 of 21 patients with an undiagnosed pleural effusion. The group at the Mayo Clinic reviewed their experience with open pleural biopsy for undiagnosed pleural effusion between 1962 and 1972 and reported that during this time no diagnosis was established in 51 such patients (27). In 31 of the patients (61%), there was no recurrence of the pleural effusion, and no cause ever became apparent. However, 13 of the patients (25.5%) eventually proved to have malignant disease (6 patients with lymphoma, 4 patients with mesothelioma, and 3 with other malignancies).

SPECIAL SITUATIONS

There are certain special situations in which a different approach is sometimes indicated. Such situations include patients with pleural effusions in the intensive care unit (ICU), patients with massive effusions and those with bilateral pleural effusions.

Pleural Effusions in the Intensive Care Unit

There is a high prevalence of pleural effusion in patients in the ICU. Mattison et al. performed ultrasound examinations of the chest and found that pleural effusions were present in 62% of 100 patients (28). In this series, 92% of the effusions were small and most were thought to be transudates (28). In a second study, Fartoukh et al. screened 1,351 patients in the medical intensive care unit (MICU) and found that 113 patients (8.4%) had a pleural effusion detectable by physical examination and obscuring one third of the lung field (29). Thoracentesis on 82 of these patients revealed transudates in 20 (24.4%), parapneumonic effusion or empyema in 35 (42.7%) and noninfectious exudates in 27 (32.9%) (29). In a third study, Tu et al. (30) performed thoracentesis on 94 patients in the MICU who had ultrasonographic evidence of pleural effusions and who had a temperature greater than 38°C for more than 8 hours. They reported that 62% of the patients had infectious exudates which included 36 parapneumonic effusions, 15 empyemas, 15 urosepsis, 2 liver abscesses, 1 deep neck infection, and 1 wound infection. The sonographic pattern of the effusion was hyperechoic and/or septated in all 15 patients with empyema (30). The studies in the preceding text proves that there is a high incidence of empyema in the patient with effusion in the MICU. A thoracentesis is recommended for patients in the ICU with more than a minimal pleural effusion particularly if the effusion is septated or hyperechoic.

Patients in the ICU who are receiving mechanical ventilation and have large pleural effusions appear to benefit if the fluid is drained. Kupfer et al. (31) compared the duration of mechanical ventilation for 80 patients who received chest tubes and 88 who did not receive chest tubes and reported that the duration of mechanical ventilation was significantly shorter (3.8 days) in the patients that received chest tubes than in the patients that did not receive chest tubes (6.5 days). All the patients had transudative effusions and the decision as to whether to insert a chest tube was made by the patient's private physician (31). When patients on mechanical ventilation are subjected to therapeutic thoracentesis their oxygenation status improves (32,33). Walden et al. (32) performed 15 thoracentesis with the removal of a mean of 1,872 ml in 10 patient on mechanical ventilation. Post thoracentesis, the mean PaO_2 increased from 82 to 115 mm Hg and the P:F ratio increased from 169 to 237 (32). These improvements were maintained for 48 hours (32). Liang and coworkers (34) have demonstrated that drainage of large pleural effusion in the ICU via pigtail catheters is effective regardless of the etiology of the effusion.

Massive Pleural Effusions

On occasion a patient is found to have a pleural effusion that occupies the entire hemithorax and such an effusion is said to be massive. As discussed in Chapter 6, it is important to assess the position of the mediastinum in such patients before proceeding with the workup. Porcel et al. (35) reviewed chest radiographs from 766 patients with pleural effusion seen at an academic medical center in Lleida, Spain, during a 10-year period. Ninety-three of the patients (12%) had a massive pleural effusion and 70 additional patients (9%) had effusions occupying more than two thirds of the hemithorax. This distribution of the diagnoses in the patients with massive and large effusions was similar. Of the 93 patients with massive effusions, 55 (59%) had malignancy, 21 (23%) had parapneumonic effusions, 9 (10%) had tuberculous effusions, 4 had other exudates, and 4 had transudative effusions. All the massive parapneumonic effusions were either empyemas or complicated parapneumonic effusions (35). Although only one patient in Porcel's series had a hepatic hydrothorax, it has been my experience that hepatic hydrothorax is one of the more common causes of massive

pleural effusions. A second study from Spain reported a similar distribution of diagnoses (36). During a 10-year period in Madrid, 1,084 patients with pleural effusions were prospectively studied and 11.2% of the effusions were massive. Of the 121 massive effusions, 65 (54%) were due to malignancy, 17 (14%) were idiopathic, 13 (11%) were parapneumonic, 12 (9.9%) were due to cirrhosis, 9 (7.4%) were due to tuberculosis, and no other diagnosis accounted for more than 2 patients.

Bilateral Pleural Effusion

The most common cause of bilateral pleural effusions is congestive heart failure and indeed most pleural effusions (approximately 90%) secondary to heart failure are bilateral. Most patients with pleural effusions due to heart failure have an enlarged heart. However, if the heart is not enlarged, an alternate diagnosis should be sought. Rabin and Blackman (37) reviewed the etiology of the effusions in 76 patients with bilateral pleural effusions and a normal-sized heart and reported the following diagnoses: 35 neoplasia, 10 pulmonary embolisms, 8 nephritis and amyloidosis, 4 systemic lupus erythematosus, 4 tuberculosis, 3 cirrhosis, 2 generalized adenitis of unknown etiology, 2 periarteritis nodosa, 3 congestive heart failure, 1 eosinophilic pneumonia, and 1 constrictive pericarditis.

Kalomenidis et al. (38) studied 27 patients with bilateral pleural effusions who underwent bilateral thoracentesis to determine if the findings were the same on both sides. They found that the pleural fluid values for the white blood cell (WBC) count and differential, RBC count, LDH, total protein, and glucose were very similar on both sides and concluded that bilateral diagnostic thoracenteses were not indicated unless there is a specific clinical indication such as effusions disparate in size or suspected pleural sepsis.

However, occasionally a patient with bilateral pleural effusions will have different explanations and this situation is known as Contarini's condition (34). Porcel et al. reviewed 546 patients with bilateral pleural effusions from a given institution (34). They reported that only five patients (1%) had effusions of different etiologies (39). Most patients with Contarini's condition have heart failure with a transudate on one side and a parapneumonic effusion or an empyema on the contralateral side (34). The second most common combination is a chylothorax on one side and a malignant pleural effusion on the other side (34).

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chapter 9

Transudative Pleural Effusions

Transudative pleural effusions occur when the systemic factors influencing the formation and absorption of pleural fluids are altered so that pleural fluid accumulates. In this chapter, the various causes of transudative pleural effusions are discussed.

CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is probably the most common cause of pleural effusion. The reason for the low incidence of pleural effusions secondary to heart failure in most studies is that researchers interested in pleural effusions usually do not see most patients with pleural effusions of this origin. In an epidemiologic study from the Czech Republic, CHF was the most common cause of pleural effusion (1). The incidence of pleural effusions in patients with CHF is high. Kataoka and Takada (2) studied 60 patients admitted to a Japanese hospital for an exacerbation of stable CHF with a computed tomography (CT) scan, ultrasound, and a chest radiograph. They reported that by CT scan, 50 patients (83%) had a right-sided pleural effusion, whereas 46 patients (77%) had a left-sided pleural effusion. Approximately one third of the effusions had volumes that exceeded 700 mL (2).

Race et al. (3) reviewed the autopsies at the Mayo Clinic between 1948 and 1953 of 402 patients who had CHF during life. The researchers found that 290 of the patients (72%) had pleural effusions with volumes greater than 250 mL. Of these, 88% had bilateral pleural effusions, whereas 8% and 4% had unilateral right-sided and left-sided effusions, respectively (3).

Pathophysiology

In recent years, concepts of pleural fluid formation and reabsorption in patients with heart failure have undergone significant modifications. In the past, it was believed that the pleural fluid that accumulated in patients with CHF was due to increased pressure in the capillaries in the visceral or the parietal pleura. These increased pressures were thought to result in an increased entry of fluid into the pleural space from the parietal pleura and a decreased removal of fluid through the visceral pleura, according to Starling's equation.

The current theories on pleural fluid formation and reabsorption give us a different entry pathway and a different exit pathway for pleural fluid in patients with CHF. It appears that most of the fluid that enters the pleural space in patients with CHF comes from the alveolar capillaries rather than the pleural capillaries (4). When the pressure in the pulmonary capillaries is elevated, increased amounts of fluid enter the interstitial spaces of the lung. The increased fluid in the interstitial spaces results in an increased interstitial pressure in the subpleural interstitial spaces (5). The fluid then moves from the pulmonary interstitial spaces across the visceral pleura into the pleural space. There appears to be relatively little resistance to fluid movement from the pulmonary interstitial spaces across the visceral pleura (4). When pulmonary edema is produced in sheep with volume overloading, approximately 25% of the pulmonary edema fluid exits the lung through the visceral pleura (6).

Currently, it is believed that almost all fluid exits the pleural space through the lymphatics in the parietal pleura rather than by passively diffusing across the visceral pleura (see Chapter 2). Pleural fluid accumulates in patients with CHF when the rate of entry of fluid into the pleural space exceeds the capacity of the lymphatics in the parietal pleura to remove the fluid. In normal sheep, the capacity of the lymphatics

to remove fluid is approximately 0.28 mL/kg/hr (7). If there is elevated pressure in the systemic veins, the lymphatic clearance is decreased and the rate of fluid formation from the capillaries in the parietal pleura is increased (8).

In the clinical situation, it appears that the accumulation of pleural fluid in patients with CHF is related more to left ventricular failure than to right ventricular failure. Wiener-Kronish et al. (9) prospectively evaluated 37 patients with CHF secondary to ischemic heart disease or to cardiomyopathy who were admitted to a coronary care unit. Nineteen patients had a pleural effusion. The mean wedge pressure in the patients with an effusion (24.1 ± 1.3 mm Hg) was significantly higher than in those without an effusion (17.2 ± 1.5 mm Hg). There was also a greater likelihood of finding pleural effusions if severe rather than mild pulmonary edema was found roentgenographically. In a subsequent study (10), these same researchers were unable to demonstrate any pleural effusions in 27 patients with chronic pulmonary hypertension or chronically elevated right atrial pressures.

Pleural effusions also occur in some patients with right ventricular failure (11–13). Tang et al (11) reviewed the records of 147 patients with idiopathic or familial hypertension and reported that 21 patients (14%) had pleural effusion for which there was no explanation. The patients with pleural effusion had significantly higher mean right atrial pressures than did those without effusion (11). The majority of the effusions were trace to small and right sided or bilateral (11). When the fluid was analyzed, it usually was a transudate (11). In another study by the same group, Luo et al. (12) reviewed the records of 89 patients with pulmonary arterial hypertension due to connective tissue disease and reported that 32.6% of the patients had a pleural effusion without an alternative diagnosis. The patients with pleural effusion had significantly higher right atrial pressures, BNP, and lower cardiac outputs (12). Patients with scleroderma had a higher incidence than did patients with systemic lupus erythematosus (12). The pleural effusions were predominantly small in size and bilateral. It therefore appears that many patients with right heart failure have pleural effusions (13).

In summary, it appears that pleural fluid accumulates in patients with CHF when they have either left or right ventricular failure. The high pressures in the pulmonary capillaries lead to increased amounts of fluid in the interstitial spaces. The fluid in the interstitial spaces enters the pleural space through the highly permeable visceral pleura. Fluid accumulates when the entry of fluid into the pleural space overwhelms the capacity of the lymphatics in the parietal pleura to remove the fluid. Small amounts of fluid may enter the pleural space from the capillaries in either pleural surface. Elevation of the systemic venous pressure also leads to the accumulation of pleural fluid because of increased fluid formation from the capillaries in the parietal pleura and decreased lymphatic clearance from the pleural space.

Clinical Manifestations

Pleural effusions due to CHF are usually associated with other manifestations of that disease. The patient often has a history of increasing dyspnea on exertion, increasing peripheral edema, and orthopnea or paroxysmal nocturnal dyspnea. The dyspnea is frequently out of proportion to the size of the effusion. Physical examination usually reveals signs of both right-sided heart failure with distended neck veins and peripheral edema and left-sided heart failure with rales and an S_3 ventricular gallop as well as signs of the pleural effusions.

The chest radiograph almost always reveals cardiomegaly and usually bilateral pleural effusions. CHF is by far the most common cause of bilateral pleural effusions, but if cardiomegaly is not present, an alternate explanation should be sought. In one series of 76 patients with bilateral pleural effusions but a normal-sized heart, only 3 (4%) were due to CHF (14). Although in the past it was thought that pleural effusions due to CHF were commonly unilateral on the right or at least were much larger on the right side, this does not appear to be the case. In the autopsy series of Race et al. (3), 88% of the patients studied had bilateral pleural effusions. Moreover, the mean volume of pleural fluid in the right pleural space (1,084 mL) was only slightly greater than the mean volume of pleural fluid in the left pleural space (913 mL). In this series, 35 patients had unilateral pleural effusions, and of these 35 patients, 16 (46%) had either pulmonary embolism or pneumonia (3). A recent letter (15) to the editor summarized the sidedness of 444 effusions due to heart failure in five separate studies. Of the effusions, 69% were bilateral, 21% were unilateral on the right, and 9% were unilateral on the left. Of the bilateral pleural effusions, most were similarly sized but either side can be larger.

In patients with pleural effusions secondary to CHF, mediastinal lymphadenopathy is common. Erly et al. (16) reported that the prevalence of mediastinal lymph nodes with a diameter greater than 1 cm

on the short axis was 81% in 36 patients with an ejection fraction less than 35%.

Diagnosis

The diagnosis of pleural effusions secondary to CHF comes readily to mind every time a patient is seen with CHF. One must be careful to avoid the trap of ascribing the pleural effusion to CHF when it has another cause. In the series of Race et al. (3), more than 25% of the patients with CHF and pleural effusions had either pulmonary emboli or pneumonia at autopsy. Certainly, if the patient is febrile, has pleural effusions that are greatly disparate in size, has a unilateral pleural effusion, pleuritic chest pain, or does not have cardiomegaly, a diagnostic thoracentesis should be performed.

If the patient has cardiomegaly and bilateral pleural effusions, is afebrile, and does not have pleuritic chest pain, we initiate treatment of the CHF and observe the patient to determine whether the pleural fluid is reabsorbed. If the effusions do not disappear within a few days, we then perform a diagnostic thoracentesis. One problem with this approach is that with diuresis, the characteristics of the pleural fluid may change from those of a transudate to those of an exudate. Romero et al. (17) performed a thoracentesis on 21 patients with CHF before and every 48 hours after diuretic therapy was initiated. Before diuretics were administered, only one effusion was misclassified as an exudate by Light's criteria, but at the time of the third thoracentesis 10 effusions were misclassified as exudates. Between the first and the third thoracentesis, the mean protein level increased from 2.3 to 3.5 gm/dL and the mean lactate dehydrogenase (LDH) level increased from 176 to 262 IU/L (17). Other authors (18,19) have also reported that the characteristics of the pleural fluid changed with diuresis.

The pleural fluid from a patient with CHF is typically a transudate with a ratio of pleural fluid to serum protein below 0.5, a ratio of pleural fluid to serum LDH under 0.6, and an absolute pleural fluid LDH level below two-thirds of the upper limit of normal for serum (Light's criteria) (20). If the foregoing criteria are satisfied in a patient with CHF, the patient has a transudative pleural effusion that can be ascribed to the CHF, and no further diagnostic studies are indicated. Such transudative pleural effusions may be blood tinged, and the pleural fluid differential cell count may reveal predominantly polymorphonuclear leukocytes, small lymphocytes, or other mononuclear cells (21).

The pleural fluid from approximately 20% to 25% of patients with CHF will be classified as exudates by Light's criteria (22). Most patients who are misclassified are receiving diuretics (22). If the pleural fluid meets exudative criteria but the effusion is thought to be due to CHF, the serum to pleural fluid protein gradient should be examined. If this gradient is greater than 3.1 g/dL, the pleural effusion in all probability is due to the CHF and additional diagnostic studies are not indicated (17). In patients with CHF on diuretic therapy, the protein gradient does not decrease much with diuresis (17). If the protein and LDH criteria are not met and the protein gradient is less than 3.1 g/dL, the pleural effusion is probably not due to the heart failure. Rather, the patient has an exudative pleural effusion, and further diagnostic tests such as pleural fluid cytologic study and a CT angiogram of the chest should be obtained. In previous editions of this book, it was recommended that in borderline pleural effusions the albumin gradient between the serum and pleural fluid be measured. If this gradient was more than 1.2 g/dL, then the effusion could be ascribed to the CHF. Currently, the protein gradient of 3.1 g/dL is preferred to the albumin gradient because the protein gradient is already available when Light's criteria are measured. Moreover, the protein gradient appears to be as effective as the albumin gradient in making the distinction (17).

Another test that should be considered for establishing the diagnosis of CHF is measurement of the serum or pleural fluid N-terminal pro-brain natriuretic peptide (NT-proBNP). When the ventricles are subjected to increased pressure or volume, the biologically active BNP and the larger aminoterminal part NT-pro-BNP are released in equimolar amounts in the circulation (23). The thresholds for the diagnosis of heart failure via the BNP recommended by the manufacturers are 100 pg/mL for the Triage BNP assay and 125 pg/mL for the Elecsys pro-BNP assay (23). However, in clinical practice, levels below 100 pg/mL are thought to make CHF unlikely, whereas levels above 500 pg/mL are considered diagnostic of CHF (24). It should be noted that serum BNP levels are increased with acute pulmonary embolism when there is right ventricular dysfunction (25).

The pleural fluid levels of NT-proBNP are elevated in patients with heart failure. Porcel et al. (26) measured NT-proBNP levels in 117 pleural fluid samples including 44 with heart failure, 25 with malignancy, 20 with tuberculous pleurisy, and 10 with hepatic hydrothorax. They reported that the median level of NT-proBNP was 6,931 pg/mL in the patients with CHF,

which was significantly higher than that of 551 pg/mL in the patients with hepatic hydrothorax or 292 pg/mL in the 63 patients with exudative effusions. A cutoff level of 1,500 pg/mL in the pleural fluid provided a sensitivity of 91% and a specificity of 93% in the diagnosis of heart failure. Tomcsányi et al. (27) compared the pleural fluid and serum NT-pro-BNP levels in 14 patients with CHF and 14 patients with pleural effusions of other etiologies. They reported that the median NT-pro-BNP levels in the patients with heart failure and other diseases were 6,295 and 276, respectively, in pleural fluid and 5,713 and 231, respectively, in serum (27). There was no overlap between the two groups. Interestingly, in the latter study, the correlation between the pleural fluid BNP levels and the serum levels was very high ($R^2 = 0.95$) (27). Kolditz et al. (28) measured the serum and pleural fluid NT-pro-BNP levels in 93 patients including 25 with CHF. They confirmed the results of the study by Tomcsányi et al. (27) in that the levels of serum and pleural fluid NT-pro-BNP again were closely correlated ($R^2 = 0.90$). They reported that an NT-pro-BNP cutoff level of 4,000 pg/mL had a sensitivity of 92% and a specificity of 93% in making the diagnosis of CHF. Moreover, in this study nine patients with heart failure met Light's exudative criteria and all of them had pleural and serum NT-pro-BNP levels greater than 4,000 pg/mL (28). From the latter two studies, it appears that there is no need to measure both the pleural fluid and the serum NT-pro-BNP levels.

We compared the pleural fluid NT-pro-BNP levels in 10 patients each with pleural effusions due to CHF, pulmonary embolism, post–coronary artery bypass surgery, and malignancy. All the patients with CHF had NT-pro-BNP levels above 1,500 pg/mL, whereas none of the other patients had such high levels (29). In view of the data given in the preceding text, it appears that a pleural fluid NT-pro-BNP level above 1,500 pg/mL is almost diagnostic that the patient has CHF.

It should be emphasized that the serum or pleural fluid BNP and NT-pro-BNP cannot be used interchangeably in the diagnosis of pleural effusions due to CHF (30). The NT-pro-BNP levels are about 10 times higher than the BNP levels. There is not a close correlation between the BNP levels and the NT-pro-BNP levels ($r = 0.78$) (31). The diagnostic usefulness of the NT-pro-BNP in making the diagnosis of heart failure is superior to that of the BNP (31,32). The pleural fluid NT-pro-BNP is also superior to the BNP and the protein gradient in identifying patients with heart failure who meet Light's criteria for exudates (31). In one study of 20 patients with heart failure who met Light's criteria for exudates, 18 had NT-pro-BNP levels above 1,300, 16 had NT-pro-BNP levels above 1,500, but only 10 had serum pleural fluid protein gradient greater than 3.1 g/dL (31).

Treatment

The preferred treatment of pleural effusion secondary to heart failure is to treat the heart failure with digitalis, diuretics, and afterload reduction. When the heart failure is successfully managed, the pleural effusion disappears. Such treatment effectively manages the pleural effusion in most patients with heart failure. For example, in a recent study of patients undergoing orthotopic heart failure, preoperatively only 19 of 60 (32%) had a pleural effusion and only 1 patient had a pleural effusion that occupied more than 25% of the hemithorax (33).

Occasionally, large pleural effusions cause patients to be very dyspneic. The removal of 500 to 1,000 mL of pleural fluid from such patients may rapidly relieve the dyspnea. If the effusions cannot be controlled with standard therapy, interventions to control the pleural effusions should be considered. One option is pleurodesis with a sclerosing agent (34) and currently, doxycycline 500 mg through a chest tube is recommended (see Chapter 10). Bleomycin is not recommended in this situation because it is not an effective agent in the rabbit model with normal pleura (35).

An alternative approach is to insert an indwelling pleural catheter or to use a pleuroperitoneal shunt. Herlihy et al. (36) inserted indwelling catheters (PleurX, CareFusion Corporation, San Diego, CA) into five patients with pleural effusions refractory to the usual therapy. Initially, the catheter was effective in controlling the effusion in all patients (36). However, after 5 and 15 months, two patient developed an empyema and after 4 months another patient developed a loculated pleural effusion (36). We have used this device in several patients with excellent results. With the PleurX, the patient connects the catheter to vacuum bottles every other day to drain the fluid (see Chapter 10). The pleuroperitoneal shunt (CareFusion Corporation, San Diego, CA) consists of two catheters connected with a valved pump chamber. The two one-way valves in the pump chamber are positioned such that fluid can only flow from the pleural space to the peritoneal cavity through the pump chamber. Because the pleural pressure is almost always more negative than the peritoneal pressure, the pumping chamber must be used to move fluid

from the pleural cavity to the peritoneal cavity. Little et al. (37) reported that two patients with refractory pleural effusions secondary to CHF were managed successfully with the pleuroperitoneal shunt.

HEPATIC HYDROTHORAX

Pleural effusions occur occasionally as a complication of hepatic cirrhosis. Pleural effusions usually occur only when ascitic fluid is present. Lieberman et al. (38) reviewed 330 patients with cirrhosis and ascites and found that 18 (5.5%) had pleural effusions. Johnston and Loo (39) found that 6.0% of 200 patients with cirrhosis had pleural effusions. In the second series, none of the 54 patients having cirrhosis without ascites had a pleural effusion (39). In some patients, the ascites is not clinically evident, but it can almost always be demonstrated with ultrasonography (40). The pleural effusion in patients with cirrhosis and ascites is usually right sided (67%), but occasionally it is left sided (16%) or bilateral (16%) (38,39).

Pathophysiology

Patients with cirrhosis frequently have decreased plasma oncotic pressure (39), and from Figure 2.1, one might hypothesize that the pleural effusions arise because of it. Indeed, in the experimental animal, the induction of decreased plasma oncotic pressure leads to the accumulation of pleural fluid (41). However, this mechanism does not appear to be the predominant cause of pleural effusions in patients with cirrhosis and ascites. Rather, the pleural effusions appear to be produced by movement of the ascitic fluid from the peritoneal cavity into the pleural cavity.

Johnston and Loo (39) demonstrated that after the intraperitoneal injection of India ink, cells in the pleural fluid contained many carbon particles, whereas cells in the peripheral blood contained none. In addition, after the intravenous injection of radiolabeled albumin, the albumin first appeared in the peritoneal fluid and then in the pleural fluid. Following the intraperitoneal injection of radiolabeled albumin, the concentration of the labeled protein was greater in the pleural fluid than in the plasma; after intrapleural injection, the labeled protein appeared in the plasma before it appeared in the peritoneal fluid (39). Because no air entered the pleural space following the intraperitoneal injection of carbon dioxide in one patient, these researchers concluded that the pleural effusion arose from the transfer of ascitic fluid from the peritoneal to the pleural space by the lymphatic vessels. This conclusion appears to have been incorrect. Datta et al. (42) injected radiolabeled human serum albumin into the peritoneal cavity of a patient with ascites and a large pleural effusion. They were able to demonstrate that when the labeled protein was picked up by the lymphatic system in the diaphragm, it flowed into normal mediastinal lymphatic channels and from them into the subclavian vein. It did not enter the pleural space.

Studies by Lieberman et al. (38) suggest that fluid passes directly from the peritoneal to the pleural cavity through pores in the diaphragm. These researchers introduced 500 to 1,000 mL of air into the peritoneal cavity of five patients with cirrhosis, ascites, and pleural effusions. In all five patients, a pneumothorax developed 1 to 48 hours after the induction of the pneumoperitoneum. Thoracoscopic examination was performed in three other patients after the induction of the pneumoperitoneum, and in one of these patients, air bubbles were seen coming through an otherwise undetectable diaphragmatic defect (38). At postmortem examination, diaphragmatic defects were demonstrated in two of the patients (38). Huang et al. (43) prospectively studied 11 patients with hepatic hydrothorax who underwent thoracoscopy. These researchers classified the morphologic findings into four morphologic types: type I, no obvious defect (one patient); type II, blebs lying on the diaphragm (four patients); type III, broken defects (fenestrations) in the diaphragm (eight patients); and type IV, multiple gaps in the diaphragm (one patient). The movement of fluid from the peritoneal cavity through the diaphragm can also be demonstrated by contrast enhanced ultrasound (44).

From the foregoing studies, it is evident that the pleural fluid in these patients originates from the ascitic fluid. It is probable that the fluid passes directly into the pleural space through defects in the diaphragm. In the patient with tense ascites and increased intraabdominal pressure, the diaphragm may be stretched, causing microscopic defects. The increased hydrostatic pressure in the ascitic fluid results in a one-way transfer of fluid from the peritoneal to the pleural cavity. My experience with the placement of chest tubes in such patients leads me to believe that the direct movement of fluid is the dominant mechanism. To control the symptoms of large hydrothoraces in several patients with cirrhosis and ascites, I have performed tube thoracostomy, followed by the injection of a sclerosing agent. In each instance, the placement of the chest tube was followed by rapid (within minutes) diminution in the amount of ascites.

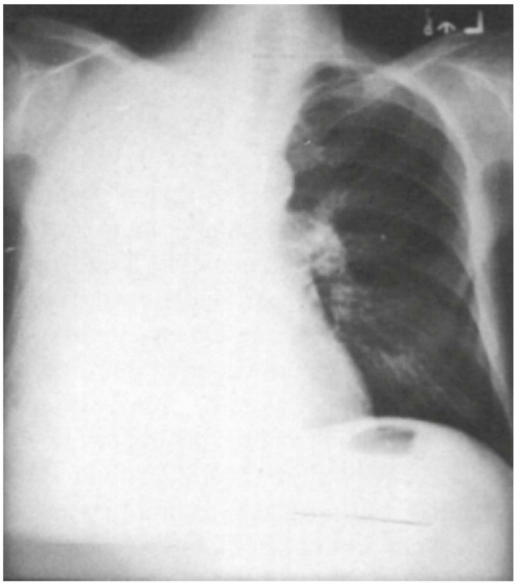

FIGURE 9.1 ■ Posteroanterior chest radiograph demonstrating a large right pleural effusion. This patient with massive ascites suddenly developed shortness of breath. A previous chest radiograph (Fig. 6.4) had suggested a subpulmonic pleural effusion.

Clinical Manifestations

Patients with pleural effusions from cirrhosis and ascites have clinical pictures dominated by the cirrhosis and ascites. At times, these patients develop acute dyspnea in association with large pleural effusions. Although the pleural effusions may be small to moderate in size, they are frequently large and occupy the entire hemithorax (Fig. 9.1). The large effusions occur because the diaphragmatic defect permits fluid to flow from the peritoneal into the pleural cavity until the pleural pressure approaches the peritoneal pressure. Indeed, the pleural pressures in patients with pleural effusions secondary to ascites are higher than in patients with other transudative pleural effusions (45).

Hepatic hydrothorax is much more common on the right side than on the left side (46). On rare occasions, hepatic hydrothorax may be bilateral. It is thought that hepatic hydrothorax is more common on the right side because the right hemidiaphragm is more likely to have embryologic developmental defects (46).

Diagnosis

The diagnosis of pleural effusion secondary to cirrhosis and ascites is usually easy. Both a paracentesis and a thoracentesis should be performed to ascertain that the ascites and pleural fluid are compatible with the diagnosis and do not have high polymorphonuclear cell counts. In one study of patients with cirrhosis and pleural effusion, a diagnosis other than hepatic hydrothorax was established in 18 of 60 patients (30%) (47). Alternative diagnoses included spontaneous bacterial pleuritis in nine, tuberculosis in two, adenocarcinoma in two, parapneumonic effusion in two, and undiagnosed exudates in three (47). Alternate diagnoses were more common when the effusion was left sided or when there was no ascites (47). With hepatic hydrothorax the pleural fluid protein level is usually higher than the ascitic fluid protein level (38), but is still below 3.0 g/dL, and the pleural fluid LDH level is low. On occasion, the pleural fluid with hepatic hydrothorax meets Light's criteria for an exudate (48). Bielsa et al. (48) reported that the pleural fluid from 18 of 102 (18%) hepatic hydrothoraces met Light's criteria for exudates. Light's criteria were met by only a little, and most patients had a serum–pleural fluid protein gradient greater than 3.1 g/dL (48). The pleural fluid is occasionally blood tinged or is frankly bloody, but such findings have no significance and are probably due to the patient's poor coagulation status. The differential cell count may reveal predominantly polymorphonuclear leukocytes, small lymphocytes, or other mononuclear cells. Amylase levels should be determined and cytologic examination performed on both fluid specimens to rule out pancreatic ascites or malignant disease.

An occasional patient with cirrhosis will develop a hepatic hydrothorax and not have clinically evident ascites. Kakizaki et al. (49) reviewed the literature on this subject and were able to find 28 cases. Twenty-seven cases were on the right side, and only one case was on the left side, and this occurred in a patient who had a tear in the left diaphragm because of a splenectomy (49). The diagnosis can be established with the intraperitoneal injection of technetium 99 m (^{99m}Tc)–sulfur colloid (50) or the intraperitoneal spraying of indocyanine green (51) and their subsequent demonstration in the pleural space or the pleural fluid.

In patients with cirrhosis, ascites, and pleural effusion, it is important to be aware of the possibility of spontaneous pleural infection, which is somewhat analogous to the spontaneous bacterial peritonitis that occurs in these patients (52). Xiol et al. (52) originally reported on 11 episodes of spontaneous pleural infection in eight patients. They used the term spontaneous bacterial empyema (52). Because the fluid

does not look like pus (53), I prefer to use the term spontaneous bacterial pleuritis to emphasize its similarity with spontaneous bacterial peritonitis. Patients are diagnosed with spontaneous bacterial pleuritis if they have cirrhosis along with a positive bacterial culture of the pleural fluid and a neutrophil count greater than 250 cells/mm^3 or a negative culture and a neutrophil count greater than 500 cells/mm^3. Patients with pneumonia are excluded. In a subsequent study, Xiol et al. (53) prospectively studied 24 episodes of spontaneous bacterial pleuritis in 16 of 120 patients (13%) admitted with a diagnosis of hepatic hydrothorax. In 14 of the 24 episodes, there was concomitant spontaneous bacterial peritonitis (53). The pleural fluid cultures were positive in 18 patients and included 8 patients with *Escherichia coli*, 4 with streptococcus species, 3 with enterococcus species, and 2 with *Streptococcus pneumoniae*. In the largest series, spontaneous bacterial pleuritis occurred in 81 (20%) of 390 patients with hepatic hydrothorax (54). Spontaneous peritonitis was concomitantly present in 54% (54). The pleural fluid with spontaneous bacterial pleuritis with the exception of the increased number of neutrophils is similar to that with hepatic hydrothorax (54). The pleural fluid/serum protein level is usually less than 0.50, the LDH ration is less than 0.6 and the pH is above 7.30 (54).

Patients with spontaneous bacterial pleuritis tend to have worse liver disease. The mortality rate in the large series was 38% (54). The diagnosis can be made at the bedside with the use of reagent strips for leukocyte esterase designed for testing urine (55). The treatment of choice is an antibiotic to which the cultured bacteria are susceptible. Tube thoracostomy is usually not indicated (54,56).

Treatment

The management of pleural effusions associated with cirrhosis and ascites should be directed toward treatment of the ascites because the hydrothorax is an extension of the peritoneal fluid. The patient should be put on a low-salt diet, and diuretics should be administered. The best diuretic therapy appears to be the combination of furosemide and spironolactone. The initial starting dose is 40 mg of furosemide and 100 mg of spironolactone. This combination appears to have the optimal ratio for the two diuretics. The doses can be increased up to 160 mg of furosemide and 400 mg of spironolactone daily (57). Serial therapeutic thoracenteses are not indicated because the pleural fluid rapidly reaccumulates.

Certain patients are refractory to salt restriction and diuretics and remain symptomatic from the presence of the large pleural effusion. In such patients, the treatment of choice is liver transplantation (58). The presence of the hepatic hydrothorax does not appear to adversely affect the results with liver transplantation (58). Interestingly, approximately 10% of living donors for liver transplant will develop a pleural effusion (59).

The next best treatment is to implant a transjugular intrahepatic portal systemic shunt (TIPS). A recent randomized controlled study demonstrated that TIPS was superior to serial thoracentesis in patients with refractory ascites (60). In this study, 60 patients were randomly assigned to TIPS or serial thoracentesis and there was a significant survival advantage with the TIPS procedure (60). A large uncontrolled series on the use of TIPS for hepatic hydrothorax was reported by Gordon et al. (61). In this series, 24 patients were treated and 14 of the patients had complete relief of symptoms after shunt placement and did not require further thoracentesis (61). Five additional patients required fewer thoracenteses, but the remaining five patients developed worsening liver function and died within 45 days (61).

If neither TIPS nor liver transplantation is feasible, the best alternative treatment is probably videothoracoscopy with closure of the diaphragmatic defects and pleurodesis (60,62). In one report, 18 patients were subjected to 21 thoracoscopies with talc insufflation (3 patients were subjected to a second procedure after the first failed) (63). Diaphragmatic defects were detected and closed in 5 of the 18 patients (28%). The procedure was effective in 10 of 21 patients (48%). The median hospital stay was 15 days. The precarious medical condition of patients with hepatothorax is reflected in the 30% mortality in the 3 months following the surgery (63). Mouroux et al. (64) performed this procedure in eight patients using talc insufflation. Diaphragmatic defects were found and closed in six of the patients, and none had a recurrent pleural effusion. No defects were found in the remaining two patients, but after talc insufflation, the effusions occupied only the lower one third of the hemithorax. Ferrante et al. (65) could find no diaphragmatic defects in 15 patients with hepatic hydrothorax subjected to thoracoscopy and talc insufflation. In this series, the hepatic hydrothorax was controlled by the talc insufflation in 8 of the 15 (53%) patients (65). I do not recommend talc insufflation for the reasons discussed in Chapter 10, but would instead recommend pleural abrasion. One small series of five

patients suggested that the results with thoracoscopy and diaphragmatic repair along with pleural abrasion would be improved if a drain were left in the peritoneal cavity (66). This would increase the likelihood of a good pleurodesis (66).

The insertion of a chest tube in patients with hepatic hydrothorax carries significant morbidity and mortality with questionable benefit (67). In one series from the University of Michigan, chest tubes were placed in 17 patients with hepatic hydrothorax and 16 had complications (67). The complications included acute kidney injury in 11, pneumothorax in 7, empyema in 5, encephalopathy in 3, and pneumonia in 3 (some of the patients had more than one complication) (67).

Although implantation of a peritoneojugular shunt might at first glance appear to be a good alternative in the management of hepatic hydrothorax, shunts frequently do not control the pleural effusion. The explanation for the ineffectiveness of the shunt is related to the pressure differences between the peritoneal cavity, the pleural space, and the systemic veins. Because the pleural pressure is less than the central venous pressure, fluid will preferentially move to the pleural space rather than to the central veins (68). Nevertheless, there is one report (69) in which six patients with hepatic hydrothorax were treated with a peritoneojugular shunt and all had a marked reduction in pleural effusion–related symptoms within a few days.

PLEURAL EFFUSION AS A COMPLICATION OF PERCUTANEOUS TRANSHEPATIC CORONARY VEIN OCCLUSION

Patients with bleeding esophageal varices are sometimes managed by injecting Gelfoam or other materials transhepatically into the coronary vein, in the hope that the injected material will lodge in the esophageal veins and stop the bleeding. To perform this procedure, the liver is entered through the diaphragm (70). In at least one patient, a large pleural effusion requiring tube thoracostomy developed following this procedure (70). On several occasions, I have observed that pleural fluid rapidly accumulates after this procedure in patients who had ascites before the procedure. I hypothesize that the pleural effusion arose because the iatrogenic diaphragmatic defect allowed the ascitic fluid to flow into the pleural space. Pleural effusions may also appear by the same mechanism after percutaneous transhepatic cholangiography.

PERITONEAL DIALYSIS

During the last 30 years, there has been an increasing use of continuous ambulatory peritoneal dialysis (CAPD) in the treatment of chronic renal failure. Pleural effusions can result from CAPD owing to the movement of the dialysate from the peritoneal cavity into the pleural cavity through a mechanism similar to that of cirrhosis and ascites. Nomoto et al. (71) reviewed 3,195 patients from 161 medical centers in Japan on CAPD. They reported that 1.6% developed this complication secondary to movement of the dialysate from the peritoneal cavity through the diaphragm into the pleural space (71). The effusion developed within 30 days of initiating the dialysis in 50% of the patients, but 18% had been on dialysis for more than a year before the effusion developed (71). The pleural effusion occurs on the right side approximately 90% of the time, but it can be bilateral or left sided (71). Pleural effusions can also develop as a complication of acute peritoneal dialysis (72).

The diagnosis of a pleural effusion secondary to peritoneal dialysis is usually very easy. The pleural fluid in these patients is characterized by a glucose level intermediate between that of the dialysate and the serum, protein level below 3 g/dL, and a low LDH level (<100 IU/L) which is higher than that in the peritoneal dialysate (73,74).

When a patient on peritoneal dialysis develops a pleural effusion, the dialysis usually must be stopped. It is recommended that the dialysis be stopped for 2 to 6 weeks (75). After this time, peritoneal dialysis can be resumed in more than 50% of patients without recurrence of the pleural effusion (75). If there is a recurrence after this waiting period or if such a waiting period is felt to be inappropriate, a procedure should be performed to create a pleurodesis. The simplest approach is to insert a chest tube with the instillation of a sclerosing agent such as doxycycline (74,75). If this approach is taken, small-volume peritoneal dialysis can be performed for 10 to 14 days after the pleurodesis is attempted (74). More recently, video-assisted thoracoscopic surgery (VATS) has been utilized. Halstead et al. (76) subjected six patients to VATS during which they clipped the communication in the diaphragm and performed a parietal pleurectomy. At a median follow-up of 40 months, all had returned uneventfully to CAPD and there were no recurrences of the hydrothorax (76). Tang et al. (73) reported that thoracoscopy with the insufflation of talc allowed 17 of the 18 patients to return to CAPD. The main advantage of thoracoscopy in this situation is that it allows one to examine the

diaphragm and clip the areas that are leaking. I would, therefore, definitely recommend that this be done. I would also recommend parietal pleurectomy rather than talc to effect the pleurodesis due to the dangers of talc inducing the acute respiratory distress syndrome.

Some patients on peritoneal dialysis develop exudative pleural effusions. Kwan et al. (77) retrospectively reviewed 82 chronic peritoneal dialysis patients that had pleural effusion and found that 22 had unexplained exudative effusions. When the dialysis therapy in these patients was intensified, the exudative effusion tended to resolve (77). The researchers concluded that these exudative effusions were uremic pleural effusions (see Chapter 23).

OTHER CAUSES OF TRANSUDATIVE PLEURAL EFFUSIONS

Nephrotic Syndrome

Pleural effusion is common in patients with the nephrotic syndrome. In one study of 52 patients, 21% had pleural effusions (78). With the nephrotic syndrome, the pleural effusions are usually bilateral and are frequently infrapulmonary in location (78). The mechanism responsible for the transudative pleural effusion associated with the nephrotic syndrome is probably the combination of decreased plasma oncotic pressure and increased hydrostatic pressure. The increased hydrostatic pressure is due to salt retention producing hypervolemia (79).

The diagnosis of pleural effusion secondary to the nephrotic syndrome is not difficult in the typical clinical situation. A diagnostic thoracentesis should be performed to ascertain that the pleural fluid is indeed a transudate. One should always consider the possibility of pulmonary emboli in patients with the nephrotic syndrome and pleural effusion. In one series of 36 patients with the nephrotic syndrome, 22% had pulmonary emboli (80). In addition, the nephrotic syndrome may be due to or complicated by renal vein thrombosis, and in such instances, the incidence of pulmonary emboli is high (80). A lung scan or a CT angiogram should be obtained in all patients with the nephrotic syndrome and pleural effusion. If the lung scan or CT angiogram is equivocal, evidence of deep venous thrombosis should be sought with venograms, impedance plethysmograms, or a pulmonary arteriogram.

The treatment of the pleural effusion associated with the nephrotic syndrome should be aimed at decreasing the protein loss in the urine to increase the plasma protein and to decrease the increased extracellular volume. This is best accomplished by administering diuretics in conjunction with a low-sodium diet, angiotensin-converting enzyme inhibitors, and using nonsteroidal antiinflammatory agents cautiously (81). Serial therapeutic thoracenteses should not be performed because they only further deplete the protein stores. In selected individuals who are symptomatic from the pleural effusion, one should consider a pleurodesis with a sclerosing agent.

Pulmonary Veno-Occlusive Disease

Pulmonary veno-occlusive disease is a rare disease that is characterized pathologically by evidence of repeated pulmonary venous thrombosis. The characteristic histologic feature of pulmonary veno-occlusive disease is obstruction of pulmonary venules and veins by intimal fibrosis; intravascular fibrous septa are nearly always present (82). The etiology of this disease is unknown and may be related to more than one source or mechanism (82).

Clinically, patients with pulmonary veno-occlusive disease typically have slowly progressive dyspnea and orthopnea punctuated by attacks of pulmonary edema. Physical examination reveals signs of pulmonary hypertension. Small pleural effusions are present in a significant fraction of patients. In one study (83), CT scans were obtained on eight patients and five of the patients had bilateral pleural effusions. The pleural effusion occupied less than 5% of the hemithorax in four patients, but in the fifth patient the effusions occupied one third the volume of the thoracic cavity. In a second study, however, pleural effusions were present in only 4 of 15 patients (27%) (84).

When a pleural effusion is seen in a patient with pulmonary hypertension, the diagnosis of pulmonary veno-occlusive disease should be considered although patients with pulmonary hypertension and right heart failure may also have pleural effusions (13). The characteristics of the pleural fluid have not been delineated, but it is likely that it is transudative (85). The pleural effusions are probably related to the increased interstitial fluid that results from obstruction of the pulmonary veins (85).

The diagnosis of pulmonary veno-occlusive disease can be definitively made only by surgical lung biopsy. The prognosis with this disease is grim, with most patients dying within 2 years of diagnosis. The only treatment that significantly improves the prognosis of patients with pulmonary veno-occlusive disease is lung transplantation (82). Patients with pulmonary veno-occlusive disease who are treated with agents for pulmonary hypertension frequently develop pulmonary edema (86).

Obstruction of the Brachiocephalic Vein

Obstruction of the brachiocephalic vein can lead to a pleural effusion. There have been case reports in which the brachiocephalic vein occlusion was due to an intrathoracic goiter (87), or thrombosis of the vein due to a central venous catheter (88), or a hemodialysis catheter (89). I have seen one case of a patient with a very large anterior chest hematoma that caused a large pleural effusion presumably due to brachiocephalic vein obstruction. The pleural fluid is a borderline transudate.

Urinothorax

Pleural effusion can develop when there is retroperitoneal urinary leakage secondary to urinary obstruction, trauma, retroperitoneal inflammatory or malignant processes, failed nephrostomy, or kidney biopsy (90–92). Such a pleural fluid accumulation is called a *urinothorax*. This is a rare cause of pleural effusions; only 58 cases had been reported till 2006 (92). The pleural effusion tends to develop within hours of the precipitating event and dissipates rapidly once the obstruction is relieved. It is believed that the urine moves retroperitoneally into the pleural space. There appear to be two distinct categories of urinothorax. The first occurs when there is bilateral obstruction of the urinary tract, and the second occurs when there is trauma to the urinary tract (92).

The diagnosis is usually easy if it is considered. The pleural fluid looks and smells like urine. It tends to have a protein level less than 1.0 g/dL, but frequently has a high LDH level (92). The pleural fluid pH level is frequently below 7.2 but can be normal, whereas the pleural fluid glucose can be normal or markedly reduced (92). Confirmation of the diagnosis can be obtained with simultaneous measurements of the pleural fluid and creatinine levels. The pleural fluid creatinine has been greater than the serum creatinine in all cases of urinothorax, but this also occurs in at least 10% of patients with pleural effusions of other etiologies (91).

Glomerulonephritis

Patients with acute glomerulonephritis frequently have pleural effusions. In a series of 76 children, 42 (55%) had pleural effusions (93). The pleural effusions are transudative and are probably due to increased intravascular pressures because most patients have cardiomegaly or peripheral edema in addition to the pleural effusions.

Myxedema

Pleural effusions occasionally occur as a complication of myxedema. In one review of 128 patients with hypothyroidism from the Massachusetts General Hospital and the Medical University of South Carolina, pleural effusion occurred in 28 patients, but it was believed to be due to the hypothyroidism in only 6 patients (94). In one of these six patients, the pleural effusion was believed to be secondary to a myxedematous pericardial effusion, whereas in the other five patients, there was no evidence of pericardial disease. When the pleural effusion occurs simultaneously with a pericardial effusion, the pleural fluid is usually a transudate (95). The isolated pleural effusion secondary to hypothyroidism can be either an exudate or a transudate (84). The diagnosis is one of exclusion in a patient with hypothyroidism. The obvious treatment for pleural effusions associated with myxedema is thyroid replacement.

Leakage of Cerebrospinal Fluid into the Pleura

On rare occasions, cerebrospinal fluid (CSF) can collect in the pleural space and produce a pleural effusion. This most commonly occurs following ventriculopleural shunting (96), but it can also occur when a ventriculoperitoneal shunt migrates to the pleural cavity (97). Other causes of subarachnoid pleural fistulas include penetrating and nonpenetrating trauma. Frequently, the trauma is surgery involving the thoracic spine (98,99). The diagnosis is suggested by the characteristics of the pleural fluid, which appears to be CSF. The fluid is clear and colorless, and the protein level is very low (98,99). If there has been recent trauma, the pleural fluid may be bloody because of the trauma and not look like spinal fluid. If there is doubt about the diagnosis, measurement of the pleural fluid β_2-transferrin is useful because only CSF contains this molecule (100). At times, the diagnosis can be made by radionuclide cisternography (99).

Hypoalbuminemia

From Starling's equation (Equation 2.1), hypoalbuminemia would decrease the oncotic pressure of the blood and increase the rate of pleural fluid formation. It is unclear how frequently hypoalbuminemia causes a pleural effusion. In patients with cirrhosis and hypoalbuminemia, the pleural effusions are related to the transdiaphragmatic transfer of ascitic fluid rather

than hypoproteinemia. Eid et al. (101) reviewed the prevalence of pleural effusions in patients with serum protein levels above 3.5 g/dL, between 2.1 and 3.5 g/dL, l.0 and 2.0 g/dL, or lower. They found that the incidence of pleural effusions was comparable in each group. In the group with serum albumin levels less than 2.0 g/dL, 3 of 21 had a pleural effusion and there were alternative explanations for the pleural effusions in each of these 3 cases. These researchers concluded that hypoalbuminemia *per se* is an uncommon cause of pleural effusion. In contrast, Mattison et al. (102) attributed 8% of 62 effusions occurring in patients in a medical intensive care unit to hypoalbuminemia. However, most of these patients had other possible explanations for their pleural effusion (102).

Meigs' Syndrome

Although the pleural fluid associated with Meigs' syndrome (benign ovarian tumors with ascites and pleural effusion) is often considered a transudate (103), the pleural fluid protein levels are usually above 3.5 g/dL, (104,105) and therefore the effusions are exudates. Accordingly, this syndrome is further discussed in Chapter 20.

Pulmonary Embolus

In the previous editions of this book, it has been stated that approximately 20% of the pleural effusions that occur with pulmonary embolization are transudates. This appears to overstate the incidence of transudates with pulmonary embolus. In a recent study, the pleural fluid from all the 60 patients with pulmonary embolus was exudative (106). This condition is discussed in detail in Chapter 17.

Superior Vena Caval Obstruction

In previous editions of this book, pleural effusions secondary to superior vena caval obstruction were discussed in this chapter. However, since the last edition it has become apparent that the pleural fluid associated with superior vena caval obstruction is usually exudative. Therefore, these effusions are now discussed in Chapter 23.

Sarcoidosis

This condition is occasionally accompanied by a transudative rather than an exudative pleural effusion (see Chapter 23).

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chapter 10

Pleural Effusions Related to Metastatic Malignancies

INCIDENCE

Malignant disease involving the pleura is the second leading cause of exudative pleural effusions after parapneumonic effusions. Because many parapneumonic effusions are small and are not subjected to thoracentesis, malignancy is probably the leading cause of exudative effusions subjected to thoracentesis. In our series from Baltimore, 42% of 102 exudative pleural effusions were due to malignant disease (1). In an epidemiologic study from the Czech Republic, malignancy accounted for 24% of all the pleural effusions (2).

Carcinomas of the lung and breast and lymphomas account for approximately 75% of malignant pleural effusions (Table 10.1). Metastatic ovarian carcinoma is the fourth leading cause of malignant pleural effusions, whereas sarcomas, particularly melanoma, account for a small percentage of malignant pleural effusions. No other single tumor accounts for more than 1% of malignant pleural effusions. In approximately 6% of patients with malignant pleural effusions, the primary tumor is not identified (3,4).

Lung Cancer

In most series, lung cancer is the leading cause of malignant pleural effusion (3). When patients with lung cancer are first evaluated, approximately 15% have a pleural effusion (5). During the course of this disease, however, at least 50% of patients with disseminated lung cancer develop a pleural effusion. Pleural effusions occur with all the cell types of lung carcinoma but appear to be most frequent with adenocarcinoma (6,7). Patients with small-cell lung carcinoma have a lower incidence of pleural effusion (~15%) (8). Patients with lung cancer who have anti-p53 antibodies are more likely to have pleural effusions. In one series, 9 of 10 patients (90%) with this antibody had pleural effusions, whereas 42 of 115 patients (36%) without the antibody had a pleural effusion (9).

Many patients have visceral pleural involvement but do not have pleural effusions. In one series of 1,074 patients undergoing pulmonary resection with intent to cure, visceral pleural involvement was present in 26.8% (10). The 5-year survival rate was significantly less in the patients with visceral pleural involvement (49.8%) than in those without it (76.0%) (10). Almost all patients undergoing lung cancer resection, who have a pleural lavage positive for malignant cells, have visceral pleural involvement (11).

At times, pleural effusions develop in patients who have undergone resection for adenocarcinoma. The incidence of pleural effusion is higher if there is either lymph node or pleural involvement by tumor, at the time of surgery (12). In one series, 18 of 19 patients who developed a cytology-positive pleural effusion after resection had either lymph node metastases, pleural involvement, or both (12). The median time from resection to diagnosis of malignant pleural effusion was 8 months. Most effusions that develop more than 24 months after surgery are due to another primary tumor (12).

It is important to emphasize that the presence of a pleural effusion in a patient with lung cancer almost always indicates that the patient is not curable with surgery whether or not the cytology is positive. Sugiura et al. (13) reviewed 197 patients with stage IIIB or IV non-small-cell lung cancer (NSCLC). They reported that the survival for stage IIIB without effusion, stage IIIB with effusion, and stage IV were 15.3, 7.5, and 5.5 months, respectively (13). The survival

TABLE 10.1 ■ Causes of Malignant Pleural Effusions in Two Different Series

	Spriggs and Boddington[a]		Anderson et al.[b]	
Tumor	*n*	%	*N*	%
Lung carcinoma	275	43	32	24
Breast carcinoma	157	25	35	26
Lymphoma and leukemia	52	8	34	26
Ovarian carcinoma	27	4	9	7
Sarcoma (including melanoma)	13	2	5	4
Uterine and cervical carcinoma	6	1	3	2
Stomach carcinoma	18	3	1	1
Colon carcinoma	9	1	0	0
Pancreatic carcinoma	7	1	0	0
Bladder carcinoma	7	1	0	0
Other carcinoma	23	4	6	4
Primary unknown	40	6	8	6
Total	634		133	

[a]From Spriggs AI, Boddington MM. *The Cytology of Effusions*, 2nd ed. New York, NY: Grune & Stratton; 1968, with permission.
[b]From Anderson CB, Philpott GW, Ferguson TB. The treatment of malignant pleural effusions. *Cancer.* 1974;33:916–922, with permission.

was similar whether the pleural fluid cytology was positive or negative (13). It has been suggested that patients with lung cancer and pleural effusion be classified as M1a which would make them a stage IV (14). Another study also demonstrated that with multivariate analysis, the presence of a pleural effusion at the time of diagnosis adversely affected prognosis (6).

How should the patient with bronchogenic carcinoma and an ipsilateral cytology-negative pleural effusion be evaluated? Rodriguez-Panadero (15) performed thoracoscopy on 21 patients with lung cancer and an ipsilateral cytology-negative pleural effusion. At thoracoscopy, only five patients were believed to be potentially resectable, but when these five were subjected to thoracotomy, their tumors were found to be unresectable because of mediastinal invasion (15). In another older study from the Mayo Clinic, 5 of 73 patients with bronchogenic carcinoma and ipsilateral cytology-negative pleural effusions had long-term survival after the lung cancer was resected (16). In view of the two studies mentioned in the preceding text, it is recommended that patients with bronchogenic carcinoma and an ipsilateral cytology-negative pleural effusion undergo thoracoscopy. If the thoracoscopy is negative, a computed tomography (CT) scan of the chest should be obtained to evaluate the mediastinal lymph nodes. If the CT scan demonstrates lymph node enlargement, a mediastinoscopy should be performed. If the CT scan demonstrates no lymph node enlargement and the thoracoscopy is negative, consideration should be given to an exploratory thoracotomy if the patient has no other contraindication to curative resection.

On occasion, a significant pleural effusion will be recognized only at the time of thoracotomy. Ruffini et al. (17) reported that 52 of 1,279 patients (4%) operated upon between 1993 and 1999 had a pleural effusion with a volume more than 100 mL. The median survival for 16 patients who were inoperable was 6 months, whereas the median survival of 8 patients who had positive cytology but who underwent resection was 9 months. However, the 3- and 5-year survivals of the 21 patients with negative cytology who underwent resection were 68% and 54%, respectively (17).

When a patient with lung cancer is found to have a pleural effusion and is not symptomatic from the effusion, should the effusion be treated? The answer to this question is probably no. Tremblay et al. (18) studied 14 such patients and reported that no patient required any specific pleural intervention for the pleural effusion.

Epidermal growth factor receptor (EGFR) mutations are strong determinants of tumor response to EGFR tyrosine kinase inhibitors in non-small-cell lung cancer. The EGFR mutation status can be determined by analyzing the DNA in malignant cells in the pleural fluid (19,20).

Breast Carcinoma

The second leading cause of malignant pleural effusion is metastatic breast carcinoma. Fracchia et al. (21)

reviewed 601 patients with disseminated breast carcinoma and found that 48% had pleural effusions. The effusions were large enough to warrant therapeutic intervention in 48% of the patients. Goldsmith et al. (22) reviewed the autopsies of 365 patients who had died of disseminated breast carcinoma and reported that 46% had pleural effusions. Pleural effusions were more common with lymphangitic spread (63%) than without lymphangitic spread (41%) (22). In this series, the pleural effusions were on the same side as the primary breast carcinoma in 58% of these patients, on the opposite side in 26%, and on both sides in 16% (22). In a second series, the effusion was ipsilateral in 70%, contralateral in 20%, and bilateral in 10% (23). Ipsilateral effusions are less common if radiotherapy was part of the initial treatment (24). With breast carcinoma, the mean interval between the development of the primary tumor and the appearance of the pleural effusion is approximately 2 and 5 years (24,25), but this interval can be as long as 20 years (26). In patients with pleural effusions secondary to breast carcinoma, determination of the steroid receptors in the effusion is useful in planning therapy.

One paper suggested that when a patient with breast carcinoma is found to have a pleural effusion, it is preferable to treat the patient with systemic therapy plus pleurodesis rather than systemic therapy alone (27). In this article, the mean pleural progression free interval was 8.5 months in the 102 patients that underwent pleurodesis compared to 4.1 months in the 78 patients that did not undergo pleurodesis originally (27). There was no difference in overall survival.

Lymphomas

Lymphomas, including Hodgkin's disease, are the third leading cause of malignant pleural effusions (28). The incidence of pleural effusion with Hodgkin's disease at presentation has varied from 7% to 21% (29,30). During the course of the disease the incidence of pleural effusion is approximately 16% (31). Patients with Hodgkin's disease who have pleural effusions almost invariably have intrathoracic lymph node involvement, frequently without microscopic pleural involvement (32). Most patients with Hodgkin's disease and pleural effusion have the nodular sclerosis type (33). Approximately only 3% of the effusions present with Hodgkin's disease are chylothoraces.

The reported incidence of pleural effusion at presentation in non-Hodgkin's lymphoma has varied from 6% to 50% (29,30,34). With this neoplasm, 20% to 70% have evidence of mediastinal disease and 90% have evidence of disease elsewhere. For non-Hodgkin's lymphoma, large-cell lymphomas more frequently have associated pleural disease than do small-cell lymphomas (33). The presence of a pleural effusion at the time of presentation does not adversely affect complete remission or survival rates with non-Hodgkin's lymphoma (35). The cytology on the pleural fluid is positive in almost all cases (34,35). During the course of the disease, as many as 40% will have a pleural effusion (36). Approximately 20% of the effusions present with non-Hodgkin's lymphomas are chylothoraces (34).

Vieta and Craver (31) also reported that 12% of 158 patients with lymphatic leukemia and 4% of 52 patients with myelogenous leukemia had pleural effusions. Parietal pleural involvement, however, was uncommon at autopsy with leukemia. The most common cause of pleural effusion in patients with chronic myeloid leukemia and acute lymphobastic leukemia is as a side-effect from the tyrosine-kinase inhibitor dasatinib (see Chapter 22) (37).

Angioimmunoblastic T-cell lymphoma was formerly called *angioimmunoblastic lymphadenopathy* (AILD) and is characterized by the acute onset of constitutional symptoms, generalized lymphadenopathy, hepatosplenomegaly, anemia, and polyclonal hypergammaglobulinemia. Pathologically, this disorder is characterized by extensive infiltration of lymph nodes with atypical lymphocytes, proliferation of arborizing small vessels, and the deposition of amorphous acidophilic material (19). Most cases of AILD contain monoclonal T-cell populations as well as clonal cytogenetic abnormalities (51). AILD is accepted as a lymphoma and a distinct clinicopathologic entity in the current World Health Organization (WHO) classification (51). A characteristic feature of angioimmunoblastic AITL, seen in more than 95% of all patients, is the presence of increased numbers of Epstein-Barr virus (EBV)–infected cells compared with both normal lymph nodes and peripheral T-cell lymphomas (51). The EBV-infected cells are mostly B cells and the EBV is not thought to have a primary role in the pathogenesis of AITL (51).

Approximately 40% of patients with AITL have pleural effusions (38). The pleural fluid is an exudate with a preponderance of mononuclear cells (39). Other findings on the chest radiograph include interstitial infiltrates and mediastinal or hilar adenopathy, each in 15% to 20% of patients (40). The diagnosis is made by biopsy examination of an enlarged lymph node.

The incidence of malignant pleural effusion in patients with multiple myeloma is approximately 1% (41). The effusions develop at an average of 12 months after the diagnosis of multiple myeloma. Most patients will have associated pleural or chest wall plasmacytomas or pulmonary parenchymal lesions on CT scan (41).

PATHOPHYSIOLOGIC FEATURES

There are several different mechanisms that can be responsible for the development of a pleural effusion in patients with malignancy (Table 10.2). Although it is frequently written that lymphatic obstruction is the primary pathophysiologic abnormality responsible for the pleural effusion with malignancy, this appears not to be true (42). The basis for the contention that lymphatic obstruction is responsible is the observation that at postmortem studies, the presence of pleural effusions is correlated with metastases to the lymph nodes (43). However, the normal rate of pleural fluid formation is thought to be only 15 mL/day. Therefore, if there was complete blockage of the lymphatics, the rate of pleural fluid accumulation should only be 15 mL/day. Certainly, the rate of pleural fluid accumulation frequently exceeds this in patients with pleural malignancy (44). Moreover, if the fluid accumulation was solely due to lymphatic obstruction, one would expect the fluid to be a transudate, but it is almost always an exudate.

We believe that the most likely explanation for the pleural effusion with metastatic disease to the pleura is increased permeability of the pleura (42). Indeed, in the series of Leckie and Tothill (45), a patient with bronchogenic carcinoma had the second highest amount of protein entering the pleural space of the 40 patients studied. The mechanism by which pleural metastases increase the permeability of the pleura is not definitely known. However, we postulate that it is due to the production of vascular endothelial growth factor (VEGF) by the tumor (42). Indeed, the median level of VEGF in pleural effusions secondary to malignancy is much higher than that in patients with effusions secondary to inflammatory disease (46,47). The pleural fluid VEGF levels are also higher in hemorrhagic malignant effusions than in nonhemorrhagic malignant pleural effusions (46). VEGF is one of the most potent agents known for increasing vascular permeability (48). Yano et al. have developed an animal model of a malignant pleural effusion by injecting human adenocarcinoma cells into the pleural space of nude mice (49). The formation of pleural fluid in this model is markedly reduced if the animals are given an inhibitor of the VEGF receptor (49) or if the cells are transfected with an antisense VEGF-165 gene (50) (see discussion on malignant pleural effusions in Chapter 4).

It is likely that lymphatic blockade and the resulting decreased clearance of fluid from the pleural space contributes to the accumulation of pleural fluid although, for the reasons outlined earlier, this is not the predominant mechanism in most cases. Leckie and Tothill (45) reported that the mean amount of protein leaving the pleural space in patients with malignant pleural effusions was less than that leaving the pleural space in patients with tuberculosis, pulmonary embolism, or congestive heart failure. This decreased lymphatic drainage can occur through two separate mechanisms. First, because the fluid leaves the pleural space through stomas in the lymphatic vessels in the parietal pleura (51), metastases to the parietal pleura that obstruct these stomas can decrease fluid clearance. Second, the lymphatic vessels of the parietal pleura drain mainly through the mediastinal lymph nodes. Therefore, neoplastic involvement of the mediastinal lymph nodes can decrease the lymphatic clearance of the pleural space.

Malignant tumors can also produce pleural effusions by obstructing the thoracic duct, in which case the resulting pleural effusion is a chylothorax. In fact, most chylothoraces that are not traumatic in origin are secondary to neoplastic involvement of the thoracic duct. Lymphomas are responsible for 75% of chylothoraces secondary to malignant disease (see Chapter 26).

TABLE 10.2 ■ Mechanisms by Which Malignant Disease Leads to Pleural Effusions

Direct Result
Pleural metastases with increased permeability
Pleural metastases with obstruction of pleural lymphatic vessels
Mediastinal lymph node involvement with decreased pleural lymphatic drainage
Thoracic duct interruption (chylothorax)
Bronchial obstruction (decreased pleural pressures)
Pericardial involvement
Indirect Result
Hypoproteinemia
Postobstructive pneumonitis
Pulmonary embolism
Postradiation therapy

Another mechanism by which malignant tumors produce pleural effusion is through bronchial obstruction. When a neoplasm obstructs the mainstem bronchus or a lobar bronchus, the lung distal to the obstruction becomes atelectatic. Therefore, the remaining lung must overexpand or the ipsilateral hemithorax must contract to compensate for the loss of volume of the atelectatic lung. These events result in a more negative pleural pressure, and it is easy to see from Figure 2.1 that such a negative pleural pressure causes pleural fluid to accumulate. My associates and I studied a patient with obstruction of the bronchus intermedius in whom the pleural pressure dropped from –12 to –48 cm H_2O as 200 mL pleural fluid was removed (52).

Pericardial involvement is frequent with metastatic malignant diseases. When a pericardial effusion is caused by such involvement and hydrostatic pressures become elevated in the systemic and pulmonary circulation, transudative pleural effusions may result. It is also likely that some of the malignant pericardial fluid is cleared through the pleural space, which can lead to an exudative effusion (see Chapter 19).

Not all pleural effusions in patients with malignant disease are related to intrathoracic involvement by the neoplasm. Pulmonary infection distal to a partially or totally occluded bronchus may produce a parapneumonic effusion (see Chapter 12). The incidence of pulmonary embolization is higher in patients with malignant disease, and emboli frequently cause exudative pleural effusions (see Chapter 17). Patients with intrathoracic neoplasms frequently receive radiotherapy for their tumors, and this treatment can also result in pleural effusions (see Chapter 23), as can some types of chemotherapy (see Chapter 22). Many patients with malignant disease are malnourished and have hypoproteinemia, and this disorder can, on rare occasions, lead to the formation of transudative pleural effusions (see Chapter 9).

AUTOPSY STUDIES

The most detailed autopsy series on pleural involvement in malignant disease are those of Meyer (43) and Rodriguez-Panadero et al. (53). It appears that pleural metastases with bronchogenic carcinoma are usually due to pulmonary arterial emboli to the ipsilateral pleura. Virtually, all patients with metastatic pleural involvement from lung carcinoma have involvement of the visceral pleura (43,53). In the series of Rodriguez-Panadero et al., pulmonary vascular invasion by the tumor was found in 19 of the 24 cases (53). Parietal pleural metastases result from direct extension from the visceral pleura (43,53).

In patients with nonbronchogenic carcinoma, the visceral pleura is also almost always involved. Involvement of the parietal pleura again appears to result from direct extension from the visceral pleura (43,53). The origin of these metastases is controversial. Meyer attributed them to tertiary spread from secondary hepatic tumors (43). In his series of 23 patients with pleural metastases, 19 (83%) had hepatic metastases. In the series by Rodriguez-Panadero et al., however, hepatic metastases could be demonstrated only in 71% of the patients and they attributed the visceral pleural metastases to blood-borne metastases from the primary (53). The latter explanation appears more plausible to me. The presence of pleural metastases does indicate systemic dissemination of the disease and renders the patient incurable with surgery alone.

Not all patients with pleural metastases have pleural effusions. In Meyer's series, only 60% of patients with pleural metastases had pleural effusion (43). In Rodriguez-Panadero's study, only 30 of 55 patients (55%) with metastatic disease to the pleura had pleural effusion (53). Meyer found that the presence of a pleural effusion was more closely related to neoplastic invasion of the mediastinal lymph nodes than to the extent of pleural involvement by nodular metastases (43).

CLINICAL MANIFESTATIONS

The most common symptom reported by patients with malignant pleural effusions is dyspnea, which occurs in more than 50% (7). Symptoms attributable to the tumor itself are also frequent. In one series, weight loss occurred in 32%, malaise in 21%, and anorexia in 14% of patients (7). When patients with malignant pleural effusions are compared to those with benign pleural effusions, patients with malignant pleural effusions are more likely to have dull chest pain (34% vs. 11%), whereas patients with benign disease are more likely to have pleuritic chest pain (51% vs. 24%) (54). Temperature elevations are significantly more common in patients with benign disease (73%) than in patients with malignant disease (37%) (54).

Chest Radiographs

The size of a malignant pleural effusion varies from a few milliliters to several liters, with the fluid occupying the entire hemithorax and shifting the mediastinum

to the contralateral side. Malignant disease is the most common cause of a massive pleural effusion and accounted for 31 of 46 (67%) of effusions occupying an entire hemithorax, in one series (55). In a more recent series, malignancy was responsible for 55% of 163 effusions that occupied more than two thirds of the hemithorax (56).

Almost all patients with pleural effusions secondary to bronchogenic carcinoma have radiographically demonstrable pulmonary abnormalities besides the effusion. At times, a therapeutic thoracentesis must be performed before the pulmonary abnormality is evident. Although almost all patients with pleural effusions secondary to lymphoma have mediastinal lymph node involvement at autopsy, this involvement is not always evident in chest radiographs (31). In a series of 22 patients with chylothorax due to lymphoma, only 5 patients (23%) had hilar or mediastinal adenopathy demonstrable on routine chest radiographs (57). In another series, however, 71% of 21 patients with pleural effusions secondary to lymphoma had visible mediastinal lymph node involvement on chest radiographs (58). In a third series of 19 patients with non–Hodgkin's lymphoma, only 4 patients had mediastinal lymphadenopathy (59). The chest radiographs of patients with pleural effusions due to malignant tumors other than lung carcinoma or lymphoma often reveal only a pleural effusion. In a series of 105 patients with pleural effusion due to breast carcinoma (26), only 9% had radiographically evident pulmonary metastases.

In patients with undiagnosed pleural effusions, the chest CT scan is useful in indicating whether the effusion has a benign or malignant etiology. Yilmaz et al. (60) reviewed the CT scans in 146 patients with pleural effusions including 59 that were malignant and 87 that were benign. They reported that the following four findings were suggestive of malignancy: (a) pleural nodularity, (b) pleural rind, (c) mediastinal pleural involvement, and (d) pleural thickening greater than 1 cm (60). In a second study, pleural surfaces assessed by CT scan were abnormal in 27 of 32 patients with malignancy but in none of the 8 patients with benign disease (61). It should be noted that both the series mentioned in the preceding text had a large percentage of mesotheliomas, which are more likely to have abnormalities of the pleural surfaces. Concurrent abnormalities are frequently present in patients with documented malignant effusions. In one study of 86 patients, the following incidences of concurrent abnormalities were reported: pericardial effusion, 3%; pericardial thickening, 14%; mediastinal adenopathy, 43%; chest wall involvement, 12%; lymphangitic carcinoma, 7%; and suspicious lung masses, nodules, or infiltrates, 53%.

Pleural Fluid

The pleural fluid from a malignant pleural effusion is almost always an exudate (62,63). Ashchi et al. (64) reviewed the medical records of 171 patients with malignant pleural effusion and found that in 8 of the cases, the fluid was transudative. There were alternative explanations for the transudative effusions in seven of the eight cases (64). In another study, 97 of 98 patients with malignant pleural effusions had exudates (63). The ratio of the pleural fluid to the serum protein level is less than 0.5 in approximately 20% of malignant pleural effusions (7,62). However, in these 20%, the ratio of the pleural fluid to the serum lactate dehydrogenase (LDH) or the absolute pleural fluid LDH almost always meet exudative criteria (62). Most pleural effusions that meet exudative criteria by the LDH level but not by the protein level are malignant pleural effusions (62).

The presence of grossly bloody pleural fluid (red blood cell [RBC] count $>100{,}000/mm^3$) suggests malignant pleural disease. In our series of 22 such effusions, 12 (55%) were due to malignant disease (1). Approximately 30% to 50% of malignant pleural effusions, however, have red blood cell counts less than $10{,}000/mm^3$ and do not appear bloody (1,65). The pleural fluid white blood cell (WBC) count with malignant pleural effusion is variable, with the usual count between 1,000 and $10{,}000/mm^3$ (1). The predominant cells in the pleural fluid differential white cell count of these effusions are lymphocytes in approximately 45%, other mononuclear cells in approximately 40%, and polymorphonuclear leukocytes in approximately 15% (1). In the past, it was stated that pleural fluid eosinophilia (>10%) made pleural malignancy unlikely. However, in a review of 392 cases of eosinophilic pleural effusions that were not associated with pleural air and/or blood, malignancy was the final diagnosis in 17% (66). A more recent paper from a single institution reported that malignancy was responsible for 34.8% of 135 eosinophilic pleural effusions (67).

The pleural fluid glucose level is reduced to below 60 mg/dL in approximately 15% to 20% of malignant pleural effusions (68–70). A low pleural fluid glucose level in association with a malignant pleural effusion indicates that the patient has a high tumor burden in the pleural space. Rodriguez-Panadero

and Lopez-Mejias (70) performed thoracoscopy on 77 patients with a malignant pleural effusion and found that the extent of the tumor was significantly greater in those with a low pleural fluid glucose level. Cytology and pleural biopsy are more likely to be positive in patients with low-glucose pleural effusions (70). Because of the large tumor burden, patients with a low pleural fluid glucose level have a worse prognosis (71). It appears that the low-glucose levels with malignant pleural effusion are due to impaired glucose transfer from blood to pleural fluid (72). Increased glucose utilization by the pleural tumor also probably plays a role in producing the low pleural fluid glucose.

Approximately one third of patients with malignant pleural effusions have a pleural fluid pH below 7.3 (70,73,74). Patients with a low pleural fluid pH level also tend to have a low pleural glucose level (70,74). As one might anticipate, they have a greater tumor burden, are more likely to have positive pleural fluid cytology and pleural biopsy, and have a shorter survival than individuals with malignant pleural effusions and a pH level above 7.3 (70,74). The pathogenesis of the low pH level with malignant pleural effusions appears to be due to the combination of acid production by the pleural fluid or the pleura and a block to the movement of carbon dioxide out of the pleural space (72).

Approximately 10% of patients with malignant pleural effusions have an elevated pleural fluid amylase level (69). Usually, the primary tumor is not in the pancreas in these patients (69,75). Analysis of the amylase isoenzymes has demonstrated that the amylase in malignant effusions is the salivary isoenzyme rather than the pancreatic isoenzyme (76), and therefore amylase isoenzyme analysis can be used to differentiate pancreatic effusions from malignant effusions.

DIAGNOSIS

The diagnosis of a malignant pleural effusion is established by demonstrating malignant cells in the pleural fluid or in the pleura itself. In most cases, this is done by cytologic examination of the pleural fluid or biopsy of the pleura.

Cytologic Examination

The easiest way to establish the diagnosis of pleural malignancy is with pleural fluid cytology. The characteristics of malignant cells in pleural fluid are described in Chapter 7. The percentage of cases in which cytologic study of the pleural fluid establishes the diagnosis of a malignant pleural effusion ranges from 40% to 87% (77–81). The reasons for this variability in the diagnostic yield with cytologic study are discussed in Chapter 7. When three separate pleural fluid specimens from a patient with malignant pleural disease are submitted to an experienced cytologist, one should expect a positive diagnosis in approximately 80% of patients. The incidence of positive results depends on the primary tumor. Most cases of metastatic adenocarcinoma can be diagnosed by pleural fluid cytology. Positive results are uncommon with squamous cell carcinoma (SCC) because the pleural effusions are usually due to bronchial obstruction or lymphatic blockade (1,3,82). With lymphoma, the cytologic test is positive in approximately 25% of patients with Hodgkin's disease and in 50% to 60% of patients with non–Hodgkin's lymphoma. By cytologic examination, the neoplasm can usually be classified into a histologic type such as adenocarcinoma, but the primary site of the tumor cannot usually be identified (82).

Immunohistochemical Tests

The use of monoclonal antibodies directed against various antigens is useful in distinguishing malignant from benign pleural effusions (83). Metastatic adenocarcinomas tend to stain positive with carcinoembryonic antigen (CEA), MOC-31, B72.3, Ber-EP4, BG-8, and TTF-1 (84), whereas malignant mesothelial cells and benign mesothelial cells stain positive with calretinin, keratin5/6, podoplanin, and WT1 (83) (see Chapter 7). TTF-1 has high specificity for lung carcinoma (83). When attempts are made to differentiate metastatic carcinoma from mesothelioma, stains should be made with two of the antibodies that stain positive for adenocarcinomas and two that stain positive for mesothelioma (84). In the situation where the cytology of the pleural fluid is positive, but the primary is unknown, immunohistochemical tests can help identify the site of the primary (see Chapter 7). The technology with these monoclonal antibodies continues to improve, and it is recommended that all laboratories that deal with significant numbers of pleural fluids develop the capability to perform these immunohistochemical tests.

Tumor Markers in Pleural Fluid

In the last decade, there have been many articles purporting to show the usefulness of tumor markers

in establishing the diagnosis of malignant pleural effusions. Tumor markers evaluated have included CEA; carbohydrate antigens (CA) 15-3, 19-9, 549 and 72-4 (85); neuron-specific enolase (85); SCC antigen; cytokeratin 19 fragments (CYFRA21-1) (85,86); and sialyl state-specific mouse embryonic antigen (SSEA-1) (87). Although the mean levels of tumor markers in the pleural fluid are significantly higher in malignant effusions than in benign effusions, there is almost always some overlap (88). For tumor markers to be useful in the diagnosis of malignant effusions, they have to be 100% specific. One does not want to misdiagnose a benign pleural effusion as a malignant effusion and inform the patient that they only have several months to live. In view of the reasons mentioned in the preceding text, the use of tumor markers for the diagnosis of pleural malignancy is not recommended (89). One possible use of pleural fluid tumor markers is to use high levels to select patients for more invasive studies (88,89). However, other criteria are probably better at predicting that a patient has malignancy. Ferrer et al. (65) found that the following four characteristics were predictive of malignancy in 93 patients undergoing thoracoscopy: a symptomatic period of more than 1 month, the absence of fever, the presence of serosanguineous pleural fluid, and a chest CT scan suggestive of pleural malignancy. All 30 patients who had all four criteria had malignancy, whereas all 20 patients with one or no criteria had a nonmalignant disease (65).

Other Noninvasive Tests

Other noninvasive tests for the diagnosis of malignant pleural effusions are discussed in Chapter 7. These include measurement of oncogenes, hyaluronic acid, lectin binding, chromosomal analysis, fluorescence *in situ* hybridization (FISH), flow cytometry and proteomics. In general, the only test that is recommended is flow cytometry when a pleural lymphoma is suspected. Demonstration of the clonality of the lymphocytes in the pleural fluid establishes the diagnosis of lymphoma (90).

Pleural Biopsy

Needle biopsy of the pleura can establish the diagnosis of a malignant pleural effusion. The percentage of positive pleural biopsies in patients with malignant pleural disease ranges from 39% to 75% (80,91,92). In general, pleural fluid cytology is superior to pleural biopsy in establishing the diagnosis of pleural malignancy. Pleural biopsy has a lower diagnostic yield than pleural fluid cytologic examination because, in approximately 50% of patients with malignant pleural disease, the costal parietal pleura is not involved (93). In one large series of 281 patients with malignant pleural disease, the cytology was positive for malignant cells in 162 patients (58%), whereas the pleural biopsy was positive in 123 (44%) (80). The diagnosis of malignancy was established by pleural biopsy alone in only 20 of the 281 patients (7.1%) (80). Another way to look at this series is to consider the 118 patients with malignancy but negative cytology. Pleural biopsy established the diagnosis of malignancy in only 20 of these 118 patients (17%).

What is the role of blind needle biopsy of the pleura in establishing the diagnosis of malignant pleural effusion in the twenty-first century? Because thoracoscopy is very effective at establishing this diagnosis and because the needle biopsy is diagnostic in less than 20% of patients with malignancy and negative cytology, I rarely perform needle biopsy of the pleura. Certainly, if the cytology is negative and thoracoscopy is unavailable or an outpatient procedure is desired, consideration can be given to performing needle biopsy of the pleura.

An alternative means by which specimens of the pleural biopsy can be obtained is with CT-guided cutting-needle biopsy. The CT-guided biopsy is made where the pleura is the most thickened. In one study, 50 patients with unilateral pleural effusion and a clinical suspicion of malignancy were randomized to pleural biopsy through an Abram's needle biopsy or a CT-guided cutting-needle biopsy (94). The Abram's needle biopsy was not necessarily aimed where the pleural thickening was greatest. The diagnosis of malignancy was made in 13 of 15 patients (87%) with the CT-guided biopsy but in only 8 of 17 patients (47%) with the Abram's needle (94). Although these results look very promising, it should be noted that 20 of the 27 patients with malignancy in this study had mesothelioma, which is notoriously difficult to diagnose with Abram's needle biopsy of the pleura.

Observation, Thoracoscopy or an Open Thoracotomy

In many patients with exudative pleural effusions, no diagnosis is apparent after the initial diagnostic thoracentesis including pleural fluid cytology and a pleural fluid marker for tuberculosis. In such instances, a CT scan of the chest is recommended. If pulmonary

emboli are demonstrated with the CT scan, the etiology of the effusion is established. If parenchymal abnormalities are present, a bronchoscopy should be performed. If the CT scan suggests mesothelioma, then a CT-guided needle biopsy or thoracoscopy should be performed to establish this diagnosis.

If the CT scan shows nothing other than the pleural effusion, the approach to the patient should be governed by the clinical picture. If there is nothing in the patient's history to suggest carcinoma and if the patient's symptoms are improving, then it is probably best to observe the patient for several weeks because only a small percentage of these patients have malignant pleural disease (95). Alternatively, if the symptoms of the patient are worsening or if there is something in the clinical picture that suggests malignancy, the patient should undergo thoracoscopy. Ferrer et al. (65) reported that the following four characteristics were predictive of malignancy in 93 patients undergoing thoracentesis including 50 with malignancy: (a) duration of symptoms more than 1 month, (b) absence of fever, (c) blood-tinged pleural fluid, and (d) chest radiograph suggestive of malignancy (pulmonary or pleural masses, pulmonary atelectasis, or lymphadenopathy). Twenty-eight patients had all four criteria and all had malignancy. Twenty-one patients had at most one criterion and none had malignancy (65). Thoracoscopy will establish the diagnosis of malignancy in approximately 90% of patients with malignancy (96,97). If facilities for thoracoscopy are not available, an alternative approach is to perform a thoracotomy with open biopsy of the pleura or to perform a needle biopsy of the pleura. If thoracoscopy or thoracotomy is performed, a procedure such as a pleural abrasion should be performed to prevent recurrence of the pleural effusion.

Mesothelioma

The possibility of a malignant mesothelioma (see Chapter11) should be considered whenever a patient's pleural fluid cytologic study or pleural biopsy suggests metastatic adenocarcinoma, because the epithelial form of malignant mesothelioma is frequently misinterpreted as adenocarcinoma on cytologic examination or pleural biopsy (98). If no primary tumor is evident, a CT scan of the thorax should be obtained. If the CT scan suggests mesothelioma, one should consider thoracoscopy or exploratory thoracotomy for staging and possible radical pleuropneumonectomy (see Chapter 11).

As discussed early in this chapter and in Chapter 7, immunohistochemical tests are useful in making this differentiation. In addition, histochemical tests using periodic acid-Schiff stain (PAS) or Alcian blue and electron microscopy are very useful in differentiating metastatic adenocarcinoma from mesothelioma (see Chapter 11).

Lipid Analysis

The possibility of a chylothorax should be considered in every patient with malignant disease and a pleural effusion. If a chylothorax is present, the mediastinal lymph nodes are probably involved, and the treatment of choice is radiation to the mediastinum or chemotherapy. The supernatant of the pleural fluid from patients with malignant pleural effusions should be examined. If the supernatant is turbid, a chylothorax should be suspected, and the triglyceride level in the pleural fluid should be determined. If the pleural fluid triglyceride level exceeds 110 mg/dL, the patient probably has a chylothorax; if the level is below 50 mg/dL, the patient does not have a chylothorax (99). If the level is between 50 and 110 mg/dL, lipoprotein electrophoresis should be performed (99) (see Chapter 26).

Other Diagnostic Tests

Numerous articles have recommended various diagnostic tests such as flow cytometry, chromosomal analysis of pleural fluid cells, or LDH isoenzymes in the diagnosis of malignant pleural effusions. These various tests are discussed in Chapter 7. In general, they are not recommended. Flow cytometry with immunophenotyping is useful in making the diagnosis of lymphoma (59).

Unknown Primary

Most patients who are diagnosed with a malignant pleural effusion are already known to have a malignancy. However, if the patient presents with a malignant pleural effusion, where is its likely origin? One study (100) reviewed 42 consecutive patients referred to the Royal Marsden Hospital with a malignant pleural effusion and no known primary. The patients included 27 men and 15 women. Despite CT scans of chest and abdomen and mammography and pelvic ultrasound in 10 patients, a primary was determined in only 15 (10 men and 5 women), and the primary was in the lung in all cases (100). The median survival in this group was 12 months from diagnosis (100).

In view of the findings mentioned in the preceding text, it is recommended that patients with a malignant pleural effusion and an unknown primary tumor have a CT scan of the chest, abdomen, and pelvis. If pulmonary parenchymal abnormalities are discovered, then a bronchoscopy is indicated with special attention to the area of abnormality. If there are no parenchymal abnormalities, then bronchoscopy will probably be nondiagnostic (100). Masses in the abdomen should be evaluated. If the patient has symptoms referable to a specific organ, that organ should be evaluated. If the patient is a woman, mammography and a careful pelvic examination should be performed. If the foregoing sequence of tests does not identify the site of the primary tumor, it is recommended that further tests not be undertaken (100).

PROGNOSIS

The prognosis of patients with malignant pleural effusions is not good. In a one report, the median survival of 417 patients with malignant pleural effusions was only 4 months (71). This 4-month median survival is on the optimistic side because all 417 patients were judged to be fit enough to undergo pleurodesis (71). The most important factor influencing the life expectancy in patients with malignant pleural effusion is the source of the tumor. In the study mentioned in the preceding text, the median survivals were 3 months for 146 patients with lung cancer, 2.3 months for 18 patients with gastrointestinal primaries, 5 months for 60 patients with breast carcinoma and 51 patients with unknown primary, and 6 months for 29 patients with mesothelioma (71). In a more recent report (101) of 284 patients with malignant pleural effusion, the overall median survival was 5.4 months following diagnosis. Again survival varied significantly depending on the primary tuber being 17.4 months for mesothelioma, 13.2 months for breast cancer, 7 months for lymphoma and 2.6 months for lung cancer (101). A second factor that is very important in determining the prognosis of patients is their Karnofsky Performance Scale (KPS) score. Burrows et al. (102) reported that the median survival of patients with a KPS score less than 30 was 34 days, whereas the median survival of patients with a KPS score greater than 70 was 395 days.

Other factors associated with a poor prognosis are a pleural fluid pH level below 7.20, a pleural fluid glucose level below 60 mg/dL, or a pleural fluid LDH level more than twice the upper limit of normal for serum (71,101,102). In addition, the greater the number of pleural adhesions at thoracoscopy (103) and the higher the VEGF level in pleural effusions due to lung cancer (104), the poorer the prognosis. All of the poor prognostic factors mentioned in the preceding text probably reflect a greater tumor burden in the pleural space (71,102).

TREATMENT

The presence of a malignant pleural effusion indicates that the malignancy cannot be cured by surgery. Management of the effusion centers on palliation of symptoms because no available treatments prolong survival (Fig. 10.1).

The initial step is to identify the location of the primary lesion. Frequently, the location of the primary is already known when the pleural effusion is first identified. If the primary is unknown, then the procedures outlined in the preceding paragraph on unknown primary should be followed.

The main reason to identify the primary tumor is to decide whether systemic chemotherapy is indicated. Systemic chemotherapy is effective at least in some patients with small-cell carcinoma, breast carcinoma non-small-cell lung cancer and lymphoma. If the patient has a chylothorax, radiation should be administered to the mediastinum.

If the patient has a tumor that is not responsive to chemotherapy or fails to respond to chemotherapy, a procedure should be considered to remove the pleural fluid. The two primary modes of treatment to control the accumulation of pleural fluid are the insertion of an indwelling pleural catheter or the creation of a pleurodesis. Only patients who are dyspneic and whose dyspnea improves after a therapeutic thoracentesis should be considered candidates for fluid removal. If the patient is not symptomatic from the pleural effusion, no treatment is recommended. Most patients who have small effusions that do not produce symptoms never become symptomatic (105). The dyspnea of patients who do not improve after a therapeutic thoracentesis should be treated with opiates and/or oxygen. Before a pleurodesis is attempted, the position of the mediastinum on the chest radiograph should be noted. If the mediastinum is shifted toward the side of the effusion, a bronchoscopy should be done before pleurodesis is attempted because it is likely that the patient has an obstructed bronchus. The presence of an obstructed bronchus is a contraindication to pleurodesis.

If the patient is dyspneic and if the dyspnea is relieved by a therapeutic thoracentesis, the procedure

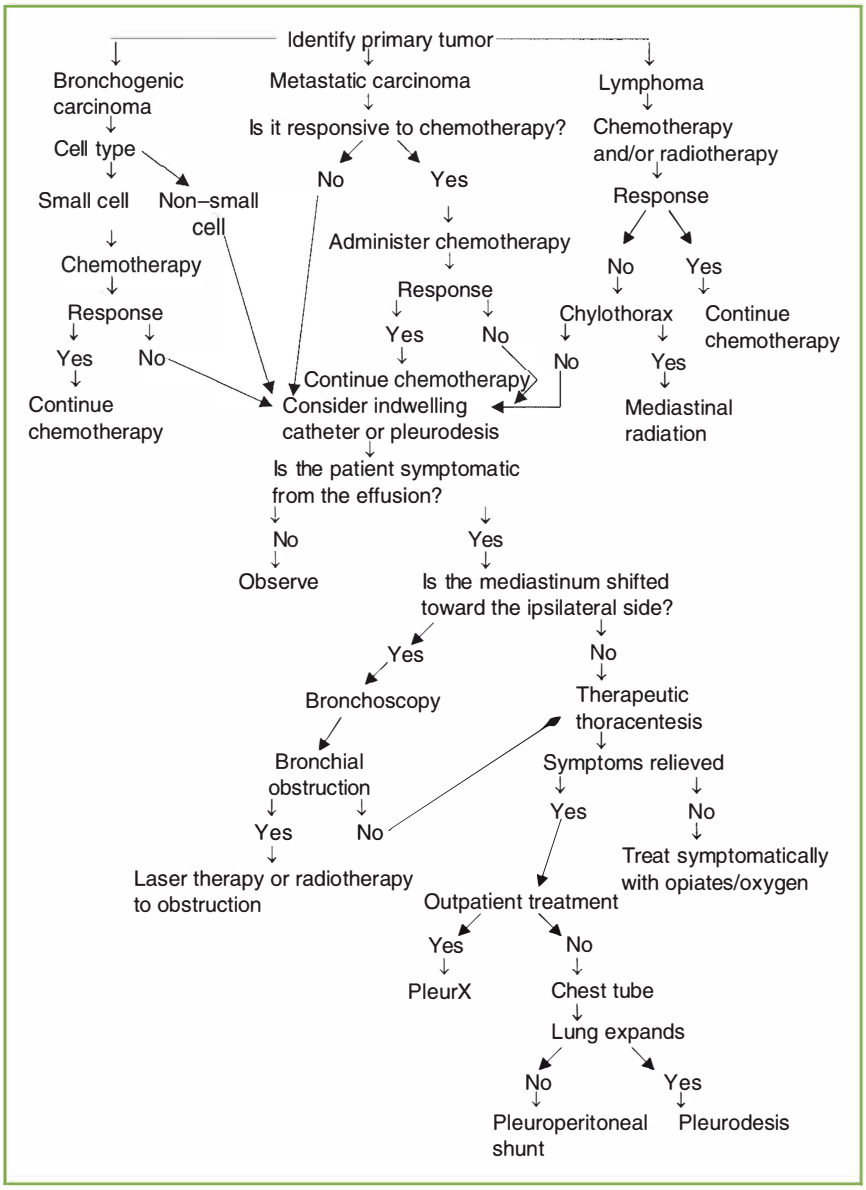


FIGURE 10.1 ■ Algorithm for managing patients with malignant pleural effusions.

of choice for outpatients who can receive home health care or who have strong family support for controlling the pleural fluid is the insertion of an indwelling catheter with periodic drainage of the pleural fluid through vacuum bottles. If patients do not meet these criteria, pleurodesis with a sclerosing agent through a chest tube is the procedure of choice. If the lung does not expand after the chest tube is inserted, pleurodesis should not be attempted (106). These patients can be treated with either an indwelling pleural catheter or a pleuroperitoneal shunt.

Systemic Chemotherapy

The presence of a malignant pleural effusion usually indicates disseminated tumor, at least for nonbronchogenic carcinoma (43). Therefore, the only hope for cure or prolonged palliation is with systemic

chemotherapy. Fentiman et al. (26) reported that pleural effusions were controlled in 7 of 22 patients (32%) with metastatic breast carcinoma who were given systemic chemotherapy, whereas Jones et al. (107) reported positive responses in 6 of 8 patients (75%) given systemic chemotherapy. There are no recent reports to my knowledge concerning the outcomes of malignant pleural effusions with breast cancer treated with systemic chemotherapy. Livingston et al. (108) reported that 19 of 53 patients (36%) with small-cell lung carcinoma had complete disappearance of their pleural effusions with chemotherapy. The median survival of patients with small-cell lung carcinoma with limited disease and a pleural effusion is 13.9 months, compared with a median survival of 18.3 months if no pleural effusion is present (109). In a second study of 62 patients with small-cell lung carcinoma, the pleural effusion disappeared after first-line chemotherapy in 34 patients (55%) (8). In addition, pleural effusions in lymphomas frequently respond to chemotherapy (35).

There is one report in which the administration of cisplatin, ifosfamide, and irinotecan to 34 patients with NSCLC and pleural effusion resulted in the complete disappearance of the effusion in 13 patients (38%), a partial resolution in 7 patients (21%), and a mean survival of 362 days. If these results can be confirmed, this regimen may prove useful in treating and extending the life of patients with adenocarcinomas of the lung. In recent years, it has been shown that the anti-VEGF antibody bevacizumab, combined with standard first-line chemotherapy, provides a statistically and clinically significant survival advantage in patients with NSCLC (110). It is important not to attempt pleurodesis in patients who are receiving an anti-VEGF drug because angiogenesis is necessary for pleurodesis and angiogenesis is inhibited by anti-VEGF drugs (111).

In patients undergoing systemic chemotherapy with methotrexate, pleural effusions should be aspirated before chemotherapy is given because the antineoplastic drugs may accumulate in the pleural space and lead to increased systemic toxicity (112,113). However, if the patients are receiving chemotherapy with pemetrexed, there is no reason to aspirate the pleural fluid (114).

Intrapleural Chemotherapy

There have been several articles that evaluated the usefulness of intrapleural chemotherapy for the management of malignant pleural effusions. In general, most have been disappointing. The presence of a malignant pleural effusion indicates that the tumor is disseminated and that local chemotherapy is unlikely to be useful. However, if intrapleural chemotherapy decreased the number of tumor cells in the pleural space, the rate of pleural fluid formation might decrease.

In one recent study, excellent results were obtained in 27 patients with NSCLC who received a combination of radiotherapy, intrapleural chemotherapy, and systemic chemotherapy (115). The regimen consisted of cisplatin 60 mg/m^2 intrapleurally on day 1; gemcitabine 1,000 mg/m^2 intravenously on days 1, 8, and 15 and every 4 weeks for three times. This was followed by radiotherapy (7,020 cGy/39 fr) and then postradiation chemotherapy (docetaxel 60 mg/m^2 every 3 weeks for three to six times). Only two patients experienced recurrence of the pleural effusion (115). The overall response rate was 55% with 7% complete and 48% partial remissions (115). The median overall survival was 18 months, which is approximately six times longer than one expects with malignant pleural effusions secondary to NSCLC. It is unclear how much one cycle of intrapleural chemotherapy contributed to the overall results.

In a second study, the therapeutic efficacy of *Staphylococcus aureus* superantigen (SSAg), a powerful T-cell stimulant, was evaluated in patients with malignant pleural effusion from NSCLC (116). In a small study of 14 patients with a median pretreatment KPS score of 40 received the pleural instillation of SSAg, 100 to 400 mg, once or twice weekly until the pleural effusions resolved (116). The effusions were completely controlled in 11 patients and the median survival was 7 months (116). If these results are confirmed in additional studies, this regimen is attractive because it not only controls the effusion, but also increases survival.

There is one case report in which the intrapleural administration of increasing doses of rituximab, a monoclonal antibody directed against the CD20 antigen on the surface of B lymphocytes, was effective in controlling a pleural effusion in a patient with a CD 20$^+$ non-Hodgkin's lymphoma (117). Interferon-gamma (118), tumor necrosis factor (119), interleukin-2 (119), cisplatin (120), and the monoclonal antibody catumaxomab (121) have all been tried in small numbers of patients with results that are not particularly impressive.

Mediastinal Radiation

When a patient with a malignant pleural effusion has a chylothorax, the thoracic duct is usually involved

by the neoplastic process. Therefore, it is logical to administer radiotherapy to the mediastinum in such patients who have tumor types that are resistant to primary chemotherapy. In one series, mediastinal radiation resulted in adequate control of the chylothorax for the remainder of the patients' lives in 68% of those with lymphomas and in 50% of those with metastatic carcinoma (122). Other means to manage chylothorax are discussed in Chapter 26.

Indwelling Pleural Catheter (PleurX)

The PleurX catheter (Fig. 10.2) or other indwelling catheters such as the Rocket (UK) allow patients with recurrent pleural effusions to have their pleural fluid drained repeatedly without having to return to the hospital. The PleurX catheter is a 15.5 F silicone rubber catheter, 66 cm in length, with fenestrations along the proximal 24 cm (CareFusion Corporation, San Diego, CA). It is inserted into the pleural space using the Seldinger technique under local anesthesia by pulmonologists, interventional radiologists, or surgeons. The catheter is maintained in place with a chest wall tunnel 5 to 8 cm in length (123,124). This particular catheter has a special valve on its distal end that is designed to enhance the safety of the product. The valve prevents fluid or air from passing in either direction through the catheter unless the catheter is accessed with the matched drainage line. The pleural fluid is drained intermittently by inserting the access tip of the drainage line into the valve of the catheter and then draining the fluid through an external tube into vacuum bottles.

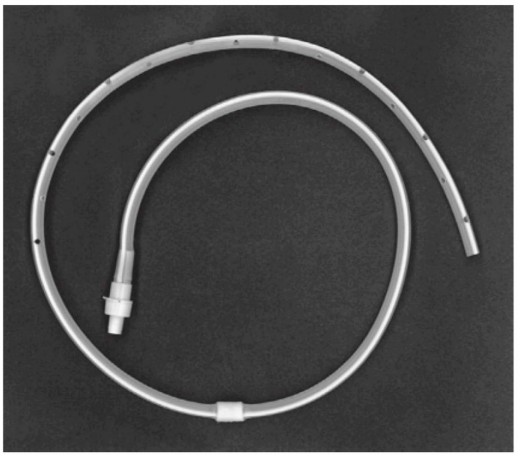


FIGURE 10.2 ■ PleurX catheter.

In the initial multicenter study using this catheter to treat malignant pleural effusions, the efficacy and safety of the catheter were compared with those of doxycycline pleurodesis through tube thoracostomy. All patients were initially hospitalized. The median hospitalization for the 94 patients who received the PleurX catheter was 1 day, whereas the median hospitalization for the 41 patients who had doxycycline pleurodesis was 6.5 days. Of the 94 patients who received the PleurX catheter, the effusion was initially controlled by the catheter in 91 (97%). The presence of the catheter leads to a spontaneous pleurodesis in approximately 50% of patients with a median time to pleurodesis of 28 days (125). Patients who experienced a pleurodesis tended to have a gradual decrease in the amount of pleural fluid formed daily (44). Several of the patients had the catheter in place for more than 1 year.

Since the original study, several studies have documented the feasibility of implanting the PleurX catheter as an outpatient. Putnam et al. (124) retrospectively compared their experience with 100 patients (including 60 outpatients) who were treated with the PleurX catheter and 68 patients treated with tube thoracostomy using either doxycycline or talc as a pleurodesing agent. The median survival was 3.4 months and did not differ significantly between treatment groups (124). The early mean charges were approximately US$8,000 in the inpatient chest tube group and US$3,400 in the outpatient pleural catheter group (126). The cost differential is decreased over longer periods as the suction bottles are expensive. This cost can be markedly decreased if the pleural fluid is drained repeatedly into an accordion drain (127). Musani et al. (128) reported their results with the outpatient insertion of the catheters in 24 patients. They reported that all patients experienced symptomatic relief and spontaneous pleurodesis occurred in 58%.

There have been two studies with at least 250 pleural catheter insertions (125,129). In the first large series regarding the utility of the indwelling catheter, Tremblay and Michaud (125) retrospectively reviewed their experience at a single center with 250 tunneled pleural catheter insertions in 223 patients for malignant pleural effusion. Home nursing support was organized for all patients to assist with catheter care. They reported that the tunneled catheter insertion resulted in complete symptom control in 38.8%, partial control in 50% and no control in 3.6%. In addition, there were 4% failed insertions and the symptoms were not evaluated in 3.6% (125). In most patients, the catheter was inserted on an outpatient

basis by pulmonologists in a bronchoscopy suite. Spontaneous pleurodesis occurred after 43% of the procedures (125). Five patients (2.2%) did develop empyema. The overall median survival was 144 days (125). These authors concluded that the insertion of a tunneled indwelling catheter should be considered as a first-line treatment option in the management of patients with malignant pleural effusions (125).

The second large study was reported by Warren et al. (129) who inserted 295 catheters in 263 patients. Spontaneous pleurodesis occurred in 173 (58.6%) of the patients after the catheters were in place an average of 29.4 days (129). Subsequently only 5/173 pleural spaces reaccumulated pleural fluid that produced dyspnea (129). These workers reported that spontaneous pleurodesis was more common in patients with breast or gynecologic primary tumors, absence of chest wall irradiation, cytologic positivity and complete reexpansion of the underlying lung.

Van Meter et al. (130) have recently performed a systematic review of 19 studies with a total of 1,370 patients who received the tunneled pleural catheter. They reported that symptomatic improvement occurred in 95.6% of the patients and that spontaneous pleurodesis occurred in 45.6% (130).

The morbidity from the catheter is relatively low (123). In the initial study early (in-hospital) morbidity occurred in 10 of 96 patients and included fever (3 patients), pneumothorax (3 patients), misplacement of the catheter (2 patients), reexpansion pulmonary edema (1 patient), and hypercapnic respiratory failure secondary to oversedation (1 patient). In the 90-day follow-up period, three patients developed tumor seeding of the catheter tract that did not require therapy. Six patients developed local cellulitis around the catheter tract that responded to oral antibiotic treatment, and seven patients reported pain during fluid drainage. In the review by Van Meter et al. (130), 2.8% developed empyema, 3.9% developed pneumothorax, and in 3.7% developed obstruction of the catheter. The use of the tunneled pleural catheter was without complication in 87.5% (130). One uncommon complication of the indwelling pleural catheter is tumor metastasis along the tract between the pleura and skin surface (131,134).

The two most significant complications with the indwelling catheter are pleural infection and obstruction of the catheter. The incidence of empyema is about 2.8% (130), but the definition of empyema has varied from study to study. The incidence of infection does not appear to be higher if the patient is receiving chemotherapy (132,135). The catheter-related empyemas should be treated on an inpatient basis with broad-spectrum intravenous antibiotics and drainage of the pleural space via the indwelling catheter (139). The incidence of obstruction of the catheter is about 3.7% (130). Such obstructions can be due to fibrin accumulations or obstruction of the holes in the catheter by tumor. If the obstruction is due to fibrin, the patency of the catheter can frequently be restored via the instillation of a fibrinolytic into the pleural space (133). The indwelling catheter may also become fractured when attempts are made to remove it (134). In one series (134), this happened in 6 of 61 cases when attempts were made to remove the catheter. However, there appears to be no ill consequences from this complication and the end of the catheter can be left in the pleural space (134).

The PleurX catheter is an advance in the management of patients with malignant pleural effusions because it allows patients to be treated easily as outpatients and obviates the necessity for return visits for a repeat thoracentesis. When the PleurX catheter is used, it is important to educate the patient and/or the family in caring for the catheter or to have home health care. It should be noted, moreover, that approximately 50% of the patients never experience a spontaneous pleurodesis and therefore are burdened with the catheter for the remainder of their lives. Because there are complications associated with prolonged use of the catheter (e.g., empyema, tumor seeding of catheter tract, loculation of the effusion), it is recommended that patients who have weekly pleural fluid production of more than 1,000 mL fluid after the catheter has been in place for 7 to 14 days have an attempt at chemical pleurodesis through the PleurX catheter.

Pleurodesis

For the last few decades, most patients with malignant pleural effusions who had symptomatic improvement with a therapeutic thoracentesis were managed by injecting a sclerosing agent through a chest tube. The creation of a pleurodesis through tube thoracostomy is still a useful way to manage a malignant pleural effusion, although most malignant pleural effusions are managed by tunneled catheters in many centers.

Pleurodesis should be considered in patients with malignant pleural effusions who are not candidates for the tunneled catheter or systemic chemotherapy and who do not have a chylothorax. This procedure should also be considered in those for whom systemic chemotherapy or mediastinal radiotherapy has failed.

When managing such a patient, the first question to answer is whether the patient is symptomatic from the effusion. The only symptom likely to be relieved with pleurodesis is dyspnea. If the patient does not have symptoms attributable to the pleural effusion, it does not make sense to insert a chest tube and to attempt a pleurodesis just to make the chest radiograph look better. In a similar vein, if the patient is moribund from disseminated tumor, he or she should not be tortured for the last few days of his or her life with chest tubes. If a patient's quality of life is diminished by dyspnea and he or she has a life expectancy of more than a few weeks, however, one should consider pleurodesis. This local therapy probably does not improve the duration of the patient's life, but it can improve the quality of life.

Before a pleurodesis is attempted, the position of the mediastinum on the chest radiograph should be evaluated, because its position tells much about the pleural pressure on the side of the effusion. If the mediastinum is shifted toward the side of the effusion (Fig. 10.3), the pleural pressure is more negative on the side of the effusion. Pleurodesis is then unlikely to be successful because the ipsilateral lung is unable to expand. In such patients, a bronchoscopic examination should be performed to assess the patency of the major bronchi. If neoplastic obstruction of the bronchi is discovered, radiotherapy, laser therapy, or an endobronchial stent should be considered for relief of the bronchial obstruction. If no obstructing lesion is found, the lung is probably encased by the tumor, and pleurodesis is likely to fail. In this situation, if the patient has symptomatic relief after a therapeutic thoracentesis, insertion of a PleurX catheter or a pleuroperitoneal shunt should be considered. In rare situations a pleurectomy (see the discussion on pleurectomy in this chapter) can be considered.

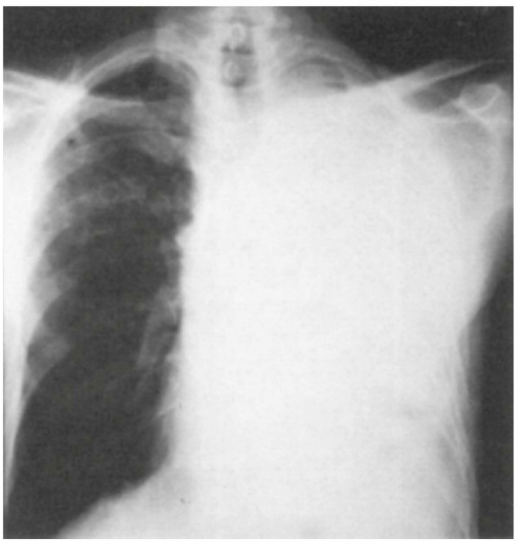


FIGURE 10.3 ■ Posteroanterior chest radiograph from a patient with a malignant pleural effusion. Note that the mediastinum is shifted toward the side of the effusion.

If the mediastinum is in midline position or has shifted to the contralateral side (Fig. 10.4), then a therapeutic thoracentesis (see Chapter 28) should be performed. The purpose of this procedure is to determine whether it relieves the dyspnea of the patient. Only those patients who experience significant symptomatic improvement from this thoracentesis should be considered to be candidates for chemical pleurodesis. The exercise tolerance does not increase in a substantial fraction of patients with a malignant pleural effusion after a therapeutic thoracentesis (135,136). In like manner, there is no decrease in the level of dyspnea at a given workload in many patients (135,136).

Prognostic Factors for Successful Chemical Pleurodesis

In the past, it has been shown that if the pleural fluid pH or glucose levels are reduced, pleurodesis is less likely to be successful (74,137). In one large series in which pleurodesis was attempted with talc insufflation during thoracoscopy, pleurodesis failed in 6 of 14 patients (43%) if the pleural fluid pH level was below 7.2 but only in 8 of 92 patients (9%) if the pleural fluid pH level was above 7.2 (137). Comparable findings have been reported when the pleurodesis was attempted with intrapleural tetracycline (74). Similar results are reported when a glucose measurement of less than 60 mg/dL was used as a predictor of pleurodesis failure. One review of 433 patients undergoing pleurodesis found that the pleural fluid pH level was the only independent predictor of pleurodesis failure (71). Interestingly, the receiver operator curves (ROC) for the pleural fluid pH, pleural fluid glucose, and pleural fluid LDH levels were virtually superimposable (71). Nevertheless, a low pleural fluid pH level should not be taken as an absolute contraindication to chemical pleurodesis because 40% of patients with a pleural fluid pH below 7 will still have a successful pleurodesis and 68% of the patients with pleural fluid pH below 7.3 will also have a successful pleurodesis (71). Interestingly, in this large series, there was no association between pleurodesis success

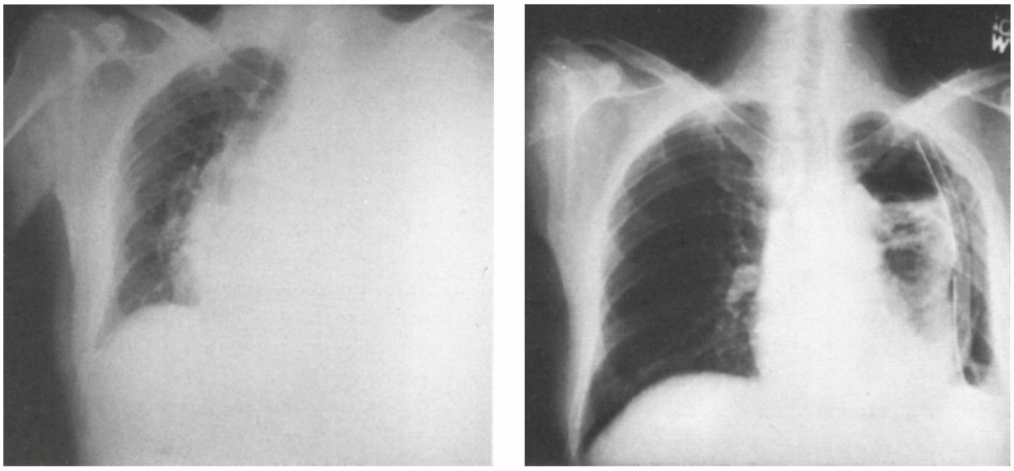


FIGURE 10.4 ■ A: Posteroanterior chest radiograph from a patient with a malignant pleural effusion. Note that the mediastinum is shifted away from the side with the pleural effusion. **B**: Posteroanterior chest radiograph from the same patient after insertion of a chest tube into the left pleural space. Note that the left lung is not well expanded. Accordingly, a sclerosing agent should not be injected into the pleural space.

and the pleurodesis technique (thoracoscopy vs. tube thoracostomy), pleurodesis agent (talc, bleomycin, or tetracycline derivative), or tumor type (71).

The success rate with pleurodesis is related to the changes in pleural pressure during thoracentesis. Lan et al. (138) measured the change in pleural pressure after 500 mL of pleural fluid had been withdrawn from 65 patients with a malignant pleural effusion. They then inserted a chest tube and continued to drain the lung until (a) the drainage was less than 150 mL/day, (b) the drainage was less than 250 mL/day for 4 consecutive days, or (c) the drainage had continued for 10 days. At this time, they attempted pleurodesis if the lung had expanded. They found that 14 patients had a pleural elastance greater than 19 cm H_2O, that is, the pleural pressure decreased by more than 9.5 cm H_2O when the 500 mL of pleural fluid was withdrawn. They found that 11 of the 14 patients had a lung that had not expanded. Pleurodesis was attempted in the remaining three patients with bleomycin and failed in all. In contrast, only 3 of the 51 patients with pleural elastance less than 19 cm H_2O had a trapped lung and bleomycin pleurodesis was successful at 1 month in 42 of 43 (98%) of the patients who returned for reevaluation.

The results of the study mentioned in the preceding text could have been anticipated because pleurodesis will fail if the two pleural surfaces cannot be brought into approximation. The rapid fall in the pleural pressure is an indication that the underlying lung is unlikely to expand with the removal of the pleural fluid.

The success rate with pleurodesis is also related to the site of the primary tumor. Bielsa et al. (139) reviewed the outcome of pleurodesis attempts in 126 patients who received doxycycline and 447 patient who received talc poudrage. They reported that in the talc group patients with lung cancer and mesothelioma had a significantly lower complete response rate (63% and 61%, respectively) than did patient with breast (77%) or other metastatic effusions (74%) (139). Similar conclusions could be made in the doxycycline group (139).

Mechanisms for Pleurodesis

Originally, antineoplastic agents such as nitrogen mustard (140) or radioisotopes (141) were injected into the pleural space in the hope that these agents would kill the tumor cells and control the pleural effusion. It was subsequently shown that the injection of these agents often controlled the pleural effusion when tumor cells persisted and that the effectiveness of intrapleural therapy was related more to the creation of a pleurodesis that prevented the accumulation of the pleural fluid than to any antineoplastic effect of the agent administered (142,143). The effectiveness of intracavitary nitrogen mustard is much greater when the instillation of this agent is combined with tube thoracostomy (4), because the apposition of the two pleural surfaces allows the fibrotic process to obliterate the pleural space.

Subsequent to the demonstration of the importance of the chemical pleuritis in controlling pleural effusions, nonspecific irritants such as talc (144), tetracycline derivatives (145), silver nitrate, iodopovidone, and quinacrine (146) were combined with tube thoracostomy in an attempt to control malignant effusions. The initial event in the production of a pleurodesis by these agents without question is an injury to the pleura. An acute exudative pleural effusion develops within 12 hours of the instillation of essentially all the agents that are currently used for pleurodesis including talc (147), tetracycline derivatives (148), quinacrine (149), mitoxantrone (150), and bleomycin (149). The pleural fluid that accumulates after the intrapleural injection of these agents is initially characterized by relatively high protein and LDH levels, and neutrophil counts (151). However, injury to the pleura, as evidenced by the production of an acute exudative pleural effusion, is not sufficient to induce a pleurodesis because many agents, when injected intrapleurally, produce an acute exudative effusion but do not produce a pleurodesis (149).

The response of the pleura to an injury is a complex and incompletely understood multifactorial process that can result in the development of fibrosis with the obliteration of the pleural space, or it can result in restoration of the pleura to its normal state. The mechanisms of pleurodesis seem to differ from agent to agent. The histologic appearance is much different with mitoxantrone (150) than it is with talc (147) or tetracycline derivatives (148). The pleurodesis that follows talc, but not tetracycline, can be blocked if corticosteroids are given systemically (152) or if tumor necrosis factor alpha-blocking antibodies (153) are given intrapleurally immediately after talc is administered.

The balance between the procoagulant system and the fibrinolytic system is also important in determining whether a pleurodesis will result after the intrapleural injection of a substance. If the procoagulant system dominates, then pleurodesis will result, whereas if the fibrinolytic system dominates, no pleurodesis will result. When rabbits are given tetracycline intrapleurally, the number of pleural adhesions that occur is reduced if the rabbits are given either heparin or urokinase intrapleurally (154). In humans, pleurodesis occurs after talc insufflation only if the intrapleural fibrinolytic activity decreases (155).

Transforming Growth Factor β

Without a doubt, cytokines are involved in the production of a pleurodesis, but the importance of various cytokines in inducing either fibrosis or repair remains to be determined. In the future, it is likely that pleurodesis will be produced by the intrapleural injection of cytokines. One cytokine that is an excellent candidate as an effective pleurodesis-producing agent is transforming growth factor-β (TGF-β). TGF-β has several characteristics that would be important for a pleurodesis agent: (a) TGF-β is a potent fibrogenic cytokine that regulates extracellular matrix production. In situations in which there is too much TGF-β, fibrosis results (156). The transient overexpression of TGF-β in the rat lung leads to marked pleural and interstitial fibrosis (157). (b) Once present, TGF-β can induce its own transcription (158), which suggests that a single injection may be sufficient. (c) Mesothelial cells express and secrete TGF-β; therefore, one intrapleural injection of TGF-β might result in prolonged secretion of TGF-β, which could result in pleurodesis. (d) The incubation of human pleural mesothelial cells with TGF-β results in secretion of increased levels of plasminogen activator inhibitor 1 (PAI-1) (159). This could facilitate pleurodesis because inhibition of the fibrinolytic system is thought to be necessary for the production of a pleurodesis (155).

Our preliminary studies in both rabbits (151) and sheep (160,161) demonstrate that the intrapleural injection of small amounts of TGF-β results in a better pleurodesis than does the intrapleural injection of either doxycycline or talc slurry. The pleurodesis after TGF-β occurs faster than after talc (162). Moreover, the pleural fluid that results from the intrapleural injection of TGF-β is characterized by a much lower WBC count and LDH level than the fluid that results from the intrapleural injection of doxycycline or talc slurry (151). The pleurodesis following intrapleural TGF-β is not inhibited by corticosteroids (163). We believe that TGF-β produces a fibrotic reaction in the pleural space without the necessity for a pleural injury. If indeed this is the situation, TGF-β will be an ideal agent for pleurodesis. Presently, the effectiveness and safety of TGF-β as an agent for pleurodesis in humans is awaiting clinical trials.

Vascular Endothelial Growth Factor

When mesothelial cells are incubated with TGF-β, the mesothelial cells produce increased amounts of VEGF (164). In addition, the pleural fluid levels of VEGF are significantly correlated with the levels of TGF-β in patients with pleural effusions (165). We noted that when pleurodesis was induced in rabbits

by the intrapleural administration of TGF-β, there was much more pleural fluid than when pleurodesis was induced with doxycycline or talc slurry (110). We therefore hypothesized that the increased amounts of pleural fluid with TGF-β were due to increased amounts of VEGF. However, when we administered anti-VEGF antibodies to the rabbits, the amount of pleural fluid was just slightly diminished, but no pleurodesis occurred (111). When the pleural tissues were assessed for the amount of vasculature, there was a close correlation between the amount of vasculature and the pleurodesis scores (111). This study demonstrated that angiogenesis is very important in the production of a pleurodesis and pleurodesis should not be attempted in patients who are receiving anti-VEGF regimens.

Choice of Sclerosing Agent

Currently, the agents that are most commonly recommended are talc (either insufflated or as a slurry), the tetracycline derivatives (minocycline or doxycycline), the antineoplastic agents (bleomycin or mitoxantrone), silver nitrate and iodopovidone. A brief discussion of the various agents proposed as sclerosing agents follows.

Talc

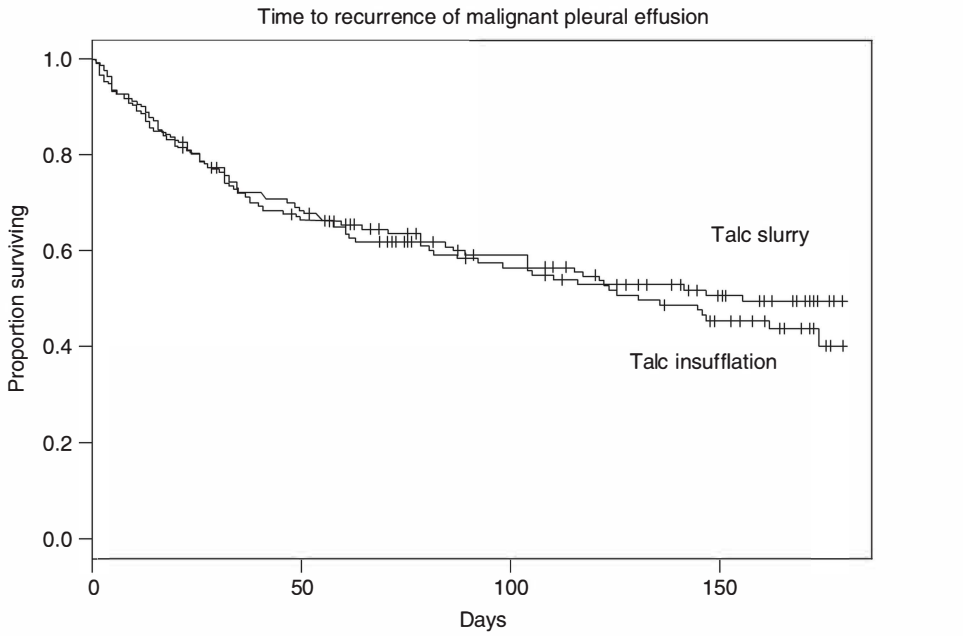
The sclerosing agent that is most commonly used for chemical pleurodesis in English speaking countries is talc (166). In a survey of 841 pulmonologists in English speaking countries, talc slurry was the agent of choice in 55.6%, whereas insufflated talc was the agent of choice in 12.2%. Talc is also the agent recommended by the Dutch Society of Pulmonologists (167) and the British Thoracic Society (168). The reason that talc is used most commonly is that it is widely available, inexpensive, and is *perceived* to be effective. Talc can be instilled into the pleural space either as slurry (suspended in saline) or insufflated (as an aerosol). Talc insufflation is usually done at the time of thoracoscopy and this procedure is discussed later in the section on Thoracoscopy for Pleurodesis.

Animal studies have demonstrated that the intrapleural administration of talc slurry can produce a pleurodesis if the pleura is normal (see Chapter 4). However, there is no convincing evidence that talc is superior to other agents. In our rabbit model, talc slurry at a dose of 400 mg/kg produces a pleurodesis (169), but doxycycline, 10 mg/kg, is at least as effective (151). Moreover, it should be noted that the dose of talc slurry necessary to produce a pleurodesis in rabbits (400 mg/kg) is much higher than that typically used in patients (~100 mg/kg) (170). Bresticker et al. (171) reported that talc insufflation (1 g) and mechanical abrasion were essentially equivalent in producing pleurodesis in dogs, whereas Jerram et al. (172) reported that mechanical abrasion was superior to talc slurry in producing pleurodesis in dogs.

It appears that talc in a slurry is effective in producing a pleurodesis in humans (172–176). Dresler et al. (176) randomized 482 patients to receive 4 to 5 g of talc, either administered as a slurry in 100 mL saline through a chest tube or insufflated during thoracoscopy. The results in this study were much poorer than those reported previously (Fig. 10.5). Of the 163 patients that received talc slurry and whose lung was more than 90% expanded, only 56% were alive without recurrence at 30 days. Moreover, 29% of those alive had a recurrence by 30 days (176). Burgers et al. (167) reported that 36% of 64 patients had a recurrence at a mean of 17 days. Other uncontrolled studies or studies with fewer patients have reported better results with talc slurry. Adler and Sayek (144) treated 44 hemithoraces with malignant pleural effusion with 10 g of talc in 250 mL of saline and reported control of the effusion in 41 (93%). Kennedy et al. (175) reported that 10 g of talc mixed in 150 to 250 mL of saline effectively controlled 38 of 47 (81%) malignant pleural effusions. Haddad et al. (177) administered 4 g of talc slurry to 37 patients with malignant effusions and reported that the success rate at 60 days was 85%.

Aydogmus et al. (178) analyzed the factors associated with successful pleurodesis with talc slurry. They found the success rate was significantly higher if the time period between the diagnosis of effusion and administration of talc slurry was less than 30 days or spontaneous expansion was attained after chest tube drain of if the daily drainage was less than 200 ml before talc slurry (178). The success rate was not related to the source of the primary tumor or the amount of drainage when chest tube drainage was terminated (178).

The primary concern with talc is that its intrapleural administration has been associated with the development of the acute respiratory distress syndrome (ARDS). The incidence of ARDS following intrapleural talc has varied markedly from series to series, and most of the reported cases have been from the United States. The highest incidence was that reported by Rehse et al. (179), who retrospectively reviewed their experience of 89 talc pleurodesis procedures in 78 patients after 1 patient developed fulminant



Number of patients at risk for given time points

Treatment	0 days	30 days	60 days	90 days	120 days	150 days	180 days
Slurry	221	135	89	66	59	44	26
Insufflation	228	144	54	61	51	38	19
Total	449	279	173	127	110	82	45

FIGURE 10.5 ■ Time to recurrence of pleural effusion after patients received either talc slurry or insufflated talc. *(Reprinted with permission Dresler CM, Olak J, Herndon JE II, et al. Phase III intergroup study of talc poudrage vs. talc slurry sclerosis for malignant pleural effusion.* Chest. *2005;127:909–915.)*

pneumonia after receiving talc. They reported that seven patients (9%) developed ARDS requiring mechanical ventilation, and one of their patients died (179). All their patients received 5 g of talc, and three patients had received insufflated talc, whereas four received talc slurry. In the multicenter study from the United States reported by Dresler et al. (176), respiratory failure developed in 8 (4%) of the patients that received talc slurry and 18 (8.1%) of the patients that received insufflated talc. Eleven of the patients with respiratory failure died (176). Brant and Eaton (126) reviewed 33 instances of talc pleurodesis performed in 29 patients and reported that major complications of hypoxemia and hypotension occurred in 7 patients, and 2 of these patients died.

In contrast, studies from Europe have reported virtually no cases of ARDS or death following the intrapleural administration of talc. Weissberg and Ben-Zeev (180) observed no cases of ARDS in 360 cases who received 2 g talc intrapleurally (some with insufflation and some with slurry) and concluded that the ARDS was dose related. This is not necessarily the case, however, because of the four fatal cases reported by Campos et al. (181) all had received only 2 g of insufflated talc. It should be noted, however, that when Montes et al. (182) injected rabbits with 50 or 200 mL/kg talc intrapleurally, there was more systemic talc deposition in the animals that received the high dose than in the rabbits that received the low dose. In Germany, Schulze et al. (183) treated 105 patients with insufflated talc and reported no cases of ARDS. Janssen and coworkers (184) in a multicenter, open-label, prospective cohort study of 558 patient who received 4 g of calibrated French large-particle size talc for malignant effusion reported that there no instances of ARDS. However, seven patients did

develop pulmonary infiltrates which they attributed to reexpansion pulmonary edema in 2, cardiogenic pulmonary edema in 1 and respiratory failure unrelated to talc in 1 (184). I am not convinced that the pulmonary infiltrates in some of these patients were not related to the talc.

The mechanism responsible for the ARDS after intrapleural talc is not definitely known. The acute lung injury could be due either to talc itself or its contaminants such as bacteria, fungi, endotoxin, dolomite, quartz, kaolinite, calcite, or chlorite. One hypothesis is that the acute pneumonitis is related to the systemic absorption of talc with the subsequent elaboration of inflammatory mediators. This hypothesis is supported by the observations in the case reported by Rinaldo et al. (185) in which there were large quantities of talc in the bronchoalveolar lavage fluid of their patient. Talc particles were also found in the bronchoalveolar lavage in all four of the patients reported by Ribas-Milanez de Campos et al. (186). In addition, one of the patients reported by Ribas-Milanez de Campos et al. died, and this patient had talc particles present in almost every organ at autopsy, including the ipsilateral and contralateral lung, brain, liver, kidney, heart, and skeletal muscle.

The systemic effects of talc are greater than those of the tetracycline derivatives. Maskell et al. (187) randomized 20 patients with malignant effusions to intrapleural tetracycline or mixed talc (most talc particles <15 μm) and measured changes in the systemic inflammation from lung clearance scans, oxygen saturations, and C-reactive protein concentrations from baseline to 48 hours after pleurodesis. The changes in the systemic inflammation, oxygen saturations, and the C-reactive protein were all significantly greater in the group that received the talc (187).

One hypothesis to explain the varying incidences of ARDS from country to country is that the incidence of ARDS is higher in countries where talc preparations with smaller particles are used. There would be more systemic inflammation from the talc preparations with smaller diameters because the smaller talc particles would be more likely to be absorbed through the stomas in the lymphatics of the parietal pleura. Then their systemic distribution would lead to systemic inflammation. When talc preparations from various manufacturers are analyzed, there is a marked variation in particle size (188). Animal studies have also demonstrated that talc is deposited extrapleurally after it is administered intrapleurally (189,190). Ferrer et al. (191) intrapleurally injected two different sizes of talc with mean maximum diameters 8.36 and 12.0 μm in rabbits. They demonstrated that the intrapleural injection of the smaller talc elicited greater pulmonary and systemic talc particle deposition (191). Rossi et al. (192) have shown that rabbits receiving small talc (median 6.4 μm) intrapleurally develop a more intense systemic inflammatory response than do rabbits that receive large talc (21.2 μm). Maskell et al. (187) provided support for this hypothesis in humans when they randomized 48 patients to receive mixed talc (most talc particles <15 μm) or graded talc (most particles <10 μm removed). They reported that with the mixed talc there was a significantly greater increase in the alveolar to arterial oxygen gradient, a significantly greater decrease in the arterial Po_2, and a significantly greater increase in the C-reactive protein. We have demonstrated (unpublished observations) that when the same two-talc preparations are injected in rabbits, those receiving the graded talc have much less systemic deposition of talc than those receiving the mixed talc. Moreover, all the talc particles detected systemically were <10 μm in their maximum diameters.

From the discussion in the preceding text, the evidence seems strong that the intrapleural injection of talc can cause ARDS and death in a small percentage of patients. The ARDS is probably more common if smaller talc particles are used. Therefore, if one is going to use talc to produce a pleurodesis, it is important to not use talc preparations that have many small talc particles (<10 μm).

Another complication of talc pleurodesis is pulmonary embolism. Montes-Worboys et al. (193) reviewed 231 patients who received talc poudrage and reported that 17 patients (7.4%) died within 15 days and thrombotic events were observed in six of these patients. Patients who survived less than 15 days tended to have higher serum IL-8 levels and these higher levels were correlated with the thrombin-antithrombin levels (193). It is unknown whether the same events happen with talc slurry.

The intrapleural injection of talc induces chronic inflammation of the pleural space as assessed via PET scan with F-18 fluorodeoxyglucose (194).

Tetracycline Derivatives

Tetracycline derivatives are now the second most common agents used for sclerosis (166). In the survey by Lee et al. (166), tetracycline derivatives were the sclerosing agent of choice for 25.8% of the respondents. During the 1980s, tetracycline was probably the most commonly used agent for creating

a pleurodesis. Tetracycline, 35 mg/kg, is effective in creating a pleurodesis in rabbits (149). Tetracycline is also effective in treating malignant pleural effusions. Sherman et al. (195) reported that tetracycline, 1,500 mg, effectively controlled 94.4% of 108 malignant pleural effusions. In a review of 11 reports involving 359 patients, the success rate with tetracycline was 67% (196).

Parenteral tetracycline is no longer available in the United States, although it remains available in some countries such as Germany (197). It has recently been shown that oral forms of tetracycline and its derivatives can be used for pleurodesis if they are dissolved in saline and then passed through a 0.2-μm sterile and nonpyrogenic polyethersulfone membrane to remove infectious materials and other particulate particles (198).

Because parenteral tetracycline is no longer available, the tetracycline derivatives minocycline and doxycycline have been evaluated for their effectiveness in producing a pleurodesis. In the rabbit, minocycline, 7 mg/kg (199), or doxycycline, 10 mg/kg (148), produces a pleurodesis that is comparable to that produced by tetracycline, 35 mg/kg. One disturbing aspect of the intrapleural administration of tetracycline derivatives in animals is that it is associated with a high incidence of hemothorax, which is frequently fatal (199). The hemothoraces and the mortality, however, are prevented if chest tubes are inserted into the animals (148).

Doxycycline and minocycline are effective in producing pleurodesis in patients with malignant pleural effusion. When five reports (200–204) with a total of 110 patients are combined, there was control of the effusion at 30 days in 91 of the patients (83%). The usual dose of doxycycline is 500 mg. There has also been one report in which the administration of minocycline, 300 to 500 mg, produced a complete response at 30 days in 62.5% of patients and a partial response (no need for further thoracentesis) in an additional 25% (205). The primary side effect when pleurodesis is performed with a tetracycline derivative is severe chest pain (206). Although the chest pain tends to be worse in patients who receive the tetracycline derivative for a pneumothorax than for a pleural effusion, it is sometimes very severe in patients with malignant pleural effusions. It is recommended that patients who receive a tetracycline derivative for pleurodesis be given lorazepam or midazolam in addition to systemic pain medications before the injection.

It is possible that pleurodesis can be induced by using combinations of sclerosing compounds at less than their usual doses. Dikensoy et al. (207) demonstrated that administration of one half (5 mg/kg doxycycline plus 200 mg/kg talc) or one fourth (2.5 mg/kg doxycycline plus 100 mg/kg talc) of both the usual doses of doxycycline (10 mg/kg) and talc (400 mg/kg) in rabbits resulted in a mean pleurodesis score that was better than the mean pleurodesis score with full-dose talc and similar to the mean pleurodesis score with full-dose doxycycline.

Antineoplastics Including Bleomycin, Nitrogen Mustard, and Mitoxantrone

Bleomycin is another agent that is sometimes used as a sclerosing agent for malignant pleural effusions. In the survey of 841 pulmonologists, it was the third most commonly used agent but was used only by 6.5% of the respondents (166). The popularity of bleomycin is due in part to an older randomized controlled study by Ruckdeschel et al. (208) comparing the results with 60 units of bleomycin and 1,000 mg of tetracycline in 44 patients. The rate of success with bleomycin at 30 days (64%) was significantly better than that with tetracycline (33%). It should be noted that less than an optimal dose of tetracycline was used in this study, the rate of success with tetracycline was much less than that generally reported and the rate of success with bleomycin was not particularly good.

Overall, it appears that bleomycin is probably less effective than talc (177) or the tetracycline derivatives in producing a pleurodesis. In a review of eight reports with a total of 199 patients using bleomycin to treat malignant pleural effusions, the overall success rate was only 54% (196). In a randomized controlled study, bleomycin failed in 41% of patients at 30 days, 59% at 90 days, and 65% at 180 days (209). In the rabbit model, bleomycin is ineffective in producing a pleurodesis (210). Much better results were reported in a more recent randomized study in which 160 patients received bleomycin 0.75 mg/kg or interferon (211). If the output from the chest tube was more than 100 mL/day on the third day after the bleomycin was administered, a second dose of bleomycin was administered (211). In this study, 70 of the 83 patients (84%) responded (211). Bleomycin is much more expensive (~US$1,000/patient) than the tetracycline derivatives or talc. Therefore, it cannot be recommended.

Nitrogen mustard was one of the first antineoplastic agents to be used intrapleurally to treat malignant pleural effusions. Interestingly, the results with nitrogen mustard on the average are better than those

with bleomycin. For example, Leininger et al. (212) administered 10 mg of nitrogen mustard through a chest tube to 18 patients and reported that the treatment was effective in 17 (94%). Kinsey et al. (213) administered 30 mg of nitrogen mustard through a tube thoracostomy in 62 patients and reported that the effusion was completely controlled in 57 (92%). Interestingly, nitrogen mustard is the only antineoplastic agent other than mitoxantrone that is effective in producing pleurodesis in animals (214). Because nitrogen mustard is at least as effective as bleomycin and costs less than US$100 per patient, it is the agent of choice if an antineoplastic agent is going to be used.

Another antineoplastic agent that has shown some promise as a pleural sclerosant is mitoxantrone. In one report, 114 patients with malignant pleural effusions from breast carcinoma were given 40 mg mitoxantrone intrapleurally and there was complete response of the effusion in 53.5% and partial response of the effusion in another 25% (215). In another report, the intrapleural administration of 40 mg mitoxantrone to 21 patients with malignant pleural effusions resulted in complete control of the effusions in all cases at 60 days (216). One advantage of mitoxantrone over bleomycin is that mitoxantrone binds to cell membranes and is therefore likely to remain in the pleural space longer (217). Interestingly, the intrapleural injection of mitoxantrone in rabbits leads to proportionately more inflammation than does the intrapleural injection of tetracycline derivatives or talc (150). In the animal model, the intrapleural administration of high doses of mitoxantrone produces a pleurodesis, but there is a significant amount of cardiotoxicity (150). Cardiotoxicity has also been reported in patients who have received mitoxantrone intrapleurally. Currently, mitoxantrone is not recommended as a sclerosing agent because it is no more effective than talc or the tetracycline derivatives, is associated with more toxicity and is very expensive (US$4,000/patient).

Another agent that has shown some promise is intrapleural cisplatin. Seto et al. (218) administered 25 mg cisplatin in 500 ml distilled water intrapleurally in 80 patients with non-small-cell lung cancer. At 4 weeks, they reported that 34% of the patient achieved a complete response and 49% achieved a partial response and the median survival was 239 days (218). If these results can be confirmed, ciplatins might become a reasonable alternative to produce a pleurodesis.

Other antineoplastic agents such as doxorubicin, etoposide, fluorouracil, and mitomycin-C have been evaluated for the treatment of pleural effusions, and the response rates have been less than 50% for almost all of them (196). Therefore, their use cannot be recommended.

Silver Nitrate

Silver nitrate was probably the first agent used to produce a pleurodesis and is very effective (219). In the 1980s, silver nitrate was replaced by tetracycline probably because of severe side effects seen after the intrapleural injection of high concentrations of this agent. Subsequent studies in rabbits demonstrated that a lower concentration of silver nitrate (0.5%) was as effective as tetracycline, 35 mg/kg, in producing a pleurodesis (220). Moreover, this dose of silver nitrate is superior to talc, 400 mg/kg, in producing pleurodesis in rabbits (221).

There has been two clinical study evaluating the efficacy of silver nitrate in inducing pleurodesis in patients with malignant pleural effusions (222). Paschoalini et al. (222) randomized 60 patients with malignant pleural effusion to receive either 5 g talc slurry or 20 mL of 0.5% silver nitrate through a chest tube. In the 47 patients who returned for follow-up, the silver nitrate tended to be more effective than talc (222). There was no recurrence of the effusion in 96% of the patients who received silver nitrate and 84% of the patients who received talc slurry (222). In a later study (223), pleurodesis was performed as an outpatient in 65 patients with malignant pleural effusion and at 30 days recurrences had occurred in 2 of 48 hemithoraces (4%). These studies suggest that silver nitrate should be considered a reasonable alternative to other commonly used pleurodesing agents such as the tetracycline derivatives or talc slurry.

Iodopovidone (Betadine)

It appears that iodopovidone is also an effective agent for producing pleurodesis. Olivares-Torres et al. (224) injected 100 mL of 2% iodopovidone into the pleural spaces of 40 patients at the end of a thoracoscopic procedure and 12 patients through tube thoracostomy. They reported that a complete response with no reaccumulation of the fluid was obtained in 50 of the 52 patients (96%). Three patients developed intense pleuritic pain and systemic hypotension after the intrapleural instillation of the iodopovidone, but there were no fatalities (224). In a second study, 37 patients were given 100 mL of 2% iodopovidone through their chest tube and there was no recurrence

of the pleural effusion in 32 (86.5%) (225). In a third study (226), 61 procedures were performed in 54 patients and there was only one recurrence with a mean follow-up of 5.6 months. In a fourth study (227), which was a randomized controlled study, 45 patients were randomized to receive 4 grams of insufflated talc or 50 ml 2% iodopovidone through a chest tube The recurrence rates were similar in each group and the side effects tended to be greater in the patients who received insufflated talc (227). In rabbits, the intrapleural administration of 2% or 4% iodopovidone is comparable in effectiveness to doxycycline 10 mg/kg in producing a pleurodesis (228). There is one report (229) from Germany in which three patients who received 200 to 500 ml of a 10% iodopovidone solution developed blindness. However, this dose is about 25 times larger than the recommended dose. None of the other studies have reported visual problems. Iodopovidone should also be considered a reasonable alternative to other commonly used pleurodesing agents such as the tetracycline derivatives or talc slurry.

Other Agents

Over the years, there have been many other articles evaluating the capability of various other agents to produce a pleurodesis. Several agents that presumably work by being immune modulators have been evaluated. Dried killed *Corynebacterium parvum,* an anaerobic gram-positive bacterium, has been evaluated in nine reports with a total of 169 patients who had an overall success rate of 76% (196). The availability of *C. parvum* worldwide is very limited, and this limits its overall use.

OK-432 is obtained from the SU strain of *Streptococcus pyogenes* and has properties similar to *C. parvum* in that it is both immunostimulating and cytotoxic. In Japan, it is considered by some to be the sclerosing agent of choice (230). Response rates as high as 75% have been obtained. In one study, the administration of the combination of OK-432 and 30 mg of doxorubicin resulted in complete control of the effusion in 80% of the patients (231). In another study, the combination of OK-432 and cisplatin resulted in complete control of the effusion for 180 days in 87% of 15 patients whereas OK-432 by itself resulted in control in only 47% of 17 patients (120). To my knowledge, OK-432 is available only in Asia.

Quinacrine, the antimalarial agent, has been used for decades for pleurodesis in Scandinavian countries. Until 1993, there were reports of quinacrine being used for malignant pleural effusion in 98 patients with a success rate of 86% (232). In a more recent report, quinacrine 500 mg was instilled through tube thoracostomy in 54 patients (233). The injection was repeated if there was more than 50 mL pleural drainage per day after 3 days. This treatment was successful at 2 months in 47 of the 54 patients (87%) (233). The intrapleural injection of quinacrine causes a systemic inflammatory response similar to that seen after talc injection (234).

Agent of Choice

The following recommendations for the selection of an agent for pleurodesis in patients with malignant pleural effusions are made based on the information provided in the preceding text. If a patient has a malignant pleural effusion and is being treated with tube thoracostomy, then the agent of choice is doxycycline, 500 mg. Alternative tetracycline derivatives are tetracycline, 1,500 mg, or minocycline, 300 mg. If a tetracycline derivative is unavailable, 20 mL of 0.5% silver nitrate or 100 mL of 2% iodopovidone are reasonable alternatives. If a patient has a malignant pleural effusion diagnosed during thoracoscopy or at thoracotomy, the patient should be subjected to pleural abrasion or parietal pleurectomy. Talc would be recommended if it were not associated with the development of the ARDS. One should only use talc if it is large particle talc.

Intrapleural Injection of Sclerosing Agent

Pleurodesis should be performed by injecting the sclerosant through a chest tube. The reason to use a chest tube rather than just injecting the sclerosing agent into the pleural effusion is that fusion of the visceral and the parietal pleura to create a pleurodesis requires that the two pleural surfaces be next to each other. If they are not in close apposition, pleurodesis is unlikely to occur.

The first question in performing a pleurodesis is on the size of chest tube to be used. There is no evidence that the use of a large tube provides better results than does the use of a small tube (235–238). There have been three randomized controlled studies (235–237) with a total of 166 patients comparing large-bore to small-bore chest tubes for pleurodesis. All three concluded that the two different tube sizes were equivalent (235–237).

The chest tube is connected to a water-sealed drainage system, and the effusion is allowed to drain (212).

It is recommended that negative pressure not be applied initially to the chest tube in this situation because the combination of a chronic pleural effusion and the application of negative pleural pressure can cause reexpansion pulmonary edema (see Chapter 24). If the lung has not expanded within 24 hours, then negative pressure should be applied to the chest tube.

The pleurodesis is less likely to be successful if the patient is on corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs). The induction of a pleurodesis usually involves the creation of intense intrapleural inflammation, which then leads to fibrosis. Therefore, it is not surprising that anti-inflammatory drugs decrease the efficacy of pleurodesis. In animal studies, the efficacy of pleurodesis is decreased in rabbits given doxycycline and corticosteroids (239) or the NSAID diclofenac (240), and in rabbits given talc slurry and corticosteroids (241), and in pigs treated with mechanical abrasion and diclofenac (242). Accordingly, it is recommended that corticosteroids and NSAIDs not be administered to patients undergoing pleurodesis.

Once the chest tube has been inserted, how long should one wait before injecting the sclerosing agent? It is important to make certain that the underlying lung has fully expanded before the injection is made. If the underlying lung has not expanded, then the injection of a sclerosing agent will lead only to additional thickening of the visceral pleura, which will further compromise the function of the underlying lung. Some authors have advocated that the sclerosing agent not be injected until the drainage from the chest tube is less than 150 mL/day (208). However, there is no supporting data for this practice. Villanueva et al. (243) randomly assigned patients to a group in which tetracycline was not instilled until the drainage was less than 150 mL/day and a group in which 1,500 mg of tetracycline was instilled as soon as the lung had reexpanded. The rate of success was the same in each group (80%), but the duration of the chest tube drainage was much less in the latter group (2 days) than in the former group (7 days). In view of this study, it is recommended that the sclerosant be injected as soon as the lung has reexpanded.

If successful reexpansion of the lung cannot be accomplished with pleural drainage, as shown in Figure 10.4B, sclerosing agents should not be injected into the pleural space. The injection can only thicken the visceral pleura and allow lesser lung expansion. Another reason for lack of expansion of the lung is loculation of the pleural fluid. One approach in both of these situations is to inject a fibrinolytic agent intrapleurally. Hsu et al. (244) injected urokinase 100,000 daily for at least 3 days in 12 patients with trapped lungs and 36 patients with loculated pleural fluid. They reported that they obtained lung reexpansion in 29 of the 48 patients (60.4%) (244). These 29 patients subsequently underwent minocycline pleurodesis which was successful at 1 month in 27 patients (93%) (244). If the lung does not expand with tube thoracostomy with or without the instillation of fibrinolytics, the pleural fluid can be drained on a chronic basis with the PleurX catheter or with a pleuroperitoneal shunt (see the discussion of pleuroperitoneal shunt later in this chapter). One of these options should definitely be performed if the mediastinum is shifted away from the side of the effusion (Fig. 10.4A).

The injection of any of the tetracycline derivatives produces an intense pleuritis that can be very painful. Accordingly, patients should be given systemic medication to control the pain. We currently use lorazepam or midazolam to produce conscious sedation. Sherman et al. (245) have suggested that the patient should be given local anesthesia such as lidocaine hydrochloride intrapleurally. There are no controlled studies evaluating the efficacy of intrapleural lidocaine, and, currently, no intrapleural anesthetic is recommended because the patient remembers no pain due to the conscious sedation.

After the sclerosant is injected, the catheter is flushed with an additional 50 to 100 mL of saline and the chest tube is clamped for at least 1 hour. Although in the past it has been recommended that the patient be moved into different positions so that the sclerosant contacts all the pleural surfaces, this does not appear to be necessary. In animals, the dispersal of radioisotopes injected intrapleurally is similar whether the animals are rotated or not (246). In humans, the dispersal of the injected radioisotopes is similar whether the patients are rotated or not (247). Rotation did not have a statistically significant effect on the results of pleurodesis in one randomized study with tetracycline derivatives (248). The rate of success with rotation was 73.7% whereas that with no rotation was 61.9% (248). However, because rotating the patient certainly does not decrease the likelihood of pleurodesis and because the patient has much less pain with rotation if the small catheters are used, it is recommended that all patients be rotated unless it is particularly uncomfortable for the patient.

After 1 to 2 hours, the chest tube is unclamped and negative pressure (–15 to –20 cm H_2O) is applied to the chest tube. Suction is maintained for at least 24 hours and until the pleural drainage is less than

150 mL/day. The chest tube is removed after 96 hours regardless of the volume of pleural fluid. The keys to the success of this procedure are the pleuritis produced by the sclerosant and the approximation of the visceral and the parietal pleura by the chest tubes so that a pleural symphysis can occur. There appears to be no advantage if the sclerosant is injected twice. In one study, 25 patients received one injection of tetracycline, 20 mg/kg, and 25 patients received instillations of tetracycline, 20 mg/kg, on 2 consecutive days. Effusions recurred in four patients in each group (249).

It would be ideal if pleurodesis could be performed on an outpatient basis. Pleurodesis accomplished on an outpatient basis has two advantages. First, the patient is not hospitalized. Because the mean hospitalization time of patients treated in hospital is approximately 6.5 days (123) and the patient has a life expectancy of only approximately 90 days, this hospitalization represents 5% of and probably the best days of the patient's remaining life. Second, it decreases the cost of the treatment because there are no hospitalization costs. Terra et al. (223) performed pleurodesis with silver nitrate as an outpatient in 65 patients with malignant pleural effusion and reported that at 30 days recurrences had occurred in 2 of 48 hemithoraces (4%). The study was performed by inserting a pigtail catheter on day 1 and then draining the pleural fluid into a collection bag. Then on the following day, 30 ml 0.5% silver nitrate was injected and allowed to remain for 1 hour. Then the patients returned after 7 days and had the catheter removed (223). Reddy et al. (250) combined talc poudrage and insertion of an indwelling catheter in 30 patients. After the patients had the talc poudrage, an indwelling catheter was placed and the catheter was drained every other day until the drainage was less than 150 ml on two consecutive days and then it was removed. They reported that pleurodesis was successful in 92% of the cases, the median hospitalization following the procedure was 1.79 days and that the catheters were removed at a median of 7.54 days. This procedure has the advantage that the hospitalizations are decreased compared with usual pleurodesis and that the indwelling catheter remains in place for a much shorter time.

Thoracoscopy for Pleurodesis

Some have recommended that pleurodesis should be performed through thoracoscopy. Indeed, it has been stated that video-assisted thoracoscopic surgery (VATS) with talc poudrage has replaced conventional instillation of talc slurry through tube thoracostomy as the procedure of choice to achieve pleurodesis (251). However, the available evidence does not support this conclusion. The randomized study by Dresler et al. (176) (Fig. 10.5) showed that there was no significant difference in recurrence rates between patients treated with thoracoscopy and talc insufflation and those treated with tube thoracostomy with injection of talc slurry through the chest tube. Moreover, Heffner et al. (71) reported that the results with thoracoscopy were not significantly better than those with tube thoracostomy. Lastly, Yim et al. (252) randomized 28 patients to pleurodesis with thoracoscopy and talc insufflation, and 27 patients to pleurodesis with tube thoracostomy and talc slurry. They found that there were no significant differences in the results with the two different methods (249). Moreover, thoracoscopy adds significantly to the expense of the procedure.

However, if thoracoscopy is performed for an undiagnosed recurrent pleural effusion, an attempt should be made to induce a pleurodesis at the time of the procedure. It should be noted that if thoracoscopy is performed and no pleural sclerosis is attempted, 62% of the patients have no recurrence of their pleural effusion for the remainder of their life (253,254).

In nonrandomized studies, thoracoscopy with the insufflation of talc has been reported to be very effective in creating a pleurodesis in patients with malignant pleural effusion. Ribas-Milanez de Campos et al. (186) treated 383 patients with malignant pleural effusions with 2 g of insufflated talc and reported a success rate of 93.4%. Kolschmann et al. (255) treated 102 patients with 8 g of insufflated talc and reported that the treatment was successful (no requirement for repeat thoracentesis) in 89% of 85 surviving patients at 30 days and in 83% of 46 patients surviving at 180 days (255). Arapis et al. (256) reported their results in 241 patients who received 5 g of insufflated talc at the time of thoracoscopy. Of the 172 patients seen at follow-up at 1 month, the chest radiograph showed no fluid in 122 (71%), a small effusion in 39 (23%), and a recurrence in 11 (6%) (253). The results in some studies have been significantly worse (176,257). Love et al. (257) reviewed 60 patients treated with 4 to 5 g insufflated talc and reported that complete control of the effusion was obtained until death in only 52% of patients. These results are similar to those reported by Dresler et al. (176) as shown in Figure 10.5.

The insufflation of talc at the time of thoracoscopy is not without significant side effects. In the multicenter study reported by Dresler et al. (176), 18 of 223 patients (8.1%) developed respiratory failure and 6 (3%) died. Froudarakis et al. (258) reported

that patients who underwent thoracoscopy with talc insufflation had a significantly greater temperature elevation, peripheral blood WBC increase, and C-reactive protein level increase than did patients who underwent thoracoscopy without talc insufflation. In a more recent study of 84 patients from Chicago, 5 (5.9%) developed acute lung injury and severe hypoxemia developed in 25 (29.8%) (259).

Because the study by Dresler et al. (176) indicates that insufflated talc can cause death, and talc is not significantly more effective than other agents, what are the alternatives? The three best alternatives appear to be pleural abrasion, the intrapleural instillation of 2% iodopovidone, or the intrapleural instillation of collagen.

In animal studies, mechanical abrasion of the pleura is at least as effective in producing pleurodesis as is talc (171,172). Mechanical abrasion is also effective in controlling malignant effusions in humans. Crnjac (260) treated 44 patients with malignant pleural effusion with mechanical pleural abrasion and reported that at 6 months there was no recurrence of the effusion in 93% of the patients. In a subsequent report, Crnjac et al. (261) randomized 87 patients with breast cancer to receive either mechanical pleurodesis or insufflated talc. They reported that both methods were equally effective in patients with pleural fluid pH level above 7.3 but that mechanical abrasion was more effective in patients with pleural fluid pH level below 7.3 (81% vs. 55%). Moreover, the duration of chest tube drainage and the duration of hospitalization were significantly longer in the patients who received talc insufflation (261).

Single center studies have shown the effectiveness of intrapleural iodopovidone and collagen. Olivares et al. (224) instilled 100 mL of 2% iodopovidone in 52 patients with pleural effusions and reported that there was no recurrence of the effusions in 50 (96%). Akopov et al. (262) instilled 1 g of bovine dermal collagen powder in 45 patients with malignant pleural effusions and reported that this was successful in 89% of patients.

In view of the discussion in the preceding text, it appears that mechanical abrasion of the pleura is the best method to induce a pleurodesis in patients who undergo thoracoscopy for an undiagnosed pleural effusion.

Choosing Between Indwelling Catheter and Pleurodesis

As mentioned earlier, these are the two main options for managing symptomatic pleural effusions (263). Other than the study by Putnam et al. (123), there have been no randomized controlled studies comparing the two modalities and each has its advantages and disadvantages and each has its supporters. The primary advantage of the indwelling catheter is that its insertion does not require hospitalization. Indeed the total hospital days associated with treatment of the pleural effusion is less when the indwelling catheter is used than when pleurodesis is performed. Fysh et al. (264) compared the number of in hospital days in 34 patients who elected to receive the indwelling catheter and 31 patients who elected talc pleurodesis. They reported that median number of hospital days was significantly greater in the pleurodesis group (18 days) than in the indwelling pleural catheter group (6.5 days). Moreover, the median number of hospital days related to the effusions was significantly greater in the pleurodesis group (10 days) than in the indwelling pleural catheter group (3 days). The patients in the indwelling catheter group also spent a smaller percentage of their remaining lives (8.0%) in the hospital compared with the pleurodesis group (11.2%). In a second study, Hunt et al. (265) retrospectively compared the course of 59 patients who had indwelling catheter placed and 50 who were treated with thoracoscopic talc pleurodesis. They reported that repeat interventions for recurrent ipsilateral pleural effusions were significantly more common with talc pleurodesis (16%) than with the indwelling catheter (2%) (265). In addition, they reported that the length of hospitalization was significantly greater in the group that received talc pleurodesis (265). They concluded that placement of an indwelling catheter should be considered for palliation of malignant pleural effusions (265).

Another advantage of the indwelling catheter is that if spontaneous pleurodesis occurs, only rarely are additional interventions necessary to treat recurrent pleural effusions (129). The indwelling pleural catheter is certainly the treatment of choice for patients who have trapped lungs (266) or who fail pleurodesis (264).

There are also several advantages to controlling the effusion with pleurodesis. The procedure is completed within 1 week, and the patient does not have to worry about draining his or her pleural space intermittently for prolonged periods. Available home health or a very reliable patient and/or family are not necessary with pleurodesis.

Side effects occur with both procedures. With the indwelling catheter, the pleural space may become infected or the catheter may become occluded. Skin infections occur. Some patients experience

pain when they drain their pleural fluid. This can be diminished if the fluid is removed slowly. Patients who undergo pleurodesis frequently have chest pain or fever after the sclerosing agent is instilled.

Since there are no good randomized controlled studies, it is probably best to present both options to the patient and let them choose. In the study of Fysh et al. (264), approximately 50% of the patients chose each option. I gave a talk at M. D. Anderson in 2010 on the treatment of malignant pleural effusions discussing both the indwelling catheter and pleurodesis. I was surprised when one of the physicians in the audience asked me why I even discussed pleurodesis—virtually all malignant pleural effusions at that institution are treated with the indwelling catheter.

Alternatives to Pleurodesis and the Indwelling Catheter

If the patient is not a good candidate for chemical pleurodesis or insertion of the PleurX catheter, there are several options available that include symptomatic treatment, the implantation of a pleuroperitoneal shunt, serial thoracentesis, and pleurectomy.

Symptomatic Treatment

The two primary symptoms associated with a malignant pleural effusion are chest pain and shortness of breath. If the patient has chest pain, sufficient analgesics should be given to control the pain. There is no reason to worry about narcotic addiction because the life expectancy of the patient is so short.

If the primary symptom is dyspnea, the patient should be given opiates or oxygen, or both, if they are not candidates for insertion of the PleurX catheter or chemical pleurodesis. Both opiates and oxygen relieve the dyspnea. The disadvantage of opiates is that their administration can be associated with an increase in the $Paco_2$, which, in turn, will lead to a decrease in the Pao_2. The disadvantage of oxygen is that it is very expensive and is not portable. Opiates are probably underused in the treatment of dyspnea associated with pleural effusions. It is recommended that they be titrated for the degree of dyspnea as they are titrated for the degree of pain.

Pleuroperitoneal Shunt

An alternative approach to the management of patients with malignant pleural effusions is the placement of a pleuroperitoneal shunt (268–270), which is marketed commercially by CareFusion Corporation, San Diego, CA. This device consists of two catheters connected with a valved pump chamber (Fig. 10.6). The two one-way valves in the pump chamber are positioned such that fluid can only flow from the pleural space to the pump chamber to the peritoneal cavity. These valves open at a positive pressure of approximately 1 cm H_2O. Because the pleural pressure is almost always more negative than the peritoneal pressure, the pump chamber must be used to move fluid from the pleural cavity to the peritoneal cavity. The capacity of the pump chamber is approximately 1.5 mL. When it is compressed, fluid is forced from the chamber into the peritoneal cavity.

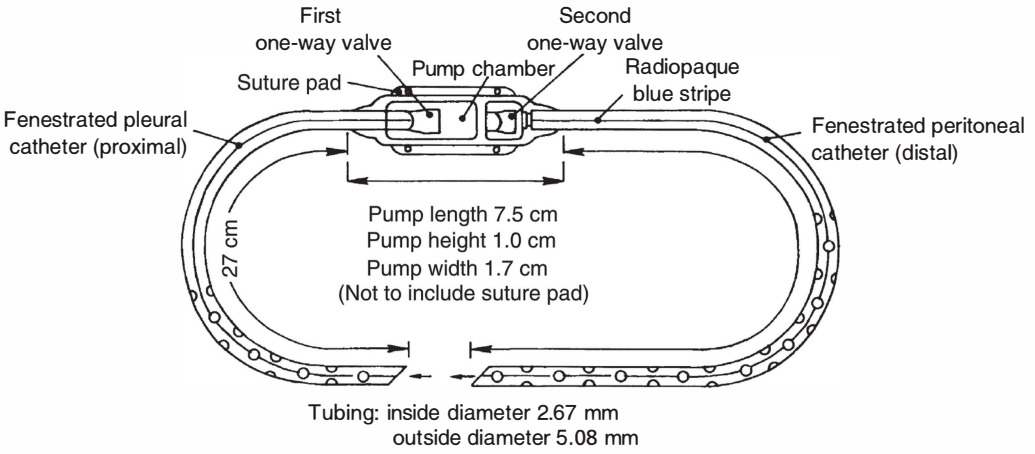


FIGURE 10.6 ■ Diagram of the Denver pleuroperitoneal shunt, which consists of a fenestrated pleural catheter, a flexible pump chamber containing two one-way valves, and a fenestrated peritoneal catheter. The one-way valves open at a positive pressure of approximately 1 cm H_2O.

Then when the pump chamber is released, negative pressure created in the pump chamber draws fluid from the pleural cavity to the pump chamber.

When the pleuroperitoneal shunt was first released, the pump chamber was always placed in a subcutaneous pocket caudal to a skin incision in the lateral part of the inframammary crease and fixed to the tissues with sutures through the sewing holes in the base of the pump chamber. Subsequently, a modification of the shunt has been developed in which the pump chamber is placed exteriorly and the volume of the chamber is 2.5 mL rather than 1.5 mL. Therefore, less pumping is required and the pumping is easier with the pump chamber exterior. The pleural catheter is inserted at the lateral and superior aspect of the incision with a Seldinger-type introducer kit. The abdominal catheter is tunneled subcutaneously across the costal margin and inserted, through a 3-cm skin incision in the anterior abdominal wall, into the peritoneal cavity through a small incision in the peritoneum. Pump compression by physicians and nurses is initiated in the recovery room and is then started by the patient or the patient's family on the first postoperative day. Within 3 days of shunt placement, pump compression usually causes no discomfort. Most patients are ready for discharge from the hospital within 48 hours of the operation. Selected patients can have the procedure performed on an outpatient basis.

The first sizable series of patients receiving the pleuroperitoneal shunt was reported by Little et al. (269) in 1988. They inserted shunts into 29 patients with excellent results overall. Eight of the patients previously had chest tube placement with attempted sclerosis with tetracycline. In most instances, shunt implantation was performed in the operating room using general anesthesia, but in four patients, local anesthesia was used. Three patients never pumped on their shunts, one obese patient was unable to localize the pump chamber, a 90-year-old man suffering from senility was simply unable to comply, and one patient developed a cancer phobia and refused to touch her shunt. Two patients died shortly after implantation from disseminated malignant disease. Excellent results were obtained in 20 of the remaining 24 patients. The 14 patients with malignant effusions had a median survival of 4 months, and there were no instances of peritoneal tumor seeding. In 5 patients, the shunts became occluded by fibrinous debris between 3 weeks and 2 months after the operation. Replacement was uneventful in all five instances.

Since this original report (269), there have been several additional reports (270–273). In these latter four studies, a total of 84 patients with malignancy were treated and 76 had either failed pleurodesis or had a trapped lung. Alleviation of dyspnea and control of the effusion was obtained in more than 90% of the patients. These results are particularly impressive when one realizes that previous treatment failed in more than 90% of the patients in these four series. The primary complication with the pleuroperitoneal shunt is that in approximately 15% of patients, the shunt becomes occluded. In such a situation, it should be replaced (274).

What should be the place of the pleuroperitoneal shunt in the management of patients with malignant pleural effusions? The shunt should certainly be considered along with the indwelling catheter in the patient in whom the lung does not expand after tube thoracostomy. Petrou et al. (275) inserted pleuroperitoneal shunts in 63 patients who had a trapped lung at thoracoscopy and reported effective palliation in more than 95%. The pleuroperitoneal shunt should also be considered in patients in whom pleurodesis has failed.

There are no studies comparing the efficacy of the shunt and chemical pleurodesis. The advantages of the shunt include the following: (a) the total hospitalization time is less than with chemical pleurodesis, (b) the amount of pain is probably less than with pleurodesis, (c) the procedure can be performed on an outpatient basis, and (d) the patient may benefit psychologically from using the pump when he or she is dyspneic. The disadvantages of the shunt include the following: (a) the shunt becomes obstructed in some patients, (b) insertion frequently requires general anesthesia, (c) the shunt must be inserted by a surgeon, and (d) the patient must use the pump daily.

Currently, when outpatient therapy of malignant pleural effusions is undertaken, the PleurX catheter is recommended because it is easier to insert. However, if a chylothorax is present, the pleuroperitoneal shunt is recommended because the nutritional status of the patient is preserved with this method. The pleuroperitoneal shunt is also preferred in patients in whom the underlying lung is trapped, because in this instance, the patient will require some type of pleural drainage for the rest of his or her life.

Pleurectomy

In carefully selected individuals, pleurectomy can be of use in controlling malignant pleural effusions. Pleurectomy may be attempted in two different

situations (276). The first is in the patient who undergoes a diagnostic thoracotomy for an undiagnosed pleural effusion. If malignant disease is found, an immediate parietal pleurectomy is useful to prevent recurrence of the effusion (276). Parietal pleurectomy consists of stripping all of the parietal pleura from the rib cage and the mediastinum. The second situation is in the symptomatic patient with a persistent pleural effusion and trapping of the ipsilateral lung so that the injection of sclerosing agents is contraindicated. The surgical procedure involves decortication of the trapped lung in conjunction with parietal pleurectomy. Pleurectomy controls the pleural effusion in more than 90% of cases (276). However, it is a substantial operation with a mortality rate of approximately 10% (276). A pleurectomy combined with decortication is recommended only in a patient who is symptomatic from the pleural effusion, who is in good overall condition, and whose primary tumor is either under control or is progressing slowly. I have yet to see such a patient, but an occasional patient with breast carcinoma meets these criteria. One recent study concluded that thoracotomy with decortication was not indicated in patients with a malignant effusion because of poor survival, a high frequency of complications, and prolonged hospital stay (277).

Thoracentesis

In the past, many patients with malignant pleural effusion were managed with repeated therapeutic thoracenteses for symptomatic relief. This regimen has several drawbacks. After therapeutic thoracentesis, malignant pleural effusions reaccumulate rapidly, usually within 1 to 3 days (4). Therefore, the patient must visit the physician frequently for the procedure. In addition, repeated thoracenteses often lead to loculation of the pleural fluid, which makes subsequent pleurodesis difficult (4). In view of these disadvantages, serial therapeutic thoracentesis should be performed only in moribund patients in whom the procedure offers symptomatic relief.

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chapter 11

Primary Tumors of the Pleura

Malignant Mesotheliomas, Solitary Fibrous Tumors, Body Cavity Lymphoma, and Pyothorax-Associated Lymphoma

MALIGNANT MESOTHELIOMAS

Malignant mesotheliomas are thought to arise from the mesothelial cells that line the pleural cavities. Individuals with a history of exposure to asbestos have a much greater risk of developing these neoplasms. Malignant mesothelioma with its dismal prognosis should be differentiated from the solitary fibrous tumor of the pleura, which has an excellent prognosis. A small percentage of mesotheliomas (<10%) arise in the peritoneal cavity (1), but only pleural mesotheliomas are discussed in this chapter.

Etiologic Factors

The occurrence of mesothelioma in many persons is related to previous exposure to asbestos. Asbestos is a fibrous silicate of various chemical types. The main types of asbestos are chrysotile and the amphiboles, which include crocidolite, amosite, tremolite, actinolite, and anthophyllite. Fibers with the greatest length-to-diameter ratio are the most carcinogenic (2,3). Exposure to the amphiboles is much more likely to induce mesothelioma than is exposure to chrysotile (3,4). In one study (5) of 118 mesotheliomas due to environmental exposure in South Africa, chrysotile was not implicated in any case. It has been estimated that the amphiboles are more than 750 times more potent that chrysotile in inducing mesothelioma (4). Indeed, in one model used to predict mesotheliomas in the future, exposure to chrysotile received no weight (6). Currently, chrysotile constitutes 99% of current global asbestos production. One of the possible reasons for the lower risk of malignancy from chrysotile exposure is that it is cleared from the lungs in a matter of hours to weeks, whereas the amphiboles are cleared only in a matter of decades (7). Crocidolite and amosite are the most carcinogenic amphiboles. Tremolite is a potent inducer of mesothelioma when the fibers have a high length-to-diameter ratio. No case of mesothelioma has been reported until now among Finnish miners exposed to anthophyllite asbestos, although there is a high incidence of pleural calcification because of this exposure.

Epidemiologic studies have implicated asbestos in the pathogenesis of malignant mesothelioma (8). In one study from Australia, 9 of 247 patients with the highest estimated cumulative exposure to asbestos had mesothelioma (8). It is thought that commercial amphiboles are responsible for most cases of mesothelioma observed in the United States (9). Occupations such as plumbing, pipe fitting, steam fitting, and mechanical engineering and industries such as ship- and boat-building have the highest risk of developing mesothelioma (10). In the United States, there have been 27 cases of pleural mesothelioma that developed in household contacts of asbestos workers (11). Most of the workers in these cases were shipyard workers or insulators, and the average latency after exposure before development of the tumor was more than 40 years (11).

Further evidence implicating asbestos as an etiologic agent in mesotheliomas comes from animal studies (see Chapter 4). Intrapleural injection of

any of the different types of asbestos results in the production of mesotheliomas in 8% to 66% of animals, depending upon the dose. Mesotheliomas can also be induced after the inhalation of various types of asbestos (12). These mesotheliomas are histologically identical to tumors in humans (13,14).

The incidence of mesotheliomas following asbestos exposure increases linearly with the intensity of the exposure but exponentially (to the third or fourth power) with time from the first asbestos exposure. The risk of malignant mesothelioma can be estimated from the following mathematic equation:

$$R = K \times F \times T^{p}$$

where R is the risk of mesothelioma, K is a coefficient dependent on the fiber size and type (highest for crocidolite and lowest for chrysotile), F is the number of fibers per milliliter, T is the time after the first exposure, and p is the exponent that is thought to be between 3 and 4 (1,2). The most recent estimates for K for chrysotile and crocidolite were 0.013 and 1.0, respectively (2). The presence of pleural plaques or pleural thickening does not increase the risk of mesothelioma when the length and duration of exposure are taken into consideration (15).

At times, the asbestos exposure may not be obvious. In one report (16), five cases of mesothelioma developed in a Native American pueblo of approximately 2,000 persons. Epidemiologic investigation revealed that asbestos mats were used to insulate worktables against the intense heat of brazing torches and molten metal in the preparation of silver jewelry. In addition, the villagers scrubbed leather with cakes of asbestos to make their leggings and moccasins a brilliant white.

The mechanism by which asbestos fibers induce malignant changes is not known. The asbestos fiber appears to have two major sources of genotoxicity: generation of reactive oxygen species and mechanical effects such as interference with mitotic spindle formation and the segregation of chromosomes (17,18). Exposure to asbestos can also damage the cellular DNA, and if the cells with the damaged DNA either do not undergo apoptosis or undergo cell cycle arrest, a malignant transformation may occur. It should be noted that, however, so far no consistent abnormalities in oncogenes or suppressor genes have been found in human mesothelioma (1).

Mineral fibers other than asbestos can induce mesotheliomas. In one area of Turkey, approximately 1% of the population dies each year of malignant mesothelioma (19). A follow-up study in 2003 of 661 adult villagers alive in 1979 revealed that 119 (18%) had died of mesothelioma, and 19% of the mesothelioma deaths were in villagers less than 40 years old (20). Asbestos does not occur in the local soil or rocks, nor is it handled in the village. The atmosphere in the area does contain increased amounts of erionite, a mineral of the zeolite family. This mineral is a major contributor to the clouds in the area. This report demonstrates that the inhalation of airborne respirable fibers other than asbestos can be associated with the subsequent development of pleural mesotheliomas (19). In North Dakota, erionite has been found to contaminate gravel used to pave more than 300 miles of roads (21). It remains to be seen whether this contamination will lead to cases of mesothelioma in the future. When erionite fibers are administered intrapleurally to rats, they are two orders of magnitude more carcinogenic than crocidolite (22).

There are probably other factors related to the development of pleural mesothelioma. Antman et al. (23) reported that mesothelioma developed in proximity to a field of therapeutic radiation administered 10 to 31 years previously in four patients. As subsequent review of 9,342 patients who received radiotherapy for breast cancer revealed the three developed mesothelioma in the ipsilateral hemithorax (24). Roviaro et al. (25) reviewed 35 cases of pleural mesothelioma and found that 3 of the patients had calcified posttuberculous fibrothorax. There is no clear evidence of a familial tendency to develop mesothelioma (26). There is no definite evidence that smoking increases the risk of mesothelioma (1).

One factor that has received much attention in the last 20 years as a possible etiologic factor in the development of malignant mesothelioma is the simian virus 40 (SV40). It should be stated that the role of SV40 in mesothelioma is controversial and the possibility that technical factors can produce false-positive results suggestive of SV40 infection has been raised (27). Two more recent well-designed studies have shown that the polymerase chain reaction (PCR) primers used to detect SV40 in many studies were targeting sequences within the SV40 genome that are also present in commonly used laboratory plasmids, leading to the false-positive detection of SV40 (28,29). A recent study using highly sensitive RT-PCR-based assays that are specific for SV40-encoded microRNAs found none in 94 malignant mesotheliomas (30). Moreover, age-specific trends in the pleural mesothelioma incidence rates are not consistent with an effect of exposure to SV40-contaminated poliovirus vaccine (31).

Incidence

The annual incidence of malignant mesotheliomas in the United States has been increasing over the last few decades and is thought to have peaked in 2004 with an annual incidence of approximately 2,300 (32,33). In comparison, the annual incidence of mesothelioma in western Europe in the year 2000 was 5,000 and is expected to peak around the year 2018 with an annual incidence of 9,000 (34). The difference in the incidence in the two locations is due to the fact that the maximal exposure to asbestos in Europe occurred around 1970, whereas the maximal exposure in the United States occurred from the 1930s to the 1960s (32). The incidence of mesothelioma in men is approximately six times that in women (10). The higher incidence in men is due, for the most part, to higher occupational exposure to asbestos. The seriousness of the problem with mesothelioma attributed to asbestos exposure is emphasized by the observation that, in Sweden, there are more deaths annually from mesothelioma due to asbestos exposure than to all fatal occupational accidents (35).

Pathologic Features

Malignant mesotheliomas in the earliest stages appear grossly as multiple white or gray granules, nodules, or flakes on normal or opaque parietal pleura (36). As the tumor progresses, the pleural surface becomes progressively thicker and nodular in appearance. The growing tumor extends in all directions to form a continuous layer encasing the lung and leading to contraction of the involved hemithorax. In advanced cases, the diaphragm, liver, pericardium, heart, contralateral pleura, and other mediastinal structures may be involved. At autopsy, hematogenously disseminated metastases are present in one third to one half of patients. In contrast to other sarcomas, however, the hematogenous metastases are usually clinically silent, and death generally results from complications arising from the primary lesion (1).

Microscopically, malignant mesotheliomas are characterized by marked structural variation within a single tumor or among different tumors with a similar gross appearance (37). Histologically, malignant mesotheliomas are classified as epithelial, sarcomatoid, or biphasic (38). Other classifications with more subtypes have also been developed (39). In a compilation of 819 cases from the literature, 50% were epithelial, 34% were biphasic, and 16% were sarcomatoid (40). The neoplastic cells of the epithelial form may show various epithelial arrangements such as papillary, tubular, tubulopapillary, cord-like, and sheet-like patterns. The epithelial cells may take various shapes but most commonly are cuboidal and uniform in size with vesicular nuclei. The sarcomatoid form resembles a spindle cell sarcoma in that the cells are spindle shaped with a parallel arrangement and have ovoid or elongated nuclei with well-developed nucleoli (41). The biphasic type has features of both the epithelial and sarcomatoid forms.

Clinical Manifestations

Two thirds of patients with malignant mesothelioma are between the ages of 40 and 70 years (42,43), and many have a history of exposure to asbestos for 20 or more years in the past. Most patients initially experience the insidious onset of chest pain or shortness of breath (44). Patients frequently have symptoms for several months before they see a physician (44). The chest pain is usually nonpleuritic and is frequently referred to the upper abdomen or shoulder because of diaphragmatic involvement. As the disease progresses, the patients lose weight and develop a dry, hacking cough and progressive dyspnea. Some patients have irregular episodes of low-grade fever (43). Physical examination may reveal clubbing. Examination of the chest reveals that the involved hemithorax is sometimes reduced in size and, at times, there is retraction of the intercostal spaces. In addition, there are the physical signs of a pleural effusion.

Radiographic Manifestations

The chest radiograph (Fig. 11.1) reveals a pleural effusion in 75% to 90% of patients (45,46). This effusion is frequently large, occupying 50% or more of the hemithorax and obscuring the pleural tumor. In about one third of patients, pleural plaques are evident in the opposite hemithorax (47). With progression of the disease, the tumor encases the ipsilateral lung and thereby produces a mediastinal shift to the side of the effusion and results in a loculated pleural effusion. In the late stages of the disease, the chest radiograph may show mediastinal widening, enlargement of the cardiac shadow due to infiltration of the pericardium, and destruction of the ribs or soft tissue masses (48). At times, rounded atelectasis is present (see Chapter 27).

Because routine chest radiographs often underestimate the extent of the disease, chest computed tomography (CT) scans are invaluable in delineating the extent of the disease (45–49). Chest CT scans

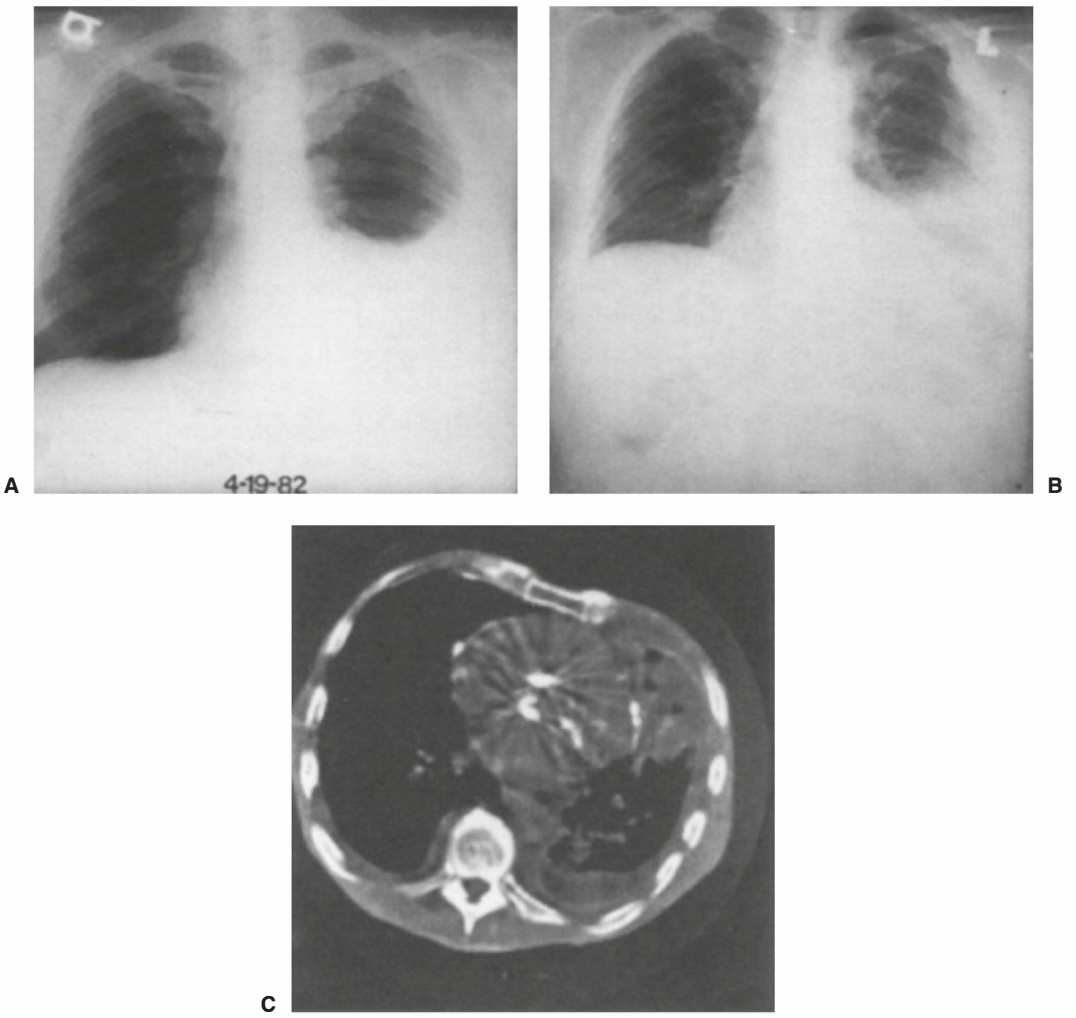

FIGURE 11.1 ■ Malignant mesothelioma. **A**: Posteroanterior chest radiograph demonstrating left pleural effusion and thickening of the pleura over the upper left lung. **B**: Posteroanterior chest radiograph from the same patient after therapeutic thoracentesis revealing a small left lung and marked pleural thickening. **C**: Computer tomography scan of the chest demonstrating shrunken left hemithorax and shift of the mediastinum toward the left. Pericardial calcifications due to previous asbestos exposure are also present.

should be obtained for all patients in whom a malignant mesothelioma is considered (Fig. 11.1C). With mesothelioma, the disease is unilateral in almost all cases (46). On CT scan, the pleura is thickened, with an irregular, often nodular internal margin that serves to distinguish this tumor from other types of pleural thickening. These changes are most pronounced at the base of the lung. The CT scan usually reveals marked thickening of the major fissure due to a combination of fibrosis, tumor, and associated fluid. The fissure may also appear nodular because of tumor infiltration (47). At times, pleural thickening is seen predominantly along the mediastinum. In such cases, the pulmonary margin is irregular, and separate nodules representing either metastases or lymph node infiltration may be seen in the juxtamediastinal tissue. In a patient with a malignant pleural effusion, features that suggest malignant mesothelioma rather than metastatic pleural disease are rind-like pleural involvement, mediastinal pleural involvement, and pleural thickness more than 1 cm (49).

The volume of the hemithorax with malignant mesothelioma is quite varied. If the patient has a pleural effusion with pleural thickening and decreased volume of the ipsilateral hemithorax, it is suggestive of mesothelioma. In one series, the volume

of the hemithorax was reduced in 42% of 50 cases of mesothelioma (45), whereas in another series, the volume of the hemithorax was reduced in 30% of 50 cases (46). It should be emphasized, however, that contralateral mediastinal shift is seen in approximately 15% to 25% of cases, and this is usually due to a large effusion (45,46).

The CT scan is also useful in demonstrating disease beyond the pleura and is thereby quite useful in staging the disease. It often reveals intrapulmonary nodules that are not apparent on the standard chest radiograph (47). The CT scan may reveal chest wall invasion, diaphragmatic invasion, or extension of the tumor to the liver or retroperitoneal space. However, CT scans are not without problems with regard to mesothelioma; CT fails to identify chest wall and mediastinal invasion in some patients who undergo surgical resections (50). In addition, it is often very difficult to distinguish pleural disease alone from associated pericardial disease, and extensive pleural disease often envelops and obscures the nodal anatomy in the hilar and middle mediastinal nodal groups (45).

Magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG) positron emission tomography (PET) are other imaging modalities that are useful in the evaluation of patients with suspected malignant mesothelioma (51,52). MRI is superior to CT in determining the extent of a malignant mesothelioma particularly when the tumor invades local structures such as the ribs and the diaphragm (52). PET scans are useful in differentiating malignant pleural disease from benign pleural disease (51,53). In one series, 28 patients with pleural thickening, including 24 with malignant and 4 with benign disease, were subjected to FDG-PET scanning. The uptake of FDG was significantly higher in the malignant lesions than in the benign lesions. In addition, the FDG-PET images provided excellent delineation of the extent of the disease (51). However, it does not appear that metastatic adenocarcinoma can be differentiated from malignant mesothelioma with this imaging technique. In a paper reporting on PET scan results in 63 patients with mesothelioma, the authors concluded that the PET scan defines metastatic disease and delineates the extent of local disease as well (54). It has also been shown that the intensity of the FDG uptake on the PET scan is a significant factor in the prediction of patient survival (53).

Pleural Fluid

The pleural fluid with mesotheliomas is yellow in approximately 50% of patients and serosanguineous in the remainder. This fluid is exudative. In approximately one third of patients, the pleural fluid glucose level is below 50 mg/dL and the pleural fluid pH level is below 7.20 (55). Patients with a low pleural fluid pH or low pleural fluid glucose level tend to have a poorer prognosis (55). The pleural fluid is generally cellular and contains a mixture of normal mesothelial cells, differentiated and undifferentiated malignant mesothelial cells, and varying numbers of lymphocytes and polymorphonuclear leukocytes (56). Although measurement of the levels of tumor markers in pleural fluid is generally not recommended (see Chapter 7), malignant mesotheliomas tend to have high levels of CYFRA 21-1 and low levels of carcinoembryonic antigen (CEA) in comparison with metastatic adenocarcinoma (57).

It has been proposed that the demonstration of elevated levels of soluble mesothelin related protein (SMRP) are useful in the diagnosis of malignant mesotheliomas (58–60). Creaney et al (61) measured the SMRP levels in pleural fluids from 192 patients presenting to a respiratory clinic including 52 with malignant mesothelioma, 56 with nonmesotheliomatous malignancies and 84 benign effusions. The pleural effusions from the patients with mesothelioma had significantly higher concentrations of SMRP than did the other patients (61). However, the SMRP in patients with sarcomatoid mesothelioma did not differ significantly from nonmalignant effusions (61). Davies et al (60) measured pleural fluid SMRP in 24 patients with mesothelioma, 67 patients with pleural metastases and 75 patients with benign conditions. Using ROC curve analysis, pleural fluid SMRP had an AUC of 0.878 in its ability to differentiate between patients with mesothelioma and all other diagnoses at an optimal cutoff value of 20 nM (60). At this cutoff, the diagnostic sensitivity and specificity were 0.71 and 0.90, respectively (60). Again, the levels of SMRP were lower in patients that had sarcomatoid mesothelioma (60). Adenocarcinomas accounted for 12 of the 13 false positives. The above two studies demonstrate that pleural fluid SMRP measurement provide additional information to cytology. However, tissue confirmation of mesothelioma is indicated in most situations.

At times, the pleural fluid of patients with malignant mesothelioma is viscid, owing to the presence of large amounts of hyaluronate, which was previously called *hyaluronic acid*. Nurminen et al. (62) assessed the diagnostic utility of hyaluronate levels by assaying the levels in 1,039 samples of pleural fluids including 50 from mesothelioma. They found that with a cutoff of 75 mg/L for hyaluronate, the assay specificity

for malignant mesothelioma was 100% and the sensitivity was 56% (62). It should be noted that another study (63) demonstrated that the hyaluronate measurements were much less useful. It appears that the poor results in the latter study are probably attributable to procedural mistakes (64). The results by Nurminen et al. (62) were obtained by high-pressure liquid chromatography (HPLC), and this assay is not generally available in the United States.

Diagnosis

The diagnosis of malignant mesothelioma should be considered in all patients with exudative pleural effusions. The suspicion of mesothelioma should be higher in middle-aged or older patients with persistent chest pain or shortness of breath, particularly if there is a history of asbestos exposure. The chest CT scan is frequently suggestive of the diagnosis. Although a diagnosis of malignancy can be established by cytologic smears or needle biopsies of the pleura, these procedures usually cannot distinguish between a metastatic adenocarcinoma and a mesothelioma. In one series (65), 80 patients with mesothelioma had pleural fluid cytology. In 20 patients (25%), cytologic examination of the pleural fluid established that the patient had malignant disease, but in none could the diagnosis of mesothelioma be established definitely with only cytology. In the remaining 60 patients, the diagnosis of malignancy could not be established (65).

There are, however, certain cytologic features that assist in making this differentiation. One report (66) compared the cytologic features of 44 cases of malignant mesothelioma and 46 cases of metastatic adenocarcinomas, and the authors concluded that the following five features separate malignant mesothelioma from adenocarcinoma with better than 95.4% accuracy. Mesotheliomas tend to have true papillary aggregation, multinucleation with atypia, and cell-to-cell apposition, whereas adenocarcinomas tend to have acinus-like structures and balloon-like vacuolation (66). In addition, immunohistochemical studies on cell blocks from pleural fluid are useful in distinguishing mesothelioma from adenocarcinoma (67–69) (see Chapter 7).

Blind needle biopsy of the pleura is usually not diagnostic of mesothelioma. In one report (65), the needle biopsy was diagnostic of mesothelioma in only 18 of 84 cases (21%). Also, there is poor concordance among different pathologists when the diagnosis of mesothelioma is based on specimens from needle biopsy (70). However, the diagnosis of mesothelioma can be established in more than 80% of patients with mesothelioma through a image-guided cutting-needle biopsy (71–73) (see Chapter 28).

More invasive procedures are often necessary to provide a larger tissue sample so that a definitive diagnosis can be made. If the patient has skin deposits, these should be biopsied. However, usually the diagnosis must be made based on a thoracoscopy or open biopsy. Thoracoscopy establishes the diagnosis of mesothelioma in more than 90% of cases. When two series (74–75) were combined, the diagnosis was established in 51 of the 56 (90%) patients. These results were similar to those with thoracotomy and open biopsy (43). Thoracoscopy is therefore the procedure of choice because its diagnostic yield is similar to that of open thoracotomy, but the procedure is less invasive (43). It should be noted that the classification of the mesothelioma with thoracoscopy is wrong in about 15% of cases (76). Most cases of misclassification are diagnosed as an epithelial subtype at thoracoscopy and a biphasic subtype as the final diagnosis (76).

Malignant mesothelioma often infiltrates needle tracts, thoracotomy scars, and chest tube drainage sites after diagnostic or therapeutic procedures. In one study (73), the incidence of seeding was 4% for image-guided core-needle biopsy and 22% for thoracoscopic biopsy. The role of small amounts of irradiation after the procedure to prevent such seeding is controversial. Randomized studies have come to different conclusions (77). A recent review (77) on the subject concluded that prophylactic radiation was not justified.

Histologic examination of hematoxylin and eosin (H&E)–stained tissue section remains the primary method by which the diagnosis of malignant mesothelioma is established. Malignant mesothelioma can have many different histologic patterns (78). However, it is frequently difficult to distinguish malignant mesothelioma from metastatic adenocarcinomas on the H&E-stained slides (36,78). Currently, immunohistochemical procedures have gained widespread acceptance as valuable adjuncts in establishing the diagnosis of malignant mesothelioma (36,79). Some of the immunohistochemical markers are positive with adenocarcinomas, whereas others are positive with malignant mesotheliomas. When one wishes to differentiate metastatic adenocarcinoma from malignant mesothelioma, the tissue sections should be stained with a panel of immunohistochemical markers (see Chapter 7). Currently,

the best markers for mesothelioma appear to be calretinin, keratin 5/6, podoplanin, and WT1, whereas the best markers for metastatic adenocarcinomas are CEA, MOC-31, B72.3, Ber-EP4, BG-8, and TTF-1 (79) (see Chapter 7). The sarcomatous type of mesothelioma usually does not stain positively with calretinin (80). Moreover, it is important to realize that nonmalignant mesothelial cells also stain positive for cytokeratin 5/6 and calretinin (81). Indeed, one of the most difficult differentials is to distinguish malignant mesothelioma cells from benign reactive mesothelial hyperplasia (82). The most reliable criterion for determining that a mesothelial proliferation is malignant is the demonstration of invasion (82).

The diagnosis of malignant mesotheliomas is usually established by the combination of the histology and the immunohistochemical stains. However, when doubt exists, two tests that have been used for decades can at times still be useful. The periodic acid-Schiff (PAS) stain can still be used to distinguish mesotheliomas from adenocarcinomas. The presence of strongly positive vacuoles after diastase digestion effectively establishes the diagnosis of adenocarcinoma, although not all adenocarcinomas have this staining characteristic. In addition, most mesotheliomas contain large amounts of hyaluronate that stain positively with colloidal iron or alcian blue stains. To be unequivocally positive, absence or attenuation of blue staining after pretreatment of a serial section with bovine testicular hyaluronidase overnight is required (83).

The diagnosis of pleural mesothelioma is made accurately in most cases without resorting to electron microscopic (EM) examination (36). However, because EM still plays a decisive role in some cases with unusual morphology or anomalous histochemical or immunohistochemical reactions, a portion of the pleural specimen should be routinely fixed at the time of pleural biopsy for possible subsequent processing for EM if malignant mesothelioma is suspected (36). Epithelial mesotheliomas are characterized by the presence of tonofilaments, desmosomes, and microvilli. The appearance of the microvilli is important in distinguishing mesotheliomas from adenocarcinomas. In mesothelioma, the microvilli are numerous and are characteristically long and thin, whereas in adenocarcinoma they are typically much less frequent and are usually short and stubby (36,84). In one study (84), with scanning electron microscopy (SEM), the mean length-to-diameter ratio of the microvilli in mesotheliomas was 19.7:1 (range 13.7–23.5:1), whereas that for adenocarcinomas was 2.5:1 (range 1.3–4:1). SEM can be used when glutaraldehyde-fixed, plastic-embedded tissue is not available for transmission EM (84). A number of subcellular structures, such as mucin granules, myelinosomes, microvilli coated by a filamentous glycocalyx, and microvillous rootlets, may be observed in some adenocarcinomas. The presence of any of these features excludes mesothelioma (37).

Flow cytometry does not appear to be particularly useful in establishing the diagnosis of malignant mesothelioma. Burmer et al. (85) performed flow cytometry on 46 cases of malignant pleural mesothelioma and 31 nonmesothelioma malignancies of the pleural space. They reported that 65% of the mesotheliomas were diploid in DNA content, with intermediate-to-low proliferative rates. In contrast, 85% of the nonmesothelial malignant neoplasms were aneuploid.

Blood Markers of Mesothelioma

In the last fifteen years, there have been many papers written on blood markers for mesothelioma. The three blood markers that have received the most attention are soluble mesothelin-related peptides (SMRP), osteopontin, and megakaryocyte-potentiating factor (MPF) (86). Mesothelin is a glycoprotein that is expressed on the surface of normal mesothelial cells, but is overexpressed in mesothelioma and various carcinomas (87). SMRP are released from the cell surface into the serum. Osteopontin is also a glycoprotein that is overexpressed in lung, breast, colorectal, gastric, and ovarian carcinoma.

The reported studies have demonstrated that the mean serum levels of SMRP, osteopontin, and MPF are all higher in patients with malignant mesothelioma than in normal individuals and patients exposed to asbestos but without mesothelioma (86,88). However, osteopontin lacks specificity for mesothelioma while both SMRP and MPF lack sensitivity for detecting nonepithelial subtypes (86). Moreover, there is significant overlap in the values in the different groups (87,89–92). In one study (88) in which the three markers were all measured, the SMRP was by far the most accurate in diagnosing mesothelioma. However, to have a specificity of 95%, the sensitivity for SMRP was only 73% (88). The SMRP is also not particularly efficient at detecting malignant mesothelioma early. In one study (93) of 106 asbestos exposed individuals who developed mesothelioma, only 17 of the 106 had elevated levels of SMRP before they were diagnosed. The practical value of using any of

these three serum markers as a diagnostic test for mesothelioma must await the assessment of their levels in other disorders that are common after extensive exposure to asbestos, such as diffuse pleural thickening with or without benign effusion, lung cancer with pleural involvement and rounded atelectasis, and metastatic adenocarcinoma of the pleura. The ERS/ESTS task force (94) concluded that at the present time there is no place for screening for malignant mesothelioma. In one study (95) of 100 patients with malignant mesothelioma, 139 with lung cancer and 75 with benign asbestosis, the best statistical cutoff for SMRP only had a sensitivity of 53% and a specificity of 82.7%. Interestingly, Scherpereel et al. (90) reported that in patients with pleural effusions, the pleural fluid SMRP levels were much higher than the simultaneous serum SMRP levels. Moreover, they reported that the pleural fluid levels of SMRP were better at distinguishing mesothelioma from pleural metastatic disease than were the serum levels (90).

These serum markers may be useful prognostically in patients with malignant mesothelioma. Cappia et al. (96) showed that osteopontin levels were significantly lower in 32 long-term survivors (>24 months) than in 69 short-term survivors (≤24 months). Higher SMRP levels have also been associated with a poorer prognosis (97). Wheatley-Price et al. (97) have shown than changes in SMRP levels but not osteopontin are indicators of the response to treatment of multiple myeloma.

Management and Prognosis

The prognosis of patients with pleural mesothelioma is more dependent on the so-called pretreatment factors than on the effect of therapeutic intervention. In general, the prognosis of patients with malignant mesothelioma is not good, with an overall median survival time of approximately 8 to 12 months after diagnosis (98,99). There is a small fraction of patients with mesothelioma who have a prolonged survival, up to 10 years (100). It should be noted, however, that the life expectancy is higher in patients with mesothelioma than in patients with metastatic malignancy, in which case, the median survival is approximately 4 to 5 months after diagnosis. The following have been identified as adverse prognostic factors: poor performance status, age greater than 75 years, chest pain, nonepithelioid histology, elevated serum lactate dehydrogenase, elevated platelet counts, male sex, and elevated peripheral white blood cell count (>8.3/mm^3) (100,101). The prognosis is better with the epithelial type when compared with the sarcomatous-type mesothelioma (98,99,102). Patients with larger tumor volumes and more advanced stages of the disease also have shorter survival times (103). Survival time is also poorer in patients with regional lymph node involvement and in patients who have a high standard uptake value (SUV) on their PET scan (104). Pleural fluid findings may also be associated with the expected survival time. It has been shown that an elevated pleural fluid hyaluranon (105) or a high pleural fluid pH level (>7.32) (106) are associated with increased survival. Survival is also less in patients with mesotheliomas that stain positively for vascular endothelial growth factor (VEGF) (107) or have a high microvessel density (108). Recently, researchers at Harvard Medical School have developed a four-gene expression ratio test (109). When this test was applied to 120 patients undergoing surgery, the mean survival in the 70 low-risk patients by the gene test was 16.8 months compared to 9.5 months in the 50 high-risk patients (110). Musk et al. (110) recently reported that the median overall survival with malignant mesothelioma gradually increased from 1960–1970 (64 days) to 2000–2005 (301 days).

Staging

When a patient is suspected of having a mesothelioma, the extent of the disease should be staged because the stage of the disease dictates the therapeutic approach. There have been several different staging systems proposed. The staging scheme recommended by the Cancer Committee of the College of American Pathologists is that developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). It is based on evaluation of tumor, nodes, and metastases (TNM) as shown in Table 11.1. To stage the disease, the following studies are required: a barium swallow to assess esophageal involvement; a bronchoscopic examination to assess involvement of the tracheobronchial tree; a chest CT scan to assess mediastinal or chest wall involvement; brain, liver, and bone scans to look for distant metastases; and possibly, a pneumoperitoneogram to look for diaphragmatic penetration (111). Rusch and Venkatraman (112) investigated prognostic factors in 231 patients who underwent thoracotomy between 1983 and 1998. They found that the median survival time was 29.9 months for stage I tumors, 19 months for stage II, 10.4 months for stage III, and 8 months for stage IV (112). A simpler staging system devised by Butchart et al. (111) is shown in Table 11.2.

TABLE 11.1 ■ Tumor, Nodes, and Metastases and Stage Grouping for Mesothelioma

Primary Tumor (T)

T0	No evidence of primary tumor
T1	Tumor limited to ipsilateral parietal or visceral pleura
T2	Tumor invades any of the following: ipsilateral lung, endothoracic fascia, diaphragm, or pericardium
T3	Tumor invades any of the following: ipsilateral chest wall muscle, ribs, or mediastinal organs or tissues
T4	Tumor directly extends to any of the following: contralateral pleural, contralateral lung, peritoneum, intra-abdominal organs, or cervical tissue

Regional Lymph Nodes (N)

N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial or ipsilateral hilar lymph nodes, including intrapulmonary nodes involved by direct extension of the primary tumor
N2	Metastasis in ipsilateral mediastinal or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes

Distant Metastasis (M)

M0	No evidence of distant metastasis
M1	Distant metastasis

AJCC/UICC TNM Stage Groupings

Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T1	N1	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0,1,2	M0
Stage IV	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

TNM, primary tumor, regional lymph nodes, and distant metastasis. AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer.

TABLE 11.2 ■ Pathologic Staging of Diffuse Malignant Mesothelioma of the Pleura

Stage	Manifestation
I	Tumor confined within the capsule of the parietal pleura, i.e., involving only the ipsilateral pleura, lung, pericardium, and diaphragm
II	Tumor involving chest wall or mediastinal structures; possible lymph node involvement inside the chest
III	Tumor penetrating diaphragm to involve the peritoneum; contralateral pleural involvement; lymph node involvement outside the chest
IV	Distant bloodborne metastases

Modified from Butchart EG, Ashcroft T, Barnsley WC, et al. The role of surgery in diffuse malignant mesothelioma of the pleura. *Semin Oncol*. 1981;8:321–328, with permission.

Palliative Therapy

No satisfactory treatment exists for malignant mesothelioma. The beneficial effects of treatment of malignant mesothelioma are moot (113). In a previous edition of this book, it was written that there were no controlled studies to demonstrate that any treatment is effective in prolonging survival. However, recently it has been shown that systemic chemotherapy with cisplatin and pemetrexed does prolong survival (see the discussion on chemotherapy in this chapter). The futility of treatment of mesothelioma in the past was demonstrated by a study of Law et al. (114) who compared the survival rates in 64 untreated patients and 52 treated patients seen at the Brompton and the Royal Marsden Hospitals between 1971 and 1980. The two groups of patients had comparable clinical conditions at the time of presentation. Whether the patient received treatment depended on the attending physician; some treated all patients, whereas others managed all patients symptomatically. The survival curves for the 64 untreated patients and the 12 patients who received radiotherapy, the 28 patients who received decortication, and the 12 patients who received chemotherapy were virtually identical. The median survival time was approximately 18 months; 10% of patients survived more than 4 years, including 7 of the 64 (11%) untreated patients (114). These results indicate that controlled

cooperative studies are needed to assess the effectiveness of the various treatment modalities proposed for malignant mesothelioma.

Shortness of breath and chest pain are the two most troublesome symptoms in patients with malignant mesothelioma. The shortness of breath can be either due to the presence of a large pleural effusion or to invasion of the lung or mediastinum by the tumor. If the patient is breathless and has a pleural effusion, a therapeutic thoracentesis should be performed. If the shortness of breath is relieved by the thoracentesis, a pleurodesis should be attempted (65), or indwelling pleural catheter (115) should be inserted. Pleurodesis should not be attempted if the mesothelioma prevents the underlying lung from expanding. In this situation, an indwelling pleural catheter should be inserted if a thoracentesis relieved the patient's dyspnea. Details concerning both these procedures are delineated in Chapter 10. If the shortness of breath is not relieved by the thoracentesis, then oxygen or opiates should be prescribed.

The other main symptom in patients with malignant mesothelioma is chest pain, frequently caused by tumor invasion of the chest wall. In such persons, local palliative radiotherapy may relieve the symptoms (48), but frequently the response is minimal or nonexistent (46,116). More often, strong analgesics must be administered to control the pain. If the pain is severe, consideration should be given to performing a percutaneous cervical cordotomy. In one series, this procedure was performed on 52 patients with intractable chest pain who were taking a median of 100 mg morphine per day (117). After the procedure, 38% of the patients were able to stop taking morphine and another 37% were able to reduce their morphine intake by more than 50%. Two patients experienced troublesome dysesthesia following the procedure, and four had persistent motor weakness. No patient became hemiplegic or was unable to walk.

Another troublesome symptom in approximately one third of patients is intermittent fever and sweating (65). Law et al. (65) reported that the administration of prednisolone was of some benefit in alleviating the fever and sweating and usually improved the appetite and the well-being of the patient.

Surgical Treatment

Surgical management appears to be the only form of therapy that offers the patient any hope for cure. Butchart et al. (111) operated on 29 patients with malignant mesothelioma between 1959 and 1972 and reported that 2 patients (7%) were alive, without evidence of recurrence, 3.5 and 6 years after the operation. The surgical resections performed by this group were extensive, with removal of the pleura, lung, lymph nodes, ipsilateral pericardium, and diaphragm. The in-hospital postoperative mortality rate was 31%. These workers concluded that radical extrapleural pneumonectomy was only indicated for patients younger than the age of 60 who are fit and who have stage I tumors of the epithelial type.

In recent years, Sugarbaker et al. (118) have reported good results in a series of 183 patients who underwent extrapleural pneumonectomy, followed by chemotherapy and radiotherapy. Patients were operated on only if they had a Karnofsky performance status greater than 70%, a creatinine level and liver function test results within normal limits, and a tumor that was judged to be completely resectable on the basis of CT and MRI scan. The extrapleural pneumonectomy entailed resection of the pleura, lung, diaphragm, and pericardium *en bloc* (118).

In the series reported by Sugarbaker, there were seven (3.8%) perioperative deaths and the median postoperative length of stay was 9 days (118). In a more recent report by the same group on 496 consecutive patients, the operative death was 4% (119). Overall, the median survival for these patients was 19 months and the 2- and 5-year survival rates were 38% and 15%, respectively. The subset of 31 patients with epithelial cell type, negative resection margins, and negative extrapleural nodal status had a median survival of 51 months, a 2-year survival rate of 68%, and a 5-year survival rate of 46% (119). In a second study, Aziz et al. (120) performed extrapleural pneumonectomies on 64 of 301 patients seen at their hospital. They reported that the median survival was no different in the 13 patients subjected to surgery and no chemotherapy than it was in the 238 patients not subjected to surgery (120). However, the median survival in the 51 patients who received both surgery and chemotherapy was 35 months (120).

It should be emphasized that the series reported by Sugarbaker et al. represent a select group of patients and the overall median survival of 19 months was disappointing. Only 1% to 5% of patients with malignant mesothelioma are candidates for extrapleural pneumonectomy (121). Whether extrapleural pneumonectomy combined with chemotherapy and/or radiotherapy improves survival time and the quality of life in patients with mesothelioma is yet

to be proved (122,123). The combination of surgery, radiotherapy, and chemotherapy is expensive, time consuming, and usually requires that the patients be away from home for considerable periods of time. The ERS/ESTS (94) task force concluded that extrapleural pneumonectomy should only be performed in clinical trials, in specialized centers as part of multimodal treatment. In a recently reported study (124) from the United Kingdom, 50 patients eligible for extrapleural pneumonectomy were randomized to receive extrapleural pneumonectomy or no surgery. All patients received induction platinum-based chemotherapy and all patients received postoperative radiotherapy to the hemithorax (124). In this study, the patients who received the extrapleural pneumonectomy lived a shorter time (14.4 months vs. 19.5 months) (124). After adjustment for sex, histological subtype, state, and age, the patients who did not undergo extrapleural pneumonectomy had a significantly longer median survival (124). There was also much higher morbidity associated with extrapleural pneumonectomy in this study (124). The results of this study suggest that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms the patient.

Other researchers have recommended that only pleurectomies be performed or that pleurectomies be performed on patients who are not candidates for extrapleural pneumonectomies (125,126). Martin-Ucar et al. (125) attempted surgical debulking in 51 patients and were able to perform the procedure with VATS without resorting to thoracotomy in 17 patients. However, the 30-day mortality was 7.8% and the median survival was only 7 months (125). Halstead et al. (126) attempted to do a VATS debulking pleurectomy-decortication in 79 patients and were successful in 51. If a decortication did not appear to be feasible, only a biopsy was attempted (126). They reported that the median survival was significantly greater in the pleurectomy group (416 days) than it was in the biopsy-only group (127 days) (126). However, the difference in survival may well have been due to the greater tumor burden in the biopsy-only group. The ERS/ESTS task force (94) concluded that this treatment can be considered in patients to obtain symptom control, especially symptomatic patients with entrapped lung syndrome who cannot benefit from chemical pleurodesis.

Rusch and Venkatraman (112) compared the survival rate in 115 patients who had extrapleural pneumonectomy and 59 patients with pleurectomy and decortication who had participated in various trials. They could find no difference in the survival rates with the two surgical methods (112). It should be noted that in most series, surgery is combined with another therapeutic modality. Controlled studies are needed to compare pleurectomy with no surgery in trimodality therapeutic plans.

Chemotherapy

A role for chemotherapy in the treatment of malignant mesothelioma has been established in the past 10 years and cisplatin in combination with pemetrexed or raltitrexed is now considered the first-line systemic therapy for select patients with mesothelioma (94). The definitive study was reported by Vogelzang et al. (127) in 2003. In this study, 456 patients were randomly assigned to receive pemetrexed, a multitargeted antifolate, 500 mg/m^2 and cisplatin 75 mg/m^2 or cisplatin 75 mg/m^2 alone on day 1 and every 21 days thereafter (127). The doses of the drugs were decreased if toxicity occurred. To be eligible for the study, the patients were required to have a Karnofsky performance status greater than 70 and have a life expectancy of more than 3 months. In this study, the response rate in the combination group was significantly better than in the cisplatin-only group (41.3% vs. 16.7%) as was the median survival (12.1 months vs. 9.3 months) (127). However, when the Kaplan-Meier survival plots are examined (Fig. 11.2), the differences between the two regimens are not particularly impressive. The combination regimen had significantly greater toxicities than did the cisplatin alone regimen with the most severe toxicities being severe neutropenia (27.9%) and severe leukopenia (17.7%). A confirmatory study was reported by Van Meerbeeck et al. (128). In this study, 250 patients were randomized to receive 80 mg/m^2 cisplatin intravenously or cisplatin plus raltitrexed, another multitargeted antifolate, 3 mg/m^2. Among the 213 patients with measurable disease, the response rate tended to be better in the combination group than in the cisplatin-only group (23.6% vs. 13.6%, $p = 0.056$). The median survival was also greater in the combination group (11.4 months vs. 8.8 months) (128). Again there was more toxicity in the combination group (128).

In view of the facts mentioned in the preceding text, it appears that the administration of the combination of cisplatin and either pemetrexed or raltitrexed is associated with an increased survival time

and an increased response rate when compared with cisplatin alone. However, it must be noted that the increase in the survival times (Fig. 11.2) and the response rates are not great and the combination has significantly more side effects than does cisplatin. Nevertheless, these are the first studies to demonstrate a survival benefit with combination chemotherapy and raise hopes that more effective treatments will be found in the future. It should also be noted that pemetrexed is quite expensive. An outpatient at Vanderbilt University Medical Center would pay more than US$18,000 for each treatment with pemetrexed, whereas they would only pay US$250 for each treatment with cisplatin. Before combination chemotherapy is initiated, the costs, benefits, and side effects of the drugs should be discussed with the patient. If systemic chemotherapy is going to be administered, it is probably better to do it as soon as the malignant mesothelioma is diagnosed. O'Brien et al. (129) randomized 43 patients with malignant mesothelioma to receive at the time of diagnosis or at the time when they had progressive symptoms. They reported that the mean survival was 14 months in the early group but only 10 months in the delayed group (129).

Intrapleural chemotherapy probably has more promise than systemic chemotherapy. It has been shown that when drugs are administered intrapleurally, there is a threefold- to fivefold-advantage on a logarithmic scale for pleural versus plasma area under the concentration–time curves for cisplatin and mitomycin (130). However, the results of clinical studies have been disappointing (131).

Radiotherapy

The results with radiotherapy in the treatment of malignant mesothelioma have been disappointing (132). External radiotherapy does not control mesotheliomas locally and is associated with severe toxicity in the underlying lung (133). Presently, it is not recommended (132). There may be a place for internal radiation therapy in the management of malignant mesothelioma (134). In one report from the Memorial Sloan-Kettering Cancer Center, 33 patients were treated with the implantation of permanent radioactive iodine-125 (^{125}I) sources in residual tumor. This report concluded that local radiotherapy improved the length of survival (134). Many patients are given external radiotherapy after extrapleural pneumonectomy or decortication, but there are no controlled trials documenting whether this additional therapy improves survival. The ERS/ESTS task force recommended that radiotherapy should not be performed after pleurectomy or decortication (94).

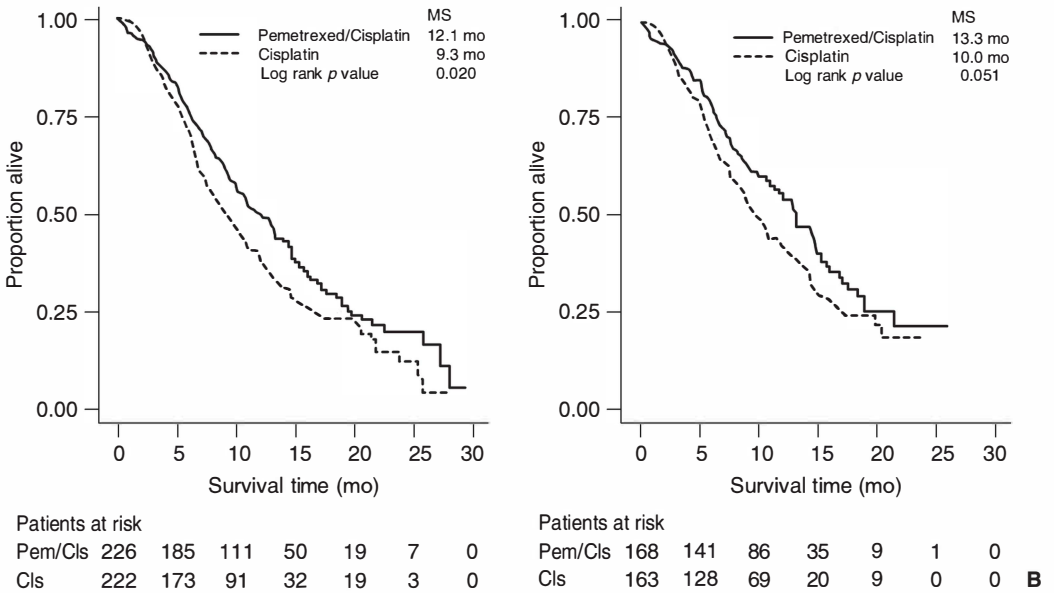

FIGURE 11.2 ■ Kaplan-Meier estimates of overall survival time for all patients (A) and for all patients supplemented with folic acid and Vitamin B_{12} (B). MS, median survival; Pem, pemetrexed; Cis, cisplatin.

Novel Therapies for Malignant Mesothelioma

Because the current therapies for mesothelioma are relatively ineffective, the search for newer therapies continues. Although none of the following therapies has proved to be effective, significant advances in the therapy for mesothelioma may arise from one or more of these therapies. Astoul et al. (135) administered interleukin 2 (IL-2) intrapleurally to 22 patients with malignant mesothelioma and reported 11 partial responses and 1 complete response. However, the median survival time of these patients was only 18 months. Marzo et al. (136) demonstrated that antisense oligonucleotides specific for transforming growth factor beta-2 inhibited the growth of malignant mesothelioma both *in vitro* and *in vivo*. Studies are underway to determine if the VEGF inhibitors are effective in mesothelioma (137).

Gene therapy for mesothelioma is in its adolescence (138). Multiple preclinical investigations and ongoing phase I trials have provided promising results (138,139). However, implementation of any of the gene therapy approaches as part of standard medical care for patients with mesothelioma remains for years in the future, but the field is finally progressing toward more definitive phase II/III studies (139).

SOLITARY FIBROUS TUMORS OF THE PLEURA

In the literature, there is a great diversity in the nomenclature of fibrous tumors of the pleura; these tumors have also been called *localized mesothelioma*, benign fibrous mesothelioma, benign localized fibroma, and submesothelial fibroma (140). The term *solitary fibrous tumor* is preferred for several reasons: (a) although the neoplasm is usually histologically and biologically benign, malignant forms clearly exist, and, in some cases, the histologic distinction between the two is difficult, if not impossible; (b) the neoplasm often shows evidence of fibroblastic differentiation; and (c) the results of ultrastructural, immunohistochemical, and experimental studies suggest that the tumor originates in the submesothelium itself (141). In comparison with malignant mesothelioma, the prognosis with solitary fibrous tumors of the pleura is excellent (142). These tumors are uncommon; at one center in Rome, however, there 110 patients were seen between July 1990 and February 2008 (143). There have now been nearly 2,000 cases reported in the literature (140). There is no relationship between asbestos exposure and solitary fibrous tumors of the pleura (141,142).

Pathologic Features

Grossly, fibrous tumors appear as firm, encapsulated yellow tumors, which may be vascular with prominent veins over their external surfaces (144). About two thirds of these fibrous tumors arise from the visceral pleura, whereas one third arises from the parietal pleura. At times, these tumors invade the lung and chest wall locally (145). Solitary fibrous tumors are characterized histologically by uniform, elongated spindle cells and varied amounts of collagen and reticulum fibers in bundles of many sizes (146). The cell of origin of this tumor is mesenchymal and appears to be the multipotential subpleural cell (147). These tumors lack expression of cytoplasmic keratins, a marker of mesothelial cells, but do express vimentin, a marker of mesenchymal cells (147). These tumors also express CD 34 which is a transmembrane cell surface glycoprotein ubiquitously observed in a novel family of interstitial spindle cells (147). The percentage of solitary fibrous tumors of the pleura that are malignant varies from 7% to 60%, a variation attributed to differences in institutional criteria for malignancy (148). The designation of a solitary fibrous tumor as malignant depends primarily on its mitotic index, mild-to-marked pleomorphism based on nuclear size, irregularity, and nuclear prominence, and bundles of high cellularity with crowding and overlapping of nuclei (147). The designation of malignancy is not based on the local invasiveness (148). Distant metastases occur in a small percentage of patients with malignant solitary fibrous tumors (148).

Classification

de Perrot et al. (147) have developed a classification that is based on whether the tumor is benign or malignant histologically and whether it is sessile or pedunculated. In one series (143) of 110 patients, 63 (57%) were pedunculated, 35 (32%) were sessile, and 12 (11%) were inverted, while 95 (86.4%) were benign and 15 (13.6%) were malignant. This classification is useful because it equates with prognosis. The solitary fibrous tumors with the worst prognosis are those that are malignant and sessile, in which approximately two thirds of patients have a recurrence and 30% die from the recurrence. Malignant pedunculated tumors recur approximately 15% of the time.

Recurrences with the benign sessile and the benign pedunculated tumors occur in less than 10% and deaths are rare with these types of tumors (147).

Clinical Manifestations

This tumor is evenly distributed between the sexes, and the median age of presentation is 57 years (145). Approximately 50% of patients with solitary fibrous tumors are asymptomatic, and the tumor is detected on routine chest radiographs (146,149). In the remaining patients, cough, chest pain, and dyspnea are the most frequent symptoms, each occurring in approximately 40% of symptomatic patients. Approximately 25% of symptomatic patients are febrile without any evidence of infection (149). The incidence of hypertrophic pulmonary osteoarthropathy is approximately 20% in patients with solitary fibrous tumors, and the incidence is much higher with larger tumors. In one series, 10 of 11 patients (91%) with lesions larger than 7 cm in diameter had hypertrophic pulmonary osteoarthropathy, whereas none of 41 patients with smaller lesions had the syndrome (146). When the tumors are surgically removed, the symptoms of hypertrophic pulmonary osteoarthropathy are relieved immediately in almost all patients (146).

Another paraneoplastic syndrome that sometimes accompanies solitary fibrous tumors of the pleura is hypoglycemia (Doege-Potter syndrome). Of the approximately 150 extrapancreatic tumors causing hypoglycemia reported by 1975, 10 were solitary fibrous tumors of the pleura. In a review of 360 cases of solitary fibrous tumors of the pleura, symptomatic hypoglycemia was reported in 4% (149). The mechanism responsible for the hypoglycemia appears to be the production of high levels of insulin-like growth factor II (IGF-II) by the tumor (150). The increased production of this insulin-like substance leads to an increased glucose utilization by peripheral tissues and decreased production of glucose by the liver. Tumors that are associated with hypoglycemia tend to be large. The hypoglycemia is relieved with surgical removal of the tumor.

Radiologically, these tumors are manifested as solitary, sharply defined, discrete masses located at the periphery of the lung or related to a fissure (42,144). At times, the mass may become very large, occupying most of the hemithorax (Fig. 11.3). The mass is frequently lobulated (42). The mass has an associated pleural effusion 10% to 20% of the time (146,151,152), but the presence or absence of an effusion apparently has no effect on the patient's prognosis (42). In one case, more than 170 L of transudative pleural fluid was produced by a solitary fibrous tumor (151). Calcifications are occasionally evident within the mass (144).

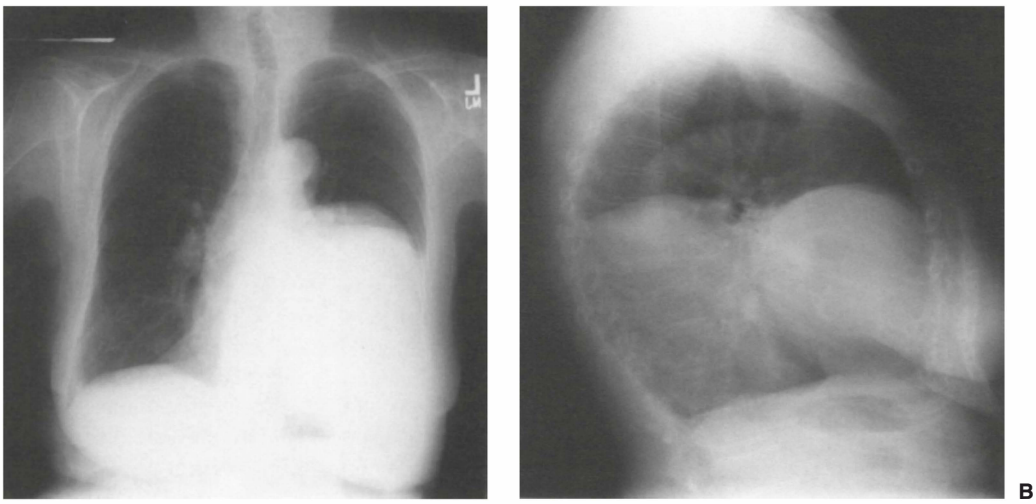

FIGURE 11.3 ■ Solitary fibrous tumor of the pleura. **A**: Posteroanterior chest radiograph demonstrating a large mass in the left hemithorax. **B**: Lateral radiograph demonstrating a large lobulated mass. These radiographs were from a 90-year-old lady who presented with severe hypoglycemia. At thoracotomy, the mass was found to be a solitary fibrous tumor of the pleura and it was completely removed. The patient became asymptomatic postoperatively with resolution of the hypoglycemia.

The appearance of the solitary fibrous tumors on CT scan is characteristic (104,141). The tumors are large, noninvasive, and tend to enhance with intravenous contrast material, but the enhancement is frequently nonhomogeneous. The intense enhancement of these tumors appears to be due to their high vascularity, whereas areas of low attenuation are due to foci of myxoid or cystic degeneration and hemorrhage in the lesion (34). There is no associated mediastinal lymphadenopathy. PET scans of patients with solitary fibrous tumors usually reveal little or no uptake of the isotope by the tumor (153).

Diagnosis

A VATS procedure or a thoracotomy is usually necessary for diagnosis, although the diagnosis has been established by transthoracic cutting-needle biopsy in some patients (154). However, because the appropriate treatment for the solitary fibrous tumor is surgical removal, most patients should be subjected to VATS or a thoracotomy for diagnosis and excision. In one series of 110 patients, the resection was performed via VATS in 59 (54%) (143). The existence of solitary tumors, such as solitary fibrous tumors of the pleura, that can produce systemic symptoms underscores the importance of obtaining histologic proof of malignant disease in patients suspected of having malignant tumors before instituting radiotherapy or chemotherapy. Obviously, bronchoscopic and sputum cytologic tests are negative with solitary fibrous tumors.

Treatment and Prognosis

The treatment of choice for solitary fibrous tumors is surgical removal by thoracotomy or by VATS (155). If the tumor originates in the visceral pleura, substantial amounts of lung parenchyma may also have to be removed (146,156). Surgical resection cures approximately 90% of these patients (143,146,149), but recurrent disease occurs in the remaining 10%. Complete resection is the best way to prevent recurrences (156). The recurrences may occur more than 10 years after the initial resection. It is recommended that annual chest radiographs be obtained postoperatively in patients with solitary fibrous tumors to detect recurrences early so that they can be surgically removed.

PRIMARY EFFUSION LYMPHOMA

Primary effusion lymphoma is an uncommon non–Hodgkin's lymphoma that grows in the liquid phase in the serous body cavities in the absence of solid tumors (157,158). Primary effusion lymphoma is also known as *body cavity–based lymphoma* and is associated with human herpesvirus 8 (HHV-8) or Kaposi's sarcoma–associated herpesvirus (KSHV) (159). HHV-8 is a gamma herpes virus with sequence homology to the Epstein-Barr virus (160). The presence of the HHV-8 appears to be specific for primary effusion lymphoma. Uphoff et al. (160) searched for the presence of HHV-8 sequences by PCR using a panel of 133 human cell lines from a variety of solid tumors, 114 hematopoietic cell lines including 50 B-cell leukemia/lymphoma-derived cell lines, and 7 cell lines established from patients with primary effusion lymphoma. All of the cell lines from the patients with primary effusion lymphoma were strongly positive for HHV-8, whereas none of the other cell lines were positive for HHV-8. This observation suggests an etiologic role for HHV-8 in primary effusion lymphoma. Castillo et al. (161) reviewed 147 patients with primary effusion lymphoma and reported that 104 (71%), were HHV-8 positive. Many of these tumors are also characterized by the presence of the Epstein-Barr virus (158).

Primary effusion lymphoma most commonly occurs in homosexual patients with acquired immunodeficiency syndrome (AIDS) (157). Primary effusion lymphoma is rare and accounts for less than 5% of all AIDS-related non–Hodgkin's lymphoma (162). Until 2012 only 147 cases had been reported in the literature (161). Mbulaiteye et al. (163) reviewed 304,439 patients with AIDS and were able to find only 4 cases of primary effusion lymphoma of the pleura. These tumors occasionally occur in patients who are not infected with the human immunodeficiency virus (HIV), particularly in elderly men (159) or those who are immunosuppressed (164,165). The tumors have a large cell morphology and their immunophenotype is null. Nevertheless, they do have a B-cell genotype (159). The cells from more than 90% of cases express the CD45 antigen (165). It has been shown that the normal counterpart of the primary effusion lymphoma tumor cells is the mature B cell or preplasma cell.

The chest radiographs and CT scans show thickening of the parietal pleura and pericardial thickening in many patients. Many patients also have pericardial effusions, and some patients also have ascites (159). The pleural fluid is a lymphocytic exudate characterized by a very high lactate dehydrogenase level. The diagnosis can usually be established with pleural fluid cytology. The primary effusion lymphoma has a distinctive morphology, bridging large cell

immunoblastic lymphoma and anaplastic large cell lymphoma. Demonstration of the HHV-8 by PCR in conjunction with the typical cytologic appearance of the cells establishes the diagnosis (166). The optimal treatment for these lymphomas remains to be established (167), but the median survival is only about 6 to 9 months (161,165). The prognosis is poorer if more than one body cavity is involved (161). Initiation of highly active antiretroviral therapy (HAART) should be done as soon as the diagnosis is established (165). There is one case report of a patient with a body cavity lymphoma, who did not have AIDS but was HHV-8 positive, whose lymphoma cells were positive for CD19, CD20, and CD22. Treatment of this patient with rituximab, a chimeric (human–mouse) anti-CD20 monoclonal antibody induced a remission that persisted for at least 13 months (168). However, the great majority of PELs are not positive for these markers.

PYOTHORAX-ASSOCIATED LYMPHOMA

Pyothorax-associated lymphoma is relatively a newly recognized entity. Most cases have been in Japan and in 2002, 106 cases were identified in Japan with a nationwide survey (169). However, one article reported 12 cases from Europe (170). Pyothorax-associated lymphoma occurs almost exclusively in patients who, several decades earlier, received artificial pneumothorax for the treatment of long-standing pleural tuberculosis. Therefore, the name should probably be pneumothorax-associated lymphoma rather than pyothorax-associated lymphoma. However, there have been cases that developed after empyema (171). Most of these lymphomas are of B-cell lineage. The Epstein-Barr virus genome has been detected in 70% of the tumors tested (169).

Patients with pyothorax-associated lymphoma commonly present with chest pain or back pain and fever (169). Some patients present with a tumor of the chest wall. The male-to-female ratio of patients with this disease is 12:1 (169). The CT scan reveals pleural masses without effusions in most patients (172,173). Frequently the chest wall, ribs, lung parenchyma, and abdomen are directly invaded (173). The treatment of choice appears to be aggressive wide-field radiation therapy of 50 Gy (172) or chemotherapy (173). If the patient can tolerate surgery, pleuropneumonectomy may be curative (173). Some patients have also had a complete response to chemotherapy (169). In one series of 98 patients, the 5-year survival was 35%.

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chapter 12

Parapneumonic Effusions and Empyema

Despite the advent of potent antibiotics, bacterial pneumonia still results in significant morbidity and mortality in the American population. The annual incidence of bacterial pneumonia is estimated to be 4 million, with approximately 25% of patients requiring hospitalization (1). Because as many as 40% of hospitalized patients with bacterial pneumonia have an accompanying pleural effusion (2), effusions associated with pneumonia, parapneumonic effusions (PPE), account for a large percentage of pleural effusions. The morbidity and mortality rates in patients with pneumonia and pleural effusions are higher than those in patients with pneumonia alone. In one study of 1,424 patients hospitalized with community-acquired pneumonia, patients with pleural effusions were 2.7 times more likely to be treatment failures than were those without pleural effusions (3). In another study, the relative risk of mortality in patients with community-acquired pneumonia was 7.0 times higher for patients with bilateral pleural effusions and 3.4 times higher for patients with unilateral pleural effusion of moderate or greater size as compared with other patients with community-acquired pneumonia alone (4). In assessing risks of patients with community-acquired pneumonia, the presence of a pleural effusion is given the same weight as a Po_2 less than 60 mm Hg (5). Espana et al. (6) recommend that any patient with pneumonia and a loculated effusion or an effusion greater than 2 cm in thickness on the decubitus be hospitalized. Some of the increased morbidity and mortality in patients with parapneumonic effusions are due to mismanagement of the pleural effusion (7).

Pleural infection (complicated parapneumonic effusion and empyema) is rising in incidence across all age groups worldwide, confirmed by reports from the United States, Canada, Europe, and Asia (8). The mortality rate of empyema has risen alarmingly. In Utah, death rates from empyema were sixfold higher in 2000–2004 compared to 1950–1975 (9). Overall in the United States, the incidence of empyema per 100,000 persons had roughly doubled between 1996 and 2008 with roughly equal increases occurring in all age groups (10). In this study, the increase was largely due to increases in nonpneumococcal empyema and staph empyema (10). The explanation for the increase in empyema incidence is not clear but has been attributed at least in part to the induction of the heptavalent pneumococcal conjugate vaccine (PCV7) in 2000. After the introduction of this vaccine, there was a reduction in invasive pneumococcal disease, but the incidences of pneumococcal empyema in children and adults have both increased (8). The decrease in incidence of empyema from serotypes covered by the vaccine was overcompensated by an emergence of disease caused by nonvaccine serotypes (particularly serotype 1) (8).

Most pleural effusions associated with pneumonia resolve without any specific therapy directed toward the pleural fluid (2), but approximately 10% of patients require operative intervention. Delay in instituting proper therapy for these effusions is responsible for some of the morbidity associated with parapneumonic effusions. In one series of 39 patients from San Francisco General Hospital selected on the basis of pus in the pleural space, a positive Gram's stain or culture, a pH of less than 7.0, or a glucose level of less than 40 mg/dL, the mean duration of pleural drainage was 21 ± 18 days, with a mortality rate of 10% (11).

HISTORY

Empyema has been recognized to be a serious problem for centuries. Around 500 B.C., Hippocrates recommended treating empyema with open drainage (12). He made the following interesting observation (12): "Those cases of empyema which are treated by incision or the cautery, if the water flows rapidly all at once certainly prove fatal. When empyema is treated, either by the incision or the cautery, if pure and white pus flows slowly from the wound, the patients recover." His observation is contrary to that which most of us would have anticipated. However, when one reflects on the observation, its validity becomes obvious. If the fluid was thin, the patient probably did not have an empyema and the lung would collapse. However, if the fluid was pus, the patient had an empyema and drainage was likely to be beneficial.

From the time of Hippocrates, the treatment of empyema remained essentially unchanged until the middle of the 19th century. At this time, Bowditch (13) in the United States and Trousseau (14) in France popularized the use of thoracentesis and demonstrated that open drainage was not necessary in many patients. The next advance in the management of empyema came in 1876 when Hewitt (15) described a method of closed drainage of the chest in which a rubber tube was placed into the empyema cavity through a cannula. He was the first to use the water seal for chest tubes.

In the 1890s, two articles appeared that described thoracoplasty as a means of obliterating the empyema cavity (16,17). Thoracoplasty involves resecting the ribs, intercostal muscles, and parietal pleural peel over the cavity, and covering the remaining defect by the few remaining muscles, the scapula, and the subcutaneous tissue and skin. At approximately the same time, the initial reports (18,19) describing decortication appeared. By 1923, Eggers (20) had reported on a series of 99 patients treated by decortication at the Walter Reed Hospital, of whom two-thirds subsequently healed.

Although Hippocrates had recognized before the birth of Christ that open drainage procedures were dangerous if the empyema fluid was not thick (12) and Paget (21) had emphasized in 1896 that open drainage should not be instituted for empyema before at least the 15th day of the illness, by World War I, open drainage was the accepted treatment for all cases of empyema. During World War I, there was a high incidence of parapneumonic empyema in American soldiers and the treatment of all such patients with open drainage had disastrous results. In a survey in 1919, the U.S. Surgeon General found an average mortality rate of 30.2% in the armed forces for individuals with pleural infections, with a range of up to 70% in some hospitals (22). The primary reason for this very high mortality rate was that many cases of parapneumonic effusions in military recruits were due to *Streptococcus hemolyticus*, which is associated with large amounts of pleural fluid but without loculation of the pleural space (23). When an open procedure is performed on such patients, there is a high likelihood that the lung will collapse. In a study from Fort Riley, Kansas, 285 patients with empyema were subjected to surgery (24). The first 85 had early surgery and the mortality was 61%, 96 had early aspiration and later surgery and the mortality fell to 15.6%, whereas the last 94 patients had early aspiration and late surgery and the mortality was only 9.5% (24).

In 1918, Graham (25) reported that when chest tubes were inserted early in dogs with experimental empyemas, the mortality rate was higher and the dogs died sooner. The Empyema Commission headed by Dr. Evarts Graham soon made the following recommendations, which really form the basis for the treatment of empyema today: (a) The pleural fluid should be drained, but one must avoid an open pneumothorax in the acute exudative phase; (b) care should be taken to avoid a chronic empyema by rapid sterilization and obliteration of the infected cavity; and (c) careful attention should be paid to the nutrition of the patient. When these guidelines were observed, the mortality rate from streptococcal empyema secondary to influenza fell to 4.3% (26,27).

The next advance in the treatment of parapneumonic effusion came about in 1950, when Tillett and Sherry proposed enzymatic debridement with a combination of streptokinase and streptodornase for parapneumonic empyema (28). Then in the 1950s and 1960s, a low pleural fluid glucose was proposed as an indicator for tube thoracostomy (29). Then in 1972, Light et al. (30) suggested that a low pleural fluid pH was an indicator for tube thoracostomy, and in 1980, the same group suggested that a high pleural fluid lactic dehydrogenase (LDH) level was an indicator for a poor prognosis (2). In the last decade, the use of video-assisted thoracoscopy (VATS) has become widespread in the treatment of loculated parapneumonic effusions (31).

DEFINITIONS

Any pleural effusion associated with bacterial pneumonia, lung abscess, or bronchiectasis is a parapneumonic effusion (30). An empyema, by definition, is

pus in the pleural space, but how many white blood cells (WBCs) need be present in pleural fluid to make it pus? Weese et al. (32) defined an empyema as pleural fluid with a specific gravity greater than 1.018, a WBC count greater than 500 cells/mm^3, or a protein level greater than 2.5 g/dL. Vianna (33) defined an empyema as pleural fluid on which the bacterial cultures are positive or the WBC is greater than 15,000/mm^3 and the protein level is above 3.0 g/dL. Because many parapneumonic pleural effusions meeting these criteria resolve without operative intervention (2), I prefer to reserve the term *empyema* for those pleural effusions with thick, purulent appearing pleural fluid. Of course, some patients with empyema have no associated pneumonic process, as shown in Table 12.1.

The main decision in managing a patient with a parapneumonic effusion is whether to insert chest tubes. Therefore, I use the term *complicated parapneumonic effusion* to refer to those effusions that do not resolve without therapeutic thoracentesis or tube thoracostomy. Many complicated parapneumonic effusions are empyemas, but some parapneumonic effusions with nonpurulent appearing pleural fluid are also complicated parapneumonic effusions.

TABLE 12.1 ■ Event or State Precipitating Empyema in 319 Patients

Event or State	Number	Percentage
Pulmonary infection	177	55
Surgical procedure	66	21
Trauma	18	6
Esophageal perforation	15	5
Spontaneous pneumothorax	7	2
Thoracentesis	6	2
Subdiaphragmatic infection	4	1
Septicemia	4	1
Miscellaneous or unknown	22	7
Total	319	100

Data from Yeh TJ, Hall DP, Ellison RG. Empyema thoracis: a review of 110 cases. *Am Rev Respir Dis.* 1963;88:785–790; Snider GL, Saieh SS. Empyema of the thorax in adults: review of 105 cases. *Chest.* 1968;54:12–17; and Smith JA, Mullerworth MH, Westlake GW, et al. Empyema thoracis: 14-years experience in a teaching center. *Ann Thorac Surg.* 1991;51:39–42, with permission.

PATHOPHYSIOLOGIC FEATURES

The evolution of a parapneumonic pleural effusion can be divided into three stages, which are not sharply defined but gradually merge together (34). First is the exudative stage, characterized by the rapid outpouring of sterile pleural fluid into the pleural space. The origin of this fluid is not definitely known, but it is probably the interstitial spaces of the lung. The origin of the pleural fluid in sheep with *Pseudomonas aeruginosa* pneumonia is the interstitial spaces of the lung (35). It is possible that some of the pleural fluid originates in the capillaries in the visceral pleura owing to their increased permeability secondary to the contiguous pneumonitis. The pleural fluid in this stage is characterized by a low WBC count, a low LDH level, and a normal glucose level and pH (36). If appropriate antibiotic therapy is instituted at this stage, the pleural effusion progresses no further, and the insertion of chest tubes is not necessary.

If appropriate antibiotic therapy is not instituted, in some instances, bacteria invade the pleural fluid from the contiguous pneumonic process, and the second, fibropurulent stage evolves. This stage is characterized by the accumulation of large amounts of pleural fluid with many polymorphonuclear leukocytes, bacteria, and cellular debris. Fibrin is deposited in a continuous sheet covering both the visceral and parietal pleura in the involved area. As this stage progresses, there is a tendency toward loculation and the formation of limiting membranes. These loculi prevent extension of the empyema but make drainage of the pleural space with chest tubes increasingly difficult. As this stage progresses, the pleural fluid pH and glucose levels become progressively lower and the LDH level becomes progressively higher.

The last stage is the organization stage, in which fibroblasts grow into the exudate from both the visceral and parietal pleural surfaces and produce an inelastic membrane called the *pleural peel*. This inelastic pleural peel over the visceral pleura encases the lung and renders it virtually functionless. At this stage, the exudate is thick, and if the patient remains untreated, the fluid may drain spontaneously through the chest wall (empyema necessitatis) or into the lung, producing a bronchopleural fistula.

Empyemas may arise without an associated pneumonic process. When three series (37–39) totaling 319 cases of empyema are combined (Table 12.1), most patients had pulmonary infections, but postsurgical empyemas were also important. A small percentage of empyemas complicate thoracentesis or tube thoracostomy for pneumothorax, hence the

necessity for maintaining sterile techniques during these procedures. The pleural effusions associated with esophageal perforation are almost always infected (see Chapter 18). Patients with rheumatoid pleural effusions frequently develop empyema (see Chapter 21); the genesis of the empyema in this situation is thought to be the formation of a bronchopleural fistula through necrotic subpleural nodules (40).

EXPERIMENTAL EMPYEMA

There has been surprisingly little work done with experimental empyema. This work is summarized in Chapter 4.

BACTERIOLOGIC FEATURES

The bacteriologic features of culture-positive parapneumonic effusions have changed since the introduction of antibiotics. Before the antibiotic era, most empyema fluids grew *Streptococcus pneumoniae* or *Streptococcus hemolyticus* (41). Then between 1955 and 1965, *Staphylococcus aureus* was the bacteria most commonly isolated from pleural fluid (41). In the early 1970s, anaerobic organisms were most commonly isolated (42). However, in the 1980s and 1990s, it appeared that the aerobic organisms were again responsible for most empyema. Brook and Frazier (43) in 1993 reviewed the microbiology of 197 patients whose pleural fluid was culture positive for bacteria in two military hospitals. In 64% of patients, only aerobic bacteria were isolated, whereas in 13% of patients, only anaerobic organisms were isolated and, in 23% of patients, both aerobic and anaerobic organisms were isolated. Alfrageme et al. (44) again in 1993 reviewed the microbiology of 82 patients treated for empyema at a respiratory unit in Spain and reported results similar to those of Brook and Frazier (43). Of their 76 patients with positive cultures, 62% had exclusively aerobic bacteria, whereas 16% had exclusively anaerobic bacteria, 17% had both aerobic and anaerobic organisms, and 5% *Mycobacterium tuberculosis* or fungi.

The organisms isolated from positive pleural fluid cultures in three separate series (42,43,45) are tabulated in Table 12.2. These series represent 342 patients, from whom 580 organisms were isolated. Aerobic organisms alone were isolated from 181 patients (53%), anaerobic organisms only were isolated from 76 patients (22%), and both aerobic and anaerobic organisms were isolated from 85 patients (25%).

Several conclusions can be made from Table 12.2. First, aerobic organisms are isolated slightly more frequently than anaerobic organisms. Second, *S. aureus* and *S. pneumoniae* account for approximately 70% of all aerobic gram-positive isolates. Third, when there is a single aerobic gram-positive organism in the pleural fluid, it almost always is *S. aureus*, *S. pneumoniae*, or *Streptococcus pyogenes*. Fourth, gram-positive aerobic organisms are isolated approximately twice as frequently as are gram-negative aerobic organisms. Fifth, although *Escherichia coli* is the most commonly isolated gram-negative aerobic organism, it is rarely the lone pathogen isolated from pleural fluid. Sixth, *Klebsiella* sp, *Pseudomonas* sp, and *Hemophilus influenzae* are the next three most commonly isolated aerobic gram-negative organisms, and these three organisms account for approximately 75% of all aerobic gram-negative empyemas with a single organism. Seventh, *Bacteroides* sp and *Peptostreptococcus* are the two most commonly isolated anaerobic organisms from infected pleural fluid. Eighth, it is uncommon for a single anaerobic organism to be isolated from pleural fluid.

The most recent comprehensive report on the bacteriology of complicated parapneumonic effusions comes from the large trial of intrapleural streptokinase in the United Kingdom (46). In this study of 434 patients, the Gram's stain was positive in 250 (58%) patients, the cultures grew a single aerobic growth in 151 (35%) patients, a single anaerobic growth in 29 (7%) patients, and a polymicrobial growth in 52 (12%) patients (46). Pleural fluid was available for molecular microbiologic analysis in 404 of the subjects. For 70 of the culture-negative cases, bacteria were identified by subsequent nucleic acid amplification. Overall, a microbiologic diagnosis was obtained in 320 patients (74%). In patients with community-acquired pneumonia, the organisms most commonly responsible were *Streptococcus intermedius-anginosus-constellatus* (milleri) group in 80, *S. pneumoniae* 71, and other streptococcus species 25, *S. aureus* 34 (7 methicillin resistant *Staphylococcus aureus* [MRSA]), gram negatives 29, and anaerobes 67. In patients with hospital-acquired parapneumonic effusions, the most common organism was *S. aureus* 21, of which 15 were MRSA (46). In a second study (47), *Streptococcus intermedius-anginosus-constellatus* (milleri) was also the most common organism isolated in culture positive complicated parapneumonic effusions.

The bacteriology of complicated parapneumonic effusions seems to be different in Taiwan. One series in the late 1990s from Taiwan reported that *Klebsiella pneumonia* was isolated from 34 of 139 patients

TABLE 12.2 ■ Organisms Isolated from Infected Pleural Fluid in Three Separate Series

Organisms	Series 1974[a]	1981[b]	1993[c]	Total	%
Gram-Positive Organisms					
Staphylococcus aureus	17 (6)	7 (4)	58 (39)	82 (49)	36
Staphylococcus epidermidis	5 (0)	0 (0)	3 (0)	8 (0)	3
Streptococcus pneumoniae	5 (2)	6 (6)	70 (33)	81 (41)	35
Enterococcus faecalis	5 (0)	4 (1)	4 (0)	13 (1)	6
Streptococcus pyogenes	4 (0)	5 (0)	9 (9)	18 (9)	8
Other streptococci	8 (0)	6 (3)	13 (0)	27 (3)	12
Total	44 (8)	28 (14)	157 (81)	229 (103)	
Gram-Negative Organisms					
Escherichia coli	11 (0)	4 (1)	17 (1)	32 (2)	30
Klebsiella species	6 (1)	1 (1)	16 (6)	23 (8)	21
Proteus species	2 (0)	1 (0)	5 (1)	8 (1)	7
Pseudomonas species	10 (2)	8 (6)	9 (3)	27 (11)	25
Enterobacter species	0 (0)	3 (3)	0 (0)	3 (3)	3
Hemophilus influenzae	1 (0)	0 (0)	12 (7)	13 (7)	12
Others	0 (0)	2 (0)	0 (0)	2 (0)	2
Total	30 (3)	19 (11)	59 (18)	108 (32)	
Anaerobic Organisms					
Bacteroides species	23 (1)	13 (4)	26 (6)	62 (11)	20
Peptostreptococcus species	26 (1)	8 (1)	28 (4)	62 (6)	20
Fusobacterium species	16 (3)	7 (2)	20 (4)	43 (9)	14
Prevotella species	13 (0)	5 (1)	22 (2)	40 (3)	13
Streptococcus species	15 (5)	4 (2)	12 (0)	31 (7)	10
Clostridium species	13 (1)	5 (3)	5 (1)	23 (5)	7
Others	34 (1)	4 (2)	14 (0)	52 (4)	16
Total	140 (12)	46 (15)	127 (17)	313 (45)	

The numbers in parentheses indicate the number of isolates that were recovered in pure culture.

[a]Data from Bartlett JG, Gorbach SL, Thadepalli H, et al. Bacteriology of empyema. *Lancet.* 1974;1:338–340, with permission.

[b]Data from Varkey B. Rose HD, Kutty CPK, et al. Empyema thoracis during a ten-year period. *Arch Intern Med.*1981;141:1771–1776, with permission.

[c]Data from Brook I, Frazier EH. Aerobic and anaerobic microbiology of empyema. A retrospective review in two military hospitals. *Chest.* 1993;103:1502–1507, with permission.

(24.4%) with positive pleural fluid cultures (48). If the patient is in the intensive care unit, gram-negative aerobic organisms are most likely to be responsible, with *K. pneumonia* being the most common organism (49). The microbiology of empyema in elderly patients and young adults is similar (50).

Several other points should be made concerning the bacteriology of infected pleural fluid. First, to a large part, the incidence of anaerobic isolates is dependent on the care with which the pleural fluid is cultured for anaerobes. The relatively high incidence of anaerobes in the series of Bartlett et al. (42) is partially explained by the intense interest these investigators had in culturing anaerobes. Second, the organisms cultured depend somewhat on the population studied. If aspiration is responsible for the underlying pneumonia, anaerobic organisms are more likely to be responsible (43). This also explains somewhat the high incidence of anaerobes in Bartlett's series because their patient population was made up of elderly veterans. In contrast, *S. pneumoniae* is more likely to be the causative factor in young ambulatory patients whereas in postthoracotomy patients, *S. aureus* is most likely to be responsible.

The bacteriology of infected pleural fluid in children varies somewhat from that in adults in that *H. influenzae* is more common and anaerobic organisms are less common. In one study of 72 culture-positive pleural fluids, aerobic organisms were found in 48 (67%), anaerobic organisms were found

in 17 (24%), and mixed aerobes and anaerobes were found in 7 (10%) (51). The most commonly isolated organisms in this series were *H. influenzae* (15 isolates), *Bacteroides* sp (15), *S. pneumoniae* (13), *S. aureus* (10), and anaerobic cocci (9). In another series of 173 culture-positive pleural fluids in children younger than 15 years, 38% were due to *S. aureus*, 28% were due to *S. pneumoniae*, 23% were due to *H. influenzae*, and 11% were due to other organisms. In this series, anaerobic isolates were rare (52).

INCIDENCE OF PLEURAL EFFUSIONS WITH VARIOUS BACTERIAL PNEUMONIAS

Once a patient has a bacterial pneumonia, the incidence of associated pleural effusion and the frequency with which the pleural fluid becomes infected largely depend on the infecting organism (Table 12.3). Infected pleural fluid is most common in anaerobic pneumonia. In one series of 143 patients with anaerobic infections of the lung (53), 50 (35%) had pleural effusions, and in 47 (94%) of these, the pleural fluid cultures were positive for anaerobic organisms. Aerobic organisms were also cultured from the pleural fluid in 18 (40%) of the patients with positive anaerobic pleural fluid cultures. Some patients with anaerobic pleural infection have no concomitant parenchymal disease.

GRAM-POSITIVE BACTERIA

S. pneumoniae is still responsible for many bacterial pneumonias, and many patients have an associated pleural effusion. Taryle et al. (54) studied 53 patients with pneumococcal pneumonia and found that 57% had an associated parapneumonic effusion, whereas my colleagues and I found that 40% of 153 patients with pneumococcal pneumonia had an associated pleural effusion (2). In a more recent paper, 40% of 52 patients with bacteremic pneumococcal pneumonia had pleural effusions as compared with 21% of patients with pneumococcal pneumonia without bacteremia (55). Pleural fluid cultures are usually negative in patients with pneumococcal parapneumonic effusions. Of the 81 patients with pleural effusions in the foregoing two

TABLE 12.3 ■ Percentage of Pleural Effusions and of Positive Pleural Fluid Cultures with Various Bacterial Pneumonias

Organism	Reference	Pleural Effusion (%)	Positive Pleural Fluid Culture (%)
Anaerobic	(53)	35	90
Gram-positive			
Streptococcus pneumoniae	(2,54)	40–60	1–5
Staphylococcus aureus			
Adults	(58,59)	50	20
Children	(54,57)	70	80
Streptococcus pyogenes	(63,63)	55–95	30–40
Bacillus anthracis	(75,76)	90–100	20–100
Aerobic gram-negative			
Escherichia coli	(65)	40	80
Pseudomonas	(66)	25–50	40–50
Klebsiella pneumoniae	(69)	50	50
Haemophilus influenza			
Adults	(64,72,73)	10–45	20
Children	(59,63,70,71)	75	80
Proteus species	(74)	20	50
Legionella species	(79–82)	25–60	?

The numbers in parentheses indicate the number of isolates that were recovered in pure culture.
[a]Data from Bartlett JG, Gorbach SL, Thadepalli H, et al. Bacteriology of empyema. *Lancet*. 1974;1:338–340, with permission.
[b]Data from Varkey B. Rose HD, Kutty CPK, et al. Empyema thoracis during a ten-year period. *Arch Intern Med*.1981;141:1771–1776, with permission.
[c]Data from Brook I, Frazier EH. Aerobic and anaerobic microbiology of empyema. A retrospective review in two military hospitals. *Chest*. 1993;103:1502–1507, with permission.

series, only 3 (4%) had pleural fluid cultures that were positive for *S. pneumoniae*. Nevertheless, as shown in Table 12.2. *S. pneumoniae* is responsible for many positive pleural fluid cultures. The explanation for this apparent paradox is the fact that such a large percentage of pneumonias is due to *S. pneumoniae*. The incidence of parapneumonic effusions is higher when patients wait 48 hours or more after the development of symptoms before seeking medical attention (54).

Pneumonia secondary to *S. aureus* is likely to have an accompanying culture-positive pleural effusion. Indeed, in one study of the causes of pleural effusion in children, staphylococcal empyema was the most frequent cause (56). Wolfe et al. (56) reviewed 98 children with pleural effusions seen at Duke University between 1952 and 1967 and reported that *S. aureus* was responsible for 35 (36%) of the effusions. In a series of 75 cases of staphylococcal pneumonia in infants and young children (57), more than 70% had pleural effusions, and the pleural fluid cultures were positive in approximately 80%. In adults, more than 50% of patients with staphylococcal pneumonia will have an accompanying pleural effusion (58), and effusions are more common with MRSA than with MSSA. Pleural fluid cultures are positive in at least 20% of adults with pleural effusions (59). In one series (60) of 14 patients with community acquired MRSA pneumonia, pleural effusions were present in nine patients (64%) and pleural fluid cultures were positive in 5 of the 9 patients (55%) with pleural effusion. Patients who have right-sided endocarditis from *S. aureus* frequently have pleural effusions, but the cultures are positive in only a small percentage (61). In this situation, the effusions are exudates with a very high pleural fluid LDH.

Pneumonias due to *S. pyogenes* are uncommon, but they are associated with parapneumonic effusion in most cases. Welch et al. (62) reported that 95% of 20 patients had an associated pleural effusion, whereas Basiliere et al. (63) reported that 57% of 95 patients with streptococcal pneumonia had a pleural effusion. The pleural fluid cultures are positive in 30% to 40% of those with pleural effusion (62,63). The pleural effusions secondary to streptococcal pneumonia are located more commonly on the left side. Of the 73 pleural effusions in the foregoing series, nearly two-thirds were on the left side. Streptococcal pneumonia occurs in epidemics, particularly among military recruits (63). In some patients, the development of the pleuritis is explosive with this organism. Patients may develop large pleural effusions with low glucose levels and pH in less than 12 hours (64).

GRAM-NEGATIVE BACTERIA

Of pneumonias due to gram-negative aerobic organisms, those caused by *E. coli* are most likely to have complicated parapneumonic effusions. In one series of 20 patients (65), 40% had pleural effusion, and in 6 of these 8 patients, pleural fluid cultures were positive. All eight patients with pleural effusion in this series had to be treated by tube thoracostomy or open thoracotomy. Rarely, however, is *E. coli* the sole isolate from pleural fluid (Table 12.2). Patients with *Pseudomonas* pneumonia are also likely to have pleural effusions. In one series of 56 patients with ventilator-associated *P. aeruginosa* pneumonia, 13 (23%) had a pleural effusion and 7 (12.5%) developed empyema (66). In another series of 28 patients with nosocomial pneumonia due to *P. aeruginosa*, 13 (46%) had bilateral effusions and an additional 5 (18%) had a unilateral effusion (67). As evident in Table 12.2, *Pseudomonas* sp and *E. coli* account for more than 50% of all aerobic gram-negative isolations from pleural fluid. In Taiwan, *K. pneumonia* is the most frequent cause of community-acquired thoracic empyema or complicated parapneumonic effusion accounting for 40 of 169 positive cultures in one study (68). Pleural effusion occurs in about 50% of patients with *Klebsiella pneumoniae* (69). The mortality rate is significantly higher in patients with pleural fluid cultures positive for *K. pneumoniae* than it is for patients with cultures positive for other organisms (68).

In recent years, *H. influenzae* has been responsible for an increasing number of pneumonias in both children (52,70,71) and adults (72). With *H. influenzae* pneumonia, the pleura is frequently involved, particularly in children (71). In a series of 65 cases of pneumonia in children, 49 (75%) had pleural effusions, and the cultures were positive in 36 of 46 patients (78%) (71). In one large series (73) of 211 patients with *H. influenzae* pneumonia, only 22 patients (10.4%) had a pleural effusion. *Proteus* sp causes a substantial proportion of gram-negative pneumonias, but associated pleural effusions are uncommon, and when they are present, they are usually small and uncomplicated (74).

ANTHRAX

Bacillus anthracis is a large gram-positive, spore-forming, rod-shaped organism that may contaminate goat hair, wool, or animal hides (75). Although only one case of anthrax was reported in the United States between 1980 and 2000, interest has been

rekindled in this organism with its use as a bioterrorism agent in Washington, D.C. in 2001 (76). This virulent organism causes pulmonary disease when the spores are inhaled into the alveoli, are engulfed by alveolar macrophages, and are carried to the hilar lymph nodes, where they multiply in their vegetative state. After causing flu-like symptoms for several days, the bacteria are disseminated hematogenously. This dissemination is marked by the acute onset of dyspnea, cyanosis, tachycardia, fever, and shock. In the cases in Washington, the medium time from exposure to symptoms was 4 days and then patients did not seek medical attention for another 3.5 days (76). The characteristic radiologic findings are mediastinal widening, patchy nonsegmental pulmonary infiltrates, and unilateral or bilateral pleural effusions.

Pleural effusions were present in all 10 of these patients treated in Washington, D.C. with the bioterrorism attack (76) and 7 patients required drainage. Indeed, when Kyriacou et al. (77) compared the clinical characteristics of 47 cases of anthrax with those of 376 patients with community-acquired pneumonia or influenza, they found that the most accurate prediction was the presence of a pleural effusion or mediastinal widening on the chest radiograph. All 47 patients with anthrax had a pleural effusion and/or mediastinal widening (77). In the recent outbreak, the pleural fluid was a bloody exudate (the pleural fluid red blood cell [RBC] count was above 70,000 cells/mm^3 in all), with a relatively low WBC count (200–3,000 cells/mm^3) and an LDH that varied from 282 to 1,762 IU/L (no upper limit of normal for serum provided) (76). Immunohistochemical stains for *B. anthracis* were positive on all pleural fluid cytologic and pleural tissue specimens (76).

It is important to make the diagnosis of anthrax early. In the outbreak in Washington, 6 of the 10 patients received antibiotics before they entered the fulminant stage and all survived. In contrast, none of the four patients who received antibiotics after they entered the fulminant stage survived (76). In a review of the world literature, Holty et al. (78) reported that the mortality rate was 97% in patients who reached the fulminant stage. The only patient who survived was a veterinarian who might have had partial immunity (78). This diagnosis should be considered in all patients with an acute illness and with mediastinal widening or pleural effusions (77). After blood cultures are obtained, appropriate antibiotics, for example, ciprofloxacin, should be started. The pleural fluid cytologic specimen should be stained immunohistochemically for anthrax.

MISCELLANEOUS PATHOGENIC ORGANISMS

Pleural effusions may also occur in 30% to 65% of patients with pneumonias due to *Legionella* sp (75,76,79). In one series (80) of 43 patients with Legionnaire's disease, pleural effusions were present in 10 patients (23%) on admission, whereas another 14 developed effusions during the first week after admission, and 3 new effusions were discovered after the first week. In some cases, the organisms can be demonstrated by direct immunofluorescence or culture of the pleural fluid (81). Usually, the pleural effusions are small and clinically unimportant, but one patient had a multiloculated pleural effusion due to *Legionella* sp and required a decortication (82).

Several unusual organisms should be considered in patients with pneumonia and pleural effusions. Tularemia may be manifested as a pneumonia, and, if so, there is frequently an accompanying pleural effusion (83). Interestingly, the pleural fluid in association with tularemia is a lymphocyte predominant exudate with a high adenosine deaminase (ADA) level (83). Pleural effusions occurred in 5 to 33% of the cases of acute melioidosis (84). As with tularemia, the pleural fluid with melioidosis can be lymphocyte predominant (84). Clostridial pleuropulmonary infections are uncommon; by 1970, only 17 cases had been reported (85). Almost all patients with clostridial pulmonary infections have a pleural effusion that is culture positive (85). Complicated parapneumonic pleural effusions have also been reported with pneumonias due to brucellosis (86), *Hemophilus parainfluenzae* (87), *Bacillus cereus* (88), *Citrobacter diversus* (89), and *Listeria monocytogenes* (90) and can probably occur with any bacterium that is a pathogen in humans.

CLINICAL MANIFESTATIONS

The clinical manifestations of parapneumonic effusions and empyema depend to a large part on whether the patient has an aerobic or anaerobic infection.

Aerobic Bacterial Infections

The clinical presentation of patients with aerobic bacterial pneumonia and a pleural effusion is no different from that of patients with bacterial pneumonia

without effusion (2,54,91). The patients first manifest an acute febrile illness with chest pain, sputum production, and leukocytosis. In one series, the incidence of pleuritic chest pain was 59% in 113 patients without effusion and 64% in 90 patients with effusion (2). The mean peripheral WBC was 17,100 in patients without effusion and 17,800 in patients with effusion. The longer the patient has symptoms before seeking medical attention, the more likely he or she is to have a pleural effusion (54). A complicated parapneumonic effusion is suggested by the presence of fever for more than 48 hours after antibiotic therapy is instituted, but, of course, the diagnosis of parapneumonic effusion should be established when the patient with pneumonia is first evaluated.

Not all patients with aerobic pneumonias and pleural effusions have acute illnesses. Sahn et al. (92) reported three cases of aerobic empyema in patients who were receiving corticosteroid therapy, and all were afebrile with minimal symptoms referable to the chest. The absence of fever or chest symptoms should not deter one from considering the diagnosis of complicated parapneumonic effusions because, in recent years, a higher percentage of such effusions has occurred in hospitalized patients, many of whom are debilitated or are receiving corticosteroids (41).

A complicated parapneumonic effusion should be suspected in febrile patients in the intensive care unit who have temperature elevations. Tu et al. (49) performed a diagnostic thoracentesis in 175 patients with a temperature elevation above 38°C for more than 8 hours and a pleural effusion. They found that 78 of the 175 patients had complicated parapneumonic effusions (49). The mortality was 41% in these 78 patients.

Anaerobic Bacterial Infections

In contrast to patients with aerobic bacterial pneumonias, patients with anaerobic bacterial infections involving the pleural space are usually first seen with subacute illnesses. In a series of 47 patients, 70% had symptoms for more than 7 days before presentation, with a median symptom duration of 10 days (53). In this same series of patients (53), 60% had substantial weight loss (mean 29 lb). Many patients have a history of alcoholism, an episode of unconsciousness, or another factor that predisposes them to aspiration. Most patients also have poor oral hygiene. Laboratory evaluation reveals leukocytosis (median WBC 23,500/mm^3) and mild anemia (median hematocrit 36%) in most patients (53).

DIAGNOSIS

The possibility of a parapneumonic effusion should be considered during the initial evaluation of every patient with a bacterial pneumonia. At this evaluation, it is important to determine whether a complicated parapneumonic effusion is present because a delay in instituting proper pleural drainage in such patients substantially increases morbidity. The possibility of a parapneumonic effusion should also be suspected in patients who do not respond to antimicrobial therapy. In one study of 49 such patients, the prevalence of pleural effusions increased from 18% on admission to 43% at the time of repeat investigation 72 hours after admission (93). Six of these patients were found to have an empyema (93).

The presence of a significant amount of pleural fluid is usually suggested by the appearance of the lateral chest radiograph. If both diaphragms are visible throughout their length and the posterior costophrenic angle is not blunted, one can assume that a significant amount of free pleural fluid is not present. If either of the posterior costophrenic angles is blunted or if a diaphragm is obscured by the infiltrate, however, the possibility of a pleural effusion should be evaluated with a computed tomography (CT) scan of the chest, ultrasound of the pleural space, or bilateral decubitus chest radiographs. The purpose of these additional studies is to document whether fluid is present and to semiquantitate the amount of fluid if it is present. Brixey et al. (94) reviewed the chest radiographs of 61 patients with pneumonia who had a pleural effusion on CT scan. They reported that the sensitivities of the lateral, PA, and AP chest radiographs were 85.7%, 82.1%, and 78.4%, respectively (94). The majority of effusions missed in each view were on films with lower lobe consolidation (94).

On the decubitus view with the suspect side down, free pleural fluid is indicated by the presence of fluid between the chest wall and the inferior part of the lung (Fig. 6.3). The view with the suspect side up is also valuable because, in this position, the free fluid gravitates toward the mediastinum and allows one to assess how much of the increased radiodensity is due to the fluid and how much is due to the parenchymal infiltrate. Of course, the chest CT scan provides more definitive information than do decubitus films and it has replaced the decubitus films for the evaluation of the possibility of pleural effusions in many institutions. It should be noted that many patients with parapneumonic effusions have mediastinal lymphadenopathy. Kearney et al. (95) reviewed the CT

scans of 50 patients with parapneumonic effusions and reported that 18 (36%) had lymph nodes in their mediastinum that were greater than 1 cm in diameter.

The possibility of a pleural effusion can also be evaluated by ultrasound. Ultrasound has two advantages: first, it is portable and can be performed easily in the intensive care unit and second, it also will delineate whether the pleural fluid is septated. However, in one study of 50 patients with parapneumonic effusions, there was no relationship between the appearance on ultrasound and whether the patient would need surgical treatment (96). In contrast, a second study (97) of 141 patients with complicated parapneumonic effusions found that patients with a complex nonseptated sonographic pattern were more frequently successfully treated with a small-bore catheter 48/60 (80%) than were patients with a complex septated sonographic pattern 41/81 (51%).

The amount of free pleural fluid can be semiquantitated by measuring the distance between the inside of the chest wall and the bottom of the lung on either the decubitus radiograph or the CT scan of the chest. This distance can also be measured with ultrasound. If this distance measures less than 10 mm, one can assume that the effusion is not clinically significant and, therefore, a thoracentesis is not indicated. My colleagues and I reported that 53 patients with acute bacterial pneumonia had such small effusions, and in each of the patients, the pneumonia and the pleural effusion cleared with only antibiotics and left no residual pleural disease (2). Moffet et al. (98) have demonstrated that a pleural fluid thickness of 2.5 cm on a CT scan correlates to a thickness of 1.0 cm on the decubitus radiograph. Moreover, a recent article (99) suggested that a thoracentesis is indicated only if the thickness of the pleural fluid is greater than 20 mm on the CT scan because effusions smaller than this are rarely complicated.

If the thickness of the fluid is greater than 10–20 mm, a therapeutic thoracentesis should be performed immediately because it is impossible to separate complicated from uncomplicated effusions without a thoracentesis. The pleural fluid is examined grossly for color, turbidity, and odor. Aliquots are sent for determination of the pleural fluid glucose, LDH, and protein levels, pH (must be analyzed with a blood gas machine), and differential and total WBC counts. Samples of pleural fluid are also sent for bacterial cultures, both aerobic and anaerobic, and for Gram's stain, as well as for cytologic studies and mycobacterial and fungal smears and cultures, if clinically indicated. When pleural fluid is sent for bacterial cultures, higher yields will be obtained if the pleural fluid is directly inoculated into blood culture bottles at the time of thoracentesis (100,101).

The pleural fluid cultures in patients with parapneumonic effusions are frequently negative, even when the fluid is pus. To identify the organism responsible for the pneumonia, nuclei acid amplification has been used to identify the bacteria responsible for a complicated parapneumonic effusion. Maskell et al. (102) performed this procedure on 404 pleural fluid specimens obtained during the First Multicenter Intrapleural Sepsis Trial (103). They reported that the nucleic acid amplification technique identified bacteria in 70 samples which were negative on culture (102).

Not all patients with an acute illness, parenchymal infiltrates, and pleural effusion have an acute bacterial pneumonia; pulmonary embolization, acute pancreatitis, tuberculosis, Dressler's syndrome, and other diseases can produce identical pictures. The possibility of pulmonary embolization should always be considered if the patient does not have purulent sputum or a peripheral leukocytosis above 15,000/mm^3. Most patients with acute tuberculous pleuritis have no infiltrate on the decubitus film with the involved side superior or on the chest CT scan.

The pleural fluid with parapneumonic effusions varies from a clear, yellow exudate to thick, foul-smelling pus. If the odor of the pleural fluid is feculent, the patient is likely to have an anaerobic pleural infection (53,104). Although Sullivan et al. (104) reported that 11% of aerobic empyemas were described as foul smelling, it is probable that these represented mixed aerobic and anaerobic pleural infections in that sophisticated anaerobic culture techniques were not used in this study. Only approximately 60% of anaerobic empyemas have a foul odor (53,104). If frank pus is obtained with diagnostic thoracentesis, a pleural fluid pH determination should not be done. When thick, purulent material is processed through blood gas machines, it is likely to plug up the machine or damage the membranes. Once laboratory personnel have this experience with one such pleural fluid, they are hesitant to process additional pleural fluids. The differential WBC on the pleural fluid usually reveals predominantly polymorphonuclear leukocytes. If many small lymphocytes, mesothelial cells, or macrophages are seen, alternate diagnoses should be considered. If food particles are seen in the pleural fluid, the patient has an esophageal-pleural fistula (105).

Not all patients with parapneumonic effusions have an acute illness, so the possibility of a

parapneumonic effusion should be considered in all patients with pleural effusion. Anaerobic pleural infections are particularly likely to produce subacute or chronic illness (53,106), and many patients with anaerobic pleural infections do not have associated parenchymal infiltrates (106). Accordingly, aerobic and anaerobic bacterial cultures should be obtained on all exudative pleural effusions of undetermined etiology.

INDICATORS OF POOR PROGNOSIS FROM PLEURAL FLUID ANALYSIS

Pleural fluid characteristics associated with a need for pleural fluid drainage are tabulated in Table 12.4. If the pleural fluid is thick pus, the patient has an empyema and drainage of the pleural space is indicated. No other tests are needed for confirmation of the need for drainage. The odor of the fluid should be noted because a feculent odor is an indication that the pleural fluid is infected with anaerobic bacteria and is hence an indication for anaerobic antibiotic coverage and pleural drainage.

If the fluid is not thick pus, then much information on the prognosis of the patient can be obtained from the Gram's stain and culture of the pleural fluid, as well as the levels of glucose, pH, and LDH in the pleural fluid. If the Gram's stain is positive, there is a large bacterial burden in the pleural space and the fluid needs to be drained. If the Gram's stain is negative but the culture is positive, it is likely that the patient will have difficulty with the pleural infection, and the pleural space should be drained.

The pleural fluid chemistries are also useful in identifying which patients have complicated parapneumonic effusions. Patients with complicated parapneumonic effusions have a lower pleural fluid glucose and pH, and a higher pleural fluid LDH than those with uncomplicated parapneumonic effusions (Fig. 12.1). If the pleural fluid pH is higher than 7.20, the pleural fluid glucose is higher than 60 mg/dL, and the pleural fluid LDH is below three times the upper normal limit for serum, the parapneumonic effusion is a Class 3 parapneumonic effusion by Light's classification (Table 12.5) and a Category 2 by the American College of Chest Physicians (ACCP) classification (Table 12.6) (107), and no further diagnostic or therapeutic maneuvers need be directed toward the pleural effusion.

A pleural fluid pH less than 7.00 or a glucose level less than 40 mg/dL is also a bad prognostic indicator in patients with parapneumonic effusions. It is important to understand that the pleural fluid pH and glucose levels should be used as indicators for pleural fluid drainage only in patients with parapneumonic effusions; patients with pleural effusions of other etiologies, including those secondary to

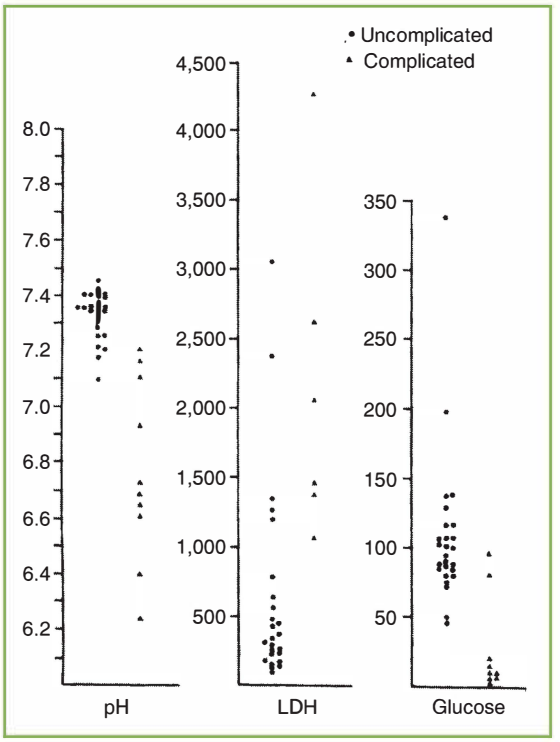

FIGURE 12.1 ■ Distribution of pleural fluid pH, lactic dehydrogenase (LDH), and glucose levels in uncomplicated and complicated parapneumonic effusions. *(From Light RW, Girard WM, Jenkinson SG, et al. Parapneumonic effusions.* Am J Med. *1980; 69:507–511, with permission.)*

TABLE 12.4 ■ Bad Prognostic Factors for Parapneumonic Effusions and Empyema

Pus present in pleural space
Gram stain of pleural fluid positive
Pleural fluid glucose below 40 mg/dL
Pleural fluid culture positive
Pleural fluid pH <7.0
Pleural fluid LDH >3 × upper normal limit for serum
Pleural fluid loculated

Listed in order of decreasing importance.
LDH, lactic dehydrogenase.

TABLE 12.5 ■ A Classification and Treatment Scheme for Parapneumonic Effusions and Empyema

Event or State	Number
Class 1 Nonsignificant pleural effusion	Small <10 mm thick on decubitus x-ray study No thoracentesis indicated
Class 2 Typical parapneumonic pleural effusion	>10 mm thick Glucose >40 mg/dL, pH >7.2 LDH <3 × upper limit normal for serum Gram's stain and culture negative Antibiotics alone
Class 3 Borderline complicated pleural effusion	7.0 <pH <7.20 and/or LDH >3 × upper limit normal and glucose >40 mg/dL Gram's stain and culture negative Antibiotics plus serial thoracentesis
Class 4 Simple complicated pleural effusion	pH <7.0 or glucose <40 mg/dL or Gram's stain or culture positive Not loculated not frank pus Tube thoracostomy plus antibiotics
Class 5 Complex complicated pleural effusion	pH <7.0 and/or glucose <40 mg/dL or Gram's stain or culture positive Multiloculated Tube thoracostomy plus fibrinolytics (rarely require thoracoscopy or decortication)
Class 6 Simple empyema	Frank pus present Single locule or free flowing Tube thoracostomy ± decortication
Class 7 Complex empyema	Frank pus present Multiple locules Tube thoracostomy ± fibrinolytics Often require thoracoscopy or decortication

LDH, lactic dehydrogenase.

rheumatoid disease, malignant tumors, and tuberculosis (30), may also have a low pleural fluid pH or glucose level and usually do not need to be treated by tube thoracostomy.

If one uses the pleural fluid pH as a guide for the placement of chest tubes, it must be measured with a blood gas machine. If the pleural fluid pH is measured with a pH meter or with a pH indicator strip paper, the results are not sufficiently accurate (108). Moreover, because the pleural fluid pH is influenced by the arterial pH (30), the arterial pH should be measured before the pleural fluid is drained, if it is to be drained solely on the basis of the pleural fluid pH. To serve as a definite indication for tube thoracostomy, the pleural fluid pH should be at least 0.30 units less than the arterial pH.

The one situation in which the pleural fluid pH is not reduced in complicated parapneumonic effusion is when the offending organism is of the *Proteus* sp. These organisms produce ammonia by their urea-splitting ability, which can lead to an elevated pleural fluid pH. Pine and Hollman (109) reported three cases of complicated parapneumonic effusions due to *Proteus* organisms in which the pleural fluid pH exceeded 7.8.

In the natural evolution of a parapneumonic effusion, the pleural fluid pH falls before the glucose level falls (30,110) and, therefore, the pH is a more sensitive indicator of complicated parapneumonic effusion than the pleural fluid glucose level. The lowered pH with complicated parapneumonic effusions appears to be caused by the metabolism of

TABLE 12.6 ■ Categorizing Risk for Poor Outcome in Patients with Percentage of Pleural Effusions

	Pleural Space Anatomy			Pleural Fluid Bacteriology			Pleural Fluid Chemistry	Category	Risk of Poor Outcome	Drainage
A_0	Minimal, free-flowing effusion (<10 mm on lateral decubitus)	AND	B_x	Culture and Gram's stain results unknown	AND	C_x	pH unknown	1	Very low	No
A_1	Small-to-moderate free-flowing effusion (>10 mm and $< \frac{1}{2}$ hemithorax)	AND	B_0	Negative culture and Gram's stain	AND	C_0	pH ≥7.20	2	Low	No
A_2	Large, free-flowing effusion ($\geq \frac{1}{2}$ hemithorax) loculated effusion, or effusion with thickened parietal pleura	OR	B_1	Positive culture and Gram's stain	OR	C_1	pH <7.20	3	Moderate	YES
A_3			B_2	Pus				4	High	YES

From Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. *Chest*. 2000;118:1158–1171, with permission.

glucose by the leukocytes in the pleural fluid, resulting in increased levels of lactate and carbon dioxide in the pleural fluid (110). When some loculi are infected and others are sterile in patients with loculated pleural effusions, the carbon dioxide probably equilibrates across the fibrin membranes, separating the different loculi, more readily than does the glucose. Accordingly, pleural fluid acidosis is present in most loculi, although some loculi may contain nearly normal glucose levels (111). It should be noted that if the pleural fluid is loculated, there might be significant differences in the pleural fluid pH from one locule to another. Maskell et al. (112) measured the pleural fluid pH from two or more locules in seven patients with parapneumonic effusions and reported that the pleural fluid pH varied markedly from locule to locule. Three of the seven patients had pHs both above and below 7.20 in different locules (112). The pleural fluid glucose levels were markedly reduced in all pleural fluids in which it was measured (112).

It should be mentioned that there is not universal agreement concerning the usefulness of using the pleural fluid glucose and pH as indicators for pleural fluid drainage. Berger and Morganroth (113) reviewed the clinical courses of 26 patients who had a pH of less than 7.20, a positive Gram's stain, or a positive culture. Sixteen patients were initially treated with intravenous antibiotics alone without tube thoracostomy, whereas the remaining 10 were treated with tube thoracostomy plus intravenous antibiotics. Only 2 of the 16 patients treated with antibiotics alone subsequently required tube thoracostomy. Three of the four patients with pleural fluid pH less than 7.00 never required tube thoracostomy. The mean duration of hospitalization was longer in the group that received a chest tube immediately. Poe et al. (114) reviewed 91 patients with parapneumonic effusions and concluded that measurement of the pleural fluid glucose, pH, and LDH has limited usefulness in predicting the need for eventual chest tube drainage or decortication, or both. However, if their data are examined closely (115), this conclusion is not supported. When patients with frank empyemas are excluded, 10 of 18 patients (56%) who had a pleural fluid pH value below 7.00 or a pleural fluid glucose below 40 mg/dL received chest tube drainage. In contrast, only 8 of 52 patients (15%) who did not meet these criteria underwent tube thoracostomy ($p < 0.005$).

Heffner et al. (116) performed a meta-analysis regarding the ability of the pleural fluid levels of pH (n = 251), LDH (n = 114), and glucose (n = 135) to identify those parapneumonic effusions that needed drainage. In general, they found that those effusions that were drained had a lower glucose, a lower pH, and a higher LDH than did those that were not drained, but there was much overlap (116). In general, the pleural fluid pH was a little better at making the differentiation than was the pleural fluid glucose or LDH, but there was much overlap in the values for all three measurements between those patients who received drainage and those who did not. Overall, one encounters several problems when trying to assess the value of these measurements. First, the individual who made the decision to institute pleural drainage knew the results of the biochemical tests. Second, the upper limit of LDH may have varied from institution to institution. Third, some of the pleural fluid pHs may have not been measured with a blood gas machine (substantial number of pleural fluid pHs above 7.50).

Jimenez Castro et al. (117) evaluated the utility of the pleural fluid glucose, pH, LDH, and volume in identifying patients who required tube thoracostomy among 238 patients admitted to one hospital. They found that the pleural fluid pH had the highest diagnostic accuracy, followed by the pleural fluid glucose, LDH, and pleural fluid volume (117). They reported that the optimal binary decision threshold was less than or equal to 7.15 for the pleural fluid pH, less than 72 mg/dL for the pleural fluid glucose, and greater than 865 IU/L for the pleural fluid LDH (upper normal limit for serum 300 IU/L) (117).

In view of the factors mentioned in the preceding text, there is no doubt that some patients with parapneumonic effusions that have a pleural fluid pH below 7.00, a pleural fluid glucose below 40 mg/dL, a positive Gram's stain or a positive pleural fluid culture can be cured with antibiotics alone. Nevertheless, it is recommended that the pleural fluid be drained in patients with parapneumonic effusions, who have a pleural fluid pH below 7.00, a pleural fluid glucose below 40 mg/dL, or a positive pleural fluid Gram's stain (115) because these are indicators that it is likely that the parapneumonic process will not resolve with antibiotics alone. It should be noted that the lower the pleural fluid pH or the pleural fluid glucose, the less likely the effusion will resolve without tube thoracostomy (118). The risk of more severe morbidity associated with delayed tube thoracostomy justifies the placement of a few extra chest tubes.

Another possible marker for a complicated parapneumonic effusion is polymorphonuclear elastase (PMN-E). Aleman et al. (119) measured the levels of PMN-E in 125 patients with parapneumonic effusions including 42 typical parapneumonic effusions, 17 borderline complicated parapneumonic effusions, and 66 complicated parapneumonic effusions or empyemas. They reported that a pleural fluid level of PMN-E greater than 3,500 μg/mL was more sensitive and specific than the pleural fluid pH or glucose in identifying parapneumonic effusion in which the cultures were positive (119). This same group has stated that a PMN-E greater than 3,000 μg/mL is useful in separating complicated and noncomplicated parapneumonic effusions (120). To my knowledge, no other group has confirmed these findings.

There have been several articles assessing the utility of other markers in pleural fluid to distinguish complicated from uncomplicated parapneumonic effusions. Markers evaluated have included interleukin-8 (121), C-reactive protein (121–124), triggering receptor expressed on myeloid cells (sTREM-1) (121), procalcitonin (121), lipopolysaccharide-binding protein (124), matrix metalloproteinase (MMP)-2 (125), MMP-8 (125), MMP-9 (125), 8-isoprostane (126), and Cu/Zn superoxide dismutase (126). None of these have proven to be superior to the pleural fluid pH, glucose, or LDH in differentiating complicated from uncomplicated parapneumonic effusions (127).

LOCULATED PLEURAL EFFUSIONS

Pleural effusions are already loculated when some patients with pneumonia and pleural effusion are first evaluated. Although small amounts of freely moving fluid can be demonstrated in most patients with loculated pleural effusion, such is invariably not the case. Loculated pleural effusions manifest as pleural-based masses without air bronchograms on the standard chest radiograph (Fig. 6.5). Frequently, it is difficult to distinguish pleural fluid loculi from peripheral parenchymal infiltrates on standard chest radiographs. Ultrasonic techniques are effective in distinguishing pleural fluid loculi from parenchymal infiltrates (128,129). As little as 5 mL of loculated pleural fluid can be identified by ultrasound. Therefore, if a loculated pleural effusion is suspected,

ultrasonic examination of the pleural space should be performed.

Loculated pleural effusion should also be suspected in patients with pneumonia who do not respond clinically to appropriate antibiotic therapy within 48 hours. If one pleural fluid loculation is identified with ultrasound, it is important to examine the entire pleural space ultrasonically because multiple loculi are often present. If pleural fluid is identified by ultrasound, thoracentesis should be performed immediately because if the skin is marked and the patient is sent back to his room, the relationship between the skin and the underlying pleural fluid may be altered with the patient in a different position. If more than one pleural fluid loculation is discovered, all should be diagnostically aspirated because the character of the pleural fluid may vary from one locule to another (53,112).

The presence of loculated pleural fluid by itself is not an indication for tube thoracostomy or a more invasive procedure. The presence of loculi does indicate that there is or has been an intense inflammatory response in the pleural space. Parapneumonic effusions that are loculated tend to have a lower pH and glucose level, and a higher LDH level than do nonloculated parapneumonic pleural effusions (130). Tube thoracostomy with loculated pleural effusions is indicated only if the pleural fluid has one or more poor prognostic factors (Table 12.4). The pleural fluid analysis from most patients with loculated parapneumonic pleural effusions indicates that tube thoracostomy should be performed.

HYDROPNEUMOTHORAX VERSUS LUNG ABSCESS

Frequently, on the standard chest radiographs, it is difficult to distinguish a loculated hydropneumothorax with a bronchopleural fistula from a peripheral lung abscess. This differentiation is important because the loculated hydropneumothorax with the bronchopleural fistula needs to be treated with chest tubes immediately to prevent discharge of the infected pleural fluid throughout the remainder of the lung. In contrast, usually only antibiotic therapy is necessary for the peripheral lung abscess. If any doubt exists as to whether the air–fluid level is in the pleural space or in the lung parenchyma, ultrasound (128,131,132) or CT scan studies (133) should be obtained to make this differentiation (see Chapter 6).

CLASSIFICATION OF PARAPNEUMONIC EFFUSIONS

It is important to realize that there is a wide range of parapneumonic effusions and empyemas (134). A patient with a very small effusion will do well regardless of treatment, as long as appropriate antibiotics are given. In contrast, a patient with multiloculated pus in the pleural space will probably require a decortication. The classification in Table 12.5 was developed to assist the practicing physician in the initial care of patients with parapneumonic effusions. This classification, however, is probably most useful for stratifying patients with parapneumonic effusions who are research subjects. Much of the literature on parapneumonic effusions and empyema is confusing because the characteristics of the patients being reported are not adequately described. The classification in Table 12.5 is based on the amount of fluid, the gross characteristics of the pleural fluid, the biochemical characteristics of the pleural fluid, and whether the pleural fluid is loculated. As one proceeds farther down Table 12.5, the treatment of the parapneumonic effusion becomes more difficult and increasingly invasive procedures are required.

The ACCP (107) has developed a second classification, which is discussed after Light's classification is discussed.

Light's Classification

Class 1: Parapneumonic Nonsignificant Effusion. Patients with Class 1 parapneumonic effusions have free-flowing fluid that is less than 10 mm thick on the decubitus chest radiograph. Individuals with Class 1 effusions should not be subjected to thoracentesis because if they are treated with appropriate antibiotics, the effusion almost always resolves (2). In addition, a thoracentesis is more difficult in patients with a small amount of pleural fluid. If a patient with a Class 1 effusion subsequently develops a larger pleural effusion, a diagnostic or therapeutic thoracentesis should be performed.

Class 2: Typical Parapneumonic Effusion. Patients with Class 2 parapneumonic effusion have pleural fluid that is free flowing, with a thickness of greater than 10 mm on the decubitus radiograph. In addition the pleural fluid glucose is above 40 mg/dL, the pleural fluid pH is above 7.20, the pleural fluid LDH is below three times the upper limit of normal for serum, and the bacterial smears and cultures are negative. Patients with Class 2

parapneumonic effusions require no invasive procedure other than the initial thoracentesis to delineate the characteristics of the pleural effusion (4). If a Class 2 effusion rapidly enlarges in size or if the patient remains toxic with significant pleural fluid, then a repeat thoracentesis should be performed.

Class 3: Borderline Complicated Parapneumonic Effusion. Patients with Class 3 parapneumonic effusions have negative bacterial smears and cultures and a glucose level above 40 mg/dL, but the pH is between 7.00 and 7.20, the LDH is above 3 times the upper limit of normal, or the pleural fluid is loculated. The relatively low pH, the relatively high LDH, and the loculated effusion all indicate a high level of inflammation in the pleural space. Some Class 3 pleural effusions resolve with no invasive procedure, whereas others do not.

Class 4: Simple Complicated Parapneumonic Effusion. Patients with Class 4 parapneumonic effusions have a pleural fluid pH less than 7.00, a pleural fluid glucose level less than 40 mg/L, or a positive Gram's stain or culture. The pleural fluid does not look like pus and it is not loculated. Patients with Class 4 parapneumonic effusions should be treated with some form of invasive therapy because many will not resolve solely with antibiotics.

Class 5: Complex Complicated Parapneumonic Effusion. Patients with Class 5 parapneumonic effusions meet the criteria for Class 4 parapneumonic effusions, but, in addition, the fluid is loculated. These patients require fibrinolytics or thoracoscopy to break down the adhesions, and some of the patients require thoracotomy with decortication.

Class 6: Simple Empyema. Patients with Class 6 parapneumonic effusions have pleural fluid that is frank pus, which is either free flowing or confined to a single loculus. These patients should be treated with a chest tube. Patients who have Class 6 parapneumonic effusions frequently have a thick peel over the visceral pleura that prevents the underlying lung from expanding. If a sizable empyema cavity remains after several days of chest tube drainage, consideration should be given to performing a decortication to eradicate the empyema cavity.

Class 7: Complex Empyema. Patients with Class 7 parapneumonic effusions have frank pus in their pleural space that is multiloculated. Although these patients should initially be treated with chest tubes and attempts can be made to facilitate drainage with fibrinolytics, more invasive measures such as thoracoscopy with the breakdown of adhesions or thoracotomy with decortication are necessary in the majority.

Classification of the American College of Chest Physicians

In 2000, the ACCP developed a classification of parapneumonic effusions on the basis of the anatomical characteristics of the fluid (A), the bacteriology of the pleural fluid (B) and the chemistries (C) of the pleural fluid (107). This classification is somewhat analogous to the TMN classification used to classify tumors. The classification is shown in Table 12.6.

The anatomy (A) of the pleural effusion is based on the size of the effusion, whether it is free flowing and whether the parietal pleural is thickened. $\mathbf{A}_0$ effusions are small effusions (<10 mm in thickness on the decubitus radiographs, ultrasound examination, or CT scans) and are free flowing. $\mathbf{A}_1$ effusions are greater than 10 mm in thickness but occupy less than 50% of the hemithorax, are free flowing, and are not associated with parietal pleural thickening. $\mathbf{A}_2$ effusions occupy more than 50% of the hemithorax or are loculated and/or are associated with thickening of the parietal pleura. I tend to ignore the thickening of the parietal pleura in this classification because it has been shown that thickening of the parietal pleura on CT scan is not related to the outcome with a parapneumonic effusion (96).

The bacteriology (B) of the effusion is based on whether smears or cultures are positive. $\mathbf{B}_x$ effusions are those in which the culture and Gram's stain results are unknown, presumably because the effusion was small and a thoracentesis was not done. $\mathbf{B}_0$ effusions have negative Gram's stains and cultures of the pleural fluid. $\mathbf{B}_1$ effusions are those in which the Gram's stain or culture are positive, but the pleural fluid is not pus. $\mathbf{B}_2$ effusions are those where the pleural fluid is pus.

The chemistry (C) of the effusion is based on the pH of the pleural fluid. $\mathbf{C}_x$ effusions are those on which the pleural fluid pH is unknown, presumably because a thoracentesis was not done. $\mathbf{C}_0$ effusions are those with a pleural fluid pH greater than 7.20. $\mathbf{C}_1$ effusions are those with a pleural fluid pH less than 7.20. To obtain an accurate pleural fluid pH, the pleural fluid must be measured with a blood gas machine (108). If a pleural fluid pH measurement with a blood gas machine is not available, an alternative measurement is the pleural fluid glucose level with a cutoff level of 60 mg/dL.

On the basis of the A, B, and C classification, the effusion is categorized. Category 1 effusion is a small

(<10 mm thickness on decubitus, CT scan or ultrasound studies) and free-flowing effusion. Because the effusion is small, no thoracentesis is performed and the bacteriology and chemistry of the fluid are unknown. The risk of a poor outcome with a category 1 effusion is very low.

Category 2 effusion is small to moderate in size (>10 mm thickness and <1/2 the size of the hemithorax) and is free flowing. The Gram's stain and culture of the pleural fluid are negative and the pleural fluid pH is more than 7.20. The risk of a poor outcome with a category 2 effusion is low.

Category 3 effusion meets at least one of the following criteria: (a) the effusion occupies more than 1/2 the hemithorax, is loculated, or is associated with a thickened parietal pleura; (b) the Gram's stain or culture is positive; or (c) the pleural fluid pH is less than 7.20 or the pleural fluid glucose is less than 60 mg/dL. The risk of a poor outcome with a category 3 effusion is moderate.

Category 4 effusion is characterized by pleural fluid that is pus. The risk of a poor outcome with a category 4 effusion is high.

MANAGEMENT

The management of parapneumonic effusions and empyemas involves two separate areas—selection of an appropriate antibiotic and management of the pleural fluid.

Antibiotic Selection

All patients with parapneumonic effusions or empyema should be treated with antibiotics. If the Gram's stain of the pleural fluid is positive, it should guide the selection of an antibiotic. The initial antibiotic selection is usually based on whether the pneumonia is community-acquired or hospital-acquired and on how sick the patient is. The initial antibiotic selection and dose are influenced to some extent by whether or not a pleural effusion is present because some antibiotics, for example, aminoglycosides, do not penetrate pleural fluid easily. The ease of penetrance of various antibiotics into the pleural space was studied in our rabbit model of empyema (108). Antibiotic levels in samples of pleural fluid and serum were collected serially for up to 8 hours after penicillin, clindamycin, gentamicin, metronidazole, vancomycin, or ceftriaxone were administered intravenously. The degree to which the different antibiotics penetrated the infected pleural space was highly variable. Metronidazole penetrated most easily, followed by penicillin, clindamycin, vancomycin, ceftriaxone, and gentamicin (Fig. 12.2) (135). Subsequent studies demonstrated that the quinolones, clarithromycin, azithromycin, linezolid, and ertapenem penetrate the infected pleural space well (136–139). This variance in the penetrance of antibiotics into the pleural fluid should be considered when an antibiotic is selected for the treatment of patients with parapneumonic effusions. No reason exists to increase the dose of antibiotics merely because a pleural effusion is present.

For patients hospitalized with community-acquired pneumonias that are not severe, the recommended agents are a fluoroquinolone alone, such as levofloxacin, moxifloxacin, gatifloxacin, or gemifloxacin, or a β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem) (140). There is no reason to add a macrolide because atypical pathogens rarely cause a pleural effusion (141). For patients with severe community-acquired pneumonia in whom pseudomonas infection is not an issue, the recommended agents are a β-lactam plus either an advanced macrolide or a respiratory fluoroquinolone (140). If a pseudomonas infection is suspected, an antipseudomonas antibiotic such as piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime should be included (140). Because anaerobic bacteria cause a sizable percentage of parapneumonic effusions, anaerobic coverage is recommended for all patients with parapneumonic effusions with either clindamycin or metronidazole (142). In patients with health care–associated pleural infection, coverage should be provided for gram-negative enteric bacteria and MRSA. A reasonable antibiotic selection in such patients is a carbapenem such as meropenem and vancomycin (141). There are no useful studies on duration of therapy for bacterial infections of the pleural space. The current standard of practice is to continue antibiotics for several weeks (143,144).

Intrapleural Antibiotics

Intrapleural antibiotics were first used to treat an infected pneumonectomy space by Clagett and Geraci (145) in 1963. Since that time, there have been several reports (146–150) regarding the use of intrapleural antibiotics in the treatment of empyema complicating pneumonia. All of these reports have indicated positive results, but none were randomized controlled studies. Until such controlled studies documenting the efficacy of intrapleural antibiotics are completed, they are not recommended for patients with parapneumonic effusions.

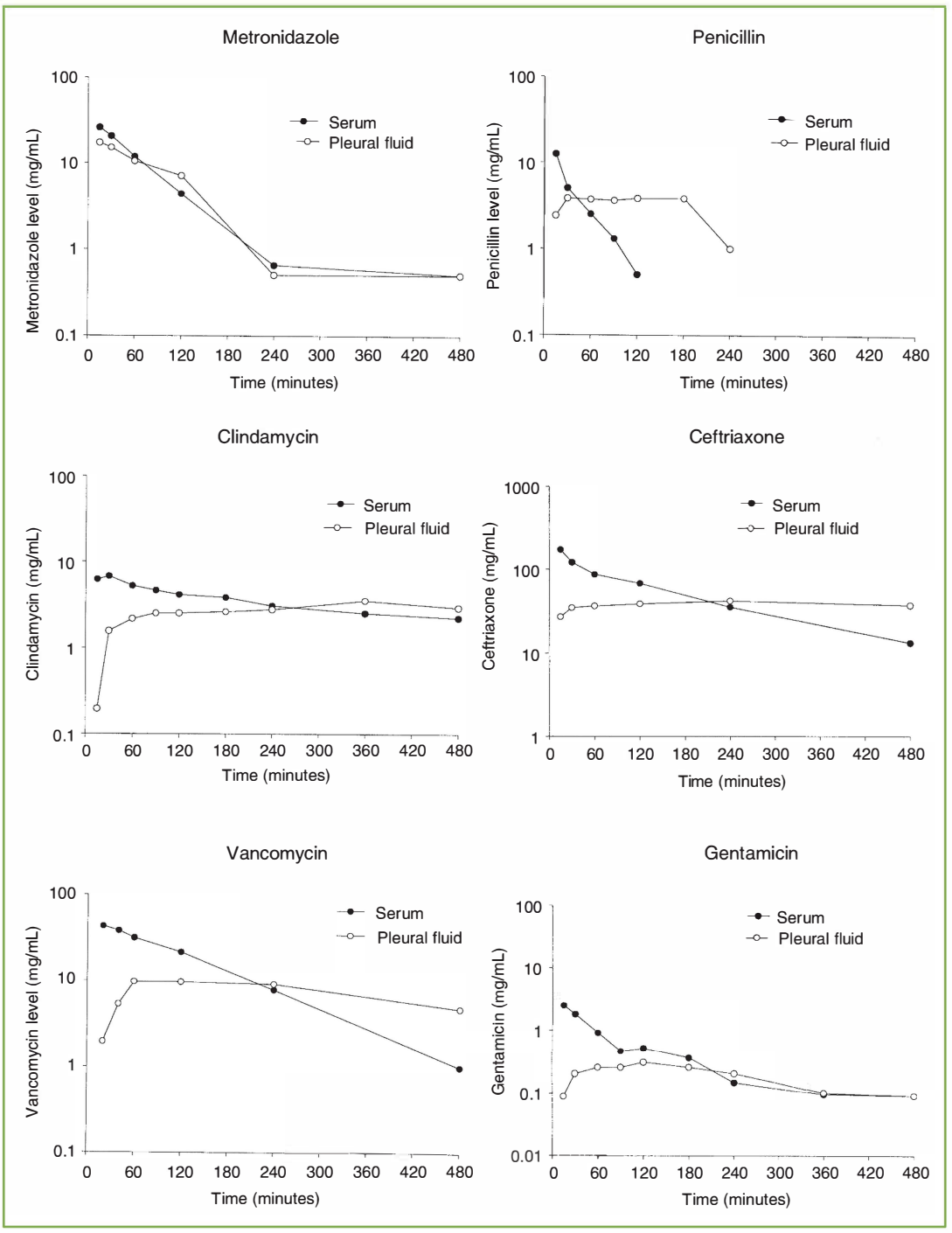

FIGURE 12.2 ■ Relationship between serum and pleural fluid antibiotic levels for six different antibiotics. *(From Teixeira LR, Sasse SA, Villarino MA, et al. Antibiotic levels in empyemic pleural fluid.* Chest. *117:1734–1739, with permission.)*

Options for Management of Pleural Fluid

There are several treatment options available for the management of the pleural fluid in patients with parapneumonic effusion and these include observation, therapeutic thoracentesis, tube thoracostomy, intrapleural instillation of fibrinolytics, VATS with the breakdown of adhesions and possible decortication, thoracotomy with decortication and the breakdown of adhesions, and open drainage.

Observation

In general, observation is not an acceptable option because the pleural fluid from patients with parapneumonic effusions should be sampled as soon as it is identified. This sampling is important because examination of the fluid is necessary to determine if drainage of the fluid is indicated (2) (Table 12.4). Although only approximately 10% of patients with parapneumonic effusions require drainage, it is important not to delay drainage in those who require it because an effusion that is free flowing and easy to drain can become loculated and difficult to drain over a period of 12 to 24 hours (53,151). Observation is the appropriate course if the patient has a Class 1 parapneumonic effusion, that is, the effusion is less than 10 mm in thickness on the decubitus chest radiograph, ultrasonography, or chest CT scan.

Therapeutic Thoracentesis

Therapeutic thoracentesis was first proposed as a treatment modality for parapneumonic effusions in the middle of the 19th century (12,13). In 1962, the American Thoracic Society (ATS) recommended repeated thoracentesis for nontuberculous empyemas that were in the early exudative phase (34). In 1968, Snider and Saleh (37) recommended that patients with empyema could be managed with two therapeutic thoracenteses, but if fluid accumulated after that time, then tube thoracostomy should be performed. Recently, however, therapeutic thoracentesis as a treatment for parapneumonic effusions has received relatively little consideration.

As discussed in the chapter on experimental animals and pleural disease (see Chapter 4), studies in our rabbit model of empyema have shown that daily therapeutic thoracentesis starting 48 hours after empyema induction is at least as effective as tube thoracostomy initiated at the same time (152). In the last 20 years, there have been studies that suggest that some patients with complicated parapneumonic effusions can be cured with therapeutic thoracentesis. Storm et al. (150) reported that 48 of 51 patients (94%) with empyema (e.g., purulent pleural fluid or positive microbiologic studies on the pleural fluid) were successfully treated with daily thoracentesis. Simmers et al. (153) treated 29 patients with complicated parapneumonic effusions with daily ultrasound-guided thoracenteses and reported that 24 (83%) were successfully treated. The drawback to this latter study was that the patients underwent an average of 7.7 ± 3.5 thoracenteses and the average hospitalization was for 31 days (153). Ferguson et al. (154) reported that 19 of 46 patients (41%) with empyema (e.g., opaque fluid in the pleural space with the cloudiness due to neutrophils or organisms) were treated successfully with repeated thoracentesis. Ozol et al. (155) recently reported that therapeutic thoracentesis cured 42 of 44 patients (95.4%) who had a mean pleural fluid pH of 6.8 and a mean pleural fluid LDH of 1,818 IU/L. There have been no controlled studies comparing therapeutic thoracentesis with small tube thoracostomy in the treatment of patients with complicated nonloculated parapneumonic effusions.

Tube Thoracostomy

For the past several decades, the initial drainage modality for most patients with complicated parapneumonic effusions has been tube thoracostomy. The chest tube should be positioned in a dependent part of the pleural effusion. Initially, the chest tube should be connected to an underwater-seal drainage system. If the visceral pleura is covered with a fibrinous peel, the application of negative pressure to the chest tube may help expand the underlying lung and hasten the obliteration of the empyema cavity. The management of patients with chest tubes is discussed in Chapter 29.

What is the size of chest tubes that should be used to treat complicated parapneumonic effusions? In the past, relatively large (28 to 36 F) tubes have been recommended because of the belief that smaller tubes would become obstructed with the thick fluid. There is, however, some data to suggest that such large tubes are unnecessary (144,156). The British Thoracic Society (BTS) guidelines (144) state that a small bore catheter 10 to 14 F will be adequate for most cases of complicated parapneumonic pleural infection. However, there is no consensus on the optimal size of the chest tube for drainage (144). The guidelines recommended regular flushing if a small bore flexible catheter is used. The flushing technique recommended is the instillation of 20 to 30 ml saline every 6 hours

via a three-way stopcock (144). It should be noted that flushing larger bore drains is technically more difficult as these do not routinely have three-way taps and disconnection for irrigation might encourage the introduction of secondary infection (144).

A recent study (157) reviewed data on 405 patients who participated in the Multi-center Intrapleural Streptokinase Trial (MIST1) (142) that was designed to assess the efficacy and safety of streptokinase in patients with complicated parapneumonic effusions. As part of the study, they collected data on the size and the complications of chest tube. They reported that there was no significant difference in the frequency with which patients either died or required thoracic surgery in patients receiving chest tube of varying sizes (size <10 F, 21/58 [36%]; size 10–14 F, 75/208 [36%]; size 15–20 F, 28/70 [40%]; size >20 F, 30/69 [44%] [p = 0.27]) (157). Moreover, patients who received the larger tubes reported significantly more pain (157). It should be noted that the patients were not randomized to the four different chest tube sizes but the size of the tube was determined by the attending physician. The patients who received the large bore chest tubes (>20 F) tended to have a significantly higher percentage of visibly purulent fluid and a significantly higher pleural fluid lactate dehydrogenase level (157).

In another study, 8 to 12 F pigtail or 10 to 14 F Malecot catheters were placed using the Seldinger technique to treat 103 patients with empyema (158). These small catheters served as the definitive treatment in 80 of the patients (78%). These results are certainly as good as those reported in recent surgical series (159,160) in which much larger tubes were used, but the parapneumonic effusions in the surgical series may have been in a higher class. The advantage of the smaller tube is that it is easier to insert and is less painful to the patient. The percutaneous catheters in the two studies referenced were placed by interventional radiologists, and it is quite likely that the excellent results are due to accurate catheter placement.

Successful closed-tube drainage of complicated parapneumonic effusions is evidenced by improvement in the clinical and radiologic status within 24 hours. If the patient has not demonstrated significant improvement within 24 hours of initiating tube thoracostomy, either the pleural drainage is unsatisfactory or the patient is receiving the wrong antibiotic. In such patients, the culture results should be reviewed. Unsatisfactory pleural drainage is frequently because the tube is positioned in the wrong location (161). Failure can also be due to loculi of the pleural fluid that prevent complete pleural drainage, or the failure may be due to fibrinous tissues coating the visceral pleura that prevent the underlying lung from expanding. If drainage is inadequate, a chest CT scan should be obtained to delineate which of the factors mentioned in the preceding text is responsible. If multiple loculi of pleural fluid are demonstrated, consideration should be given to performing VATS with the lysis of adhesions.

If the patient responds clinically and radiologically to closed-tube drainage of the pleural space, how long should the chest tubes be left in place? In general, chest tubes should be left in place until the volume of the pleural drainage is less than 50 mL for 24 hours and until the draining fluid becomes clear yellow. The amount of sediment (representing WBCs and debris) in the collection system should be quantitated daily and the chest tube should not be removed if more than 5 mL sediment collects daily. If the chest tube ceases to function (no spontaneous fluctuation with respiratory efforts), it should be removed because it serves no useful purpose and can be a conduit for pleural superinfection.

At times, a patient responds clinically and radiologically to closed-tube drainage, but purulent drainage continues from the chest tube. In this situation, the decision to take a more aggressive approach, for example, thoracoscopy or thoracotomy, can be aided by the injection of contrast material through the chest tube into the pleural space (162). When only a tube tract remains, the chest tube is gradually withdrawn over a few days, and the cavity is allowed to fill in with granulation tissue. When a larger cavity (greater than 50 mL) is demonstrated, empyemectomy with decortication or an open drainage procedure should be performed.

How effective is tube thoracostomy alone in treating patients with complicated parapneumonic effusions? The ACCP consensus statement concluded that therapeutic thoracentesis or tube thoracostomy alone appears to be insufficient treatment for managing most patients with category 3 or 4 parapneumonic effusion (107). Although I was on the committee that produced this consensus statement, I disagree with it. Different series have reported widely varying success rates with tube thoracostomy, but all are above 25%. Earlier in this section, a success rate of more than 75% was reported with the use of small chest tubes (158). Lim and Chin (163) reported a 28% success rate, whereas Athanassiadi et al. (164) reported that 75% of patients with complicated

parapneumonic effusions were managed successfully with tube thoracostomy. In a recent study, 67% of 70 patients with complicated parapneumonic effusions were managed successfully with tube thoracostomy (28 to 32 F) (165).

Intrapleural Fibrinolytics

Difficulties arise in the drainage of complicated parapneumonic effusions as a result of pleural fluid loculation. The pleural fluid loculations are produced by fibrin membranes that prevent the spread of the infected pleural fluid throughout the body, but which make drainage of the pleural space difficult. The theory behind the use of intrapleural fibrinolytics is that they will destroy the fibrin membranes and facilitate drainage of the pleural fluid (166). Many years ago, Tillett et al. (28) reported that the intrapleural injection of streptokinase and streptodornase facilitated pleural drainage in patients with empyemas. Subsequently, the use of intrapleural streptokinase and streptodornase was largely abandoned because its intrapleural injection was associated with systemic side effects, including febrile reactions, general malaise, and leukocytosis (167). In the late 1970s, Bergh et al. (168) reported the results with the intrapleural injection of streptokinase alone in 12 patients with empyema. They reported radiologic improvement in 10 of their 12 patients.

The rightful place for fibrinolytics in the management of loculated parapneumonic effusions remains to be determined. In a landmark study (103) on the use of intrapleural fibrinolytics for the treatment of complicated parapneumonic effusion, the administration of streptokinase had no effect on the need for surgery or the duration of hospitalization (Fig. 12.3) (103). In this multicenter, randomized, controlled,

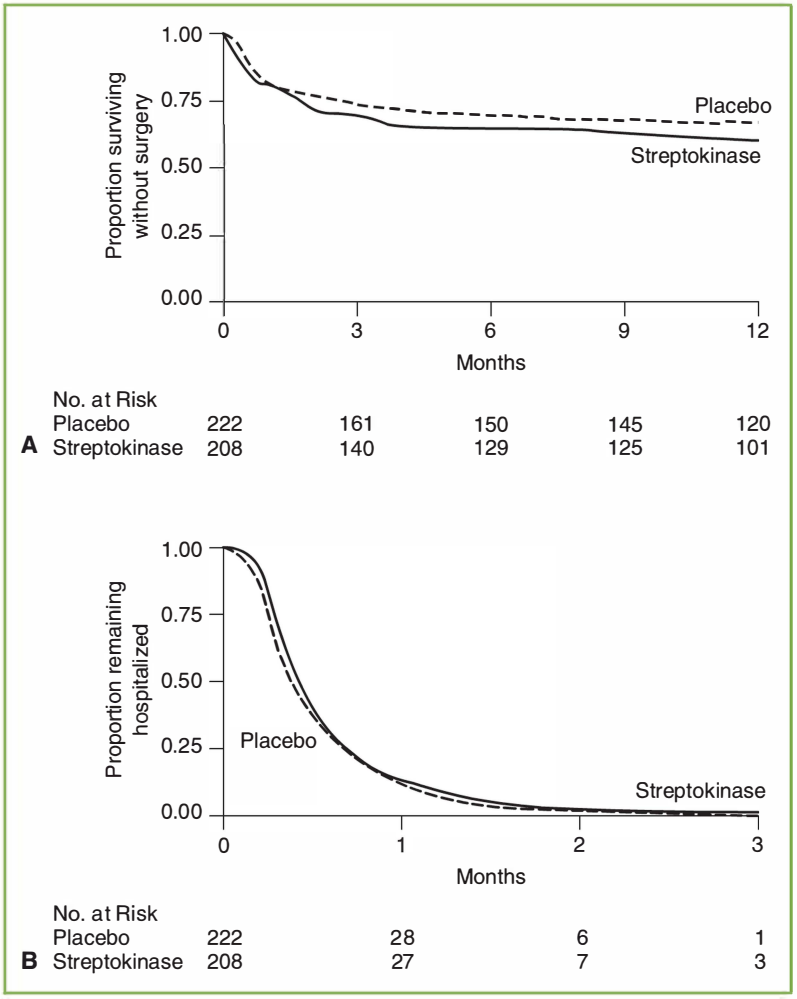

FIGURE 12.3 ■ A: Proportion of patients surviving without requiring pleural drainage surgery. **B**: Proportion remaining hospitalized during follow-up. *(From Maskell NA, Davies CW, Nunn AJ, et al. U.K. controlled trial of intrapleural streptokinase for pleural infection.* N Engl J Med. *2005; 352:865–874, with permission.)*

double-blind study, 454 patients were randomized to receive 250,000 IU of streptokinase or saline, twice daily for 3 days, both with a total volume of 30 mL. To be eligible for the study, patients had to have pleural fluid that was macroscopically purulent, that was positive for bacteria on Gram's stain, or that had a pH below 7.20. As can be seen from Figure 12.3, the patients in the placebo group actually had a slightly higher survival rate without surgery than those in the streptokinase group (103). One criticism of this study is that loculation of the pleural fluid was not required and the fibrinolytics theoretically would be most useful if the pleural fluid were loculated. However, when the subgroups with loculation were analyzed, there was no benefit from streptokinase in this group.

In a second study, Diacon et al. (169), in a single-center, randomized, double-blind study, assigned 44 patients to receive daily pleural washes with streptokinase or saline for 4 or 5 days. Eligibility criteria for this study included frank pus in the pleural space or a complicated parapneumonic effusion (pH $<$7.00 or pH $<$7.20 and evidence of pleural fluid loculation on chest x-ray or ultrasound) (169). After 3 days, there was no significant differences in the groups, but after 7 days, streptokinase-treated patients had a higher clinical success rate (82% vs. 48%, $p < 0.01$) and fewer referrals for surgery (9% vs. 43%, $p < 0.02$) (169). The patient characteristics were somewhat different in the two double-blind studies. The patients in the Diacon study were younger (38 vs. 66 years old) and had lower values for pleural fluid pH (6.6 vs. 6.8). In addition the patients in the Diacon study received antibiotics longer.

There have been five other controlled studies in which a fibrinolytic was compared with a saline control (165,170–173). None of these studies was double blind. Four of the five studies concluded that fibrinolytics were effective. In addition, there have been at least five uncontrolled studies (174–178), each with more than 20 patients, which concluded that fibrinolytics are useful in the management of patients with loculated parapneumonic effusions. Success has been reported with both streptokinase (174–177) and urokinase (174,177,178). Each agent is administered intrapleurally in a total volume of 50 to 100 mL as long as it appears to be facilitating pleural drainage. Some of the positive results were based on the observation that there is more pleural fluid drainage after the intrapleural administration of a fibrinolytic. It should be noted, however, that the intrapleural injection of a fibrinolytic in rabbits with empyemas increases the drainage by a large amount, but does not improve the empyema score (179). A meta-analysis including the UK randomized study with streptokinase concluded that there was no support for the routine use of fibrinolytic therapy for patients who require chest tube drainage (180).

The original articles on enzymatic debridement for loculated parapneumonic effusions used Varidase, which consists of a fibrinolytic (streptokinase) and a DNase (streptodornase). It is unclear how much the DNase contributed to the efficacy of the preparation. We have shown that when thick empyemic material from rabbits is incubated with either streptokinase or urokinase, there is no significant liquefaction of the fluid (167). In contrast, when the fluid is incubated with Varidase, the fluid becomes completely liquefied over 4 hours. Although Varidase is currently not available in the United States, recombinant human DNase (Pulmozyme, Genentech, San Francisco, CA) is available. Simpson et al. (181) have demonstrated that recombinant DNase by itself is very effective at reducing the viscosity of human empyema fluid. They also reported that the intrapleural administration of 5 mg recombinant DNase for 3 days resulted in the resolution of an empyema in one patient who refused surgery (182). We demonstrated that in our rabbit model of empyema the intrapleural injection of recombinant DNase in combination with tissue plasminogen activator (tPA), but not by itself, resulted in a significant improvement in empyema score (179). It has been hypothesized that streptokinase may be ineffective because plasminogen levels in the pleural fluid are probably low and so may have been excessively bound by the streptokinase into activator complex. Direct plasminogen activators, such as tPA, may overcome this problem as they do not require the generation of an activator complex.

The recently reported MIST2 study (183) evaluated the efficacy of tPA, DNase, tPA plus Dnase, and placebo in the treatment of complicated parapneumonic effusions. In this double dummy, double placebo randomized study 210 patients were randomized to one of the above four regimens. The interventions were given twice daily for 3 days (tPA 10 mg, DNase 5 mg). The primary outcome measure was the absolute change in the pleural opacity on the chest radiograph from the day of randomization until 7 days post randomization (183).

The administration of the combination of tPA and DNase resulted in a significantly greater reduction in the pleural opacity (−29.5%) than did the administration of tPA (−17.2%), DNase (−14.7%), or placebo (−17.2%) (183). There were no significant differences between tPA, DNase, and placebo (183). When the secondary endpoints were examined, the patients who received the combination had a significant decrease in surgical referrals and a significantly shorter hospital stay than did the patients who received placebo (183). tPA alone did not differ significantly from placebo on either of these secondary endpoints while DNase alone was actually associated with more surgical referrals than was placebo (183).

In view of the discussion in the preceding text, what is the rightful place of fibrinolytics in the therapy of loculated parapneumonic effusions? The results of the two multicenter studies (103,183) from the United Kingdom cast doubt on the effectiveness of intrapleural fibrinolytics alone for the therapy of complicated parapneumonic effusions. However, the second study (183) demonstrates that the combination of tPA plus DNase is significantly better than placebo, while either agent by itself is not more effective than placebo. It is recommended that the combination of tPA and DNase be used if one elects to use fibrinolytic therapy. Randomized studies are needed to compare VATS with the intrapleural administration of tPA and DNase. It should be noted that a rare patient who receives a fibrinolytic intrapleurally will develop a hemothorax (184,185).

Video-Assisted Thoracoscopy with Lysis of Adhesions and/or Decortication

One option for the patient with an incompletely drained parapneumonic effusion is VATS. Although medical thoracoscopy is occasionally used in this situation, VATS is usually preferred because if the lung cannot be expanded, the VATS can be converted to a full thoracotomy. A chest CT scan should be obtained before VATS to provide anatomic information about the size and extent of the empyema cavity and whether the pleural surfaces are thickened (186). However, it should be noted that some patients will need a decortication even when no pleural thickening was evident on the CT scan (187). With VATS, the loculi in the pleural space can be disrupted, the pleural space can be completely drained, and the chest tube can be optimally placed (186). In addition, if the lung is trapped, an attempt can be made to perform a decortication. In one study of 172 patients undergoing decortication, the decortication could be completed with VATS in 66 (38%) (188). If with VATS, the lung cannot be mobilized sufficiently to reach the chest wall and diaphragm, the VATS incision can be enlarged so that the decortication can be completed with a full thoracotomy (186).

VATS is very effective at treating incompletely drained parapneumonic effusions. Between the third and fourth editions of this book, there were four articles that reported the results of VATS in this situation (189–192). When these four studies with a total of 232 patients are combined, VATS was the definitive procedure in 178 of the patients (77%). The overall mortality rate was 3%, and the median time for chest tube drainage after the procedure ranged from 3.3 to 7.1 days. The median hospital stay after VATS ranged from 5.3 to 12.3 days (189–192). Since the fourth edition of this book there has been one large study with 234 patients reported from Taiwan (193). In this study, 194 of the 234 patients (83%) had satisfactory results with the first VATS procedure, although 24 (10%) required open thoracotomy and 16 (7%) required reoperation (183). In general, patients who require open thoracotomy had their complicated parapneumonic effusion for a longer period before thoracoscopy was attempted (193,194).

There was one small study that randomized 20 patients with either a loculated pleural effusion or a pleural fluid pH less than 7.20 to receive either chest tube drainage plus streptokinase or VATS (195). In this study, VATS was the definitive procedure in 10 of 11 patients (91%), whereas streptokinase was definitive in 4 of 9 patients (44%) (195). The authors of this study concluded that in patients with loculated parapneumonic effusions, a primary treatment strategy of VATS is associated with a higher efficacy, shorter hospital duration, and less cost than a treatment strategy that uses catheter-directed fibrinolytic therapy (195).

An alternate use of VATS in the management of parapneumonic effusions is to use a VATS procedure to insert the initial chest tube. At the time that the chest tube is inserted, VATS is used to irrigate the pleural space and break down all the fibrous strands (196). One randomized study of 70 patients compared the results when the chest tube was inserted in the standard manner and when it was inserted in conjunction with VATS (196). In this study, patients with chest tubes inserted through VATS had a shorter hospital stay (8.3 vs 12.8 days) and required less decortication (17% vs 37%) (196). It appears to me that this approach to complicated parapneumonic effusions is advantageous.

Decortication

With decortication, all the fibrous tissue is removed from the visceral and parietal pleura, and all pus is evacuated from the pleural space (197). Decortication eliminates the pleural sepsis and allows the underlying lung to expand.

Decortication can be performed with VATS or with a full thoracotomy. In one study (171), decortication was performed on 308 patients including 123 who underwent open thoracotomy and 185 who underwent VATS. The patients who underwent open thoracotomy had their surgery between 1996 and 2001 while those undergoing VATS were treated between 2000 and 2006. Only 11 of the 185 patients (5.9%) who underwent VATS needed to be converted to an open thoracotomy (198). In this study, the group who received VATS had significantly less pain, shorter operative time, shorter hospital stay, and a more rapid return to work (198). The postoperative hospitalization was 3.9 days in open thoracotomy group and 2.8 days in the VATS group (198). The results of this and other studies suggest that when decortication is necessary, VATS is the procedure of choice (199). VATS decortication can be performed with the patient awake using epidural anesthesia (200).

When managing patients with pleural infections in the acute stages, decortication should only be considered for the control of pleural infection. Decortication should not be performed just to remove thickened pleura because such thickening usually resolves spontaneously over several months (201,202). If after 6 months the pleura remains thickened and the patient's pulmonary function is sufficiently reduced to limit activities, decortication should be considered. However, this is an uncommon event. The prevalence of residual pleural thickening greater than 10 mm 6 months after 348 patients were hospitalized with parapneumonic effusions was 13.8% (202). Residual pleural thickening was more common when patients had pus in their pleural space or when there was delayed resolution of the parapneumonic effusion (202). The results of pulmonary function in patients with and without residual pleural thickening did not differ significantly (202).

Open Drainage

Chronic drainage of the pleural space can be achieved with open drainage procedures. Two different types of procedures can be performed (203). The simplest procedure involves resecting segments of one to three ribs overlying the lower part of the empyema cavity and inserting one or more short, large-bore tubes into the empyema cavity. Following this procedure, the tubes are irrigated daily with a mild antiseptic solution. The drainage from the tubes can be collected in a colostomy bag placed over the tubes. The advantage of this method over closed-tube drainage is that drainage is more complete and the patient is freed from attachment to the chest tube bottles.

A similar but more complicated procedure is open-flap drainage, in which a skin and muscle flap is positioned so that it lines the tract between the pleural space and the surface of the chest (203) after two or more overlying ribs are resected. The advantage of this open flap (Eloesser flap) is that it creates a skin-lined fistula that provides drainage without tubes. Therefore, it can be more easily managed by the patient at home and permits gradual obliteration of the empyema space.

It is important not to convert to an open drainage procedure too early in the course of a complicated parapneumonic effusion. With an open drainage procedure, the pleural space is exposed to atmospheric pressure. If the visceral and parietal pleura adjacent to the empyema cavity have not been fused by the inflammatory process, exposure of the pleural space to atmospheric pressure will result in a pneumothorax. Before open drainage procedures, this possibility can be evaluated by leaving the chest tube exposed to atmospheric pressure for a short period and determining radiologically whether the lung has collapsed. If the lung does collapse in this situation, an open drainage procedure can still be performed by creating an airtight seal and connecting the large tube to a water-seal drainage apparatus (204). The high mortality rate in patients with parapneumonic effusions during World War I has been attributed to performing open drainage procedures too early (26).

A patient treated with an open procedure can expect to have an open chest wound for a prolonged period. In one series (53) of 33 patients treated using open drainage procedures, the median time for the drainage site to heal was 142 days. With decortication, the period of convalescence is much shorter (205), but decortication is a major surgical procedure that cannot be tolerated by markedly debilitated patients.

Recommended Management of Parapneumonic Effusions

When a patient with pneumonia is initially evaluated, one should ask if the patient has a parapneumonic effusion. If the diaphragms are not visible throughout

the entire length on the lateral radiographs, decubitus radiographs, ultrasonic examination, or chest CT scan should be obtained to determine whether free pleural fluid is present. If free pleural fluid is present and the distance between the inside of the chest wall and the outside of the lung is more than 10 to 20 mm, the pleural fluid needs to be sampled. If there is doubt as to how much of the density in a hemithorax is parenchymal and how much is pleural, a CT scan of the chest should also be obtained. If more than minimal fluid is demonstrated on the CT scan, the pleural fluid should be sampled. The reason for sampling the pleural fluid in these situations is to determine whether any bad prognostic factors are present (Table 12.4).

The options for the invasive treatment of complicated parapneumonic effusions are listed in Table 12.7. In general, one moves from the less invasive treatments to the more invasive treatments. It is important to abandon a treatment within 1 or 2 days if it is ineffective. Not every treatment needs to be used. If a patient is going to need a decortication, it should be performed within 10 to 14 days of the initial identification of the parapneumonic effusion. Even in the 21st century, there are frequent delays in performing the definitive procedures in patients with complicated parapneumonic effusions. For example, Chu et al. (206) reported that the mean time from admission until a surgical consult was requested for 26 patients with empyema in Regina, Saskatchewan, Canada, was 44 days.

An outline of the recommended treatment for a patient with a parapneumonic effusion is presented in Figure 12.4. If a patient has sufficient pleural fluid to warrant a thoracentesis, it is recommended that a therapeutic rather than a diagnostic thoracentesis should be performed initially. Although there are no controlled studies validating this approach, the reasoning behind this recommendation is as follows. If no fluid reaccumulates after the initial therapeutic thoracentesis, one need not worry about the parapneumonic effusion. If the pleural fluid reaccumulates and there were no bad prognostic factors at the time of the initial thoracentesis, no additional therapy is indicated as long as the patient is doing well. If the fluid reaccumulates and there were bad prognostic factors present at the time of the initial thoracentesis, a second therapeutic thoracentesis should be performed. If the fluid reaccumulates a second time, a tube thoracostomy should be performed if any of the bad prognostic factors were present at the time of the second therapeutic thoracentesis.

TABLE 12.7 ■ Treatment Option for Complicated Parapneumonic Effusions

Therapeutic thoracentesis
Tube thoracostomy
Tube thoracostomy with the intrapleural administration of fibrinolytics
Thoracoscopy with the breakdown of adhesions
Thoracotomy with decortication

Listed in order of increasing invasiveness.

Performance of the therapeutic thoracentesis also delineates whether the pleural fluid is loculated. If the pleural fluid is loculated, and if any of the other bad prognostic factors listed in Table 12.4 are present, then more aggressive therapy should be initiated. The patient should be subjected to VATS if it is available and the patient is an operative candidate. Otherwise, a chest tube should be inserted and 10 mg tPA plus 5 mg DNase should be administered intrapleurally twice a day for 3 days (MIST2). If the lung does not expand, then decortication should be performed. If the patient was not subjected to VATS originally and the pleural fluid remains incompletely drained after 10 or more days, consideration should be given to performing a VATS if the patient is an operative candidate or an open drainage procedure if the patient is not an operative candidate.

The ACCP (107) and the BTS (144) have both published guidelines for the management of complicated parapneumonic effusions. The guidance given by the ACCP guidelines (107) is rather vague in that they say most category 3 and category 4 effusions (Table 12.6) are not cured with tube thoracostomy or therapeutic thoracentesis. They recommend the intrapleural instillation of fibrinolytics, VATS, or open thoracotomy rather than a stepwise progression as I recommend. The BTS recommends a diagnostic thoracentesis rather than a therapeutic thoracentesis and then the insertion of a chest tube if any bad prognostic factors are present. If the fluid is not drained adequately after 5 to 7 days, they recommend consultation with a thoracic surgeon (143).

SPECIAL SITUATIONS WITH EMPYEMA

Empyema in Children

Parapneumonic effusions are the most common cause of pleural effusion in children (207). As mentioned earlier in this chapter, the bacteriology of empyema

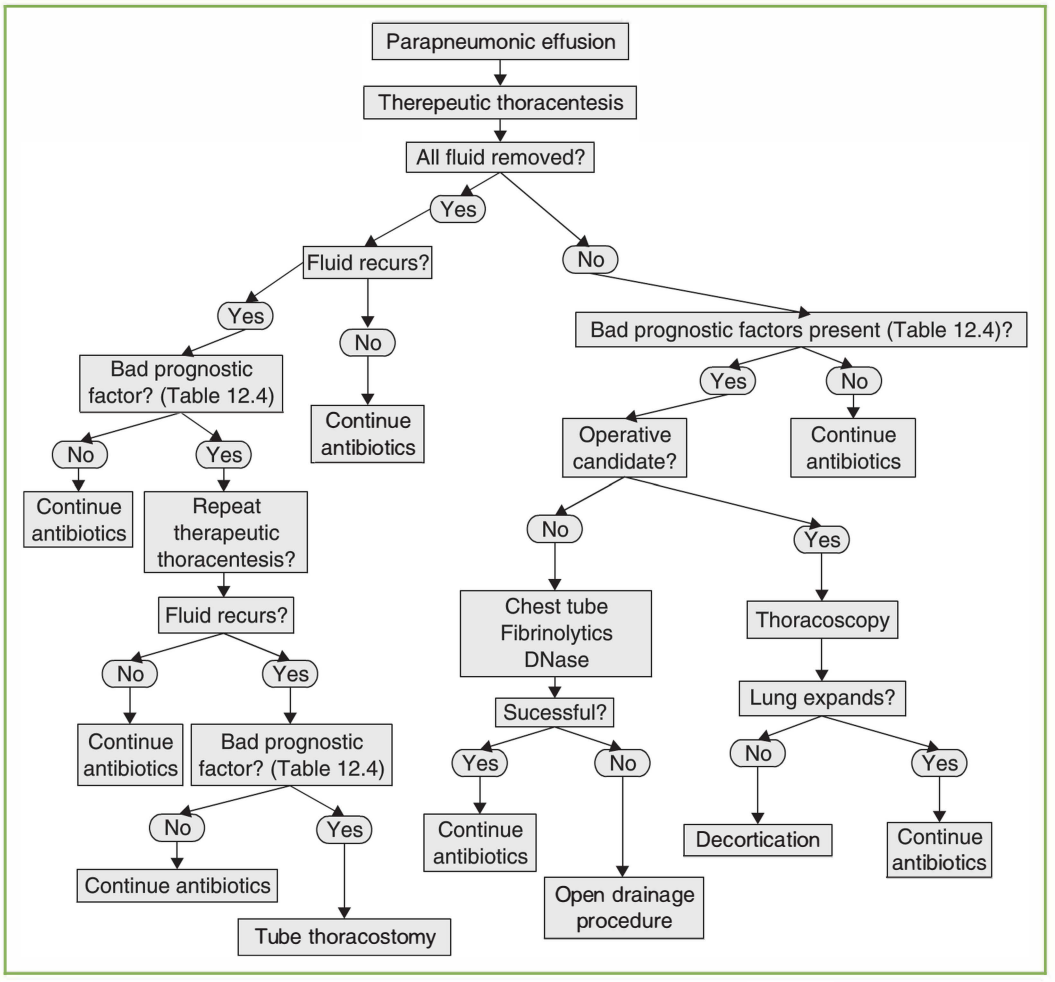

FIGURE 12.4 ■ Algorithm for managing patients with parapneumonic effusions.

in children varies somewhat from that in adults. In children the incidence of anaerobic infection is lower, whereas that of *H. influenzae* is higher. In Texas, the most common bacterial cause of empyema in children now is MRSA (208). However, other recent studies have reported that *S. pneumoniae* serotype 1 is the most common pathogen isolated (209,210). The bedside diagnosis of *S. pneumoniae* infection can be made with the Binax NOW *S. pneumoniae* kit which had a sensitivity of 83.3% and a specificity of 93.5% in one study of 130 patients with pediatric empyema (211). It is noteworthy that the vaccines available in the United States and the United Kingdom are not directed against this serotype (209,210). The majority of children with complicated parapneumonic effusions have negative pleural fluid cultures. However, the application of real-time polymerase chain reaction (PCR) for bacterial DNA can improve the positive results to more than 80% (212).

Since the introduction of the 7-valent PCV7 in the United States, the pneumococcal pneumonia hospitalization rates decreased 61%, but the pneumonia hospitalizations complicated by empyema increased 2.01-fold (213). Rates of pneumococcal and streptococcal empyema remained stable, whereas the rates for staphylococcal and other empyema increased by 4.08- and 1.89-fold, respectively (213). A second study (214) reported similar findings. In a study from Australia, nonvaccine serotypes accounted for 51 of 53 pneumococcal isolates (215). It is possible that the vaccine results in the selection of pneumococci which are more likely to cause empyema. There have

also been increases in the incidence of empyema in Taiwan, a country without a pneumococcal vaccination program (216). The reason for the increased incidence of empyema is unknown (217).

Another difference between children and adults is that the complicated parapneumonic effusions can lead to scoliosis in the children. Mukherjee et al. (218) reported that scoliosis of 10 degrees or more was noted in 71 of 122 pediatric patients (71%). Patients with scoliosis did not require more decortications. The scoliosis resolved in all patients (218). The percentage of children with pneumonia who require surgery for pleural complications has ranged from 3% in a study in Brazil (219) to 28% in a study from Salt Lake City, Utah, USA (209).

The treatment for children with complicated parapneumonic effusions is similar to that for adults with parapneumonic effusions. One difference between the management of parapneumonic effusions in children and adults is that a diagnostic thoracentesis is frequently not performed in children because this requires sedation (219). Another big difference between children and adults is that children are almost always in good general health and the final results are usually excellent (220).

In 2005, the BTS has published guidelines on the management of pleural infection in children (221). Highlights of the guidelines include the following recommendations: (a) ultrasound must be used to confirm the presence of a pleural fluid collection; (b) ultrasound should be used to guide thoracentesis; (c) biochemical analysis of pleural fluid is unnecessary in the management of parapneumonic effusion; (d) effusions that are enlarging and/or compromising respiratory function should not be managed by antibiotics alone; (e) if a child has significant pleural infection, a chest tube should be inserted; (f) small rather than large chest tubes should be used to minimize discomfort; (g) when the effusion consists of thick pus or is loculated, intrapleural fibrinolytics should be given; and (h) patients should be considered for surgical treatment if they have persisting sepsis in association with a persistent pleural fluid collection, despite a chest tube and antibiotics (221).

Although the BTS guidelines state that the pleural fluid pH and glucose levels should not be used in selecting which pediatric patients with parapneumonic effusions should undergo tube thoracostomy, a low pleural fluid pH or a low pleural fluid glucose appears to be important in indicating which children will have a poor outcome (209,222–224). Additional indicators of a poor outcome in children are significant scoliosis, evidence of parenchymal entrapment, and anaerobic infection. Tube thoracostomy, VATS, or decortication should be instituted if the patient has two or more of these indicators of a poor prognosis.

In general, the management of children with empyema is very similar to that for adults. The children are usually healthy, so there is very little, if any, role for open drainage procedures. If the fluid is not drained adequately with tube thoracostomy the two main options are intrapleural fibrinolytics and VATS. Gates et al. (223) reviewed the literature in 2004 and found that patients treated with VATS or thoracotomy had significantly shorter hospitalizations (9.9 and 10.5 days, respectively) than did patients treated with chest tube only or chest tube plus fibrinolytics (16.4 and 18.9 days, respectively). Early VATS (within 48 hours of admission) leads to significantly shorter hospitalizations that if the VATS is performed later (225).

However, some series show that patients treated with fibrinolytics usually do not require VATS or thoracotomy. Wells and Havens (226) treated 71 patients with 25,000 to 100,000 IU urokinase or 0.1 mg/kg alteplase and reported that the treatment was successful in 70 patients (99%). Randomized controlled studies evaluating the effectiveness of intrapleural fibrinolytics have produced conflicting results. In one study, 40 patients with Light's class 5, 6, or 7 parapneumonic effusions were randomized to receive saline or streptokinase 15,000 IU/kg/dose intrapleurally for 3 consecutive days. There was no difference in the duration of fever or the median duration of drainage (227). In a second study that was double blind and multicenter, 60 children with a persistent fever of greater than 38°C after more than 24 hours of parenteral antibiotic therapy or the presence of a pleural collection causing respiratory distress were randomized to receive intrapleural urokinase 40,000 IU in 40 mL of saline or saline only 12 hourly for 3 days (228). In this study, the mean hospital stay was significantly shorter with urokinase (7.4 days) than it was with saline (9.5 days) but the need for surgery in the urokinase group ($n = 2$) and the saline group ($n = 3$) did not differ significantly (228). Since the MIST1 (103) and MIST2 (183) double-blind randomized placebo controlled studies in adults have failed to demonstrate any benefit from a thrombolytic itself, one should be cautious in using fibrinolytics in children. To my knowledge, the utility of the combination of a fibrinolytic and DNase has not been assessed in children.

Several authors have recommended that VATS be the primary means of therapy for pediatric patients (229). In one series of 41 patients, all were cured with VATS and the median length of stay was only 7 days (230). In a second series, 49 children had VATS performed within 48 hours of admission and the median total length of stay was 9.9 days (208). In a third study (231), 114 children had VATS for empyema. The median hospital stay postoperatively was 7 days, and the procedure was successful in 96 patients (93%). Five patients needed to be converted to thoracotomy and three patients developed a recurrent empyema (231). In the one randomized study comparing fibrinolytics and VATS, 60 patients were randomized to receive tube thoracostomy with urokinase or VATS if they had a pleural effusion and remained febrile for more than 24 hours after parenteral antibiotics were initiated or if they had respiratory distress (232). In this study, there was no difference in the median hospital stay (VATS 8 days, urokinase 7 days), the need for additional therapy (VATS 4, urokinase 5), or radiologic outcome after 6 months (232). In a second randomized study (233) with 36 patients comparing VATS with 4 mg tPA, there was no difference in days of hospitalization after intervention, days of oxygen requirement but VATS was associated with higher charges. If VATS is performed and the sepsis is still not controlled, then the patient should be subjected to decortication (222,230), but this is an unusual event in children (208,234). It should be emphasized that decortication is indicated only for pleural sepsis. If the patient has extensive pleural thickening without pleural fluid, the thickening can be expected to resolve completely over the next 6 months without surgery (235).

Two recent reviews (236,237) of randomized controlled studies comparing VATS with chest drain and fibrinolytics concluded that the best available evidence does not support the contention that VATS is superior to chest drain with fibrinolytics. Clinicians should consider local expertise in the interventions, potential adverse events, and patient preference when deciding between these two treatment options.

Empyema Associated with Bronchopleural Fistula

When an empyema is complicated by the presence of a bronchopleural fistula, adequate pleural drainage is crucial (Fig. 12.5). Pleural fluid that is not drained exteriorly with chest tubes is likely to drain interiorly into the lung through the fistula. The bacteria are then spread throughout the bronchopulmonary tree and an overwhelming pneumonia can result. It should be emphasized that the presence of a bronchopleural fistula in conjunction with infected pleural fluid is a medical emergency. Drainage should be instituted immediately to prevent the possibility of contaminating the entire respiratory system by the infected pleural fluid (Fig. 12.5).

The presence of a bronchopleural fistula should be suspected when a patient with a pleural fluid collection raises more sputum than would be expected from the associated pulmonary disease. If the patient raises large amounts of sputum only when lying in one position, a bronchopleural fistula is strongly suggested. Radiologically, a bronchopleural fistula is manifested by the presence of an air–fluid level in the pleural space when the radiograph is obtained with the patient in the upright position (Fig. 12.5). It is sometimes difficult to determine whether the air–fluid levels are in the lung parenchyma or in the pleural space. The utility of ultrasound and CT studies in making this differentiation is discussed in Chapter 6.

Empyema Distal to an Obstructed Bronchus

One contraindication to the placement of chest tubes in patients with complicated parapneumonic effusions is the presence of a malignant tumor obstructing a lobar or main stem bronchus. If chest tubes are placed in such patients, the bronchial obstruction will prevent expansion of the lung underlying the pleural effusion and the unfortunate patient will be saddled with a chest tube or an open chest wound for the remainder of his life. When a patient is discovered to have a complicated parapneumonic effusion distal to an obstructed bronchus, appropriate antibiotics should be administered in conjunction with therapy for the obstructed bronchus, which could include radiotherapy, an endobronchial stent, or laser therapy. Tube thoracostomy can be instituted if the obstruction is relieved with the therapy. If the obstruction persists, the patient can be sent home with a prescription of appropriate oral antibiotics. In my experience, continuous administration of oral antibiotics to patients with pleural sepsis and bronchial obstruction allows them to live in symbiosis with their pleural infection without excessive systemic toxicity.

Postpneumonectomy Empyema

Empyemas following thoracic surgical procedures account for approximately 25% of all empyemas (32,37,45), and the procedure is usually a

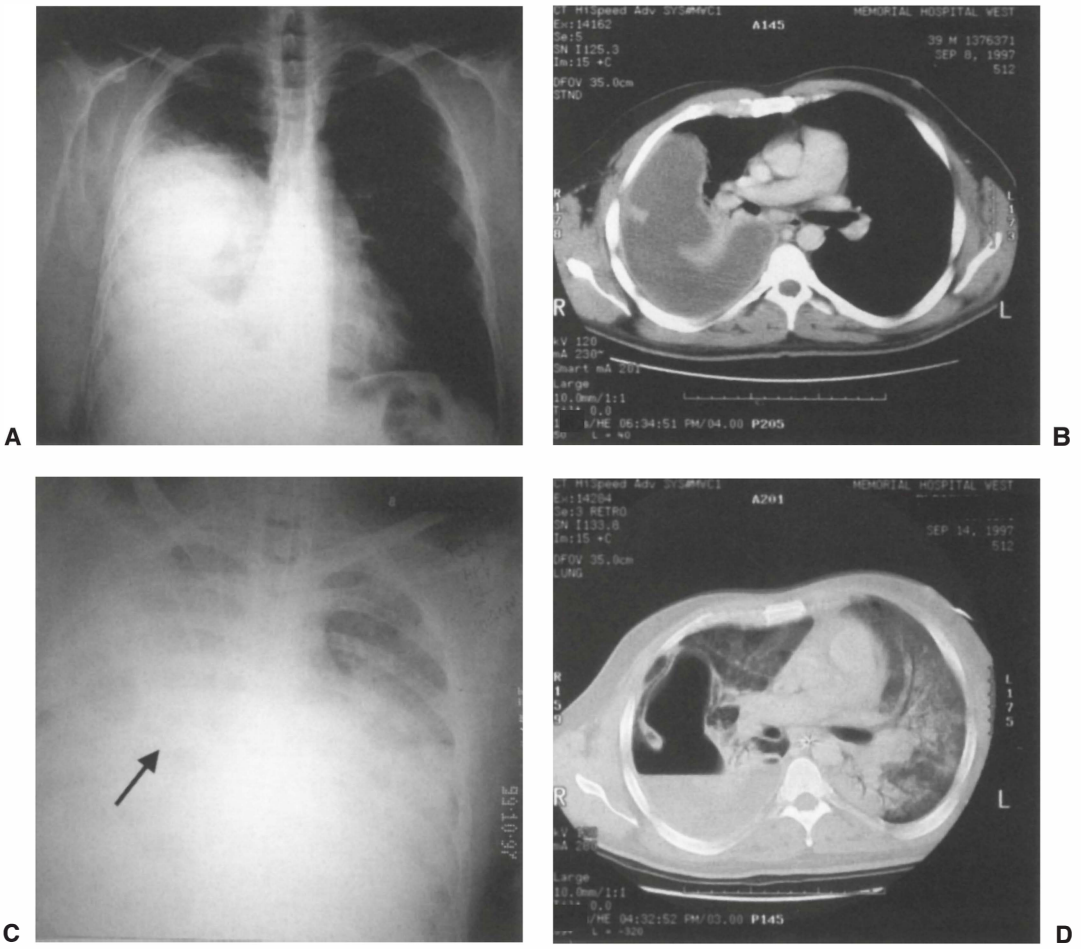

FIGURE 12.5 ■ A: Posteroanterior (PA) chest radiograph of a 44-year-old man who had pleuritic chest pain, fever, and leukocytosis for 1 week. **B**: Computed tomography (CT) scan demonstrating that most of the opacity in the right lung field in the PA chest radiograph is pleural fluid. **C**: Anteroposterior (AP) chest radiograph 2 days later demonstrating extensive infiltrates throughout both lungs in addition to pleural effusion. Note lucent area (*arrow*) in right midlung field indicating an area in the pleural space that had drained. The infiltrates are a result of the pleural pus entering the tracheobronchial tree. **D:** CT scan 1 day after the AP chest radiograph demonstrating extensive bilateral pulmonary infiltrate. Note that there is no chest tube in place so that the pus in the pleural space continues to drain through the tracheobronchial tree.

pneumonectomy. After a pneumonectomy, there is a characteristic evolution of radiologic findings, and deviations from this pattern suggest the possibility of postpneumonectomy empyema. Immediately after pneumonectomy, the ipsilateral pleural space contains air, the mediastinum is shifted to the ipsilateral side, and the hemidiaphragm is elevated (Fig. 12.6A). The postpneumonectomy space then begins to fill with serosanguineous fluid at a rate of approximately two rib spaces a day. In most patients, the pleural space becomes 80% to 90% filled with fluid within 2 weeks and completely filled within 2 to 4 months (238). During this period, the mediastinum progressively shifts ipsilaterally (Fig. 12.6B). Failure of the mediastinum to shift in the postoperative period indicates an abnormality in the postpneumonectomy space (238). Similarly, the most sensitive indicator of late complications in the pneumonectomy space is the return to the midline of a previously shifted mediastinum or a shift of the mediastinum to the contralateral side (Fig. 12.7) (238).

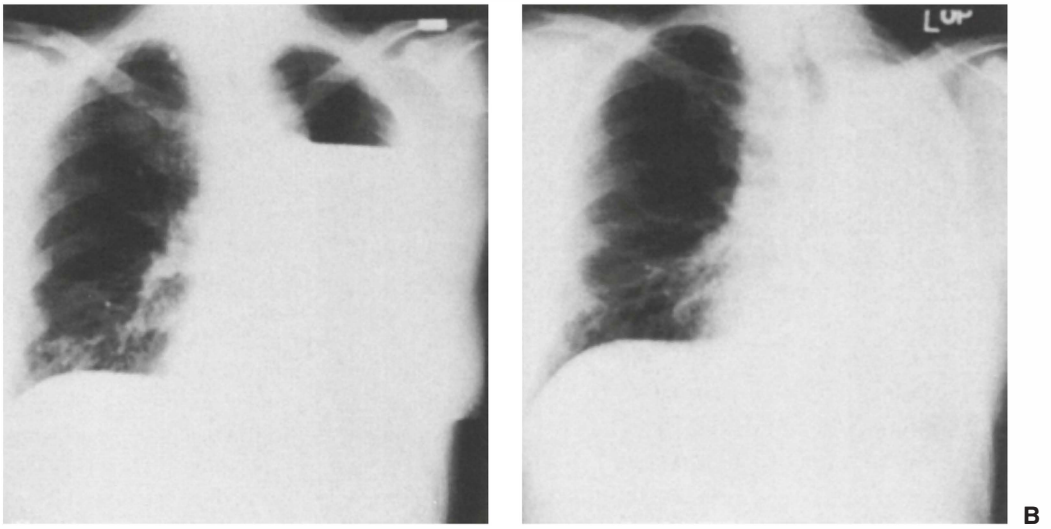

FIGURE 12.6 ■ Appearance of chest radiograph after pneumonectomy. **A**: Posteroanterior chest radiograph from a patient 1 week after pneumonectomy. Note that the postpneumonectomy space contains an air–fluid level and that the mediastinum is shifted toward the side of the pneumonectomy. **B**: Posteroanterior chest radiograph from the same patient 1 year after pneumonectomy. The mediastinum has shifted more toward the side with the pneumonectomy, and the hemithorax is completely opacified.

The postoperative occurrence of empyema is a dreaded complication of pneumonectomy. The complication is particularly serious because it is impossible to eliminate the space containing the infection, and, consequently, it is difficult to sterilize the space. Approximately 80% of patients with postpneumonectomy empyema have a bronchopleural or an esophagopleural fistula as a complication (239,240).

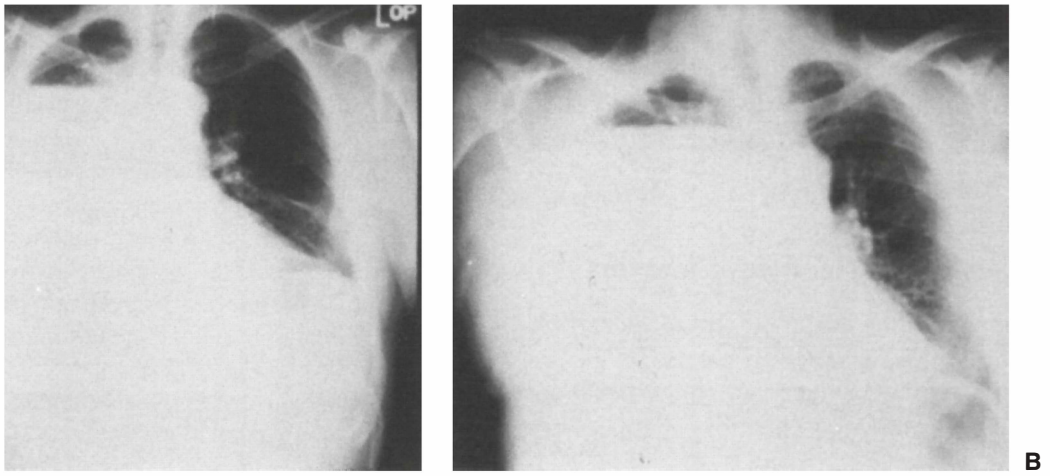

FIGURE 12.7 ■ **A**: Posteroanterior chest radiograph from a patient who had undergone a right pneumonectomy 2 weeks previously. **B**: Posteroanterior chest radiograph from the same patient a week later. Note the marked interval shift in the mediastinum. This patient had a *Staphylococcus aureus* infection of his pneumonectomy space.

Therefore, all patients with this type of empyema should have a barium swallow and a bronchoscopic examination (240).

The incidence of empyema following pneumonectomy is approximately 5% (239,240), and the mortality rate from postpneumonectomy empyema is approximately 12% (239). Between 1985 and 1998, 713 patients underwent pneumonectomy at the Mayo Clinic and empyema developed in 53 of the patients (7.5%), and 32 of these had a bronchopleural fistula (241). The administration of antibiotics prophylactically starting before surgery and continuing until the pleural drains are removed resulted in a significant reduction in postpneumonectomy empyema in one study (242). An infected pneumonectomy space usually becomes manifest in one of four ways: (a) a febrile illness with signs of systemic toxicity; (b) expectoration of large amounts of pleural fluid; (c) an air–fluid level in the pneumonectomy space; or (d) the drainage of purulent material from the surgical incision. The time from pneumonectomy to the development of an empyema ranges from 2 days to 7 years, with most infections evident within 4 weeks (243,244). The diagnosis should be suspected in any patient who, following this operation, becomes febrile, starts expectorating large amounts of pleural fluid, has purulent drainage from his thoracotomy wound, or has a mediastinum that is at midline or is shifted to the contralateral side (Fig. 12.7). Other causes of a contralateral mediastinal shift post pneumonectomy are hemothorax and chylothorax (245). Diagnosis is established by a thoracentesis, demonstrating bacteria on the Gram's stain of the pleural fluid. If more than several weeks have passed since the patient's pneumonectomy, ultrasound examination of the pleural space should be performed to identify the appropriate location for the thoracentesis. *S. aureus* is the bacterium responsible for most postpneumonectomy empyemas (243,246,247), but gram-negative organisms such as *E. coli, Pseudomonas* sp, and *Proteus* sp, as well as fungi are at times responsible.

All patients with postpneumonectomy empyema should be treated with a chest tube and appropriate antibiotics. Placement of a chest tube more than 1 week following the pneumonectomy may be difficult, because the evacuated hemithorax rapidly loses volume by apposition of ribs and shift of the mediastinum. Therefore, a chest CT scan is useful to assess the size and location of the residual space and to determine the optimal line of approach. Placement of the tube in the fourth or fifth intercostal space in the anterior axillary line is usually appropriate (240). In the first few weeks following pneumonectomy, the mediastinum is not stable. Therefore, suction should not be applied to the chest tube and an open drainage procedure should not be performed.

After the initial drainage, the treatment is largely dependent on whether the patient has a bronchopleural fistula. If the patient does not have a bronchopleural fistula, then the treatment of choice is closed-tube drainage of the pleural space in conjunction with antibiotic irrigation (147,239,246). A chest tube is inserted into the most dependent portion of the patient's empyema cavity and is connected to an underwater-seal drainage apparatus. The antibiotics to which the offending organisms are susceptible can be instilled by this tube, if a double-lumen tube is used (147), or through a separate, smaller tube inserted into the second or third intercostal space at the midclavicular line. The antibiotics can be infused through the pleural space continuously. Alternatively, with the drainage tube clamped, several hundred milliliters of antibiotic solution can be instilled into the pleural space and allowed to remain for several hours. The pleural fluid is then drained, and the sequence is repeated. When the drained fluid becomes clear, the irrigation fluid is changed to normal saline solution for 24 hours. If the culture of this drainage is sterile, 100 mL of concentrated irrigation fluid is left in the pleural space, and the chest tubes are removed. Gossot et al. (248) recommend thoracoscopic debridement shortly after the initial chest tube is placed. The debridement facilitates sterilization of the postpneumonectomy space.

Antibiotic irrigation of the pneumonectomy space is also effective in patients in whom the bronchopleural fistula is repaired surgically. Gharagozloo et al. (239) reported that this approach was successful in all 22 patients who had their bronchopleural fistula repaired primarily. At the time that the bronchopleural fistula was repaired, the pleural space was meticulously debrided. In 20 patients, the Gram's stain pleural fluid was negative on day 8 of the irrigation, and in the remaining 2 patients, Gram's stain of the pleural fluid was negative on day 16 after the operation.

An accelerated treatment program for postpneumonectomy empyema has been described by Schneiter et al. (249). With their procedure, they perform repeated surgical debridement of the chest cavity under general anesthesia every 48 hours with temporary closure of the chest which is filled with

povidone-iodine-soaked towels and an antibiotic solution based on the infecting organism (249). In a series of 75 patients, they reported that 97.3% were successfully, the mean hospitalization was 18 days and the mortality rate was only 4% within the first 90 days (249).

An alternate approach to postpneumonectomy empyema involves the creation of a large opening in the chest by resecting several inches of the rib inferior to the thoracotomy incision and one or more ribs superior to it. The procedure is called the *Clagett procedure* after the surgeon who first described it (145). The superficial fascia is sutured down to the periosteum of the resected ribs to leave a large window in the thoracic wall. Each day, the empyema cavity is irrigated with a mildly antiseptic solution such as half-strength Dakin's solution or chlorhexidine (Hibitane) (247). These irrigations are continued for several weeks until the drainage is no longer purulent and the empyema cavity appears to be well debrided. At this time, the opening in the chest wall is closed, and a 0.25% solution of neomycin is placed in the cavity. It has been recommended by some (250), the that Clagett procedure be followed by a thoracoplasty but I see no reason for this as a thoracoplasty is a disfiguring procedure.

Goldstraw (247) treated 29 patients with postpneumonectomy empyemas in the foregoing manner and attempted closure in 22 of the patients. In 17 of these 22 patients (77%), closure was successful in that no evidence was seen of a recurrence of the empyema from 5 weeks to 9 years after closure. The five patients in whom closure failed initially were subjected to a second fenestration, and a successful closure was eventually obtained in two of these patients. Other workers have reported much poorer results with the Clagett procedure. Shamji et al. (251) achieved successful closure in only 2 of 31 patients (6%) managed in this manner, whereas Bayes et al. (252) reported success in 10 of 28 patients (36%). This treatment is time consuming, with a mean interval between fenestration and closure of 40 days (range 21–74 days), and patients usually have to remain hospitalized for the entire period (202). The closed irrigation method is the procedure of choice in my opinion.

If a bronchopleural fistula is present, several different procedures can be used in an attempt to close the fistula. On occasion, the bronchopleural fistula will close with continuous irrigation of the infected pleural space, but usually more extensive procedures must be done. If the bronchopleural fistula develops within the first few weeks of surgery, attempts can be made to close the bronchopleural fistula directly. Recently, Gharagozloo et al. (239) reported the successful primary repair of all 22 bronchopleural fistulas. None of the patients had a bronchial stump opening that was more than 25% of the diameter of the bronchus. Attempts can be made to close the bronchopleural fistula with fibrin glue endoscopically. In one study, 8 of 36 patients had their bronchopleural fistula successfully treated using fibrin sealant and decalcified spongy calf bone (251). Pairolero et al. (253) advocate the intrathoracic transposition of extrathoracic skeletal muscle to facilitate closure of the fistula. They attempted this procedure in 28 patients following open drainage and reported success in 24. The median number of operations was 5, with a range of 1 to 19. The median hospitalization time was 34 days, with a range of 4 to 137. A related method closes the fistula with an omentopexy (254,255).

Posttraumatic Empyema

Empyema remains a distressing complication after thoracic injury. In one study published in 1997, the incidence of empyema requiring decortication was 4% in 584 patients who were treated with tube thoracostomy (256), whereas in another series, the incidence was 1.8% of 5,474 patients (257). Factors that predicted the development of an empyema were retained hemothorax (odds ratio, 12.5), pulmonary contusion (odds ratio, 6.3), and multiple chest tube placement (odds ratio, 2.5). Factors that did not predict empyema were severity of injury, mechanism of injury, the setting in which tube thoracostomy was performed, number of days chest tubes were in place, and antibiotics at the time of tube thoracostomy (256). Aguilar et al. (256) recommend the early drainage of the pleural space with the VATS technique in posttrauma patients with fluid collections in the pleural space. In general, the management of posttraumatic empyema is the same as that of parapneumonic empyema.

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chapter 13

Tuberculous Pleural Effusions

The diagnosis of tuberculous pleuritis should be considered in any patient with an exudative pleural effusion. A pleural effusion as an isolated manifestation of tuberculosis (TB) has been likened to a primary chancre as a manifestation of syphilis. Both are self-limited and of little immediate concern, but both may lead to serious disease many years later.

PATHOGENESIS AND PATHOPHYSIOLOGIC FEATURES

When a tuberculous pleural effusion occurs in the absence of radiologically apparent TB, it may be the sequel to a primary infection 6 to 12 weeks previously or it may represent reactivation TB (1). In industrialized countries, more pleural effusions may be due to reactivation than are due to postprimary infection (1). However, in a relatively recent study from San Francisco, pleural TB cases were approximately two times more likely to be clustered (as assessed by genotyping of the mycobacterial organisms) than were pulmonary TB and three times more likely to be clustered than nonrespiratory TB cases (2). Thirty-five percent of the pleural TB cases were clustered (2). These findings suggest that at least in San Francisco, primary infection accounts for a large percentage of pleural TB (2). However, two subsequent studies from Houston (3) and Baltimore (4) were unable to confirm these findings.

The tuberculous pleural effusion is thought to result from rupture of a subpleural caseous focus in the lung into the pleural space (5). Supporting evidence comes from the operative findings of Stead et al. (6), who reported that they could demonstrate a caseous tuberculous focus in the lung contiguous with the diseased pleura in 12 of 15 patients with tuberculous pleuritis. The remaining three patients in this series were found to have parenchymal TB, although these patients did not have caseous foci adjacent to the pleura.

It appears that delayed hypersensitivity plays a large role in the pathogenesis of tuberculous pleural effusion. As mentioned in the previous paragraph, the hypersensitivity reaction is initiated when tuberculous protein gains access to the pleural space. When guinea pigs are immunized to tuberculous protein by injecting Freund's adjuvant containing dead tubercle bacilli into their footpads, an intrapleural injection of purified protein derivative (PPD) of tuberculin 3 to 5 weeks later causes the rapid appearance (~within 12 to 48 hours) of an exudative pleural effusion (7). The development of the pleural effusion is suppressed when the animals are given antilymphocyte serum (8).

The neutrophil appears to play a key role in the development of experimental tuberculous pleuritis. When bacillus Calmette-Guérin (BCG)–sensitized rabbits are given BCG intrapleurally, the resulting pleural fluid contains predominantly neutrophils for the first 24 hours (9). If the animals are made neutropenic, the accumulation of pleural fluid and inflammatory cells, particularly macrophages, is decreased. The intrapleural injection of neutrophils in the neutropenic animals restores the response to control levels. The neutrophils in the pleural space appear to secrete a monocyte chemotaxin that recruits monocytes to the pleural space and thereby contributes to the formation of granulomas (9).

In this BCG model of experimental tuberculous pleuritis, macrophages predominate in the pleural fluid from day 2 to day 5 (9). It has been shown that

mesothelial cells stimulated with BCG or interferon-gamma produce macrophage inflammatory protein and monocyte chemotactic peptide (10). These two proteins account for more than 75% of the mononuclear chemotactic factor in tuberculous pleural fluid (10). After this period, lymphocytes are the predominant cells in the pleural fluid (11). When the lymphocytes first appear in the pleural fluid approximately on day 3, they do not respond to PPD. From day 5 onward, however, reactivity to PPD is found in most cases (12). The reactivity of the lymphocytes in the peripheral blood parallels that of the pleural lymphocytes (12). (See Chapter 4 for further discussion of these experimental models of tuberculous pleuritis.)

It is probable that delayed hypersensitivity also plays a large role in the development of tuberculous pleural effusions in humans. The mycobacterial cultures of the pleural fluid from most patients with tuberculous pleural effusions are negative (2,13,14). T lymphocytes specifically sensitized to tuberculous protein are present in the pleural fluid (15). In one report, approximately 1 in 2,000 of the lymphocytes in the pleural fluid was specifically sensitized to tuberculous protein (15). In the same report, only 1 in 15,000 of the lymphocytes in the peripheral blood was specifically sensitized to the tuberculous protein. It is unknown whether the increased percentage of specifically sensitized lymphocytes in the pleural fluid is due to their clonal expansion in the pleural fluid or is due to the migration of PPD-responding T lymphocytes from the blood to the pleural space. When pleural lymphocytes from patients with tuberculous pleural effusions are cocultured with PPD, lymphokines are produced (16). The level of lymphokine production is much greater with pleural lymphocytes than with peripheral blood lymphocytes (16).

Although delayed hypersensitivity to tuberculous protein is probably responsible for most clinical manifestations of tuberculous pleuritis, many patients when first evaluated have a negative PPD skin test. The explanation for this paradox may be a combination of two factors. First, in some (17), but not in all (18) patients with tuberculous pleuritis, a circulating mononuclear adherent cell suppresses the specifically sensitized circulating T lymphocytes in the peripheral blood. Second, there may be sequestration of PPD-reactive T lymphocytes in the pleural space involving both Leu-2 (suppressor/cytotoxic) and Leu-3 (helper) positive T cells (18).

Tuberculous pleural effusions are enriched with many potentially immunoreactive cells and substances that comprise the vigorous local cell-mediated immune response (19). Compared with peripheral blood, pleural fluid is enriched with T lymphocytes. The CD4 (helper–inducer) to CD8 (suppressor/cytotoxic) ratio is 3:4 in pleural fluid, compared with 1:7 in blood (19). Pleural fluid lymphocytes from patients with tuberculous pleuritis show greater responsiveness to PPD than do peripheral blood lymphocytes (20).

The obvious explanation for the development of the tuberculous pleural effusion is that the delayed hypersensitivity reaction increases the permeability of the pleural capillaries to protein, and the increased protein levels in the pleural fluid result in a much higher rate of pleural fluid formation and accordingly result in the accumulation of pleural fluid. However, this does not appear to be the mechanism for the pleural fluid accumulation. Apicella and Allen (21) were unable to demonstrate any striking increase in the inflow of protein into the pleural space in their experimental model of delayed hypersensitivity tuberculous pleuritis. They did, however, demonstrate a dramatic decrease in the clearance of protein from the pleural space (21). Leckie and Tothill (22) reported that the pleural lymphatic flow from patients with TB was approximately 50% that of patients with congestive heart failure. It is probable that the intense inflammatory reaction in the parietal pleura impedes the lymphatic drainage from the pleural space (see Chapter 2) and leads to the accumulation of pleural fluid. It should be noted, however, that when mesothelial cells are cultured in the presence of BCG, vascular endothelial growth factor (VEGF) is released from the mesothelial cells, and the expression of adherens junction protein is down regulated (23). However, extrapolation of these results in monolayers to the *in vivo* situation remains to be verified.

INCIDENCE

In many areas of the world, TB remains the most common cause of pleural effusions in the absence of demonstrable pulmonary disease. For example, in one series of 642 pleural effusions from northern Spain in the mid-1990s, TB was the most common etiology of pleural effusion, accounting for 25% of all pleural effusions (24). A study from Saudi Arabia about the same time demonstrated that TB was also the most common cause of pleural effusions in that country, accounting for 37% of all pleural effusions (25).

In the United States, the annual incidence of tuberculous pleuritis has been estimated to be approximately 1,000 cases, and it is said that 3% to 5% of patients with TB will have tuberculous pleuritis (3,26,27).

It is likely that both these numbers are low. Patients with tuberculous pleuritis tend to be underreported because their mycobacterial cultures are frequently negative. Between 1988 and 1994, there were 2,817 cases of TB in patients without the acquired immunodeficiency syndrome (AIDS) who were reported to the South Carolina state TB registry; 6% of these patients had pleural effusions (28). However, in non-AIDS patients with new-onset intrathoracic TB, pleural effusions occur in more than 25% of patients in Burundi (29) and 20% in South Africa (30).

Patients who are immunocompromised are more likely to develop TB than nonimmunocompromised individuals. Pleural TB also occurs frequently in the immunocompromised individual. Mycobacterial infection occurred in 27 of 1,261 patients (2.1%) who received renal transplants in Valencia, Spain and 3 of these had pleural effusions (31). TB occurred in 48 of 330 patients (14.5%) who were on renal dialysis in Saudi Arabia and 5 of them had pleural effusions (32).

One might anticipate that the incidence of tuberculous pleuritis would be relatively low in patients with AIDS and TB because the patient with AIDS has a compromised immunologic system, and pleural TB is thought to be due to hypersensitivity. However, overall it appears that the incidence of pleural effusions is higher in patients with AIDS. One possible explanation for this apparent paradox is that the pleural effusion in patients with AIDS is related to pleural invasion by the mycobacteria rather than to delayed hypersensitivity (33). The fact that smears and cultures are more often positive in the human immunodeficiency virus (HIV)–positive patient lends support to this hypothesis.

Although in the series referenced in the preceding text from Burundi, a slightly smaller percentage of HIV-positive patients (24%) than HIV-negative patients (28%) had pleural effusions (29), other series have shown that pleural effusions are more common in HIV-positive patients. The percentage of patients with thoracic TB who also had a pleural effusion was higher in HIV-positive patients than in HIV-negative patients in series from South Africa (38% vs. 20%) (29), Uganda (23% vs. 11%) (34), and Zimbabwe (27% vs. 13%) (35).

CLINICAL MANIFESTATIONS

Although TB is usually considered a chronic illness, tuberculous pleuritis most commonly manifests as an acute illness. In one series of 71 patients, 25 (35%) had initial symptoms of less than 1 week in duration, whereas 50 (70%) had been symptomatic for less than a month (36). In another series, 31 of 49 patients (63%) had an acute illness that most commonly mimicked acute bacterial pneumonia (5). Most patients (~70%) have a cough, usually nonproductive, and most (~75%) have chest pain, usually pleuritic in nature (1,5,37). If both cough and pleuritic chest pain are present, the pain usually precedes the cough. Most patients are febrile, but a normal temperature does not rule out the diagnosis. In one series, 7 of 49 patients (14%) were afebrile (5). Occasionally, the onset of TB is less acute, with only mild chest pain, perhaps with a low-grade fever and a nonproductive cough, weight loss, and easy fatigability.

In general, patients with tuberculous pleuritis are younger than patients with parenchymal TB. In one recent series from Qatar, the mean age of 100 patients with tuberculous pleuritis was 31.5 years (38). In industrialized countries, the mean age of patients with TB tends to be older. In a recent study from the United States, the mean age of the 14,000 patients with tuberculous pleuritis reported to the Communicable Disease Center in the United States between 1993 and 2003 was 49.9 years (27). Patients with pleural effusions secondary to reactivation tend to be older than those with postprimary pleural effusion (1).

Pleural effusions secondary to tuberculous pleuritis are usually unilateral and can be of any size. In one series, the effusions occupied more than two thirds of the hemithorax in 18%, between one third and two thirds of the hemithorax in 47%, and less than one third of the hemithorax in 34% (39). In another series of 46 patients with massive pleural effusions (40), 4% of the effusions were due to TB. In approximately 20 to 25% of patients with pleural effusions secondary to TB (39,41), coexisting parenchymal disease is visible on the chest radiograph. If chest CT scans are done, approximately 90% will have parenchymal abnormalities (41,42). In such patients, the pleural effusion is almost always on the side of the parenchymal infiltrate and invariably indicates active parenchymal disease. On rare occasions, pleural TB can present with pleural-based nodules and thickening (43).

Clinical Manifestations in HIV-Positive Patients

The clinical manifestations of pleural TB tend to be somewhat different in the HIV-positive patient. Patients with HIV tend to have a longer duration of illness and a lower incidence of chest pain (44).

Systemic signs and symptoms such as night sweats, fatigue, diarrhea, hepatomegaly, splenomegaly, and lymphadenopathy are significantly more common in HIV-infected patients (37). Patients with HIV are more likely to have concomitant parenchymal lesions (3). Their pleural fluid is more likely to be smear positive for acid-fast bacilli (AFB) and culture positive for AFB (44,45). If the CD4 count is less than 100, approximately 50% have a positive smear for AFB on their pleural fluid (44). HIV patients have significantly lower lymphocyte counts (45). Interestingly, the viral load per mL pleural fluid was higher than that in simultaneously obtained serum in each of eight patients in one study (46).

NATURAL HISTORY OF UNTREATED TUBERCULOUS PLEURITIS

Without treatment, tuberculous pleuritis usually resolves spontaneously, only to return as active TB at a later date. Patiala (47) followed up for at least 7 years all 2,816 members of the Finnish Armed Forces who developed pleural effusions between 1939 and 1945. They reported that 43% of this large group of young men developed TB during the follow-up period. Even in the 1-year observation period 5 years following the initial episode, 5% of the total population studied developed active TB.

Confirmatory evidence for this large series comes from the series of Roper and Waring (48) in the United States, who followed up 141 military personnel first seen from 1940 to 1944 with a pleural effusion and a positive PPD test. In most patients, the effusions resolved and all the other symptoms disappeared within 2 to 4 months. Nevertheless, 92 of the 141 individuals (65%) subsequently developed some form of active TB. Manifest TB did not develop in the lung or elsewhere in any of the patients within 8 months of the onset of the original pleurisy. The incidence of subsequent TB was 60% in those with initially negative pleural fluid cultures for TB and 65% in those with initially positive pleural fluid cultures. In addition, the size of the original effusions and the presence or the absence of small radiologic residual pleural disease were not correlated with the subsequent appearance of active TB (48). The foregoing series emphasize the importance of making the diagnosis of tuberculous pleuritis.

Because the administration of antituberculous chemotherapy reduces the incidence of subsequent TB (5,49), it is important to establish the diagnosis of tuberculous pleuritis and initiate proper treatment. Moreover, patients in whom the diagnosis cannot be established but is considered likely should also be treated.

DIAGNOSIS

The diagnosis of tuberculous pleuritis depends on the demonstration of tubercle bacilli in the sputum, pleural fluid, or pleural biopsy specimen, or the demonstration of granulomas in the pleura. The diagnosis can also be established with reasonable certainty by demonstrating elevated levels of adenosine deaminase (ADA) or interferon-gamma in the pleural fluid (50). Study of the peripheral blood is not useful; most patients do not have leukocytosis (5). The chest radiograph usually demonstrates only the pleural fluid, but as previously mentioned, approximately 20 to 25% of the patients also have a parenchymal infiltrate due to TB (39).

Tuberculin Skin Testing

In the past, the tuberculin skin test was an important diagnostic aid in patients suspected of having tuberculous pleuritis. However, a negative skin test does not rule out the diagnosis of tuberculous pleuritis. In one series from Spain, the PPD was positive in only 66.5% of 254 patients with tuberculous pleuritis (39). In another series from Hong Kong, more than one half of the patients tested had a negative PPD (14). The factors responsible for the negative skin test in patients with tuberculous pleuritis are discussed earlier in this chapter. If a patient with a negative tuberculin skin test and tuberculous pleuritis is skin tested more than 8 weeks after the development of symptoms, the skin test will almost always be positive. Therefore, in patients with an undiagnosed exudative pleural effusion, a negative tuberculin skin test performed 8 weeks after the development of symptoms can be used to exclude the diagnosis of tuberculous pleuritis. However, if the patient is markedly immunosuppressed with HIV infection or is severely malnourished, the PPD may remain negative.

Pleural Fluid Analysis

Pleural fluid analysis is useful in the diagnosis of tuberculous pleuritis. The fluid is invariably an exudate. Frequently, the pleural fluid protein level is above 5 g/dL, and this finding suggests tuberculous pleuritis. In most patients, the pleural fluid

differential white blood cell (WBC) count reveals more than 50% small lymphocytes (5,39,51–53). In one series of 254 patients with tuberculous pleuritis (39), only 17 (6.7%) had fewer than 50% lymphocytes in the pleural fluid. In patients with symptoms of less than 2 weeks' duration, the pleural fluid differential WBC is more likely to reveal predominantly polymorphonuclear leukocytes (36,54). In a second series of 214 patients, 11% had more than 50% pleural fluid polymorphonuclear leukocytes (54). If serial thoracenteses are performed, the differential WBC usually reveals a change to predominantly small lymphocytes (5). The separation of the lymphocytes into T lymphocytes and B lymphocytes is not useful diagnostically (see Chapter 7). If eosinophils are found in the pleural fluid in significant numbers (>10%), one can virtually exclude the diagnosis of tuberculous pleuritis, unless the patient has a pneumothorax or has had a previous thoracentesis (see Chapter 7).

A useful study for ruling out tuberculous pleuritis is analysis of the pleural fluid for mesothelial cells (Fig. 7.1A). Four separate series have confirmed that pleural fluid from patients with TB rarely contains more than 5% mesothelial cells (51,52,55,56). Unfortunately, the absence of mesothelial cells is not diagnostic of TB because with any condition in which the pleural surfaces are extensively involved by an inflammatory process, mesothelial cells are not found in the pleural fluid. It has been suggested that HIV-infected patients with tuberculous pleuritis may have significant numbers of mesothelial cells in their pleural fluid (57). In one report (57), three HIV-infected patients with tuberculous pleuritis had significant numbers of mesothelial cells in their pleural fluid. Each of the patients had CD4 counts of less than 100/mm^3 in their peripheral blood.

Adenosine Deaminase

Demonstration of an elevated pleural fluid ADA level is useful in establishing the diagnosis of tuberculous pleuritis. ADA is the enzyme that catalyzes the conversion of adenosine to inosine. ADA is a predominant T-lymphocyte enzyme, and its plasma activity is high in diseases in which cellular immunity is stimulated. In an early study, Ocana et al. (58) measured the pleural fluid ADA levels in 221 pleural or peritoneal effusions (Fig. 13.1). All patients with a pleural fluid ADA level above 70 U/L had TB, whereas no patient with a pleural fluid ADA level below 40 U/L had tuberculous pleuritis. Subsequent studies of larger numbers of patients with tuberculous pleural

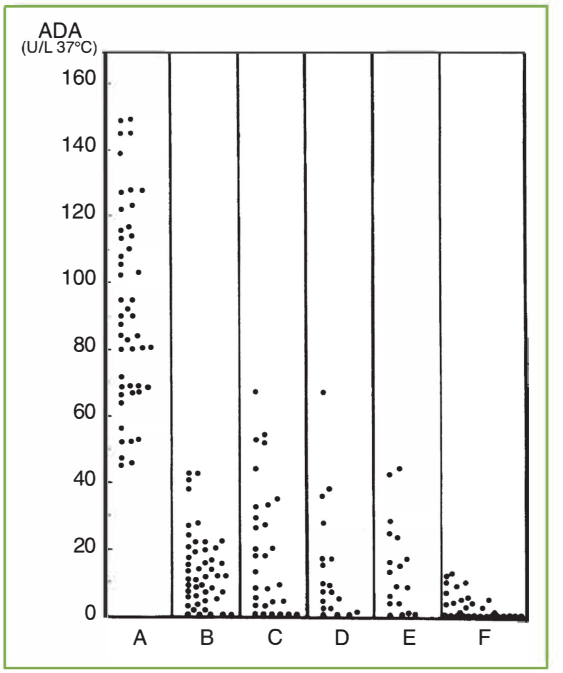

FIGURE 13.1 ■ Levels of adenosine deaminase (ADA) activity in pleuroperitoneal effusions. Tuberculosis **(A)**; malignancies **(B)**; pleuropneumonia **(C)**; miscellaneous **(D)**; unknown origin **(E)**; transudates **(F)**. *(From Ocana I, Martinez-Vazquez JM, Segura RM, et al. Adenosine deaminase in pleural fluids. Chest. 1983;84:51–53, with permission.)*

effusions have demonstrated that the pleural fluid ADA level is higher in patients with tuberculous pleuritis than in patients with other types of pleural effusions (59–62). Different authors have used various cutoff levels for the pleural fluid ADA between 30 and 70 U/L for the diagnosis of pleural TB. The higher the pleural fluid ADA level, the more likely the patient is to have tuberculous pleuritis. Liang et al. (63) performed a meta-analysis of 63 articles evaluating the diagnostic usefulness of ADA that included 2,796 patients with tuberculous pleuritis and 5,297 patients with other diseases. They reported that the mean sensitivity was 0.92, the mean specificity was 0.90, the mean positive likelihood ratio was 9.03 and the mean negative likelihood ratio was 0.10 (63).

In general, the two main diseases other than tuberculous pleuritis that are associated with a high pleural fluid ADA are empyema and rheumatoid pleuritis. However, it should be easy to differentiate these two diseases from tuberculous pleuritis by the clinical picture and the fact that these latter two diseases do

not have pleural fluid lymphocytosis. Indeed, if the diagnostic criteria for tuberculous pleuritis includes a pleural fluid lymphocyte-to-neutrophil ratio of 0.75 or more, the specificity of the test is increased (64–66). This increase in specificity is due to excluding the cases with rheumatoid pleuritis or empyema. The pleural fluid ADA is elevated in patients with tuberculous pleuritis who have predominantly PMNs in their pleural fluid (54).

There are a few other instances in which the pleural fluid ADA level will be elevated. Patients with pleural effusions due to Q fever (67) or brucellosis (68) will have elevated pleural fluid ADA levels. An occasional patient with a pleural effusion due to lymphoma or malignancy will have a lymphocytic effusion with a high ADA (69).

Almost all patients with tuberculous pleuritis have an ADA level above 40 U/L. Immunosuppressed patients with tuberculous pleuritis have elevated pleural fluid ADA levels. The levels of ADA in patients with and without AIDS are comparable (62). Renal transplant patients who develop a pleural effusion have elevated pleural fluid ADA levels (70).

The pleural fluid ADA level can be used to exclude the diagnosis of tuberculous pleural effusions in patients with undiagnosed pleural effusions. Ferrer et al. (71) followed up 40 patients with undiagnosed pleural effusions and a pleural fluid ADA level below 43 U/L for a mean of 5 years and reported that none of the patients developed TB. Lymphocytic pleural effusions not due to tuberculous pleuritis usually have pleural fluid ADA levels below 40 U/L. Lee et al.(69) measured the pleural fluid ADA in 106 patients with lymphocytic pleural effusions not due to TB, including 45 post–coronary artery bypass pleural effusions and 26 malignant pleural effusions. They reported that only 3 of the 106 fluids (3%) had ADA levels above 40 U/L (69). The three patients included two with lymphoma and one with a late complicated parapneumonic effusion (69). Jimenez Castro et al. (72) measured the pleural fluid ADA levels in 410 lymphocytic nontuberculous pleural fluids and found that the ADA was above 40 U/L in only 7 (1.7%).

There are two molecular forms of ADA—ADA1 and ADA2. ADA1 is found in all cells, but has its greatest activity in lymphocytes and monocytes (73). ADA2 is found only in monocytes, and most of the ADA in tuberculous pleural fluid is ADA2, whereas most of the ADA in other pleural fluids is ADA1 (73). Although the use of a ratio of the ADA1 to ADA total of less than 0.42 will slightly increase the sensitivity and specificity of the ADA in diagnosing tuberculous pleuritis, the separation of ADA into its isoenzymes is not necessary in the vast majority of cases (73,74).

When preservatives are added to pleural fluid, the pleural fluid ADA levels remain stable during transportation. Miller et al. (75) have shown that if 0.9 mL pleural fluid is maintained in a test tube containing 0.10 mL of a mixture of 50% glycerol and 50% ethylene glycol, the pleural fluid can be mailed by regular mail with no loss of ADA activity. The pleural fluid ADA levels were virtually identical in specimens that were shipped in the preservative through regular mail and those that were shipped in dry ice by air (75). However, if pleural fluid is maintained at ambient temperatures without preservatives, the ADA levels will linearly decrease (75). The ADA levels remain stable for long periods in pleural fluid frozen at −70°C (69).

In summary, measurement of the pleural fluid ADA level is useful in the diagnosis of tuberculous pleurisy. In patients with lymphocytic pleural effusion, demonstration of an ADA level above 40 U/L is strongly suggestive of the diagnosis of tuberculous pleurisy. If a lymphocytic pleural effusion is not due to TB, the pleural fluid ADA level is almost always below 40 U/L. Pleural fluid for ADA assay can be transported at ambient room temperatures if preservatives are added to the pleural fluid (75).

Interferon-Gamma

Another test that is useful in the diagnosis of tuberculous pleuritis is the level of interferon-gamma in the pleural fluid (59,76–80). Interferon-gamma is produced by the $CD4^+$ lymphocytes from patients with tuberculous pleuritis (78). Patients with tuberculous pleuritis tend to have higher pleural fluid interferon-gamma levels than do patients with pleural effusions of other etiologies. In the largest series published until now, Villena et al. (81) measured the pleural fluid interferon-gamma levels in 595 patients, including 82 with TB, and reported that a cutoff level of 3.7 IU/mL yielded a sensitivity of 0.98 and a specificity of 0.98. Most of the false positives in this study occurred in patients with hematologic malignancies. Unfortunately, ADA levels were not measured in this article for comparison (81). The pleural fluid interferon-gamma levels were elevated in 14 immunocompromised patients and 3 transplantation patients with tuberculous pleuritis (81). Comparable results have been reported in other series (76–79), but comparison of the series is difficult because the units have differed from one study to another. Patients with

empyema frequently have elevated pleural fluid levels of interferon-gamma (59). Jiang et al. (80) performed a meta-analysis on the diagnostic usefulness of pleural fluid interferon-gamma levels in 22 studies with 782 patient with tuberculous pleuritis and 1,319 patients with pleural effusions due to other diseases. They reported that the mean sensitivity was 0.89, the mean specificity was 0.97, the mean positive likelihood ratio was 23.45, and the mean negative likelihood ratio was 0.11 (80).

Adenosine Deaminase versus Interferon-Gamma

Which is the better test for the diagnosis of tuberculous pleuritis—ADA or interferon-gamma? Greco et al. (82) performed a meta-analysis comparing ADA and interferon-gamma for the diagnosis of tuberculous pleuritis. After a review of 31 papers on ADA which included 4,738 patients and 13 papers on interferon-gamma which included 1,189 patients, they reported that the summary receiver operating characteristic curve yielded a maximum joint sensitivity and specificity of 93% for ADA and 96% for interferon-gamma (82). They concluded that both ADA and interferon-gamma are reasonably accurate at diagnosing tuberculous pleuritis. Gupta et al. (83) have pointed out that in articles that directly compare ADA and interferon-gamma, some conclude that ADA is better and some conclude that interferon-gamma is better. In general, measurement of the pleural fluid ADA level is preferred to measurement of the pleural fluid interferon-gamma level in evaluating patients suspected of having pleural TB because the ADA measurement is less expensive (84).

Interferon-Gamma Release Assays (IGRA)

The IGRAs are inferior to the pleural fluid interferon-gamma levels in diagnosis tuberculous pleuritis (85,86). Zhou et al. (85) performed a meta-analysis of the available reports on IGRA on the pleural fluid for diagnosing tuberculous pleuritis. The analyzed seven reports with a total of 213 patients with tuberculous pleuritis and 153 patients with pleural effusions of other etiologies and reported that the mean sensitivity was 0.75, the mean specificity was 0.82, the mean positive likelihood ratio was 3.49 and the mean negative predictive ratio was 0.24 (85). Since these results are markedly inferior to those with ADA or interferon-gamma, the IGRA should not be used in assessing whether patients have tuberculous pleuritis.

Polymerase Chain Reaction

In the field of infectious diseases, the polymerase chain reaction (PCR) tests and other nucleic acid amplification (NAA)–based tests have been quite useful in establishing the diagnosis of viral diseases. Therefore, it was hypothesized that the NAA-based tests would be useful in diagnosing tuberculous pleuritis. It appears, however, that the NAA-based tests are certainly not superior to either the pleural fluid ADA or interferon-gamma levels in establishing the diagnosis of tuberculous pleuritis. Pai et al. (87) performed a meta-analysis on 14 studies utilizing NAA-based tests for the diagnosis of tuberculous pleuritis using three different commercial kits including 127 patients with tuberculous pleuritis and 1,400 patients with pleural effusions due to other diseases. They reported that the mean sensitivity was only 0.62 while the mean specificity was 0.98 (87). The mean positive likelihood ratio was 25.4 while the mean negative likelihood ratio was 0.40 (87). Currently, PCR of the pleural fluid should be considered to be an investigative test until there is more data available regarding its sensitivity and specificity.

Pleural Fluid Tuberculous Proteins or Antibodies

In recent years, the possibility of establishing the diagnosis of tuberculous pleuritis by the demonstration of tuberculous antigens or specific antibodies against tuberculous proteins in the pleural fluid has been investigated. None of these tests have proved to be useful in the diagnosis of tuberculous pleuritis. The presence of antituberculous antibodies in the pleural space appears to result from their passive diffusion from the serum rather than local antibody production (88). Therefore, it is unlikely that measurement of such antibodies in the pleural fluid will ever be diagnostically useful.

Other Chemical Tests

Other chemical analyses of the pleural fluid are of limited value in establishing the diagnosis of tuberculous pleuritis. Although in the past it was believed that the pleural fluid glucose level was reduced in most cases of tuberculous pleuritis (89), more recent studies show that most patients with tuberculous pleuritis have a pleural fluid glucose level above 60 mg/dL (5,44). A low pleural fluid pH level was once thought to be suggestive of tuberculous pleuritis (90), and I concluded that tuberculous pleural

effusions had a lower pleural fluid pH level than malignant pleural effusions in the first article Light et al. wrote on pleural fluid pH levels (91). Subsequent articles (92,93), however, and my own observations indicate that the pleural fluid pH has approximately the same distribution in malignant as in tuberculous pleural effusions. The mean level of C-reactive protein (CRP) is higher in tuberculous effusions than in other exudative effusions (94). Chierakul et al. (94) reported that the optimal cutoff level for the pleural fluid CRP level was 30 mg/dL and this level had a sensitivity of 72% and a specificity of 93%. Garcia-Pachon et al. (95) in a study of 144 patients reported that a CRP level greater than 50 mg/L had a 95% specificity for TB, whereas a CRP level less than 30 mg/L had a 95% sensitivity for excluding tuberculous pleuritis. However, both the pleural fluid ADA and interferon gamma are superior to the pleural fluid CRP levels in establishing the diagnosis of tuberculous pleuritis.

The levels of lysozyme in the pleural fluid have been proposed to be useful diagnostically, and there is no doubt that the mean level of lysozyme in the pleural fluid from patients with tuberculous pleuritis is higher than it is in other exudative pleural fluids (96,97). A value of 1.2:1 for the ratio of the pleural fluid to the serum lysozyme has been proposed as a good test for diagnosing tuberculous pleuritis (97). When the utility of this ratio is compared with that of the pleural fluid ADA or interferon-gamma level, the lysozyme ratio is distinctly inferior (59). For this reason, the measurement of the lysozyme ratio is not recommended (59). Measurement of the levels of tumor necrosis factor alpha (TNF-α) in the pleural fluid or the ratio of the pleural fluid to the serum TNF-α is inferior to measurements of the pleural fluid ADA in making the diagnosis of tuberculous pleuritis (98). There have been many other studies on cytokine levels in the pleural fluid and although the mean cytokine levels in tuberculous effusions differ significantly from those in pleural fluids of other etiologies (see Chapter 5), there is always so much variation in the levels that their measurement has not proved as diagnostically useful as that of ADA or interferon-gamma.

Sputum Smears and Cultures

One test that is frequently overlooked in the diagnostic workup of patients with a pleural effusion is examination of the sputum for mycobacteria. Conde et al. (99) prospectively evaluated the diagnostic yield of AFB smear and culture of the sputum in 84 patients with tuberculous pleuritis. Sputum was induced in those unable to spontaneously produce sputum. They reported that the sputum studies were positive in 44 of the 84 patients (52%) (99). In 10 of the 44 patients, sputum smears were positive, whereas cultures were positive in all 44 (99). Sputum was induced in 64 patients with a normal radiograph (except for the effusion) and was positive in 35 (55%).

Pleural Fluid Stains and Cultures

For nonimmunosuppressed patients, routine smears of the pleural fluid for mycobacteria are not indicated because they are usually negative, unless the patient has a tuberculous empyema (13,39). Cultures for mycobacteria should be obtained, however. If the patient is HIV-positive, the smears may be positive in more than 20% (44). In most series of patients with tuberculous pleuritis, the pleural fluid cultures are positive for mycobacteria in fewer than 40% (5,39). For mycobacterial cultures, use of a BACTEC system with bedside inoculation provides higher yields and faster results than do conventional methods. In one study, the median time for the BACTEC cultures to become positive was 18 days (range 3–40 days), whereas the median time for conventional cultures was 33.5 days (range 21–48 days) (100). In a second study, the pleural fluid cultures were positive by the BACTEC system in 24% of HIV-negative and 75% of HIV-positive individuals, whereas the cultures were positive by the Lowenstein–Jensen medium in 12% of HIV-negative patients and 56% of HIV-positive patients (45). In this same study, the mean time to positive culture with the BACTEC system was 3.5 weeks compared with 4.7 weeks with the Lowenstein–Jensen medium (45).

Pleural Biopsy

For the last 40 years, the diagnosis of tuberculous pleuritis has been most commonly made with needle biopsy of the pleura. The demonstration of granuloma in the parietal pleura suggests tuberculous pleuritis; caseous necrosis and AFB need not be demonstrated. Although other disorders including fungal diseases, sarcoidosis, tularemia (101), and rheumatoid pleuritis may produce granulomatous pleuritis, more than 95% of patients with granulomatous pleuritis have TB. Even when granulomas are not demonstrated in the pleural biopsy, the biopsy specimen should be examined for AFB because organisms are occasionally

demonstrated when no granulomas are present in the biopsy. In one study of 248 patients with tuberculous pleuritis who underwent needle biopsy of the pleura, the biopsy showed granulomas in 198 patients (80%), the acid-fast stain of the biopsy was positive in 64 (25.8%), the culture of the biopsy tissue was positive in 140 (56%), and at least one of the preceding three tests was positive in 227 (91%) (39). PCR has also been tried on pleural biopsy specimens, but it is not clear that the PCR adds to the regular microscopic examination (102).

In recent years, the availability of tests on the pleural fluid, such as the ADA, which are at least as sensitive in diagnosing tuberculous pleuritis as is needle biopsy of the pleura, have resulted in a decreased use of needle biopsy of the pleura (103). A possible criticism of relying on the pleural fluid tests rather than the pleural biopsy is that with pleural fluid markers, no culture results are obtained. Accordingly, the sensitivities of the organisms cannot be determined. It should be noted that although the cultures of the biopsy are positive in approximately 55%, cultures of the fluid itself are positive in 35%. Therefore, the culture of the biopsy itself provides additional positive cultures in only 20% of the patients. One study reported that multidrug resistance occurred in only approximately 1% of patients with pleural TB and that any first-line drug resistance occurs in less than 10% (27).

Recommended Diagnostic Approach in Patients with Undiagnosed Exudative Pleural Effusion

When a patient is seen with a pleural effusion, the diagnosis of tuberculous pleuritis should always be considered. When the initial thoracentesis is performed, the pleural fluid should be analyzed for the ADA level and differential cell count, and the fluid should be cultured for mycobacteria. If the pleural fluid ADA is above 70 U/L and the pleural fluid has a lymphocyte-to-neutrophil ratio of more than 0.75, the diagnosis of TB is virtually established. If the pleural fluid ADA level is between 40 and 70 U/L and the patient has a lymphocyte-to-neutrophil ratio of more than 0.75, a presumptive diagnosis of TB can be made. In this situation, consideration can be given to further studies (thoracoscopy or needle biopsy of the pleura) if the patient's clinical picture is not typical for tuberculous. If the patient's pleural fluid ADA level is below 40, the diagnosis of TB is unlikely. However, if the patient has a clinical picture typical of TB and, particularly, if the pleural fluid has a high percentage of lymphocytes, the possibility of TB can be further evaluated with thoracoscopy or needle biopsy of the pleura.

TREATMENT

The treatment of tuberculous pleuritis has three goals: (a) to prevent the subsequent development of active TB, (b) to relieve the patient symptoms, and (c) to prevent the development of a fibrothorax.

Chemotherapy

The recommendations for the treatment of all pulmonary and extrapulmonary TB are as follows (104,105). The initial phase of a 6-month regimen should consist of a 2-month period of isoniazid (INH), rifampin, and pyrazinamide. Ethambutol should be included in the initial regimen until the results of drug susceptibility studies are available, unless there is little possibility of drug resistance. The second phase of the treatment should be INH and rifampin given for 4 months. Directly observed therapy (DOT) is recommended. Nine-month regimens using INH and rifampin are also effective when the organisms are fully susceptible to the drug. One study demonstrated that the penetration of INH into pleural fluid was excellent, but the penetration of pyrazinamide was very poor, whereas the penetration of rifampin was intermediate (106). The clinical significance of these findings remains to be determined.

The recommendations mentioned in the preceding text may be somewhat intensive for isolated tuberculous pleuritis. Less intensive regimens appear to be effective. In one study, Canete et al. (107) treated 130 patients with 5 mg/kg of INH and 10 mg/kg of rifampin daily for 6 months and reported no treatment failures. In a second study, Dutt et al. (108) administered 300 mg of INH plus 600 mg of rifampin daily for 1 month, followed by 900 mg of INH plus 600 mg of rifampin twice a week for the next 5 months to 198 patients. This regimen failed in only one patient (108).

The patient with isolated tuberculous pleuritis appears to have a small bacterial burden because many of the symptoms are due to delayed hypersensitivity. In the series of Patiala and Mattila (49), the administration of chemotherapy decreased the subsequent incidence of TB from 28% to 9%, although most of their patients received only one drug for less than

6 months. Falk and Stead (109) reported that antituberculous therapy reduced the incidence of subsequent TB from 19% to 4%, and, again, many of their patients did not receive two drugs for even 6 months. From the foregoing studies, it appears that 6 months of INH and rifampin administration are sufficient if the patient does not have resistant organisms.

With treatment, the patient's symptoms and radiologic abnormalities gradually abate. The average patient becomes afebrile within 2 weeks, but temperature elevations may persist for as long as 2 months (110). If a therapeutic thoracentesis is performed at the same time that antituberculous therapy is initiated, most patients become afebrile within 5 days (111,112). The mean duration for complete resorption of the pleural fluid is approximately 6 weeks, but it can be as long as 12 weeks (110). No reason exists to keep the patient in bed (5), and patients need be isolated only if their sputum tests are positive for mycobacteria.

The incidence of pleural thickening at 6 to 12 months after beginning treatment is approximately 50% (113). In one study (114), 8 of 81 patients (10%) had a forced vital capacity (FVC) less than 80% of predicted at the end of the follow-up period for their TB treatment. In this study, there was only a weakly negative correlation ($r = -0.298$) between the degree of pleural thickening and the reduction in the FVC (114). The incidence of residual pleural thickening is not closely related to the initial pleural fluid findings; patients with a low glucose, high lactate dehydrogenase (LDH), and high cytokine levels are only slightly more likely to have residual pleural thickening (113,115). One randomized controlled study of 52 patients demonstrated that the intrapleural administration of 2.5 mL of a hyaluronate-based gel resulted in significantly faster fluid absorption and significantly less pleural thickening at 3 months (0.57 vs. 1.14 cm) (116). Residual pleural thickening is more common if the pleural effusion is initially loculated (117). Residual pleural thickening will continue to improve for at least 18 months after the antituberculous therapy is completed (117).

It appears that complete removal of the pleural fluid does not decrease the amount of residual pleural thickening. Lai et al. (118) randomized 61 patients to receive pigtail drainage until the drainage was less than 50 mL/day or no drainage. The degree of residual pleural thickening was basically identical in both groups (118).

In patients with loculated tuberculous pleural effusions, the intrapleural administration of a fibrinolytic may decrease the degree of residual pleural thickening. Kwak et al. (119) randomized 43 patients to receive only antituberculous chemotherapy or antituberculous chemotherapy plus 100,000 urokinase daily administered through a pigtail catheter starting when the amount of pleural fluid drainage was less than 100 mL/day and finishing when the amount of pleural fluid was less than 50 mL/day. Patients received a mean of 3.8 urokinase instillations (119). After the cessation of treatment, the width of the pleural thickening was 0.46 cm in the urokinase group and 1.86 cm in the control group (119). Chung et al. (120) randomized 44 patients with loculated TB pleural effusions to receive pigtail drainage of the effusion with saline or streptokinase irrigations for three consecutive days. They reported that the group that received streptokinase had less residual pleural thickening and had a faster radiological improvement (120).

An occasional patient will develop paradoxical worsening of their disease after antituberculous therapy is initiated as part of the immune reconstitution inflammatory syndrome. Al-Majed (121) serially studied 61 patients with tuberculous pleural effusion who were started on a standard regimen of rifampin, INH, pyrazinamide, and ethambutol for the first 2 months. He reported that the size of the effusion worsened in 10 of the 61 patients (17%) after the initiation of antituberculous therapy. Six of the patients developed increasing dyspnea and were treated with pleural aspiration and oral prednisolone with complete resolution of the pleural effusion. A second report suggested that such paradoxical responses might be due to INH-induced lupus pleuritis (122). An occasional patient with tuberculous pleuritis will also develop a peripheral lung nodule while being treated for the pleuritis (123). The nodules represent pulmonary TB and disappear when the antituberculous therapy is continued (123).

An occasional patient will also develop a pleural effusion during antituberculous chemotherapy. Gupta et al. (124) reported 29 patients who developed pleural effusions while receiving chemotherapy for pulmonary (16 cases) or extrapulmonary TB. The pleural effusion developed between the 5th and 8th week of starting chemotherapy in 13, between the 9th and 12th week in 9, and between the 13th and 24th week in 5 (124). The pleural fluid was exudative in all cases and the culture was positive for *Mycobacterium tuberculosis* in four (124). Most patients had a good response to the same chemotherapeutic regimen without any interruption.

Corticosteroids

The role of oral corticosteroids in the treatment of tuberculous pleurisy is controversial. There were no benefits with systemic corticosteroids in two controlled studies in which therapeutic thoracentesis was also performed (111,112). In a third study, however, the duration of fever and the time required for fluid resorption were decreased; but in this study, no therapeutic thoracentesis was performed (125). In none of the three reports did the administration of corticosteroids influence the degree of residual pleural thickening at 6 or 12 months after therapy was initiated. In one randomized controlled study of 197 patients with HIV-associated pleural TB, the administration of prednisolone was associated with an increased risk of Kaposi sarcoma (126).

In view of the factors mentioned in the preceding text, if the patient is more than mildly symptomatic with tuberculous pleuritis, a therapeutic thoracentesis is recommended. It should be noted, however, that although the studies outlined earlier suggested a beneficial effect of therapeutic thoracentesis, an older study by Large and Levick (127) was unable to demonstrate any difference in the clinical courses of 33 patients who had serial therapeutic thoracenteses and those of 19 patients who had only a single diagnostic thoracentesis. If the patient continues to have severe systemic symptoms (fever, malaise, pleuritic chest pain) after a therapeutic thoracentesis, and a definite diagnosis has been established, the administration of 80 mg of prednisone every other day until the acute symptoms have subsided is recommended. Thereafter, the corticosteroids are rapidly tapered.

Engel et al. (128) conducted a meta-analysis of randomized studies of corticosteroids in the treatment of tuberculous pleuritis. They concluded that there was no evidence of an effect of corticosteroids on death from any cause, respiratory function, residual pleural fluid at 8 weeks, or pleural adhesions. They also concluded that randomized controlled trials that are sufficiently powered to evaluate the effects of corticosteroids on both morbidity and mortality are needed (128).

Surgical Procedures

If the patient is dyspneic from a large pleural effusion, a therapeutic thoracentesis should be performed. Surgery should not be performed early for pleural thickening. Although the pleura may be thickened when the patient's disorder is first diagnosed, the thickening decreases with treatment, so decortication should not be considered until the patient has undergone treatment for at least 6 months. After this period of observation, decortication is rarely necessary. At this time, decortication should only be performed if the patient's quality of life is diminished by dyspnea.

TUBERCULOUS BRONCHOPLEURAL FISTULA

Tuberculous bronchopleural fistulas are uncommon today because most cases of TB are easily controlled with modern antituberculous chemotherapy. These fistulas are usually seen in patients with old, healed TB, and especially in patients with a previous therapeutic pneumothorax who were never treated with chemotherapy (129–131). When such patients develop a bronchopleural fistula, their sputum production usually increases in variable amounts, and superinfection of the pleural space by bacteria sometimes occurs (129). The diagnosis is suggested by the presence of an air–fluid level in the pleural space, particularly if the level fluctuates with serial chest radiographs (129). The fistula can be confirmed by the injection of methylene blue or a radiopaque dye into the pleural space and then observing whether the dye appears in the sputum or in the tracheobronchial tree.

A tuberculous bronchopleural fistula is dangerous to the patient for three reasons. First, the communication between the bronchus and the pleural space allows bacteria to gain access to the pleural space and to cause pleural infection with its attendant toxicity. Second, once the pleural space becomes superinfected, the patient is at risk for a fulminant pneumonia caused by entrance of the infected material from the pleural space into the remainder of the tracheobronchial tree. Third, the tuberculous bacilli in the pleural space are likely to become resistant to antituberculous drugs (129).

The initial treatment of tuberculous bronchopleural fistulas should be the institution of appropriate antituberculous chemotherapy in addition to the insertion of chest tubes into the lower part of the pleural cavity, because a tuberculous bronchopleural fistula does not heal spontaneously (129). Insertion of the chest tubes eliminates the danger of contamination of the contralateral lung by the infected pleural fluid and controls the systemic toxicity from the bacterial infection. Before a definitive surgical procedure is attempted, the patient should be given antituberculous chemotherapy for 90 to 120 days, or until sputum tests become negative for AFB.

Definitive surgical treatment consists of decortication, which sometimes must be combined with thoracoplasty because the underlying lung has usually been damaged by the TB to such an extent that it cannot expand to fill the pleural space (129,131). This is a major operation and is dangerous to the patient with severely damaged lungs. In Jensen's series (130) of 15 patients with tuberculous bronchopleural fistulas, 3 were cured with conservative treatment, 2 were deemed unfit to undergo definitive surgical treatment and died within a year, and 10 were operated on with an operative mortality rate of 20%.

TUBERCULOUS EMPYEMA

Tuberculous empyema is a rare entity characterized by purulent pleural fluid that is loaded with tuberculous organisms on AFB stains (132). It usually develops in fibrous scar tissue resulting from pleurisy, artificial pneumothorax, or thoracoplasty (133). In one series of 12 patients from Italy, 9 patients had received artificial pneumothorax therapy, 1 had received a thoracoplasty, and 2 had received inadequate antituberculous therapy (133). The mean duration between the therapy with the artificial pneumothoraces and the development of the empyema was more than 40 years (133). Frequently, the underlying pleura is heavily calcified. The patient usually has a subacute or chronic illness characterized by fatigue, low-grade fever, and weight loss. On rare occasions, a tuberculous empyema may produce an empyema necessitatis where the empyema ruptures through the chest wall (134). Indeed, TB is the most common cause of empyema necessitatis (134). Radiographically, there may be an obvious pleural effusion, but frequently the chest radiograph only shows pleural thickening. The chest CT scan usually demonstrates a thick, calcific pleural rind and rib thickening surrounding loculated pleural fluid. The diagnosis is established with diagnostic thoracentesis, which yields thick pus on which the AFB smear is markedly positive.

Treatment is difficult, and decortication, extrapleural pneumonectomy, and thoracoplasty have all been recommended. All of these procedures have substantial morbidity and some mortality, at least in part, because of the compromised pulmonary status of the patient. Because intensive chemotherapy coupled with serial thoracentesis can be curative at times (135), this approach should be attempted initially. It is important to use a multiple (three or more) drug regimen and to employ agents at their maximal tolerated dosages, because these patients have a strong tendency to develop resistant organisms. This is probably because the antituberculous drugs frequently do not reach their normal levels in the pleural space owing to the thick, fibrous, and often calcified pleura (136).

ATYPICAL MYCOBACTERIA

Pleural effusions due to atypical mycobacteria are rare. Pleural effusions without parenchymal disease analogous to the post primary pleural effusion with *Mycobacterium tuberculosis* do not occur. However, approximately 5% of patients with parenchymal disease due to either *M. kansasii* or *M. intracellulare* have an associated small pleural effusion, an incidence similar to that seen with parenchymal disease due to *M. tuberculosis* (137). Approximately 15% of patients with parenchymal disease due to *M. intracellulare* or *M. avium* (collectively referred to as the *Myobacterium avium* complex [MAC]) have marked pleural thickening (>2 cm), as compared with fewer than 3% of patients with disease due to *M. tuberculosis* or *M. kansasii* (137).

If the cultures of the pleural fluid yield a nontuberculous mycobacterium, one must be cautious in attributing the pleural effusion to that organism. Gribetz et al. (138) reviewed the case records of 22 patients whose pleural fluid grew nontuberculous mycobacterium. In 16 of the patients, there was another explanation for the pleural effusion, and in only 3 did the nontuberculous mycobacterium appear to be responsible for the pleural effusion. All three patients had nontuberculous mycobacterial infection of other tissues. These authors concluded that nontuberculous mycobacteria isolated from pleural fluid should not be considered etiologic, unless there is evidence of the same organism infecting other tissues (138). However, in another study (139) for a single center in Taiwan, pleural fluid cultures from 35 patients grew atypical mycobacterium over a 7-year period including 16 MAC, 6 *M. fortuitum*, 3 *M. kansasii*, 3 *M. chenonae*, and 7 others. Before the AIDS epidemic, disseminated nontuberculous mycobacterial infections were very uncommon. However, disseminated disease due MAC is an important cause of infection in patients with AIDS (140). Some autopsy studies have shown that more than 50% of patients with AIDS who die have disseminated disease due to MAC (140). Pleural effusions do occur in some patients with disseminated disease due to MAC (140), and pleural fluid

cultures are sometimes positive for MAC. Nevertheless, it is unclear whether the atypical mycobacteria are responsible for the effusion (140). Overall, disease due to MAC accounts for at most only a small percentage of the pleural effusions in patients with AIDS.

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chapter 14

Pleural Effusion Secondary to Fungal Infections, Actinomycosis, and Nocardiosis

In this chapter, pleural disease resulting from fungal infections is discussed. Although fungal diseases account for less than 1% of all pleural effusions, it is important to identify correctly patients with fungal disease of the pleura because effective treatment is available. Actinomycosis and nocardiosis are also included in this chapter because they produce a chronic disease similar to that caused by the fungi, although they actually are bacteria.

ASPERGILLOSIS

Occasionally, the pleural space becomes infected with the *Aspergillus* species of fungus. The usual infecting organism is *Aspergillus fumigatus* (1), but other species such as *Aspergillus niger* may also be responsible (2). Pleural aspergillosis is uncommon, but 13 cases were observed in one institution during a recent 5-year period (3).

Clinical Manifestations

Pleural aspergillosis usually occurs in one of two settings. Most commonly, it occurs in patients who were treated in the past with artificial pneumothorax therapy for tuberculosis (2–4). Such patients have signs and symptoms of a chronic infection, including weight loss, malaise, a low-grade fever, and a chronic, productive cough (1). The chest radiograph reveals increasing degrees of pleural thickening and usually an air–fluid level in the pleural space indicating the presence of a bronchopleural fistula (1). Fungus balls, although uncommon, may be evident radiographically either in the lungs or the pleural space (1,5).

The second situation in which pleural aspergillosis occurs is postoperatively after lobectomy or pneumonectomy for lung cancer, tuberculosis, or aspergillosis (3,4,6). A bronchopleural fistula is almost invariably present. The clinical picture is similar to that of a pleural bacterial infection after lung resection (see Chapter 12). On rare occasions, the pleural fluid becomes infected with aspergillus in the immunosuppressed patient with systemic aspergillosis (7). One report cited two patients with pleural effusion complicating allergic bronchopulmonary aspergillosis (8), but the relationship between the pleural effusion and the allergic aspergillosis was not convincing.

There has been one case report of a patient with allergic bronchopulmonary aspergillosis who presented with a large recurrent pleural effusion (9). The pleural fluid was an exudate and the effusion responded to corticosteroid therapy (9).

Diagnosis

The diagnosis of pleural aspergillosis should be suspected in any patient with a history of artificial pneumothorax therapy for tuberculosis who has a chronic pleural infection, particularly when a bronchopleural fistula is present. Similarly, the diagnosis should be suspected in any patient with a pleural infection after lung resection. The diagnosis is confirmed by the demonstration of aspergillus on fungal cultures of the pleural fluid. The presence of brown clumps containing fungal hyphae in the pleural fluid suggests the diagnosis (4). Patients with pleural aspergillosis almost always have positive precipitin blood tests for antibodies against aspergillus (1,4). Aspergillus antigens can also be demonstrated in the pleural fluid

by radioimmunoassay (10). The presence of calcium oxalate crystals in the pleural fluid suggests an infection due to *A. niger* (2). The presence of the black-pigmented spores of *A. niger* can impart a black color to the pleural fluid (11).

Treatment

The optimal treatment for pleural aspergillosis is early excision of the involved pleura with resection of the upper lobe or the entire ipsilateral lung, if necessary (1). When this definitive surgical treatment is undertaken, itraconazole or voriconazole should be administered systemically before and after the operation because the incidence of postoperative pleural infection with aspergillus is high if systemic antifungal drugs are not administered (1,12,13). The reason for performing this extensive operation is that the infection is likely to invade and destroy the underlying lung. The longer the surgical procedure is postponed, the more severe the damage to the underlying lung and the more debilitated the patient becomes (1). The bronchopleural fistulas are often difficult to manage and frequently require muscle transpositions or omentoplasty (3). Even if there is no bronchopleural fistula, muscle transpositions are sometimes necessary because the pleural space cannot be obliterated with just the damaged underlying lung (3).

Some patients with pleural aspergillosis are too debilitated to undergo a surgical procedure, or their pleural aspergillosis is a complication of pulmonary resection. In such patients, a chest tube should be inserted, and the pleural space should be irrigated daily with amphotericin B or nystatin (4,5,14). The usual dose of amphotericin B is 25 mg, and the usual dose of nystatin is 75,000 U (5). After instillation of the antifungal agents, the chest tube is clamped for an hour. In addition voriconazole and micafungin should be given as they penetrate the pleural space well (15). One patient with an aspergillus empyema was cured with the combination without chest tubes (15). An open-drainage procedure (see Chapter 12) can be performed for the patient's comfort (5). Although this treatment takes many months, it is successful in most patients (4,5,14).

BLASTOMYCOSIS

Infection with *Blastomyces dermatitidis* is frequently associated with pleural disease. In one series of 118 patients with pulmonary blastomycosis, 4 (3%) had pleural effusions (16). In a more recent study of 63 cases with proven pulmonary blastomycosis, 13 of the patients (21%) had a pleural effusion. The effusions in this series were small and caused only mild-to-moderate blunting of the costophrenic sulci (17). However, an occasional patient with pleural blastomycosis has an effusion that occupies more than 50% of a hemithorax (18).

Patients with pleural blastomycosis have signs and symptoms similar to those with tuberculous pleuritis (see Chapter 13). In addition to the pleural effusion, there may be an associated parenchymal infiltrate (19,20). With pleural blastomycosis, the pleural fluid is an exudate containing predominantly lymphocytes or polymorphonuclear leukocytes (18–20). The pleural fluid glucose level is normal, and the lactate dehydrogenase (LDH) level is usually not higher than the upper limits of normal for serum (18). Microscopic examination of the pleural fluid at times reveals the budding yeasts typical of *B. dermatitidis* (18). Pleural biopsy may reveal noncaseating granulomas (19,20). Therefore, one should consider the diagnosis of blastomycosis in patients with a clinical picture suggestive of tuberculous pleuritis, and one should obtain fungal cultures of the pleural fluid in all such patients. The complement-fixation test is the most widely used test for the serologic diagnosis of blastomycosis; however, its clinical value is limited because fewer than 25% of culture-proven cases are detected using this method (21). There is no commercially available skin test for blastomycosis.

Patients with pleural blastomycosis should be treated with itraconazole 400 mg/day for 6 months, ketoconazole 400 to 800 mg/day for 6 months, or amphotericin B with a total dose of 2 g. It appears that the treatment of choice is itraconazole (12,22), which cures virtually all immunocompetent individuals with pulmonary blastomycosis. Amphotericin B remains the drug of choice for all forms of blastomycosis in the immunosuppressed host (12,22).

COCCIDIOIDOMYCOSIS

Coccidioides immitis is an infectious fungus endemic to southwestern United States, particularly the San Joaquin Valley in California. The disease is acquired by inhaling the light, fluffy, and infectious arthrospores produced by the mycelial form growing in appropriate soil. Once inhaled, the arthrospores develop into the yeast form that produces disease in humans. Pleural disease of two types occurs in association with coccidioidomycosis (23). The first type is a pleural effusion associated with the primary benign

infection and may or may not have concomitant parenchymal involvement. The second type occurs when a coccidioidal cavity adjacent to the pleura ruptures to produce a hydropneumothorax with a bronchopleural fistula.

Primary Infection

The pleura is frequently involved in primary infections with *C. immitis*. As many as 70% of patients have pleuritic chest pain, and approximately 20% have blunting of the costophrenic angles radiologically (24). Approximately 7% of all symptomatic patients with primary coccidioidomycosis have pleural effusions (24). However, on one study (25), 22 of 146 patients (15%) hospitalized with coccidioidomycosis had a pleural effusion. Patients with pleural effusions secondary to coccidioidomycosis are almost always febrile, and more than 80% have pleuritic chest pain (24). Approximately 50% of patients have either erythema nodosum or erythema multiforme (24). The chest radiograph reveals parenchymal infiltrates in addition to the pleural effusion in approximately 50% of patients. The pleural effusion varies in size, but it often occupies more than 50% of the hemithorax (24). In one series of 28 patients, all pleural effusions were unilateral (24).

Pleural fluid analysis reveals an exudate that usually contains predominantly small lymphocytes (24). Although approximately 50% of patients have peripheral eosinophilia, pleural fluid eosinophilia is uncommon and occurred in only 1 of 15 patients in one series (24). However, in another series (25) the mean percentage of eosinophils in the pleural fluid was 10.3%. The pleural fluid glucose level is almost always above 60 mg/dL (24), and the pH is normal unless the patient has an empyema, which occurred in 5 of 15 patients (33%) in one series (25). The pleural fluid cultures are positive for *C. immitis* in approximately 20% of patients, but cultures of pleural biopsy specimens are positive in almost all patients (24). In one series, eight of eight pleural biopsy cultures were positive, and cocci spherules were identified in six of eight specimens (24). The pleural biopsy may reveal caseating or noncaseating granulomas (24). The cocci skin tests are usually positive, and the mean complement fixation (CF) titer 6 weeks after the onset of symptoms is 1:32 (24).

Most patients with primary coccidioidomycosis and pleural effusion require no systemic antifungal therapy (24). In a series of 28 such patients, 23 (82%) recovered completely without specific therapy. Two patients with disseminated disease died within a short period, whereas the other three patients had minor complications and were treated with amphotericin B. Although the CF titers are high in patients with pleural coccidioidomycosis (24) and high (>1:16) CF titers are used by some as an indication of dissemination (26), patients with pleural coccidioidomycosis and high CF titers should be treated only if their skin tests are negative or if other evidence of dissemination exists. The treatment of choice is either itraconazole or amphotericin B (12). If the patient has a coccidioidal empyema, treatment should be with fluconazole or itraconazole plus tube thoracostomy (25).

Rupture of Coccidioidal Cavity

The second situation in which pleural disease occurs with coccidioidomycosis is when a coccidioidal cavity adjacent to the pleura ruptures into the pleural space to produce a bronchopleural fistula and a hydropneumothorax. Hydropneumothoraces develop in 1% to 5% of patients with chronic cavitary coccidioidomycosis and occasionally occur without a prior cavitation (23). Many patients who experience rupture of a coccidioidal cavity have no history of coccidioidomycosis (27). Accordingly, in endemic areas, all patients with spontaneous hydropneumothoraces should be evaluated for the possibility of coccidioidomycosis.

When a coccidioidal cavity ruptures into the pleural space, the patient usually becomes acutely ill, with systemic signs of toxicity. The pleural fluid cultures are usually positive for *C. immitis* and the CF tests are almost always positive (27). In one case report, the pleural fluid glucose was 0 mg/dL and the lactic acid dehydrogenase was more than 3,500 U/mL (26). Patients with a hydropneumothorax should have a chest tube inserted immediately to drain the air and the fluid from the pleural space. They should also be given itraconazole or amphotericin B systemically. Most of them require additional surgery such as a partial lobectomy for control of the cavity. In one series of 23 patients, all but 2 required surgical treatment in addition to the tube thoracostomy (27). In view of this observation, it is recommended that patients who have a persistent bronchopleural fistula for more than 7 days be subjected to surgery.

CRYPTOCOCCOSIS

Cryptococcus neoformans, a fungus distributed worldwide, lives in soil, particularly that contaminated by

pigeon excreta. On rare occasions, infection with *C. neoformans* produces a pleural effusion. Until 1980, only 30 cryptococcal pleural effusions had been reported (28). With the advent of the acquired immunodeficiency syndrome (AIDS) epidemic, pleural effusions secondary to cryptococcosis have become much more frequent. In one series of 12 patients with pulmonary cryptococcal involvement proved by culture, 3 (25%) had a pleural effusion (29). In another series of 75 patients with AIDS and pleural effusion from Paris, 4 (5%) had pleural cryptococcosis (30). Pleural cryptococcosis appears to result from an extension of a primary subpleural cryptococcal nodule into the pleural space (31).

In patients with pleural cryptococcosis, the disease is localized to the hemithorax in approximately 50% and is disseminated in the remaining 50% (28). More than half the patients have serious underlying disease, most commonly leukemia, lymphoma, or AIDS (28,32). In 27 of the 30 cases reported up to 1980, the pleural effusion was unilateral (28) and most of the effusions associated with AIDS are also unilateral. The size of the pleural effusion ranges from minimal to massive (28). Most patients also have an accompanying parenchymal lesion in the form of a nodule, a mass, or an interstitial infiltrate (28). The pleural fluid is an exudate, usually with a predominance of small lymphocytes. In one case report (33), the pleural fluid adenosine deaminase level was elevated making the differentiation from tuberculous pleuritis difficult. One case report cited an effusion in which the pleural fluid contained 15% eosinophils (34). Cultures of the pleural fluid were positive in 11 of 26 patients in the 1980 series (28). In the remaining patients, the diagnosis was made by histologic study or by culture of lung tissue obtained at operation or autopsy (28). Patients with cryptococcal pleural effusion have high titers of cryptococcal antigen in their pleural fluid and serum (28).

It is not clear whether treatment with systemic antifungal agents is necessary for all patients with pleural cryptococcosis. Several patients have recovered without any specific therapy (28,35,36). Therefore, it is recommended that blood and cerebrospinal fluid (CSF) be studied for cryptococcal antigen. If cryptococcal antigen is detected in the CSF, the patient should be treated with amphotericin B and 5-fluorocytosine (37). If the cryptococcal antigen in the CSF is negative and the patient is symptomatic or the blood antigen is positive, then the patient should be treated with fluconazole (37). Immunosuppressed patients, such as those with AIDS, leukemia, lymphoma, diabetes mellitus, or sarcoidosis, and patients receiving corticosteroids or immunosuppressant agents should also be treated (37). If any of the foregoing conditions are met, it is recommended that the patient be treated with 400 mg/day of fluconazole for 6 months (22). On rare occasions in immunosuppressed individuals, the pleural infection is so overwhelming that tube thoracostomy is indicated (38).

HISTOPLASMOSIS

Histoplasma capsulatum is a fungus that lives in the mycelial form in soil and is distributed throughout the temperate zones of the world but is most heavily endemic in central United States (39). Infection with *H. capsulatum* only rarely produces pleural effusions. Although it has been estimated that 500,000 persons are infected annually in the United States (39), fewer than 20 pleural effusions secondary to histoplasmosis have been reported. In a review of the radiographic manifestations of pulmonary histoplasmosis, only 1 patient of 259 with abnormal chest radiographs had a pleural effusion (40).

Patients with pleural effusions secondary to histoplasmosis usually have a subacute illness characterized by a low-grade fever and pleuritic chest pain. The chest radiograph usually reveals an infiltrate or a subpleural nodule in addition to the pleural effusion (41–44). Pleural fluid analysis reveals an exudate containing predominantly lymphocytes. In two of the reported cases (41,43), pleural fluid eosinophilia was present. The pleural biopsy may reveal noncaseating granulomas. The diagnosis is made by culturing *H. capsulatum* from the pleural fluid, sputum, or biopsy material by routine fungal cultures or by demonstrating the organism in biopsy material with appropriate stains. A presumptive diagnosis can sometimes be established by demonstrating a high histoplasmosis CF titer (>1:32) or an M band on counterimmunoelectrophoresis (45). It appears that treatment is not necessary for pleural effusions secondary to histoplasmosis (42,44,46). The pleural effusion usually resolves spontaneously over several weeks (41,42,47). On rare occasions, however, a patient develops a fibrosing pleuritis for which a decortication should be considered if the patient is symptomatic (42,48).

An isolated pleural effusion due to infection with *H. capsulatum* has been reported in a patient with AIDS (49). This patient presented with fever and bilateral small pleural effusions. Thoracentesis revealed an exudate with many organisms typical of *H. capsulatum* on the Wright-Giemsa stain of the

pleural fluid. This patient appeared to respond to therapy with amphotericin B (49). Pleural effusions can also occur in patients with AIDS and disseminated histoplasmosis (50), but pleural involvement is not a prominent part of the disease picture.

On rare occasions, patients with parenchymal histoplasmosis may develop a bronchopleural fistula with the subsequent development of a loculated fungal empyema (51). Such patients should be treated with drainage and decortication.

CANDIDIASIS

On occasion, pleural fluid cultures are positive for candida. Pleural infection with candida usually occurs because of a leak from the gastrointestinal tract and often occurs in the postoperative period (52,53). There is coinfection with bacteria in most patients. In patients with pleural infection with candida, the possibility of esophageal perforation should always be suspected (see Chapter 18). The most important aspect in the treatment of these patients is to repair the esophageal perforation if one is present. In addition, appropriate antibiotics should be administered and purulent fluid should be drained through percutaneous catheter drainage (52). For antifungal therapy both conventional amphotericin B (0.7 mg/kg daily) and fluconazole (400 mg daily) are options suggested in the 2004 Infectious Diseases Society of America (IDSA) guidelines (54).

ACTINOMYCOSIS

Actinomyces israelii, an anaerobic or microaerophilic gram-positive bacterium, is a normal inhabitant of the mouth and oropharynx. Although this organism and *Nocardia asteroides* are actually bacteria, they are usually grouped with fungi because they cause chronic illness.

Clinical Manifestations

Actinomycosis is characterized by the formation of abscesses and multiple sinus tracts (55). The infection arises from endogenous sources such as infected gums, infected tonsils, or carious teeth (55). The pleura is involved in more than 50% of patients with thoracic actinomycosis. In one series of 15 cases of this disorder, 6 patients had pleural effusions, and an additional 6 patients had marked pleural thickening (56). The pleura is particularly likely to be thickened in areas where parenchymal actinomycosis has extended through the chest wall to produce a chest wall abscess or a draining sinus. In a more recent series using computed tomography (CT) scans, pleural effusions were present in five of eight patients (62.5%) with actinomycosis, although there was only enough pleural fluid for thoracentesis in three (57). Pleural thickening was demonstrated with CT scans in all eight of the patients in this latter series (57).

The pleural fluid with actinomycosis may be either frank pus with predominantly polymorphonuclear leukocytes (58) or serous fluid with predominantly lymphocytes (59). I have seen a patient with thoracic actinomycosis in which the associated pleural effusion was serous and contained more than 50% eosinophils.

Diagnosis

The diagnosis of thoracic actinomycosis should be suspected in any patient with a chronic infiltrative pulmonary disease, particularly when the parenchymal disease crosses lung fissures. The presence of chest wall abscesses or draining sinus tracts suggests the diagnosis, as do bone changes consisting of periosteal proliferation or bone destruction (56). Thoracic actinomycosis sometimes becomes disseminated and produces peripheral abscesses in the skin, subcutaneous tissues, or muscles (60). The diagnosis is suggested by the presence of sulfur granules in the draining exudate or the pleural fluid. These granules are 1 to 2 mm in diameter and consist of clumps of thin bacterial filaments that possess peripheral radiations with or without clubbing at their ends. Sulfur granules may be associated with cutaneous nocardiosis, but their presence in viscera only occurs in actinomycosis.

Gram's stains of the exudate should be carefully examined for the presence of the slender, gram-positive, long-branching filaments characteristic of actinomycosis (60). The definitive diagnosis is established with the demonstration of *A. israelii* by anaerobic cultures. The diagnosis of thoracic actinomycosis cannot be established from cultures of expectorated sputum or bronchoscopic washings because *A. israelii* can frequently be cultured from such specimens in the absence of invasive disease. Bacterial culture of the pleural fluid frequently reveals other organisms in addition to *A. israelii* (58,60). The organism most commonly isolated is *Actinobacillus actinomycetemcomitans*, a gram-negative aerobic coccobacillus (60). It has been suggested that the aerobic actinobacillus

reduces the oxygen level in the lesion to facilitate the growth of *A. israelii* (60).

Treatment

The cornerstone of treatment of actinomycosis is the administration of high doses of antibiotics for prolonged periods. Penicillin is the antibiotic of choice, and a dose of 10 million units per day for 4 to 6 weeks is recommended, followed by 12 to 18 months of therapy with oral penicillin phenoxymethyl potassium (60). Tetracycline, erythromycin, lincomycin, and clindamycin have been used successfully in the treatment of patients with actinomycosis and a history of penicillin hypersensitivity. The management of the pleural effusion in patients with actinomycosis is similar to that of patients with any other type of bacterial pneumonia (see Chapter 12). If the pleural fluid is serous and contains predominantly lymphocytes or eosinophils, the insertion of chest tubes is not necessary. Alternately, if the pleural fluid is frank pus, tube thoracostomy should be performed (61). Decortication is sometimes necessary for resolution of the process (58).

NOCARDIOSIS

Nocardia asteroides is an aerobic, gram-positive, filamentous bacterium that has a worldwide distribution and can be cultured from the soil (62).

Clinical Manifestations

The disease produced by this organism is similar to actinomycosis, but there is less abscess and sinus tract formation and more hematogenous dissemination with nocardiosis (55). Nocardiosis also has a greater propensity to occur in patients with AIDS and other immunosuppressed patients than does actinomycosis. Because most patients who develop nocardiosis are immunosuppressed (63), the incidence of nocardiosis is increasing because there are more immunosuppressed patients due to AIDS, organ transplantation, and chemotherapy. The lung is involved in approximately 75% of patients with nocardiosis (64), and as many as 50% of patients with pulmonary nocardiosis have a pleural effusion (50,65,66). Patients with pleural effusions secondary to nocardiosis usually have associated parenchymal infiltrates (64,65,67). The pleural fluid is an exudate, which can range from serous fluid to frank pus. Pleural fluid cultures may or may not be positive for *N. asteroides*.

Diagnosis

The diagnosis of nocardiosis should be suspected in patients with subacute or chronic pulmonary infiltrates and pleural effusion, particularly if the patient is immunosuppressed. Support for the diagnosis is obtained from a Gram's stain of sputum, bronchoscopic washings, or pleural fluid revealing the typical gram-positive, branching, filamentous bacteria or from an acid-fast stain revealing variably acid-fast, filamentous bacteria (62). The definitive diagnosis is made by the demonstration of *N. asteroides* with aerobic bacterial cultures of the sputum, bronchoscopic washings, or pleural fluid. Because *N. asteroides* is a slow-growing organism, when nocardiosis is suspected, the bacterial cultures must be flagged so that they can be maintained for at least 2 weeks (67). Not all patients with positive sputum cultures for *N. asteroides* have nocardiosis. In a series of 20 patients with positive sputum cultures for *N. asteroides*, 9 of the patients (45%) did not have radiographic abnormalities (68).

Treatment

The cornerstone of treatment for nocardiosis is the administration of sulfonamides. The preferred agent for treating nocardiosis is trimethoprim–sulfamethoxazole at a dose of 15 mg/kg/day in two to four divided doses (69). Antimicrobial susceptibility testing is strongly recommended; however, few laboratories can routinely do this testing. Alternative agents include imipenem, amikacin, minocycline, and ceftriaxone (69). The medications are continued for at least 6 weeks after the disease is completely cleared, and lifelong therapy has been recommended by some (64). The recommended management of the pleural effusion with nocardiosis is the same as the management of the pleural effusion with actinomycosis (see the discussion on actinomycosis in this chapter).

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chapter 15

Pleural Effusion Due to Parasitic Infection

Pleural effusions secondary to parasitic infections are uncommon in the United States, but in some countries, they account for a sizable percentage of all pleural effusions. With worldwide travel being more prevalent, one can anticipate that the incidence of pleural effusions secondary to parasitic disease will gradually increase in the United States.

AMEBIASIS

Amebiasis, the disease caused by *Entamoeba histolytica*, occurs throughout the world. Humans acquire the disease by ingesting the cyst, which is the infectious form of the organism. After ingestion by the host, eight daughter trophozoites develop and colonize the proximal large intestine. The trophozoites, which can proliferate, are the potentially invasive form. These trophozoites may migrate through the portal system to the liver, where the liberation of cytolytic enzymes gives rise to liver abscesses. The trophozoite can also revert to a cyst. When the cyst is passed in the stool, it can be ingested by another individual to complete the parasite's life cycle. Trophozoites can also be passed in the stool but are not infectious (1).

The prevalence of amebiasis is most dependent on the level of sanitation in the community, as would be expected from the life cycle of this parasite. Approximately 5% of the population in the United States are carriers. Amebiasis is most prevalent in southeastern United States, but the condition is reported with low frequency from every state. Amebic abscess is not unusual in the United States. For example, there were 30 patients seen with hepatic amebiasis at the Santa Clara Valley Medical Center in San Jose, California, during the period from 1981 to 1988. None of the patients, however, were born in the United States (2).

Pathogenesis

Pleural effusions arise by two mechanisms in association with amebic liver abscess. The first occurs when an amebic abscess produces diaphragmatic irritation and a sympathetic pleural effusion in a manner analogous to that seen with pyogenic liver abscesses (3,4) (see Chapter 18). Amebic liver abscesses also produce pleural effusions when the abscess ruptures through the diaphragm into the pleural space (3,4). In this situation, the pleural fluid is described as "chocolate sauce" or "anchovy paste" (1). Such pleural fluid does not contain purulent material but is rather a mixture of blood, cytolyzed liver tissue, and small solid particles of liver parenchyma that have resisted dissolution.

Clinical Manifestations and Diagnosis

The sympathetic effusion seen with amebic liver abscess is more common than rupture of an abscess through the diaphragm into the pleural space (2,3,5). Approximately 20% to 35% of patients with an amebic liver abscess will have a sympathetic pleural effusion (2). Patients with the sympathetic effusion frequently experience pleuritic chest pain referred to the tip of the scapula or the shoulder. Most patients have a tender enlarged liver (6). Eosinophilia is not associated with extraintestinal amebiasis. The level of alkaline phosphatase is elevated in more than 75% of patients, whereas the levels of transaminases are elevated in 50% (1). The chest radiograph reveals a pleural effusion of small-to-moderate size, often with a concomitant elevation of the hemidiaphragm and plate-like atelectasis at the base (2–4). The pleural fluid in this situation has not been well characterized, but is an exudate (2,5).

The diagnosis of amebiasis should be considered in all patients with right-sided pleural effusions for which no other explanation is obvious. Ultrasonic studies and computed tomography (CT) scan can demonstrate the hepatic abscess but cannot differentiate the pyogenic from amebic abscesses (7). The diagnosis is aided by the use of serologic tests. The sensitivity of antibody tests for *E. histolytica* is 95% for patients with extraintestinal amebiasis (8). Serology is limited as a diagnostic tool in highly endemic areas, as individuals will remain seropositive for years after an infection has cleared and seropositivity rates of greater than 25% may exist in some areas (8). Polymerase chain reaction (PCR) techniques are being more frequently used for the diagnosis of amebiasis but there is yet no standardized commercially available test (8).

Treatment

The treatment of choice is metronidazole, 500 to 750 mg t.i.d. orally, for 10 days (8). If the patient is dyspneic from the pleural effusion, a single therapeutic thoracentesis is usually sufficient to control the symptoms. More than 90% of patients can be cured with the aforementioned regimen. Catheter drainage adds no significant benefit to amebicidal therapy alone (1).

Transdiaphragmatic Rupture of Liver Abscess

The transdiaphragmatic rupture of an amebic liver abscess is usually signaled by an abrupt exacerbation of pain in the right upper quadrant and may be accompanied by a tearing sensation (3). These symptoms are followed by the development of rapidly progressive respiratory distress and sepsis, occasionally with shock (3). The pleural effusion is frequently massive, with opacification of the entire hemithorax and shift of the mediastinum to the contralateral side (3). The rupture is into the right pleural space in more than 90% of patients. The symptoms are sometimes subacute or chronic in nature (9). The diagnosis of amebic abscess with transdiaphragmatic rupture is suggested by the discovery of anchovy paste or chocolate sauce pleural fluid on diagnostic thoracentesis. Amebas can be demonstrated in the pleural fluid in fewer than 10% of patients. Concomitant rupture into the airways occurs in approximately 30% of patients (3), and this complication is usually manifested by the expectoration of chocolate sauce sputum that may be confused with hemoptysis by the patient and the physician.

The diagnosis is established by the characteristic appearance of the pleural fluid and can be confirmed by serologic tests for amebiasis. Ultrasound or CT scanning of the abdomen can delineate the extent of the intrahepatic disease and the presence or absence of a subphrenic abscess. Patients with transdiaphragmatic rupture should be treated with the same drugs as patients with sympathetic pleural effusions due to amebic hepatic abscess. Patients with transdiaphragmatic rupture should also undergo percutaneous drainage of both the liver abscess and the collection of material in the pleural space. The drainage can be accomplished with small tubes (12 to 14 F) (10). The combination of the drugs and the percutaneous drainage tubes results in clinical cure in almost all patients (10).

Approximately one third of patients with transhepatic rupture also have a bacterial infection of their pleural space (4,9). Such patients should be treated with the appropriate antibiotics. In addition, an open-drainage procedure or decortication is frequently necessary, indications for which are outlined in Chapter 12. In patients who undergo decortication, the visceral pleura is found to be covered with a thick membrane (9), but this membrane can easily be stripped off the visceral pleura (9). Even when no bacterial superinfection is present, decortication should be performed if the lung has not fully expanded in 10 days (9). The prognosis with transdiaphragmatic rupture is excellent if the patient is not too debilitated initially or if the diagnosis is not delayed (3,4,9).

ECHINOCOCCOSIS (HYDATID DISEASE)

Echinococcosis is caused by the tapeworm *Echinococcus granulosus.* The definitive host for this small tapeworm is the dog or wolf. When dog feces containing the parasite's eggs are ingested by humans, larvae emerge in the duodenum, enter the blood, and usually lodge in either the liver or the lung. In these tissues, the parasite grows gradually, and years may pass before symptoms appear. It takes approximately 6 months for the cyst to reach a diameter of 1 cm and thereafter it increases in size by 2 to 3 cm/year (11). The dog becomes infected by eating meat containing the larvae. Echinococcosis is seen in most sheep- and cattle-raising areas of the world including Australia, New Zealand, Argentina, Uruguay, Chile, parts of Africa, Eastern Europe, and the Middle East. The disease is particularly common in Turkey, Lebanon, and Greece.

Pathogenesis

Pleural involvement with hydatid disease can occur in one of four situations (12,13): (a) a hepatic hydatid cyst or, on rare occasions, a splenic cyst may rupture through the diaphragm into the pleural space; (b) a pulmonary hydatid cyst may rupture into the pleural space; (c) on rare occasions, the pleura may be primarily involved by the slowly enlarging cyst (12); or (d) a pulmonary or hepatic hydatid cyst may be accompanied by a pleural effusion (14–16). The incidence of pulmonary and hepatic cyst rupture into the pleural space is equivalent (12). Fewer than 5% of hepatic (12,13) or pulmonary hydatid cysts (16) are complicated by intrapleural rupture. Approximately 5% of patients with a hepatic or a pulmonary hydatid cyst have a pleural effusion (14). The pleural fluid has been described as an exudate (16) which can be eosinophilic (17).

Patients who are being treated medically for hydatid cysts may develop pleural complications. In one retrospective study, 11 of 36 patients who were treated medically developed pleural complications (18). All the patients who developed complications had cysts that exceeded 6 cm in diameter. The complications included pleural empyema in seven and pulmonary abscess with pleural fluid in four (18). The authors of the article recommended that large pulmonary hydatid cysts should not be treated medically (18).

Clinical Manifestations and Diagnosis

When a hepatic cyst ruptures into the pleural space, the patient usually becomes acutely ill, with sudden tearing chest pain, dyspnea, and shock from the antigenic challenge to the body (19). In approximately 50% of patients with rupture into the pleural space, simultaneous rupture into the tracheobronchial tree occurs (19). Such patients may cough up large quantities of pus and membranes of the cyst. When a pulmonary cyst ruptures into the pleural space, similar symptoms are frequently present. In addition, a bronchopleural fistula often produces a hydropneumothorax that may become secondarily infected.

The diagnosis of pleural echinococcosis is established by the demonstration of echinococcal scolices with hooklets in the pleural fluid (20). A CT scan demonstrating multiple round cysts is suggestive of the diagnosis (21). Most patients who have a ruptured hydatid cyst have a hydropneumothorax (16). An occasional patient will even have a tension hydropneumothorax (22). Eosinophils are frequently present in the pleural fluid unless it becomes secondarily infected (13,20). The Casoni skin test is positive in approximately 75% of patients (19), and the Weinberg complement fixation (CF) test is positive in a higher percentage.

Treatment

Attempts should be made to remove the cyst in patients with hydatid disease. In the past, all thoracic cysts have been removed through thoracotomy. However, it appears that the cysts can be removed by percutaneous catheter drainage (23) or thoracoscopy (24).

An immediate thoracotomy is recommended for patients who have rupture of a hepatic cyst into the pleural space (19). When a hepatic cyst has ruptured, the objectives of surgical treatment are to remove the parasite, to drain the hepatic cavity, and to reexpand the lung immediately (19). If the surgical procedure is delayed, a decortication may also be required (19). An exploratory thoracotomy should also be performed when a pulmonary hydatid cyst ruptures into the pleural space, to remove the parasite, to excise the original cyst, and to close the bronchopleural fistula. Patients with hydatid cysts should be treated with antiprotozoal therapy if all the cysts cannot be removed or when rupture of a cyst has occurred. The treatment of choice is albendazole, 400 mg b.i.d. over 28 days (25).

PARAGONIMIASIS

Paragonimiasis is caused by the lung flukes *Paragonimus westermani*, *Paragonimus miyazakii* (26), *Paragonimus heterotremus* (27), and *Paragonimus kellicotti* (28) which have a fascinating life cycle. Humans acquire the disease by eating raw or undercooked crabs or crayfish containing the larvae of these parasites (29,30). Once ingested, the larvae bore through the intestinal wall and enter the peritoneal cavity. They then migrate upward in the peritoneal cavity to the diaphragm, bore through the diaphragm, and then, after traversing the pleural space, bore through the visceral pleura and enter the lung (29,30). In the lung, the larvae lodge near small bronchi and mature into the adult lung flukes that persist in the lungs for years while producing approximately 10,000 eggs daily. The eggs produced by the mature flukes are expectorated or are swallowed and excreted in the feces. Once in water, the eggs develop into ciliated miracidia that infect freshwater snails. Another larval

form develops in the snails and is eventually liberated as cercariae that penetrate crayfish and crabs, to complete the cycle (29,30).

Pathogenesis and Incidence

The pleural disease associated with paragonimiasis is thought to arise when the parasites traverse the pleural space and penetrate the visceral pleura. Pleural disease is common with paragonimiasis (31,32). In a series of 71 cases of pleuropulmonary paragonimiasis from Korea, 43 patients (61%) had pleural disease including 26 with pleural effusions, 12 with hydrothorax, and 5 with pleural thickening (32). Twelve of these patients had bilateral pleural effusions or hydrothoraces (32). In another series from Japan, 9 of 13 patients (69%) had a pleural effusion (31). The prevalence of pleural disease was less in a more recent study of 31 patients from Korea who underwent chest CT scans (33). In this study, only nine patients (29%) had pleural disease that included six pleural effusions, two hydropneumothoraces, and one pneumothorax (3).

Although paragonimiasis is confined mainly to residents of the Far East, there was an increased incidence of this disease in the United States in the 1980s with the influx of refugees from Southeast Asia (29,34). Johnson and Johnson (34) reported a series of 25 cases of paragonimiasis that occurred in Indo-Chinese refugees between March 1980 and December 1982. Seventeen cases occurred in Minneapolis, whereas eight cases occurred in Seattle (34). Twelve of the patients (48%) had pleural effusions. The effusions were bilateral in three individuals and were massive in six. Non-Asian individuals in the United States have developed paragonimiasis from ingesting infected crayfish (35) or crabs (36). Indeed between July 2006 and September 2010, nine patients in Missouri developed paragonimiasis after eating raw or undercooked crayfish and all had a pleural effusion (28).

Diagnosis

The diagnosis of pleural paragonimiasis should be suspected in Asian patients or in patients with a pleural effusion who have recently traveled to the East. The diagnosis of paragonimiasis is made either by detecting eggs in sputum, stool, fluid from bronchoscopic lavage, or biopsy specimens, or by a positive anti-Paragonimus antibody test (29). Enzyme-linked immunosorbent assay (ELISA) is highly sensitive and specific in detecting antibodies, whereas eggs are demonstrable in less than 50% of cases (32).

The characteristics of the pleural fluid are virtually pathognomonic for paragonimiasis. The pleural fluid with paragonimiasis is an exudate with a low glucose level (<10 mg/dL), a low pH (<7.10), and a high lactic dehydrogenase (LDH) level (>1,000 IU/L) (29,34). Pseudochylothorax with cholesterol crystals in the pleural fluid occurs frequently with pleural paragonimiasis (37). Most patients with pleural paragonimiasis have significant eosinophilia in their pleural fluid (26,34,38,39). In patients with pleural paragonimiasis the pleural fluid interleukin 5 levels are markedly elevated and correlate with the percentage of eosinophils in the pleural fluid (39). The only other disease that produces an eosinophilic exudate with a low glucose level and a low pH is the Churg-Strauss syndrome (40).

Yokogawa et al. (26) reported that pleural fluid immunoglobulin E (Ig-E) levels are elevated and are higher than the simultaneous serum IgE levels in patients with pleural paragonimiasis. Subsequently Ikeda et al. (41) used ELISA to measure *P. westermani*-specific IgE and IgG in seven patients. They reported that the levels of parasite-specific IgE and IgG were significantly higher in the pleural effusion than in the serum in all patients (41). This latter study suggests that measurement of parasite-specific IgE and IgG is useful diagnostically and indicates that these antibodies are produced in the pleural space.

Treatment

The treatment of choice is praziquantel, 25 mg/kg body weight three times a day for 3 days. If symptoms relapse, retreatment with praziquantel should be considered (42). Bithionol, 35 to 50 mg/kg on alternate days for 10 to 15 doses, is also effective, but its toxic gastrointestinal effects can be troublesome (41). If pleural disease has been present for such a prolonged period that the pleural surfaces are abnormally thickened, penetration of the drugs into the pleural space is insufficient to eradicate the infection, and thoracotomy with decortication may be necessary (29,43).

OTHER PARASITIC INFECTIONS

Pleural disease due to other parasites is uncommon. A rare patient with *Pneumocystis carinii* pneumonia has a pleural effusion, but the effusion hardly ever dominates the clinical picture. Because *P. carinii* infection usually occurs in patients with acquired immunodeficiency syndrome, this entity is discussed in Chapter 16. Patients who die from malaria

frequently have pleural effusions (6). The pleural effusions in this circumstance are probably secondary to the pulmonary edema and have little, if any, clinical significance (5). There have been case reports of pleural effusions due to *Strongyloides sterocoralis* (44), *Trichomonas* (45), *Toxocara canis* (46), loiasis (47), gnathostomiasis (48), anisakiasis (49), toxoplasmosis (50), and sporotrichosis (51).

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chapter 16

Pleural Effusion Due to Acquired Immunodeficiency Syndrome, Other Viruses, *Mycoplasma Pneumoniae*, and Rickettsiae

Over the last three decades, the acquired immunodeficiency syndrome (AIDS) epidemic has had a profound impact on the practice of medicine. Accordingly, the first part of this chapter deals with pleural effusions in patients with AIDS. Because the organism responsible for AIDS is a virus, pleural diseases due to viruses are included in this chapter. Additionally, the pleural effusions resulting from infection with *Mycoplasma pneumoniae*, ehrlichia, and the rickettsial diseases, Q fever, and Rocky Mountain spotted fever are discussed in this chapter because they produce clinical pictures simulating viral pneumonias.

PLEURAL EFFUSIONS IN PATIENTS WITH AIDS

Pleural effusions are not uncommon in patients with AIDS. In one series of 1,225 consecutive hospital admissions of patients with AIDS in Jacksonville, Florida, the incidence of pleural effusion was 14.6% (1). In an older series from Metropolitan Hospital Center in New York, the incidence was 1.7% in a series of 4,511 hospitalized human immunodeficiency virus (HIV)-positive patients (1). The distribution of the diseases responsible for pleural effusions in patients with AIDS varies widely from series to series. In the series of 160 patients from Jacksonville, the five leading causes of pleural effusions were pneumonia and empyema (33%), renal failure (9%), hypoalbuminemia (8%), tuberculosis (6%), and pancreatitis (4%) (1). In a second, older series of 61 patients from Paris, 52% of the effusions were due to Kaposi's sarcoma (KS) (2), 18% had aerobic bacterial infections, 15% had tuberculosis, 10% had opportunistic infections, and 5% had effusions due to other malignancies (2). In a third series from Rwanda (3), tuberculosis was responsible for the pleural effusion in 82 of 91 (90%) of patients who were HIV positive.

Kaposi's Sarcoma

KS is one of the more common causes of a pleural effusion in patients with AIDS. KS occurs almost exclusively in male homosexual patients with AIDS (4). Human herpesvirus 8 (HHV-8) is associated with the development of this malignancy. Although HHV-8 is necessary, additional factors not yet fully delineated need to be present for a person to develop KS (5,6). It is thought that HHV-8 is particularly likely to be spread by male homosexual contacts. In the past, KS occurred in 20% to 25% of individuals with AIDS (4). In recent years, there has been a precipitous decline in the prevalence of KS (5). For example, in the state of Washington, the prevalence of KS in the homosexual HIV-positive population was 6% in 1990, but had fallen to 2% by 1997 and apparently has fallen more in the next 3 years (5). It is likely that the decrease in the prevalence of KS is, at least in part, related to the introduction of the highly active antiretroviral therapy (HAART) (5).

Cutaneous violaceous plaques are the most common presentation of KS. At autopsy, 50% to 75% of patients with cutaneous KS have pulmonary involvement (5), but clinically apparent pulmonary involvement is less common during life (5). Most patients

with pleuropulmonary KS present with progressive shortness of breath, nonproductive cough, and fever. Patients with pulmonary KS generally have abnormal chest roentgenograms characterized by bilateral infiltrates (4). The incidence of pleural effusion with pulmonary KS is approximately 50% (4). Most patients with a pleural effusion due to KS also have bilateral parenchymal infiltrates (4). The pleural effusions may be unilateral or bilateral. Bilateral pleural effusions, focal airspace consolidation, intrapulmonary nodules and/or hilar adenopathy are very suggestive of KS (7). The computed tomography (CT) scans are somewhat characteristic with KS. In a review of 53 patients with pulmonary KS, 42 patients (79%) had nodules, 35 (66%) had bronchovascular bundle thickening, 28 (53%) had tumoral masses, and 29 (55%) had pleural effusions (8). The effusions were bilateral in 40 (76%) and were usually at least medium sized (8). Autopsy studies demonstrate multiple cherry red to purple lesions on the visceral surface but not on the parietal pleural surface (4).

The pathogenesis of the pleural effusions in KS is not conclusively defined. Approximately 20% of the pleural effusions with KS are chylothoraces, and, in these instances, the pleural effusion is probably due to involvement of the thoracic duct by the sarcoma (4). In the remaining patients, lymphatic blockade is probably not the responsible mechanism because the lymphatic drainage of the pleura is through the parietal pleura and KS does not involve the parietal pleura. It has been hypothesized that the effusion is due to the elaboration of vascular endothelial growth factor (VEGF) by the tumor (9). VEGF increases the permeability of the microvessels and is present in large quantities in AIDS-KS cell–derived conditioned media (10).

The diagnosis of pulmonary KS is usually established at bronchoscopy, which demonstrates erythematous or violaceous macules or papules in the respiratory tree (11). It is important to remember that many patients with pulmonary KS have a coexisting opportunistic infection (5). If the CT scan reveals ground-glass opacities, alternative diagnoses must be sought (8). The definitive diagnosis of pleural KS is not easy and is virtually one of exclusion. The pleural fluid is an exudate that is usually serosanguineous or hemorrhagic. The differential cell count shows a mononuclear cell–predominant pattern (4). In one series of 10 patients, the pleural fluid glucose and pH levels were normal in 9 patients but were reduced to 63 mg/dL and 7.02, respectively, in 1 patient (4). Cytologic examination of the pleural fluid is not helpful because the diagnosis requires a characteristic architectural appearance and not a particular neoplastic cell type (12). Mesothelial cells from patients with KS are infected with the HHV-8 virus (13). Needle biopsy of the pleura does not establish the diagnosis of KS because the parietal pleura is not involved (4). It is probable that the diagnosis could be established with thoracoscopy given the characteristic appearance of the KS lesions on the visceral pleura (4).

The prognosis of a patient with pleuropulmonary KS is poor. In one study, the average interval from diagnosis of pulmonary KS to death was 4 ± 3 months (4). The presence of the pleural effusion is a significant problem for many patients with pleuropulmonary KS. In one series, recurrent, massive, progressive effusions dominated the final days of a substantial percentage of patients and contributed significantly to the death of approximately 50% (4).

The treatment of the pleural effusion associated with KS is difficult. Tube thoracostomy with the instillation of tetracycline is usually not successful (4). If the diagnosis is made with thoracoscopy, pleural abrasion or parietal pleurectomy is probably the treatment of choice. Otherwise, the best alternatives are probably the insertion of a pleuroperitoneal shunt or an indwelling catheter (e.g., PleurX).

Primary Effusion Lymphoma

This rare lymphoma occurs almost exclusively in patients with HIV infection and is discussed in Chapter 11.

Parapneumonic Effusion and Empyema and AIDS

Community-acquired bacterial pneumonia (CAP) occurs frequently in patients with AIDS. It appears that patients with AIDS are probably more likely to develop pleural complications with their pneumonias than are other patients because they are more likely to have bacteremia with their pneumonia (14). Moreover, once there are bacteria in the pleural space, patients with low $CD4^+$ counts probably have more trouble clearing the bacteria. When *Staphylococcus aureus* bacteria are injected intrapleurally in $CD4^+$ knockout mice, there is a decreased pleural chemokine response, decreased neutrophil influx into the pleural space, and impaired bacterial clearance from the pleural fluid (15). In one series of 81 cases of community-acquired pneumonia, pleural effusion occurred in 21 (26%) patients (14). The pleural fluid was culture positive in 11 of these 21 (52%) patients. However, in a

more recent study of 1,415 patients hospitalized with HIV-associated CAP from 1995 to 1997 at 86 hospitals in seven metropolitan areas, the prevalence of pleural effusion was only 7.8% and the presence of a pleural effusion was not associated with a higher mortality (16). The distribution of organisms responsible for CAP in AIDS is similar to that of patients without AIDS (14). The management of the patient with AIDS and a parapneumonic effusion or an empyema is the same as that for any patient with a parapneumonic effusion (see Chapter 12). HIV-positive patients with empyema and $CD4^+$ counts less than 200/mm^3 more commonly have complex empyemas that require open decortication and drainage (17).

Pneumocystis jiroveci Pneumonia and AIDS

Although pleural effusions due to *Pneumocystis jiroveci* account for only a small percentage of pleural effusions in patients with AIDS, they do occur. By 1993, a total of seven cases of pleural effusion due to *P. jiroveci* infection had been reported (18,19). In most cases, the diagnosis was established by visualization of Pneumocystis in pleural fluid stained with Gomori methenamine silver. All seven of the reported patients were receiving aerosolized pentamidine, and five of the seven had documented underlying *P. jiroveci* pneumonia. Two patients presented with primary pleural infection with Pneumocystis. It appears that Pneumocystis pleural disease is an anatomic extension of smoldering subpleural Pneumocystis pneumonia, and the prognosis is not worse than with pneumonia alone. Four of the seven patients with pleural Pneumocystis also had a bronchopleural fistula (18).

The pleural fluid is an exudate with pleural Pneumocystis. The pleural fluid lactate dehydrogenase (LDH) has been higher than 400 IU/L, and the ratio of the pleural fluid to serum LDH level has exceeded 1:0. Interestingly, the pleural fluid protein level has been below 3.0 g/dL, and the ratio of the pleural fluid to the serum protein has been below 0:50 in all patients. The pleural fluid glucose and pH levels are not reduced, and the differential cell count can reveal either neutrophils or mononuclear cells (18). The treatment of pleural Pneumocystis is the same as that of pulmonary Pneumocystis.

Tuberculous Pleural Effusions and AIDS

In some series, tuberculosis is the most common etiology for pleural effusions associated with AIDS (3). The clinical picture of tuberculous pleuritis in patients with and without AIDS is similar, but there are some differences. In patients with tuberculosis, some reports have demonstrated that a higher percentage of patients with AIDS have a pleural effusion (20), whereas others report a similar incidence (21). The percentage of cases of tuberculosis that have pleural effusions in patients with AIDS is higher in patients with $CD4^+$ counts above 200 than in those with $CD4^+$ counts below 200/mm^3 (22).

The purified protein derivative (PPD) skin test is less frequently positive in patients with AIDS who have tuberculous pleuritis. In one series of patients with tuberculous pleuritis, the PPD was positive in 76% of patients without AIDS but in only 41% of patients with AIDS (23). The lower the $CD4^+$ count, the less likely the PPD is to be positive. HIV-positive patients have a lower percentage of $CD4^+$ lymphocytes and a higher percentage of $CD8^+$ lymphocytes in their pleural fluid than do HIV-negative patients with tuberculous pleuritis (24). In patients without AIDS, the pleural fluid acid-fast bacilli (AFB) stain is only rarely positive (~1%), but in one series, the AFB pleural fluid smear was positive in 15% of patients with AIDS (23). In another series, the pleural fluid smear was positive in 37% of patients with AIDS and a $CD4^+$ count less than 200/mm^3 (25). The pleural fluid cultures for AFB are more likely to be positive in patients with AIDS. In one study, the pleural fluid culture was positive in 75% and 24% of the HIV-positive and HIV-negative patients with BACTEC, respectively; with Lowenstein-Jensen medium, comparable numbers were 43% and 12%, respectively (26). The levels of pleural fluid interferon-gamma are higher in HIV-positive than in HIV-negative patients (24). The granuloma on pleural biopsy are less well formed in some patients with AIDS, and there are numerous AFB (27). Patients with poorly defined granuloma appear to respond less well to antituberculous therapy (27). The incidence of granuloma on pleural biopsy is comparable in patients with and without AIDS (23). The treatment of the patient with AIDS and tuberculous pleuritis is the same as the treatment of the HIV-negative individual. However, prednisone should not be given to the AIDS patient with tuberculous pleuritis because its administration is associated with a risk of developing KS (28).

Miscellaneous Pleural Effusion in Patients with AIDS

Other opportunistic diseases such as cryptococcosis (29), histoplasmosis (30), nocardiosis (31), and

atypical mycobacteria (32) are at times responsible for a pleural effusion in patients with AIDS. In their terminal stages, some patients with AIDS develop hypoproteinemia and this may lead to a transudative pleural effusion (33). Patients with AIDS may also develop hypervolemia owing to heart failure or renal failure, which can lead to a pleural effusion (34). In one series, pancreatitis was the fifth leading cause of pleural effusion in patients with AIDS (1). The diagnosis and management of pleural effusions due to these different entities are described in the appropriate chapters in this book.

Approach to the Patient with AIDS and Pleural Effusion

Patients with AIDS and pleural effusion should undergo a diagnostic thoracentesis. Studies on the fluid should include smears and cultures for bacteria, mycobacteria, and fungi; cytology with special consideration for primary effusion lymphoma; and either an interferon-gamma or an adenosine deaminase measurement for pleural tuberculosis. If the patient has a positive PPD (>5 mm) or if there are no mesothelial cells in the pleural fluid, chemotherapy with isoniazid and rifampin for 9 months is recommended. If the patient is receiving aerosolized pentamidine, silver stains of the pleural fluid should be obtained to rule out *P. jiroveci*.

If the diagnosis is not apparent after the thoracentesis and the patient has an exudative pleural effusion, what should be the next diagnostic procedure? Possible courses of action include a needle biopsy of the pleura, thoracoscopy, bronchoscopy, or observation. In general, a thoracoscopy is recommended, if any procedure is going to be done. With thoracoscopy one can establish the diagnosis of KS, other intrathoracic malignancies, tuberculous pleuritis, or other opportunistic pleural infections. In addition, a pleural abrasion or a partial parietal pleurectomy can be performed to prevent reaccumulation of the pleural fluid.

VIRUSES

Viral infections probably account for a larger percentage of pleural effusions than is generally realized. The diagnosis usually depends on isolation of the virus or the demonstration of a significant increase in the antibodies to the virus. Because most pleural effusions secondary to viruses are self-limiting, paired sera from patients in the acute and convalescent phases of disease are not usually obtained for diagnosis. Moreover, most hospitals are not equipped to culture viruses. In recent years, the diagnosis of more and more viral infections have been made by PCR (35). In one study (35) of patients with a positive PCR and symptoms of a lower respiratory tract infection, 19 of 91 patients (20%) had a pleural effusion.

The most interesting epidemic of pleural effusions attributed to viral infection occurred in Turkey in 1955, when 559 individuals at a military base developed a pleural effusion in conjunction with an acute illness characterized by fever, cough, malaise, anorexia, and shortness of breath (36). None of the patients had parenchymal infiltrates, but approximately 30% had an enlarged hilar shadow. The peripheral white blood cell (WBC) count was normal or reduced, with an increased percentage of lymphocytes. The differential WBC on the pleural fluid revealed mostly mononuclear cells. The disease was self-limited, and almost all patients recovered completely within 90 days. Because all bacterial cultures were negative, as were serologic tests for Q fever, and because the patients recovered without any specific therapy, it was concluded that the disease was due to a viral infection (36). This report is important because it documents that viral infections can cause pleural effusions and in large numbers. One wonders what fraction of undiagnosed pleural effusions is due to viral infections.

Small pleural effusions frequently accompany primary atypical pneumonia. Fine et al. (37) prospectively studied 59 patients with atypical pneumonia that satisfied serologic criteria for association with either a mycoplasma, viral, or cold-agglutinin–positive pneumonia. Twelve of these patients (20%) had small pleural effusions, and in four patients the effusions were evident only on the lateral decubitus radiographs. This finding compares with a 45% incidence of pleural effusions in patients with acute bacterial pneumonia (38). In the series of Fine et al. (37), 6 of 29 (21%) patients with *M. pneumonia*, 1 of 7 (14%) with adenoviral pneumonia, 1 of 4 (25%) with influenza pneumonia, and 4 of 19 (21%) with only increased titers of cold agglutinins had pleural effusions.

In patients with viral infections, the pleural effusions are usually small (36,37), but may occasionally be large (39). The pleural fluid is an exudate (37), and usually mononuclear cells are predominant on the pleural fluid differential WBC (36,40). I have seen a patient with a viral pneumonia, however, in whom the initial thoracentesis revealed predominantly

polymorphonuclear leukocytes, but a subsequent thoracentesis 48 hours later revealed predominantly mononuclear cells. The diagnosis of pleural effusions secondary to viral infections is established by documenting increasing titers with the specific serologic tests or by culturing viruses from the pleural fluid (40,41). At times, with pleural effusions secondary to herpes infections or cytomegalovirus, the cytologic findings in the pleural fluid, consisting of intranuclear inclusions and multinuclear giant cells with gelatinous nuclear changes, suggest the diagnosis (42,43).

Hantavirus Infections

The hantavirus pulmonary syndrome is due to infection with a previously unknown hantavirus species now called Sin Nombre virus. As of May 31, 1996, 139 cases had been confirmed from 24 states, representing all regions of the United States, with a mortality rate of 49.6% (44). An additional 12 cases had been reported from Canada (44). Most cases have occurred in the Four Corners Region, where New Mexico, Arizona, Colorado, and Utah meet. The deer mouse, *Peromyscus maniculatus*, has been identified as the likely principal reservoir of the Sin Nombre virus (45,46). There are several other hantaviruses that can produce a similar syndrome including the New York virus, which produces disease in New York State; the Bayou virus, which produces disease in Louisiana; and the Black Creek Canal virus, which produces disease in Florida and southeastern United States (47). Hantaviruses have also been recognized in several locations in South America (47).

The hantavirus pulmonary syndrome is characterized by a brief prodromal illness, followed by rapidly progressive, noncardiogenic pulmonary edema (45,46). The median age of infected individuals is approximately 30 years, and 50% of the patients have been Native American Indians (45). Most patients present with fever or chills, and gastrointestinal complaints such as nausea or vomiting, abdominal pain, or diarrhea. Most patients report myalgias and cough. Dyspnea tends to be a late-developing symptom, occurring just before respiratory decompensation.

Patients who present with the hantavirus pulmonary syndrome have many abnormal laboratory tests. They characteristically have the triad of thrombocytopenia, a left shift in the myeloid series, and large immunoblastoid lymphocytes. The Pao_2/Fio_2 is usually severely reduced, and 50% of the patients require mechanical ventilation. The chest radiograph of patients who progress to respiratory failure initially shows bibasilar infiltrates, which rapidly spread to include all four quadrants of the lung. The heart size is normal. Patients with the hantavirus pulmonary syndrome tend to decompensate rapidly with refractory hypoxemia and hypotension. The mean duration of hospitalization before death is only approximately 3 days.

Pleural effusions were common in the 23 patients seen at the University of New Mexico Hospital (44). At the time of admission, 21 of the 23 patients had pleural effusions. Effusions of similar size were present bilaterally in most patients. The maximum size of the effusion was achieved within 24 to 48 hours of admission. Three of the patients had effusions of sufficient size that chest tubes were inserted. A thoracentesis was performed in four of the patients. Although none of the fluids was very inflammatory, all four met exudative criteria with a pleural fluid LDH greater than two thirds of the upper normal serum limit. However, the pleural fluid protein level was below 2.5 g/dL in three of the four patients, and the pleural fluid WBC was below 200/mm^3 in all patients (44). At autopsy, patients dying of the hantavirus pulmonary syndrome have large serous effusions with severe edema of the lungs. It is probable that the pleural effusion results from interstitial fluid traversing the visceral pleura to the pleural space.

It is important to make the diagnosis of the hantavirus pulmonary syndrome early because antiviral therapy requires time to be beneficial. The diagnosis can be established by serologic tests for immunoglobulin M (Ig-M) and IgG antibody, which are usually demonstrated by enzyme-linked immunosorbent assay (ELISA) (47). The broad-spectrum antiviral agent ribavirin is active against hantavirus *in vitro*, but an open-label trial of intravenous ribavirin in patients with the hantavirus syndrome was inconclusive (47).

An animal model of the hantavirus syndrome has been described. When adult Syrian hamsters are exposed to the *Andes virus* (ANDV), a South American hantavirus, they develop a syndrome very similar to the hantavirus syndrome (48). Animals that died had a large volume (3–5 mL) pleural effusion.

Adenovirus Pneumonia

After *M. pneumoniae*, adenoviruses are the second leading cause of primary atypical pneumonia. Pleural effusions occur in 15% to 62% of patients with adenoviral pneumonia (49,50). The pleural effusions are usually bilateral, and most are moderate to large

in size. When adenovirus infection results in a pleural effusion, a concomitant parenchymal infiltrate is usually present (49,50).

Infectious Hepatitis

Pleural effusions occasionally occur in conjunction with infectious hepatitis and at times precede the development of icterus (40,51–55). In a review of 2,500 patients with viral hepatitis, 4 patients (0.16%) had pleural effusions (51). In another prospective study of 156 patients with hepatitis, however, 70% of the patients had at least a small pleural effusion (55). Patients with pleural effusions secondary to viral hepatitis do not have parenchymal infiltrates. The pleural fluid is an exudate with predominantly mononuclear cells (40,56). The pleural effusion frequently resolves before the hepatitis (52). One must be careful in handling pleural fluid when infectious hepatitis is suspected because the infectious hepatitis B e antigen has been demonstrated in pleural fluid secondary to hepatitis (54,56).

Epstein-Barr Virus and Infectious Mononucleosis

It appears that infection with the Epstein-Barr virus (EBV) can cause pleural effusions. The EBV infects more than 90% of the population worldwide and is able to establish a lifelong latent infection with intermittent reactivation to lytic replication (57). Primary infection usually occurs subclinically in infancy and childhood. Thijsen et al. (58) reported that the polymerase chain reaction (PCR) for the EBV was positive in 24 of 60 (40%) of pleural fluids including 20 of 34 (59%) with no etiology. The PCR in the serum was negative in 12 of the 18 fluids in which the pleural fluid PCR was positive. The pleural fluid PCR was also positive in pleural fluids from 15% of patients with another clear diagnosis (57). The possibility that EBV DNA came from latently infected B cells present in the fluid rather than from lytic replication could not be excluded. It is possible that many undiagnosed pleural effusions are due to EBV.

Infectious mononucleosis is due to infection with the EBV, and pleural effusions occasionally occur in the course of infectious mononucleosis (59–61). Lander and Palayew (59) reviewed the chest radiographs of 59 patients with infectious mononucleosis and reported that 3 (5%) had pleural effusions. Two of the patients had bilateral interstitial infiltrates and small bilateral pleural effusions, whereas the third patient had a moderate-sized, left-sided pleural effusion without any parenchymal infiltrates (59). The pleural effusions are exudates and usually take several months to resolve (60,61).

Dengue Hemorrhagic Fever

Dengue fever is caused by four antigenically distinct dengue viruses, and the disease is transmitted to human beings by mosquitoes. Classic dengue fever is not uncommon among travelers to tropical areas but dengue hemorrhagic fever is rare. The characteristics of dengue hemorrhagic fever are increased capillary permeability with leakage of plasma and abnormal hemostasis (62). In one study (63) involving 363 patients with dengue hemorrhagic, 25% had small effusion, 4.5% had moderate effusion, and 1.9% had massive effusion. Thoracentesis was performed in seven patients and all were transudates. The effusions are usually bilateral but sometimes are right sided only, and rarely, if ever, left sided only (64). It appears that the pathogenesis of the effusions is similar to that with the hantavirus syndrome, namely, a systemic increase in the permeability of capillaries induced by cytokines (63). In one study, the interleukin 8 (IL-8) levels in the pleural fluid were very high (65).

Influenza Viruses

Pleural effusions can occur in patients with influenza infections (37,66,67). Pleural effusions appear to be particularly common with avian influenza A (H5N1). In one report (66), 17 of 19 patients (89%) of patients with H5N1 had a pleural effusion. Thoracentesis was done in nine patients and showed a variable WBC and differential (66). Pleural effusions also occur in patients with influenza A (H1N1) also known as swine flu (67). In one series of 42 patients (67), 12 had abnormal chest radiographs and pleural effusions were present in 7 (58%). The pleural effusion does not seem to be a big problem in these patients.

Other Viral Infections

Pleural effusions have also been reported to result from infection with respiratory syncytial virus (68,69), measles after the administration of inactivated virus vaccine (70), herpes simplex virus (71), Lassa fever virus (39), and HHV-6 associated pleurisy after hematopoietic stem cell transplantation (72). Pleural effusions probably result from infection by

many other viruses as well. However, pleural effusions appear to be distinctly uncommon with the severe acute respiratory syndrome (SARS). In one study of 108 patients, no pleural effusions were identified (73).

Mycoplasma Pneumoniae

This organism is actually a small bacterium rather than a virus. It is included in this chapter because the disease it produces more closely resembles a viral than a bacterial disease. Pleural effusions occur in 5% to 20% of patients with pneumonias due to *M. pneumoniae* (37,74). The effusions are usually small (37) but can be large (74–77). In one series of 10 patients with pneumonia and pleural effusion due to *M. pneumoniae*, 4 of the patients' pleural fluid were positive by PCR for *M. pneumoniae* DNA (77). The clinical courses of the patients with a positive pleural fluid PCR were more prolonged than those of patients with negative pleural fluid PCR (77). The diagnosis, suggested by increased titers of cold agglutinins, is established by increasing specific antibody titers. It may take several weeks for a fourfold rise in specific antibody titer to become evident. In an occasional patient, the diagnosis can be established by isolating *M. pneumoniae* from the pleural fluid (78). The treatment of choice is tetracycline or erythromycin administration. No specific treatment need be directed toward the pleural effusion, but a diagnostic thoracentesis should be performed to ensure that a complicated parapneumonic effusion is not present.

RICKETTSIAE

Q Fever

The causative agent for Q fever is the rickettsial agent *Coxiella burnetii*. This disease is sometimes manifested as a primary atypical pneumonia. Q fever is acquired by the inhalation of contaminated dust particles or by drinking infected, unpasteurized milk. Because the infection is prevalent among livestock in the United States, farmers and stockyard workers are particularly likely to contract the disease. Patients with Q fever pneumonia present with the clinical picture of primary atypical pneumonia, with a high fever, cough, headache, and myalgias. Approximately half of the patients have no respiratory symptoms, although one third of them have pleuritic chest pain (79). Pleural involvement is relatively common with Q fever pneumonia. In one series of 164 cases from the Basque country of Spain, 12% had a pleural effusion (79). In another review, 5 of 25 patients (20%) with chest radiographic abnormalities due to Q fever had a pleural effusion, and in one of these patients the effusion was large (80). The pleural fluid is an exudate, and the differential reveals predominantly mononuclear cells (81) or eosinophils (82). In one report, the pleural fluid adenosine deaminase level was increased to 64 IU/L with Q fever (81). The diagnosis is usually established by demonstrating a fourfold increase in the antibody titers in the patient's serum. This increase becomes apparent in most patients within 2 weeks of the onset of the illness. The treatment of choice is tetracycline or doxycycline, which appear to be superior to erythromycin (79).

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever is due to *Rickettsia rickettsii*, and humans acquire the infection after a tick bite. Most infections occur in the southeastern and coastal Atlantic states. Classically, Rocky Mountain spotted fever is manifested by the triad of fever, rash, and a history of tick exposure. The usual onset of illness is 5 to 7 days after the tick bite. Fever, malaise, frontal headache, myalgia, and vomiting are common. A pleural effusion is present in 10% to 36%, and a pulmonary infiltrate is present in a comparable percentage (83). The infiltrates are probably due to vasculitis with increased permeability of the blood vessels. The pleural fluid probably develops from a capillary leak syndrome (84). The pleural fluid can be either a transudate or an exudate, but when it is an exudate the LDH and protein levels are relatively low (84). The treatment of choice is doxycycline 200 mg/day in two divided doses.

EHRLICHIOSIS

Ehrlichiae are obligate intracellular bacteria that grow within membrane-bound vacuoles in leukocytes. Humans acquire ehrlichiosis through a tick bite. The two most important human ehrlichial diseases are human monocytic ehrlichiosis (HME), which is caused by *Ehrlichia chaffeensis*, and human granulocytic ehrlichiosis (HGE), which is caused by a species currently known as the human granulocytic ehrlichia. Ehrlichiosis is not uncommon; at Saint Thomas Hospital in Nashville, Tennessee, there have been more than 20 confirmed cases within the last 5 years. Clinical illness begins approximately 7 days after a tick bite and is characterized by high fever with headache. Frequently, there is also malaise, myalgia,

nausea, vomiting, and anorexia. Pulmonary infiltrates develop in approximately 50% of patients (83) and at least some patients develop a pleural effusion (85). Frequently the chest radiograph is normal initially, but the condition then progresses rapidly with the development of bilateral pulmonary infiltrates and pleural effusions. It is probable that the infiltrates represent noncardiogenic pulmonary edema with a pathogenesis similar to those with hantavirus syndrome or Rocky Mountain spotted fever. The treatment of choice for ehrlichiosis is doxycycline.

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chapter 17

Pleural Effusion Due to Pulmonary Embolization

The disorder most commonly overlooked in the workup of a patient with pleural effusion is pulmonary embolization (1,2). The possibility of pulmonary embolization should be excluded in every patient with a pleural effusion of uncertain origin.

INCIDENCE

It is estimated that at least 800,000 persons have a pulmonary embolic event each year in this country (3). The incidence of pulmonary embolus increased 50% between 1998 and 2005 (3). Because pleural effusions occur in 30% to 50% of patients with pulmonary emboli (4–6), 240,000 to 400,000 pleural effusions secondary to pulmonary emboli should occur annually. Therefore, one should expect to see more cases of pleural effusions secondary to pulmonary embolization than due to bronchogenic carcinoma. Nevertheless, in most large series, pulmonary embolization accounts for less than 5% of the pleural effusions. There are two explanations for this discrepancy. First, individuals interested in pleural effusion do not see many of the patients that have pleural effusions due to pulmonary emboli as the effusions are small and a thoracentesis is not performed (7). Second, the diagnosis of pulmonary embolus is frequently not considered in patients with undiagnosed pleural effusions. Indeed, in an epidemiologic study from the Czech Republic, pulmonary embolism was the fourth leading cause of pleural effusion (8).

It is likely that pulmonary embolism is responsible for a substantial fraction of undiagnosed pleural effusions. Gunnels (9) followed 27 patients with exudative pleural effusions in whom no diagnosis was established after an initial workup, including pleural biopsy. Of the 19 patients who did not have malignant disease, 2 subsequently died, and both had pulmonary emboli at autopsy. One wonders how many of the remaining 17 patients might have had pulmonary emboli if this diagnosis had been considered. Along the same lines, Storey et al. (10) reported on a series of 133 patients with pleural effusions in which only 3 were due to pulmonary emboli, but causes were not determined in 25 patients. Because these authors do not mention any evaluation of their patients for pulmonary emboli, one wonders how many of the 25 patients would have been switched from the undetermined category to the pulmonary embolus category if the possibility of pulmonary embolus had been explored.

PATHOPHYSIOLOGIC MECHANISMS

The primary mechanism by which pulmonary emboli produce pleural effusion is by increasing the permeability of the capillaries in the lung. The interstitial fluid that results from this increased permeability traverses the visceral pleura and leads to the accumulation of pleural fluid. In the experimental situation, it has been shown that more than 20% of the fluid formed in the lung with increased permeability pulmonary edema is cleared through the pleural space (11). It is probable that ischemia of the capillaries in the visceral pleura plays at most a minor role because these capillaries are supplied by the bronchial circulation (12). Leckie and Tothill (13) have demonstrated that patients with a pleural effusion secondary to pulmonary emboli have a large amount of protein entering and leaving the pleural space. The main factor responsible for the increased permeability of the pulmonary

capillaries is probably the release of inflammatory mediators from the platelet-rich thrombi. It is possible that vascular endothelial growth factor (VEGF) may play a role in the formation of pleural fluid in at least some patients. Indeed a very high pleural fluid VEGF level was reported in one patient with pulmonary embolism (14). The release of such mediators can increase the permeability of the capillaries in either the visceral pleura or the lung. Ischemia of the pulmonary capillaries distal to the embolus may also contribute to the increased permeability.

CLINICAL MANIFESTATIONS

Symptoms and Signs

There are three symptom complexes associated with pulmonary emboli: (a) pleuritic pain or hemoptysis, (b) isolated dyspnea, and (c) circulatory collapse. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, 56% of the 119 patients with pleuritic chest pain or hemoptysis had pleural effusion, 26% of the 31 with isolated dyspnea had pleural effusion, and none of the 5 with circulatory collapse had pleural effusion (15). More than 75% of patients with pleural effusions secondary to pulmonary emboli have pleuritic chest pain (16), which is almost invariably on the side of the effusion (4). Indeed, the presence of pleuritic chest pain in a patient with pleural effusion is suggestive of pulmonary embolus. In one series, pulmonary emboli were present in 12 of 22 patients (55%) younger than the age of 40 who presented as outpatients with pleural effusion and pleuritic chest pain (17). Dyspnea, also present in more than 70% of patients (16,18), is usually out of proportion to the size of the pleural effusion. Cough and apprehension are present in approximately 50% of patients (16,18). Approximately 50% of these patients are febrile (18) but less than 10% have temperatures above 38.5°C (16,18). Approximately 15% have hemoptysis (16). Most patients have a respiratory rate above 20 per minute, and a heart rate above 100 per minute occurs in approximately 40% (7,15). In the PIOPED study, 113 of 117 patients (97%) with no preexisting cardiac or pulmonary disease had dyspnea or tachypnea or pleuritic chest pain (16).

Chest Radiograph

When a pleural effusion is secondary to pulmonary emboli, an associated parenchymal infiltrate may or may not be present. In one series of 62 patients with pleural effusions secondary to pulmonary embolism, 28 (45%) had no associated infiltrate (4), but in another series of 20 patients, only 1 (5%) did not have an associated infiltrate (19). In a third series of 10 patients with pulmonary emboli and bilateral pleural effusions, only 3 (30%) had parenchymal infiltrates (20). Infiltrates are usually in the lower lobes, are pleural based, and are convex toward the hilum. Patients with an embolic occlusion of segmental pulmonary arteries are more likely to have infiltrates than those with an embolic occlusion of the central arteries (19).

The pleural effusions secondary to pulmonary emboli are small, with the mean size equal to approximately 15% of the hemithorax (4). In the PIOPED study, 48 of the 56 effusions (86%) were manifest only as blunting of the costophrenic angle and in no patient did the pleural effusion occupy more than one third of a hemithorax (7,16). In a second series of 73 patients (7), effusions occupied less than a third of the hemithorax in 66 (90%), occupied 50% of the hemithorax in 3 (4%), and occupied more than two thirds the hemithorax in 4 (6%). If parenchymal infiltrates are present, the pleural effusions are larger. In one series, the pleural effusion occupied greater than 15% of the hemithorax in 74% of the patients with parenchymal infiltrates but in only 21% of those without parenchymal infiltrates (4). The pleural effusions are usually unilateral, but about 15% to 35% are bilateral (7,21). The pleural effusions with pulmonary emboli may be loculated, particularly if the diagnosis has been delayed for more than 10 days (7,22). There is not a close relationship between the sidedness of the pleural effusion and that of the pulmonary embolus (7). In one study of 93 patients (7), the pulmonary embolus was unilateral in 61 and the pleural effusion was ipsilateral in 38, on the contralateral side in 7, and bilateral in 16.

Pleural Fluid Findings

In patients with pulmonary emboli, analysis of the pleural fluid is not helpful in establishing the diagnosis because the pleural fluid associated with pulmonary emboli can vary widely. Nevertheless, a thoracentesis should be performed in patients suspected of having pulmonary emboli to exclude other causes of pleural effusion such as tuberculosis, malignant disease, or pneumonia with a parapneumonic effusion.

Although in the past it has been stated that the pleural effusion with pulmonary embolus may be a transudate or an exudate, it appears that almost all

pleural effusions secondary to pulmonary emboli are exudates (7,23). Romero et al. (23) reported that the pleural fluid was an exudate in 60 of 60 pleural fluids secondary to pulmonary embolus. The pleural fluid is not always blood tinged or bloody. In the series of Romero et al. (23), the pleural fluid red blood cell (RBC) count was above 100,000/mm^3 in 11 patients (18%), was between 10,000 and 100,000/mm^3 in 29 patients (48%), and was below 10,000/mm^3 in 20 patients (33%). The differential white blood cell (WBC) count may reveal predominantly polymorphonuclear leukocytes or lymphocytes (23,24). Spriggs and Boddington (25) have reported that pleural effusions secondary to pulmonary emboli frequently have large numbers of mesothelial cells or eosinophils.

CLINICAL PROBABILITY OF PULMONARY EMBOLUS

There have been several analyses developed to assess the clinical probability of pulmonary embolus. The most well known until recently were those reported in 2001 by Wells et al. (26) and in the same year by Wicki et al. (27). There were significant problems with both. The Geneva score (27) required a blood gas on room air for its calculation, whereas with the score of Wells (26), much weight is given to whether the physician thinks that pulmonary embolism is the most likely diagnosis.

In 2006, Le Gal et al. (28) reported a new scoring system that is reproduced in Table 17.1. This scoring system was developed by analyzing 965 patients with new-onset shortness of breath or chest pain, of whom 23% turned out to have pulmonary embolus. The higher the score, the more likely the patient was to have a pulmonary embolus. Only 8% of the patients with scores less than 3 had emboli, whereas 28.5% of those with intermediate scores had pulmonary emboli and 74% of patients with high scores had pulmonary emboli (28). It should be noted that findings on the chest radiograph including pleural effusion are not included in the revised Geneva score.

TABLE 17.1 ■ The Revised Geneva Score

Risk Factors	Points
Age >65 yr	1
Previous DVT or PE	3
Surgery or fracture of a lower limb within 1 mo	2
Active malignant condition	2
Symptoms	
Unilateral lower-limb pain	3
Hemoptysis	2
Heart rate	
75–94 beats/min	3
>95 beats/min	5
Pain on lower-limb deep venous palpation and unilateral edema	4
Clinical probability	
Low	0–3 total
Intermediate	4–10 total
High	≥11

DVT, deep vein thrombosis; PE, pulmonary embolus.

DIAGNOSIS

The diagnosis of pulmonary embolization should be considered in every patient with an undiagnosed exudative pleural effusion. If the patient has a high probability of pulmonary embolus, the patient should be started immediately on low-molecular-weight heparin or unfractionated heparin, and a test for pulmonary embolism should be performed before a thoracentesis is attempted (1). It should be noted that patients with pleural effusions and obvious congestive heart failure may have pulmonary emboli. In an autopsy series of 290 patients with congestive heart failure and pleural effusions, 60 (21%) had pulmonary emboli (29). The possibility of pulmonary embolization should be considered in patients with heart failure in whom the effusions are unilateral or bilateral but greatly disparate in size, particularly if the pleural fluid is an exudate.

In the past, perfusion lung scan was the procedure of choice as the initial screening procedure for pulmonary emboli. More recently, contrast-enhanced CT, which is now called *CT angiography*, has become the method of choice (30). For the reasons detailed later, CT angiography appears to be the initial procedure of choice for the patient with an undiagnosed pleural effusion.

D-Dimer Levels

The best screening test for pulmonary embolus appears to be measurement of the D-dimers in the peripheral blood. D-dimers are degradation products that result from the breakdown of cross-linked fibrin by plasmin. Fibrin is cross-linked

by factor XIII and is the primary component of thrombus material. Increased levels of D-dimer are found in conditions that result in the activation of the fibrinolytic system. Therefore, D-dimer tests lack specificity for thromboembolism, although it appears that normal levels are useful in excluding it (31). Elevated levels of D-dimer are also found in patients with recent surgery, malignancy, and liver disease (32). In fact, more than 50% of hospitalized patients have elevated levels of D-dimer. Nevertheless, if the levels are normal and an appropriate test is used, the diagnosis of pulmonary embolus can be excluded. However, if the D-dimer test is positive, an additional test is necessary to definitely diagnose pulmonary embolism (31).

It is important for physicians to understand the characteristics and limitations of the test that is performed at their hospital (31,33). For example, I recently ordered a D-dimer test on a young lady with acute shortness of breath to rule out pulmonary embolism and subsequently discovered that the only D-dimer test available at my hospital was a latex agglutination test, which was only useful in the detection of disseminated intravascular coagulation and had no role in screening for deep vein thrombosis.

The enzyme-linked immunosorbent assay (ELISA) tests have a high sensitivity in screening for pulmonary embolism, but are expensive and must be performed in batches. The latex agglutination tests in general are much less sensitive (29). Recently newer tests such as the Nycocard assay, the VIDAS D-dimer assay and the Minutex D-dimer assay have been developed that appear to have a higher sensitivity and can be performed rapidly (31).

The utility of using a D-dimer test for screening is demonstrated by a study by Wells et al. (26). These researchers prospectively studied 930 patients suspected of having pulmonary embolus. In their initial evaluation, they obtained a D-dimer test (SimpliRED whole-blood agglutination) and assessed the clinical probability of pulmonary embolus as high ($n = 64$), moderate ($n = 339$), and low ($n = 527$). If the D-dimer test was negative and the clinical probability was low, no additional tests were performed. If the D-dimer test was negative but the clinical probability was moderate or high, additional diagnostic tests were performed. When the D-dimer test was performed on the 527 patients with low probability, it was negative in 437 (83%). These patients did not undergo further evaluation, and only one (0.1%) developed a pulmonary embolus during the subsequent 3 months (26). One disturbing aspect of the study by Wells et al. is that the D-dimer test was negative in 18 of the 66 patients with pulmonary embolism (26). However, Kelly and Hunt (34) concluded that patients presenting with a low pretest probability of pulmonary embolus and a negative D-dimer test with a modern test need not undergo imaging or treatment for pulmonary embolism (34). It has been shown that the higher the D-dimer levels, the more likely the diagnosis of pulmonary embolism (35).

Lung Scans

In general, the perfusion lung scan has significant limitations in the diagnosis of pulmonary embolism. If the perfusion lung scan is negative, a pulmonary embolus is virtually ruled out. If the perfusion lung scan is a high-probability one, 87% of the patients will have pulmonary emboli, and when coupled with a high clinical probability of embolism, the positive predictive value increases to 96% (36). However, the patients most likely to have a pleural effusion are those with pleuritic pain or hemoptysis, and less than one third of these patients will have a high-probability lung scan (15).

If a pleural effusion is present, the perfusion lung scan is even more difficult to interpret (Fig. 17.1). A large effusion severely restricts the ability of the lung to expand and causes a shift of perfusion to the contralateral lung (37). Small, mobile effusions of any origin may gravitate to different regions of the pleural space, depending on the position of the patient at the time of the examination. For example, fluid may enter the major fissures when the patient lies down and produce a perfusion defect on the lung scan, when no comparable defect is seen on the erect chest radiograph. Similarly, mismatching of the ventilation and perfusion lung scans can be produced by the pleural fluid itself when the scans are obtained in different positions (Fig. 17.1) (37). For these reasons, consideration should be given to performing a therapeutic thoracentesis (see Chapter 28) before obtaining the lung scan.

Computed Tomography Angiography

In more and more centers, a CT angiography scan is being used rather than the perfusion scan as the initial imaging study for pulmonary emboli. The diagnosis of pulmonary embolism is based on the presence of partial or complete filling defects in the pulmonary

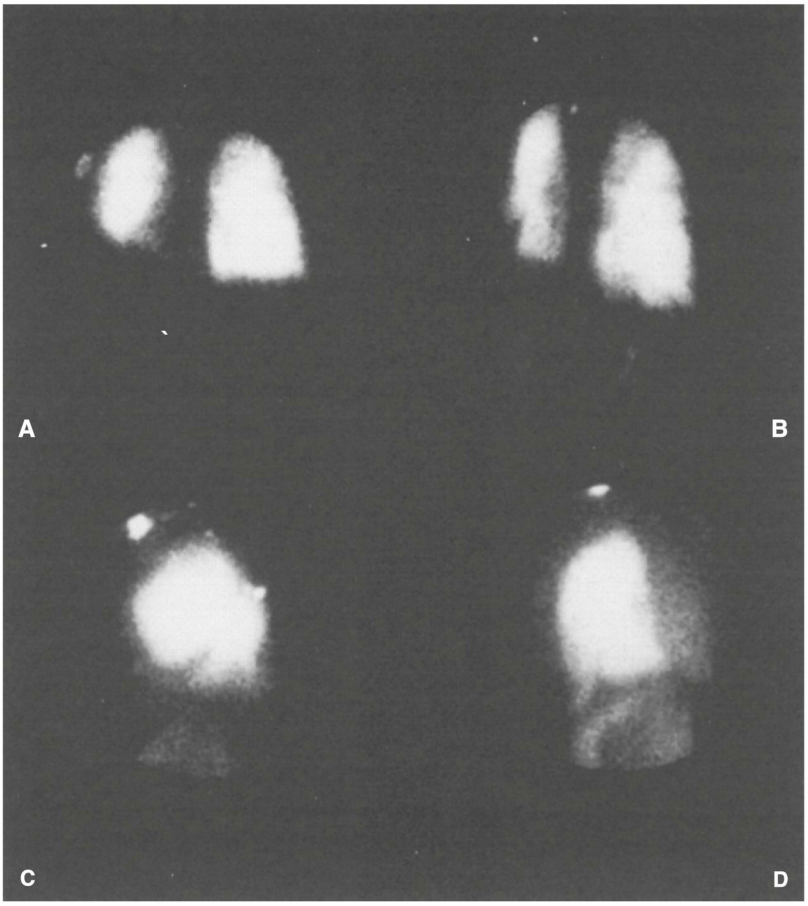

FIGURE 17.1 ■ Influence of pleural fluid on lung scans. Posterior perfusion lung scans with the patient upright **A**: and in the left lateral decubitus **B**: position from a patient with a left pleural effusion. Note the marked difference in the configuration of the left lung as the patient's position is changed, owing to shifts in the pleural fluid. Left lateral scans with the same patient upright **C**: and supine **D**: The perfusion defect seen posteriorly with the patient upright disappears when the patient is supine. (Courtesy of Norah Milne, MD)

artery on the contrast-enhanced CT (Fig. 17.2). In general, CT angiography detects between 75% and 100% of emboli and the specificity of the test exceeds 90% (38,39). These numbers are improving with the latest generation of scanners (40). Indeed in a recent survey, 86.7% of respondents believed that CT angiography was the most useful procedure for patients with acute pulmonary embolism (40). If CT angiography is used for the diagnosis of pulmonary emboli, it is important that the pulmonary arteries be examined on the video monitor and not just on the hard copies of the scans. False-positive and false-negative results are common when the length of the pulmonary artery is not scrutinized on the monitor. CT angiography has its greatest sensitivity for detecting emboli in the main, lobar, or segmental pulmonary arteries (41). This should not be too much of a problem because in the PIOPED study, only 6% of the patients with pulmonary emboli had isolated subsegmental emboli (42).

I believe that CT angiography is the best way to evaluate the possibility of pulmonary emboli in patients with a pleural effusion. Patients with a pleural effusion are likely to have an embolus in the central, lobar, segmental, or subsegmental pulmonary arteries, and these are the areas in which CT angiography can detect an embolus. The additional advantage of obtaining a CT angiogram in a patient with pleural

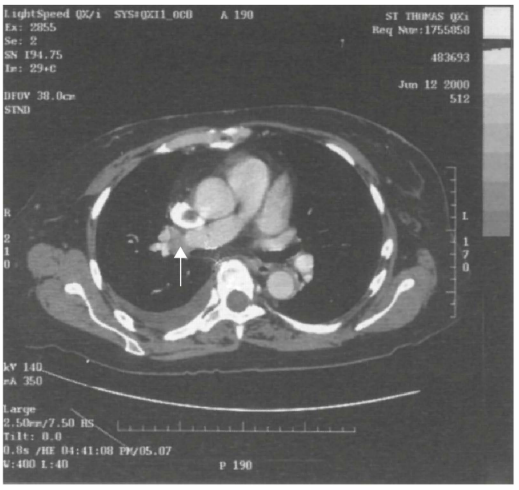

FIGURE 17.2 ■ Computed tomographic angiography showing a small right pleural effusion, a peripheral infiltrate in the right lower lobe, and a dark area in the artery to the right lower lobe *(arrow)* that represents the pulmonary embolus.

effusion who is being evaluated for pulmonary embolism is that the CT angiogram can also demonstrate pulmonary infiltrates, pulmonary masses, pleural masses, or mediastinal abnormalities that may provide clues to the etiology of the pleural effusion if a pulmonary embolus is not present.

Duplex Ultrasonography of Leg Veins

An alternative approach in diagnosing pulmonary embolism is to study the legs to see if there is any evidence of deep venous thrombosis. The basis for this approach is that approximately 90% of pulmonary emboli originate in the legs (1). Probably the best method to evaluate the proximal veins of the legs is duplex ultrasonography with venous compression. The sensitivity of this exceeds 90% while the specificity exceeds 95% (43). If the ultrasonography demonstrates deep venous thrombosis, the diagnosis of pulmonary embolism is likely. The patient needs to be anticoagulated and usually no further diagnostic tests directed toward the pleural effusion are indicated. Unfortunately, deep venous thrombosis is not demonstrable in approximately 40% of patients with pulmonary embolism (44,45) and additional tests are necessary in these patients to delineate the etiology of the pleural effusion (1).

TREATMENT

The treatment of the patient with pleural effusion secondary to pulmonary embolization is the same as that for any patient with pulmonary emboli. If the patient has a moderate or a high probability of having a pulmonary embolus, treatment should be started immediately before any imaging studies are obtained. Low-molecular-weight heparins (LMWHs) are now the initial drugs of choice for the treatment of pulmonary embolism (46). The advantages of LMWHs, compared with unfractionated heparin, include the following: (a) improved bioavailability and a longer half-life; (b) a more predictable dose–response curve so that laboratory monitoring is rarely needed; (c) less frequent heparin-induced thrombocytopenia; and (d) less heparin-associated osteopenia. After the initial administration of LMWHs, the patient should be treated with oral anticoagulants. With treatment, pleural effusions gradually resolve, particularly if no infiltrates are present. In one series, the effusions had cleared completely after 7 days of therapy in 18 of 28 patients (64%) without parenchymal infiltrates, but in none of the 30 patients with parenchymal infiltrates (4).

An alternative to heparin in the treatment of pulmonary emboli is fondaparinux. This is a synthetic antithrombotic agent. In one large study involving more than 2,000 patients, its efficacy was equivalent to heparin (47). It is the agent of choice in patients with heparin-induced thrombocytopenia.

An alternative to Coumadin for the treatment of pulmonary embolism is rivaroxaban. It is approved in Europe and Canada for the prevention of venous thromboembolism in patients undergoing major orthopedic surgery. Its mechanism of action is as an active inhibitor of coagulation factor Xa. It is an oral once a day agent that does not require blood monitoring. Trials are under way assessing whether it is an effective agent for treating pulmonary embolism and deep venous thrombosis (48).

The presence of bloody pleural fluid is not a contraindication to the administration of heparin or LMWHs. Bynum and Wilson (24) treated three patients who had pleural fluid RBC greater than 100,000/mm^3 with intravenous heparin, and in none did the effusion increase in size.

If the pleural effusion increases in size with anticoagulant therapy or if a contralateral pleural effusion develops, the patient probably has recurrent emboli or another complication. In one series, two patients developed an enlarged ipsilateral effusion and one

had recurrent pulmonary emboli, whereas the other had developed infected pleural fluid (4). Two other patients developed contralateral pleural effusions, and both had recurrent emboli.

On rare occasions, the administration of anticoagulants to patients with pulmonary emboli can lead to the development of a hemothorax. Rostand et al. (49) reviewed 11 such cases and reported that the clotting studies were within an acceptable range when the hemothorax occurred in 7 of the patients. Hemothorax developed within the first week of anticoagulation in 9 of the 11 reported cases and developed on the side of the embolus in each of these patients. In two patients, the hemothorax developed while they were receiving long-term anticoagulation. When a pleural effusion increases in size in a patient with pulmonary emboli, a diagnostic thoracentesis should be performed to rule out a complicated parapneumonic effusion or a hemothorax. If bloody pleural fluid is obtained, the hematocrit of the pleural fluid should be determined. If the hematocrit on the pleural fluid is greater than 50% of that of the peripheral blood, anticoagulation should be discontinued and chest tubes should be inserted (see Chapter 25).

PLEURAL EFFUSIONS WITH RIGHT-SIDED ENDOCARDITIS AND SEPTIC EMBOLI

Patients who have right-sided endocarditis may have septic pulmonary emboli and pleural effusions (50). The incidence of pleural effusion with right-sided endocarditis is approximately 25% to 67% (50,51). The pleural fluid is an exudate, and the cultures are usually negative. The differential cell count can reveal neutrophils, lymphocytes, or monomesothelial cells (49). The pleural fluid lactate dehydrogenase (LDH) level is usually higher than the serum LDH level and may be elevated to 10 times or more the upper limit for serum.

PLEURAL EFFUSIONS WITH LEMIERRE SYNDROME

Lemierre syndrome is a rare life-threatening septic thrombophlebitis of a jugular vein with anaerobic septicemia (52). The most common pathogen associated with the syndrome is *Fusobacterium necrophorum*. The diagnosis is established with evidence of metastatic infection and internal jugular vein thrombophlebitis. The diagnostic procedure of choice is a contrast-enhanced CT of the neck and chest that typically reveals distended veins with enhancing walls, low-attenuation intraluminal filling defects, and localized soft tissue edema (53). The treatment should include an extended course of a β-lactamase–resistant antibiotic and surgical drainage of any purulent fluid collection (53).

Pleural effusions occur with Lemierre syndrome as with any septic emboli. In one review of 59 patients reported in the literature between 1990 and 2000, 19 (32%) had pleural effusion, 8 (14%) had empyema, and 7 (12%) had pneumothorax (54). If the pleural effusion is infected, tube thoracostomy or thoracoscopy with the breakdown of adhesions may be necessary.

PLEURAL EFFUSIONS WITH SICKLE CELL ANEMIA

There is a high incidence of pleural effusions in patients with sickle cell anemia who develop the acute chest syndrome. In one series of 107 episodes of the acute chest syndrome in 77 adults, unilateral pleural effusions were present in 35%, whereas bilateral pleural effusions were present in 14% (55). The pathogenesis of these effusions is not definitely known but is believed to be either *in situ* thrombosis of the pulmonary arteries or fat embolization (55). The characteristics of the pleural fluid associated with the acute chest syndrome with sickle cell anemia are not known.

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chapter 18

Pleural Effusion Secondary to Diseases of the Gastrointestinal Tract

Diseases of the gastrointestinal tract are sometimes associated with pleural effusion. In this chapter, the exudative pleural effusions resulting from pancreatic disease, intraabdominal abscesses, esophageal perforation, abdominal operations, diaphragmatic hernia, variceal sclerotherapy, hepatic transplantation, and disease of the biliary tract are discussed. Transudative pleural effusions that occur with cirrhosis and ascites are discussed in Chapter 9.

PANCREATIC DISEASE

Four different types of nonmalignant pancreatic disease can have an accompanying pleural effusion: acute pancreatitis, pancreatic abscess, chronic pancreatitis with pseudocyst, and pancreatic ascites.

Acute Pancreatitis

In older reports, the incidence of pleural effusion with acute pancreatitis was relatively low (3% to 17%) (1,2). More recent reports, however, have documented a much higher incidence of pleural effusion. Lankisch et al. (3) obtained computed tomography (CT) scans of the chest within 72 hours of admission in 133 consecutive patients with their first attack of acute pancreatitis and reported that 50% of the patients had a pleural effusion. The effusions were bilateral in 77%, left sided in 16%, and right sided in 8%. The thickness of the fluid on the CT scan was less than 10 mm in 32 patients, 1 to 2 cm in 18 patients, and greater than 2 cm in 16 patients with the CT scans (3).

The presence of a pleural effusion in patients with acute pancreatitis is an indication of more severe pancreatitis (4). In one series, the incidence of pleural effusion was 84% in 19 patients with severe pancreatitis but only 8.6% in 116 patients with mild pancreatitis (4). The presence of a pleural effusion is also associated with the development of a pseudocyst. In the series of Lankisch et al. (3), 29% of 66 patients with pleural effusions had pancreatic pseudocysts compared with 6% of 67 patients without pleural effusions.

The exudative pleural effusion accompanying acute pancreatitis results primarily from the transdiaphragmatic transfer of the exudative fluid arising from acute pancreatic inflammation and from diaphragmatic inflammation (2). Numerous lymphatic networks join on the peritoneal and pleural aspects of the diaphragm (1). Anatomically, the tail of the pancreas is in direct contact with the diaphragm. Hence, the exudate resulting from acute pancreatic inflammation, which is rich in pancreatic enzymes, enters the lymphatic vessels on the peritoneal side of the diaphragm and is conveyed to the pleural side of the diaphragm. Because this fluid contains high levels of pancreatic enzymes, the permeability of the lymphatic vessels is increased and fluid leaks from the pleural lymphatic vessels into the pleural space. The high enzymatic content of the pancreatic exudate may also cause partial or complete obstruction of the pleural lymphatic vessels that leads to more pleural fluid accumulation (1). Of course, the diaphragm itself may be inflamed from the adjacent inflammatory process, and this inflammation may increase the permeability of the capillaries in the diaphragmatic pleura. This mechanism cannot be entirely responsible for the pleural fluid accumulation, because the pleural fluid amylase concentration is almost always higher than the simultaneous serum amylase.

In the patient with acute pancreatitis, the clinical picture is usually dominated by abdominal symptoms including pain, nausea, and vomiting. At times, however, respiratory symptoms consisting of pleuritic chest pain and dyspnea may dominate the clinical picture. The chest radiograph may reveal, in addition to the small to moderate-sized pleural effusion, an elevated diaphragm, and basilar infiltrates (5). In addition, on ultrasound or fluoroscopy, the diaphragm is sluggish or immobile. The clinical picture may look much like that of pneumonia or pulmonary embolism complicated by pleural effusion.

The diagnosis is usually established by demonstrating an elevated serum amylase or lipase level in a patient with abdominal symptoms. In a patient with the typical clinical picture for pancreatitis, a thoracentesis need not be performed. If the patient has a large pleural effusion and the patient is dyspneic, a therapeutic thoracentesis should be performed to relieve the dyspnea. If the patient is persistently febrile, a thoracentesis should be performed to rule out an empyema.

In patients with acute pancreatitis, the pleural fluid amylase level is usually elevated (5). Light and Ball (6) reported on five patients with pleural effusions secondary to pancreatic disease, and in one of the patients, the pleural fluid amylase was originally within normal limits for serum, but subsequently the amylase level in this pleural fluid became elevated. The pleural fluid amylase level is usually higher than the serum amylase and remains elevated longer than the serum amylase (1,6). The pleural fluid amylase level in patients with acute pancreatitis tends to be lower than that in patients with chronic pancreatic disease (2). Pleural fluid levels of phospholipase A2 are also elevated in patients with acute pancreatitis (7).

Other characteristics of the pleural fluid with pancreatic disease are as follows. The pleural fluid is an exudate with high protein and lactate dehydrogenase (LDH) levels. Frequently, the pleural fluid is serosanguineous, and it can be bloody. The pleural fluid glucose level is comparable to that of the serum (6). The pleural fluid differential white blood cell (WBC) count usually reveals predominantly polymorphonuclear leukocytes, and the pleural fluid WBC can vary from 1,000 to 50,000 cells/mm^3 (6).

In the patient with acute pancreatitis, the pleural effusion usually resolves as the pancreatic inflammation subsides. If the pleural effusion does not resolve within 2 weeks of treatment of the pancreatic disease, the possibility of a pancreatic abscess or a pancreatic pseudocyst must be considered.

Pancreatic Abscess

Pancreatic abscess usually follows an episode of acute pancreatitis. Typically, the acute pancreatitis initially responds to therapy, but 10 to 21 days later, the patient becomes febrile with abdominal pain and leukocytosis (8). The diagnosis is also suggested if a patient with acute pancreatitis does not respond to the usual therapy within several days (8). It is important to establish the diagnosis because the mortality rate approaches 100% if the abscess is not drained surgically (8). Both ultrasound (8) and abdominal CT scanning (9) are useful in establishing the diagnosis of pancreatic abscess preoperatively. Pleural effusion occurs commonly in patients with pancreatic abscess. In one series of 63 patients, 38% had pleural effusions on chest radiographs (8). Although pleural fluid findings were not described in this series, a patient described in a different paper had a high pleural fluid amylase level in a pleural effusion associated with a pancreatic abscess (10). The other complication that can cause a pleural effusion to persist in patients with acute pancreatitis is a pancreatic pseudocyst.

Pancreatic Pseudocyst and Chronic Pancreatic Pleural Effusion

A pancreatic pseudocyst is not a true cyst but rather a collection of fluid and debris rich in pancreatic enzymes near or within the pancreas. The walls consist of granulation tissue without an epithelial lining (11). Approximately 10% of patients with acute pancreatitis have a clinically significant pseudocyst (12). Approximately 5% of patients with a pancreatic pseudocyst have a pleural effusion (12). Pleural effusions due to pancreatic pseudocysts are relatively uncommon. Between 1983 and 1989, there were only seven cases at the Moffitt-Long and San Francisco General Hospitals (12).

The mechanism responsible for pleural effusion in patients with a chronic pseudocyst is the development of a direct sinus tract between the pancreas and the pleural space (10,13). When the pancreatic ductal system is disrupted, the extruded pancreatic fluid sometimes passes through the aortic or esophageal hiatus into the mediastinum. Once in the mediastinum, the process either can be contained, to form a mediastinal pseudocyst, or may decompress into one or both pleural spaces. Once fluid enters the pleural space, the pancreaticopleural fistula is likely to result in a massive chronic pleural effusion.

Most patients with chronic pancreatic pleural effusion are men. In more than 90% of male patients, the pancreatic disease is a result of alcoholism (12,14).

Chest symptoms usually dominate the clinical picture of the patient with chronic pancreatic disease and a pleural effusion (14). These patients report chest pain and shortness of breath. In one series of 101 patients from Japan, 42 complained of dyspnea and 29 complained of chest and back pain, whereas only 23 complained of upper abdominal pain (14). The explanation for the lack of abdominal symptoms is that the pancreaticopleural fistula decompresses the pseudocyst. Weight loss is common in patients with chronic pancreatic pleural effusions (12).

Pleural effusion is usually large, sometimes occupying the entire hemithorax. In most cases the effusion is unilateral and left sided, but approximately 20% are unilateral and right sided. Fifteen percent are bilateral (12,14). If a therapeutic thoracentesis is performed, the pleural effusion reaccumulates rapidly. In one patient, more than 13 L of pleural fluid was removed during three separate thoracenteses over a short period (15). Because chest symptoms dominate the clinical picture and some patients have no history of prior pancreatic disease, the diagnosis is easily missed unless the pleural fluid amylase is measured.

The diagnosis of a chronic pancreatic pleural effusion should be suspected in any individual with a large pleural effusion who appears to be chronically ill or has a history of pancreatic disease or abdominal trauma (16). Many patients have no history of pancreatic disease (12). The best screening test for chronic pancreatic pleural effusion is to measure the pleural fluid amylase. The pleural fluid amylase is usually markedly elevated (>1,000 U/L) (16), whereas the serum amylase may be normal or mildly elevated (16). An elevated pleural fluid amylase level is not diagnostic of pancreatic disease, as discussed in Chapter 7.

The other main diagnosis to consider in a patient with a chronic pleural effusion with a high amylase level is malignant disease. Approximately 10% of patients with a malignant pleural effusion have an elevated pleural fluid amylase level (6). With malignancy, the cytology is frequently positive. In addition, it is uncommon to have a malignant pleural effusion with an amylase above 1,000 U/L. If there is difficulty in distinguishing between these two entities, the differentiation can be made by obtaining amylase isoenzymes on the pleural fluid. With malignant effusions, the amylase is of the salivary rather than the pancreatic type (17).

Diagnosis can usually be established by CT of the chest and abdomen, which frequently shows both the pseudocyst and the sinus tract (12). Magnetic resonance imaging is complimentary to CT in establishing the presence of pseudocyst and the site of the ductal disruption (18). Endoscopic retrograde cholangiopancreatography (ERCP) also plays an important role in the evaluation and management of patients with pancreaticopleural fistula. ERCP is useful in delineating the ductal structure, the pseudocyst, and the fistulous connection to the pleura through the sinus tract (12). The greatest utility for ERCP is in defining the precise anatomic relationship preoperatively so that a direct and expeditious surgical procedure can be planned. Recently, some patients have been successfully treated by placing stents in the pancreatic duct at the time the ERCP is performed (19,20). In one series (18), five of six patients were successfully treated with a stent.

The initial therapy of a patient with a pancreatic pseudocyst and a pleural effusion should probably be nonoperative. The theory behind conservative therapy is that if pancreatic secretions are minimized, the pseudocyst will regress and the sinus tract will close. Accordingly, a nasogastric tube is inserted and the patient is given intravenous hyperalimentation. It is probable that the patients are benefited if they are given somatostatin or octreotide, a synthetic analog of somatostatin (21). Somatostatin has numerous inhibitory actions on gastrointestinal functions, one of which is its inhibitory effect on pancreatic exocrine secretion (12). It has been shown that somatostatin decreases the output from an external pancreatic fistula by more than 80% (22). Some authors recommend serial thoracentesis and subsequent tube thoracostomy if the effusions recur, but there is no evidence that such procedures are beneficial.

If after 2 weeks, the patient remains symptomatic and the pleural fluid continues to accumulate, surgical intervention should be considered. Approximately 50% of patients require surgery. Surgery is more likely to be required in patients with more severe pancreatic disease (21). Before surgery, an endoscopic retrograde pancreatogram and an abdominal CT scan should be performed to aid in planning the surgical procedure (23). For example, if a leak from the duct or pseudocyst is demonstrated in the distal portion of the gland, distal pancreatectomy will be curative. If a direct pancreatic duct leak is found in the more proximal portion of the gland, without a pseudocyst, a direct anastomosis between the leak and a Roux-en-Y jejunal loop or a Whipple resection should be considered. Conversely, if a large cyst is present within the body of the gland, internal drainage should be performed either into the stomach or with a Roux-en-Y jejunal loop. Procedures that do not focus on removal of the disrupted portion of the gland or on drainage

of the pseudocyst usually fail. If the preoperative ERCP is unsuccessful, pancreatography may be performed at the time of surgery (12).

An alternative approach to the patient with a pancreatic pseudocyst is to drain the pseudocyst percutaneously. Under CT guidance, a catheter is introduced through the anterior abdominal wall, and then through the anterior and then the posterior wall of the stomach into the pseudocyst cavity. Side holes are cut into the part of the catheter that lies in the pseudocyst and that which lies in the stomach. Maintenance of this drainage for 15 to 20 days is thought to create a fistulous tract between the pseudocyst and stomach akin to surgical marsupialization. In one series, 20 of 26 patients (77%) were cured by this procedure (24). To my knowledge, there are no randomized studies comparing the results with surgery and with percutaneous drainage of pseudocysts.

The prognosis of patients with pancreaticopleural fistula appears to be favorable (12). In the series of 96 patients reviewed by Rockey and Cello (12), the overall mortality rate was 5%, and 3 patients died of unrelated illnesses during their follow-up period. Both patients who died as a direct result of the pancreatic process were managed conservatively and died of sepsis.

In patients with chronic pleural effusions secondary to pancreatic disease, the pleural surfaces may become thickened, and in several patients, decortications have been performed (25). However, because the pleural thickening gradually improves spontaneously, decortication should be delayed for at least 6 months following definitive treatment of the pancreatic disease to ascertain whether the pleural disease will resolve spontaneously.

One rare complication of pancreatic pleural effusion is the development of a bronchopleural fistula. Kaye (1) reported one such patient in whom the development of the bronchopleural fistula was heralded by the expectoration of copious quantities of clear yellow fluid. In this situation, chest tubes should be inserted immediately to drain the pleural space and to protect the lung from the fluid with its high enzymatic content.

Pancreatic Ascites

Some patients with pancreatic disease develop ascites characterized by high amylase and protein levels (21,26). The genesis of the ascites is through leakage of fluid from a pseudocyst directly into the peritoneal cavity or a sinus tract from the pseudocyst into the peritoneal cavity. If such a patient should happen to have a defect in his diaphragm, he will develop a large pleural effusion as a result of the flow of fluid from the peritoneal to the pleural cavity in the same way that pleural effusions develop secondary to ascites due to cirrhosis (see Chapter 9). Approximately 20% of patients with pancreatic ascites have a pleural effusion (26).

Most patients with pancreatic ascites and pleural effusion are initially thought to have cirrhosis and ascites. The diagnosis is easily established if amylase determinations are made on the peritoneal and pleural fluid in such patients (26). Most patients have a protein level above 3.0 g/dL in their ascitic fluid. The treatment for pancreatic ascites is the same as for pancreatic pleural effusion, except that serial paracenteses rather than serial thoracenteses are performed (26).

SUBPHRENIC ABSCESS

Subphrenic abscess continues to be a significant clinical problem despite the development of potent antibiotics.

Incidence

In most large medical centers, between 6 and 15 subphrenic abscesses are seen each year (27–29). Subphrenic abscesses are discussed in this chapter because a pleural effusion is present in approximately 80% of cases.

Pathogenesis

Approximately 80% of subphrenic abscesses follow intraabdominal surgical procedures (30,31). Splenectomy is likely to be complicated by a left subphrenic abscess (31), as is gastrectomy. Deck and Berne (32) noted a high incidence of subphrenic abscess after exploratory laparotomy for trauma; in their study, 59% of subphrenic abscesses occurred after such an operation. Overall, approximately 1% of abdominal operations are complicated by subphrenic abscess (29). Sanders (29) reviewed the incidence of subphrenic abscesses following 1,566 abdominal surgical procedures at the Radcliffe Infirmary in 1965 and found 15 patients with subphrenic abscess. Sanders also reviewed the cases of 23 patients with pleural effusion following intraabdominal surgical procedures during the same period. He found that 12 of the 23 patients had definite subphrenic abscesses, and he believed that another 5 patients possibly had subphrenic abscesses.

Subphrenic abscess may also occur without antecedent abdominal surgical procedures. It may result from processes such as gastric, duodenal, or appendiceal perforation; diverticulitis; cholecystitis;

pancreatitis; or trauma (30). In such patients, the diagnosis of subphrenic abscess is frequently not considered. In one series of 22 patients in whom abscesses occurred without antecedent abdominal operations, the diagnosis was established before the patient's death in only 41% (30).

The pathogenesis of the pleural effusion associated with subphrenic abscess is probably related to inflammation of the diaphragm. Although Carter and Brewer (27) proposed that the pleural effusion arose from the transdiaphragmatic transfer of abscess material by the lymphatic vessels, this hypothesis is unlikely because fluid from these pleural effusions is only rarely culture positive. If the pleural effusion arose from the transdiaphragmatic transport of abscess material, bacteria as well as leukocytes should be transported. The diaphragmatic inflammation resulting from the adjacent abscess probably increases the permeability of the capillaries in the diaphragmatic pleura and causes pleural fluid to accumulate.

Clinical Manifestations

The clinical picture of a patient with subphrenic abscess can be dominated by either chest or abdominal symptoms. In the series of 125 cases of Carter and Brewer (27), chest findings dominated the clinical picture in 44% of patients. The main chest symptom is pleuritic chest pain. Radiographic abnormalities include pleural effusion, basal pneumonitis, compression atelectasis, and an elevated diaphragm on the affected side. Pleural effusions occur in 60% to 80% of patients and are usually small to moderate in size, but may be large, occupying more than 50% of the hemithorax (27,28,31–33).

Most patients with postoperative subphrenic abscesses have fever, leukocytosis, and abdominal pain (27,28,29), but frequently no localizing signs or symptoms are present. The symptoms and signs of subphrenic abscess are variable. In a series of 60 patients, 37% had no abdominal pain, 21% had no abdominal tenderness, 15% had no temperature elevation greater than 39°C, and 8% had no leukocytosis above 10,000/mm^3 (28). The interval between the surgical procedure and the development of the subphrenic abscess is usually 1 to 3 weeks but can be as long as 5 months (30,31).

Examination of the pleural fluid from patients with subphrenic abscesses usually reveals an exudate with predominantly polymorphonuclear leukocytes. Although the pleural fluid WBC may approach or even exceed 50,000/mm^3, the pleural fluid pH and glucose level remain above 7.20 and 60 mg/dL, respectively. It is distinctly uncommon for the pleural fluid to become infected (27). However, empyemas have resulted from contamination of the pleural space when the abscesses were drained percutaneously (34).

Diagnosis

The diagnosis of subphrenic abscess should be considered in any patient who develops a pleural effusion several days or more after an abdominal surgical procedure or in any other patient who has an undiagnosed exudative pleural effusion containing predominantly polymorphonuclear leukocytes. The chest radiographs from such a patient are shown in Figure 18.1.

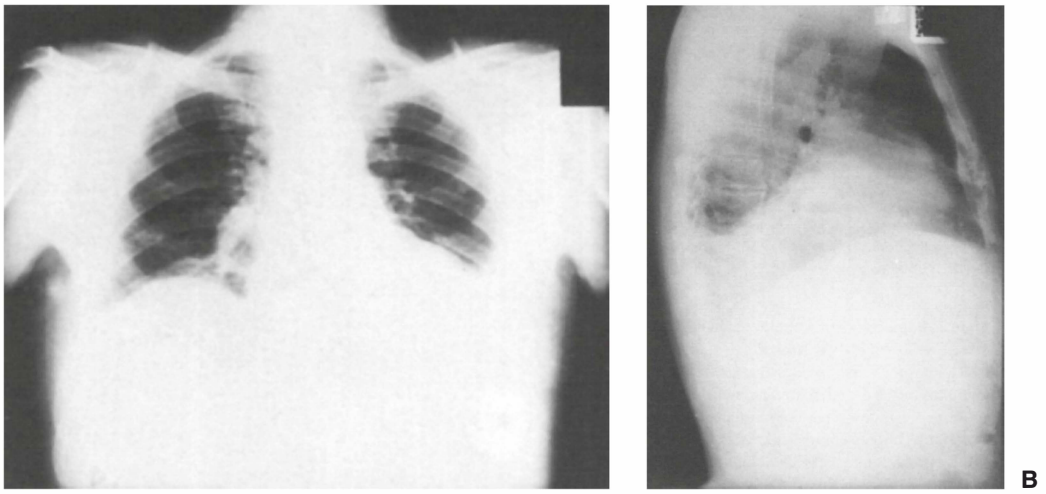

FIGURE 18.1 ■ Posteroanterior chest radiograph **A**: and left lateral radiograph **B**: demonstrating elevated left diaphragm and blunting of the left diaphragm posteriorly.

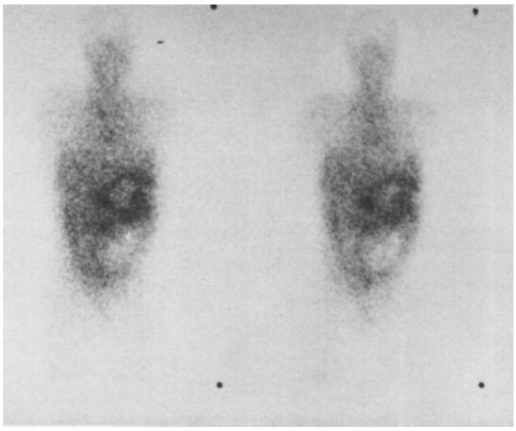

FIGURE 18.2 ■ Gallium scan from the patient whose radiographs are shown in Figure 18.1. Note the increased activity in the left upper abdominal quadrant with the "cold" spot in the center of the area with the increased uptake.

This patient had left-sided chest pain and a low-grade fever without any abdominal symptoms. Thoracentesis revealed an exudate with a WBC of 29,000, an LDH level of 340 IU/L (upper normal limit for serum 300 IU/L), a glucose level of 117 mg/dL, and a pH of 7.36. He was treated with parenteral antibiotics for a presumed parapneumonic effusion but had little clinical response. Two subsequent thoracenteses revealed similar pleural fluid findings. Two weeks after admission, a gallium scan revealed increased uptake of the gallium in the left upper quadrant (Fig. 18.2). At laparotomy, this patient was found to have a left subphrenic abscess resulting from a colonic perforation secondary to a colonic carcinoma. At no time did this patient have more than mild left upper quadrant tenderness.

Routine chest or abdominal radiographs frequently establish the diagnosis of subphrenic abscess. A pathognomonic radiologic finding is an air–fluid level below the diaphragm outside the gastrointestinal tract. These air–fluid levels are best demonstrated with heavily exposed abdominal films that include the diaphragm, with the patient upright and in the lateral decubitus position (31). In one series of 82 patients, these routine radiographs demonstrated air within the abscess in 70% (31). In more than 25% of the patients with air in the abscess, the air had been overlooked on the initial radiologic interpretation (35). A second radiographic sign sometimes seen on routinely obtained radiographs is displacement of intraabdominal viscera. Contrast studies including upper gastrointestinal series and barium enemas are helpful in demonstrating the extraluminal location of gas, leakage, and deformity or displacement of normal structures. Some investigators have recommended water-soluble contrast material for these studies because of the possibility of perforation or leakage and because retained barium can make subsequent CT scans and ultrasound studies more difficult.

In recent years, CT scans, ultrasound studies, and gallium scans have proved useful in diagnosing subphrenic abscesses. As demonstrated in Figure 18.2, gallium scans can be helpful in establishing the diagnosis. Gallium scans are not always positive when subphrenic abscesses are present. In one series, four of 11 patients (36%) with subphrenic abscesses had negative gallium scans (32). Abdominal CT scans are probably the best means by which to establish the diagnosis of subphrenic abscess (36). One advantage of CT scans over gallium scans is that, with CT scans, the precise anatomic location and extent of the abscess can be defined (31). Ultrasonic examination effectively demonstrates fluid-filled abscess cavities, but ultrasound is technically difficult in the left subphrenic region because of overlying lung, ribs, and gas in the gastrointestinal tract (31). In one series, ultrasonic examinations were negative in 41% of 22 patients with subphrenic abscesses (31).

Treatment and Prognosis

The two main aspects of treatment are the administration of appropriate antibiotics and drainage. Sepsis is an ever-present threat to the patient with a subphrenic abscess. In a series of 125 cases, 29 patients (23%) developed positive blood cultures, and the mortality rate in these 29 patients was 93% (27). Most subphrenic abscesses contain more than a single organism; *Escherichia coli, Staphylococcus aureus*, and anaerobic organisms are most commonly isolated (37). Broad-spectrum antibiotics with anaerobic coverage should be instituted before any drainage procedure is attempted to prevent bacteremia during this procedure.

Drainage of the subphrenic abscess can be accomplished either percutaneously or with surgery. Because the results with the two procedures seem comparable (38), it is recommended that percutaneous drainage be used in most cases, although posterior subphrenic abscesses are best approached surgically (39). The results with percutaneous drainage by experienced individuals are excellent. Voros et al. (39) reported that 92% of 185 patients with intraabdominal abscesses were successfully treated with percutaneous drainage. These investigators

inserted the catheters under CT guidance and left the catheters in place for a mean of 6 days (39).

Mortality rates among patients with subphrenic abscesses remain high, ranging from 20% to 45% (27, 28,30,33). Because much of the mortality is due to delayed diagnosis or lack of a diagnosis before autopsy, the possibility of a subphrenic abscess must be considered in every patient with an exudative pleural effusion containing predominantly polymorphonuclear leukocytes. In such patients, heavily penetrated abdominal radiographs should be examined for extravisceral gas, and one should consider obtaining an abdominal CT scan.

INTRAHEPATIC ABSCESS

Pleural effusions accompany intrahepatic abscesses in approximately 50% of patients (40). The pathogenesis of the pleural fluid and the pleural fluid findings with intrahepatic abscess are similar to those for subphrenic abscess, as previously discussed. Because the mortality rate of patients with untreated liver abscesses approaches 100% (35), the diagnosis of intrahepatic abscess should be considered in every patient with a right-sided exudative pleural effusion with predominantly polymorphonuclear leukocytes on the pleural fluid differential. Amebic liver abscesses are discussed in Chapter 15.

Clinical Manifestations

Most patients with pyogenic intrahepatic abscesses have fever and anorexia (35), and approximately 50% give a history of shaking chills. Approximately 50% of patients with hepatic abscesses have hepatobiliary disease, most commonly hepatolithiasis, whereas 50% have no illness that predisposes them to liver abscess (41). Abdominal pain is common, but it is frequently not localized to the right upper quadrant. Most patients have an enlarged, tender liver. Laboratory tests usually reveal leukocytosis, anemia, elevated alkaline phosphatase levels, and hyperbilirubinemia. However, because none of these findings are invariably present in patients with pyogenic liver abscesses, this diagnosis should be pursued in all patients with right-sided exudative pleural effusions containing polymorphonuclear leukocytes.

Diagnosis

The best way to establish the diagnosis of pyogenic liver abscess is with an abdominal CT scan (42). With CT scanning, abscesses with diameters as small as 0.5 cm can be readily appreciated. Abdominal ultrasound studies can also identify fluid-filled intrahepatic lesions, but because CT scanning provides more precise anatomic information, it is the procedure of choice (43). Not all fluid-filled intrahepatic lesions are pyogenic abscesses; cysts, hematomas, hemangiomas, and amebic abscesses can produce identical findings on ultrasound studies and CT scans. The definitive diagnosis can be established by percutaneous aspiration guided by CT scanning or ultrasound.

Treatment

The treatment of a pyogenic liver abscess consists of the administration of appropriate parenteral antibiotics and drainage of the abscess. The preferred method of drainage is image-guided aspiration with or without catheter drainage (40,41). Emergency laparotomy is indicated when there are signs of peritonitis, ongoing deterioration of the patient's condition despite aspiration or catheter drainage, or CT evidence of persistent abscess (41). In a recent study (43), the mortality rate of 84 patients was 19%.

INTRASPLENIC ABSCESS

Splenic abscess is an unusual entity. In the 30 years between 1950 and 1980, there were only 11 cases diagnosed at Johns Hopkins Hospital (44). In a more recent series from the University of California at Davis Medical Center, nine patients were seen between 1980 and 1990 (45). In this latter series, all patients had an associated pleural effusion, but in prior series only 20% to 50% of patients with splenic abscess had a left-sided pleural effusion (44,46). In most patients, the splenic suppuration arises from primary hematogenous seeding such as with endocarditis. Splenic abscess appears to be more common in individuals with diseases producing splenic abnormalities, such as chronic hemolytic anemia or sickle cell anemia (44).

Most but not all patients with a splenic abscess have localized pain in the left upper quadrant. One combination that is particularly suggestive of the diagnosis is a left pleural effusion plus thrombocytosis. In the series of Ho and Wisner (45), seven of nine patients (78%) had this combination. The diagnosis can be made presumptively with ultrasonography or CT scan and can be confirmed by fine-needle aspiration (47). Although most patients are treated with splenectomy plus antibiotics (45,48), some patients have been cured with catheter drainage (47,48).

ESOPHAGEAL PERFORATION

Esophageal rupture should always be considered in the differential diagnosis of pleural effusions, because if this entity is not rapidly treated, the mortality rate rapidly increases.

Incidence

Esophageal perforation is uncommon. Michel et al. (49) reported only 85 cases at the Massachusetts General Hospital over a 21-year period, whereas Reeder et al. (50) found 41 cases at The University of Chicago Hospitals over a 14-year period. Ryom et al. (51) reported that there were 286 cases of esophageal perforation in Denmark between 1997 and 2005.

Pathogenesis and Pathophysiologic Mechanisms

Esophageal perforation most commonly arises as a complication of esophagoscopic examination. In one series of 108 cases, 67% occurred as a complication of esophagoscopy (52). Esophageal perforation is particularly common with esophagoscopy when one has attempted to remove a foreign body or to dilate an esophageal stricture (52). Overall, between 0.15% and 0.70% of all esophagoscopic examinations are complicated by esophageal perforation (49). The insertion of a Blakemore tube for esophageal varices can also be complicated by esophageal rupture; this mechanism accounted for 11% of all esophageal perforations in one series (49). Frequently, the diagnosis of esophageal perforation is missed in patients with Blakemore tubes because they are so ill with multiple problems (49).

Esophageal perforations may also arise from foreign bodies themselves, carcinomas, gastric intubation, chest trauma, and chest operations. Finally, esophageal rupture may occur as a complication of vomiting (Boerhaave syndrome). Spontaneous rupture almost always involves the lower esophagus, just above the diaphragm.

The clinical symptoms of esophageal perforation are due to contamination of the mediastinum by oropharyngeal contents, which produces an acute mediastinitis. When the mediastinal pleura ruptures, a pleural effusion develops, frequently complicated by a pneumothorax. Most of the morbidity from esophageal perforation is due to the infection of the mediastinum and the pleural space by the oropharyngeal bacterial flora (53).

Clinical Manifestations

With esophageal perforation secondary to esophagoscopic examination, the endoscopist usually does not realize that the esophagus has been perforated (54). However, patients usually report persistent chest or epigastric pain within several hours of the procedure (55), and such complaints should serve as indications for an emergency contrast study of the esophagus.

Patients with spontaneous rupture of the esophagus usually have a history of vomiting, followed by chest pain, and they frequently describe a sensation of tearing or bursting in the lower part of the chest or the epigastrium (56). The chest pain is characteristically excruciating and is often unrelieved by opiates. Small amounts of hematemesis are present in more than 50% of these patients (56). Dyspnea is frequently a prominent symptom. The presence of subcutaneous emphysema that first appears in the suprasternal notch suggests esophageal perforation, but this appears late in the course of perforation. Abbott et al. (56), in a series of 47 patients, found that only four (9%) had subcutaneous emphysema within the first 4 hours. The clinical picture may be much less dramatic than that described. Chandrasekhara and Levitan (57) described a patient with a ruptured esophagus and symptoms that were present for 5 days, who had only mild distress.

In patients with esophageal perforation, the chest radiograph reveals a pleural effusion in approximately 60% and a pneumothorax in approximately 25% (49). Most patients with spontaneous rupture have a pleural effusion (58). The pleural effusion is usually left sided, but it may be right sided or bilateral. Other radiographic findings may include widening of the mediastinum and air visible within the mediastinal compartments. The chest CT scan is useful in suggesting the diagnosis of esophageal perforation because it demonstrates periesophageal air tracks suggestive of esophageal perforation in most cases (59).

Diagnosis

Because the mortality rate approaches 60% (58) when treatment is delayed for more than 24 hours, the diagnosis of esophageal rupture should be entertained any time one sees a patient with an exudative pleural effusion, particularly when the patient appears acutely ill. Examination of the pleural fluid is helpful in suggesting the diagnosis of esophageal perforation because it is characterized by (a) a high amylase level, (b) a low pH, (c) the presence of squamous epithelial cells, (d) ingested food particles, and (e) multiple pathogens on smear or culture.

An elevated pleural fluid amylase level appears to be the best indication of esophageal rupture. In the experimental model, the pleural fluid amylase level is elevated within 2 hours of esophageal rupture (53). In one clinical series, all seven patients with esophageal rupture had elevated pleural fluid amylase levels (56). The origin of the amylase is salivary rather than pancreatic because the saliva, with its high amylase content, enters the pleural space through the defect in the esophagus (60). To my knowledge, in only two reported cases have pleural fluid amylase levels been within normal limits with esophageal perforation and pleural effusion (61,62). One of these patients had Sjögren's syndrome and essentially no production of saliva (62). The other had a chronic perforation due to esophageal carcinoma (61).

The pleural fluid pH is usually decreased with esophageal rupture (63,64). In fact, Dye and Laforet (64) concluded that a pleural fluid pH below 6.0 was highly suggestive of esophageal rupture and attributed the low pleural fluid pH to the leakage of acidic gastric juice through the esophageal tear. Both of these conclusions appear to be wrong. Patients with severe infections of the pleural space and an intact esophagus frequently have a pleural fluid pH below 6.0.

Good et al. (65) demonstrated, in an experimental model, that the pleural fluid pH falls just as rapidly after esophageal perforation when the esophagogastric junction is ligated. These authors concluded that leukocyte metabolism was the major contributor to the low pleural fluid pH with esophageal rupture. Nevertheless, the presence of a pleural fluid pH below 7.00 increases the likelihood that the patient has a ruptured esophagus.

Another useful test in diagnosing esophageal perforation is examination of the Wright's stain of the pleural fluid for squamous epithelial cells. Eriksen (66) demonstrated the presence of squamous epithelial cells in the pleural fluid from all 14 patients with esophageal perforation. Again, as with amylase, the squamous epithelial cells enter the pleural space through the esophageal perforation. Obviously, the demonstration of food particles in pleural fluid is diagnostic of esophageal perforation.

The pleural fluid glucose level with esophageal rupture is usually decreased. If, however, the patient has recently ingested food with a high glucose level, the glucose level in the pleural fluid may exceed 500 mg/dL (67). The only two other conditions associated with such a high pleural fluid glucose level are diabetes, when the serum glucose level is very high, and instances where intravenous fluids with high glucose levels enter the pleural space.

Another characteristic of the pleural fluid from patients with esophageal rupture is that smear and cultures frequently reveal multiple organisms. The diagnosis of esophageal rupture should be considered in any patient with a polymicrobial empyema, particularly when the daily pleural fluid output is high.

The diagnosis of esophageal perforation is established when esophageal disruption is confirmed by contrast studies of the esophagus. The contrast agent of choice is probably meglumine and ioxaglate sodium (Hexabrix, 320 mg/mL) (68). Barium has a greater radiographic density, better mucosal adherence, and causes minimal irritation to the tracheobronchial tree, but it is not absorbed once it leaks into the mediastinum or pleura and produces a marked inflammatory reaction in the pleura. When water-soluble agents, such as Hexabrix or meglumine and diatrizoate sodium (Gastrografin), are injected in the pleural space, they are almost completely absorbed after 24 hours and neither creates much of an inflammatory response (68). Hexabrix is considered the agent of choice because Gastrografin creates marked bronchospasm when it is aspirated and Hexabrix does not create such a reaction (68). The contrast studies are positive in approximately 85% of patients (49). If the perforation is small or has already closed spontaneously, the esophagogram may not be diagnostic. It has been suggested that contrast studies of the esophagus be done in the decubitus position when perforation is suspected (69). In this position, the contrast material fills the whole length of the esophagus and thereby allows the actual site of the perforation and its interconnecting cavities to be demonstrated in almost all patients (69).

If the esophageal perforation is not demonstrated by the contrast study of the esophagus, chest CT scan may facilitate the diagnosis (70). White et al. (70) performed chest CT scans on 12 patients with esophageal perforation. They found esophageal thickening in 9 patients, periesophageal fluid in 11 patients, extraluminal air in 11 patients, and pleural effusion in 9. The site of the perforation was visible on CT scan in two patients. The finding that most commonly pointed to esophageal rupture was extraluminal air (70).

Treatment

The treatment of choice for esophageal rupture is exploration of the mediastinum with primary repair of the esophageal tear and drainage of the pleural space and mediastinum (50,71,72). Parenteral antibiotics should be given to treat the mediastinitis and pleural infection.

Although conservative treatment consisting of antibiotics and nasogastric suction is adequate in some patients with esophageal perforation (72), in patients with pleural effusion or pneumothorax complicating esophageal perforation, mediastinal exploration should be performed. It is important to perform the mediastinal exploration as soon as possible after the diagnosis is established because a delay of even 12 hours increases the mortality rate (58). However, primary repair can be attempted if the perforation has been present for more than 24 hours. In one series, the mortality rate for 16 patients operated upon with primary repair 2 to 17 days after the perforation was only 13% (73). If primary repair is not possible because the damaged tissue cannot hold the sutures, the patient can be managed with T-tube intubation of the esophageal defect (74). Operative repair of the esophageal perforation can be performed thoracoscopically if the patient is relatively stable and has only mild mediastinal inflammation (75). Nonoperative management of iatrogenic perforations is frequently successful, provided the mediastinal and pleural spaces are not soiled with ingested food or bacteria (76,77).

ABDOMINAL SURGICAL PROCEDURES

The incidence of small pleural effusions after abdominal operations is high. George and I (78) reported a series of 200 patients who had bilateral decubitus chest radiographs 48 to 72 hours following abdominal surgical procedures. Pleural effusions were identified in 97 patients (49%). In a more recent series, Nielsen et al. (79) reported that 89 of 128 patients (69%) undergoing upper abdominal surgery had pleural effusions in the first 4 days postoperatively. Most of the pleural effusions are small; only 21 patients (22%) in our series had pleural fluid that measured more than 10 mm in thickness on the decubitus films (78). Larger left-sided pleural effusions are particularly common after splenectomy. Postoperative pleural effusions are more common in patients undergoing upper abdominal surgical procedures (78), in patients with postoperative atelectasis (78,79), and in those with free abdominal fluid at the time of operation (78). In our series (78), a thoracentesis was performed on 20 patients, and in 16 of these, the pleural fluid was an exudate. The pleural effusions in all but a single patient, who had a staphylococcal pleural infection, resolved spontaneously without any specific therapy. In summary, pleural effusions frequently occur after abdominal surgical procedures and are usually related to diaphragmatic irritation or atelectasis. If the pleural effusion measures more than 10 mm in thickness on the decubitus film, a diagnostic thoracentesis should be performed to rule out pleural infection. Although pulmonary embolization and subphrenic abscess can cause pleural effusion postoperatively, most effusions occurring within the first 72 hours of abdominal surgery are not due to these factors and resolve spontaneously.

Patients with advanced epithelial ovarian cancer sometimes undergo removal of the peritoneum from the diaphragm or diaphragmatic resection to render the patients more likely to respond to chemotherapy (80). In a series (80) of 59 patients who underwent one of these two procedures, the incidence of pleural effusion in the 40 patients who did not have a pleural effusion preoperatively and who were not treated with tube thoracostomy was 60%. The effusions tend to resolve with time and drainage is indicated only if the patient becomes symptomatic (80).

DIAPHRAGMATIC HERNIA

Hernias through the diaphragm are important in the differential diagnosis of pleural effusions from two viewpoints. First, they may mimic a pleural effusion. Second, pleural effusions are usually present in patients with a strangulated diaphragmatic hernia (81).

Diaphragmatic hernia should be considered whenever an apparent pleural effusion has an atypical shape or location (Fig. 18.3). Air in the herniated intestine is usually the clue to this diagnosis. Occasionally, an upper gastrointestinal series and a small bowel follow-through study in conjunction with a barium enema are necessary for accurate diagnosis.

The possibility of a strangulated diaphragmatic hernia should always be considered in patients with a left pleural effusion and signs of an acute abdominal catastrophe (82,83). At least 90% of strangulated diaphragmatic hernias are traumatic in origin, and at least 95% are on the left side because the liver protects the right diaphragm. Strangulation can occur months to years after the original injury, which is usually an automobile accident. Strangulation typically occurs suddenly and progresses rapidly. Left shoulder pain is generally present due to diaphragmatic irritation. Serosanguineous exudative pleural fluid with predominantly polymorphonuclear leukocytes is almost always present. The diagnosis is usually suggested by air–fluid levels in the viscera strangulated in the left pleural space. Contrast studies of the gastrointestinal tract are sometimes necessary to make the diagnosis. Immediate surgical treatment is imperative to prevent gangrene of the strangulated viscera (81–83).

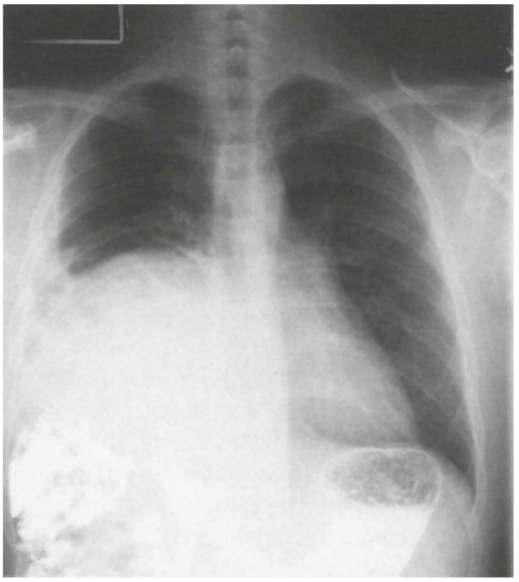

FIGURE 18.3 ■ Posteroanterior chest radiograph from a 31-year-old man who presented with increasing dyspnea. He was in an automobile accident 15 years previously and was told that he had injured his right diaphragm. Note the collections of air in the upper part of the apparent mass. At surgery, both the liver and colon had herniated through the diaphragm.

There is a high incidence of pleural effusions in babies after they have a congenital diaphragmatic hernia repaired (84). In one study (84) of 76 patients, pleural effusion occurred in 16 of 23 patients (70%) who received a Dacro patch and in 6 of 53 patients (11%) who did not received a Dacron patch. The pleural effusions where chylothoraces in 15 of the 22 cases (68%) (84).

ENDOSCOPIC VARICEAL SCLEROTHERAPY

Although currently used less than in the past due to the development of banding procedures for esophageal varies, endoscopic variceal sclerotherapy (EVS) is still used on occasion for patients who have bled from ruptured esophageal varices. Frequently, EVS is followed by the development of a pleural effusion. Saks et al. (85) reviewed the chest radiographs following 38 different EVS procedures and reported that 50% of the procedures were followed by the development of a pleural effusion, whereas Bacon et al. (86) reported pleural effusions following 48% of 65 procedures. The sclerosant used in both of these series was 5% sodium morrhuate. Parikh et al. (87) reported that the incidence of pleural effusion was only 19% in 31 patients in whom absolute alcohol was used as the sclerosant. Left, right, and bilateral effusions occur with approximately equal frequency (88). Most of the effusions are small and resolve within a week (89).

In the Bacon study group (86), 11 pleural fluids were analyzed and all were exudates, primarily by the LDH criteria. There is no relationship between the incidence of fever, the patient's fluid status, or the presence of ascites and the occurrence of postsclerotherapy effusions (86). Patients who develop pleural effusion are more likely to experience chest pain requiring medication after the procedure (86). It is hypothesized that the development of the pleural effusion is related to extravasation of the sclerosant into the esophageal mucosa, which results in an intense inflammatory reaction in the mediastinum and pleura (86). No treatment is necessary for the pleural effusion secondary to EVS. However, if the effusion persists for more than 24 to 48 hours and is accompanied by fever or if the effusion occupies more than 25% of the hemithorax, a thoracentesis should be performed to rule out an infection or an esophagopleural fistula (88). The latter diagnosis is suggested by a high pleural fluid amylase level (see the discussion on esophageal perforation earlier in this chapter).

Small pleural effusions also occur in about 20% of patients who undergo balloon-occluded retrograde transvenous obliteration with 5% ethlanolamine oleate (90).

BILIOUS PLEURAL EFFUSIONS

Bilious pleural effusions are a rare complication of biliary tract disorders. With all cases of bilious pleural effusions, there is a fistula from the biliary tree to the pleural space. Historically, the most common cause has been thoracoabdominal trauma (91); other causes have included parasitic liver disease, suppurative complications of biliary tract obstruction, and postoperative strictures of bile ducts (92). Bilious pleural effusions have also been reported to occur after percutaneous biliary drainage (93) or after placing an internal stent for an obstructed biliary system (94). In two cases with spontaneous biliary pleural fistula, the tract was large enough to allow the passage of gallstones into the pleural space (92,95).

When bile is instilled into the pleural space of rabbits, an inflammatory reaction is produced. The influx of fluid plus the rapid reabsorption of the bile results in

the pleural fluid having a much lower bilirubin than one would anticipate (93). In one patient who developed a pleural effusion as a complication of percutaneous biliary drainage, the pleural fluid bilirubin was only 2.1 mg/dL (93). However, the pleural fluid bilirubin has exceeded 25 mg/dL in some patients (93).

The diagnosis of a bilious pleural effusion should be suspected in any patient with an obstructed biliary system. It is important to remember that the pleural fluid may not appear to be bile, although the ratio of the pleural fluid to serum bilirubin is greater than 1.0 (93). The appropriate treatment for this condition is the reestablishment of the biliary drainage. Most patients who have a bilious pleural effusion after trauma require decortication and diaphragmatic repair (91). The incidence of empyema with bilious pleural effusions approaches 50%, and one should constantly be aware of this complication.

PLEURAL EFFUSIONS AFTER LIVER TRANSPLANTATION

Most patients who undergo an orthotopic liver transplantation develop a pleural effusion postoperatively. Golfieri et al. (96) reviewed the chest x-rays of 300 consecutive patients who had undergone 333 liver transplants over a 11-year period. They reported that 68% of the patients had a pleural effusion and the effusion occupied more than 25% of the hemithorax in 21 patients (7%). The effusion was unilateral on the right side in 153 patients and bilateral in 53. The effusion lasted for more than 1 week in 59 patients. Only 37 of the patients underwent a thoracentesis. Other authors have also reported a high prevalence of pleural effusion following liver transplantation (97,98).

The pleural effusion after liver transplantation may be large. In one series of liver transplants in 48 children, effusions that were large enough to cause clinically detectable respiratory compromise occurred in 23 (19 right sided and 4 left sided) (99). Fifteen of the patients in this latter series were treated with chest tubes (99).

The pathogenesis of the pleural effusions after liver transplantation is not definitely known. It has been suggested that the effusion is due to injury or irritation of the right hemidiaphragm caused by the extensive right upper quadrant dissection and retraction. The natural history of a pleural effusion after transplantation is that it increases in size over the first 3 postoperative days and then gradually resolves over a period ranging from several weeks to several months (97). In one series, the effusion increased in size after the first 3 days in 10 of 42 patients. Seven of these 10 patients had subdiaphragmatic pathology, including 4 with hematomas, 1 with a biloma, and 2 with abscesses (97). Accordingly, patients with enlarging pleural effusions after liver transplantation should be evaluated for subdiaphragmatic pathology.

There is little data on characteristics of the pleural fluid after liver transplantation. In one series (100), thoracentesis was done in 37 patient post lung transplantation and the fluid was exudative in 16 (43%) and the bacterial cultures were positive in 7 (19%).

The pleural effusion that occurs after liver transplantation can be largely prevented if a fibrin sealant is sprayed on the undersurface of the diaphragm around the insertion of the liver ligaments at the time of transplantation. When Uetsuji et al. (101) used the fibrin sealant in 25 liver transplant patients, none developed a pleural effusion postoperatively.

PLEURAL EFFUSIONS AS COMPLICATIONS OF THERAPY FOR TUMORS OF THE LIVER

Several different therapies for hepatic tumor are associated with the development of pleural effusion. When hepatic tumors are treated surgically, there is a high incidence of pleural effusion. In one study (102), the incidence of pleural effusion with an abdominal approach was 43% of 28, whereas the incidence was 73% of 70 with a thoracoabdominal approach. With the thoracoabdominal approach, 17% of the patients required thoracentesis and a mean of three thoracenteses was done on each patient (102). Pleural effusions are also common after magnetic resonance imaging-guided laser-induced thermotherapy. In one study of 899 patients in which 2,132 procedures were performed, 171 of the procedures (8.1%) were complicated by pleural effusion and thoracentesis was required in 16 (0.8%) (103). Tajima et al. (104) reported that the incidence of pleural effusion following transcatheter hepatic chemoembolization through the inferior phrenic vein was 41% in 44 patients who underwent this procedure.

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chapter 19

Pleural Effusion Secondary to Diseases of the Heart

In this chapter, the pleural effusions that occur after coronary artery bypass graft (CABG) surgery, those that occur after cardiac injury (Dressler's syndrome), those that occur concomitantly with pericardial disease, and those that occur after heart transplantation are discussed.

POST–CORONARY ARTERY BYPASS SURGERY

More than 500,000 CABG procedures are now performed annually in the United States (1). Because pleural effusions complicate many of these procedures, pleural effusions that occur after CABG are one of the most common types of effusion.

Incidence

In the period immediately following CABG, there is a very high incidence of pleural effusion. In one study of 152 patients who had undergone CABG surgery, the incidence of pleural effusion on routine chest radiographs 7 days postoperatively was 42% (2). In a subsequent study, patients underwent chest ultrasound on the 7th, 14th, and 30th postoperative day (3). In this latter study, the incidence of pleural effusion was 89.4% on the 7th postoperative day, 76.6% on the 14th postoperative day, and 57.4% on the 30th postoperative day (3). In a more recent prospective study, the prevalence of pleural effusions in 349 patients was 63% 30 days postoperatively (4). The prevalence of pleural effusion appears similar whether the patient has valve surgery or not in addition to the CABG (4).

In patients who have undergone CABG, there is a substantial incidence of large pleural effusions although most effusions are small (5). In a recent study of 349 patients, the incidence of pleural effusion that occupied more than 25% of the hemithorax 30 days after CABG was 9.7% (4). In this study, the incidence of larger effusions was higher in the patients who received internal mammary grafts (10.9%) than it was in patients who received only saphenous vein grafts (4.5%) (4). Hurlbut et al. (6) reported that 4% of 100 patients who had undergone CABG developed moderate-to-large effusions. If 10% of all the patients undergoing CABG develop a moderate-to-large pleural effusion, then the exudative pleural effusion following CABG is one of the most common types of exudative pleural effusion.

Pathogenesis and Pathologic Features

In general the larger pleural effusions, those occupying more than 25% of the hemithorax, that occur after CABG surgery can be divided into those that reach their maximal size within the first 30 days of surgery and those that reach their maximal size more than 30 days after surgery (7). The etiology of the large early pleural effusion after CABG surgery is probably related to trauma to the pleura during surgery (3). Patients undergoing internal mammary artery (IMA) grafting are more likely to have a pleural effusion than those undergoing only saphenous vein grafting (SVG) (3). Patients undergoing bilateral IMA bypasses are more likely to have a pleural effusion than those undergoing unilateral IMA bypasses (8). Patients with a pericardial effusion postoperatively are more likely to have a pleural effusion, but it is likely that both are a result of trauma rather than one being responsible for the other (3). The effusions

occurring early in the postoperative period are frequently bloody. In one series, the mean pleural fluid red blood cell count in 45 patients with large pleural effusions within the first 30 days of surgery exceeded 2,000,000/mm^3 (7), which is equivalent to a hematocrit of 20%.

The etiology of the effusions that occur more than 30 days after CABG is not known. The fluid is an exudate with predominantly lymphocytes (7). Because the fluid is an exudate, the effusion is probably not due to congestive heart failure. The presence of the lymphocytes suggests an immunologic basis. Pleural biopsies obtained within the first few months of surgery demonstrate an intense lymphocytic pleuritis (9). Immunohistochemical staining demonstrates that the lymphocytes in the pleural tissue are both T lymphocytes and B lymphocytes with a predominance of B lymphocytes (9). The effusions have been attributed to the post–cardiac injury syndrome (PCIS) (10). This explanation, however, is unsatisfactory because patients with PCIS usually have fever, chest pain, pericarditis, and pneumonitis in addition to the pleural effusion. Patients with the late pleural effusions after CABG usually do not have fever, chest pain, pericarditis, or pneumonitis (4). Possibly, the late pleural effusion after CABG is a variant of or a limited variety of the PCIS (7).

The administration of topical hypothermia through iced slush during CABG surgery appears to be associated with a higher prevalence of pleural effusion. In one study of patients receiving only saphenous venous grafts, the prevalence of pleural effusion was 50% in 50 patients receiving topical hypothermia, but only 18% in 50 patients not receiving topical hypothermia (11). In a second study of 505 nonrandomized, consecutive patients undergoing CABG surgery, 60% of the 191 patients who received topical hypothermia had a pleural effusion, whereas only 25% of the 314 patients who did not receive topical hypothermia had a pleural effusion (12). The explanation for the association between iced slush and the presence of pleural effusion is not known, but it has been speculated that cold injury to the phrenic nerve may cause atelectasis (5).

It has been hypothesized that the development of the pleural effusion post-CABG is due, at least in part, to the patients being on cardiopulmonary bypass. This is not definitely the case, however, because in two small series (13,14) the prevalence of pleural effusion was actually higher in patients who had off-pump coronary artery bypass surgery than in those who had on-pump surgery. However, in a series from Nashville, the prevalence of effusion at 30 days postoperatively that occupied more than 25% of the hemithorax was only 3% in the off-pump group (15) whereas in a previous study from the same hospital it had been 10% in the on-pump group (4).

Clinical Manifestations

Dyspnea is the only symptom that most patients with pleural effusions experience after CABG (4). Pleuritic chest pain, chest wall tenderness, fever, pneumonitis, and pericarditis are all unusual. In one series of 29 patients with large pleural effusions, 75.9% complained of dyspnea, 10.3% complained of chest pain, and only 1 (3.4%) complained of fever (4).

The pleural effusions that occur after CABG surgery tend to be unilateral on the left side. In the study using ultrasound in which 42 of 47 patients had pleural effusions on the seventh postoperative day, 17 (40%) of the effusions were unilateral on the left, 24 (57%) were bilateral, and 1 (2%) was unilateral on the right (3). By the 30th postoperative day, there were 27 patients with effusions, and 18 (67%) of these were unilateral left sided, 8 (30%) were bilateral, and 1 (4%) was unilateral right sided (3).

In studies of patients who have larger pleural effusions, the effusions are usually left sided, or if they are bilateral, they are larger on the left. In the study by Sadikot et al. (7) of 71 patients with post-CABG pleural effusions who underwent thoracentesis, 42 of the effusions (59%) were unilateral left sided, 18 (25%) were bilateral and usually larger on the left, and 11 (15%) were unilateral on the right.

As mentioned in the preceding text, the larger pleural effusions that occur after CABG can be divided into those that occur within the first 30 days of the surgery and those that occur more than 30 days after surgery (7,16). The late effusions do not appear to evolve from the early effusions. The characteristics of the pleural fluid in the two situations are quite different. The pleural fluid with the early effusions is bloody, with a mean red blood cell count of approximately 2,000,000/mm^3 (7,16). The pleural fluid is frequently eosinophilic, with a mean eosinophil percentage of greater than 40% (7). The pleural fluid eosinophilia is probably due to the blood in the pleural space. Patients with eosinophilic pleural effusions post-CABG also tend to have peripheral eosinophilia (17). There is a significant correlation between the percentage of eosinophils in the pleural fluid and the serum, although the percentage of eosinophils in the serum is lower (17). In these patients, the eosinophilia is correlated with the

levels of interleukin-5 and eotaxin-3 in the pleural fluid, which are higher than the corresponding levels in the serum (17). The mean pleural fluid lactate dehydrogenase (LDH) with the bloody effusions is approximately twice the upper limit of normal for serum (7). It is likely that much of the pleural fluid LDH is LDH-1, which is the LDH from the red blood cells. The pleural fluid protein is in the exudative range, and the pleural fluid glucose level is not reduced (7).

In contrast to the bloody exudates that were discussed in the preceding text, the pleural fluid that occurs more than 30 days after CABG is a clear yellow lymphocyte-predominant exudate. The mean lymphocyte percentage for 26 late effusions in one series was 61%, whereas the mean eosinophil percentage was only 2% (7). The pleural fluid LDH tends to be lower with the late effusions than with the early effusions and averages about the upper limit of normal for serum (7). As with the early effusions, the pleural fluid protein is in the exudative range and the pleural fluid glucose level is not reduced (7). A small percent of patients will develop dyspnea from a pleural effusion more than 90 days post-CABG surgery (18). Most effusions occurring this long after surgery are transudates due to heart failure (18).

Diagnosis

The diagnosis of pleural effusion secondary to CABG is one of exclusion. In the days immediately after CABG, the main diagnoses to exclude are congestive heart failure, pulmonary embolus, parapneumonic effusion, and chylothorax. Congestive heart failure is excluded if the patient has an exudative pleural effusion. Chylothorax is excluded if the fluid is clear yellow or if the triglyceride levels are low. Pulmonary embolus is more difficult to exclude, and a computed tomography (CT) angiography is necessary in some cases (see Chapter 17). However, the pleural effusion with pulmonary embolus usually occupies less than 25% of the hemithorax and disappears spontaneously within a couple of weeks. Patients with parapneumonic effusions are usually febrile, and the pleural fluid differential white blood cell (WBC) count reveals predominantly neutrophils and a very low percentage of eosinophils.

The differential diagnosis is somewhat different for the late pleural effusion occurring after CABG, and the main diagnoses to consider are congestive heart failure, chylothorax, tuberculosis, malignancy, constrictive pericarditis, and pulmonary embolus. As with the early effusion, the diagnosis of congestive heart failure is eliminated if the patient has an exudative pleural effusion and the diagnosis of chylothorax is excluded if the patient's pleural fluid is clear or has a low triglyceride level. With a lymphocyte-predominant pleural effusion, one must exclude tuberculosis. Because the adenosine deaminase (ADA) level is less than 40 IU/L in patients with pleural effusions after CABG (19) and is above this level in patients with tuberculous pleuritis, demonstration of an ADA below 40 IU/L virtually excludes the diagnosis of tuberculous pleuritis. Patients with constrictive pericarditis will usually have other signs and symptoms such as bilateral pedal edema and ascites.

Treatment

Most patients with smaller pleural effusions post-CABG require no treatment as the effusion gradually disappears (5). When a patient is identified with a large pleural effusion after CABG (occupying more than 25% of the hemithorax), a thoracentesis should be performed to exclude the other diagnoses in the differential outlined earlier. Because most of these patients are dyspneic (4) and the therapy of choice for these effusions is a therapeutic thoracentesis, it is recommended that the initial thoracentesis be a therapeutic thoracentesis (5).

If the other diagnostic possibilities are excluded and the fluid recurs, a second and then a third therapeutic thoracentesis are indicated. Many patients are also given nonsteroidal anti-inflammatory agents (NSAIDs) or oral prednisone, but there are no controlled studies documenting the efficacy of this approach. There is one study that evaluated the effectiveness of diclofenac, an NSAID, in preventing pleural effusion in the immediate postoperative period (20). Niva et al. (20) randomized patients to receive 50 mg diclofenac (22 patients) or placebo (19 patients) orally every 8 hours in the postoperative period. They reported that the control group had a higher incidence of pleural effusion (42.1%) at discharge than did the diclofenac-treated group (22.7%) (20). In a second study, Imazio et al. (20a) studied whether colchicine would reduce the incidence of effusions post cardiac surgery in a double-blind randomized study of 360 patients. They reported that the incidence of pleural effusion was significantly less (12.2%) in the group that received colchicine starting on the third postoperative day and continuing for a month than it was in the group that received placebo (22.8%) (21).

Some patients have been managed successfully with chemical pleurodesis. Before one becomes too aggressive in managing this condition, it is important to realize that most patients will do well with no more than a couple of thoracenteses. In our prospective study, we followed 30 patients with pleural effusions occupying more than 25% of the hemithorax for 12 months. During this period, 8 (27%) received no invasive treatment for the pleural effusion, 16 (53%) received a single thoracentesis, 2 (7%) received two thoracenteses, and 4 (13%) received three or more thoracenteses. Only one patient was still receiving periodic thoracenteses 12 months after CABG (4). Twenty-two of the 25 patients who underwent thoracentesis reported that their dyspnea was alleviated with the thoracentesis (4).

On occasion, the effusion persists despite several therapeutic thoracenteses. We have subjected eight such patients to thoracoscopy in recent years. At thoracoscopy, several patients had thin sheets of fibrous tissue that coated the lung and prevented it from expanding (9). It is likely that this sheet of fibrous tissue "trapped" the lung and prevented it from reexpanding. After the fibrous tissue coating the visceral pleura was removed, the lung expanded and the effusion did not recur (9). However, because most had a mechanical or a chemical pleurodesis at the same time, one cannot be certain that the decortication was responsible for the effusion not recurring. Recurrent pleural effusions post-CABG surgery have also been managed successfully with video-assisted thoracic surgery with talc insufflation (21). No mention was made in this latter paper about membranes encasing the visceral pleural (21).

In view of the series mentioned in the preceding text, thoracoscopy is recommended for an effusion after CABG that continues to recur for several months despite several therapeutic thoracenteses. At thoracoscopy, any fibrous tissue coating the visceral pleura should be removed and the parietal pleura should be abraded to create a pleurodesis.

Pleural Effusion After Ventricular Assist Device Placement

Patients who receive ventricular assist devices are being used more frequently as bridges to cardiac transplantation or to facilitate patient transfers. It appears that most placements of this device are associated with the development of a pleural effusion (22). Guha et al. (22) reviewed the placement of 22 of these devices and reported that every patient had a pleural effusion after placement (22). Six of the 22 patients (18%) had effusions before surgery. Nine patients required thoracentesis to relieve dyspnea and the median time from placement to thoracentesis was 23 days. All the pleural fluids examined were blood-tinged exudates (22).

POST–CARDIAC INJURY (DRESSLER'S) SYNDROME (PCIS)

PCIS is characterized by the onset of fever, chest pain, pleuropericarditis, and parenchymal infiltrates in the weeks following injury to the pericardium or myocardium (23,24). There is no universal agreement on the definition of the PCIS (22). Mott et al. (25) defined noncomplicated PCIS as the presence of a temperature greater than 100.5°F, patient irritability, pericardial friction rub, and a small pericardial effusion with or without pleural effusion following cardiac trauma (25). They defined complicated PCIS as a noncomplicated PCIS plus the need for hospital readmission with or without the need for pericardiocentesis or thoracentesis (25). I prefer the proposed definition of Imazio et al. (26) who define the PCIS as the presence of at least two of the following: fever without alternative explanation, pleuritic chest pain, pericardial friction rub, new or worsening pleural effusion, and new or worsening pericardial effusion. This syndrome has been described following myocardial infarction, cardiac surgery, blunt chest trauma, percutaneous left ventricular puncture, pacemaker implantation, angioplasty, and repair of pectus excavatum (27).

Incidence

The incidence of the PCIS was thought by Dressler to be 3% to 4% after an acute myocardial infarction (23). Subsequent studies have demonstrated that the incidence is probably less than 1% (28), but the incidence is much higher in patients with large transmural infarctions in which the pericardium is involved (29). In one series, 15% of patients with an acute myocardial infarction and pericarditis developed the post–myocardial infarction syndrome during the follow-up period (29). The incidence of the syndrome is much higher following surgical procedures involving the pericardium than after an acute myocardial infarction (24,30). Engle et al. (24) reported that 30% of 257 children undergoing cardiac operations developed the syndrome. Miller et al. (31) reported an incidence of 17.8% in 944 patients undergoing cardiac surgery at Johns Hopkins Hospital during a 1-year period. In a recent study (32), the incidence of PCIS was 15% in 360 patients undergoing cardiac surgery.

Etiologic Factors

The cause of the syndrome is unknown, but it appears to have an immunologic basis. The syndrome is thought to be initiated by a combination of damage to the pericardium and/or pleura and especially bleeding into the pericardium (33). Then this damage is thought to initiate immunologic events in susceptible individuals. (33). In patients undergoing surgical procedures involving the pericardium, a close relationship exists between the development of the syndrome and the presence of antimyocardial antibodies. Engle et al. (24) prospectively followed up 257 patients undergoing cardiac operations and found that 67 (26%) had high titers of antimyocardial antibodies, and all of these patients developed the syndrome. None of the 102 patients without a rise in antibody titers developed the syndrome, and only 4 of 93 patients with intermediate titers developed the syndrome. In a second study conducted by De Scheerder et al. (34), antibodies to actin and myosin were measured preoperatively and postoperatively in 62 patients undergoing CABG. Eight patients (13%) developed the PCIS, and all of them had more than a 60% increase in their antibodies to both actin and myosin postoperatively. Thirty-eight patients did not develop the syndrome, and none of these patients had more than a 50% rise in either of the antibodies. The remaining patients developed an incomplete syndrome and had intermediate increases in their antibody titers. No such clear-cut relationship has been demonstrated between antimyocardial antibodies and the syndrome in patients with myocardial infarction. Liem et al. (28) were unable to find any association between the development of the syndrome and the presence of antimyocardial muscle antibodies in 136 patients with an acute myocardial infarction. In postoperative patients, it is unclear whether the antimyocardial antibodies precipitate or result from the syndrome.

Other factors also appear to be associated with the development of PCIS. Epidemiologic studies indicate that there is a seasonal variation in the PCIS, with the highest incidence corresponding to the time of the highest prevalence of viral infection in the community (35). It has been hypothesized that a concurrent viral infection may trigger the immune response (34). In patients undergoing cardiac surgery, the incidence is approximately the same after all types of surgery (31). Younger patients and those who are asymptomatic preoperatively are more likely to develop the syndrome (31). There is also a higher incidence of the syndrome if the patient has a history of pericarditis or if the patient had taken corticosteroids previously (31).

Clinical Manifestations

PCIS is characterized by fever, chest pain, pericarditis, pleuritis, and pneumonitis occurring after cardiac trauma or an acute myocardial infarction. The symptoms following myocardial infarction usually develop in the second or third week; an occasional patient develops symptoms within the first week (35), and a larger percentage of patients develops symptoms only after the third week. The syndrome is seen at an average of 3 weeks following cardiac operations but can occur any time between 3 days and 1 year (36). The two cardinal symptoms of the syndrome are fever and chest pain (23,36). The chest pain often precedes the onset of fever and varies from crushing and agonizing, mimicking myocardial ischemia, to a dull ache, to pleuritic chest pain (23). Almost all patients have a pericardial friction rub, and many of them also have a pericardial effusion. As many as 75% of patients with these syndromes have pulmonary infiltrates, either linear or in patches, mostly located in the base of the lungs (37). Laboratory evaluation reveals a peripheral leukocytosis (10,000 to 20,000/mm^3) and an elevated erythrocyte sedimentation rate or CRP in most patients (23,32,36).

Pleural involvement is common in the PCIS. Dressler (23) reported that 68% of 35 patients with the post–myocardial infarction syndrome had pleural effusions. In another series of 35 patients with PCIS, 29 patients (83%) had a pleural effusion; the effusion was unilateral in 18 and bilateral in 11 of the patients (37). Imazio et al. (32) reported that 93% of 54 patients with the PCIS post-cardiac surgery had a pleural effusion. In general, the pleural effusion is small, and pericarditis is the dominant feature. The pleural fluid is an exudate with a normal pH and a normal glucose level (37). The pleural fluid is frankly bloody in approximately 30% of patients, and the differential WBC may reveal predominantly polymorphonuclear leukocytes or mononuclear cells, depending on the acuteness of the process (37).

Diagnosis

The diagnosis of the syndrome should be considered in any patient who develops a pleural effusion following myocardial infarction, a cardiac operation or other trauma to the heart, particularly when signs of pericarditis are present. The diagnosis of the syndrome is established by the clinical picture and by ruling out

congestive heart failure, pulmonary embolism, and pneumonia. Congestive heart failure as a cause of the pleural effusion is excluded by the demonstration of an exudative pleural fluid. A pulmonary CT angiogram or a perfusion lung scan should be obtained to exclude the diagnosis of pulmonary embolization. It is important not to mistakenly diagnose pulmonary embolism rather than the PCIS because anticoagulation is contraindicated in the PCIS (23). Patients with the syndrome are at risk for developing hemopericardium. One report suggested that the diagnosis of the syndrome could be established by demonstrating a high titer of antimyocardial antibodies and a low complement level in the pleural fluid (38). However, a subsequent publication (39) and our own unpublished observations have failed to confirm that levels of antimyocardial antibodies in the pleural fluid are elevated in patients with the PCIS.

Treatment

This syndrome usually responds to treatment with antiinflammatory agents such as aspirin or indomethacin (33). In the more severe forms of the syndrome, corticosteroids may be necessary (33). However, the prophylactic administration of intravenous methylprednisolone at a standard anti-inflammatory dose in children after cardiac surgery with cardiopulmonary bypass neither prevents nor attenuates the PCIS (25). A recent placebo-controlled double-blind randomized study (40) of 360 patients reported that the administration of colchicine on the third postoperative day and continuing for 30 days was associated with a reduction in the incidence of pericardial effusion from 22.8% to 12.8% and a reduction in the incidence of pleural effusion from 26.5% to 12.2%

It is important to establish the diagnosis of the PCIS in patients who have undergone CABGs because the pericarditis may cause graft occlusion. Urschel et al. (36) reported that graft occlusion occurred in 12 of 14 patients (86%) who developed the syndrome after CABGs and who were treated symptomatically. When 31 subsequent patients were treated with prednisone, 30 mg/day for a week and tapering doses for 5 weeks thereafter, in addition to aspirin 600 mg q.i.d., only 5 (16%) of the grafts became occluded (36).

PERICARDIAL DISEASE

A substantial percentage of patients with pericardial disease develop a pleural effusion, which is usually left sided. Weiss and Spodick (41) reviewed the charts of 133 consecutively discharged patients with pericardial effusion. Thirty-five of the patients (26%) had a roentgenographically demonstrable pleural effusion and no other lung disease. Twenty-one of the patients had inflammatory pericardial disease without congestive heart failure, and 15 of them had only a left-sided pleural effusion, 3 had more fluid on the left than on the right, and in 3, the effusions were of the same size on both sides. Of the five patients with inflammatory pericarditis and congestive heart failure, the effusions were equal bilaterally in two, greater on the right side in two, and left sided in one. Two of the three patients with constrictive pericarditis had a unilateral left-sided effusion. Sun et al. (42) performed CT scans on 74 patients with pericardial effusions and reported that 52 (70%) had a pleural effusion. The incidence of effusion was comparable whether the patient had benign or malignant pericardial disease (42). Tomaselli et al. (43) reviewed 30 cases of constrictive pericarditis and found that a pleural effusion was present in 18 (60%). In 12 of the 18 patients, the effusion was bilateral and approximately symmetric. Three effusions were left sided, and three were right sided. We described one patient with constrictive pericarditis who had a large unilateral right-sided pleural effusion, which we attributed to the transdiaphragmatic transfer of his ascitic fluid (44).

The mechanism responsible for the pleural effusion associated with pericardial disease is not clear. The obvious explanation is that the pulmonary and systemic capillary pressures are elevated secondary to the pericardial disease, resulting in a transudative pleural effusion. However, if this were the sole explanation, one would not expect most of the effusions to be left sided in patients with inflammatory pericardial disease and also that some patients with constrictive pericarditis would have exudative pleural effusions (43). It is probably that in patients with pericardial effusions, some of the fluid passes directly from the pericardial space into the pleural space. Gibson and Segal (45) showed that 20% of protein injected into the pericardium entered the pleural space within an hour of the injection. The pericardial inflammation itself may increase the ease by which fluid passes from the pericardial to the pleural space (41). In addition the pericardial inflammation may also cause inflammation of the pleura covering the pericardium which could lead to a pleural effusion.

The characteristics of the pleural fluid seen in conjunction with pericardial disease are not well described. Tomaselli et al. (43) reported that the fluid was exudative in three patients and transudative in

one patient with constrictive pericarditis. We described one patient with a large right-sided pleural effusion with constrictive pericarditis who had a pleural fluid protein of 4 g/dL (44). In another recent report of two patients with constrictive pericarditis secondary to bromocriptine therapy, the pleural fluid in one had a protein level of 4 g/dL (simultaneous serum level of 6.4 g/dL) (46). I would suspect that the pleural fluid with inflammatory pericardial disease is also exudative.

Obviously, the treatment of choice for the pleural effusion secondary to pericardial disease is to treat the pericardial disease.

POST–HEART TRANSPLANTATION

Pleural effusions are common after heart transplantation. Misra et al. (47) retrospectively reviewed the charts and imaging studies of 72 patients who had undergone orthotropic heart transplants over a 6-year period and reported that 61 patients (85%) had a pleural effusion postoperatively while only 19 (26%) had effusions preoperatively. Most of the effusions were small and bilateral, but 16% of the patients had effusions that occupied more than 25% of the hemithorax (47). All of these effusions were attributed to the transplantation procedure. The effusions were largest at median hospital day 6.5. Most of them resolved within the first year after transplantation (47). Pleural fluid was examined in four of the patients and was exudative in two (47).

A second study (48) reviewed all the pulmonary complications in 157 patients that received 159 transplants. Ten of the patients (6.3%) developed pleural effusions that warranted a diagnostic thoracentesis and/or specific therapeutic intervention with diuretics, antibiotics, or chest tubes (48). The etiology of the effusion was found to be parapneumonic in four cases, chylothorax in one, hemothorax secondary to Aspergillus pneumonia in one, sepsis in one, and probable transudates in three cases (48). There was one case report of a pleural effusion due to post–transplant lymphoproliferative disorder (49). At autopsy, the patient had pleural-based tumor nodules compatible with post–transplant lymphoproliferative disorder (49).

The management of patients with pleural effusions depends on the size of the effusion and the patient's clinical picture. If the effusion occupies more than 25% of the hemithorax, a diagnostic thoracentesis should be performed immediately in an attempt to ascertain the etiology of the effusion. The main considerations are pleural infection, chylothorax, congestive heart failure, and a pleural effusion post–heart transplant similar to the effusions post-CABG surgery. If the effusion is very small, it can probably be ignored because these effusions are very common (47). If the effusion occupies less than 25% of the hemithorax but represents more than just blunting of the costophrenic angle, a diagnostic thoracentesis should be performed if the patient is complaining of shortness of breath or if the patient is not feeling up to par. It is important to remember that these patients are immunosuppressed and accordingly are more likely to have infections. Moreover, patients with pleural infections may not be febrile because of the immunosuppression.

PULMONARY VEIN STENOSIS AFTER CATHETER ABLATION OF ATRIAL FIBRILLATION

A procedure that is being used more and more commonly for the treatment of chronic atrial fibrillation is circumferential pulmonary-vein ablation (50). A known complication of this procedure is pulmonary vein stenosis (51), which occurs in approximately 3% of patients who undergo this procedure (52). Presenting symptoms with pulmonary vein stenosis include shortness of breath, cough, and hemoptysis (53). In one series, 5 of 18 patients (28%) had a pleural effusion whereas 7 (39%) had a parenchymal infiltrate (53). The pleural fluid was described in one case, and it was exudative with a pleural fluid protein of 4.7 g/dL (serum 7.1 g/dL) and a pleural fluid LDH level of 1,308 U/L (serum 302 U/L) (54). Pathologic examination of the areas of infiltrate reveal hemorrhagic infarctions. The pathogenesis of the infiltrates and the effusion is probably ischemia from the lack of perfusion of the lung drained by the occluded vein. The perfusion lung scan shows decreased perfusion to the areas drained by the stenotic vein. Treatment is stenting or balloon angioplasty of the stenotic vein (55).

FONTAN PROCEDURE

With the Fontan procedure, the right ventricle is bypassed by an anastomosis between the superior vena cava and the inferior vena cava and, the right atrium, or the pulmonary artery (56). The procedure is typically performed for tricuspid atresia or univentricular heart. Pleural effusion is a significant problem after the Fontan procedure. Persistent pleural drainage is the primary cause of prolonged postoperative hospital stay in patients who have had a Fontan procedure (57).

Zellers et al. (58) analyzed pleural fluid formation after this procedure on 46 patients. They reported that the median amount of pleural drainage was 3,220 mL, with a range of 155 to 31,000 mL. Most patients had pleural drainage from both sides. Gupta et al. (59) reviewed the pleural fluid drainage in 100 consecutive patients who underwent the Fontan operation and reported that the median duration of chest tube drainage was 10 days and the median volume of drainage was 14.7 mL/kg/day.

The pathogenesis of the formation of the large amounts of pleural fluid postoperatively in these patients is not definitely known. It is probably related to the increased systemic venous pressure. It is unclear, however, whether increased pleural fluid transudation from the parietal pleura, lymphatic leakage into the pleural space (60), or hormonal changes are responsible for the large accumulations of pleural fluid. Spicer et al. (61) analyzed the factors that were related to the development of pleural effusions after the Fontan procedure in 71 children. They found that patients with significant aortopulmonary collateral vessels evidenced by angiographic opacification of the pulmonary arteries or veins had more prolonged pleural drainage. They believed that the aortopulmonary collateral vessels contributed to volume loading of the systemic ventricle and to elevation of the pulmonary artery, and right atrial and caval pressures, all of which increase the rate of formation of the pleural fluid. When 13 patients were subjected to preoperative embolization of these vessels, the median duration of the effusion postoperatively was only 6.5 days (61). Gupta et al. (59) performed a multivariate analysis for significant risk factors for pleural effusions lasting more than 2 weeks or more than 20 mL/kg/day in 100 children undergoing the Fontan procedure. They found that a lower preoperative oxygen saturation, a smaller conduit size, and a longer duration of cardiopulmonary bypass were associated with the longer and larger amounts of fluid drainage. The authors were unable to demonstrate a relationship between the presence of aortopulmonary collateral vessels and the amount of pleural fluid drainage (59). Yun et al. (62) studied 85 patients undergoing the Fontan procedure and reported that prolonged pleural drainage was associated with a low pulmonary vascular compliance and cardiopulmonary bypass time. The Fontan procedure is also performed in adults and persistent pleural effusion is a problem in adults as it is in children. Burkhart et al. (62a) reported that 36 of 121 adults who underwent the Fontan procedure had pleural effusions that persisted more than 2 weeks.

It appears that creation of a fenestration at the time of surgery will reduce the amount of pleural fluid drainage. Lemler et al. (63) randomly assigned 49 patients to receive or not receive a fenestration at the time of the Fontan procedure. The fenestration consisted of a single 3- to 6-mm communication between the Fontan channel and the pulmonary venous atrium (63). Performance of the fenestration was associated with a reduction in the median chest tube drainage from 4,588 to 1,734 mL and a decreased hospital stay from 23 to 12 days (63). The disadvantage to the creation of a fenestration is that it creates a right-to-left shunt which can lead to increased hypoxemia (63). Not all studies have found that fenestration is associated with decreased amounts of pleural fluid drainage. In a study in which the patients were not randomized, Atik et al. reported that pleural drainage was less in patients who did not receive fenestration (64).

It has been hypothesized that alterations in the hormones that regulate fluid and electrolyte homeostasis may also play a role (65). Indeed in one study, patients who developed effusions following surgery had an elevated serum renin and angiotensin compared with those who did not (65). In one study, patients who were given enalapril 5 μg/kg intravenously within 1 hour of surgery and every 12 hours thereafter until they were able to tolerate enteral feeding had significantly less total pleural fluid drainage (10.6 mL/kg) than did patients who did not receive enalapril (19.6 mL/kg) (66). However, the administration of captopril had no effect on pleural fluid formation in a subsequent study (57).

The pleural fluid with the Fontan procedure is an exudate in almost every case (67). In one series of 15 patients, the mean pleural fluid LDH was 1,575 IU/L suggesting a very inflammatory state (67). The pleural fluid triglycerides were elevated in 4 of the 15 patients indicating that these patients had chylothoraces (67).

The optimal treatment for the patient who has prolonged pleural drainage after a Fontan procedure remains to be determined. The intrapleural administration of tetracycline at the end of the surgical procedure had no effect on the amount or the duration of the fluid drainage (58). One study by Cava et al. demonstrated that the duration of pleural drainage was shorter and the total volume was less when the patients postoperatively were placed on a regimen consisting of diuretics (hydrochlorothiazide and spironolactone), fluid restriction, captopril, a low-fat diet, and a minimum of 0.5 L of supplemental oxygen by nasal cannula than when they were not placed on

such a protocol (68). In patients who have markedly prolonged pleural fluid drainage, consideration should be given to the implantation of a pleuroperitoneal shunt (69), the insertion of an indwelling catheter such as the Pleurx Pleural Catheter (Care Fusion, San Diego, California) or an attempt at pleurodesis with a sclerosing agent such as doxycycline (70). Some patients have been managed successfully with medium-chain triglycerides or with pleurectomy and ligation of the thoracic duct (60). Caverly and coworkers administered octreotide to 10 patients with persistent effusions after the Fontan procedure and reported resolution of the effusion with octreotide in 6 of the patients (71).

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chapter 20

Pleural Disease in Obstetrics and Gynecology

In this chapter, the pleural effusions seen in the practice of obstetrics and gynecology are discussed. The ovarian hyperstimulation syndrome (OHSS) occurring before pregnancy, fetal pleural effusions, postpartum pleural effusion, Meigs' syndrome, and finally, the pleural effusions secondary to endometriosis are addressed.

OVARIAN HYPERSTIMULATION SYNDROME

OHSS is a serious complication of ovulation induction with human chorionic gonadotropin (hCG) and occasionally clomiphene (1). This syndrome is characterized by ovarian enlargement, ascites, pleural effusion, hypovolemia, hemoconcentration, and oliguria (2). A rare complication is the occurrence of thromboembolism related to hemoconcentration (2). The severe form with ascites or pleural effusion, or both, occurs in approximately 3% of patients undergoing ovulation induction for *in vitro* fertilization, but radiologically evident pleural effusions develop only in approximately 1% (3).

Pathogenesis

OHSS has two primary components: (a) enlargement of the ovaries accompanied by the formation of follicular, luteal, and hemorrhagic ovarian cysts and edema of the stroma, and (b) an acute shift of fluid out of the intravascular space (3). The syndrome is more frequent in cycles resulting in pregnancy (4). The exact pathogenesis of this syndrome is not clear. At one time, it was thought that the OHSS resulted from high local concentrations of estrogen in the ovaries causing altered capillary permeability and ascites, which, in turn, led to the pleural effusion. This does not appear to be the sole explanation, however, because the syndrome can still be produced in rabbits when the ovaries are exteriorized (5). This indicates that there must be systemic effects involved in the fluid shifts into the peritoneal and pleural cavities. It is now believed that the syndrome is precipitated by an ovarian product, vasoactive peptide, or cytokine that has been released into the peritoneal cavity by the ovary or that has gained access to the systemic circulation directly from the corpus luteum or serosal vessels. Three likely candidates are vascular endothelial growth factor (VEGF) (6,7), interleukin 8 (IL-8) (7), and interleukin 6 (IL-6) (6). All three have been shown to be markedly elevated in the follicular fluid and ascites. Antibodies to VEGF reduce the ascites-induced endothelial permeability to 44% of control and antibodies to IL-8 reduce the ascites-induced endothelial permeability to 34% of control (7). Antibodies to IL-6 do not significantly affect ascites-induced endothelial permeability (7). It has also been shown that hCG upregulates the VEGF expression of granulosa cells in the OHSS, but not in control groups (8). The serum levels of VEGF are elevated in patients with OHSS (8). The mean levels of VEGF in ascitic fluid with the OHSS (7) are higher than the mean level of VEGF in any type of pleural effusion (7). The mean level of VEGF in the pleural fluid with the OHSS is elevated but is only about 60% that in ascitic fluid (9).

There are probably two factors responsible for the accumulation of pleural fluid with OHSS. In patients with bilateral effusions, the probable mechanism is a generalized capillary leak syndrome. In patients with large right-sided pleural effusions, it is probable that the fluid moves directly from the peritoneal space to the

pleural space. Evidence supporting this mechanism is the fact that the effusions are frequently large and right-sided, many patients have ascites, and the observation in one patient that the pleural fluid IL-6 level was more than 100 times higher than the simultaneously obtained serum level (10). Obviously, the pleural fluid in this case was not due to a generalized capillary leak syndrome.

Clinical Manifestations

Patients with OHSS initially develop abdominal discomfort and distension, followed by nausea, vomiting, and diarrhea. As the syndrome worsens, the patients develop evidence of ascites and then hydrothorax or breathing difficulties. In the most severe stages, the patients develop increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminishing renal function (3). Respiratory symptoms develop 7 to 14 days after the hCG injection (4).

The pleural effusions with OHSS are usually right sided. In the series of 33 patients with pleural effusions reported by Abramov et al. (11), 17 effusions (52%) were right sided, 9 (27%) were bilateral, and 7 (21%) were unilateral left sided. At times, a pleural effusion may be the sole manifestation of OHSS (12). The pleural effusion can be a significant problem, as evidenced by one patient who had 8,500 mL pleural fluid aspirated from her pleural space over 14 days (13). The pleural fluid in patients with OHSS is an exudate. In the series of Abramov et al. (14), the mean pleural fluid protein was 4.1 g/dL, whereas the mean serum protein was 4.4 g/dL.

The incidence of the syndrome can be reduced if the serum estrogen levels and the number of ovarian follicles are monitored. If the serum estrogen levels are very high or if there are more than 15 ovarian follicles with a high proportion of small and intermediate size follicles, hCG should be withheld (2).

Treatment

The treatment of the OHSS is primarily supportive (1). Hemoconcentration should be treated with intravenous fluids, because hypovolemia can lead to renal failure and even death. If the patient has a large pleural effusion and is dyspneic, a therapeutic thoracentesis should be performed. Rarely is more than one therapeutic thoracentesis necessary (1).

FETAL PLEURAL EFFUSION

The ability to diagnose fetal abnormalities prenatally has been facilitated by diagnostic ultrasound. One abnormality now diagnosed on occasion is fetal pleural effusion. Almost all neonatal pleural effusions are probably persistent fetal pleural effusions. The prevalence of fetal pleural effusion is approximately 1 in 10,000 deliveries (15). The prevalence is approximately twice as high in boys as in girls (16). There is one report of a patient who had three children, each of whom had a fetal pleural effusion (17).

Very early in pregnancy, the incidence of pleural effusion is higher. In one study of 965 pregnancies evaluated by ultrasound between 7 and 10 weeks, the incidence of pleural effusion was 1.2% (18). These early pregnancies complicated by effusion had poor outcomes with miscarriages in 86% (18).

If the fetal pleural effusion is untreated, there is a high mortality rate. In one series of untreated patients, the mortality rate was 37% for 54 untreated fetuses (15). The high perinatal mortality rate in cases of fetal pleural effusion is related to three factors: development of nonimmune hydrops, prematurity, and pulmonary hypoplasia (15). Intrathoracic compression of the developing lung produces pulmonary hypoplasia. This pulmonary hypoplasia can sometimes result in perinatal death. The mortality rate is also higher if there are associated chromosomal abnormalities or structural abnormalities. Ruano et al. (19) reported that the mortality of fetuses with isolated pleural effusions was 5 of 14 (36%), of those with structural abnormalities and no chromosomal abnormalities 19 of 19 (100%), of those with chromosomal abnormalities 20 of 23 (87%). The most common chromosomal abnormality in the series of Ruano et al. (19) was Turner syndrome, which occurred in 15 of the 23 patients (65%).

Pathogenesis and Clinical Manifestations

The pathogenesis of fetal pleural effusion is not known and is possibly multifactorial. There is some evidence that the fetal pleural effusions are actually chylothoraces. Benacerraf and Frigoletto (20,21) analyzed the pleural fluid from two fetuses and reported abundant lymphocytes in both, but one had almost all T lymphocytes, whereas the other had a mixture of T and B lymphocytes. The presence of the lymphocytes was suggestive of a chylous effusion. A ratio of the pleural fluid to serum IgG that exceeds 0.6 is very suggestive of a neonatal pleural effusion (22). In addition, most neonatal pleural effusions, which in many cases are continuations of fetal pleural effusions, are chylothoraces (23). Analysis of the pleural fluid for chylomicrons is not useful in the diagnosis of fetal chylothorax because the fetuses are not eating any lipids.

In a review of the literature for isolated fetal pleural effusion in 1998, 204 cases were found (24). The fetal pleural effusions were bilateral in 74%, unilateral right sided in 11%, and unilateral left sided in 14% (24). Polyhydramnios was noted in 72% and hydrops fetalis in 57% (24). The reason for the polyhydramnios is not clear, but it has been suggested that the increased intrathoracic pressure may interfere with normal fetal swallowing. There is a high frequency of chromosomal abnormalities in fetuses with pleural effusions. In one series, the prevalence of chromosomal abnormalities was 50% in 152 fetuses with other sonographic abnormalities and 12% in 94 patients with isolated pleural effusion (25).

Treatment

The optimal management for fetuses with pleural effusions is controversial (15). If the pleural effusions are not treated, some resolve spontaneously whereas others deteriorate to generalized hydrops. In one review of 204 cases, spontaneous remission occurred in 22% (24). Characteristics of cases that resolved spontaneously included diagnosis made early in the second trimester, unilateral effusion, and no associated polyhydramnios or hydrops (24). Some infants die from pulmonary hypoplasia after delivery, whereas others survive. In a review of 82 cases in 1993, the mortality rates of those treated surgically and those treated conservatively were comparable (15). Overall, the mortality rate in cases not terminated by abortion was 36% (15). However, in a second review in 1998, 43% of the fetuses with treatment had a good outcome whereas only 22% without treatment had a favorable outcome (24). In a more recent review (26) of 172 fetuses with isolated pleural effusion, the overall survival rate was 63% with various treatment approaches.

The following scheme is suggested for the management of fetal pleural effusion. When a pleural effusion is discovered in a fetus, a thoracentesis is performed immediately if there is fetal distress or if there is diaphragmatic inversion or shift of the mediastinum to the contralateral side (27). Otherwise the fetus is evaluated for other abnormalities. Then a repeat ultrasound is obtained in 2 to 3 weeks. If the effusion has decreased in size, then the fetus is followed with scans every 2 to 3 weeks. If the effusion is stable, then serial scans are performed and a thoracentesis is performed immediately before delivery to facilitate neonatal resuscitation. If the effusion increases in size, then a diagnostic amniocentesis should be performed for chromosomal analysis and culture of amniotic fluid to screen for bacterial or viral infection. At the same time, a diagnostic thoracentesis should be performed and the pleural fluid sent for culture, cell analysis, and biochemical study. The lung size and the fetal lung distensibility are assessed through ultrasound before and after the thoracentesis. Fetuses that have less-than-normal lung expansion are then subjected to surgical intervention.

The possible surgical interventions for fetal pleural effusion are pleuroamniotic shunt or repeated therapeutic thoracentesis. Rodeck et al. (28) reported their results with the implantation of pleuroamniotic shunts in eight human fetuses with pleural effusion. These shunts were established with double-pigtail nylon catheters with external and internal diameters of 0.21 and 0.15 mm, respectively. The shunts were introduced transamniotically under ultrasound visualization through the fetal midthoracic wall into the effusion. All eight fetuses in this series had large pleural effusions with hydramnios. Twelve pleuroamniotic shunts were placed in these fetuses. One shunt was noted to be free in the amniotic cavity 1 week after insertion and a second shunt was inserted. The remaining 11 shunts functioned until delivery (median 2.5 weeks; range 1–14 weeks). In six fetuses, the pleural effusions almost completely resolved and the hydramnios disappeared. Three of the six fetuses had hydrops that resolved after the insertion of the shunt. All six infants survived, and five had no respiratory difficulty at birth. Fetal hydrothoraces did not resolve in two patients, both of whom had hydrops and died shortly after delivery. In a second study, Blott et al. (29) inserted shunts into 11 fetuses between 24 and 35 weeks of gestation and reported that the effusions were successfully drained in all cases and that 8 of the 11 fetuses survived. It should be noted that the shunts become displaced intrathoracically in a sizeable percentage of fetuses, but there appears to be no long-term pulmonary complications and they do not need to be removed (30).

An alternative approach to the management of the fetal pleural effusion is to perform serial thoracenteses. Benacerraf and Frigoletto (20,21) performed three to five thoracenteses on two fetuses between 20 and 24 weeks of gestation with massive pleural effusions. The effusion did not recur after the last thoracentesis, and normal babies resulted from both pregnancies.

There have been case reports of attempts to create a pleurodesis in the fetus by the intrapleural injection of the immunostimulant OK-432 (31) or maternal blood (32). In general, pleurodesis is not recommended because the long-term side effects from a fetal pleurodesis remain to be determined. In fetuses that

are known to have large effusions just before delivery, if a cesarean section is performed, a thoracentesis can be performed while the fetoplacental circulation is still intact (33). Performance of the thoracentesis in this manner preserves systemic oxygenation (33).

Long-Term Prognosis

The prognosis of fetuses that have pleural effusion and that receive pleuroamniotic shunting appears to be good. Thompson et al. (34) studied 17 infants who had undergone pleuroamniotic shunting for a fetal pleural effusion at a median age of 12 months. They reported that respiratory symptoms and respiratory function were no different in these 17 infants than those in a control group (34).

Other Causes of Neonatal Pleural Effusion

Although most neonatal pleural effusions are persistent fetal pleural effusion, there are other cause of neonatal pleural effusions that should be considered if the neonate was not known to have a fetal pleural effusion. Other possible etiologies include parapneumonic effusions and empyema, hemothorax, congestive heart failure, chylothorax following chest surgery, and central venous catheters that are misplaced so that the infusion enters the pleural space (35,36). If the etiology is unknown, a diagnostic thoracentesis should be performed.

PLEURAL EFFUSION DURING PREGNANCY

There has never been a systematic study on the diseases causing pleural effusion in pregnancy to my knowledge. There is a high incidence of small pleural effusion demonstrable by ultrasonography in pregnant women. Kocijancic et al. (37) performed ultrasound on 47 patients studied at a mean gestation of 24.4 weeks and reported that 28 (59.5%) had free pleural fluid that was bilateral in 18 (38.3%) and unilateral in 10 (21.2%) (37). The mean thickness of the pleural fluid was 2.9 ± 1.1 mm. Patients with pleural fluid were asymptomatic. These same workers reported that the prevalence of demonstrable pleural fluid was 25% in 106 normal individuals (38).

When patients develop symptomatic pleural effusions, several different diseases should be considered. Early in pregnancy, one diagnosis that should always be considered is the OHSS, which is discussed earlier in this chapter.

The distribution of the other causes of pleural effusions in the pregnant individual is probably similar to that in nonpregnant women of the same age (39). In general, I would guess that the leading cause of pleural effusion during pregnancy is pulmonary embolism. The risk of venous thromboembolism among pregnant or postpartum women is 4.29 times greater compared with nonpregnant women (40). The risk of pulmonary embolism is much higher (~15 times) in the postpartum period than during pregnancy (40). Other common causes of pleural effusions include pneumonia with effusion and viral illnesses. The incidence of pleural effusions is low (~3%) in patients with severe preeclampsia or the hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome (41). If the patient has a transudative effusion, peripartum cardiomyopathy, which complicates approximately 1 in 300 pregnancies, should be considered.

POSTPARTUM PLEURAL EFFUSION

As mentioned earlier, there is a high incidence of pulmonary embolism in the postpartum period and this diagnosis should always be considered in the postpartum patient with a pleural effusion. Pleural effusions may develop in the immediate postpartum period or a week or more after delivery. The pathogenesis of the pleural effusions at these two different times is different.

Immediate Postpartum

The prevalence of small pleural effusions in the immediate postpartum period is uncertain (42,43). Hughson et al. (42) retrospectively studied 112 patients who had delivered vaginally and had posteroanterior and lateral chest radiographs within 24 hours of delivery. They reported that 46% of the patients had small pleural effusions, which were bilateral in 75%. The same workers then conducted a prospective study of 30 similar patients who were requested to have a lateral decubitus radiograph if fluid was suggested on the standard radiographs. In this group of 30 women, 20 (67%) had a pleural effusion, and in 11, the effusion was bilateral. Ten of the women had a decubitus radiograph, and free fluid was demonstrated in seven. In two subsequent studies using ultrasound (44,45), 6 of 34 patients (18%) and 7 of 31 patients (23%) had pleural effusions within the first 24 hours of delivery. No correlation was found between postpartum pleural effusion and age, weight gain during pregnancy, duration of labor, use of intravenous fluid, or presence of preeclampsia (44,45). Because ultrasound is more sensitive than the chest radiograph, it is likely that the true incidence is closer to that reported by the latter two groups.

The mechanism responsible for the pleural effusion is unknown. No therapeutic intervention is necessary in the absence of symptoms or signs of illness (42).

Delayed Postpartum

There have been two reports with a total of four patients that have documented the occurrence of a systemic illness with pleural effusions and pulmonary infiltrates occurring in the first few weeks after delivery (46,47). All four of the patients had biologically false-positive tests for syphilis early in the course of their pregnancy. Three of the four patients had severe preeclampsia and three had a cesarean section. All four patients had either lupus anticoagulant or anticardiolipin antibodies, or both, in conjunction with a negative antinuclear antibody test (46,47). Two of the four patients had serious cardiac manifestations, and two of the four patients had intravascular thrombosis within 4 weeks of delivery. Patients who experience pleuropulmonary complications in the first few weeks after delivery should be evaluated for antiphospholipid antibodies. Patients with positive assays may benefit from immunosuppressive therapy and prophylactic anticoagulation to prevent thromboembolic disease (46,47).

PNEUMOTHORAX AND PREGNANCY

Spontaneous pneumothorax complicating pregnancy is rare. Only 56 cases had been reported up until 2008 (48). The average age of these patients was 26.4 (48). Risk factors most commonly associated with pneumothorax in these patients were asthma, cocaine use, hyperemesis gravidarum, history of previous pneumothorax, and underlying infection (48).

MEIGS' SYNDROME

Meigs originally described a syndrome characterized by the presence of ascites and pleural effusions in patients with benign solid ovarian tumors (49). When the ovarian tumor was removed, the ascites and the pleural effusion both resolved. Subsequent to this original report, it has become apparent that a similar syndrome can occur with benign cystic ovarian tumors, with benign tumors of the uterus (fibromyomata), with low-grade ovarian malignant tumors without evidence of metastases (50), and with endometrioma (51). Meigs still prefers to reserve his name for only those cases in which the primary neoplasm is a benign solid ovarian tumor (50). Meigs-type syndromes not associated with benign solid ovarian tumors are frequently called *pseudo-Meigs' syndrome* (52). Nevertheless, I classify any patient with a pelvic neoplasm associated with ascites and pleural effusion, in whom surgical extirpation of the tumor results in permanent disappearance of the ascites and pleural effusion, as having Meigs' syndrome.

Etiologic Factors

The pathogenesis of the ascitic fluid in patients with Meigs' syndrome appears to be a generalized secretion of fluid from the primary tumor. Such tumors secrete a large amount of fluid even when they have been resected and placed in dry containers (50). The serum levels of IL-1, IL-6, IL-8, tumor necrosis factor alpha and VEGF are all elevated in patients with Meigs' syndrome as compared with controls (53,54). Interestingly, cytokine levels in the pleural and ascitic fluid are higher than the simultaneously obtained serum levels (53). The role of these cytokines in the development of Meigs' syndrome remains to be defined.

Only large tumors appear to be associated with free peritoneal fluid at the time of surgical procedures. Samanth and Black (55) found that only tumors with diameters greater than 11 cm were associated with free peritoneal fluid. Approximately 15% of patients with ovarian fibromas have free ascitic fluid (56), but not all patients with ascites have pleural effusions. The genesis of the pleural fluid in Meigs' syndrome is probably similar to that in patients with ascites and cirrhosis (see Chapter 9); that is, fluid passes through pores in the diaphragm (57). Evidence for this pathogenesis includes the similar characteristics of ascitic and pleural fluids, the rapid reaccumulation of the fluid following thoracentesis, and the absence of pleural effusions in some patients with ovarian tumors and ascites (56). Other investigators, however, have concluded that the pleural fluid arises from the transdiaphragmatic transfer of ascitic fluid by the lymphatic vessels (56,58,59).

The tumor most commonly responsible for Meigs' syndrome is the ovarian fibroma, followed by ovarian cysts, thecomas, granulosal cell tumors, and leiomyomas of the uterus (50).

Clinical Manifestations

Patients with Meigs' syndrome usually have a chronic illness characterized by weight loss, pleural effusion, ascites, and a pelvic mass (56). It is important to remember that not all such patients have disseminated pelvic malignant disease. Patients with Meigs' syndrome may even have markedly elevated serum CA 125 levels (60). The pleural effusion is right sided

in approximately 70% of patients, is left sided in 10%, and is bilateral in 20% (59). The only symptom referable to pleural effusion is shortness of breath. Ascites may not be evident on physical examination.

The pleural fluid is usually an exudate. Although several authors have stated that the pleural fluid with Meigs' syndrome is a transudate (56,61), this opinion appears to be based on the gross appearance of the fluid rather than on its protein levels. Most pleural fluids secondary to Meigs' syndrome have a protein level above 3.0 g/dL (56,61–64). The pleural fluid usually has a low white blood cell (WBC) count (fewer than 1,000/mm^3) and is occasionally bloody (56,64). At times, the level of CA 125 in the pleural fluid is elevated and this should not be taken as an indication of malignancy (52,65).

Diagnosis and Management

The diagnosis of Meigs' syndrome should be considered in all women who have pelvic masses, ascites, and pleural effusions. If in such patients cytologic examination of the ascitic and pleural fluid is negative, an exploratory laparotomy or at least a diagnostic laparoscopy should be performed with surgical removal of the primary neoplasm. The diagnosis is confirmed when the ascites and the pleural fluid resolve postoperatively and do not recur. Postoperatively, the pleural fluid disappears from the chest rapidly and is usually completely gone within 2 weeks (63).

ENDOMETRIOSIS

At times, severe endometriosis is complicated by massive ascites (66). In a substantial proportion of patients, a pleural effusion is also present. Muneyyirci-Delale et al. (66) presented 4 cases and reviewed the literature with 23 additional cases and found that 8 of the 27 patients (30%) also had a pleural effusion. The pleural effusion was described as a bloody exudate and in one instance had an elevated pleural fluid level of CA 125 (66). The pleural effusion is thought to be due to ascitic fluid gaining entrance to the pleural cavity through the diaphragm, as in Meigs' syndrome. The pleural effusion is either right sided or bilateral (67).

Most patients initially present with abdominal distension, pain, anorexia, and nausea. Because significant weight loss occurs in many of the patients, the usually presumptive diagnosis is malignancy. However, a large proportion also has clinical manifestations of endometriosis, such as progressive dysmenorrhea and cul-de-sac and uterosacral ligament nodularity. Some patients have exacerbation of their symptoms coincident with menses.

The treatment of the massive ascites, pleural effusion, and endometriosis is difficult. Hormonal therapy (progestational agents, danazol, or luprolide acetate [Lupron]) fails in at least 50% of cases. The most common treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy, but this is difficult owing to the pelvic endometriosis (66).

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chapter 21

Pleural Disease Due to Collagen Vascular Diseases

RHEUMATOID PLEURITIS

Rheumatoid disease is occasionally complicated by an exudative pleural effusion that characteristically has a low pleural fluid glucose level.

Incidence

Patients with rheumatoid arthritis (RA) have an increased incidence of pleural effusion. In a review of 516 patients with RA, Walker and Wright (1) found 17 cases of pleural effusions (3.3%) without other obvious causes (1). Pleural effusions were more common in men (7.9%) than in women (1.6%). These authors also found a high incidence of chest pain in their patients with RA; 28% of the men and 18% of the women gave a history of pleuritic chest pain (1). In a separate study, Horler and Thompson (2) studied 180 patients with rheumatoid disease and found that 9 (5%) had an otherwise unexplained pleural effusion. In this latter study, 8 of 52 men (15%) but only 1 of 128 women (1%) had rheumatoid pleural effusions.

Pathologic Features

Examination of the pleural surfaces in patients with rheumatoid pleuritis at the time of thoracoscopy reveals a visceral pleura with varying degrees of nonspecific inflammation. In contrast, in most cases the parietal pleural surface has a "gritty" or frozen appearance. The parietal surface looks slightly inflamed and thickened, with numerous small vesicles or granules approximately 0.5 mm in diameter (3).

Histopathologically, the most constant finding is a lack of a normal mesothelial cell covering (3). Instead there is a pseudostratified layer of epithelioid cells that focally forms multinucleated giant cells of a type different from those of Langerhans or foreign body giant cells (3). The histologic features in nodular areas are those of a rheumatoid nodule with palisading cells, fibrinoid necrosis, and both lymphocytes and plasma cells (4,5). This picture is virtually diagnostic of rheumatoid pleuritis. However, even with tissue obtained from open thoracotomy, this specific histologic picture may not be seen (6). At times, the thickened pleura contains cholesterol clefts (5).

Clinical Manifestations

Rheumatoid pleural effusions classically occur in the older male patient with RA and subcutaneous nodules. Almost all patients with rheumatoid pleural effusions are older than 35 years of age, approximately 80% are men, and approximately 80% have subcutaneous nodules (1,2,6,7). Typically, the pleural effusion appears when the arthritis has been present for several years. When two series totaling 29 patients are combined (1,7), the pleural effusion preceded the development of arthritis in 2 patients by 6 weeks and 6 months, occurred simultaneously (within 4 weeks) with arthritis in 6 patients, and occurred after the development of arthritis in the remaining 21 patients. In this last group of patients, the mean interval between the development of arthritis and the pleural effusion was approximately 10 years.

The reported frequency of chest symptoms in patients with rheumatoid pleural effusions has varied markedly from one series to another. In one series of 24 patients, 50% of the patients had no symptoms referable to the chest (8). In a second series of 17 patients,

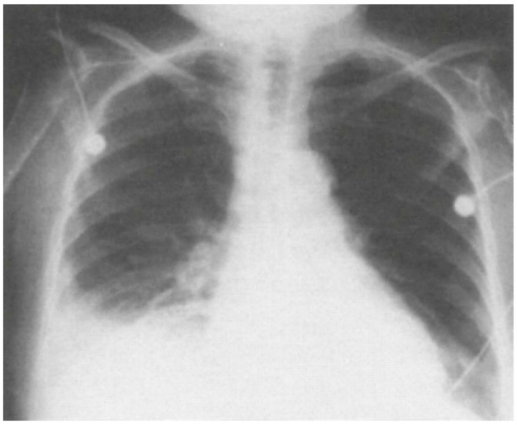

FIGURE 21.1 ■ Posteroanterior radiograph from a patient with long-standing rheumatoid arthritis. Note the right pleural effusion and the destructive changes in the shoulders. *(Courtesy of Dr. Harry Sassoon.)*

15 complained of pleuritic chest pain (1), whereas in a third series, 4 of 12 complained of pleuritic chest pain, and of these, 3 were febrile (7). Other patients complained of dyspnea secondary to the presence of fluid. In one reported patient, the pleural effusion was large enough to cause respiratory failure (9).

The chest radiograph in most patients reveals a small-to-moderate-sized pleural effusion occupying less than 50% of the hemithorax (Fig. 21.1). The pleural effusion is most commonly unilateral, and no predilection exists for either side (6). In approximately 25% of patients, the effusion is bilateral (1). The effusion may eventually alternate from one side to the other or may come and go on the same side. As many as one third of these patients may have associated intrapulmonary manifestations of RA (1). PET scans of patients with rheumatoid pleuritis show intense pleural uptake (10).

Diagnosis

The diagnosis of a rheumatoid pleural effusion is not difficult if the patient is a middle-aged man with RA and subcutaneous nodules.

Pleural Fluid Examination

Examination of the pleural fluid is useful in establishing the diagnosis because the fluid is an exudate characterized by a low glucose level (<40 mg/dL), a low pH (<7.20), a high lactate dehydrogenase (LDH) level (>700 IU/L or >2 times the upper limit of normal for serum), low complement levels, and high rheumatoid factor titers (>1:320), which are at least as high as those in serum (7) (see Chapter 7). Occasionally, the pleural fluid glucose is not reduced when the patient is first seen, but serial pleural fluid glucose determinations reveal progressively lower pleural fluid glucose levels. In the patient with arthritis and pleural effusions, the main differential diagnosis is between rheumatoid pleuritis and lupus pleuritis. Patients with lupus pleuritis have higher pleural fluid glucose levels (>60 mg/dL), higher pleural fluid pH (>7.35), and lower pleural fluid LDH levels (<500 IU/L or <2 times the upper limit of normal for serum) than patients with rheumatoid pleuritis (7). Other immunologic tests are discussed in Chapter 7, but they are not generally recommended.

The pleural fluid differential can reveal predominantly polymorphonuclear or mononuclear leukocytes, depending on the acuteness of the process. The cytologic picture from most patients with rheumatoid pleural effusion is suggestive of the diagnosis (8). The cytologic picture with rheumatoid pleuritis is characterized by three distinct features: (a) slender, elongated multinucleated macrophages; (b) round giant multinucleated macrophages (Fig. 21.2); and (c) necrotic background material (8). When Naylor (8) reviewed the cytologic picture of 24 patients seen at the University of Michigan over a 32-year period with rheumatoid pleuritis, the pleural fluid from each patient had at least one of the three characteristics mentioned in the preceding text. Twenty-three fluids demonstrated granular necrotic material, 17 multinucleated giant macrophages, and 15 elongated macrophages (8).

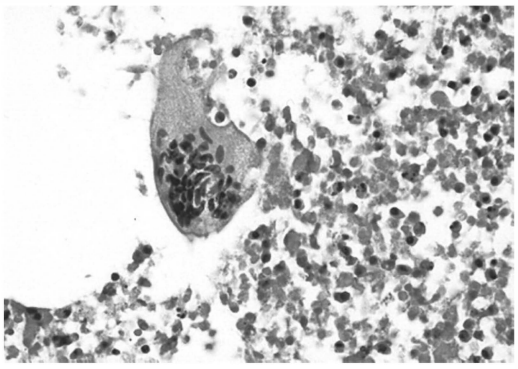

FIGURE 21.2 ■ Multinucleated giant cell on a background of amorphous material, which is characteristic of pleural effusions secondary to rheumatoid pleuritis *(bw version of Figure 7.6).*

These features were not seen in any of 10,000 other pleural fluids due to diverse causes (8).

The pleural fluid from patients with rheumatoid pleuritis may contain "ragocytes" or RA cells. The term *ragocyte* was coined by Delbarre et al. (11) who described small, spherical, cytoplasmic inclusions in neutrophilic leukocytes and occasionally in monocytes in unstained wet films of the sediment obtained from the synovial fluid of patients with various types of arthritis. These inclusions were reminiscent of raisin seeds; hence, the adoption of the prefix *rago,* which is derived from the Greek word for grape. The inclusion bodies have been shown to represent phagocytic vacuoles or phagosomes, which are of greater size than normal lysosomes of granular leukocytes (12). The presence of these cells is not useful diagnostically because pleural effusions of other etiologies, particularly those with a low glucose level, contain these cells (8,13).

Concomitant Infection

When a patient is seen with RA and a pleural effusion characterized by a low glucose level (<20 mg/dL), a low pH (<7.20), and a high LDH level, one must rule out pleural infection, which can produce pleural fluid with the same characteristics (see Chapter 12). Hindle and Yates (14) first reported a pyopneumothorax in a patient with a rheumatoid pleural effusion. At thoracotomy, it was found that a necrobiotic nodule in the visceral pleura had broken down, producing a bronchopleural fistula. Jones and Blodgett (15) subsequently reported that 5 of 10 patients with rheumatoid pleural effusion followed for a 5-year period developed empyemas. These investigators found that empyemas were more common in patients who had been treated with corticosteroids, and they attributed the pleural infection to the creation of a bronchopleural fistula through necrobiotic subpleural rheumatoid nodules.

When a patient with an apparent rheumatoid pleural effusion is seen, it is important to obtain both aerobic and anaerobic cultures of the pleural fluid. In addition, the pleural fluid should be centrifuged, and the sediment should be Gram stained because stains made in this manner are more sensitive than those made on uncentrifuged pleural fluid.

Glucose Levels

The most striking characteristic of the rheumatoid pleural effusion is its low glucose content. In a review of 76 patients with rheumatoid pleuritis, 48 (63%) had pleural fluid glucose levels below 20 mg/dL, whereas 63 (83%) had pleural fluid glucose levels below 50 mg/dL (6). The explanation for the low pleural fluid glucose in this condition is not known precisely. If the serum level of glucose is increased in patients with rheumatoid pleural effusions, little change is seen in the pleural fluid glucose levels (16–18), but similar results are obtained in patients with low pleural fluid glucose levels from other diseases (19). In contrast, when patients with rheumatoid pleural effusions are given oral urea (18) or intravenous d-xylose (17) loads, the pleural fluid and serum levels of these substances equilibrate over several hours.

Carr and McGuckin (18) have suggested that the rheumatoid inflammatory process alters the normal state of one or more enzymes that constitute the carbohydrate transport mechanism of cellular membranes. This interpretation should be viewed with some caution. The relationship between the serum and pleural fluid glucose levels is dictated not only by the ease with which glucose passes from the serum into the pleural fluid but also by the rate at which the pleural surfaces and fluid use the glucose. Because the pleural fluid glucose level falls within 30 minutes from 2,000 to 236 mg/dL after the intrapleural injection of glucose in patients with rheumatoid pleuritis (16), there must be either rapid glucose uptake by the pleura or no great barrier to its diffusion.

The pleural surfaces with rheumatoid pleuritis appear to be active metabolically, as manifested by the high pleural fluid LDH and the low pleural fluid glucose levels, although the metabolic activity of rheumatoid pleural fluid is virtually nil even when glucose is added (17). The thickened pleura in rheumatoid pleuritis probably limits the movement of glucose into the pleural space, and because glucose consumption by the pleural surfaces is high, an equilibrium is formed in which the pleural fluid glucose level is much lower than the serum glucose level.

Cholesterol Levels

Another interesting characteristic of rheumatoid pleural effusions is their tendency to contain cholesterol crystals or high levels of cholesterol. Ferguson (5) first reported on two patients with rheumatoid pleural effusions in whom the pleural fluid contained numerous cholesterol crystals. Subsequently, Naylor (8) reported that 5 of 24 rheumatoid pleural fluids (21%) contained cholesterol crystals. Some rheumatoid pleural effusions contain high levels of cholesterol without cholesterol crystals (6).

Lillington et al. (6) measured the lipid levels in seven rheumatoid pleural effusions and found levels

above 1,000 mg/dL in four of the seven fluids. One of the two patients whom I have seen with cholesterol crystals in the pleural fluid had rheumatoid pleuritis. The cholesterol crystals impart a sheen to the fluid when viewed with the naked eye under proper lighting. High cholesterol levels make the pleural fluid turbid. The significance of the presence of high levels of cholesterol or cholesterol crystals in the pleural fluid is unknown. Cholesterol pleural effusions are discussed more extensively in Chapter 26.

Biopsy

Closed pleural biopsies have a limited role in the diagnosis of rheumatoid pleuritis. Although a pleural biopsy specimen may reveal a rheumatoid nodule diagnostic of rheumatoid pleuritis in an occasional patient, the pleural biopsy usually reveals only chronic inflammation or fibrosis. Pleural biopsy is not recommended in the typical case of rheumatoid pleuritis. In atypical cases, however, such as in patients without arthritis or in those with a normal pleural fluid glucose level, thoracoscopy, or pleural biopsy should be performed to rule out malignant disease and tuberculosis.

Prognosis and Treatment

The natural history of rheumatoid pleuritis is variable. In the series of Walker and Wright (1), 13 of 17 patients (76%) had spontaneous resolution of their pleural effusions within 3 months, although 1 of the 13 patients had a subsequent recurrence. One patient had a spontaneous resolution after 18 months of observation, whereas another had a persistent effusion for more than 2 years. One patient developed progressive severe pleural thickening and eventually had to undergo a decortication. The last patient developed an empyema.

Little information is available in the literature on the efficacy of therapy in rheumatoid pleural disease. Some patients have appeared to respond to systemic corticosteroids (1), whereas in others no beneficial effects were observed (20–22). The degree of activity in the pleural space and in the joints is not necessarily parallel. In one report, the administration of methotrexate was associated with improvement in the arthritis but also with the development of a pleural effusion (23). The main goal of therapy should be to prevent the progressive pleural fibrosis that may necessitate a decortication in a small percentage of patients (1,4,21,24,25). There are no controlled studies evaluating the efficacy of corticosteroids or nonsteroidal anti-inflammatory drugs in the treatment of rheumatoid pleural effusion. It is recommended that patients be treated with nonsteroidal anti-inflammatory drugs such as aspirin or ibuprofen for 8 to 12 weeks initially. If the pleural effusion persists and if the joint symptoms are not well controlled, then appropriate therapy should be directed toward the rheumatologic problem. If the only symptomatic problem is the pleural disease, then the patient should have a therapeutic thoracentesis and possibly an intrapleural injection of corticosteroids. There have been two reports concerning the intrapleural injection of corticosteroids; the first (22) had two patients, and the intrapleural corticosteroids were ineffective; the second (26) had one patient who seemed to respond to one injection of 120 mg of depomethylprednisolone.

Decortication should be considered in patients with thickened pleura who are symptomatic with dyspnea. Computed tomographic examination is useful in delineating the extent of the pleural thickening. In patients with pleural effusions, the significance of the pleural thickening can be gauged by measuring the pleural pressure serially during a therapeutic thoracentesis (see Chapter 28). If the pleural pressure drops rapidly as pleural fluid is removed, the lung is trapped by the pleural disease (27), and decortication should be considered. The decortication procedure is difficult to perform in patients with rheumatoid pleuritis because it is not easy to develop a plane between the lung and the fibrous peel. Therefore, air leaks persist longer than usual after decortication (25). Nevertheless, decortication can substantially improve the quality of life of some patients with dense pleural fibrosis secondary to rheumatoid disease.

As mentioned earlier, patients with rheumatoid pleural effusions have a high incidence of complicated parapneumonic effusions. The management of such patients is the same as for any patient with complicated parapneumonic effusion (see Chapter 12). The incidence of persistent bronchopleural fistula is higher in the patient with rheumatoid disease, and more exploratory thoracotomies are required (25).

Still's Disease

Pleural effusions sometimes occur with adult onset Still's disease. Uppal et al. (28) reported 17.9% of 28 patients with adult onset Still's disease had a pleural effusion. The pleural fluid with adult onset Still's disease is an exudate with a predominance of neutrophils (29).

SYSTEMIC LUPUS ERYTHEMATOSUS

Both systemic and drug-induced lupus erythematosus (LE) may affect the pleura.

Incidence

The pleura is involved more frequently in systemic lupus erythematosus (SLE) than in any other collagen vascular disease. In a review of 138 patients with SLE, Harvey et al. (30) found that 16% had pleural effusions and that 56% complained of pleuritic chest pain some time during the course of their illness. Winslow et al. (31) reviewed the chest radiographs of 57 cases of SLE and found pleural effusions without other apparent cause in 21 (37%). Alarcon-Segovia and Alarcon (32) reviewed 48 patients with SLE and found that 21 (44%) had pleural effusions some time during their course. In a study from Hong Kong, 30 of 309 patients (9.7%) with at least four of the American College of Rheumatology criteria for SLE had either pleuritis or pleural effusion (33). These figures may overestimate the incidence of pleural effusions with SLE because almost all of these patients had severe disease. A comparable incidence of pleural effusions has also been reported with drug-induced SLE (34).

Pathologic Features

Surprisingly, little has been written concerning the pathologic features of the pleura with SLE. In an autopsy series of 54 patients with SLE, acute fibrinous pleuritis was seen in approximately 40% and evidence of previous pleural inflammation in the form of pleural fibrosis and thickening was seen in approximately 33% (35). Pleural biopsy usually reveals chronic inflammation, although on rare occasions, hematoxylin bodies can be demonstrated in pleural biopsy specimens (36).

Clinical Manifestations

Most patients with pleural effusions secondary to SLE are women (7,31), and any age-group can be affected. Pleuritic chest pain is the most common symptom of the pleural disease. All 9 patients in the series by Halla et al. (7) had pleuritic chest pain, as did 12 of the 14 patients in a more recent series (37). Thirteen of the 23 patients (57%) in these two series were febrile. In a large series (38) of 876 patients from Canada, 34% of the patients had pleuritic chest pain and/or pleural effusion. Most patients with lupus pleuritis have arthritis or arthralgias before the pleuritis. The pleuritis frequently dominates the clinical picture (37) and may precede any other symptoms (31).

The pleural effusions secondary to SLE are usually small, but, at times, they may occupy nearly the entire hemithorax. The pleural effusions are bilateral in approximately 50% of patients, left sided only in 17%, right sided only in 17%, and alternate from one side to another in 17% (31). The effusion may be the only abnormality on the chest radiograph, but frequently the cardiac silhouette is enlarged (39). Nonspecific alveolar infiltrates, usually basilar, or atelectasis may also be seen (36,37).

TABLE 21.1 ■ Drugs Associated with Lupus-like Syndromes

Definitely Associated	Possibly Associated
Hydralazine	Carbamazepine
Procainamide	D-Penicillamine
Isoniazid	Ethosuximide
Phenytoin	Ethylphenacemide
Chlorpromazine	Guanoxan
—	Griseofulvin
—	Mephenytoin
—	Methyldopa
—	Methylthiouracil
—	Methysergide
—	Oral contraceptives
—	PAS
—	Penicillin
—	Phenylbutazone
—	Primidone
—	Propylthiouracil
—	Reserpine
—	Streptomycin
—	Sulfonamides
—	Tetracycline
—	Troxidone

PAS, para-aminosalicylic acid.

It is important to recognize that a lupus-like syndrome may develop after taking many different drugs (Table 21.1). The first five drugs in this table have been definitely incriminated in producing the lupus-like syndrome (40). They cause SLE in many individuals and elicit antinuclear antibodies (ANA) in a still higher percentage of patients. The remainder of the drugs occasionally induce a lupus-like syndrome and are not associated with an increase in the ANA (40). The incidence of pleuritic chest pain and pleural effusion is comparable in patients with drug-induced SLE and naturally occurring SLE. The main clinical difference between drug-induced SLE and idiopathic SLE is the lower incidence of renal involvement in the drug-induced SLE. The symptoms associated with drug-induced SLE characteristically abate within days of discontinuing the offending drug (34).

Occasionally, a patient with SLE will develop the shrinking lung syndrome which is characterized by unexplained dyspnea, small lung volumes, elevation of the diaphragm, and restrictive physiology. Toya and

Tzelepis (41) reviewed 77 cases of the shrinking lung syndrome from 1965 to 2008 and reported that 65% had pleuritic chest pain.

Of course, patients with SLE may have pleural effusions for reasons other than SLE. Patients with the nephrotic syndrome may have hypoproteinemia and pleural effusions on this basis. In addition, patients with SLE may have uremia, pericardial effusions, pneumonia, pulmonary emboli, congestive heart failure, or other disorders that can produce pleural effusions.

Diagnosis

The possibility of lupus pleuritis should be considered in any patient with an exudative pleural effusion of unknown etiology.

Pleural Fluid Examination

The pleural fluid is usually a yellow or serosanguineous exudate. The differential white blood cell (WBC) count on the pleural fluid may reveal a preponderance of polymorphonuclear leukocytes or mononuclear cells (37).

Halla et al. (7) reported that measurement of the pleural fluid glucose, LDH, and pH levels were useful in distinguishing rheumatoid pleural effusions from lupus effusions. They reported that patients with lupus pleuritis had a pleural fluid glucose level above 80 mg/dL, an LDH level less than two times the upper limit for serum, and a pH above 7.20, whereas patients with rheumatoid pleuritis had a glucose level below 25 mg/dL, an LDH level more than two times the upper limit for serum, and a pH below 7.20. These biochemical tests do not always distinguish between lupus and rheumatoid pleuritis because an occasional patient with lupus pleuritis will have a low pleural fluid glucose, a high pleural fluid LDH, or a low pleural fluid pH (37). In one report of a pleural effusion due to procainamide, the pleural fluid was an exudate with a WBC count of 53,200/mm^3, an LDH of 4,296 IU/L, a pH of 7.195, and a glucose of 79 mg/dL (42).

Although in the past it was believed that the most useful test for establishing the diagnosis of lupus pleuritis was the measurement of the ANA level in the pleural fluid, this does not appear to be the case. In one study of 82 patients, including 8 with known SLE, the pleural fluid ANA levels were less useful than had been reported previously. The pleural fluid ANA titers were increased to 1:320 or above in six patients with lupus pleuritis and were below 1:160 in two patients with SLE and effusions due to other factors (43). In the six patients with lupus pleuritis, the ANA titers in the pleural fluid and in the serum tended to be within one dilution of each other. However, the pleural fluid ANA titers were above 1:40 in 8 of the 74 patients (10.8%) who did not appear to have lupus and in 3 of the patients the titers were greater than 160. The staining pattern in the patients with lupus pleuritis tended to be homogeneous, whereas it tended to be speckled in the patients without lupus, but again there was some overlap. The patients with lupus also tended to have higher titers for specific ANA to single-stranded DNA (ssDNA), double-stranded DNA (dsDNA), smooth muscle, and ribonucleoprotein (43). In another series (44), ANA titers were performed on 266 pleural fluids including 16 with SLE. The titers were ≥ 1:160 in all patients with SLE but also exceeded this level in 16 patients (6.4%) with pleural effusion due to other diseases (44).

Another study evaluated the ANA titers of 126 pleural fluids including 7 due to SLE (45). In this study, the ANA tests were performed using a commercially available kit that used an indirect immunofluorescent antibody method with a human epithelial 2 (HEP-2) cell line. Although all the pleural fluids from patients with SLE had titers greater than 1:320, the pleural fluid ANA titer and pattern essentially mimicked the titer and pattern in the serum (45). In addition, the pleural fluid ANA titers were greater than 1:160 in 13 other patients, including 11 patients with malignant effusions, 1 with tuberculous pleuritis, and 1 with an empyema due to amebiasis. In each instance, the pleural fluid ANA titer was within one dilution of the serum ANA titer (45).

The demonstration of LE cells in pleural fluid is suggestive of lupus pleuritis (46). In one recent study, the LE cell test was positive in 8 of 11 patients who were thought to have lupus pleuritis. Moreover, the LE cell test on the pleural fluid was negative in 13 patients with serum and effusion ANA titers greater than 1:160 who were not thought to have SLE. However, because the LE cell tests on the pleural fluid always correlated with the LE test results on the serum, the same test on the pleural fluid provided no additional information (46). There have been false-positive reports with the LE cell test on the pleural fluid (47).

On the basis of the studies mentioned in the preceding text, it appears that tests for ANA or LE cells on the pleural fluid add very little to the information obtained from these tests on the serum. Accordingly, they are not recommended.

Biopsy

Pleural biopsy is useful in establishing the diagnosis of lupus pleuritis if immunofluorescence is combined with light-microscopic examination. Chandrasekhar

et al. (48) performed immunofluorescent studies on pleural biopsy specimens from 36 patients with exudative pleural effusions. These researchers found that their three patients with drug-induced SLE had a specific immunofluorescent pattern characterized by diffuse and speckled staining of the nuclei of the cells in the pleural biopsy with anti-immunoglobulin G (IgG), anti-IgM, or anti-C3.

Other workers have reported that pleural specimens obtained at autopsy from patients with SLE have the same specific nuclear immunofluorescence (49). Many pleural biopsy specimens have positive immunofluorescence outside the nuclei; only positive nuclear immunofluorescence is thought to be diagnostic of SLE (50). It is my impression, however, that these stains are rarely used in establishing the diagnosis of lupus pleuritis.

Treatment

In contrast to rheumatoid pleuritis, the pleuritis with SLE definitely responds to corticosteroid administration. Hunder et al. (51) treated six patients with lupus pleuritis with corticosteroids and reported that the pleural effusions in five of the six patients rapidly cleared once therapy was begun, and the sixth effusion gradually subsided over 6 months. In the series of Winslow et al. (31), 11 patients were treated with corticosteroids and the effusions cleared rapidly in 10 of these patients. In contrast, only 10 of 16 effusions cleared spontaneously without corticosteroids. In view of the responsiveness of the pleuritis to corticosteroids and the much lower incidence of side effects with alternate-day corticosteroid therapy, corticosteroid therapy should be initiated with 80 mg prednisone every other day, with rapid dose tapering once the symptoms are controlled. Of course, if the patient has drug-induced SLE, adequate therapy consists of withdrawing the drug.

At times, the pleural effusion is large and does not respond to corticosteroid therapy. If the SLE is not controlled systemically, the treatment of choice is intense immunosuppression with regimens such as high-dose steroids and cyclophosphamide (52). If systemic measures fail or if the only disease manifestation is the pleural disease, the alternatives are similar to those for malignant pleural effusion and include chemical pleurodesis or the insertion of an indwelling catheter (52). On rare occasions, the pleura becomes markedly thickened with lupus pleuritis resulting in severe restrictive ventilatory dysfunction (53). Decortication has been shown to be efficacious in such patients (53).

MIXED CONNECTIVE TISSUE DISEASE

The term *mixed connective tissue disease* (MCTD) was coined to distinguish the patients with combined clinical features of SLE, scleroderma, and polymyositis-dermatomyositis. A prerequisite for the diagnosis of MCTD is the presence of high titers of autoantibodies against small nuclear ribonucleoprotein (snRNP) (54). Other characteristic laboratory abnormalities in MCTD include high titer (>1:1,000) of speckled antibody and high levels of antibody to RNA-sensitive extractable nuclear antigen (ENA) (54). The Smith (Sm) antibodies and high titers of anti–native DNA that are characteristic of SLE are uncommon in MCTD (54).

Most patients are women, and the average age at diagnosis is 37. Common clinical features of MCTD include Raynaud's phenomenon, polyarthritis, sclerodactyly, and inflammatory myositis (54). Approximately 50% of patients with MCTD have a pleural effusion, and it tends to be bilateral (55). The pleural effusions are usually small and resolve spontaneously (54). The pleural fluid is an exudate and has a normal glucose (55). In rare instances, the pleural effusion may be the presenting manifestation of MCTD. The pleural fluid is an exudate with normal glucose and complement levels.

OTHER COLLAGEN VASCULAR DISEASES

Pleural effusions occasionally occur in the course of several other collagen vascular diseases.

Sjögren's Syndrome

Sjögren's syndrome is a chronic inflammatory disease characterized by dryness of the mouth, eyes, and other mucous membranes (20). It is frequently associated with other collagen vascular diseases, most notably RA, but sometimes SLE, dermatomyositis, or scleroderma. Pathologically, lymphocytic infiltration of the lacrimal and salivary glands occurs. It appears that Sjögren's syndrome can have an associated pleural effusion.

In a review of the pulmonary manifestations of Sjögren's syndrome, 31 of 349 patients (9%) had pulmonary involvement, and of these, 5 (1%) had pleural effusions (56). Of these five patients, three had RA or SLE, but two had no other connective tissue disease (56). In another series, 1 of 24 patients with primary Sjögren's syndrome who had a high-resolution CT scan had a pleural effusion (57). There have now been nine cases of pleural effusion reported in patients who

had Sjögren's syndrome without other connective tissue disease (58). The pleural fluid has been described in two patients and was a lymphocyte-predominant exudate with normal pH and glucose level and a low adenosine deaminase level (59,60).

Familial Mediterranean Fever

Familial Mediterranean fever, also known as *familial paroxysmal polyserositis*, is a rare cause of paroxysmal attacks of fever and pleuritic chest pain, sometimes with pleural effusion (61,62). The hallmark of the disease is the recurrent, acute, self-limited febrile episodes of peritonitis, pleuritis, synovitis, or an erysipelas-like syndrome. Familial Mediterranean fever is an autosomal recessive disease that occurs almost exclusively in Armenians and Sephardic Jews who have their origin in the Mediterranean countries.

The initial attack usually occurs before age 20 and is typically dominated by peritoneal symptoms and signs. The initial attack is characterized by pleuritic chest pain and fever in fewer than 10% of patients, but approximately 40% have an attack of febrile pleurisy during the course of their disease (61). Chest radiographs during the acute pleuritic attacks reveal elevation of the ipsilateral diaphragm and frequently small pleural effusions (62). The pleural fluid can contain predominantly polymorphonuclear leukocytes (63) or lymphocytes (64). The radiographic abnormalities and the symptoms are usually completely gone within 48 hours. Approximately 40% of the patients also have amyloidosis (65). The attacks are recurrent, with irregular intervals of days to months between the attacks. Because the administration of colchicine, 0.5 mg orally twice daily, decreases the frequency of the attacks (66,67), it is worthwhile to establish this diagnosis in patients with recurrent episodes of polyserositis.

Churg-Strauss Syndrome

Churg-Strauss syndrome is a disorder characterized by hypereosinophilia and systemic vasculitis occurring in individuals with asthma and allergic rhinitis (68). The American College of Rheumatology has proposed six criteria for the Churg-Strauss syndrome, with four being necessary for the diagnosis with an 85% sensitivity and 99.7% specificity; the six criteria are asthma, eosinophilia greater than 10%, paranasal sinusitis, pulmonary infiltrate, histologic proof of vasculitis, and mononeuritis multiplex (69). Typically, this disease begins with allergic rhinitis, with the subsequent development of asthma and peripheral blood eosinophilia. The systemic vasculitis with the Churg-Strauss syndrome resembles that of periarteritis nodosa, but severe renal disease is uncommon. The classic histologic picture consists of a necrotizing vasculitis, eosinophilic tissue infiltration, and extravascular granulomas, but all three components are found in a minority of cases. In recent years, it has been suggested that there is an association between the administration of leukotriene receptor antagonists and the development of the Churg-Strauss syndrome (70).

Pleural involvement occurs on occasion with the Churg-Strauss syndrome. In Lanham et al.'s (68) review of the literature in 1984, 18 of 61 patients (30%) in whom chest radiograph results were reported had a pleural effusion. However, in a recent review of 96 patients, pleural effusions were said to be rare (69). High-resolution CT scans demonstrate ground glass opacities and consolidations in the majority of patients (71). The pleural fluid findings with the Churg-Strauss syndrome are relatively unique. Erzurum et al. (72) reported on one patient with bilateral effusions and pleural fluid with an LDH of 2,856 IU/L, a pH of 7.08, a glucose level less than 10 mg/dL, and 10,400 WBC with 95% eosinophils. The only other disease with comparable pleural findings is paragonimiasis.

Patients with Churg-Strauss syndrome respond well to treatment with steroids, although some patients benefit from the addition of immunosuppressive agents. The vasculitic illness is usually of limited duration, but relapses can occur, and they should be detected and treated early (68).

Wegener's Granulomatosis

Wegener granulomatosis, characterized by necrotizing granulomatous vasculitis of the small vessels, typically involves the upper and lower respiratory tracts and produces glomerulonephritis (20). Radiologically, the most common patterns in the lung are solitary or multiple nodular densities, either poorly defined or sharply circumscribed (67). An associated small pleural effusion is frequently seen (73,74).

In one series of 11 patients, 6 (55%) had small pleural effusions (74), whereas in another series of 18 patients, 4 (22%) had pleural effusions (73). The pleural fluid in patients with Wegener's granulomatosis has not been well characterized, but it is probably an exudate. Because effective treatment for this disease is now available (20), it is important to consider this diagnosis in patients with parenchymal infiltrates and a pleural effusion. Measurement of serum antineutrophil cytoplasmic antibodies (ANCA) is useful in the diagnosis of Wegener's granulomatosis. There are

two major patterns of ANCA immunofluorescence—c-ANCA shows granular staining in the cytoplasm that is accentuated in the cleft between the neutrophil nuclear lobes and p-ANCA shows perinuclear accentuation around the periphery of the neutrophil nucleus. Most patients with Wegener's granulomatosis are c-ANCA positive (75).

Eosinophilia–Myalgia Syndrome

In the late 1980s, an epidemic of the eosinophilia–myalgia syndrome was linked to the dietary ingestion of contaminated l-tryptophan. The clinical manifestations of the eosinophilia–myalgia syndrome include myalgias, arthralgias, skin rashes, muscle pain, edema, fatigue, neuropathy, and marked peripheral eosinophilia (76). A similar syndrome appears sporadically without exposure to contaminated l-tryptophan (77). More than half of the patients with the eosinophilia–myalgia syndrome have respiratory complaints, with dyspnea occurring most frequently.

Pleural effusions can occur with the eosinophilia–myalgia syndrome. In one large series of 1,531 patients, 718 patients had chest radiographs and pleural effusions were present in 12% (78). The pleural effusions are usually bilateral and are sterile eosinophilic exudates (77,79). Although some patients have improved with the discontinuation of l-tryptophan or corticosteroid therapy, the response is often incomplete and the disease may be chronic and progressive.

Miscellaneous Diseases

Occasionally, patients with other collagen vascular diseases such as scleroderma (80), temporal arteritis (81), ankylosing spondylitis, polyarteritis nodosa, Behçet's syndrome (82), Kawasaki's disease (83), eosinophilic pneumonia (84), or dermatomyositis have a pleural effusion, but it appears that the pleural effusions in such patients usually result from complications of the disease, such as heart failure, pneumonia, or pulmonary embolism, rather than from the primary disease. However, there has been one case report of a patient with Behçet's syndrome who presented with life-threatening chylothorax and chylopericardium (82).

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chapter 22

Pleural Effusion Due to Drug Reactions

Adverse reactions to drugs produce only a small percentage of all pleural effusions. Because the pleural disease in most cases rapidly resolves when the drug is discontinued; however, it is important to consider the possibility of drug-induced pleural disease in all patients with pleural effusions. The lupus-like syndromes associated with various drugs are described in Chapter 21. In this chapter, the pleural diseases resulting from the administration of nitrofurantoin, dantrolene, ergot alkaloids, dasatinib, amiodarone, interleukin 2 (IL-2), procarbazine, methotrexate, interleukin 11 (IL-11), all-trans-retinoic acid, valproic acid and clozapine are discussed. These are the only drugs convincingly incriminated in the production of pleural disease other than drugs that produce the lupus-like syndrome. At the end of the chapter, there is a summary of other drugs that have been implicated but not proved to cause pleural effusions.

NITROFURANTOIN

Nitrofurantoin (Furadantin) is widely used in the treatment of urinary tract infections. Israel and Diamond (1) first reported that the administration of nitrofurantoin could be associated with the development of an acute febrile illness with pulmonary infiltrates and pleural effusion. A subsequent review of the literature and the records of the company that produces nitrofurantoin in 1969 revealed that approximately 200 cases of this syndrome had been reported (2). Now, there have been more than 2,000 cases reported (3). It is thought that nitrofurantoin injures the lung through the production of oxygen radicals (4).

Pulmonary reactions to nitrofurantoin may develop in two distinct patterns characterized by the length of treatment before the development of the syndrome (4). The acute presentation occurs within 1 month of initiating therapy with the drug. The symptoms with the acute presentation include dyspnea, nonproductive cough, and fever. The chest radiograph is usually abnormal. In one series of 335 patients, 186 (56%) had infiltrates, 65 (19%) had infiltrates and effusion, 14 (4%) had only an effusion, and 70 (21%) had a normal chest radiograph (5).

Most patients with acute pleuropulmonary reactions to nitrofurantoin have both peripheral eosinophilia ($>350/mm^3$) and lymphopenia ($<1,000/mm^3$) (6). The only reported pleural fluid analysis showed 17% eosinophils (6).

The chronic syndrome occurs when the patient has been taking nitrofurantoin from 2 months to 5 years and is much less frequent than the acute syndrome. The presentation is insidious, with the gradual onset of dyspnea on exertion and a nonproductive cough (4). Patients with the chronic syndrome always have abnormal chest radiographs; diffuse bibasilar infiltrates are the most common abnormality (5). Pleural effusions, which are less common with the chronic form, occur in fewer than 10% of patients. No patients with the chronic syndrome have had a pleural effusion without an infiltrate (4).

The diagnosis of nitrofurantoin pleuropulmonary reaction should be suspected in all patients with a pleural effusion who are taking nitrofurantoin. If the drug is discontinued, the patient with the acute syndrome usually improves clinically within 1 to 4 days, and the chest radiograph becomes normal within a week (5). Symptoms and signs with the chronic syndrome resolve much more slowly (5).

DANTROLENE

Dantrolene sodium (Dantrium) is a long-acting skeletal muscle relaxant used in treating patients with

spastic neurologic disorders. The chemical structure of dantrolene is similar to that of nitrofurantoin (7,8). The chronic administration of dantrolene can lead to an eosinophilic pleural effusion (7,8). At one of my previous institutions, the Veterans Affairs Medical Center in Long Beach, we saw more than 10 instances of pleural effusions due to dantrolene during a 10-year period. This institution had a large population of patients with spinal cord injury for whom dantrolene was frequently prescribed. In one report, four patients developed an eosinophilic pleural effusion 2 months to 3 years after the initial administration of dantrolene (7). In one case, the eosinophilic effusion developed 12 years after dantrolene therapy was initiated (8). The pleural effusions in all patients were unilateral, and no associated pulmonary infiltrates were seen. In the reported series of four patients, one had a pericardial friction rub and another had a pericardial rub with a pericardial effusion (7). Two of the patients were febrile, and two had pleuritic chest pain.

All reported patients have had at least 5% eosinophils in their peripheral blood (7). The pleural fluid is an exudate with normal glucose and amylase levels. The differential white blood cell count on the pleural fluid has revealed at least 35% eosinophils in all cases. When dantrolene is discontinued, the patients improve symptomatically within days, but it takes several months for the pleural effusions to resolve completely. Administration of corticosteroids may accelerate the resolution of the eosinophilic effusion (9). The mechanism by which dantrolene produces the eosinophilic pleural effusion is unknown.

ERGOT ALKALOIDS

Ergot alkaloid drugs such as bromocriptine, ergotamine, dihydroergotamine, nicergoline, pergolide, and dopergine are sometimes used in the long-term treatment of Parkinson's disease. Ergot derivatives have also been used in the treatment and prophylaxis of migraine and cluster headaches (methysergide, ergotamine). The long-term administration of any of these drugs can lead to pleuropulmonary changes (10–18). It has been suggested that the pleural changes are due to increased serotonin levels with a subsequent increase in fibroblast activity (19).

Methysergide (Sansert) is a serotonin antagonist used to treat migraine headaches. The association of methysergide administration with the development of retroperitoneal fibrosis and fibrosing mediastinitis is well established (10). One report described 13 cases of "pleurisy" secondary to methysergide treatment (11). It is not clear what these authors meant by the term pleurisy, but apparently all the patients had pleural effusions or pleural thickening (11). The pleurisy developed 1 month to 3 years after methysergide therapy was initiated, and in five patients, it was bilateral. Only 1 of the 13 patients had concomitant retroperitoneal fibrosis. Although no description of the pleural fluid was included in this report, in another report of a patient with bilateral pleural effusions, the fluid was bloody on one side and clear on the other (12). When methysergide was discontinued, the patients' symptoms and signs improved. At follow-up 6 months or more after discontinuation of the drug, pleural fibrosis was not detectable or was slight in seven patients, moderate in three patients, and severe in two patients. The two patients with severe fibrosis were those who had continued to take methysergide for the longest period (18 and 36 months) after the onset of this pleurisy (11). Therefore, the occurrence of a pleural effusion or pleural thickening in a patient taking methysergide is a strong indication for the prompt discontinuation of the drug.

Rinne (13) reviewed the chest radiographs of 123 patients taking bromocriptine for Parkinson's disease and found that 7 patients (6%) had pleural effusions, pleural thickening, and pulmonary infiltrates. As of 1988, there had been a total of 23 patients reported who developed pleuropulmonary disease while taking bromocriptine (14). All the patients were men, and most of them have had a history of long-term cigarette smoking. The prevalence of symptomatic pleuropulmonary disease among individuals taking bromocriptine is 2% to 5% (14). Patients had taken the drug for 6 months to 4 years before symptoms developed. The chest radiograph reveals unilateral or bilateral pleural thickening or effusion with or without pulmonary infiltrates. An occasional patient has only pulmonary infiltrates. Analysis of the pleural fluid reveals an exudate with predominantly lymphocytes and frequently eosinophils (14,19). The erythrocyte sedimentation rate (ESR) is sometimes markedly elevated in these patients (18). There is some suggestion that patients taking bromocriptine-type drugs are more likely to develop pleural disease if they have a history of exposure to asbestos (18,20).

As of 2002, there had been a total of 87 patients reported who developed one or more symptoms of serosal fibrosis after taking pergolide, including 38 cases with pleural effusion and 21 cases with pleural fibrosis (21). The mean age of the patients was 64 years, and approximately three fourths of the patients were men (21). Most patients had been taking the drug for

more than 1 year and had not recovered at the time that they were reported (21).

The natural history of pleuropulmonary disease during treatment with ergot alkaloids is unclear. The disease progresses only in some of the patients who continue taking the drug (14). On discontinuation, most patients improve, but complete resolution of the process is rare. It is recommended that annual chest radiographs be obtained in patients who are taking ergot alkaloids on a long-term basis. If the radiograph reveals pleural or parenchymal infiltrates, strong consideration should be given to stopping the ergot alkaloids and using an alternative drug for the treatment of the Parkinson's disease.

DASATINIB

Dasatinib is a tyrosine-kinase inhibitor approved for the treatment of BCR-ABL positive chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (ALL) after imatinib failure. The incidence of dasatinib-associated pleural effusions is approximately 20% to 40% (22), which is probably the highest incidence of pleural effusion associated with any drug. Administration of dasatinib once daily is associated with fewer pleural effusions than is administration twice daily and is equally effective (23). In one study (23), 319 patients were randomized to receive dasatinib 140 mg qd or 70 mg bid. The incidence of pleural effusion was 39% in the bid group and 20% in the qd group (23). In a subsequent study (24), 662 patients were randomized to dasatinib 100 mg qd, 50 mg bid, 140 mg qd, or 70 mg bid. In this series (24), the incidence of pleural effusions was lower in the 100 mg qd group (14%) than in the 140 mg qd group (26%), the 70 mg bid group (25%), or the 50 mg bid group (23%). The mean time to the development of the pleural effusion was about 200 days, and it tended to be longer in the groups that received 100 mg per day (24). Pleural effusion was cited as the reason for discontinuing the drug in less than 5% of patients. Peripheral lymphocytosis was more common in the patients that developed pleural effusion than in those that did not (24). Most of the pleural effusions were symptomatic (24).

The characteristics of the pleural fluid secondary to dasatinib therapy have not been well described. Bergeron et al. (25) performed thoracentesis on six patients and reported that the fluid was exudative in all and five were lymphocytic and one was a chylothorax. Quintás-Cardama et al. (26) reported that seven of nine pleural fluids were exudative while two were transudative. Seven of the nine effusions were lymphocyte predominant and one was a chylothorax (26). Pleural biopsy has shown lymphocytic infiltration (25).

The mechanisms responsible for the development of the pleural effusion is unknown. It is thought that it is immune mediated given the predominance of lymphocytes in the pleural effusion, the high incidence of patients who have lymphocytosis, and the lymphocytic infiltrates on the pleural biopsy.

The optimal management of a patient with a dasatinib-related pleural effusion has yet to be defined. If dasatinib is discontinued, the effusion usually resolves (22). If the patient is given corticosteroids, it will resolve more rapidly. Dasatinib can be reinstituted after the effusion resolves. Since effusion are least common with the 100 mg/day dose, this is recommended when dasatinib is reinstituted. An alternative approach after the patient has been off dasatinib is to institute therapy with nilotinib, which is another tyrosine kinase inhibitor (27).

AMIODARONE

Amiodarone is an antiarrhythmic drug that may produce severe and potentially lethal pulmonary toxicity. The current incidence of pulmonary toxicity in patients receiving amiodarone is 5% to 10% (28), and 5% to 10% of those with pulmonary toxicity die of pulmonary fibrosis. The pulmonary toxicity is characterized by the insidious onset of nonproductive cough, dyspnea, weight loss, and, occasionally, fever. The chest radiograph reveals parenchymal infiltrates, which are predominantly interstitial (28). The toxicity rarely begins before 2 months of therapy, and it rarely occurs in patients receiving less than 400 mg/day.

Pleural effusions occur as a manifestation of amiodarone toxicity, but they are uncommon (29–31). Gonzalez-Rothi et al. (29) reviewed 11 cases of pleural disease attributed to amiodarone and found that all 11 had concomitant parenchymal involvement. Subsequently, a case has been reported in which there was no parenchymal involvement (30). The pleural fluid is an exudate (29–31) and may have predominantly lymphocytes (31), macrophages (30), or polymorphonuclear leukocytes (29). Pleural fluid eosinophilia has not been reported with amiodarone toxicity. The pleural abnormalities resolve when the amiodarone is discontinued.

INTERLEUKIN-2

Recombinant IL-2 is sometimes used in the treatment of malignancy, most commonly melanoma

or renal cell carcinoma. The administration of IL-2 is accompanied by multiple acute but generally reversible toxic effects, including fever, chills, lethargy, diarrhea, anemia, thrombocytopenia, eosinophilia, confusion, and diffuse erythroderma, among others (32).

One of the primary side effects of IL-2 administration is the development of pulmonary infiltrates and pleural effusion (32,33). Vogelzang et al. (32) reviewed the chest radiographs of 54 patients who were receiving high-dose IL-2 with or without lymphokine-activated killer cell therapy for advanced cancer and reported that 28 (52%) had a pleural effusion (32). Other abnormalities on the chest radiograph included pulmonary edema in 41% and focal infiltrates in 22%. The abnormalities were more frequent in patients receiving bolus rather than constant intravenous therapy (32). These pulmonary reactions were clinically significant in that 19 patients (35%) either developed dyspnea at rest or required intubation. The pleural effusions tend to resolve, but they persisted in 17% of patients 4 weeks following therapy. In a second study, 26 of 54 patients (48%) developed a pleural effusion after IL-2 therapy (33). In this series, 80% of the patients had either alveolar edema or interstitial edema. Two of the patients without parenchymal infiltrates had a pleural effusion (33).

The pathogenesis of the pleural effusion with IL-2 therapy is probably related to the generalized capillary leak syndrome that sometimes occurs after IL-2 therapy. It is likely that the pleural fluid originates from the leaky capillaries in the lung. Therefore, the pleural fluid would be expected to be an exudate, but to my knowledge, there is no published description of the pleural fluid characteristics. It is unclear as to why the pleural effusion persists so much longer than does the pulmonary edema.

INTERLEUKIN-11

Recombinant human IL-11 is used to prevent severe thrombocytopenia in patients receiving myelosuppressive chemotherapy in patients with nonmyeloid malignancies. The administration of IL-11 to normal individuals is associated with an increase in the plasma volume of approximately 20% due to sodium retention (34). This increase in plasma volume is thought to be responsible for most side effects from IL-11, which include dyspnea, edema, and pleural effusions (34). In one study of patients with stage IV breast cancer, 7 of 40 patients (18%) developed a pleural effusion or a worsening of an existing pleural effusion, but none required thoracentesis (35). In a subsequent study in which diuretics were given, no patient developed a pleural effusion (34).

ALL-TRANS-RETINOIC ACID

This drug is used in the treatment of acute promyelocytic leukemia. Up to one fourth of patients treated with this drug develop a life-threatening reaction that resembles the capillary leak syndrome which is attributed to IL-2 (36,37). Symptoms develop 1 to 22 days after the initiation of treatment and include fever, fluid retention, dyspnea, multiple organ failure, and hemorrhagic and thrombotic manifestations. In one series, 11 of 15 patients with the syndrome had pleural effusion 7 of which were right sided and 2 each bilateral and left sided (36). Many patients also have lung parenchymal ground glass opacities, consolidation, or nodules (36). The characteristics of the fluid have not been reported (38).

The seriousness of this syndrome is emphasized by the observation that 9 of 148 patients treated with all-trans-retinoic acid died. Early administration of high-dose corticosteroids usually leads to prompt symptomatic improvement, although full radiographic recovery may require several days and residual pleural thickening may remain in the occasional patient (36,37).

PROCARBAZINE

Procarbazine hydrochloride (Matulane), a methylhydrazine derivative, is effective in the treatment of Hodgkin disease and other lymphomas. Two detailed case reports have described pleuropulmonary reactions consisting of chills, cough, dyspnea, and bilateral pulmonary infiltrates with pleural effusions occurring after treatment with procarbazine (39,40). In both instances, rechallenge with procarbazine again produced the infiltrates and pleural effusions. Both patients had peripheral eosinophilia. When the drug was discontinued, the patients' symptoms and radiologic changes resolved within several days (39,40). This syndrome appears to be identical to that associated with nitrofurantoin.

METHOTREXATE

One report exists of pleural effusion occurring after methotrexate therapy for trophoblastic tumors (41). Walden et al. (41) treated 317 patients with

methotrexate, 50 mg intramuscularly, followed by folinic acid for trophoblastic disease and reported that 14 of the patients developed pleuritic chest pain after the second to the fifth injection. Four of the patients also developed pleural effusions, but no peripheral eosinophilia was noted. In a second report, pleural disease was reported in 18 of 210 patients (9%) being treated for osteogenic sarcoma with high-dose methotrexate (42). Most of the patients had severe chest pain. The mechanism of the pleuritis in those patients is unknown.

VALPROIC ACID

This antiepileptic drug has been incriminated in causing eosinophilic pleural effusion. In a recent case report (43) and review of the literature, 12 cases were found. Patients took the drugs from 3 weeks to chronically before the effusion was diagnosed. The eosinophil count in the pleural fluid varied from 35 to 84% (43). There was peripheral eosinophilia in most cases, but at a lower level than in the simultaneously obtained pleural fluid.

CLOZAPINE

Clozapine is an antipsychotic drug that is used in the treatment of severely ill schizophrenic patients. There have been at least four reports of pleural effusions that have been attributed to clozapine (44–47). The pleural effusions develop within 7 to 14 days of starting the drug and resolve when the drug is discontinued. Some but not all patients have had a concomitant skin rash or peripheral eosinophilia. The pleural fluid is an exudate without significant eosinophilia (48). When two of the patients mentioned in the preceding text underwent rechallenge, the symptoms and the effusions recurred (47,48).

OTHER DRUGS

Several other drugs have been incriminated in causing pleural effusions.

Cilazapril. There has been one report (49) of a lymphocytic pleural effusion in a patient who was taking cilazapril which is a novel angiotensin-converting-enzyme inhibitor. Six months after beginning cilazapril, the patient developed a moderate-sized pleural effusion. Thoracoscopy nondiagnostic. The effusion disappeared when the drug was discontinued (49).

Dapsone. The sulfone syndrome consists of a constellation of symptoms secondary to a hypersensitivity reaction to dapsone. The clinical manifestations include fever, malaise, acute hepatitis, exfoliative dermatitis, and hemolytic anemia (50). The syndrome typically develops 2 to 6 weeks after the institution of dapsone therapy. There is one report in which a patient had a large unilateral right-sided exudative pleural effusion (50).

Daptomycin. Daptomycin is a cyclopeptide antibiotic with outstanding coverage for Gram-positive bacteria. There is one case report (51) of a patient who developed eosinophilic pneumonia with a pleural effusion containing 15% eosinophils. The pneumonia and the pleural effusion both resolved rapidly when the daptomycin was stopped. (51).

Fluoxetine hydrochloride. There has been one case report of a 49-year-old man who developed a small painful right-sided pleural effusion 8 weeks after starting fluoxetine therapy (52). The pleural fluid contained 36% eosinophils and the effusion gradually disappeared in the weeks following discontinuation of the fluoxetine.

Gliclazide. There is one case report of a diabetic patient who developed a moderate-sized pleural effusion 2 weeks after beginning therapy with gliclazide, a new oral hypoglycemic agent. The patient had a peripheral eosinophil count of 20%, and the pleural fluid was an exudate with 80% eosinophils. When gliclazide was discontinued, the effusion resolved (53).

Imatinib. This is a chemotherapeutic agent used primarily for chronic myelogenous leukemia, ALL, and gastrointestinal stromal tumors. Goldsby et al. (54) reported three patients who developed clinically significant pleural effusions shortly after starting treatment with this agent. The characteristics of the pleural fluid were not described, and two of the patients also had significant peripheral edema (54). It should be noted that imatinib is a tyrosine kinase inhibitor like dasatinib, the administration of which is associated with a much higher incidence of pleural effusions.

Immunoglobulin. Bolanos-Meade et al. (55) reported a patient who was receiving intravenous immunoglobulin every 4 to 6 weeks for idiopathic thrombocytopenic purpura, who

developed bilateral exudative pleural effusions on the second day of her seventh or eighth course. The effusion resolved within 2 weeks, but recurred when the intravenous immunoglobulin was readministered. However, when a different preparation of immunoglobulin was given, there was no recurrence of the pleural effusion (55). This observation suggests that the pleural effusion represents a reaction to a component of the first preparation and not of the immunoglobulin itself (38).

Interferons. There is one case report of a 54-year-old man who developed a moderate right pleural effusion 9 days after starting therapy with recombinant interferon-α-2a for chronic hepatitis (56). Although there was a slight increase in serum antinuclear antibody titer, the patient's symptoms and signs did not satisfy the criteria of drug-induced lupus. The effusion gradually resolved upon discontinuation of the interferon.

Isotretinoin. There is one report of a 49-year-old woman who developed an eosinophilic pleural effusion 7 months after starting isotretinoin therapy for systemic sclerosis (38). When isotretinoin was discontinued, the chest radiograph became normal within 3 months. There is another case report of a similar case (57), and the manufacturer of isotretinoin has on file three other cases of pleural effusion occurring in patients who took isotretinoin for acne.

Mesalamine. Trisolini et al. (58) reported a 36-year-old patient who developed fever and bilateral areas of parenchymal infiltration with eosinophilic pleural effusions several weeks after starting mesalamine therapy. The fever and effusions which had persisted for weeks, disappeared shortly after the mesalamine was stopped (58). A similar case has been reported by Sesin (59). There was also one case report in which a patient was thought to have developed pleuropericarditis 7 months after starting this treatment (60). In this instance, the patient was felt to have drug-induced lupus (60).

Metronidazole. Kristenson and Fryden (61) reported an interesting case of a patient who developed fever and pleural effusions on two different occasions within a day of starting a course of oral metronidazole. On the initial occasion, pulmonary infiltrates were also present.

Minoxidil. Siddiqui et al. (62) reported a case of a patient who developed a unilateral exudative pleural effusion with a pleural fluid protein level of 7.5 g/dL while taking minoxidil. After a therapeutic thoracentesis, the effusion recurred. The effusion gradually resolved after minoxidil was discontinued (62). The patient had no renal disease. Minoxidil had previously been implicated in pleural effusions in patients with renal disease, but it was unclear whether the effusions were due to uremic pleuritis or fluid overload (62).

Mitomycin. Small pleural effusions are frequently present in patients who have interstitial infiltrates secondary to mitomycin (63).

Propylthiouracil. Middleton et al. (64) have reported one patient who developed left pleuritic chest pain and an eosinophilic pleural effusion 3 weeks after starting propylthiouracil (PTU). A thoracentesis 5 weeks after starting therapy revealed 16% eosinophils. The patient continued taking the PTU for 2 more weeks, and the effusion enlarged and the eosinophils increased to 45%. The effusion then resolved after PTU was discontinued (64). Sen et al. (65) reported a patient who developed an eosinophilic pleural effusion 11 years after starting PTU which went away with steroid therapy and discontinuation of the drug. The effusion recurred when PTU therapy was reinstituted (65).

Simvastatin. Simvastatin is a member of the statin family of drugs used to treat hypercholesterolemia. There is one case report of a patient who developed a moderate-sized right-sided pleural effusion and interstitial infiltrates after taking simvastatin for 6 months. Thoracoscopy revealed no pleural abnormalities. He had concomitant marked elevations of his liver function test results. The patient improved after the simvastatin was stopped and prednisone was administered (66). There is another case report (67) of a patient who developed an eosinophilic pleural effusion after taking simvastatin for 13 years. The effusion went away when the simvastatin was discontinued.

Tizanidine. There is one case report of a patient who developed a large pleural effusion 6 weeks after starting tizanidine, a muscle relaxant (68). The effusion was an exudate with 10% eosinophils. The effusion gradually disappeared after tizanidine was discontinued (68).

Warfarin. There is one case report of a patient who developed a dry cough, low-grade fever, right-sided exudative pleural effusion with 57% eosinophils, and blood eosinophilia 9 months after starting warfarin therapy. When it was discontinued, the peripheral eosinophilia decreased somewhat, and when it was reinstituted, the peripheral eosinophilia again increased and a pleural effusion developed on the left. When the therapy was discontinued a second time, the peripheral eosinophilia and the pleural effusions gradually resolved (69). There is another case (70) of a patient who developed an eosinophilic pleural effusion after being on warfarin for 1 month. His effusion went away when warfarin was discontinued.

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chapter 23

Pleural Effusion Due to Miscellaneous Diseases

ASBESTOS EXPOSURE

The exposure to asbestos is definitely associated with the occurrence of benign exudative pleural effusions.

Incidence

Epler et al. (1) reviewed the medical histories of 1,135 asbestos workers whom they had followed for several years and found that 35 of the workers (3%) had pleural effusions for which there was no other ready explanation (1). In contrast, no unexplained effusions were seen in the control group of 717 subjects. These authors found a direct relationship between the level of asbestos exposure and the development of a pleural effusion. In patients with heavy, moderate, and mild asbestos exposure, the incidence of pleural effusion was 9.2, 3.9, and 0.7 effusions/1,000 person-years, respectively (1). Pleural effusions occur sooner after asbestos exposure than do pleural plaques or pleural calcification. In the series mentioned in the preceding text, many patients developed pleural effusions within 5 years of the initial exposure, and almost all did so within 20 years of the initial exposure. This finding is in direct contrast to the occurrence of pleural plaques and pleural calcifications, which usually do not occur until at least 20 years after the initial exposure. Other investigators, however, have reported a much longer period between the initial exposure and the development of the effusion. Hillerdal and Ozesmi (2) reviewed 60 patients with asbestos pleural effusions and found that the mean latency after the initial exposure was 30 years and that only 4 of their patients had developed a pleural effusion within 10 years of the initial exposure.

Pathogenesis and Pathologic Features

The pathogenesis of the pleural effusion that occurs after asbestos exposure is not known but is probably similar to that of pleural plaques, which are described in Chapter 27. In the series of Epler et al. (1), 20% of the affected individuals had pleural plaques, whereas in the Hillerdal and Ozesmi series (2), 39 of 60 patients (65%) had bilateral pleural plaques. It is likely that the presence of submicroscopic asbestos particles in the pleural space provides a constant stimulation to the pleural mesothelial cells (3). When mesothelial cells are cultured in the presence of asbestos particles, they synthesize and release a protein fraction with chemotactic activity for neutrophils, which appears to be interleukin 8 (IL-8) (4). When crocidolite is instilled into the pleural spaces of rabbits, chemotactic activity rapidly appears in the pleural fluid and this chemotactic activity is significantly inhibited by a neutralizing antibody to human IL-8 (4). In addition, when rat mesothelial cells are incubated in the presence of crocidolite or chrysotile asbestos fibers, they secrete the fibroblast chemoattractant fibronectin (5).

The gross pathologic findings in patients with pleural effusions secondary to asbestos are not well defined. Mattson (6) performed a thoracoscopy on nine patients with asbestos pleural effusion and found that the visceral pleural surface was completely normal in all patients but the parietal pleura was inflamed. In contrast, Gaensler and Kaplan (7) reported that both the visceral pleura and the parietal pleura of their patients were thickened, and an irregular pleural symphysis was seen in all patients. Perhaps the difference between these series is that pleural disease had been

present longer in the second group. Microscopic examination of the pleura reveals chronic fibrosing pleuritis with varying degrees of inflammation and vascularity, depending on the acuteness of the process (7,8).

Clinical Manifestations

Patients with pleural effusions secondary to asbestos have surprisingly few symptoms (1,2). In Hillerdal and Ozesmi's (2) series of 60 patients, 47% had no symptoms, 34% had chest pain, 6% had dyspnea, and the remainder had various other symptoms. Mattson (6) reported that his patients often complained of feeling heavy in their chest. Most of Gaensler and Kaplan's (7) patients complained of pleuritic chest pain or progressive dyspnea, but these patients were referred for symptoms rather than having their disorder diagnosed on the basis of serial chest radiographs.

The chest radiograph usually reveals a small-to-moderate-sized pleural effusion, which is bilateral in approximately 10% of patients (1). Many patients have pleural plaques, whereas fewer than 5% have pleural calcifications, and approximately 50% have some evidence of parenchymal asbestosis (1,7).

The pleural fluid associated with asbestos pleural effusion is an exudate that is serous or serosanguineous (6). The pleural fluid white blood cell (WBC) count can be as high as 28,000/mm^3, and the pleural fluid differential WBC can reveal either predominantly polymorphonuclear leukocytes or mononuclear cells (2). Pleural fluid eosinophilia appears to be a characteristic of asbestos pleural effusions. In one series, more than 50% eosinophils were found in 5 of 11 asbestos pleural effusions, and an additional 2 effusions had more than 15% eosinophils (6). In a second series (2), 26% of 66 asbestos effusions had pleural fluid eosinophilia. Most asbestos pleural effusions contain mesothelial cells (2).

Diagnosis

The diagnosis of asbestos pleural effusion is one of exclusion. Patients with a strong history of exposure to asbestos and a pleural effusion should be closely evaluated for mesothelioma or metastatic bronchogenic carcinoma because these diseases occur much more commonly in individuals exposed to asbestos. If these diseases as well as tuberculosis and pulmonary embolism are ruled out, the patient probably has an asbestos pleural effusion and should be watched. The occupational history of any patient with an undiagnosed exudative pleural effusion should be evaluated for exposure to asbestos. If such exposure is found and the patient is asymptomatic with a small pleural effusion, the effusion is probably due to asbestos exposure.

Prognosis

The natural history of the patient with an asbestos pleural effusion is one of chronicity with frequent recurrences and sometimes the development of fibrosis of the parietal pleura (1,6–8). The pleural effusion on the average lasts several months, but eventually it clears and leaves no residual pleural disease in most patients (2). In the series of 35 patients followed by Epler et al. (1) for a mean period of 9.7 years, 29% of the patients developed recurrent benign effusions, more commonly on the contralateral side. In approximately 20% of patients, massive pleural fibrosis follows the asbestos pleural effusion, whereas in an additional 20%, the ipsilateral costophrenic angle remains blunted after the effusion has resolved. At times, malignant mesotheliomas follow asbestos pleural effusions. Three of the 61 patients (5%) in the series of Epler et al. developed a mesothelioma during the follow-up period. These mesotheliomas occurred 6, 9, and 16 years after the initial pleural effusion (1).

POST–LUNG TRANSPLANTATION

Pleural effusions are common after lung transplantation. Normally, 80% of the fluid that enters the interstitial spaces of the lungs is cleared from the lung through the lymphatics, whereas 20% is cleared through the pleural space (see Chapter 2). In the patient with a lung transplant, however, the lymphatics are transected, and, accordingly, almost all the fluid that enters the lung exits through the pleural space. The continuity of the lymphatics is restored within 2 to 4 weeks of lung transplantation (9).

Pleural effusions are usually not evident in the immediate posttransplant period because the patients have chest tubes. The amount of fluid that drains through the chest tube may be very large, particularly if the patient has the reperfusion syndrome. In one patient with a severe reperfusion syndrome, the chest tube drained more than 600 mL/hour (10). Prolonged chest tube drainage is necessary in many patients. In one series of 100 patients, the mean time for chest tube drainage was 19.3 days with a range of 5 to 52 days (11). Most patients do not have large amounts of chest tube drainage. Judson et al. (12) performed serial analyses on the chest tube drainage

from seven patients who had undergone lung transplantation. They reported that the mean output from the chest tube fell from 400 mL/day on day 1 to 200 mL/day on day 4 and that these mean outputs were similar to those seen in patients undergoing coronary artery bypass or other cardiothoracic surgeries (12). The pleural fluid on day 1 is a bloody neutrophil-predominant exudate, and on day 7 is still bloody with a mean protein of 2 g/dL and a mean lactate dehydrogenase (LDH) level of more than twice the upper limit of normal. Over the same time, the mean WBC decreased from 10,600 to 637 cells/mm^3 and neutrophils decreased from 90% to 49% (12). Teixeira et al. (13) performed serial measurements of IL-1β, IL-6, IL-8, and VEGF in the pleural fluid of 20 patients who had undergone lung transplantation. They found that the levels of all four cytokines were much higher in the pleural fluid than in the serum and were highest at 6 hours after the transplantation (13). With time the levels of these cytokines tended to gradually decrease (13).

Pleural abnormalities are common on imaging studies of the chest posttransplantation. Ferrer et al. (11) reported that on thoracic computed tomography (CT) at 3 months posttransplantation, 34 of 58 patients (59%) had a pleural effusion whereas at 12 months posttransplantation 4 of 50 patients (8%) had a pleural effusion. Most patients (62%) at 3 months and (96%) at 12 months posttransplantation had pleural thickening (11).

It appears that some patients may develop a benign effusion 2 to 6 weeks posttransplantation. Shitrit et al. (14) reported that 10 of 35 patients (29%) developed more than a minimal pleural effusion between 2 and 12 weeks posttransplantation. Two of these patients had a parapneumonic effusion and one had rejection, but there was no explanation for the effusion in the other seven patients (14). A thoracentesis was performed in all the patients. In each instance, the pleural fluid was a lymphocyte-predominant exudate (13). Most did not recur after thoracentesis (14). It is likely that these effusions have a pathogenesis similar to those that occur after coronary artery bypass graft surgery (see Chapter 19).

It appears that patients who develop complications after their lung transplantation are likely to have a pleural effusion. In one series in children, radiologic findings were correlated with histopathologic diagnoses in 62 instances (15): pleural effusions occurred with 14 of 19 (74%) episodes of acute rejection, 7 of 8 (88%) instances of chronic rejection, 6 of 11 (55%) episodes of infection, 3 of 4 (75%) instances with lymphoproliferative diseases, and 15 of 20 (75%) episodes in which the histopathology was nonspecific. The high prevalence of effusion with the different entities after transplantation is probably due to the fact that a larger percentage of interstitial fluid exits through the pleural space in the patient after lung transplantation. The pleural effusion that accompanies acute lung rejection is a lymphocyte-predominant exudative pleural effusion (16).

After lung transplantation, patients are at risk of developing empyema. In one series of 392 patients from the University of Pittsburgh, empyema developed in 14 patients (3.6%) at a mean time of 46 days after transplantation (17). Four of the 14 patients (29%) died from complications of pneumonia or sepsis, or both (17). In a more recent study (18) from the Duke University, pleural infection occurred in 27% of 455 lung transplant recipients within 90 days of transplantation. Pleural infection in this study was defined as a positive bacterial, fungal, or viral culture or a pleural fluid WBC greater than 20,000 (18). Fungal pathogens accounted for more than 60% of the infections and *Candida albicans* was the predominant organism found (18).

The omental flap used to prevent dehiscence of the bronchial anastomosis may result in a pseudoeffusion on the chest radiograph. The omentum with its blood supply is introduced into the chest cavity through a small incision in the diaphragm. It is particularly likely to mimic an effusion on a supine radiograph (19).

The management of the patient with a pleural effusion post–lung transplantation is dependent upon the size of the effusion and the symptoms of the patient. If the effusion occupies more than 25% of the hemithorax, a thoracentesis should be performed immediately in an attempt to ascertain the etiology of the effusion. A therapeutic thoracentesis is recommended because if the patient has the typical post–lung transplant pleural effusion, this procedure is likely to be curative (14). The other main considerations are pleural infection, chylothorax, congestive heart failure, and rejection of the lung. If the effusion recurs after the therapeutic thoracentesis, consideration should be given to small-bore catheter drainage (20). If the effusion is very small, it can probably be ignored as these effusions are very common (11). If the effusion occupies less than 25% of the hemithorax but represents more than just blunting of the costophrenic angle, a diagnostic thoracentesis should be performed if the patient is complaining of shortness of breath or if the patient is not feeling up to par. It is important to remember that these patients

are immunosuppressed and accordingly are more likely to have infections. Moreover, patients with pleural infections may not be febrile because of the immunosuppression.

POST–BONE MARROW TRANSPLANTATION

Pleural effusions can occur o n occasion as a complication after bone marrow transplantation. Adam et al. (21) reviewed 860 patients who underwent bone marrow transplantation between 1998 and 2006 at Wayne State University and reported that pleural effusions occurred in 64 (7.4%). Malignancy was responsible for nine effusions while four patients had parapneumonic effusions or empyema (21). Diagnoses were not established in the remaining patients (21). Seber et al. (22) reviewed the medical records of 1,905 patients who received bone marrow transplants between 1974 and 1993 at the University of Minnesota. They found seven patients who had unexplained multiple effusions involving two or more of the pleural, pericardial, or peritoneal cavities. The pleura was involved in all patients. All of these cases of polyserositis occurred in recipients of allogeneic transplants. The pleural fluid was characterized by a WBC count below 1,000 cells/mm^3 and a protein level below 3.0 g/dL. Because all patients had concomitant severe graft versus host disease, the effusions were also attributed to the same disease (22).

PLEURAL EFFUSION IN LIVING DONORS

The lungs for some lung transplantations are being obtained from living donors. In one series of 62 living donors, 4 patients (6.4%) had a pleural effusion requiring drainage with a pigtail catheter and 2 additional patients (3.2%) had a loculated pleural effusion (23). In a second report (24), 2 of 21 donors (9.5%) had to be readmitted to the hospital for the development of a pleural effusion.

The livers for some liver transplantations are also being obtained from living donors. Pleural effusions may occur in the living donor partial hepatectomy. In one large series of 386 donors, pleural effusion occurred in 9 (2.3%) (25). Five of these patients received a drainage catheter that remained in place for a median of 5 weeks (25). In a second study (26) of 112 living donors, a CT scan was obtained on day 7 which revealed pleural effusion in 75% which were bilateral in 55% and right sided in 45%. Three patients developed a right-sided empyema and an additional five patients developed a pleural effusion requiring a thoracentesis (26).

YELLOW NAIL SYNDROME

The yellow nail syndrome consists of the triad of deformed yellow nails, lymphedema, and pleural effusions. Until 1986, only 97 patients had been reported with this syndrome (27). In one series, 89% of the reported cases had yellow nails, and these were the presenting manifestation in 37%. Lymphedema of various degrees was encountered in 80% of the reported cases and was the initial manifestation in 34%. Pleural effusions were found in 36% of all cases (27). The three separate entities may become manifest at widely varying times. For example, one patient developed lymphedema in childhood, chronic nail changes at age 78, and a pleural effusion in her ninth decade (28). An occasional patient with the yellow nail syndrome also has a pericardial effusion (29,30) or chylous ascites (30). In a series (31) of 41 patients from the Mayo Clinic, other chronic respiratory manifestations were present including bronchiectasis (44%), chronic sinusitis (41%), and recurrent pneumonia (22%). In this series, the median age at diagnosis was 61 years (31). There appears to be a relationship between rheumatoid arthritis and the yellow nail syndrome. Since 1979, 10 patients have been reported who had both the yellow nail syndrome and rheumatoid arthritis (32). Lastly, a recent report (33) demonstrated that the yellow nail syndrome could be associated with either common variable immunodeficiency or the specific antibody deficiency syndrome.

The basic abnormality in this syndrome appears to be hypoplasia of the lymphatic vessels. Lymphangiograms of the lower extremity demonstrate hypoplasia of at least some lymphatic vessels in most patients with the syndrome (28). Emerson (34) has postulated that pleural effusions may develop when a lower respiratory tract infection or pleural inflammation damages previously adequate but impaired lymphatic vessels. Subsequently, the lymphatic drainage of the pleural space is insufficient to maintain a fluid-free pleural space. In one report, biopsy of the parietal pleura revealed abnormally dilated lymphatics, neogenesis of lymphatic channels, and edematous tissues in some areas, suggesting some deficit in lymphatic drainage (35). However, the albumin turnover in the pleural fluid is not greatly decreased in patients with this syndrome (36). There has been one report (37) of the familial occurrence of the yellow nail syndrome.

In this report, the mother, three of four of her children, and her grandmother had the yellow nail syndrome (37).

With this syndrome, the nails are yellow, thickened, and smooth and may show transverse ridging (38). They are excessively curved from side to side, and the actual color is pale yellow to greenish. Onycholysis (separation of nail from bed) is frequently present, and nail growth is slow (38).

The pleural effusions are bilateral in approximately 50% of patients and vary in size from small to massive (38). Once pleural effusions have occurred with this syndrome, they persist and recur rapidly after a thoracentesis (28). The pleural fluid is usually a clear yellow exudate with a normal glucose level and predominantly lymphocytes in the pleural fluid differential WBC (28,34,38). The pleural fluid LDH tends to be low relative to the pleural fluid protein level. In one series (31), 5 of 16 patients (31%) had a chylothorax. The pleural biopsy reveals fibrosis, nonspecific inflammation, or lymphocytic cellular infiltrates, none of which is diagnostic of the disease (39).

The diagnosis is made when a patient has a chronic pleural effusion in conjunction with yellow nails or lymphedema. No specific treatment exists for the syndrome, but if the effusion is large and produces dyspnea, pleurodesis with a tetracycline derivative or thoracoscopy with pleural abrasion should be considered (31,35,38,40). One patient with pleural effusion secondary to the yellow nail syndrome has been treated successfully with a pleuroperitoneal shunt (41).

SUPERIOR VENA CAVAL SYNDROME

In sheep, elevation of the pressure in the superior vena cava leads to the accumulation of pleural fluid. Allen et al. (42) demonstrated that once the pressure in the superior vena cava was elevated above 15 mm Hg, pleural fluid accumulated. The higher the pressure in the superior vena cava, the greater the rate of fluid accumulation. The fluid was transudative in that the ratio of the pleural fluid to serum protein was less than 0:5. These workers attributed the pleural fluid formation to either lymph leakage out of the lymphatics that pass through the chest or obstruction of lung or chest lymphatics with subsequent leakage of interstitial fluid into the pleural space.

Ligation of the superior vena cava also leads to the formation of pleural fluid in dogs. Blalock et al. (43) ligated the superior vena cava of dogs and reported that within a few days of the procedure, bloody, nonchylous pleural effusions developed almost universally. Subsequently chylous effusions developed in about half the animals between 4 and 25 days after the ligation. An increase in the intravascular hydrostatic pressure in the external jugular vein above 10 cm H_2O correlated with the development of both chylous and bloody effusions in these animals (43).

In the clinical situation, pleural effusions are very common with superior vena caval obstruction. Rice et al. (44) reviewed the chest radiographs of 67 patients with the diagnosis of the superior vena caval syndrome at a tertiary referral hospital. They reported that the incidence of pleural effusions was 70% in the 43 cases due to malignancy and was 58% in the 24 cases with benign etiologies (44). The location of the effusions was 23% unilateral on the left, 39% unilateral on the right, and 39% bilateral (44). Most of the effusions occupied less than 25% of the hemithorax (44). The pleural fluid was analyzed in 22 of the patients and was found either to be an exudate or a chylothorax in each instance (44). The etiology of the effusions in the patient with malignancy could well have been the malignancy itself, and one would expect these effusions to be exudative. Only five of the effusions with benign etiologies were sampled and of these, two were exudates, two chylous, and one reported as "bloody." It is not clear why the effusions secondary to the benign processes are exudative.

In neonates, superior vena caval thrombosis is also associated with the development of bilateral pleural effusions. Dhande et al. (45) reported a series of five babies who developed superior vena caval obstruction as a complication of the use of central venous catheters. The effusions occurred 7 to 19 days after the initial placement or change of a central venous catheter. All the infants required repeated thoracenteses to remove pleural fluid that accumulated at a rate of up to 200 mL/kg/day. The fluid was a clear transudate (protein level 1.2–2.2 g/dL) but became chylous when feedings were given. These workers attributed the pleural fluid accumulation to obstruction of thoracic lymph flow into the venous system. The incidence of superior vena caval thrombosis in infants who receive central venous catheters for total parenteral nutrition is approximately 10% (46). Approximately 3% of neonates who undergo neonatal cardiac surgery will develop the superior vena caval syndrome, and approximately half of these will develop a chylothorax (47). Fibrinolytic therapy is sometimes useful in treating the venous thrombosis, particularly if it is started within a few days of the development of the syndrome (47).

SARCOIDOSIS

Sarcoidosis is occasionally complicated by a pleural effusion (48–51). The incidence of pleural effusion with sarcoidosis is probably approximately 1% to 2% (48,50,52), although it has been reported to be as high as 7% (48). Patients with sarcoid pleural effusion usually have extensive parenchymal sarcoidosis and frequently also have extrathoracic sarcoidosis (48). The symptoms of pleural involvement with sarcoidosis are variable; many patients have no symptoms (48), although an equal number of them have pleuritic chest pain or dyspnea.

The pleural effusions with sarcoidosis are bilateral in approximately one third of cases. The pleural effusions are usually small but may be large (53). The pleural fluid is generally an exudate with predominantly small lymphocytes on the differential WBC (48,51–53). In one case, 90% of the cells in the pleural fluid were eosinophils at the time of the initial thoracentesis. The adenosine deaminase level in sarcoid pleuritis is not elevated (54). There are nine reported cases of chylothorax secondary to sarcoidosis in the literature (53). In another report, seven patients were described as having transudative pleural effusions with no pleural fluid protein concentration above 2.5 g/dL (49). This report is so much at variance with other reports (48,50,51) concerning the protein levels in the pleural fluid, however, that it can probably be ignored. Needle biopsy of the pleura, thoracoscopic biopsy, or open pleural biopsy reveals noncaseating granulomas in the pleura (55).

The diagnosis of a sarcoid pleural effusion should be suspected in any patient with bilateral parenchymal infiltrates and a pleural effusion. A pleural biopsy demonstrating noncaseating granulomas is further support for the diagnosis, but most patients with pleural effusions and noncaseating granulomas on their pleural biopsy have tuberculosis rather than sarcoidosis. Fungal disease involving the pleura (see Chapter 14) must also be considered when noncaseating granulomas are seen on pleural biopsy examination. If a patient has typical, symmetric bilateral hilar adenopathy, parenchymal infiltrates, a negative purified protein derivative (PPD) test, and noncaseating granulomas in tissue besides the pleura, however, he or she probably has sarcoidosis. An elevated serum angiotensin-converting enzyme level gives strong support to the diagnosis. The administration of corticosteroids to patients with pleural sarcoidosis leads to a rapid amelioration of symptoms (if any) and a resolution of the pleural effusion (51).

Necrotizing sarcoid granulomatosis is a disease in which the primary pathologic abnormality is a sarcoid-like granuloma, which is also characterized by vasculitis and necrosis (56). By 1989, approximately 80 cases had been described. Clinically, patients may be asymptomatic or may present with cough, fever, sweats, malaise, dyspnea, hemoptysis, or pleuritic pain. Extrapulmonary findings are usually absent. Roentgenographically, most patients manifest multiple well-defined nodules or ill-defined opacities. There seems to be a greater pleural component with necrotizing sarcoid granulomatosis than with typical sarcoid. In one recent report, seven patients presented with pleuritic chest pain (56). Pleural involvement was seen on CT scanning in six patients, and two patients had pleural effusion. The pleural fluid findings with necrotizing sarcoid granulomatosis have not been described. The prognosis of patients with necrotizing sarcoid granulomatosis is favorable, and most patients improve rapidly after corticosteroid therapy is initiated (56).

UREMIA

In 1836, Richard Bright (57) noted, when reviewing patients who died of nephritis, that "of all the membranes, the pleura has decidedly been most often diseased." Seventy-one of his 100 cases demonstrated pleural involvement at autopsy; 41 had a serous effusion, 16 showed evidence of recent inflammation, and 40 had old adhesions. In a more recent series, fibrinous pleuritis has been found in approximately 20% of patients who died of uremia (58). During life, this fibrinous pleuritis can be manifested as pleuritic chest pain with pleural rubs (59), pleural effusions (59–61), or progressive pleural fibrosis producing severe restrictive ventilatory dysfunction (61–63). The pathogenesis of the pleural disease associated with uremia is not known, but it is probably similar to that of pericarditis that is seen with uremia.

The pleural effusion and the restrictive pleuritis have been likened to the hemorrhagic pericarditis and constrictive pericarditis seen with uremia.

The incidence of pleural effusions with uremia is approximately 3% (60). No close relationship exists between the degree of uremia and the occurrence of a pleural effusion (60). More than 50% of these patients are symptomatic, with fever (50%), chest pain (30%), cough (35%), and dyspnea (20%) being the most common symptoms (60). The pleural effusions are bilateral in approximately 20% of patients and may be large. In a series of 14 patients with uremic pleural effusions, more than 50% of the hemithorax was occupied by pleural fluid in 6 patients (43%) (60).

Another patient had opacification of the entire hemithorax, with contralateral mediastinal shift.

The pleural fluid in uremic pleuritis is an exudate that is frequently serosanguineous or frankly hemorrhagic (59–61,64). The glucose level is normal, and the differential WBC reveals predominantly lymphocytes in most patients (60). In one series of seven patients, the mean WBC was 1,231 cells/mm^3, the mean neutrophil percentage was 22, the mean protein was 3.9, and the mean LDH was slightly more than 50% the upper limit of normal for serum (65). Pleural biopsy specimens invariably reveal chronic fibrinous pleuritis.

The diagnosis of uremic pleuritis is one of exclusion in the patient with chronic renal failure (66). Specifically, fluid overload (in such a case the fluid is a transudate), chronic pleural infection, malignant disease, and pulmonary embolism need to be excluded. There is one report (67) that suggests that measurement of the pleural fluid levels of neopterin might be useful in diagnosing uremic pleural effusions. In this report, eight of nine patients (89%) with a uremic pleural effusion had a pleural fluid neopterin level above 200 nmol/L, whereas none of the 85 other patients with pleural effusions of varying etiologies had levels this high (67).

Dialysis is the treatment of choice for patients with uremic pleuritis. With dialysis, the effusion gradually disappears within 4 to 6 weeks in approximately 75% of patients. In the remaining 25%, the effusion persists, progresses, or recurs.

In an occasional patient, the pleural thickening is progressive and leads to severe restrictive ventilatory dysfunction and marked shortness of breath (61–64). At least three such patients have undergone a decortication procedure, and the operation was not complicated by severe bleeding in any of these patients (61–63). All three patients reported marked symptomatic improvement, and one patient's vital capacity increased from 850 mL preoperatively to 1,600 mL 9 months postoperatively. On the basis of these reports and the progressive nature of uremic pleuritis, decortication should be considered in uremic patients with pleural thickening and severe respiratory symptoms.

There is a high incidence of pleural effusions in patients who are receiving chronic hemodialysis. Coskun et al. (68) reviewed the thoracic CT findings of 117 uremic patients on long-term hemodialysis and reported that a pleural effusion was present in 51%. The effusions were bilateral in 63%. Jarratt and Sahn (65) reviewed the medical records of hospitalized patients who had received hemodialysis for at least 3 months and reported that 21% had pleural effusion. They had a total of 100 patients with pleural effusions while receiving dialysis, and the effusions had the following etiologies: heart failure, 46; uremia, 16; parapneumonic, 15; atelectasis, 11; and miscellaneous, 12 (65). Some patients on dialysis will develop rounded atelectasis with their pleural effusions (64). These patients seem particularly likely to develop pleural fibrosis and early pleurodesis has been recommended (64).

Patients receiving peritoneal dialysis have a high prevalence of unexplained exudative pleural effusions (69). The transudative pleural effusion due to the dialysate passing through the diaphragm is discussed in Chapter 9. Kwan et al. (69) reviewed 1,038 patients who received peritoneal dialysis from 1995 to 2004 and reported that 22 patients (2%) had unexplained exudative effusions. They felt that the effusions were due to uremia and recommended that the dialysis be intensified in such patients (69).

AMYLOIDOSIS

A significant percentage of patients with primary systemic amyloidosis have a persistent pleural effusion. Berk et al. (70) reviewed the charts of 636 patients with primary systemic amyloidosis seen at Boston University between 1994 and 2001. They found a total of 35 patients (5.5%) who had persistent pleural effusions that were defined as pleural effusions which failed to resolve despite thoracentesis and aggressive diuresis (70). The patients underwent a median of three thoracenteses (70). The seriousness of the pleural effusions is underscored by the fact that 18 patients had chest tubes placed and 11 underwent pleurodesis (7). An additional 10% to 15% of their patients had less significant effusions (71). Overall, there have been relatively few reports of pleural effusions due to amyloid in the literature. Berk (71) could only find 23 such cases in the English literature between 1977 and 2004. In 21 of these 23 cases, amyloid infiltration in the pleura was demonstrated (71).

The pleural fluids in general were transudates with a mean pleural fluid–serum protein ratio of 0:3 and a mean pleural fluid–serum LDH ratio of 0:38. However, 10 of the 27 effusions on which pleural fluid analysis was available met Light's exudative criteria (70). The median pleural fluid WBC count was only 306 cells/mm^3 and no one cell type predominated (70). Two of the patients had chylothoraces (71). Pleural biopsies were performed in six patients and all revealed amyloid (70).

The etiology of the pleural effusions has been attributed to direct disruption of pleural lymphatics by deposits of amyloid in the parietal pleural. When patients with primary systemic amyloidosis and persistent pleural effusions and those with primary systemic amyloidosis with heart failure and no effusion are compared, there is no difference in septal thickness, left ventricular systolic function, or diastolic compliance. However, right ventricular hypokinesis did occur more frequently in the patients with the effusions (70). Because right ventricular hypokinesis is not usually associated with the development of pleural effusions and as there are amyloid deposits in the parietal pleura, the effusions have been attributed to the amyloid deposits. I have some reservations about this explanation because the amyloid deposits do not explain the very high daily pleural fluid production in amyloid patients with chest tubes.

The management of patients with persistent pleural effusions due to primary systemic amyloidosis is difficult. Initially, aggressive diuresis with therapeutic thoracentesis as needed should be attempted. If thoracentesis is required more frequently than weekly, more aggressive measures are indicated (71). In the series of Berk (71), chest tubes were used to manage the pleural effusions in 18 patients and in each case daily fluid loss exceeded 500 mL for 5 to 12 days despite aggressive diuresis and fluid restriction. Berk (71) reported that thoracoscopy with talc insufflation was successful only if the fluid output per chest tube was less than 200 mL/day. He reported two patients who were managed successfully with an indwelling PleurX catheter (71).

Anti-vascular endothelial growth factor (anti-VEGF) antibodies may have a role in the treatment of refractory pleural effusions (72,73). There is one report (72) in which four patients with systemic amyloidosis and pleural effusions refractory to diuretic therapy were treated with bevacizumab, an anti-VEGF antibody. Three of the four patients had improvement in their pleural effusions, peripheral edema, and functional status (72). In a case report (73), the administration of bevacizumad resulted in a decrease in the pleural fluid production from 600 ml/day to 0 after two treatments 4 weeks apart.

ACUTE EOSINOPHILIC PNEUMONIA

Acute eosinophilic pneumonia is associated with diffuse pulmonary infiltrates on the chest radiograph and an increased number of eosinophils and an elevation of IL-5 (74). The prevalence of pleural effusion is high in patients with acute eosinophilic pneumonia. In one study, 10 of 14 patients had pleural effusions on CT scan (75). Five patients underwent diagnostic thoracentesis, and the mean percentage of eosinophils in four patients was 38%. One patient had pleural fluid lymphocytosis without pleural fluid eosinophilia (75). In a second article, Daimon et al. (76) reported that pleural effusions were present in 23 of 29 patients (79%) with eosinophilic pneumonia. The effusions were bilateral in 22 of the patients (76).

EXTRAMEDULLARY HEMATOPOIESIS

Extramedullary hematopoiesis occurs as a compensatory phenomenon in various diseases in which there is inadequate production or excessive destruction of blood cells. Although the liver and the spleen are the most common sites of extramedullary hematopoiesis, foci can occur in many other organs, including the paravertebral areas of the thorax and the pleura.

An occasional patient with extramedullary hematopoiesis will develop a symptomatic pleural effusion (77–79). The diagnosis of extramedullary hematopoiesis is suggested in the patient with severe anemia by the presence of immature blood cells and megakaryocytes in the pleural fluid. However, the presence of immature blood cells in the pleural fluid is not diagnostic of extramedullary hematopoiesis as it can be seen in patients with sepsis or pleural infection or in patients who have undergone transplantation and are receiving cyclosporine (80). Many patients also have multiple paravertebral masses (77). Patients with pleural effusions secondary to extramedullary hematopoiesis have been managed successfully by both chemical pleurodesis (77,81) and radiotherapy to the masses of hematopoietic tissue (79).

RUPTURE OF A MEDIASTINAL CYST

On rare occasions, pleural effusions result from rupture of a benign germ cell tumor or a bronchogenic cyst into the pleural space (82–84). In one series of 17 cystic mediastinal teratomas, 4 of the patients had preoperative rupture with pleural effusion (83). Chemical analysis of the pleural fluid is confusing at times in these cases. Hiraiwa et al. (82) reported one patient who developed a right pleural effusion after rupture of a benign mediastinal teratoma in which the pleural fluid carcinoembryonic antigen (CEA) level was elevated to 160 ug/L. I have seen another case in which the pleural fluid amylase level was elevated due to high amylase levels in the germ cell tumor. Khalil et al. (84) reported two cases of bronchogenic cysts with associated pleural effusion. No description of the fluid was provided (84).

WHIPPLE DISEASE

Whipple disease is characterized by weight loss, diarrhea, arthralgias, and abdominal pain. Whipple disease is due to chronic infection with the bacterium *Tropheryma whippelii* (85). At times, patients with Whipple disease have pleural effusions, but the pleural effusions are usually not an important manifestation of the disease. In one case, polymerase chain reaction (PCR) on the cells from a pleural effusion demonstrated *T. whippelii*–specific ribosomal ribonucleic acid (rRNA) (86).

SYPHILIS

On rare occasions, syphilis can cause a pleural effusion. There was one case report of a patient with an exudative pleural effusion with predominantly lymphocytes in the fluid and granuloma on the pleural biopsy who turned out to have syphilis (87).

TRAPPED LUNG

A fibrous peel may form over the visceral pleura in response to pleural inflammation. This peel can prevent the underlying lung from expanding (88,89). Therefore, the lung is said to be trapped. When the lung is trapped, the pleural pressure becomes more negative as the chest wall is pulled in. The negative pleural pressure increases pleural fluid formation and decreases pleural fluid absorption (see Fig. 2.1) resulting in a chronic pleural effusion.

The incidence of pleural effusion secondary to trapped lung is not known, but it is probably much higher than is generally recognized. The event producing the initial pleural inflammation is usually pneumonia or a hemothorax, but spontaneous pneumothorax, thoracic operations including coronary artery bypass surgery (90), uremia, and collagen vascular disease can cause the initial pleural inflammation. The pleural effusion in some patients with malignancy is due to malignancy encasing the underlying lung (91), and this situation is sometimes called lung entrapment rather than trapped lung. The presence of a transudative pleural effusion for many months on occasion can lead to the formation of a visceral pleural peel and a trapped lung.

Patients with pleural effusions secondary to trapped lung have either shortness of breath due to restrictive ventilatory dysfunction or an asymptomatic pleural effusion. Symptoms of acute pleural inflammation such as pleuritic chest pain or fever are distinctly uncommon, but the patient often gives a history of such events in the past. One characteristic of the pleural effusion secondary to trapped lung is that the amount of fluid is remarkably constant from one study to another (88). Following thoracentesis, the fluid reaccumulates rapidly to its previous level.

Although one would expect that the pleural fluid with trapped lung would be exudative because the pleural surfaces are involved, the pleural fluid is usually a borderline exudate. The ratio of pleural fluid to serum protein is approximately 0:5, and the ratio of the pleural fluid LDH level to the serum LDH level is approximately 0:6. The pleural fluid glucose level is normal, and the pleural fluid WBC is usually less than 1,000/mm^3, with the differential WBC revealing predominantly mononuclear cells (92).

The diagnosis of pleural effusion secondary to trapped lung should be suspected in any patient with a stable chronic pleural effusion, particularly in a patient with a history of pneumonia, pneumothorax, hemothorax, or thoracic operation. The injection of 200 to 400 mL air at the time of a diagnostic thoracentesis frequently permits demonstration of the thickened visceral pleura. Measurements of the pleural pressure as fluid is withdrawn during therapeutic thoracentesis (see Chapter 28) are useful in supporting this diagnosis. The initial pleural pressure is low, and the rate of decline of pleural pressure as fluid is removed is high in patients with trapped lung. If the initial pleural pressure is below –10 cm H_2O, or if the pleural pressure falls by more than 20 cm H_2O per 1,000 mL of the fluid removed, the diagnosis is suggested if the patient does not have bronchial obstruction (89). The pleural pressures can be measured either with a U-shaped manometer (89) or with pressure transducers (93).

The definitive diagnosis of trapped lung requires a thoracotomy and decortication, with the demonstration that the underlying lung will expand to fill the pleural space. This operation also cures the patient, but such a surgical procedure is probably not indicated in the asymptomatic or minimally symptomatic patient with trapped lung. Such patients can be observed if the clinical picture, pleural fluid findings, and pleural pressure measurements are compatible with the diagnosis (89).

THERAPEUTIC RADIATION EXPOSURE

Pleural effusions can occur as a complication of radiotherapy to the chest. Bachman and Macken (94) followed up 200 patients treated with radiation of 40 to 60 cGy to the hemithorax for breast carcinoma. These researchers reported that 11 patients (5.5%) developed pleural effusions with no other obvious explanation.

The pleural effusions, therefore, were attributed to the radiation (94). All patients developed their pleural effusions within 6 months of completing radiation therapy, and every patient had concomitant radiation pneumonitis (94). The pleural fluid with radiation pleuritis has not been well characterized, but one report described the fluid as an exudate with many vacuolated mesothelial cells (95). Most pleural effusions were small, but at least one occupied approximately 50% of the hemithorax. In 4 of the 11 patients, the fluid gradually disappeared spontaneously in 4 to 23 months. In the remaining patients, the pleural effusions persisted, gradually decreasing in size over the follow-up period of 10 to 40 months.

Pleural effusions can also occur as a late complication of radiotherapy to the chest. Morrone et al. (96) reported one case of bilateral pleural effusion that developed in a patient 19 years after receiving mediastinal radiotherapy for Hodgkin's disease. The effusions were exudates with predominantly lymphocytes. Thoracoscopy revealed that there were enlarged lymphatic vessels in the visceral pleura. In a second report, a patient developed bilateral pleural effusions 8 years after receiving radiotherapy for Hodgkin's disease. In this instance, thoracoscopy demonstrated diffuse thickening of the pleura (97).

ELECTRICAL BURNS

Individuals who have suffered major electrical burns may develop a pleural effusion secondary to the burn. If the contact point for the electrical burn is over the chest, the underlying pleura is damaged. Accordingly, a pleural effusion develops within the first week of the accident, and an accompanying pneumonitis may be seen (98). The pleural fluid is an exudate that gradually resolves over a period of several months.

DROWNING

Individuals who drown have a substantial amount of pleural fluid at autopsy. Morild (99) reviewed the autopsies of 133 individuals who had drowned between 1987 and 1991. He found that pleural effusions were present in 71 of the patients (53%). The mean amount of fluid was 433 mL, with a maximum of more than 3,000 mL. Effusions were more common if the patient had been in the water for more than 8 hours and were more common with saltwater drowning (99).

Analysis of the electrolytes in the pleural fluid of drowning victims shows significant differences depending on whether the drowning occurred in seawater or freshwater (100). After rats are drowned, the mean pleural fluid sodium and chloride levels after seawater drowning were 117 and 98 mEq/L, respectively, whereas those after freshwater drowning were 71 and 54 mEq/L, respectively (100). The potassium levels did not differ in the two types of drowning and were very high (>60 mEq/L). Similar results have been found in humans (101). In one study (101) of 24 cases of seawater drownings and 9 cases of freshwater drownings, the mean sodium levels were 175 mEq/L in the seawater drownings and 75 mEq/L in the freshwater drownings while the mean chloride levels were 179 mEq/L in the seawater drownings and 57 mEq/L in the freshwater drownings. Although there are no reports of pleural effusion occurring in patients who survive near-drowning, it is likely that some have pleural effusion because one of the patients who died in Morild's series (99) had 900 mL of pleural fluid and had been in the water only 6 to 7 minutes.

MILK OF CALCIUM PLEURAL EFFUSION

Milk of calcium is a colloidal suspension of precipitated calcium salts. It has been seen in various cystic spaces such as the gallbladder, renal calyceal diverticula, adrenal cysts, and breast cysts (102). Milk of calcium can also collect in the pleural space. The radiographic picture is characteristic, showing a half-moon or hemispherical calcium–fluid level (102).

Im et al. (102) reported five patients with pleural milk of calcium who showed a loculated pleural collection with double contour on radiography and homogeneous calcification on CT scan. Four of the five patients gave a history of pleurisy more than 10 years previously. Aspirated materials from the pleural space consisted of thick yellow fluid containing gritty particles. The concentration of calcium in the aspirated material was greater than 500 mg/dL (102). The five patients were essentially asymptomatic from the milk of calcium–fluid collections and received no therapy for the pleural effusion (102).

ACUTE RESPIRATORY DISTRESS SYNDROME

There appears to be a high prevalence of small pleural effusions in patients with the acute respiratory distress syndrome (ARDS). The origin of the pleural fluid in patients with ARDS is probably the interstitial spaces of the lung. Tagliabue et al. (103) reviewed the CT findings in 74 patients with ARDS. They reported

that pleural effusions were present in 37 (50%). On the chest radiograph, the effusion was apparent in 25 of the 37 (68%). The effusions were bilateral in 21, unilateral and right sided in 6, and unilateral and left sided in 10. The effusions were small in 22 and moderate in 15. In a second study, Talmor et al. (104) prospectively studied 199 patients with ARDS in a surgical intensive care unit who required ventilation with positive end-expiratory pressure (PEEP). These investigators found that 19 patients (10%) who had unsatisfactory oxygenation status had effusions visible on the supine chest radiograph. When chest tubes were inserted into these patients, their oxygenation status and their lung compliance improved (104). Patients with ARDS with significant pleural fluid should undergo a thoracentesis to delineate the characteristics of the pleural fluid. If the patient is having trouble with oxygenation or with being weaned off the ventilator, a therapeutic thoracentesis should be performed.

IATROGENIC PLEURAL EFFUSIONS

At times, physicians are responsible for the development of pleural effusions in their patients. The iatrogenic effusions secondary to various pharmaceutical agents, radiation therapy, endoscopic esophageal sclerotherapy, the ovarian hyperstimulation syndrome, and fluid overload are discussed elsewhere in this book, as are those that occur following coronary artery bypass surgery, various transplantations and abdominal surgery. In this section, the iatrogenic pleural effusions that result from misplacement of percutaneously inserted catheters or enteral feeding tubes, those associated with translumbar aortography, and those resulting from rupture of silicone bag mammary prosthesis are discussed.

Superior Vena Cava Perforation by a Central Catheter

An uncommon but potentially fatal iatrogenic cause of pleural effusion is the misplacement of a percutaneously inserted catheter into the mediastinum or the pleural space. As of 1995, there had been 35 reports describing 69 patients with central venous catheter–induced hydrothorax (105). The incidence of this complication has been estimated to be as high as 0.5% (105). The two major risk factors for the development of this complication are (1) catheter insertion from the left and (2) large-bore catheters (106).

The average time interval from catheter placement to the onset of symptoms is 2 days, with a range of 1 to 60 days (106). The more common clinical symptoms and signs are dyspnea (82%), chest pain (46%), respiratory failure (18%), hypotension (13%), and cardiac arrest (5%). The chest radiograph may reveal unilateral or bilateral pleural effusions with or without a widened mediastinum. A unilateral pleural effusion may be ipsilateral or contralateral to the catheter's insertion site (106).

The pleural fluid may be pure blood resulting from laceration or puncture of one of the vessels (107). More frequently, the pleural fluid reflects the characteristics of the infusate. If the patient is receiving an intravenous fat emulsion, the pleural fluid may appear milky and is easily confused with a chylothorax (108). If the patient is receiving 5% of dextrose-containing solutions, the pleural fluid glucose level is invariably higher than the simultaneous serum glucose level (106). The only other situations in which the pleural fluid glucose is significantly higher than the simultaneously obtained serum glucose is with peritoneal dialysis with dialysates containing a high glucose level and with esophageal rupture when food with high glucose levels enters the pleural space. The pleural fluid protein and LDH levels are usually very low (105).

The diagnosis should be suspected in any patient with a central line who has a large pleural effusion. If aspiration of the central catheter yields blood, a perforation may still be present (109). Analysis of the pleural fluid usually confirms the diagnosis. The treatment is to remove the catheter immediately. If the patient is in respiratory distress, a therapeutic thoracentesis should be performed. If fresh blood is present, a chest tube should be inserted immediately, and if bleeding persists, an exploratory thoracotomy may be necessary (107).

Many central lines are inserted to infuse chemotherapy. When such lines perforate the vein and enter the mediastinum, the chemotherapeutic agents may be quite toxic. Bozkurt et al. (110) were able to find seven such cases in the literature. The agents extravasated included vincristine, vinblastine, 5-fluorouracil, epirubicin, and daunorubicin. Pleural effusions developed in four of the patients. The pleural effusion was described as a transudate in one of the patients (110).

Perforation of Pleura with a Nasogastric Tube

The development of soft, flexible, small-bore polyurethane feeding tubes has made nasogastric and nasoenteric feeding more practical and comfortable for patients. The increasing awareness by physicians of the importance of malnutrition and metabolic

support has led to an increase in the use of such tubes. However, their use has been associated with significant pleural complications. In an 11-month period in one institution, there were four instances in which nasogastric tubes were placed in the tracheobronchial tree for an incidence of approximately 0.3% of all intensive care unit patients who received nasogastric tubes (111). These tubes are often inserted into patients who have taken an overdose. Because such patients are obtunded, sometimes the tubes enter the pleural space without producing respiratory symptoms immediately. There have been several instances in which charcoal has been instilled into the pleural space (112).

Pneumothorax is the most common complication (113), but the infusion of the enteral formula into the pleural space or the development of an empyema also occurs relatively frequently (114). The stylets used for ease of insertion provide stiffness and strength to the tubing and allow easier advancement of the device. With the stylet in place, the tubing becomes stiff and is able to perforate structures relatively easily. There are frequently no clinical clues that the tube has entered the bronchial tree instead of the esophagus. The risk of this complication is much greater if the patient has an endotracheal tube in place or if he or she is obtunded (113). To prevent this complication, these tubes should only be inserted by experienced individuals, and the tube should be removed immediately if the patient starts coughing. If any resistance is felt, no further attempts should be made to advance the tube. Before feeding is initiated, the position of the tip of the tube should be confirmed radiographically (114). The standard tests for the placement of nasogastric tubes such as the insufflation of air with auscultation over the left upper quadrant or the aspiration of fluid are often misleading with the small nasogastric tubes (114).

If the tube enters the pleural space and the enteral solutions or charcoal are infused, tube thoracostomy should be performed after the nasogastric tube has been removed. In such a situation, the possibility of an empyema should be evaluated because the incidence of empyema is high when these small tubes enter the pleural space (113).

Translumbar Aortography

Pleural effusion may also complicate translumbar aortographic examination (114). Small pleural effusions requiring decubitus radiographs for their demonstration occur frequently after translumbar aortographic studies (114) and are thought to be secondary to the passage of the needle through the most inferior part of the pleural space. An exudative pleural effusion may result from irritation of the pleural space by the extravasated contrast medium. The pleural effusion following translumbar aortographic examination is sometimes frankly bloody and probably results from blood leaking from the aorta into the pleural space. In such situations, a therapeutic thoracentesis is usually sufficient treatment because the leak stops spontaneously (114).

After Mammoplasty

There have been at least three case reports of a pleural effusion developing after rupture of a silicone bag mammary prosthesis (115–117). One patient developed left-sided pleuritic chest pain 24 hours after she had sustained a blow of moderate severity on the left anterior chest wall. Five years previously, she had undergone bilateral augmentation mammoplasties with insertion of silicone bag prostheses. On physical examination, the breasts appeared equal in size. The chest radiograph revealed a large left pleural effusion. Thoracentesis revealed slightly turbid fluid with a protein level of 4.6 g/dL and an LDH level of 372 IU/L. A subsequent pleural biopsy revealed a dense mixed cellular infiltrate with several granulomas and large multinucleated giant cells suggestive of a foreign body reaction. Two liters of pleural fluid were aspirated, and an oily layer was observed on the top of the fluid, which was consistent with the presence of silicone gel in the aspirate. After the aspiration, the pleural effusion did not recur. Two other patients developed pleural effusions approximately 1 year after their implants had ruptured (116,117). In one patient, there was viscid, yellowish pasty material that could only be obtained with a 14-gauge needle (116). The other fluid was yellow, and scanning electron microscopy was necessary to demonstrate material with the electron energy pattern of silicone (117). These three reports demonstrate that silicone can reach the pleural space, but once there, it does not elicit much of an inflammatory reaction.

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chapter 24

Pneumothorax

A pneumothorax is air in the pleural space, that is, air between the lung and the chest wall. Pneumothoraces can be divided into *spontaneous pneumothoraces*, which occur without antecedent trauma or other obvious cause, and *traumatic pneumothoraces*, which occur from direct or indirect trauma to the chest. A subcategory of traumatic pneumothorax is *iatrogenic pneumothorax*, which occurs as an intended or inadvertent consequence of a diagnostic or therapeutic maneuver. Spontaneous pneumothoraces are further divided into *primary* and *secondary spontaneous pneumothoraces*. Primary spontaneous pneumothoraces occur in otherwise healthy individuals, whereas secondary spontaneous pneumothoraces occur as a complication of underlying lung disease, most commonly chronic obstructive pulmonary disease (COPD).

PRIMARY SPONTANEOUS PNEUMOTHORAX

Incidence

The most complete figures on the incidence of primary spontaneous pneumothorax probably come from a study of the residents of Olmsted County, Minnesota, where complete medical records are kept on all residents. Between 1959 and 1978, 77 cases of primary pneumothorax occurred among the county's population that averaged 60,000 over this period. The age-adjusted incidence of primary spontaneous pneumothorax was 7.4/100,000/year for men and 1.2/100,000/year for women (1). If these figures are extrapolated to the entire population of 250 million in the United States, one can anticipate approximately 10,000 new cases of primary spontaneous pneumothorax per annum. In a more recent study from the United Kingdom, the incidence of spontaneous pneumothorax in males and females aged 15 to 34 was 37.0 and 15.4/100,000/year, respectively. Since most patients in this age range have primary spontaneous pneumothorax, it appears that the incidence in the United Kingdom is greater than that previously reported in the United States (2).

Etiologic Factors

The general consensus is that primary spontaneous pneumothorax results from rupture of subpleural emphysematous blebs that are usually located in the apices of the lung (3,4). In one older study, Gobbel et al. operated on 31 patients with primary spontaneous pneumothorax and found subpleural blebs or bullae in each patient (3). In a more recent study, Lesur et al. (4) obtained computed tomography (CT) scans on 20 young (mean age 27) patients with spontaneous pneumothorax and could demonstrate apical subpleural emphysematous lesions in 16 of the 20 patients (80%). In another study, Bense et al. obtained CT scans on 27 nonsmoking patients with primary spontaneous pneumothorax and reported that 22 (81%) had emphysema-like changes, mostly in the upper lobes (5). It appears that the apical blebs present on direct visualization and the emphysema-like changes seen on CT scan represent the same abnormality. It should be noted, however, that there is some controversy concerning the significance of the subpleural blebs. Noppen et al. have identified abnormal regions of the visceral pleura by fluorescein-enhanced autofluorescence thoracoscopy and suggest that leakage of air through these areas, rather than rupture of blebs, may be responsible for primary spontaneous pneumothorax (6). I believe that most primary spontaneous pneumothoraces are due to

rupture of a bleb. The reason that I believe this is that the symptoms of primary spontaneous pneumothorax start suddenly. If the pneumothorax were due to slow leakage through the visceral pleura, the symptoms should not start abruptly.

The pathogenesis of these subpleural blebs is probably related to airway inflammation. Respiratory bronchiolitis was found in 70 of 79 patients (89%) who underwent a surgical procedure for recurrence or persistence of primary spontaneous pneumothorax (7). All the patients in this study were smokers, and cigarette smoking can certainly produce airway inflammation. Cigarette smoking is known to be strongly associated with the development of primary spontaneous pneumothorax. When the smoking habits of 505 patients from four separate studies were analyzed (8–11), 461 of the patients (91%) were smokers. Furthermore, the occurrence of a spontaneous pneumothorax appears to be related to the level of cigarette smoking. Compared with nonsmokers, the relative risk of a pneumothorax in men is seven times higher in light smokers (1–12 cigarettes/day), 21 times higher in moderate smokers (13–22 cigarettes/day), and 102 times higher in heavy smokers (>22 cigarettes/day). For women, the relative risk is 4, 14, and 68 times higher in light, moderate, and heavy smokers than in nonsmokers, respectively (11). Disease of the small airways related to smoking probably contributes to the development of the subpleural blebs (12). Interestingly, the prevalence of smoking in Chinese patients with primary spontaneous pneumothorax is only about 50% (13,14).

Two studies concluded that spontaneous pneumothoraces were more likely to develop following days when there are broad swings in the atmospheric pressure (15,16). It was postulated that the air in the apical blebs was not in free communication with the airways. Therefore, when the atmospheric pressure falls, the distending pressure of the bleb may increase and could result in its rupture (15). It should be noted that three other studies found no relationship between change in the atmospheric pressure and the occurrence of a spontaneous pneumothorax (17–19). In one study, however, there was a significant relationship between thunderstorms and the occurrence of pneumothoraces (17). Noppen et al. described the development of five episodes of primary spontaneous pneumothorax in four patients upon exposure to loud music (20).

Patients with primary spontaneous pneumothorax are usually taller and thinner than control patients. In a study of military recruits with pneumothorax, Withers et al. (21) found that those with pneumothoraces were 2 in. taller and 25 lb lighter than the average military recruit (21). Because the gradient in pleural pressure is greater from the lung base to the lung apex in taller individuals (see Chapter 2), the alveoli at the lung apex are subjected to a greater mean distending pressure in taller individuals. Over a long period, this higher distending pressure could lead to the formation of subpleural blebs in taller individuals who are genetically predisposed to bleb formation.

The tendency to develop a spontaneous pneumothorax may be genetically determined (22). There is a high incidence of pneumothorax in patients with the *Birt-Hogg-Dubé syndrome.* This syndrome is autosomal dominant (23) and is characterized by an increased incidence of spontaneous pneumothorax, benign skin tumors, and renal tumors (23,24). The gene has been mapped to chromosome 17p11.2 (23). Mutations in the folliculin (FLCN) gene are responsible for the Birt-Hogg-Dubé syndrome (25). At least 53 different germline mutations and 31 SNPs have been identified in patients with the Burt-Hogg-Dubé syndrome (26). Pneumothorax occurred in 25 of 111 patients (22.5%) in one study (27). Radiographically, 15% to 83% have pulmonary cysts and/or bullae (28). When these patients are explored surgically, they are found to have apical blebs (27). Microscopic examination of the resected lung tissue reveals cysts comprising intraparenchymal collections of air surrounded by normal parenchyma or a thin fibrous wall or blebs consisting of collections of air within the pleura (28).

There have been other reports of a familial tendency for the development of primary spontaneous pneumothorax. In one study of primary spontaneous pneumothorax in the Israeli Defense Forces, 11.5% of 286 patients with spontaneous pneumothorax had a positive family history for primary spontaneous pneumothorax (29). A more in-depth analysis of 15 families suggested that the mode of inheritance for the tendency for pneumothorax was either autosomal dominant with incomplete penetrance or X-linked recessive (30). These reports were written before the Birt-Hogg-Dubé syndrome was described and the patients may have had this syndrome. In another report of patients with familial pneumothorax, individuals with human leukocyte antigen (HLA) haplotype A_2, B_{40} were found to be much more likely to have a pneumothorax (31). Other studies of familial pneumothorax have been unable to document any association with the HLA haplotypes (32).

Well-known inherited diseases associated with pneumothorax include Marfan's syndrome, homocystinuria, Ehlers-Danlos syndrome, and α_1-antitrypsin deficiency (24).

There is a very high prevalence of bronchial abnormalities in nonsmoking patients with spontaneous pneumothorax. Bense et al. (33) performed fiberoptic bronchoscopy on 26 people who had never smoked but had a history of spontaneous pneumothorax. They reported that 25 of 26 (96%) of the patients had bronchial abnormalities bilaterally. In comparison, only 1 of 41 control patients had such abnormalities (33). The bronchial abnormalities included disproportionate bronchial anatomy (smaller than normal dimensions and deviating anatomic arrangements of the airways at various locations), an accessory bronchus, or a missing bronchus. The most common abnormality was the disproportionate bronchial anatomy (33).

Pathophysiologic Features

When resected specimens from the lungs of patients with spontaneous pneumothorax are examined, there is frequently an eosinophilic pleuritis (34). In addition, some patients have mild pulmonary vascular and perivascular eosinophilia (34). Many patients also have pulmonary artery intimal fibrosis and pulmonary vein intimal fibrosis (35). The eosinophilic pleuritis is probably directly related to the air in the pleural space, and the presence of abnormalities in the pulmonary vessels should not serve as an indication to investigate the patient for pulmonary vascular disease.

The physiological consequences of a pneumothorax are discussed in Chapter 3.

Clinical Manifestations

The peak age for the occurrence of a primary spontaneous pneumothorax is the early 20s, and primary spontaneous pneumothorax rarely occurs after age 40. The main symptoms associated with the development of primary spontaneous pneumothorax are chest pain and dyspnea. In a series of 39 patients reported by Vail et al. (36), every patient had chest pain or dyspnea, and both symptoms were present in 25 of the 39 patients (64%). Seremetis (10) reported chest pain in 140 of 155 patients (90%). The chest pain usually has an acute onset and is localized to the side of the pneumothorax. On rare occasions, the patient has neither chest pain nor dyspnea. The pneumothorax is bilateral in less than 2% of patients (13). In the series of Seremetis (10), five patients (3%) complained only of generalized malaise. On rare occasions, the pneumothorax is discovered on a routine chest radiograph (37). Horner's syndrome has been reported as a rare complication of spontaneous pneumothorax and is thought to be due to traction on the sympathetic ganglion produced by shift of the mediastinum (38).

Primary spontaneous pneumothorax usually develops while the patient is at rest. In the series of 219 patients of Bense et al. (39), 87% were at rest at the onset of symptoms and none were exerting themselves heavily when symptoms began. Other series have reported comparable findings (8,10).

Many patients with spontaneous pneumothorax do not seek medical attention immediately after the development of the symptoms. Eighteen percent of the patients in one series had symptoms for more than a week before seeking medical attention (10), whereas 46% in a second series waited more than 2 days before seeing a physician (8). Patients with symptoms for more than 3 days should not have negative pressure applied to their chest tubes in view of the higher incidence of reexpansion pulmonary edema with prolonged pneumothorax (see Chapter 28).

Changes on Physical Examination

Physical examination of patients with primary spontaneous pneumothorax reveals vital signs that are usually normal, with the exception of a moderate tachycardia. If the pulse rate exceeds 140 or if hypotension, cyanosis, or electromechanical dissociation is present, a tension pneumothorax should be suspected (see the section later in this chapter on tension pneumothorax). Examination of the chest reveals that the side with pneumothorax is larger than the contralateral side and moves less during the respiratory cycle. Tactile fremitus is absent, the percussion note is hyperresonant, and the breath sounds are absent or reduced on the affected side. The trachea may be shifted toward the contralateral side. With right-sided pneumothoraces, the lower edge of the liver may be shifted inferiorly.

Electrocardiographic Changes

Patients with spontaneous pneumothorax may show electrocardiographic changes due to the pneumothorax (40). In a study of seven patients with spontaneous left pneumothorax, Walston et al. (41) found that a rightward shift of the frontal QRS axis, a diminution of precordial R voltage, a decrease in QRS amplitude,

and precordial T-wave inversion could all occur. A different study (40) reports that the V_{2-6} amplitude was decreased with left-sided pneumothorax. In a study (42) of patients with right-sided pneumothorax, prominent R-wave voltage in lead V_2 with loss of S-wave voltage, mimicking posterior myocardial infarction, and reversible reduced QRS voltage were reported. In another study (40), the QRS amplitude was increased in V_{5-6} with right-sided pneumothorax (40). In addition, marked PR-segment elevation in the inferior leads with reciprocal PR-segment depression in aVR has been reported (43). These changes should not be mistaken for an acute non–Q wave myocardial infarction. There has also been a report of a patient with a tension pneumothorax who developed pronounced ST-segment elevation in II, III, a VF, and V_{4-6} (44). When a chest tube was inserted, the ST changes resolved and studies of myocardial enzymes were negative (44).

Diagnosis

In a young, thin, tall man, the diagnosis is usually suggested by the clinical history and physical examination. The diagnosis is established by demonstrating a pleural line on the chest radiograph (Fig. 6.12) (45). Because expiratory chest radiographs have little or no advantage over inspiratory chest radiographs in making the diagnosis of pneumothorax (46), they are not routinely recommended. However, if there is a strong suspicion of a pneumothorax and the inspiratory film is nondiagnostic, many clinicians will obtain expiratory films (45). The diagnosis of pneumothorax can also be established with ultrasound (47) (see Chapter 6). It is important to realize that the presence of air in a hemithorax does not always represent a pneumothorax. If abdominal viscera herniate through a diaphragm, intravisceral air can be confused with pneumothorax (48). Chest CT scans are not routinely indicated in patients with primary spontaneous pneumothoraces since there is no close correlation between the presence of subpleural blebs and the recurrence of pneumothorax (49–51).

Approximately 10% to 20% of patients have an associated pleural effusion, which is usually small and is manifested radiographically as an air–fluid level (10,36). The pleural fluid with pneumothorax is characterized by eosinophilia, and the median percentage of eosinophils exceeds 20% after 1 day and 60% after 7 days (52). There is a significant correlation between the interleukin 5 (IL-5) levels in the pleural fluid and pleural fluid eosinophilia (52). When pneumothoraces are induced in mice, the number of eosinophils in the pleural space is reduced in tumour necrosis factor (TNF)-alpha knockout mice and in wild type mice who are given dexamethasone (53). In a small percentage of patients, the pleural effusion turns out to be a hemothorax that can be associated with life-threatening hemorrhage (54) (see Chapter 25).

Quantitation

One should estimate the amount of lung collapse when treating a patient with a pneumothorax. The volume of the lung and the hemithorax are roughly proportional to the cube of their diameters. Therefore, one can estimate the degree of collapse by measuring an average diameter of the lung and the hemithorax, cubing these diameters, and finding the ratios.

Mathematically,

$$\%\ \text{pneumothorax} = 100\left(1 - \frac{(\text{diameter lung})^3}{(\text{diameter hemithorax})^3}\right)$$

For example, in Figure 6.12, the average diameter of the hemithorax is approximately 10 cm, and the distance between the lung and chest wall is 4 cm. Therefore, the ratio of the diameters cubed 6^3:10^3 equals 22% and approximately a 80% pneumothorax is present, although it appears substantially smaller at first glance. This method of estimating the size of primary spontaneous pneumothorax has been called the *Light index* (55). Noppen et al. have demonstrated that there is a close correlation between the Light index and the actual amount of air in the pleural space, as quantitated by manual aspiration (55).

Collins et al. (56) have described an alternate method for estimating the percentage of collapse. With their method, the distance between the apex of the partially collapsed lung and the apex of the thoracic cavity (distance A), and the midpoints of the upper (distance B) and lower (distance C) halves of the collapsed lung and the lateral chest wall were measured in centimeters. They found that the percentage pneumothorax size could be calculated by the formula,

$$\%\ \text{pneumothorax} = 4.2 + [4.7 \times (A + B + C)]$$

When the volume calculated from a helical CT scan was compared with the volume measured with this formula, the correlation coefficient in 20 patients was 0.98 (56). Even though the correlation coefficient

was very high, improvements can be made in the preceding formula because it does not take into account the patient's size. Obviously, a very large person will have a smaller pneumothorax in relation to the overall size of the lung than a small person with identical distances between the lung and the chest wall.

A third method for estimating the size of a pneumothorax, the Rhea method, uses a nomogram that relates the average intrapleural distance to the pneumothorax size (57). On this nomogram, there is a 10% pneumothorax for every centimeter of intrapleural distance. A recent article found that there was a close correlation when the Collins method and the Rhea method were used to calculate pneumothorax percentage (58). However, there is no close agreement between the Collins method and the Light index (59). In general, the Rhea method or the Collins method is recommended.

The size of a pneumothorax can also be calculated from a CT scan of the thorax (60). Cai et al. (60) demonstrated that was very close agreement for the volume of a pneumothorax calculated via a computer from the chest CT scan and the volume of air aspirated from the hemithorax.

Position papers have used much simpler schemes for semiquantitating the size of pneumothoraces. In the British Thoracic Society's (BTS) guidelines for the management of spontaneous pneumothorax, small pneumothoraces were defined as those in which the rim of air between the pleura and the chest wall at the level of the hilum was less than 2 cm and large as greater than 2 cm (61). In their consensus statement of the management of spontaneous pneumothorax, the American College of Chest Physicians defined a small pneumothorax as one in which the apex-to-cupola distance was less than 3 cm whereas a large pneumothorax was one in which this distance was greater than 3 cm (62). Collins method and Rhea method are preferred to measuring just the apex-to-cupola distance because they give a more precise estimate of the size of the pneumothorax.

Recurrence Rates

A patient who has had a primary spontaneous pneumothorax is at risk of having a recurrence. Sadikot et al. (63) followed up 153 patients with primary spontaneous pneumothorax for a mean of 54 months and found that the recurrence rate was 54.2%. In this study, the recurrence rates were less in men (46%) than in women (71%) and were less in individuals who stopped smoking (40%) than in those who continued smoking (70%). There was no significant relationship between the size of the original pneumothorax or the treatment of the original pneumothorax and the recurrence rates. Twenty-four of their patients (16%) had a pneumothorax on the contralateral side; in only one patient did the pneumothoraces occur simultaneously (63). Gobbel et al. (3) followed a group of 119 patients with spontaneous pneumothorax for a mean of 6 years. These investigators found that, of the 110 patients who did not have a thoracotomy at the time of their initial pneumothorax, 57 (52%) had an ipsilateral recurrence. Once a patient had second and third pneumothoraces without thoracotomy, the incidence of subsequent recurrence was 62% and 83%, respectively.

Older studies suggested that there is substantial risk of recurrence over many years. In the series of Gobbel et al. (3), the average interval between the first and the second pneumothorax was 2.3 years, although the average interval for recurrence in the series of Seremetis was 17 months (10). However, more recent studies have suggested that most recurrences occur within the first year (49,64,65).

Attempts have been made to predict which patients with a primary spontaneous pneumothorax are more likely to have recurrence. If one could predict which patients are more likely to have a recurrence, then those patients could be treated more aggressively to prevent a recurrent pneumothorax at the time of their first pneumothorax. The presence of blebs or bullae on chest CT scan does not predict whether the patient will develop a recurrent pneumothorax (49,51). Abolnik et al. (29) did report that taller, thinner individuals were more likely to have a recurrence. Guo et al. (66), using a multivariate analysis of 138 patients, demonstrated that recurrences were more frequent in taller patients and patients with lower weights (66).

In a recent study, Ganesalingam et al. (67) carefully studied the chest radiographs taken on the initial presentation of 100 patients for spontaneous pneumothorax for pleural thickening, blebs/bullae, pleural irregularities, and pleural adhesions. Over a mean follow-up period of 57 months, 52% of the patients had a recurrence. Patients having one, two, and three or more abnormalities were 3.0, 5.3, and 12.6 times more likely to develop a recurrence, respectively (67). They recommended that surgical treatment be offered to patients in whom two or more radiological abnormalities were identified (67).

Treatment

Therapy for the patient with primary spontaneous pneumothorax has two goals: (a) to rid the pleural

space of its air and (b) to decrease the likelihood of a recurrence.

Several different treatments can be used for the management of a patient with a primary spontaneous pneumothorax. These include observation; supplemental oxygen; simple aspiration; tube thoracostomy with or without the instillation of a sclerosing agent; medical thoracoscopy with the insufflation of talc; video-assisted thoracoscopy with stapling of blebs, instillation of a sclerosing agent, or pleural abrasion; and open thoracotomy. In selecting the appropriate treatment for any given patient, it should be remembered that a primary spontaneous pneumothorax is mainly a nuisance and is rarely life threatening to the patient. In the following sections, discussions of the various treatments are provided. At the end of the section, recommendations for the management of primary spontaneous pneumothorax are given.

Observation

If the communication between the alveoli and the pleural space is eliminated, the air in the pleural space will be reabsorbed for the reasons discussed in Chapter 2. The rate of spontaneous absorption is slow, however. Kircher and Swartzel (68) estimated that 1.25% of the volume of the hemithorax was absorbed every 24 hours. Therefore, a pneumothorax occupying 15% of the hemithorax would take 12 days to be completely reabsorbed. In another study, Kelly et al. (69) used the Collins method to assess the rate of absorption of pneumothoraces. They reported that the mean rate of absorption was 2.2% per day, but there was much variation from patient to patient (69). It is not clear whether some of their patients were on oxygen which would increase the rate of absorption.

It is recommended that only patients with pneumothoraces occupying less than 15% of the hemithorax be considered for this type of treatment. If the patient is hospitalized, supplemental oxygen should be administered to increase the rate of pleural air absorption.

Supplemental Oxygen

The administration of supplemental oxygen accelerates the rate of pleural air absorption in experimental and clinical situations. Chernick and Avery (70) administered humidified 100% oxygen to rabbits with experimentally induced pneumothoraces and found that the oxygen increased the rate of air absorption by a factor of 6. Northfield (71) reported that the rate of absorption was increased fourfold when patients were treated with high-flow supplemental oxygen through a face mask. It is recommended that hospitalized patients with any type of pneumothorax who are not subjected to aspiration or tube thoracostomy be treated with supplemental oxygen at high concentrations.

Aspiration

The initial treatment for most patients with primary spontaneous pneumothoraces greater than 15% of the volume of the hemithorax should probably be simple aspiration (61,72–74). With this procedure, a 16-gauge needle with an internal polyethylene catheter is inserted into the second anterior intercostal space at the midclavicular line after local anesthesia. An alternate site is selected if the pneumothorax is loculated or if adhesions are present. After the needle is inserted, it is extracted from the cannula. Alternatively, one of the commercially available thoracentesis trays such as the Arrow-Clark Thoracentesis Kit manufactured by Arrow International or the Argyle Turkel Safety Thoracentesis Set distributed by Sherwood can be used. These kits have an outer cannula with an inner needle. If they are used, it is important to make a large-enough skin incision so that the catheter does not become crumpled during its insertion.

A three-way stopcock and a 60-mL syringe are then attached to the catheter. Air is manually withdrawn until no more can be aspirated. If no resistance has been felt after aspirating a total of 4 L, it is assumed that no expansion has occurred, and a tube thoracostomy is performed. After no more air can be aspirated, the stopcock is closed and the catheter is secured to the chest wall. After 4 hours of observation, a chest radiograph should be obtained. If adequate expansion persists, the catheter can be removed and the patient discharged. Patients should return in 24 to 72 hours for a follow-up chest radiograph.

One multicenter, prospective, randomized study compared manual aspiration versus chest tube drainage for the first episode of primary spontaneous pneumothorax. Sixty patients were randomized and immediate success was obtained in 16 of 27 patients (59.3%) in the manual aspiration group and 28 of 33 (85%) in the chest tube drainage group (72). Importantly, 13 of the 27 manual aspiration patients did not require hospitalization (72). Devanand et al. (75) performed a meta-analysis of three randomized controlled studies comparing manual aspiration and chest tube drainage and concluded that simple aspiration is advantageous in the initial management of primary spontaneous pneumothorax because of a shorter hospitalization. A recent study randomized

137 patients with their first episode of primary spontaneous pneumothorax to aspiration versus tube thoracostomy (74). The aspiration was initially successful in 40 of the 65 patients (62%). Only 17 of the 65 patients in the aspiration group were admitted to the hospital, and their mean hospital stay was 1.8 days. All patients in the tube thoracostomy group were admitted with a mean stay of 4.04 days (74).

One might worry that the use of manual aspiration would be associated with a higher recurrence rate in the patients who were successfully aspirated. This does not appear to be the case. For the patients in the study of Noppen (72), the recurrence rate in patients successfully treated with aspiration was 3 of 16 (19%), whereas it was 4 of 11 (36%) in patients in whom the aspiration was unsuccessful (73). In a recent study, Ayed et al. (74) reported that the recurrence rate over 2 years was 29% in 40 patients in whom aspiration was successful compared with 25% in 72 patients who were treated with tube thoracostomy. One might hypothesize that the patients in whom aspiration is successful have smaller blebs than those in whom it fails (73). One study (76) reported that the administration of 300 mg minocycline after a successful air aspiration reduced the incidence recurrent pneumothorax from 11 of 33 (33%) to 4 of 31 (12.9%).

One complication that has been reported with anterior needle aspiration of pneumothoraces is life-threatening hemorrhage (77). In one report, three cases were described that developed life-threatening hemorrhage after the procedure (77). I know of no other similar reports, but the authors of this article suggested that it would be preferable to do the aspiration in the fifth intercostal space in the anterior axillary line (77).

If aspiration fails, the two primary alternatives are tube thoracostomy and VATS. Chen et al. (78) reported that the recurrence rates were less after VATS and the duration of hospitalization was less.

Tube Thoracostomy

With tube thoracostomy, the air in the pleural space can be rapidly evacuated. The chest tube should be positioned in the uppermost part of the pleural space, where residual air accumulates. The management of chest tubes in general is discussed in Chapter 29. Tube thoracostomy effectively evacuates the pleural air if the tube is properly inserted. In one series of 81 patients, only 3 patients (4%) had persistent air leaks after several days of chest tube drainage (10). The average duration of hospitalization in this series was only 4 days, with a range of 3 to 6 days. Although one might think that the placement of chest tubes would irritate the pleura and produce at least a partial pleurodesis, diminishing the likelihood of a recurrent pneumothorax, the incidence of recurrent pneumothorax is similar whether the initial episode is treated by bed rest alone or by tube thoracostomy (10).

When patients with spontaneous pneumothorax are managed with tube thoracostomy, several questions need to be addressed, such as what size of tube needs to be used, whether the patient can be managed as an outpatient, whether to apply suction, when to remove the tube, and when to resort to more aggressive therapy. Although one earlier study (79) concluded that the success rates were poor when patients with spontaneous pneumothorax were treated with small chest tubes (13 F), subsequent studies have reported that most pneumothoraces are effectively managed with small chest tubes (80–82). Minami et al. (80) treated 71 episodes of spontaneous pneumothorax using a small caliber catheter (No. 5.5 or 7.0 F) connected to a Heimlich valve. They reported that the treatment was successful in 60 patients (84.5%) and ineffective in the remaining 11 patients. Only 6 of these latter 11 patients were successfully managed when a large chest tube was placed (80). Liu et al. (82) retrospectively reviewed the results of treating 102 patients with spontaneous pneumothoraces with 8- to 10-Fr pigtail catheters or conventional chest tubes. They demonstrated that the results with both treatments were comparable (82).

When patients with pneumothorax are treated with tube thoracostomy, small tubes (7–14 F) should be tried initially because their insertion is much less traumatic than that of larger tubes (61,62,83). They are best inserted using a guidewire technique, as described in Chapter 28. If the lung does not reexpand with the small tube, then a larger tube can be inserted; however, it appears that most patients can be successfully managed with the small tube.

Patients with primary spontaneous pneumothorax can be managed with tube thoracostomy on an outpatient basis (84,85). Ponn et al. (84) inserted 12-F or 16-F short catheters in 96 patients with spontaneous pneumothorax. To prevent kinking, the tube was placed intracorporeally for most of its length, with only 1 or 2 cm plus the flared end left outside the body. A Heimlich valve was connected and secured with tape. An occlusive dressing covered the entry site, and a gauze sponge was secured over the open end of the valve with a rubber band. Patients returned every 2 to 5 days for physical examination and a chest radiograph. Using this procedure,

92 of 96 patients (96%) were treated successfully. Dernevik et al. (85) reported that they managed 31 of 35 patients (88.5%) on an outpatient basis with a device called a *Tru-Close Thoracic Vent* (Uresil, Sweden). This device is self-contained and consists of a chest tube, a Heimlich valve, and a thoracic vent (85). The cost reduction associated with outpatient management is obvious; most patients with primary spontaneous pneumothorax who are subjected to tube thoracostomy should be treated as outpatients.

It is recommended that no suction be applied to chest tubes inserted for spontaneous pneumothorax (61). The chest tubes can either be connected to a Heimlich valve or an underwater seal. Two studies (79,86) have concluded that the rate at which the lung reexpands is similar whether suction is applied or not. Because the risk of reexpansion pulmonary edema is greater when suction is applied to the chest tube (87), and because the suction appears to offer no benefit, suction is not recommended. In one series (88), reexpansion pulmonary edema occurred in 16 of 84 patients (19%) with spontaneous pneumothorax who had -20 cm H_2O suction applied to the chest tube. Although this is a much higher incidence than in most other studies, it does emphasize the recommendation to not use suction. If the lung does not expand after 24 hours of water-seal drainage or Heimlich valve drainage, suction should be applied to the chest tube. A Heimlich valve comes with some of the commercially available kits (see Chapter 28). It is important to hook up the Heimlich valve in the right direction, or a tension pneumothorax can result (89).

The chest tube should remain in place for 24 hours after the lung reexpands and the air leak ceases. If the chest tubes are removed too soon after the lung reexpands and the air leak ceases, there is a high likelihood of an early recurrence. Sharma et al. (86) reported a recollapse rate of 25% in 20 patients in whom the chest tubes were removed within 6 hours of lung expansion, but a recollapse rate of 0% in 20 patients in whom the chest tubes were removed 48 hours after lung expansion. There is controversy as to whether the chest tube should be clamped if the lung has reexpanded and if there is no air leak. The thought behind this procedure is that if there is a small air leak that is not obvious, then a small pneumothorax will develop if the tube is clamped and then chest tube drainage can be reinitiated. There are no studies to my knowledge evaluating how many pneumothoraces will be detected with this approach. Chest tubes should certainly *not* be clamped if there is an air leak because clamping in this situation could lead to a tension pneumothorax.

Not all primary spontaneous pneumothoraces are treated successfully with a small chest tube. If the patient is initially treated with a small caliber chest tube and the lung does not expand within 48 hours, a larger chest tube should be placed. If the lung has not expanded or a bronchopleural fistula persists after 3 or 4 days, consideration should be given to more invasive therapy such as thoracoscopy or thoracotomy or to performing an autologous blood patch (see later sections in this chapter). The insertion of additional chest tubes is not recommended (90).

Tube Thoracostomy with Instillation of a Sclerosing Agent

Approximately 50% of patients with an initial primary spontaneous pneumothorax have a recurrence whether they are treated with observation, aspiration, or tube thoracostomy. Efforts have been made to diminish the recurrence rates by injecting various agents into the pleural space in an attempt to create an intense inflammatory reaction that would obliterate the pleural space. Many different materials including quinacrine (91), talc slurry (92), olive oil (93), and tetracycline (65,94) have been instilled through the chest tube at the time of the initial pneumothorax in an effort to create a pleurodesis and prevent a recurrence.

The two agents that appear to be the best sclerosing agents are talc slurry and the tetracycline derivatives. Most commonly, when talc is used as an agent to affect a pleurodesis, it is insufflated at the time of thoracoscopy or thoracotomy (see the discussion in the following text). There have been two reports (92,95), however, with a total of 32 patients in whom 5 to 10 g of talc suspended in 250 mL of saline was administered intrapleurally. The recurrence rate in these 32 patients was less than 10%.

The primary drawback to using talc is that a small percentage of patients develop the acute respiratory distress syndrome (ARDS) from its instillation intrapleurally (96). The mortality rate is not inconsequential. In one recent study in which talc slurry was used to treat 240 patients with malignant pleural effusion, the incidence of respiratory failure was 4%, and 5 (2%) of the patients died (97). Although most deaths following talc slurry have occurred in patients who were being treated for malignant pleural effusions rather than pneumothorax, the fact that ARDS and death do occur after administering talc slurry intrapleurally should make one hesitant to use it for a benign condition in young healthy individuals (96). Talc insufflation for prevention of pneumothorax

recurrence has also been associated with the development of chronic debilitating pain requiring thoracotomy (98). A more in-depth discussion of the side effects of talc can be found in Chapter 10.

An alternative agent for pleurodesis in patients with pneumothorax is a tetracycline derivative. In the Veterans Administration (VA) cooperative study on pneumothorax, 229 patients who were being treated with tube thoracostomy for spontaneous pneumothorax were randomized to receive 1,500 mg of tetracycline or nothing through their chest tube. During the 5-year study period, the 25% recurrence rate in the tetracycline group was significantly less than the 41% recurrence rate in the control group (65). In a second study, Alfageme et al. (99) reported that the recurrence rate was 9% in 66 patients treated with tetracycline intrapleurally, whereas the recurrence rate was 36% for the 79 patients treated with observation or chest tubes only (99). In a more recent study of 138 patients that was not randomized, Guo et al. used proportional hazards analysis and demonstrated that the administration of a sclerosing agent (tetracycline 45 patients, gentamicin 23 patients) was associated with a significantly lower recurrence rate (66).

In summary, the evidence presented earlier strongly suggests that the intrapleural injection of a sclerosing agent in patients with spontaneous pneumothorax significantly reduces the subsequent recurrence rates. It appears that at least in rabbits, the effectiveness of the pleural sclerosant is decreased if the animal is receiving corticosteroids (100,101). The administration of the nonsteroidal anti-inflammatory agent diclofenac (2 mg/kg body weight) also decreased the effectiveness of pleurodesis from mechanical abrasion in pigs (102). Therefore, one should attempt to minimize corticosteroids and anti-inflammatory agents in patients in whom pleurodesis is attempted. Which patients with spontaneous pneumothorax should receive the intrapleural injection of an agent in an attempt to produce a pleurodesis and decrease recurrence rates? It is recommended that all patients with primary or secondary spontaneous pneumothorax who are treated with tube thoracostomy receive an agent unless they are subjected to thoracoscopy or thoracotomy.

What agent should be used? Currently, the recommended agent for an attempted pleurodesis through a chest tube is a tetracycline derivative. If it were not for the reported cases of ARDS after the administration of talc slurry to patients with malignant pleural effusions, talc slurry would be the recommended agent. Parenteral tetracycline is no longer available in most countries due to increasingly stringent manufacturing requirements for parenteral antibiotics. Tetracycline derivatives appear comparable in effectiveness to tetracycline. In the rabbit model, minocycline (103) or doxycycline (104) is as effective as tetracycline in producing a pleurodesis at approximately one fourth the dose of tetracycline. Intrapleural doxycycline is also an effective treatment for malignant pleural effusion (see Chapter 10). Accordingly, 500 mg of doxycycline intrapleurally is recommended for patients with spontaneous pneumothorax who are treated with chest tubes. An alternative agent is minocycline (300 mg intrapleurally) (78). Bleomycin should not be used because it is ineffective in producing a pleurodesis in rabbits with a normal pleura (105) and expensive.

The intrapleural injection of tetracycline derivatives is an intensely painful experience for many patients. In the VA cooperative study (65), more than 50% of the patients reported severe pain at the time of the tetracycline injection, and 70% of the individuals stated that the pain was greater at the time of the tetracycline injection than at either the onset of pneumothorax or at the time the chest tube was placed. The intrapleural administration of 100 mg of lidocaine (Xylocaine) was not effective in ameliorating the intense chest pain. However, some have recommended that when a tetracycline derivative is administered intrapleurally for pneumothorax, the injection be preceded by 4 mg/kg of Xylocaine up to a maximal dose of 250 mg (106). The patient should also be premedicated with an agent such as a short-acting benzodiazepine (e.g., midazolam).

It is recommended that the tetracycline derivative be injected as soon as the lung has reexpanded. The patient should be positioned so that the tetracycline comes into contact with the apical pleura. In experimental animals, the presence of a small pneumothorax at the time of the injection does not decrease the efficacy of the pleurodesis (107). A persistent air leak is not a contraindication to tetracycline injection. There is, however, no evidence that the intrapleural injection of tetracycline leads to an earlier closure of the bronchopleural fistula (65,108).

Autologous Blood Patch for Persistent Air Leak

In the past decade, there have been approximately 50 papers reporting on the use of the autologous blood patch for the treatment of a persistent air leak in patients with spontaneous pneumothorax (109,110). With this technique, 50 to 100 mL of blood is drawn from a vein and then promptly injected, without anticoagulation, through the chest tube into the pleural

space (109). The chest tube is elevated about 60 cm to prevent the blood from being drained. The chest tube should not be clamped because with the airleak this could lead to a tension pneumothorax. Chambers et al. (109) reviewed the literature on utilizing the blood patch technique for airleaks in conjunction with pneumothorax and reported that the airleak ceased in 91.7% of 107 patients. It is possible that the blood-patch technique might also decrease the incidence of recurrence. In the study of Cagirici (111), there were no recurrences in any of the 32 patients treated with the blood-patch technique during a follow-up of 12 to 48 months. When the blood-patch technique has been used in patients undergoing needle aspiration of the lung, it was ineffective in preventing pneumothorax in two studies (112,113), but it was effective in preventing larger pneumothoraces in the most recent study (114).

Other agents have been injected intrapleurally in an attempt to stop the airleak. Cobanoglu et al. evaluated 50 patients with persistent airleaks from spontaneous pneumothorax and reported that the airleak stopped in 30 of 40 (75%) with the blood patch, in 16 of 19 (84%) with talc, and in 6 of 11 with tetracycline. They concluded that the blood patch was the technique of choice because the airleak ceased more quickly and that it had less effect on the pulmonary function (115).

Intrapleural Fibrin Glue for Persistent Air Leak

There has been one article (116) that suggested that the intrapleural administration of a large amount of diluted fibrin glue might be effective in patients with persistent air leaks. Kinoshita et al. (116) diluted both the compounds used with regular fibrin glue to 60 mL and then injected the 120 mL total into 40 high-risk patients with persistent bronchopleural fistula. They reported that the bronchopleural fistula closed after one injection in 35 patients, after two injections in 4 patients, and after three injections in 1 patient. The air leaks ceased within 12 hours of injection. During the follow-up period of 2.5 to 6.5 years, the pneumothorax recurred in five patients (12.5%), but an additional single treatment with fibrin glue resulted in resolution of the pneumothorax with no further recurrences (116). If these results can be duplicated by others, the intrapleural administration of fibrin glue represents a significant advance in the treatment of high-risk patients with pneumothorax. However, since this article was published in 2003, I have been unable to find additional articles using intrapleural fibrin glue to treat airleaks with spontaneous pneumothorax.

Medical Thoracoscopy

Medical thoracoscopy is performed with the patient under local anesthesia, usually combined with conscious sedation (see Chapter 30). In contrast, video-assisted thoracoscopic surgery (VATS) is performed almost exclusively under general anesthesia with double-lumen endotracheal intubation, which allows single-lung ventilation and the collapse of the lung on the operated side (117). However, there is one report (118) in which VATS was performed with the patient awake using spinal anesthesia. There are strong advocates for using medical thoracoscopy for the treatment of primary spontaneous pneumothorax (117,119–121). Tschopp et al. (119) treated 89 patients for persistent or recurrent spontaneous pneumothorax from 1986 to 1994 with talc insufflation at the time of medical thoracoscopy. They reported that the initial medical thoracoscopy was successful in 80 patients (90%) and that the subsequent recurrence rate was 7.5% (6 of 80 patients). In a second study, 108 patients were randomized to receive medical thoracoscopy with talc insufflation or tube thoracostomy (120). In this study, the recurrence rate over 5 years in the patients who received talc was 5% and the authors concluded that medical thoracoscopy was more cost-effective than drainage alone (120). There have been reports that talc insufflation was associated with the development of ARDS and death. However, a recent report (122) on 418 patients who received talc insufflation with graded talc reported no instances of ARDS.

The primary difference between medical thoracoscopy with talc insufflation and VATS is that with medical thoracoscopy no attempt is made to treat the blebs. The advocates of medical thoracoscopy do not believe that the blebs are important in the pathogenesis of the pneumothorax (121). However, there are no randomized controlled studies comparing these various techniques. Nevertheless, the general consensus is that recurrence rates are slightly higher with medical thoracoscopy (~5%) than with VATS (~3%) (123). One advantage that medical thoracoscopy has over VATS is that it is much less expensive.

Video-Assisted Thoracoscopic Surgery

VATS is effective in the treatment of spontaneous pneumothorax and the prevention of recurrent pneumothorax. With VATS, there are two primary objectives: (a) to treat the bullous disease responsible for the pneumothorax and (b) to create a pleurodesis. Currently, the most common means by which bullae

are treated is with an endoscopic stapling device. The primary disadvantage of the endostapler is its expense. The Endo-GIA model costs approximately US$500, and additional cartridges (of which an average of two per procedure are used) cost US$500 each (124). Previously, the bullae were treated with electrocoagulation, which was associated with a higher recurrence rate (125). An alternative method of dealing with the apical bullae is to ligate the bullae with a Roeder loop (126). However, Inderbitzi et al. (126), who have reported one of the largest series using VATS for the treatment of pneumothorax, have reported a relatively high recurrence rate after use of the loop and recommend that it be abandoned in favor of wedge resection with the endostapler. One series concluded that endostapling of the lung apex was associated with a decreased recurrence rate even if no blebs are visible (127). The recurrence rate during a mean follow-up of 38.7 months was 7% in the 57 patients who did not receive the stapling, whereas there were no recurrences in the 69 patients who received the stapling (127).

Once the lesion in the lung is treated, some attempt should be made to create a pleurodesis. Recurrence rates are higher when only the blebs are treated (128,129). The primary alternatives are mechanical abrasion of the pleura, partial parietal pleurectomy, talc insufflation, and argon beam coagulation (130). Of these four, mechanical abrasion of the pleura is the simplest. In one study (131) of 569 patients treated with VATS for spontaneous pneumothorax, the recurrence rates over a 5-year follow-up period were 3.6% for abrasion, 1.1% for poudrage, and 2.5% for pleurectomy, which did not differ significantly. Since there is no other evidence that partial pleurectomy, talc poudrage, or argon beam coagulation is associated with less recurrences than mechanical abrasion, it is the method of choice. In another approach, Marcheix et al. (132) treated 603 patients with stapling of the blebs and spraying 1% silver nitrate on the parietal pleural and reported that the long-term recurrence rate was only 1.1%.

There have been several series, each with more than 100 patients, in which patients with spontaneous pneumothorax were treated with VATS. In general, VATS with stapling of bullae is very effective at managing spontaneous pneumothorax, with an overall recurrence rate of approximately 3% (133–137). Yim and Liu (133) treated 483 patients with VATS using mechanical pleurodesis plus some other procedures such as endostapling or endoloop for management of the bullae. They reported that their median postoperative hospital stay was only 3 days and the recurrence rate was 1.74%, with a mean follow-up of 20 months (133). Cardillo et al. (134) used VATS to treat 432 patients with primary spontaneous pneumothorax between 1992 and 1998. They used subtotal pleurectomy to induce a pleurodesis in some patients and talc insufflation in others. The conversion rate to open procedures was 2.3%, most often due to extensive pleural adhesions. The mean time to chest tube removal was 5.4 days, and the mean hospital stay was 6.1 days. The recurrence rate was 4.4%, with a mean follow-up of 38 months (134). In a more recent study, Margolis et al. (138) performed VATS with stapling of blebs and pleural abrasion in 156 young (median age 19) patients with their first spontaneous pneumothorax and reported no recurrences with a mean follow-up of 62 months. The mean total hospital stay was 2.4 days (138).

Cardillo et al. (139) reported the largest series ever reported from a single institution. They treated 861 patients with VATS and talc poudrage. If the patients had no visible blebs, they were treated with only talc poudrage. If blebs or bullae were visible, they were stapled (139). After a mean follow-up of 52.5 months, the recurrence rate was 2.4% in the group without blebs and 1.7% in the group with blebs (139). Since I would expect the group with no blebs to have less recurrences, this study suggests to me that treatment of the blebs is important.

One paper randomly assigned 202 patients to resection of blebs plus pleural abrasion or resection of blebs plus pleural abrasion plus the instillation of 300 to 400 mg minocycline at the end of the procedure (140). The group of patients that received minocycline had more pain postoperatively, but there was a significant decrease in the recurrence rate for pneumothorax (1.9% vs. 8.1%) (140). However, it should be noted that the recurrence rates in the patients treated with resection of blebs plus pleural abrasion is much higher than in most series. Accordingly, minocycline in addition to pleural abrasion is not recommended currently.

Patients with hemopneumothoraces in which there is significant pleural hemorrhage are probably best managed with VATS. Hwong et al. (141) performed VATS on 25 patients with spontaneous hemopneumothorax and reported that the bleeding was controlled in all the patients. VATS also appears to be effective in patients who have had a recurrence after talc insufflation with medical thoracoscopy (142). Doddoli et al. (142) successfully managed 27 of 39 such patients (69%) with VATS. VATS is also an effective management strategy

for recurrent pneumothorax after a previous VATS procedure (143–145).

Open Thoracotomy

The indications for open thoracotomy are the same as those for thoracoscopy. If VATS is available, thoracotomy is recommended only after VATS has failed. The reason for this recommendation is that the hospitalization is shorter and the postoperative pain is less severe after thoracoscopy (124,146,147). However, in a meta-analysis of 29 studies (148) the recurrence rate after open thoracotomy (1.1%) was significantly lower than that after VATS (5.4%), but many of the studies were done when thoracoscopy was first being used for pneumothorax and recurrence rates fell as the surgeons became more experienced. It should be mentioned, however, that some surgeons still prefer axillary mini-thoracotomy to VATS for the treatment of spontaneous pneumothorax (148,149). The reason for this preference is that time is saved because double-lumen intubation is not required, the operating time is short, there is a good cosmetic result, and it is less expensive (149).

At thoracotomy, the apical pleural blebs are oversewn and the pleura is scarified. This procedure is effective in controlling the pneumothorax and diminishing the rate of recurrence. In one large series in which 362 patients underwent parietal pleurectomy, only two documented ipsilateral recurrences were reported, with an average follow-up of 4.5 years in 310 patients (150). The low rates of morbidity and mortality of the procedure are attested to in the same article (150). Only 1 operative death was reported in the 362 operative procedures, and the average postoperative period of hospitalization was only 6 days. Various methods proposed for scarification of the pleura range from visceral and parietal pleurectomy to mere abrasion of the pleura with dry sponges. All of these procedures appear to be effective (8), but because pleural abrasion with dry gauze is less traumatic than pleurectomy and does not affect a potential later thoracotomy, it is the procedure of choice.

Air Travel

If a patient has a spontaneous pneumothorax, when should they be allowed to travel by air? Commercial airlines have adopted a 6-week "no fly" rule between pneumothorax occurrence and air travel (151). This rule seems very arbitrary and there are no data to support it. Currie et al. (152) reported two patients with loculated pneumothoraces who flew without incident. I believe that the 6-week "no fly" rule is very conservative, and I will allow my patients to fly 7 days after resolution of the pneumothorax.

Recommendations

My recommendations for the management of a patient with a primary spontaneous pneumothorax are as follows. If the pneumothorax is small (<15% of the hemithorax) and the patient is asymptomatic, observation is recommended. If the patient is at a site where oxygen is available, high-flow supplemental oxygen should be administered. If the pneumothorax is >15% of the hemithorax, an attempt should be made to aspirate the pneumothorax. If this is successful and there is no recurrence over several hours, the patient can be sent home. If the aspiration is unsuccessful, then the patient should be admitted to the hospital. If possible, thoracoscopy should be performed as soon as possible. Thoracoscopy is preferred to tube thoracostomy because it is associated with less recurrences, a shorter mean hospital stay, and a shorter duration of chest tube drainage (153). In general, if both medical thoracoscopy and VATS are available, VATS is preferred because with it the apical blebs can be treated. If thoracoscopy is not available, tube thoracostomy should be performed with the injection of a sclerosing agent. The sclerosing agent of choice is doxycycline 500 mg. Talc is not recommended because its administration intrapleurally can lead to ARDS that can be fatal. If a patient has a recurrent pneumothorax, VATS or medical thoracoscopy should be performed. VATS or medical thoracoscopy should also be performed if the patient has an occupation, for example, airplane piloting, or an avocation, for example, diving, where the occurrence of a pneumothorax might be life threatening. VATS or medical thoracoscopy is not indicated if the aspiration is successful because most such patients will never have a recurrence.

SECONDARY SPONTANEOUS PNEUMOTHORAX

Secondary spontaneous pneumothoraces are more serious than primary spontaneous pneumothoraces because they decrease the pulmonary function of a patient with already compromised pulmonary function. The secondary spontaneous pneumothoraces that occur in patients with the acquired immunodeficiency syndrome (AIDS), cystic fibrosis, tuberculosis, lymphangioleiomyomatosis (LAM), and Langerhans cell histiocytosis are discussed in separate sections.

Incidence

The incidence of secondary spontaneous pneumothorax is similar to that of primary spontaneous pneumothorax. In the study from Olmsted County, Minnesota, the incidence was 6.3 and 2.0/100,000/year for men and women, respectively (1). If these figures are extrapolated to the entire population of the United States, approximately 10,000 new cases of secondary spontaneous pneumothorax will be seen each year. In a more recent study from the United Kingdom, the incidence of spontaneous pneumothorax for males and females above 55 was 32.4 and 10.9/100,000/year, respectively (2). Interestingly, the incidence in men kept increasing as the age increased (2).

Etiologic Factors

Most secondary spontaneous pneumothoraces are due to COPD, although almost every lung disease has been reported to be associated with secondary spontaneous pneumothorax. In one series of 505 patients from Israel with secondary spontaneous pneumothorax, the etiologies were as follows: COPD, 348; tumor, 93; sarcoidosis, 26; tuberculosis, 9; other pulmonary infections, 16; and miscellaneous, 13 (154).

There appears to be a tendency for patients with more severe COPD to develop spontaneous pneumothorax. In the VA cooperative study, which included 171 patients with secondary spontaneous pneumothorax, 51 of the patients (30%) had a forced expiratory volume$_1$ (FEV_1) $<$1,000 mL and 56 of the patients (33%) had an FEV_1/forced vital capacity (FVC) $<$0.40 (65).

Clinical Manifestations

In general, the clinical symptoms associated with secondary spontaneous pneumothorax are more severe than those associated with primary spontaneous pneumothorax. Most patients with secondary spontaneous pneumothorax have dyspnea (155,156), which frequently seems out of proportion to the size of the pneumothorax (157). In one series of 57 patients with COPD, all complained of shortness of breath, whereas 42 (74%) had chest pain on the side of the pneumothorax (155). In addition, five patients were cyanotic and four patients were hypotensive.

The occurrence of a pneumothorax in a patient with underlying lung disease is a serious event. Because the pulmonary reserve of these patients is already diminished, the partial or total loss of the function of a lung can be life threatening. In one series of 18 patients in whom arterial blood gases were obtained at the time of admission, the mean Pao_2 was 48 mm Hg and the mean $Paco_2$ was 58 mm Hg (155). In the VA cooperative study, the Pao_2 was below 55 mm Hg in 20 of 118 (17%) and was below 45 mm Hg in 5 of 118 (4%). The $Paco_2$ exceeded 50 mm Hg in 19 of 118 (16%) and exceeded 60 mm Hg in 5 of 118 (4%) (65).

A substantial mortality rate is associated with secondary spontaneous pneumothorax. When three older series totaling 120 patients are combined, the mortality rate was 16% (155,157,158). Causes of death included sudden death before chest tubes could be inserted in three patients, respiratory failure within the first 24 hours of treatment in three patients, late respiratory failure in three patients, and massive gastrointestinal bleeding in three patients. However, in the VA cooperative study, none of the 185 patients with secondary spontaneous pneumothorax died from a recurrent ipsilateral pneumothorax. However, the overall mortality rate in the 5-year follow-up period was 43% (65). The high mortality rate probably reflects the severity of the underlying disease. The leading causes of death were COPD, lung cancer, pneumonia, and heart disease (65).

The physical examination of patients with secondary spontaneous pneumothorax is less helpful than it is in primary spontaneous pneumothorax. These patients already have hyperexpanded lungs, decreased tactile fremitus, hyperresonant percussion notes, and distant breath sounds over both lung fields. Accordingly, when a pneumothorax develops, side-to-side differences in the physical examination may not be apparent. The possibility of a pneumothorax should be considered in any patient with COPD who has increasing shortness of breath, particularly if chest pain is also present.

Diagnosis

As with primary spontaneous pneumothorax, the diagnosis of secondary spontaneous pneumothorax is established by the chest radiograph. In patients with COPD, the radiographic appearance of the pneumothorax is altered by the loss of elastic recoil of the lung and the presence of air trapping. Normal areas of the lung collapse more completely than diseased areas with large bullae or severe emphysema in the absence of adhesions. In addition, the deflation of the diseased lung is limited by its decreased elastic recoil. Although ultrasound can be used to establish the

diagnosis of pneumothorax in patients with primary spontaneous pneumothorax and traumatic pneumothorax, it is less reliable in patients with COPD (159). If pleural gliding is present, one can be confident that there is no pneumothorax. However, pleural gliding is sometimes absent in patients with COPD who do not have a pneumothorax (159).

The diagnosis of pneumothorax is established by the demonstration of a visceral pleural line. It is sometimes difficult to see this line because the lung is hyperlucent and little difference exists in radiodensity between the pneumothorax and the emphysematous lung. Frequently, the presence of the pneumothorax is overlooked on the initial chest radiograph. One must distinguish a spontaneous pneumothorax from a large, thin-walled, air-containing bulla. The pleural line with a pneumothorax is usually oriented in convex fashion toward the lateral chest wall, whereas the apparent pleural line with a large bulla is usually concave toward the lateral chest wall. If there is any doubt as to whether the patient has a pneumothorax or a giant bulla, CT scan should be obtained because the two conditions are easily differentiated with this procedure (45,160). It is important to make the distinction between a large bulla and a pneumothorax because only the pneumothorax should be treated with tube thoracostomy.

In patients with cystic lung disease, the presence of cysts and pleural adhesions sometimes makes it difficult to determine whether a pneumothorax is present on the routine chest radiographs. If patients with cystic lung disease present with increased shortness of breath, the possibility of a pneumothorax should be considered, particularly if the hemithoraces are asymmetric in size. In such cases, the CT scan will delineate whether a pneumothorax is present and will also assist in selecting the appropriate site for chest tube placement (161).

Occasionally, secondary spontaneous pneumothoraces result from primary carcinoma of the lung with bronchial obstruction. One must recognize the radiologic signs of bronchial obstruction in these patients because the insertion of chest tubes is contraindicated. When a patient has a totally collapsed lung, one should search for air bronchograms in the lung. Air bronchograms are absent when there is an obstructing endobronchial lesion, but otherwise they are present (162). If no air bronchograms are present, a bronchoscopic examination should be performed before a chest tube is inserted.

Recurrence Rates

The recurrence rates for secondary spontaneous pneumothorax appear to be somewhat higher than those for primary spontaneous pneumothorax (64,65,163). Videm et al. (163) followed a total of 303 patients for a median period of 5.5 years and reported that 24 of the 54 patients (44%) with COPD had a recurrence. In patients without COPD, 96 of 249 (39%) had a recurrence (163). In the VA cooperative study, 92 patients with secondary spontaneous pneumothorax were treated with chest tubes without pleural sclerosis and the recurrence rate was 47% with a median follow-up of 3 years (65). In this study, the recurrence rate with primary spontaneous pneumothorax was 32% (65). Guo et al. in a multivariate analysis of the factors related to recurrent pneumothorax found that patients with secondary spontaneous pneumothoraces were significantly ($p < 0.007$) more likely than patients with primary spontaneous pneumothorax to have a recurrence (66).

Treatment

The goals of treatment of the patient with secondary spontaneous pneumothorax, as with primary spontaneous pneumothorax, are to rid the pleural space of air and to decrease the likelihood of a recurrence. Achievement of these goals, particularly the second, is more important in the patient with secondary spontaneous pneumothorax, however. A primary spontaneous pneumothorax or its recurrence is mostly just a nuisance. In contrast, the occurrence of a pneumothorax in a patient with lung disease may be life threatening, even though the mortality rate from recurrent secondary spontaneous pneumothorax is low (65).

The treatment options for the patient with a secondary spontaneous pneumothorax are the same as those for a patient with a primary spontaneous pneumothorax, as discussed earlier in this chapter. There are far fewer articles written on the treatment of secondary spontaneous pneumothorax than there are on primary spontaneous pneumothorax. The recommendations for the treatment of the patient with a secondary spontaneous pneumothorax differ from those of the patient with a primary spontaneous pneumothorax in the following ways.

Nearly every patient with a secondary spontaneous pneumothorax should initially be hospitalized and managed by tube thoracostomy (90). Aspiration of the pneumothorax is not recommended because it is less likely to be successful (164,165) and does nothing to diminish the likelihood of a recurrence. Even if the pneumothorax is small, its evacuation can lead to a rapid improvement in symptoms. Pigtail catheters appear efficacious in treating secondary spontaneous pneumothorax (166). Arterial blood gases usually

improve within 24 hours of instituting tube thoracostomy (158). If the patient has respiratory failure necessitating mechanical ventilation, a chest tube should definitely be placed because the pneumothorax is likely to enlarge during mechanical ventilation.

Tube thoracostomy is less efficacious in secondary spontaneous pneumothorax than in primary pneumothorax, however. In primary spontaneous pneumothorax, the lung usually expands, and the air leak ceases within 3 days. In secondary spontaneous pneumothorax due to COPD, the mean time for the lung to expand is 5 days. In approximately 20% of patients with secondary spontaneous pneumothorax, the lung remains unexpanded or an air leak persists after 7 days (158,162,163,167,168).

Once the lung has expanded, it is recommended that attempts be made to prevent the recurrence of a pneumothorax (90). This can be done with VATS, medical thoracoscopy, mini-thoracotomy, or the instillation of a sclerosant through the chest tube. If VATS is available, it is the procedure of choice because the stapling of blebs and pleural abrasion reduces the likelihood of recurrence to less than 5%. Onuki et al. (169) subjected 53 patients with a mean age of 65.1, most of whom had persistent air leaks, to VATS. They reported that during the mean follow-up period of 988 days, there was only one recurrence (169). Shaikhrezal et al. (131) performed VATS plus a procedure to create a pleurodesis in 94 patients with secondary spontaneous pneumothorax and reported that only 3.9% needed an additional operation over the next 5 years. Medical thoracoscopy with the insufflation of talc also appears to be an effective treatment. Lee et al. (170) insufflated 3 g talc in 41 patients with secondary spontaneous pneumothorax whose mean age was 70.7 and whose mean FEV_1 was 41% of predicted. Although the mortality was 10%, there were only two recurrences in the 37 surviving patients (170). If these procedures are not available, or if the patient refuses or is too sick to undergo surgery, then doxycycline can be injected through the chest tube, as described earlier. However, the intrapleural injection of a tetracycline derivative will only decrease the recurrence rate from approximately 50% to 30% (65). It should be emphasized that there is a dearth of randomized controlled studies comparing the different treatment modalities with secondary spontaneous pneumothorax (171).

When one contemplates an attempt to prevent a recurrent pneumothorax, the effect that the agent will have on a future lung transplant should be considered if the patient has a disease such as LAM, cystic fibrosis, interstitial pulmonary fibrosis, or COPD that might be managed with lung transplantation. In the past, patients were excluded from lung transplantation if attempts at pleurodesis had been made on the side of the proposed transplant owing to the increased difficulty of the procedure and the risk of excessive bleeding. However, a consensus conference statement in 1998 on lung transplantation concluded that pleurodesis was not a contraindication to lung transplantation in patients with cystic fibrosis (172). In one study, the outcome of 18 patients with a previous intrapleural procedure was compared with 18 paired controls without previous intrapleural procedures and there was no difference in the outcomes of the two groups (173).

If the lung does not expand within 72 hours or if there is a persistent air leak for more than 3 days, strong consideration should be given to performing VATS or medical thoracoscopy (174,175). At thoracoscopy, the blebs are excised with a stapling instrument and some other procedure is done to create a pleurodesis. In one study, 22 patients with secondary spontaneous pneumothorax due to COPD, with a mean age of 70 and a mean preoperative FEV_1 that was 48% of predicted, were subjected to VATS for either persistent air leak (18 patients) or recurrent pneumothorax (4 patients) (174). The mean duration of the procedure was only 57 minutes, and only one patient required mechanical ventilation during the immediate postoperative period. The mean duration of postoperative hospitalization was 9 days. The fact that the mean hospitalization was 18 days before surgery suggests that the hospitalization would have been shortened if the procedure had been performed sooner. VATS failed in 4 of the 22 patients (18%), in that there was a large air leak postoperatively that necessitated thoracotomy. There were two deaths in this series; one patient developed a contralateral tension pneumothorax and a subsequent fatal myocardial infarction, and the other developed bronchopneumonia after revisional thoracotomy and died of respiratory failure. None of the surviving patients had a recurrent pneumothorax (174).

The three studies detailed earlier (169,170,174) document that elderly patients with severe COPD and pneumothorax can be managed successfully with VATS or medical thoracoscopy with acceptable rates of morbidity and mortality. Since the results with these procedures are so good, it is recommended that they be considered if the lung remains unexpanded or if there is a persistent air leak after 3 days. If facilities are available for VATS, it is advisable to attempt it relatively early rather than attempting to reexpand the lung with several chest tubes. Indeed, some authors

have recommended that all patients with secondary spontaneous pneumothorax undergo VATS (90,175). If the patient is a good operative candidate and if thoracoscopy is readily available, I would agree with this recommendation.

One procedure that should be considered in patients with persistent airleaks due to secondary spontaneous pneumothorax is a blood patch as discussed in the section on primary spontaneous pneumothorax. Aihara et al. (176) reported that the blood-patch technique was successful in treating the airleak in 16 of 22 patients (73%) of patients with secondary spontaneous pneumothorax due to interstitial lung disease.

In patients who have a persistent airleak, procedures can be performed endobronchially in an attempt to stop the air leak. Zeng et al. (177) studied 40 patients with persistent air leaks. They first attempted to identify the bronchus from which the air originated by occluding the various bronchi with a balloon. Then they attempted to occlude the bronchus with a mixture of fibrin and autologous blood. They reported that they were able to identify the bronchus leading to the air leak in 36 patients and were successful in stopping the airleak in 28 of the 40 (70%) patients (177). An alternative to occluding the bronchus with a mixture of fibrin and autologous blood is to occlude it with an endobronchial valve (178).

PNEUMOTHORAX SECONDARY TO ACQUIRED IMMUNODEFICIENCY SYNDROME

In the 1990s, a substantial proportion of secondary spontaneous pneumothoraces occurred in patients with AIDS. Between 1983 and 1991, 120 patients with a spontaneous pneumothorax were seen at Parkland Memorial Hospital in Dallas, Texas, and 32 (27%) occurred in patients with AIDS (167). Most patients with AIDS who have a spontaneous pneumothorax have a history of *Pneumocystis jirovecii* infection are on prophylactic pentamidine and have a recurrence of the *P. jirovecii* infection (179–181). Pulmonary tuberculosis and pulmonary cryptococcosis are also associated with spontaneous pneumothorax in patients with AIDS. In one series, 13 of 35 patients (37%) with spontaneous pneumothorax and AIDS had tuberculosis (182). Most patients have a $CD4^+$ count less than 100 cells/mm^3 (181). The reported prevalence of pneumothorax in patients who have a history of *P. jirovecii* infection and who receive prophylactic pentamidine has varied widely. In one series of 408 patients who were receiving prophylactic pentamidine therapy in San Francisco, there were 17 cases (4%) of spontaneous pneumothorax but only approximately one fourth of the 408 patients had had *P. jirovecii* pneumonia previously (183). Renzi et al. (184) reported that 5 of 48 patients (10%) with a history of *P. jirovecii* infection who were receiving prophylactic pentamidine therapy developed a spontaneous pneumothorax. In another small series of 13 hemophiliacs who were infected with human immunodeficiency virus (HIV) and who were receiving prophylactic pentamidine, 4 patients (31%) developed a spontaneous pneumothorax (185).

The etiology of pneumothorax in the patient with AIDS may be changing. In a review (186) of 9,831 nontreated HIV-infected patients, 105 (1.06%) of the patients had a spontaneous pneumothorax. The most common etiology was bacterial pneumonia (34.3%) followed by *P. jirovecii infection* (29.5%) and tuberculosis (15.2%). Patients with $CD4^+$ counts above 200 were more likely to have bacterial pneumonia while those with $CD4^+$ counts below 200 were more likely to have *P. jirovecii infection.*

The explanation for the high incidence of spontaneous pneumothorax in these patients with *P. jirovecii infection* appears to be the presence of multiple subpleural lung cavities, which are associated with subpleural necrosis (187–190). These bullous changes and pulmonary cysts develop because of repeated episodes of inflammation and cytotoxic effects of HIV on pulmonary macrophages (188). Most patients have radiologic evidence of fibrocystic parenchymal disease (Fig. 24.1) (187). If these patients are subjected to surgery, there is diffuse involvement of the lung parenchyma with greater involvement in the upper lobe than in the lower lobe. Areas of necrosis are usually present in consolidated areas of the lung, and these areas are exceedingly friable and prone to laceration with the slightest manipulation. Emphysematous blebs are located on the surface of the lungs, and the apex of the lungs contains multiple cysts based on consolidated parenchyma (191). Microscopically, the tissue specimens invariably reveal extensive necrosis with a complete loss of the inherent architecture (191). When patients are studied prospectively, those with a lower diffusion capacity are more likely to develop a spontaneous pneumothorax (184). The reason for the relationship between the aerosolized pentamidine and the occurrence of the pneumothorax is not clear, but it is probably related to the fact that the aerosolized pentamidine does not reach the periphery

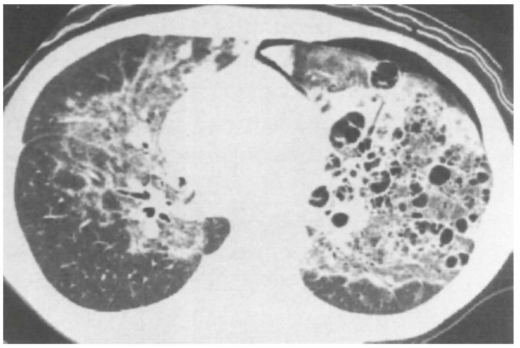

FIGURE 24.1 ■ CT scan of a patient with acquired immune deficiency syndrome and *Pneumocystis jirovecii* infection. Note the numerous cysts in the left lung and the large subpleural cyst anteriorly in the left lung, which is probably responsible for the pneumothorax seen anteriorly *(Courtesy of Dr. David P. Naidich)*.

of the upper lobes. Accordingly, a low-grade infection persists and destroys the lung, leading to the development of the cysts and the bronchopleural fistulas.

The occurrence of a spontaneous pneumothorax in a patient with AIDS and *P. jirovecii* infection is ominous prognostically. In one series, the in-hospital mortality rate was 50% in 32 patients with *P. jirovecii* infection and spontaneous pneumothorax (192). In a second series, 17 of 22 patients (77%) with spontaneous pneumothorax died, with a mean survival of 147 days after the diagnosis of the pneumothorax (191). In another series, the in-hospital mortality rate was 10 of 35 (29%) for patients with spontaneous pneumothorax (193). However, the in-hospital mortality rate was only 6% in the patients reported by Wait (194) who were managed with VATS.

Once a patient with AIDS and *P. jirovecii* infection has a spontaneous pneumothorax, he or she is very likely to have a recurrent pneumothorax or a contralateral pneumothorax. In one series of 20 patients, contralateral pneumothoraces occurred in 13 (65%) and ipsilateral recurrences occurred in 13 (65%) (179). In another series of 22 patients, 8 (36%) had synchronous or sequential bilateral pneumothoraces (191).

Owing to the necrotic lung surrounding the ruptured cavity, the spontaneous pneumothorax associated with AIDS and *P. jirovecii* infection is notoriously difficult to treat. Conservative therapy consisting of tube thoracostomy is rarely successful. In one report of 20 patients, the median length of hospitalization was 42 days and a chest tube was required for a median of 20 days but was successful in only 4 patients. In this series, the pneumothorax resolved in 11 patients with sclerotherapy, whereas 5 patients required thoracotomy (179). In a second series, 35 patients were treated with chest tubes and tetracycline or doxycycline pleurodesis, and this treatment was effective in only 9 (26%) (193).

In view of the poor results with tube thoracostomy alone, alternate procedures are necessary. It is recommended that alternate therapies be initiated if the patient still has an air leak after 3 days, because the leak will probably not close spontaneously. The simplest alternative is to attach a Heimlich valve to the chest tube and send the patient home, not worrying about the closure of the bronchopleural fistula (181,195,196). This treatment gets the patient home fastest and is associated with the least morbidity. It is not always successful, however, in that in some patients the Heimlich valve cannot handle the airflow through the large bronchopleural fistula and the lung does not remain expanded. Vricella and Trachiotis (181) discharged two patients had bilateral pneumothoraces and reported that there was no incidence of morbidity or mortality related to the Heimlich valve. Two patients died in a hospice, and the others were successfully managed as outpatients.

If the patient cannot be managed with a Heimlich valve, or if definitive treatment of the pneumothorax is desired, the treatment of choice is probably VATS. The optimum procedure to perform with VATS remains to be defined. Wait (194) performed VATS with the insufflation of 5 to 10 g of asbestos-free talc without treating the air leaks directly and reported success in 30 of 32 patients (94%) (194). The mean hospital stay after VATS was 3.9 days, and no patient was discharged with a Heimlich valve (194).

An alternative aggressive approach is thoracotomy with stapling of blebs and pleural abrasion (197–199). Crawford et al. (198) reported successful management for 13 of 14 patients using thoracotomy with direct closure of the bronchopleural fistula and parietal pleurectomy. Horowitz and Oliva (199) reported the successful management of seven of seven patients with this procedure. Because the incidence of contralateral pneumothorax is so high in these patients, one group has recommended the use of a median sternotomy incision with bilateral pleurodesis for those patients who require surgery (197).

Pleural sclerosis has a limited role in the management of the secondary pneumothorax in patients with AIDS because it is usually ineffective (179,193). The reason for its ineffectiveness is unknown, but it is probably related to the size of the bronchopleural fistula

or the inability of the immunocompromised host to mount a brisk inflammatory response. If pleurodesis is attempted through a chest tube, doxycycline is recommended. There has been one report in which six of seven spontaneous pneumothoraces in patients with AIDS were managed successfully with intrapleural doxycycline (200).

PNEUMOTHORAX SECONDARY TO CYSTIC FIBROSIS

Secondary spontaneous pneumothorax is also frequent with cystic fibrosis, a disease with a high prevalence of severe COPD. Flume et al. (201) reviewed the Cystic Fibrosis Foundation Patient Registry of more than 28,000 cystic fibrosis patients and reported that 3.4% of the patients had had a spontaneous pneumothorax and that the annual incidence was 0.64%. The mean age of the patients at the time of their initial pneumothorax was 21.9 years (201). Pneumothorax occurs more frequently in patients with severe respiratory impairment. Seventy-five percent of cystic fibrosis patients with pneumothorax will have an FEV_1 <40% of that predicted (201). Cystic fibrosis patients with a pneumothorax have a higher mortality than those without even when the level of pulmonary dysfunction is taken into consideration (201). Approximately 16% to 20% of patients with cystic fibrosis who are older than 18 years will experience a pneumothorax some time in their lives (202).

The treatment of the secondary spontaneous pneumothorax associated with cystic fibrosis is similar to the treatment of that associated with COPD. Because the recurrence rate approaches 50% (203), consideration should be given to preventing a recurrence. Almost all patients should initially be treated with tube thoracostomy unless the pneumothorax is small. If the air leak ceases and the lung remains expanded, consideration should be given to the prevention of a recurrence with either thoracoscopy or the intrapleural injection of a sclerosant. However, the Cystic Fibrosis Pulmonary Guidelines do not recommend either procedure after the initial pneumothorax (204). Because many patients with cystic fibrosis are candidates for lung transplantation, one has to consider the effect of the preventive measures on the subsequent lung transplantation. As discussed earlier, it appears that efforts to create a pleurodesis do not preclude a lung transplantation and do not add appreciably to its complications (172,173,205). Accordingly, the procedure of choice for prevention is VATS with the stapling of blebs and pleural abrasion. Thoracoscopy should also be performed if the air leak persists or the lung remains unexpanded for 3 days after tube thoracostomy is performed. Indeed, one can make a good case for thoracoscopy for all cases of pneumothorax secondary to cystic fibrosis as soon as the patient is stabilized with tube thoracostomy.

PNEUMOTHORAX SECONDARY TO TUBERCULOSIS

The prevalence of secondary spontaneous pneumothorax in patients hospitalized with pulmonary tuberculosis is between 1% and 3% (206). In one series from Spain, tuberculosis was the second leading cause of secondary spontaneous pneumothorax after COPD (207). All patients with pneumothorax secondary to tuberculosis should be treated with tube thoracostomy. In one older series of 28 patients, 11 were treated by observation or repeated pleural aspiration, and 7 of the 11 (64%) died. In contrast, of the 17 patients treated with chest tubes, only 1 (6%) died. Once chest tubes are placed in such patients, a long period of chest tube drainage can be anticipated. The duration of tube thoracostomy ranged from 5 days to 6 months, with a mean duration of 50 days in one series (206). Patients with pneumothorax secondary to TB should have surgery if the airleak persists more than a few days or if they have a relapse. Recently Freixinet et al. (208) reviewed the cases of pneumothorax secondary to tuberculosis at a hospital in the Canary Islands and reported that there were 47 cases between 1989 and 2010. They inserted chest tubes in all but one patient (208). They performed thoracotomy or VATS in patients in whom the airleak lasted more than 10 days or who had a recurrent pneumothorax. An atypical pulmonary segmentectomy was performed in 10 patients for persistent air leak and 3 patients for recurrence. Five patients had a lateral thoracotomy and 7 patients had VATS (208). There were no postoperative deaths and the duration of hospitalization ranged from 4 to 73 days (208).

PNEUMOTHORAX DUE TO LYMPHANGIOLEIOMYOMATOSIS (LAM)

LAM is a rare condition characterized by peribronchial, perivascular, and perilymphatic proliferation of abnormal smooth muscle cells. LAM almost exclusively affects women of childbearing age and presents with slowly progressive breathlessness, chylothorax, recurrent spontaneous pneumothorax, or hemoptysis (209). There is a high incidence of spontaneous

pneumothorax with LAM. When three series (209–211) with a total of 154 patients are combined, 101 of the patients (66%) had experienced at least one episode of spontaneous pneumothorax. It has been estimated that 5% of women between 25 and 54 with a spontaneous pneumothorax have LAM (212). It has been recommended that all women in this age range undergo a high-resolution CT for assessment of LAM (212). When patients in the LAM registry were questioned, 66% of 395 patients reported at least one pneumothorax (213). When patients were questioned about the treatment of their pneumothorax, 66% had a recurrence after chest tube therapy, 27% had a recurrence after chemical pleurodesis therapy and 32% had a recurrence after surgery (213). The explanation for the high recurrence rate after surgery is unknown (213). Since the recurrence rates are so high, chemical pleurodesis or surgery is recommended after the first pneumothorax.

PNEUMOTHORAX DUE TO LANGERHANS CELL HISTIOCYTOSIS

Pulmonary Langerhans cell histiocytosis is an uncommon interstitial lung disease that results from the accumulation of specific histiocytic cells known as *Langerhans cells* in the lung. Almost all patients with this disease are smokers. Pneumothorax is relatively common with Langerhans cell histiocytosis. The incidence of pneumothorax was 16% in a series of 102 patients older than 18 years from the Mayo Clinic (214). These 16 patients had a total of 37 episodes of pneumothorax. Since the recurrence rate was 58% in patients managed without an attempt at pleurodesis (214), the recommended management of pneumothoraces in patients with pulmonary Langerhans cell histiocytosis is the same as that for patients with cystic fibrosis.

CATAMENIAL PNEUMOTHORAX

A catamenial pneumothorax occurs in conjunction with menstruation and is usually recurrent (215). Alifano et al. (216) have defined a catamenial pneumothorax as a recurrent pneumothorax that occurs between the day before and within 72 hours after onset of menses. It is unusual, with only 195 cases reported up to 2004 (217). However, catamenial pneumothorax may be more common than generally realized. In one center in France, 49 patients were seen with a catamenial pneumothorax between 2000 and 2009 (218). The mean age at the initial pneumothorax in one series of 156 patients was 34 years (218). Patients with catamenial pneumothorax classically develop chest pain and sometimes dyspnea within 24 to 48 hours of the onset of the menstrual flow (215). Frequently, the patients give a history of recurrent thoracic or scapular pain (218). Catamenial pneumothorax may be more likely if the patient's menstrual period is preceded by mental or physical stress. These pneumothoraces are usually right sided, but left-sided and even bilateral pneumothoraces have been reported (219).

Pathogenesis

The pathogenesis of catamenial pneumothorax is not definitely known (220). When Maurer et al. (221) initially described the syndrome, they hypothesized that air gained access to the peritoneal cavity during menstruation and then entered the pleural cavity through a diaphragmatic defect because their initial patient had a diaphragmatic defect. However, in a subsequent review by Lillington et al. (215) of 18 patients who had undergone thoracotomy, only 3 patients had diaphragmatic defects, whereas 6 had pleural or diaphragmatic endometriosis. These reviewers concluded that the most plausible explanation was leakage of air from the lung owing to subpleural endometrial implants. Korom et al. (217) in 2004 reviewed the literature on catamenial pneumothorax and found 195 patients who had adequate information. Of these, 140 were treated surgically and had detailed findings reported. Seventy-three (52.1%) had thoracic endometriosis and 54 (38.8%) had diaphragmatic lesions (217). In a recent study (222) from France, 28 cases were seen at a single hospital over a 6-year period. At thoracoscopy, diaphragmatic perforations were seen in 21 patients and diaphragmatic nodules felt to be endometriosis were found in 11 patients (222). Both abnormalities were found in 10 patients. Eleven patients had visceral pleura brown nodules, and 4 patients had parietal pleura brown nodules felt to represent endometriosis (222). It is likely that either of the mechanisms can be responsible for the syndrome. There is one case report in which a woman simultaneously had a catamenial pneumothorax and air under her diaphragm on three different occasions (223). There is another series (222) of three patients who had a pneumoperitoneum at the time they had their catamenial pneumothorax.

Diagnosis and Treatment

The diagnosis of catamenial pneumothorax is not difficult if the possibility is considered. Any woman older than 20 years who develops a pneumothorax

during the first 48 hours of her menstrual flow should be considered to have a probable catamenial pneumothorax. The medical treatment of catamenial pneumothorax is aimed at treating the endometriosis by suppressing the ectopic endometrium (215,219,224). This can be accomplished by administering gonadotropin-releasing hormone antagonists such as Luprin (225). Hormonal therapies that allow for menses do not always prevent catamenial pneumothorax and the recurrence rate for patients on hormonal therapy exceeds 50% (225,225). The surgical treatment for catamenial pneumothorax is thoracoscopy with closure of the diaphragmatic defects, stapling of any blebs in the lung, and pleural abrasion. However, the recurrence rates in patients with catamenial pneumothorax after this procedure are approximately 30% (226) and are higher than with any other condition. Bagan et al. (227) recommend the coverage of the diaphragmatic surface by a polyglactin mesh even when the diaphragm appears normal. If facilities for thoracoscopy are not available, then the same procedures can be performed with a thoracotomy (215,228). There has been one case report in which recurrent pneumothoraces developed after thoracoscopy with pleural abrasion and thoracotomy with partial pleurectomy and plication of the diaphragm; however, after bilateral tubal ligation, there were no recurrences (229).

NEONATAL PNEUMOTHORAX

Spontaneous pneumothorax occurs more commonly in the newborn period than at any other age. In radiologic surveys, a pneumothorax is present shortly after birth in 1% to 2% of all infants (230), and a symptomatic pneumothorax is present in approximately 0.5% (230). Spontaneous neonatal pneumothorax is twice as common in boys as in girls, and the infants are usually full term or postterm (230). In most instances, the baby has a history of fetal distress requiring resuscitation or a difficult delivery with evidence of aspiration of meconium, blood, or mucus (230).

The incidence of pneumothorax in infants with respiratory distress syndrome (RDS) is high (230,231). The more severe the RDS, the more likely the infant will develop a pneumothorax. In one series of 295 infants with RDS, 19% developed a pneumothorax (231). Pneumothorax developed in only 3.5% of those not requiring respiratory assistance, but it occurred in 11% of those requiring continuous positive airway pressure and in 29% of those requiring intermittent positive-pressure ventilation with positive end-expiratory pressures (231). Overall, pneumothorax develops in 5% to 8% of babies with birth weights 500 to 1,500 g (232).

Pathogenesis

The pathogenesis of neonatal pneumothorax in infants without RDS is related to the mechanical problems of first expanding the lung. Karlberg (233) has demonstrated transpulmonary pressures averaging 40 cm H_2O during the first few breaths of life, with occasional transpulmonary pressures as high as 100 cm H_2O. At birth, the alveoli usually open in rapid sequence, but if bronchial obstruction occurs from the aspiration of blood, meconium, or mucus, high transpulmonary pressures may lead to rupture of the lung (230). A transpulmonary pressure of 60 cm H_2O ruptures adult lungs (230), whereas a transpulmonary pressure of only 45 cm H_2O ruptures neonatal rabbit lungs (234). There has been one family reported in which the maternal grandfather, a maternal aunt, and an older sister, along with the patient had spontaneous neonatal pneumothorax (235).

In infants with RDS, the pneumothoraces also occur because of high transpulmonary pressures. With the infant breathing spontaneously, abnormally negative transpulmonary pressures can be generated because of the reduced lung volumes and the noncompliant lung. Intermittent positive-pressure ventilation is even more likely to produce high transpulmonary pressures and pneumothorax.

Clinical Manifestations

Depending on the size of the pneumothorax, the signs vary from none to severe acute respiratory distress. In the infant with a small pneumothorax, no clinical signs or mild apneic spells with some irritability or restlessness may be present. Large pneumothoraces incur varying degrees of respiratory distress, and, in severe cases, marked tachypnea (up to 120/minute), grunting, retractions, and cyanosis are present (230). The detection of pneumothorax by physical examination is often difficult because abnormal physical signs are often not found. The most reliable sign is a shift of the apical heart impulse away from the side of the pneumothorax. Because breath sounds are widely transmitted in the small neonatal thorax, appreciation of diminished breath sounds on the affected side is difficult (230).

In infants who develop pneumothorax as a complication of RDS, the onset of the pneumothorax is frequently heralded by a change in the vital signs (231). In the series of Ogata et al. (231) of 49 infants with pneumothorax complicating RDS, cardiac arrest marked the development of the pneumothorax in 12 (24%). Most of the other babies had a decrease in the pulse of 10 to 90 beats/minute, a decrease in the blood pressure of 8 to 22 mm Hg, or a decrease in the respiratory rate of 8 to 20 breaths/minute (231). Although the Pao_2 decreased with the development of pneumothorax, no consistent changes were seen in the pH or $Paco_2$. The infant with RDS who develops hypotension as a result of a pneumothorax is at high risk of having an intraventricular hemorrhage. In one series, 32 of 36 infants (89%) with pneumothorax associated with hypotension had a grade 3 or 4 intraventricular hemorrhage. In contrast, only 3 of 31 (10%) infants with pneumothorax and normal blood pressure developed an intraventricular bleed (236). It is hypothesized that the hypotension results in a cerebral infarction, with the intraventricular hemorrhage occurring after the systemic blood pressure has been raised to normal values (236). The infants who developed hypotension had a higher mortality rate and more residual brain damage than did those who maintained their blood pressure (236).

Diagnosis

The diagnosis of pneumothorax should be entertained in any neonate with respiratory distress or in any infant with RDS who deteriorates clinically. A radiograph of the chest is essential to differentiate pneumothorax from pneumomediastinum, hyaline membrane disease, aspiration pneumonia, congenital cyst of the lung, lobar emphysema, and diaphragmatic hernia. A clinically significant pneumothorax should be evident on a high-quality anteroposterior or posteroanterior chest radiograph (230). Transillumination of the chest with a high-intensity transilluminating light is also a rapid, accurate, and easy way to make the diagnosis of pneumothorax in the neonate (237).

Treatment

The neonate without RDS who is asymptomatic or is mildly symptomatic can be treated by close observation, and the pneumothorax resolves in most patients over a few days. Close observation is necessary because of the possibility that the pneumothorax will enlarge or that a tension pneumothorax (see the section later in this chapter) will develop (230). Supplemental oxygen can increase the speed at which the pneumothorax is absorbed, but it should be administered with care, particularly in the preterm infant because of the dangers of retrolental fibroplasia (230). A thoracentesis should be performed or a chest tube should be inserted in the neonate who is more than mildly symptomatic (238). Smith et al. (238) reported that 22 of 54 neonates at the University of Michigan with neonatal pneumothorax required tube thoracostomy. In this study (238), 10 of these 22 patients required mechanical ventilation for progressive respiration failure. In addition (238), 10 of these 22 neonates had pulmonary hypertension necessitating treatment with inhaled nitric oxide in 7 and extracorporeal membrane oxygenation in 4. All these neonates survived (238).

It is important to be careful about the location on the chest wall where the chest tube is placed. Rainer et al. (239) reported two teenagers who had significant breast deformities due to chest tube placement when they were infants. The chest tube should be placed in the anterior axillary line at a distance 4 to 5 cm inferior to the nipple in the fifth or sixth intercostal space (239).

Tube thoracostomy should almost always be performed in infants with RDS and pneumothorax because the pneumothorax compromises the patient's already poor ventilatory status and often increases in size. Usually, the air leak is small, and intermittent positive-pressure ventilation can maintain adequate gas exchange. In certain patients, however, air leaks are so large that most of the ventilation delivered by the respirator exits the lung through the bronchopleural fistula. In such patients, high-frequency ventilation may be the only method by which adequate gas exchange can be maintained (240) (see the discussion on bronchopleural fistulas at the end of this chapter).

IATROGENIC PNEUMOTHORAX

The incidence of iatrogenic pneumothorax is high and is likely to increase as the use of invasive procedures continues to increase. In Olmsted County, Minnesota, between 1950 and 1974, 102 instances of iatrogenic pneumothorax were reported, as compared with 77 cases of primary and 64 cases of secondary spontaneous pneumothorax (1). In the VA cooperative study on spontaneous pneumothoraces

in the 1980s, data were collected on the incidence of iatrogenic pneumothoraces at the same time (241). These investigators reported that during the 4-year study period, there were 538 instances of iatrogenic pneumothorax and 520 instances of spontaneous pneumothorax. This study probably underestimates the relative incidence of iatrogenic pneumothorax because some of the medical centers did not appear to be diligent in searching for iatrogenic pneumothoraces (241). The major causes of iatrogenic pneumothorax in this study are shown in Table 24.1. There is a significant cost for iatrogenic pneumothoraces. Zhan et al. (242) reported that iatrogenic pneumothoraces occur in 0.67/1,000 hospitalized patients and that these patients stayed in hospitals for an average of 4.4 extra days, incurred approximately US$18,000 in excess charges, and had a 6% higher risk of death in the hospital.

The incidence of iatrogenic pneumothoraces is particularly high in patients in the intensive care unit. In one prospective study of 3,430 patients admitted for more than 24 hours to an intensive care unit, the incidence of pneumothorax was 3.0% (243). The etiologies of the iatrogenic pneumothoraces in these patients were mechanical ventilation in 42, central venous catheters in 28, thoracentesis in 21, and miscellaneous in 3 (243).

There is a substantial rate of morbidity and even some deaths associated with iatrogenic pneumothorax. Despars et al. (244) reviewed the cases of iatrogenic pneumothoraces at the VA Medical Center in Long Beach, California, and reported that between October 1983 and December 1988, there were 105 cases of iatrogenic pneumothorax in comparison to 90 cases of spontaneous pneumothorax. The most common cause of iatrogenic pneumothorax was transthoracic needle aspiration (35), followed by thoracentesis (30), subclavian venipuncture (23), and positive-pressure ventilation (7). There was substantial morbidity from the iatrogenic pneumothoraces in this series. Most patients (65 of 98) were treated with large chest tubes that were in place 4.7 ± 3.9 days. Nine of the patients required a second chest tube. Two patients died from the iatrogenic pneumothorax (244).

TABLE 24.1 ■ Leading Causes of Iatrogenic Pneumothorax in the Veterans Administration Cooperative Study

Procedure	Number	Percentage
Transthoracic needle aspiration	128	24
Subclavian needle stick	119	22
Thoracentesis	101	19
Transbronchial biopsy	53	10
Pleural biopsy	45	8
Positive-pressure ventilation	38	7
Supraclavicular needle stick	24	5
Nerve block	16	3
Miscellaneous	5	1

At present, the leading cause of iatrogenic pneumothorax is transthoracic needle aspiration of lung masses. The incidence of iatrogenic pneumothorax with this procedure in five series, each with more than 300 patients, ranged from 19% to 40% (245–249). The percentage of patients undergoing needle aspiration of the lung who are treated with chest tubes ranges from 2 to 8 (245–249). The two primary factors related to the development of the pneumothorax are the depth of the lesion and the severity of the underlying lung disease (245,247). In one study, the incidence of pneumothorax was 15% if no aerated lung was traversed and approximately 50% if aerated lung was penetrated (247). In this same study, the incidence of pneumothorax was 49% if emphysema was present on the CT scan and 35% if emphysema was absent. Patients with emphysema were three times more likely to undergo chest tube drainage than were patients without emphysema (247). In a more recent study (250) of 1,098 CT fluoroscopy-guided lung biopsies with a #20 coaxial cutting needle, the overall incidence of pneumothorax was 42.3% and 11.9% of the patients required a chest tube. Multivariate analysis in this study (250) revealed that lesions in the lower lobe, greater lesion depth, and a needle trajectory $<45°$ were associated with an increased incidence of pneumothorax.

In one study, the use of a smaller coaxial needle (#19) in comparison to a larger needle (#18) reduced the incidence of pneumothorax from 38% to 23% (249). Positioning the patient with the biopsied lung down is not effective (246,251), even though it is in animals. Similarly, the use of a blood-patch technique was ineffective in decreasing the incidence of pneumothorax in two studies (112,113), but it did decrease the incidence of large pneumothoraces in a third study (114). The pneumothorax following transthoracic needle biopsy may be delayed. Choi et al. (252) reported that a delayed pneumothorax, that is, one not visible on radiograph at 3 hours but which was subsequently visible, developed in 3.3% of 458 patients.

A preliminary study (253) suggested that the incidence of pneumothorax could be reduced with a lung biopsy tract plug. The plug consists of a desiccated polyethylene glycol hydrogel which is extruded as a solid cylinder (253). Upon contact with moist tissue, the hydrogel absorbs fluids and expands to fill the void created by the needle puncture. It then absorbs over time. In one randomized multicenter study with 339 patients, the incidence of pneumothorax was significantly lower (19%) in the treatment group than in the control group (31%) (253). There were also significantly fewer chest tubes placed in the treatment group (4%) than in the control group (11%).

Another preliminary study (216) suggested that the use of fibrin glue as a sealant might decrease the incidence of pneumothorax after lung aspiration. In a prospective randomized study in patients with COPD, 26 patients received 1 mL of fibrin glue as the needle was withdrawn, whereas 32 control patients received nothing. The incidence of pneumothorax was 19.2% in the group that received the fibrin glue compared with 40.6% in the control group. In the group that received the fibrin glue, one patient (3.8%) received a chest tube, whereas six patients (18%) in the control group received a chest tube (254). In a third preliminary study (255), 140 patients were randomized to receive 2 to 4 ml of saline into the whole puncture access during extraction of the trocar needle. The incidence of pneumothorax with the saline (8%) was significantly less than in the control group (34%) (255). It remains to be seen which of the above three techniques survives the test of time. However, the big advantage of the saline technique is that its cost is minimal.

It appears that it is safe to travel by air within 24 hours of having a transthoracic needle aspiration. Tam et al. (256) contacted 179 patients who underwent air travel within 14 days of having a transthoracic needle aspiration including 65 who developed a pneumothorax. No patient required in-flight medical attention or flight diversion (256). Most patients traveled less than 48 hours after the biopsy (256).

The second leading cause of iatrogenic pneumothorax is probably the insertion of a central line (241). The reported incidence of iatrogenic pneumothorax following subclavian vein catheterization has varied from 0% to 12%, with the average being approximately 2% (257–261). The importance of monitoring the incidence of complications in individual institutions is demonstrated by the report of Lockwood (257). In this report, the incidence of pneumothorax fell dramatically from 12% once training programs were initiated (257). Because more than 1 million subclavian catheters are inserted annually in the United States, this procedure is responsible for a substantial number of pneumothoraces. In one recent study from Denmark, only 2 of 473 patients (0.4%) developed a pneumothorax following central venous catheter insertion (262). The authors of this study recommended that routine postprocedure radiographs not be obtained unless a complication was suspected (262). Maury et al. (263) recommend ultrasound rather that chest radiographs to assess the possibility of pneumothorax and the placement of the catheter. Pneumothoraces appear to be more common with internal jugular cannulations (2.6%) as opposed to subclavian cannulations (1.3%) and with Swan-Ganz catheters as opposed to central venous catheters. One recent paper (264) suggests strongly that the incidence of pneumothorax can be markedly reduced if the catheter is inserted using ultrasound guidance. In this paper (264), 1,948 catheters were inserted in the internal jugular for cancer treatment and there were no pneumothoraces. It is important to note that the pneumothorax following the insertion of a central line may not be apparent on the immediate postprocedure radiograph (265).

Thoracentesis is probably the third leading cause of iatrogenic pneumothorax. At present, the incidence of pneumothorax after thoracentesis is approximately 6%, with approximately 34% of those with a pneumothorax receiving a chest tube (266). The incidence of pneumothorax is higher if the patient has COPD. Pneumothorax is more common following therapeutic than diagnostic thoracentesis (266). The incidence of pneumothorax can be decreased if the thoracentesis is performed by experienced interventional radiologists or pulmonologist trained in thoracentesis methods with ultrasound guidance. At my previous institution, the incidence of pneumothorax was 2.5% after the performance of 941 thoracenteses with ultrasound guidance and only 0.8% received tube thoracostomy (267). At the Mayo Clinic, the incidence of pneumothorax was 8.6% in the pulmonary outpatient clinic in 2001–2002 (268). This incidence fell to 1.1% after a program was instituted where all thoracenteses were performed with ultrasound guidance and only by physicians who had undergone a training program (268). If tactile fremitus is present over the upper lung field after thoracentesis, if the patient is not symptomatic, and if the physician does not suspect a pneumothorax, a chest radiograph after thoracentesis is not indicated (269).

Although mechanical ventilation was the leading cause of iatrogenic pneumothorax in the 1970s (270), it is probably now only the third or fourth leading cause of iatrogenic pneumothorax. The relative decrease in the incidence of iatrogenic pneumothorax caused by mechanical ventilation is probably due to a combination of two factors. First, procedures such as transthoracic needle aspiration and subclavian vein catheterization were used much less commonly 40 years ago. Second, newer ventilatory modes have made it possible to ventilate patients with lower peak inspiratory pressures and lower mean airway pressures. In a series of 553 patients requiring ventilatory support from nearly 35 years ago, the incidence of iatrogenic pneumothorax was 4% (271). In this series, the frequency of pneumothorax was increased if the patient had aspiration pneumonia (37%), COPD (8%), intubation of the right main stem bronchus (13%), or treatment with positive end-expiratory pressure (15%) (271).

The incidence of pneumothorax is relatively high in patients with ARDS. Weg et al. (272) reported that the incidence of pneumothorax was 9.2% in a series of 644 patients with ARDS. Although the occurrence of pneumothoraces in this situation in the past had been attributed to high inspiratory pressures or mean airway pressures, these pressures were very similar in patients with and without pneumothorax in Weg's series (272). In this series, the mortality rate was not significantly different in those with and without pneumothorax. Boussarsar et al. (273) reviewed the literature on the relationship between pneumothorax and ARDS and concluded that there was a higher incidence of pneumothorax with plateau pressures above 35 cm H_2O and lung compliances less than 30 mL/cm H_2O. The presence of mediastinal emphysema may precede the development of the pneumothorax. In one series of 20 patients who developed a pneumothorax while on mechanical ventilation, previous chest radiographs had shown the presence of mediastinal emphysema in 10 (50%) (274).

Overall, the incidence of pneumothorax with severe acute respiratory syndrome (SARS) is relatively low. Sihoe et al. reported that only 1.7% of 356 SARS patients had a pneumothorax (275), but most of their patients did not receive mechanical ventilation. Kao et al. (276) reported that 5 of 41 patients (12%) who were treated with mechanical ventilation developed a pneumothorax.

Other procedures associated with iatrogenic pneumothorax and their approximate incidence are pleural biopsy, 10% (277); radiofrequncy ablation of lung neoplasms, 11.3% to 42% (278,279); transbronchial lung biopsy, 1% to 2% (280,281); laparoscopy, 0.2% (282); cardiac surgery 1.4% (283), intercostal nerve block for fractured rib 5.6% (284), and liver biopsy 0.35% (285). Bronchoscopy with an ultrafine bronchoscopy without transbronchial biopsy has been associated with pneumothorax (286). In this instance, the ultrathin bronchoscope perforates the visceral pleura (286). The reported incidences are probably minimum percentages because the authors of articles are usually more experienced in the various procedures they describe than is the average physician. Iatrogenic pneumothorax may occur following tracheostomy, when air passes into the mediastinum and pleural space via the cervical fascial planes. Iatrogenic pneumothorax also frequently complicates cardiopulmonary resuscitation. In an autopsy series, 12 patients had tension pneumothoraces that were undiagnosed during life, and 9 of these patients had undergone cardiopulmonary resuscitation (287). Resuscitation-related rib fractures were found in only three of the nine patients.

Physicians treating heart–lung transplant recipients or other patients who have undergone mediastinal surgery should be aware of the fact that these patients do not have an intact mediastinum. Because they are likely to undergo procedures that are associated with iatrogenic pneumothorax such as transthoracic needle aspiration, bronchoscopy, thoracentesis, and central line insertion, they may develop life-threatening bilateral pneumothoraces. Paranjpe et al. (288) reported that 15 of 72 heart–lung transplant recipients developed iatrogenic pneumothoraces, and the pneumothoraces were bilateral in six of the patients. Lee et al. (289) reported the development of a contralateral tension pneumothorax following the unilateral chest tube drainage of bilateral pneumothoraces.

Clinical Manifestations

The clinical manifestations of iatrogenic pneumothorax depend both on the patient's condition and on the initiating procedure. If the pneumothorax occurs as a complication of mechanical ventilation, the patient is likely to demonstrate a sudden clinical deterioration. A sensitive indicator of the development of a pneumothorax in such patients is an increasing peak and plateau pressure on the respirator if the patient is on volume-controlled ventilation, or a decreasing tidal volume if the patient is on pressure support. The development of a pneumothorax during cardiopulmonary resuscitation is heralded by more difficulty

in ventilating the patient. In contrast, many patients who develop pneumothorax after thoracentesis, pleural biopsy, transbronchial biopsy, or percutaneous lung aspiration have no symptoms referable to the pneumothorax.

Diagnosis

The diagnosis of iatrogenic pneumothorax should be suspected in any patient treated by mechanical ventilation. The presence of mediastinal emphysema should serve as an indicator to look closely for a pneumothorax. Recognition of the pneumothorax in the patient on mechanical ventilation is more difficult because the chest radiographs are obtained with the patient supine or semisupine. When the patient is in this position, the most superior part of the chest (where the air accumulates) is the anterior costophrenic sulcus. In one series of 112 pneumothoraces seen on supine radiographs, the most common location of air was anteromedial in 38%, followed by subpulmonic in 26%, apicolateral in 22%, and posteromedial in 11% (290). Air in the anterior costophrenic sulcus is manifested as hyperlucency over the upper abdominal quadrants (290). Pneumothoraces are frequently not recognized on the supine radiographs. Kollef (291) prospectively reviewed all 464 medical intensive care unit admissions at Fitzsimons Army Medical Center over a 1-year period and reported that 9 of 28 pneumothoraces (32%) were not originally recognized. Three of these nine patients subsequently went on to develop a tension pneumothorax.

The occurrence of an iatrogenic pneumothorax should also be suspected in patients who become more short of breath after a medical or surgical procedure known to be associated with the development of an iatrogenic pneumothorax. The signs and symptoms of the pneumothorax are similar to those of primary and secondary pneumothorax, and the diagnosis is confirmed by chest radiographs. Ultrasound can also be used to diagnose the pneumothorax (292).

Treatment

The treatment of iatrogenic pneumothorax differs from that of spontaneous pneumothorax in that recurrence is not likely, and, therefore, one need not try to create a pleurodesis, as is done frequently with spontaneous pneumothorax. When a pneumothorax occurs during positive-pressure ventilation, tube thoracostomy should be performed immediately in most cases to prevent the development of a tension pneumothorax. With mechanical ventilation, positive pressure in the alveoli leads to increased entry of air into the pleural space and the likelihood that a tension pneumothorax will develop. The chest tube should be left in place for at least 48 hours after the air leak stops if the patient continues to receive mechanical ventilation. At times, an ipsilateral recurrent pneumothorax develops in a patient on mechanical ventilation while the chest tube is still in place. This development is usually due to placement of the chest tube in a fissure (293). Malpositioning of the chest tube is suggested if the chest tube is perpendicular to the lateral chest wall; the chest tube should be relatively parallel to the chest wall (293). Bronchopleural fistulas and mechanical ventilation are discussed later in this chapter.

When an iatrogenic pneumothorax develops after a procedure, symptoms vary from none to severe respiratory distress. In general, if the patient has no symptoms or just mild symptoms and the pneumothorax occupies less than 40% of the hemithorax, the patient can be managed with observation. The administration of supplemental oxygen will increase the rate at which air is absorbed from the pleural space (see Chapter 2) (71). If the patient is more than mildly symptomatic, if the pneumothorax occupies more than 40% of the hemithorax, or if the pneumothorax continues to enlarge, however, one should consider removing the intrapleural air.

In general, most iatrogenic pneumothoraces should first be treated with aspiration. If the initial aspiration is unsuccessful, then a Heimlich valve should be attached to the catheter. Only when the lung does not expand and remains expanded with the Heimlich valve is a larger chest tube inserted (294). Delius et al. (295) treated 79 needle-induced iatrogenic pneumothoraces by aspiration through an 8-F radiopaque Teflon catheter. The initial aspiration was successful in 59 patients (75%), and an additional 9 patients (15%) were successfully managed with a Heimlich valve attached to this small catheter (295). In another study (296) in which 102 patients were treated with aspiration after developing a pneumothorax post needle aspiration of a nodule, only 15 required a chest tube. A chest tube was more likely to be necessary if more than 670 ml of pleural air was aspirated (296). Patients can be managed as outpatients with small intrapleural catheters and Heimlich valves (297). In one study, 17 of 20 patients (85%) who developed pneumothorax after transthoracic needle aspiration and were treated with manual aspiration did not require a chest tube (298). The injection of 15 ml blood after aspiration is complete may decrease the subsequent need for tube

thoracostomy (299). In general, patients are more likely to require a chest tube if they have COPD (300).

TRAUMATIC (NONIATROGENIC) PNEUMOTHORAX

Traumatic pneumothorax can result from either penetrating or nonpenetrating chest trauma.

Mechanism

The mechanism of the pneumothorax is easily understood with penetrating chest trauma because the wound allows air to enter the pleural space directly through the chest wall. In addition, the visceral pleura is frequently penetrated, allowing air to enter the pleural space from the alveoli. With nonpenetrating trauma, the ribs may become fractured or dislocated, and the visceral pleura may thereby be lacerated, leading to a pneumothorax. In most patients with pneumothorax secondary to nonpenetrating trauma, however, no associated rib fractures occur (301,302). The mechanism of the pneumothorax in such patients is thought to be as follows (301,302). With sudden chest compression, the alveolar pressure increases and this may cause alveolar rupture. Air then enters the interstitial spaces and dissects either toward the visceral pleura or toward the mediastinum to produce mediastinal emphysema. A pneumothorax results when either the visceral or the mediastinal pleura ruptures.

Incidence and Diagnosis

The diagnosis of traumatic pneumothorax should be considered in any patient who suffers significant trauma. In most instances, the initial chest radiograph on trauma patients is obtained in the supine position and small pneumothoraces may not be apparent. These supine chest radiographs are insensitive in diagnosing both pneumothorax and hemothorax. In one series of 103 patients with blunt chest trauma, thoracic CT scans revealed pneumothorax in 44 patients whereas supine chest radiographs revealed pneumothorax in only 17 patients (303). In the same series, the CT scan revealed hemothorax in 44 patients whereas the supine chest radiograph revealed hemothorax in only 23 patients (303). In view of this series, a case can be made for obtaining a thoracic CT scan in all severely injured patients with blunt chest trauma.

Pneumothoraces seen only on the CT scan are labeled as occult pneumothoraces. Overall, approximately 5% of multiple trauma patients have a pneumothorax and at least 40% of the pneumothoraces are occult (304). For example, in one series of 2,048 multiple trauma patients, there were 90 patients (4.4%) who had a pneumothorax (305). Thirty-five of these pneumothoraces (38.8%) were occult (305). In a second study of 3,712 trauma patients, a pneumothorax was present in 230 (6.2%) and the pneumothorax was occult in 126 of them (54.8%) (306).

An alternative imaging procedure to diagnose traumatic pneumothorax is ultrasound. The presence of pneumothorax is characterized by two features: (a) absence of pleural lung sliding and (b) absence of comet-tail artifacts (307,308). Ultrasound appears to be better at diagnosing pneumothorax than the supine radiograph (309,310,311). Soldati et al. (310) performed supine chest radiographs, ultrasound, and CT scan on 186 patients with blunt chest trauma. Using the CT scan as the gold standard, they reported that ultrasound identified 55 of 56 (98%) pneumothoraces while the chest radiograph only identified 30 of 56 (54%) (310). In a second study, Blaivas et al. (311) examined supine chest radiographs and bedside ultrasound performed by the emergency room physicians for the delineation of pneumothorax in 176 trauma victims of whom 53 had a pneumothorax on CT scan which they used as the gold standard (311). They reported that the sensitivity and specificity of ultrasound were 98.1% and 99.2%, respectively, whereas the sensitive and specificity of the supine chest radiograph was 75.5% and 100%, respectively (311).

Treatment

Most traumatic pneumothoraces should be treated with tube thoracostomy. Small tubes 10 to 14 Fr are adequate in almost all instances (312). If a hemopneumothorax is present, one chest tube should be placed in the superior part of the hemithorax to evacuate the air and another should be placed in the inferior part of the hemithorax to remove the blood (see Chapter 25). With traumatic pneumothorax, the lung expands and the air leak usually ceases within 72 hours. If the lung does not expand or an air leak persists, VATS should be performed within the first few days to evaluate the reason for the air leak (313). Carrillo et al. (314) reported their results in 13 patients who had persistent air leaks or unexpanded lung 72 hours post trauma. They obtained chest CT scans and performed bronchoscopy on all patients to ascertain that there were no significant problems causing the pneumothorax. At thoracoscopy,

the source of the air leak was sought by inspecting the lung surface from apex to base. If there was no obvious air leak, 250 mL saline solution was instilled with slight lung ventilation to identify the air leak. Once the air leak was identified, a topical surgical sealant CoSeal (Baxter, Freemont, CA) was applied. They did not attempt to surgically close the leak. This procedure was successful in all patients in that 11 of the 13 patients had their chest tubes removed within 24 hours and the remaining 2 patients had their chest tubes removed without 48 hours (314).

Tube thoracostomy may not be necessary for patients with small pneumothoraces or those with occult pneumothoraces. Knottenbelt and van der Spuy (315) observed 333 patients with small (<1.5 cm from lung to chest wall) pneumothoraces due to chest trauma and reported that only 33 (10%) required subsequent drainage for an enlarging pneumothorax. Ordog et al. (316) observed 47 patients with small pneumothoraces (<20%) secondary to stab wounds of the chest and reported that only 32% required a chest tube or showed progression of the pneumothorax within 24 hours. They recommend that such patients be admitted to the hospital and have repeat radiographs at 6 hours, 24 hours, and again at 48 hours. The patients are then discharged if the pneumothorax is unchanged or shows evidence of resolving (316).

Most patients with occult pneumothoraces need not be treated with tube thoracostomy (317–319). Wolfman et al. (319) classified occult pneumothoraces as minuscule (<1 cm in greatest anteroposterior thickness and seen on no more than four contiguous CT images), anterior (>1 cm but not extending beyond the midcoronal line), and anterolateral (extending posteriorly beyond the midcoronal line). Of the 28 occult pneumothoraces in their series, 6 were minuscule, 14 were anterior, and 8 were anterolateral. The patients with the minuscule and the anterior occult pneumothoraces were less likely to receive tube thoracostomy (319). De Moya et al. (320) developed another system for semiquantitating the size of an occult pneumothorax. They took the maximum distance from the chest wall in millimeters and added 10 if the pneumothorax did not go below the hilum and 20 if the pneumothorax went below the hilum (320). They reported in a series of 1,295 patients with pneumothorax that the average score of those with chest tubes was 34 while the average score for those without chest tubes was 21 (320).

Some patients who have an occult pneumothorax and receive mechanical ventilation have been managed without tube thoracostomy (321,322). Indeed, the practice guidelines for management of occult pneumothorax states that occult pneumothoraces subjected to mechanical ventilation may be observed (323). However, if the patient does not receive a chest tube, they should be observed closely because of the possibility of the development of a tension pneumothorax, which could be fatal. Supplemental oxygen should be administered to facilitate the reabsorption of the pleural air (324).

Whenever a patient with a traumatic pneumothorax is seen, two uncommon diagnostic possibilities, both indications for immediate thoracic operation, should be considered. One is fracture of the trachea or a major bronchus; the second is traumatic rupture of the esophagus. Bronchial rupture should be suspected in patients with persistent air leak following a traumatic pneumothorax, particularly if there is subcutaneous emphysema, pneumomediastinum, deep cervical emphysema, hemoptysis, or rib, or clavicular fractures (325,326). The possibility of bronchial rupture should be assessed in such patients with fiberoptic bronchoscopy. Thoracic CT scan does not definitively establish the diagnosis in most patients (326). The treatment of choice is surgical repair.

Traumatic rupture of the esophagus usually produces a hydropneumothorax. Therefore, if a patient with a traumatic pneumothorax also has a pleural effusion, the possibility of esophageal rupture should be entertained. A reliable screening test for esophageal rupture is measurement of the pleural fluid amylase level (327). If the patient's pleural fluid amylase level is elevated, contrast radiographic studies of the esophagus should be performed.

If a patient has suffered a traumatic pneumothorax, how long should they wait before they travel by air? The Aerospace Medicine Association has suggested that patients should be able to fly 2 to 3 weeks after radiologic resolution of the pneumothorax (328). The following study appears to have validated these recommendations. Cheatham and Safcsak (329) studied 12 consecutive patients with recent traumatic pneumothorax who desired to travel by commercial airline. Ten patients waited at least 14 days and all were asymptomatic in-flight. One of two patients who flew earlier than 14 days developed respiratory distress in-flight with symptoms suggesting a recurrent pneumothorax.

TRAUMATIC PNEUMOTHORAX SECONDARY TO DRUG ABUSE

Intravenous drug abuse has become endemic in many urban areas. It appears that there is a high incidence

of traumatic pneumothorax in intravenous drug users. Douglass and Levison (330) reviewed 525 diagnoses of pneumothorax between January 1, 1982 and December 31, 1984 at the Detroit Receiving Hospital. They reported that 113 (21.5%) occurred because of drug abuse. The user or a companion had attempted to inject the drug into the subclavian or internal jugular vein. It has been recommended that intravenous drug users with traumatic pneumothorax be managed with tube thoracostomy (330). In the series of Douglass and Levison (330), the average number of days for chest tube management was 4.4. It is probable, however, that many such cases could be managed with simple aspiration.

PNEUMOTHORAX *EX VACUO*

Pneumothorax *ex vacuo* is said to occur when patients develop a pneumothorax secondary to acute bronchial obstruction. The theory is that the acute collapse of the lung results in negative intrapleural pressure, which leads to the accumulation of gas that originated in the ambient tissues and blood in the pleural space (331).

Recently, the definition has been altered to indicate the development of a pneumothorax after a thoracentesis because the lung is unable to reexpand and fill the pleural space (332). In one series of 282 patients undergoing 437 thoracenteses, 10 patients (4%) developed what the authors called *pneumothorax ex vacuo* (332). These pneumothoraces tend to persist and the authors recommend that they not be treated with chest tubes (332).

It is not obvious to me that this entity actually exists. In order for air to come out of the tissues and into the pleural space, the pleural pressure would have to be more negative than -60 cm H_2O (see Chapter 2). Heidecker et al. (333) performed manometry in eight patients who developed an unintentional pneumothorax after a thoracentesis. In none of the cases were the pleural pressures below -20 cm H_2O (333). All theses pneumothoraces were associated with radiographic signs of unexpandable lung. These investigators speculated that the pneumothoraces developed from transient, parenchymal-pleural fistulae caused by nonuniform stress distribution over the visceral pleura that develop during large-volume drainage if the lung cannot conform to the shape of the thoracic cavity (333).

TENSION PNEUMOTHORAX

A tension pneumothorax is said to be present when the intrapleural pressure exceeds atmospheric pressure throughout expiration and often during inspiration as well. Most tension pneumothoraces occur in patients who are receiving positive-pressure ventilation either from mechanical ventilation or during resuscitation. If the patient is not receiving positive-pressure ventilation, then the mechanism by which a tension pneumothorax develops is probably related to some type of one-way valve process in which the valve is open during inspiration and closed during expiration. During inspiration, owing to the action of the respiratory muscles, the pleural pressure becomes negative and air moves from the alveoli into the pleural space. Then, during expiration, with the respiratory muscles relaxed, the pleural pressure becomes positive. A one-way valve mechanism must be implicated; otherwise, on expiration, when the pleural pressure is positive with respect to the alveolar pressure, gas would flow from the pleural space into the alveoli and no positive pressure would develop in the pleural space.

Pathophysiologic Features

The development of a tension pneumothorax is usually heralded by a sudden deterioration in the cardiopulmonary status of the patient. The precise explanation for sudden deterioration is not known, but it is probably related to the combination of a decreased cardiac output due to impaired venous return and marked hypoxemia (334). Older studies in unventilated animals suggested that the primary pathophysiologic abnormality was a precipitous fall in the Pao_2 to below 30 mm Hg (335,336). However, more recent studies in ventilated animals have suggested that the primary problem is decreased cardiac output. Carvalho et al. (337) induced right-sided tension pneumothoraces with mean pleural pressures of $+10$ and then $+25$ cm H_2O in 10 mechanically ventilated adult sheep. The mean cardiac output in these animals fell from 3.5 L/minute to approximately 1.2 L/minute, and the mean blood pressure fell from 80 mm Hg to less than 50 mm Hg as the pleural pressure increased from -5 to $+25$ cm H_2O (337). The decrease in the Pao_2 was much less life threatening; the Pao_2 was 150 mm Hg at baseline and fell to 59 mm Hg when the pleural pressure was 25 cm H_2O (337). The inspiratory airway pressure nearly doubled from 19 to 35 cm H_2O (337). However, studies by Barton et al. (338) in ventilated swine suggested that the fall in the Sao_2 was at least as important as the fall in cardiac output. They measured the cardiac output and the Sao_2 as 100 mL aliquots of air were introduced into the pleural space.

They found that when the mean intrapleural pressure had increased to 11 mm Hg with the introduction of 700 mL of air, the mean cardiac output had fallen from 2.8 to 1.9 L/minute, the mean arterial pressure had fallen only from 90 to 73 mm Hg, but the Sa_{O_2} had fallen from 97% to 55% (338).

In humans, for obvious reasons, there are no systematic studies of the blood gases or the hemodynamics associated with tension pneumothorax. Beards and Lipman (339) did report on the hemodynamics of three patients receiving mechanical ventilation who developed tension pneumothorax. In their three patients, the cardiac indices, which were 7.3, 4.8, and 3.6, respectively, at baseline, fell to 3.0, 3.1, and 1.4 l/min/m^2, respectively, with the development of a tension pneumothorax, whereas the baseline mean arterial pressures, which were 97, 96, and 68, respectively, fell to 33, 68, and 57, respectively. The oxygenation status did not deteriorate nearly as dramatically (339). The patients in this study did not have consistent changes in their heart rates (339). In another report, a 67-year-old man with COPD developed a tension pneumothorax while on mechanical ventilation. This patient's cardiac output fell from 7.11 to 3.80 L/minute and the stroke volume fell from 56 to 27 mL, whereas the pulse increased from 127 to 142 (340). In the same patient, the Pa_{O_2} fell from 76 mm Hg to 47 mm Hg with the development of tension pneumothorax.

In summary, the disastrous effect of a tension pneumothorax in patients appears to be the result of the combination of a marked decrease in the cardiac output and in the Pa_{O_2}. In patients, the decrease in the cardiac output is most life threatening, but the marked decrease in the Pa_{O_2} should not be ignored.

Clinical Manifestations

Although tension pneumothorax occasionally evolves from a spontaneous pneumothorax, it is much more frequent in patients who develop pneumothorax while receiving mechanical ventilation or during cardiopulmonary resuscitation (341). The clinical status of patients with tension pneumothorax is striking. The patient appears distressed with rapid labored respirations, cyanosis, and usually profuse diaphoresis, hypotension, and marked tachycardia. Arterial blood gases reveal marked hypoxemia and, sometimes, respiratory acidosis. The physical findings are those of any large pneumothorax, but in addition, the involved hemithorax is larger than the contralateral hemithorax with the interspaces widened. The trachea is usually shifted toward the contralateral side.

Diagnosis and Treatment

The diagnosis of tension pneumothorax should be suspected in patients whose condition suddenly deteriorates, who are receiving mechanical ventilation and who have undergone a procedure known to cause a pneumothorax. If difficulty is encountered in the ventilation of a patient during cardiopulmonary resuscitation or a patient has electromechanical dissociation, a tension pneumothorax should also be suspected. In a series of 3,500 autopsies, unsuspected tension pneumothorax was found in 12 patients; 10 of these had been supported by mechanical ventilators, and 9 had undergone cardiopulmonary resuscitation (287). There is one report of three cases of tension pneumothorax that occurred during hyperbaric oxygen therapy for acute carbon monoxide poisoning (340). The presence of a chest tube in a patient with a pneumothorax does not preclude the possibility of a tension pneumothorax because the chest tube might be malpositioned (342). There is a report of two cases of tension pneumothorax that occurred when the Heimlich valve used for treating pneumothorax was attached backward (343).

It is important to assess carefully the chest radiograph for pneumothorax in patients who are receiving mechanical ventilation. Patients with unrecognized pneumothoraces who are receiving mechanical ventilation are those most likely to develop a tension pneumothorax. Kollef (291) reviewed 464 medical intensive care unit admissions at Fitzsimons Army Medical Center over a 1-year period and reported that 28 patients acquired a pneumothorax during their stay in the intensive care unit. Pneumothorax was not originally recognized in nine of the patients, and three of them (33%) subsequently developed a tension pneumothorax. In a second series, Tocino et al. (290) reported that a pneumothorax was originally missed in 34 of 112 patients in an intensive care unit and 16 of these 34 patients developed tension pneumothorax. The diagnosis of pneumothorax on the supine chest radiograph is discussed earlier in this chapter in the section on iatrogenic pneumothorax.

Tension pneumothorax is a medical emergency. Although the diagnosis of tension pneumothorax can be established radiographically by demonstrating severe contralateral mediastinal shift and ipsilateral diaphragmatic depression, valuable time should not be wasted on radiologic studies because the clinical situation and the physical findings are usually sufficient to establish the diagnosis. When the diagnosis is suspected, the patient should immediately be

given a high concentration of supplemental oxygen to combat the hypoxia. Then, the elevated pressure in the pleural space must be eliminated. Optimally, this is done with a silicon catheter such as that advocated for thoracentesis (see Chapter 28). Ideally, the catheter should be attached to a three-way stopcock and a 50-mL syringe partially filled with sterile saline solution. After the catheter is inserted into the pleural space, it is connected through the three-way stopcock to the syringe. Then the stopcock is opened to the syringe, and the plunger is withdrawn. A rush of air bubbling outward through the fluid in the syringe establishes the diagnosis of tension pneumothorax.

If a tension pneumothorax is confirmed, the catheter should be left in place and in communication with the atmosphere until air ceases to exit through the syringe. Additional air can be withdrawn from the pleural space with the syringe and the three-way stopcock. There have been instances reported where 16-gauge cannulae were insufficient in the drainage of air from tension pneumothorax (344). If a tension pneumothorax is present, preparations should be made for the immediate insertion of a large chest tube. If no bubbles escape from the syringe, the patient does not have a tension pneumothorax and the catheter should be withdrawn from the pleural space.

In recent years, some emergency medical services have begun performing needle thoracostomies prehospital in patients suspected of having a tension pneumothorax (345). The outpatient use of needle thoracostomy is controversial, and its utilization varies markedly from region to region (345). Warner et al. reviewed 20,330 advanced life support calls in the Seattle area and found that 39 had a needle thoracostomy placed for suspected tension pneumothorax. Four of these patient had unexpected survivals. It appears that if the emergency medical technicians are well trained in needle thoracostomy, its benefits are *greater than its risks.*

BRONCHOPLEURAL AND ALVEOLAR–PLEURAL FISTULAS

When a chest tube is in place, there will be an air leak through the tube if there is communication between a bronchus or the pulmonary parenchyma and the pleural space. A *bronchopleural fistula* is present when there is a communication between a mainstem, lobar, or segmental bronchus and the pleural space. An *alveolar–pleural* fistula is a communication between the pulmonary parenchyma distal to a segmental bronchus and the pleural space. Most air leaks are due to alveolar–pleural fistulas. Bronchopleural fistulas occur almost exclusively after pneumonectomy, lobectomy, or segmentectomy and almost always require reoperation or some type of surgical intervention. Alveolar–pleural fistulas rarely require reoperation. Air leaks occurring concomitantly with spontaneous pneumothorax have been discussed earlier in this chapter. In this section, the problem of air leaks in patients on mechanical ventilation and in patients after pulmonary surgery is discussed.

Classification of Air Leaks

When a patient is seen with an air leak, it is important to semiquantitate the amount of leak. Cerfolio (346) has developed the following classification that is quite useful. In his classification, there are four types of air leaks. The largest and the most uncommon is the continuous (C) leak that is present throughout the entire respiratory cycle. There is continuous bubbling in the air leak chamber as the patient breathes in and out. These types of leaks are rare and are usually seen only in the patient who is using a ventilator or who has a bronchopleural fistula (346). The second largest type of air leak, which is also uncommon, is an inspiratory (I) air leak. These leaks are present only during inspiration. They are seen almost exclusively in the patient who is using a ventilator and has a sizable alveolar–pleural fistula or a small bronchopleural fistula. The third largest type of air leak, which is very common, is an expiratory (E) air leak. An E leak is present only during expiration. This type of leak is commonly seen after pulmonary surgery and its presence suggests an alveolar–pleural fistula. The smallest type of air leak is the forced expiratory (FE) leak that is present only when the patient performs a forced expiration or coughs. As leaks begin to resolve or heal, they usually go from an E leak to an FE leak.

A new method of quantitating air leaks was reported by Anegg et al. (347) who used a device (AIRFIX) that would provide digital readouts of the leak per breath and per minute. They reported that if the leakage volume was less than 1 mL/breath or 20 mL/minute, the chest tube could be removed with no recurrence of the pneumothorax (347). If these results can be confirmed, use of this device could certainly diminish the time that chest tubes remain in place postoperatively. This paper suggests that the air leak need not be zero before the tube is removed.

Air Leaks and Mechanical Ventilation

The management of a patient on mechanical ventilation with a large air leak is frequently difficult. In general, hypoxia rather than hypercapnia is the main threat to the patient because the air that exits through the chest tube has a carbon dioxide level comparable to that in mixed expired air (348). In other words, the air that exits through the chest tube is effective in removing carbon dioxide from the patient. Indeed, Prezant et al. (349) reported on a patient whose total ventilatory requirements could be maintained through a chronic large air leak. At times, however, when a high percentage of the minute ventilation exits through the chest tube, the patient's oxygenation may suffer (350).

The first question that must be addressed when dealing with a patient with an air leak who is receiving mechanical ventilation is the management of the chest tubes. How much suction? How many chest tubes? It appears that the level of flow through the fistula is decreased when the side with the air leak is placed in the dependent position (351). The number and size of the chest tubes should be sufficient to effect a complete expansion of the underlying lung. The amount of suction should probably be established on an individual basis. Powner et al. (352) have shown that the level of suction at which the air leak is minimized varies from patient to patient. In some patients, the flow is minimized at no suction, whereas in others, it is minimized at an intermediate level (10 to 15 cm H_2O), and in still others, it is minimized with high suction (25 cm H_2O).

One approach to decreasing the flow through a bronchopleural fistula is to place the patient on a high-frequency jet ventilator. Although high-frequency ventilation appears to decrease the flow through the fistula and improve gas exchange in the experimental model (353), it is not recommended because it has not been demonstrated to be effective in patients. Two separate studies in adults (354,355) demonstrated no benefits of high-frequency ventilation as compared with conventional mechanical ventilation with respect to the size of the air leak or gas exchange. In infants, Gonzalez et al. (356) applied conventional ventilation at a rate of 60/minute and high-frequency jet ventilation with a rate of 420/minute to six infants with continuously bubbling chest tubes. They recommended that jet ventilation be used in such instances because the mean flow through the air leak dropped from 227 to 104 mL/minute as the infants were switched to the jet ventilator. However, the Pao_2 dropped from 49 to 44 mm Hg when the patients were switched to the jet ventilator. Therefore, it is difficult to agree with their recommendation.

Multiple agents and devices, including silver nitrate, Gelfoam, cyanoacrylate-based agents, and fibrin agents, have been passed through a bronchoscope in attempts to stop the air leak (357,358). A recent review summarizes the results with the various agents (358). The cyanoacrylate agents have been recently improved with an additive that slows drying time to permit greater time for modeling of the agent into the fistula site and show the most promise (357). There are, however, no sizable series on the use of any of these agents in the treatment of air leaks in patients on mechanical ventilation (359).

Different agents such as tetracycline derivatives, talc, and fibrin glue have also been injected into the pleural space in an attempt to treat the air leak (359). The most promising agent is dilute fibrin glue. Kinoshita et al. (116) injected fibrin glue into the pleural spaces of five patients with persistent air leaks receiving mechanical ventilation. They reported that the air leaks closed within 12 hours in 4 of the 5 patients (116).

Postoperative Bronchopleural and Alveolar–Pleural Fistulas

After pulmonary resections of lesser magnitude than a pneumonectomy, there is frequently an air leak from the residual raw parenchymal surface. If the lung has expanded and the pleural space is obliterated, the leak usually stops in 2 or 3 days. The persistence of a leak beyond 7 days is considered abnormal and generally used to define a "prolonged" air leak (360). In one study (361) of 24,113 patients undergoing pulmonary resection in France, the incidence of prolonged air leak was 6.9%. Patients who have a prolonged air leak and are otherwise ready for discharge can be discharged with a Heimlich valve in place (362).

Procedures during surgery can reduce the incidence and duration of air leaks. The administration of fibrin glue or synthetic sealants at the end of lung surgery appears to reduce the incidence and duration of the postoperative air leak. Fabian et al. (363) randomized 100 patients to receive 5 mL fibrin glue sprayed over the lung or nothing. In the patients that received fibrin glue, the incidence of air leak was significantly less (34% vs. 68%), the mean time to chest tube removal was decreased (3.5 vs. 5.0 days)

and the incidence of prolonged air leak was reduced (2% vs. 16%) (363). Wain et al. (364) demonstrated that the application of a synthetic sealant at the end of the surgical procedure in 189 patients decreased the incidence of air leaks from 49% to 11% and decreased the mean time to the last observable air leak from 52.3 to 30.9 hours.

The management of the chest tubes postoperatively also influences the duration of air leaks. Cerfolio et al. (365) demonstrated that when chest tubes were managed with water seal the air leak stopped sooner than when they were managed with suction. However, in a larger study Brunelli et al. (366) were unable to confirm these findings. Patients who had large air leaks on the first postoperative day were more likely to have prolonged air leaks (365). In a meta-analysis of six studies, Deng et al. (367) found that there was no significant difference in the duration of air leaks or the incidence of prolonged pneumothorax for patients who received suction or no suction although the trends favored no suction. Interestingly Waller et al. (368) demonstrated that flutter valves were more effective than water-seal systems for the management of postoperative air leaks (368). Prolonged air leaks are a very frequent problem after lung volume reduction surgery. In one study, prolonged air leaks occurred in 35 of 197 patients (17.8%) undergoing lung volume reduction surgery, but only three leaks persisted after 14 days (366). Shackcloth et al. (369) randomized 20 patients with prolonged air leaks after lobectomy to receive 120 ml autologous blood intrapleurally or nothing and reported that the treatment group had a significantly shorter hospital stay and duration of chest tube drainage. In general, this treatment results in cessation of the air leak in >70% of patients within 24 hours (369,370). Since this is such a simple procedure, it should be tried first in patients with prolonged air leaks.

A bronchopleural fistula is observed in approximately 4% of patients after a pneumonectomy and less frequently after lobectomy, segmentectomy, or lesser procedure (360). In patients with lung cancer, significant risk factors for the development of a bronchopleural fistula include residual carcinomatous tissue at the bronchial stump, preoperative irradiation, and diabetes mellitus (371). A bronchopleural fistula is more common after resections for inflammatory disease of the lung, especially in patients with active tuberculosis and positive sputum cultures (360).

After pulmonary surgery, a bronchopleural fistula may develop immediately or weeks to months later. The early appearance of a fistula (e.g., 1–6 days) is frequently due to a technically poor closure of the bronchial stump. After a pneumonectomy, the early fistula is massive and persistent. The patient frequently develops massive subcutaneous emphysema and may exhibit varying degrees of respiratory insufficiency (360).

When the bronchial leak occurs later in the postoperative course (e.g., 7–10 days), it may be caused by failure of healing because of inadequate viable tissue coverage of the stump, or as the result of infection of the fluid within the space and rupture of the empyema through the suture line of the bronchial stump. At this stage, the patient coughs up variable quantities of serosanguineous, frothy fluid from the respiratory tract. The patient should be placed with the affected side down to decrease the danger of flooding the remaining lung.

When a bronchopleural fistula occurs more than 2 weeks after pneumonectomy, it is usually due to rupture of a frank empyema through the bronchial stump, although, at times, it may be due to failure of healing of the bronchial stump (360). The patient appears chronically ill with a cough and fever. Thoracentesis reveals that the pleural fluid is infected.

The management of a postoperative bronchopleural fistula depends on the time of its development and its underlying cause. If the bronchopleural fistula occurs early in the postoperative period, it can sometimes be managed with reoperation and repair of the bronchial stump. If primary repair of the bronchial stump is attempted, it is imperative that the new bronchial suture line be covered. This can be done with a transposed muscle flap (372), the pericardial fat pad, or an omental pedicle flap (360). With direct closure, the bronchial stump should be shortened as much as possible (373).

If primary repair of the bronchopleural fistula is not attempted or is unsuccessful, the patient should be treated with a chest tube. Several studies have reported on the implantation of different materials in the bronchus through a bronchoscope in an attempt to close the air leak. When the patient has undergone less than a pneumonectomy, a Fogarty balloon catheter is passed down the working channel of the bronchoscope, and systematic occlusion of all lung segments on the side of the air leak is undertaken. The segment or segments leading to the fistula can be noted by observing decreases or disappearance of the air leak (374). Materials placed in the appropriate bronchus to close the fistula have included Gelfoam (374), doxycycline and blood (375), fibrin glue (376,377), vascular occlusion coils (378), self-expandable stents (379), and endobronchial one-way valves (380). Fibrin glue appears to be the most promising material. Hollaus et al. (377) applied

fibrin glue to 45 patients with bronchopleural fistula after pneumonectomy (40 patients) or lobectomy (5 patients). They reported that 9 of 29 patients who were treated only endoscopically were cured. Small fistulas (<3 mm) were particularly likely to respond. The ultimate place of this approach in the management of patients with a postoperative bronchopleural fistula remains to be determined.

Bronchopleural fistulas that occur late after surgery are almost always associated with empyema. Such fistulas are discussed in Chapter 12 in the section on postpneumonectomy empyema.

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chapter 25

Hemothorax

Hemothorax is the presence of a significant amount of blood in the pleural space. Most hemothoraces result from penetrating or nonpenetrating chest trauma. An occasional hemothorax results from iatrogenic manipulation such as the placement of central venous catheters percutaneously by the subclavian or internal jugular route or from translumbar aortography. On rare occasions, a hemothorax results from a medical condition such as pulmonary embolism or rupture of an aortic aneurysm.

Blood may enter the pleural space from injury to the chest wall, diaphragm, lung, or mediastinum. Blood entering the pleural space coagulates rapidly. Presumably as a result of physical agitation produced by movement of the heart and the lungs, the clot may be defibrinated. Loculation occurs early in the course of hemothorax, as with empyema.

When a diagnostic thoracentesis in a medical patient reveals pleural fluid that appears to be pure blood, a hematocrit should always be obtained on the pleural fluid. Frequently, although the pleural fluid appears to be blood, the hematocrit on the pleural fluid is less than 5%. A hemothorax should be considered to be present only when the pleural fluid hematocrit is equal to or greater than 50% of the peripheral blood hematocrit. If a measured hematocrit is not available, a rough estimate of the hematocrit can be obtained by dividing the pleural fluid red blood cell (RBC) count by 100,000. For example, a pleural fluid RBC count of 1,000,000 equates with a pleural fluid hematocrit of 10%.

TRAUMATIC HEMOTHORAX

Traumatic hemothoraces are a frequent occurrence, particularly in centers that treat victims of trauma. In one Houston hospital, more than 300 patients with hemothorax due to penetrating trauma were seen in a 1-year period (1). The relative incidence of hemothorax due to penetrating and blunt thoracic trauma depends on whether the medical center cares primarily for victims of automobile accidents or of stab and gunshot wounds.

There is a high incidence of hemothorax with blunt trauma. In a retrospective analysis of 515 cases of blunt chest trauma, 193 patients (37%) had hemothoraces (2). In patients with rib fractures, hemothorax is more common if the fracture is displaced (3). Pneumothorax occurring concomitantly with hemothorax is common whether the trauma is blunt or penetrating (Fig. 25.1).

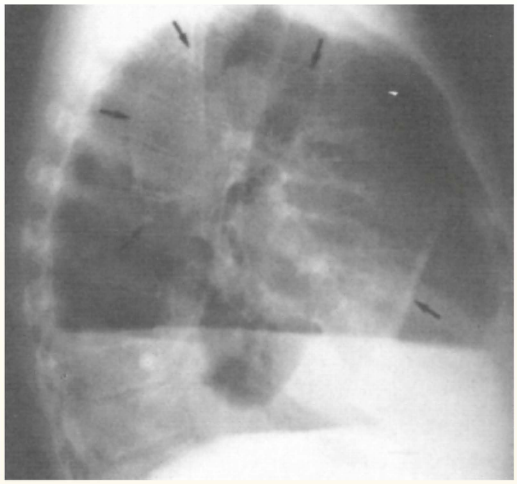

FIGURE 25.1 ■ Traumatic hemopneumothorax. Lateral chest radiograph, obtained from a patient shortly after he was stabbed in the chest, that shows a pleural effusion and a pneumothorax. The pleural line (*arrows*) is easily seen outlining the lung. *(Courtesy of Dr. Harry Sassoon.)*

In a series of 114 patients with hemothorax secondary to blunt trauma, 71 (62%) also had pneumothorax (4). In another series of 373 patients with hemothorax secondary to penetrating trauma, 307 (83%) also had pneumothorax (1).

Diagnosis

The diagnosis of a traumatic hemothorax should be suspected in any patient with penetrating or nonpenetrating trauma to the chest. The diagnosis is usually established by the demonstration of a pleural effusion with a chest radiograph or with ultrasound. As an initial screening test, surgeon-performed ultrasonography appears to be as sensitive as a supine chest radiograph in detecting hemothorax. In one study of 360 patients, 39 of 40 effusions were detected by ultrasound and 37 were detected by chest radiograph. The performance time for ultrasonography was significantly faster than that for chest radiography (1.3 vs. 14.2 minutes) (5). In some patients, a hemothorax becomes apparent only after some delay. In one series of 167 hemothoraces from Toronto due to blunt trauma, the initial chest radiograph revealed no hemothorax in 7 patients, but a hemothorax was subsequently diagnosed 22 hours to 16 days later in these 7 (4.2%) (6). All seven patients had multiple rib fractures, which were displaced in five (6).

A case can be made for obtaining chest computed tomography (CT) scans in all patients with severe chest injuries. Trupka et al. (7) obtained supine chest radiographs and chest CT scans in 103 patients with severe chest injuries and reported that the chest radiograph missed hemothoraces in 21 patients, lung contusion in 33 patients, and pneumothorax in 27 patients. In a second study of 93 patients with blunt trauma to the chest, 25 had normal supine chest radiographs and the chest CT scan showed multiple injuries in 13 patients including two aortic lacerations, three hemothoraces, and one pericardial effusion (8).

Treatment

The treatment of choice for patients with traumatic hemothorax is the immediate insertion of a chest tube. Obviously, if there is only a very small hemothorax, tube thoracostomy is not necessary. An occult hemothorax is one that is seen on CT scan but not apparent on the supine chest radiograph. Tube thoracostomy is not necessary for most patients with occult hemothorax (9). In one study, tube thoracostomy was performed if either diaphragmatic dome was obscured or if the fluid was more than 2 cm in thickness on the lateral decubitus radiograph (10). Most patients need tube thoracostomy for a relatively short period. In one study of 1,845 patients from South Africa, chest tubes were checked every 6 hours and were removed when there was no air leak and there was less than 50 mL drainage in the previous 6 hours (10). With this protocol, the average drainage time was 27.1 hours and 82% of the patients were discharged in less than 48 hours (10). Chest tubes should be removed as soon as they stop draining or cease to function because they can serve as conduits for pleural infection.

In the past, it was believed by some that the insertion of a chest tube would decrease pleural pressure and would thereby augment the pleural bleeding. If the bleeding originates from lacerated pleura, however, apposition of the pleural surfaces will produce a tamponade and will stop the bleeding (11). If the bleeding is from larger vessels, the slight decrease in the pleural pressure with a chest tube is insignificant in comparison to the transvascular pressure (11). The advantages of the immediate institution of tube thoracostomy are as follows: (a) it allows more complete evacuation of the blood from the pleural space; (b) it stops the bleeding if the bleeding is from pleural lacerations; (c) it allows one to quantitate easily the amount of continued bleeding; (d) it may decrease the incidence of subsequent empyema because blood is a good culture medium (12); (e) the blood drained from the pleural space may be autotransfused (1); and (f) the rapid evacuation of pleural blood decreases the incidence of subsequent fibrothorax (13).

Large-bore chest tubes (size 24 to 36 F) should be inserted in patients with hemothorax because the blood frequently clots (14). Beall et al. (12) recommend inserting the chest tube high (fourth or fifth intercostal space) in the midaxillary line because the diaphragm may be elevated by the trauma. Immediate thoracotomy or thoracoscopy is indicated for suspected cardiac tamponade, vascular injury, pleural contamination, debridement of devitalized tissue, sucking chest wounds, or major bronchial air leaks (15). Vascular injury is suggested if the initial chest tube output is more than 1,500 mL.

Continued pleural hemorrhage is another indication for immediate thoracotomy or video-assisted thoracic surgery (VATS). There is no precise criterion for the amount of pleural bleeding that should serve as an indication for surgery, because each case must be considered individually (11); however, if the

bleeding is at a rate of more than 200 mL/hour and shows no signs of slowing, thoracotomy or VATS should be seriously considered. Approximately 10% to 20% of patients with hemothorax require thoracotomy or VATS (1,3,4,10,12).

One must ensure that the bleeding is not from a misplaced central venous catheter (16,17). Mattox and Fisher (16) reported seven patients with a traumatic hemothorax in whom continued bleeding originated from a misplaced central venous catheter. This diagnosis is readily established by examining the appearance of the pleural drainage when the character of the infusion fluid is changed. If blood is obtained when fluid is withdrawn from the central catheter, the catheter may still be misplaced in the pleural space (18).

VATS is replacing thoracotomy in some patients with traumatic hemothorax who otherwise would have been subjected to thoracotomy. Thoracotomy rather than VATS should be performed if there is exsanguinating hemorrhage through the chest tubes (19,20). However, in the hemodynamically stable patient with persistent bleeding VATS is very effective (21). Villavicencio et al. (22) in a literature review found that VATS was effective in controlling the bleeding in 33 of 40 (82%) such cases. VATS was effective in controlling the bleeding when the bleeding arose from intercostal vessels and lung lacerations. Manlulu et al. (20) reported that VATS was the definitive procedure in all 19 patients in a single institution on whom it was attempted. Indications for VATS in this study included continued hemorrhage in six, retained hemothorax in six, and suspected diaphragmatic injury in three (20).

An alternative approach to the patient with persistent bleeding is to perform a contrast-enhanced CT scan and then perform transcatheter arterial embolization in patients who exhibit contrast extravasation. Hagiwara et al. (23) used this approach in 6 patients who were draining >200 ml/hour from their chest tube and reported that 5 had contrast extravasation and the bleeding was controlled in all five via transcatheter arterial embolization.

The efficacy of prophylactic antibiotics for the prevention of empyema in patients with tube thoracostomy for hemothorax is unclear. In an early study, Brunner et al. (24) randomly allowed 90 such patients to receive cefazolin or nothing immediately before and then every 6 hours until tube removal. They reported that there were six empyemas and three pneumonias in the control group, but only one pneumonia and no empyema in the group that received the antibiotic (24). However, in a more recent study, Maxwell et al. (25), in a randomized, double-blind study, gave cefazolin for 24 hours, for the duration of tube thoracostomy or placebo to 224 patients. The use of antibiotics did not significantly affect the incidence of empyema or pneumonia (25). However, only 1.3% of the patients who received antibiotics developed empyema while 5.6% of the patients receiving no antibiotics developed empyema. A longer duration of tube thoracostomy and a higher thoracic trauma score were associated with a higher incidence of empyema (25).

It appears that prehospital autotransfusion has a role in the management of life-threatening hemothorax. Barriot et al. (26) developed a system by which autotransfusions could be administered in ambulances. The system consists of a 28-to-30 F plastic chest tube and an autotransfusion device. The latter is basically a 750-mL bag with filters. The blood drains by gravity into the collection bag and is then reinfused without anticoagulation into a central line. They reported the use of their system on 18 patients in Paris with life-threatening traumatic hemothorax. During transfer to the hospital, the patients received 4.1 ± 0.6 L of autotransfused blood, without anticoagulation. Thirteen of the 18 patients (72%) survived, and there were no complications. They believed that the 13 patients would have died had it not been for the autotransfusions.

Complications of Hemothorax

The four main pleural complications of traumatic hemothorax are the retention of clotted blood in the pleural space, pleural infection, pleural effusion, and fibrothorax.

Retention of Clotted Blood

Although most traumatic hemothoraces are managed nonoperatively by tube thoracostomy, some of these blood collections remain only partially drained. The residual blood, already potentially contaminated by the insertion of the chest tube, may be the nidus for significant complications such as empyema or fibrothorax. Surgical evacuation of retained hemothoraces decreases this risk (27). In one study from California, 20 of 703 patients (3%) treated with tube thoracostomy for hemothorax were found to have retention of clotted blood (27). The chest radiograph may be misleading in patients with hemothorax who are suspected of having retention of clotted blood. Velmahos et al. (27) obtained chest CT scans on 58 consecutive

patients with hemothorax who had opacification extending above the costophrenic angle on standard chest radiograph 1 day after tube thoracostomy for hemothorax. They found that the prediction of fluid from the chest radiograph was correct in less than 50% of cases by both the chest surgeon and the radiologist (27). This study suggests that a CT scan should be obtained before an operative procedure is undertaken to remove the clotted blood.

When a patient is identified as having retention of clotted blood in the pleural space, three questions need to be asked: (a) Does the clot need to be removed? (b) If so, when should it be removed? (c) How should it be removed? If the residual clot occupies at least one third of the involved hemithorax 48 to 72 hours or more after the initial tube thoracostomy, it should probably be removed (28,29). The clot is most easily disrupted and removed by thoracoscopy 48 to 72 hours after the initial injury. After 7 to 9 days, the clot adheres to the lung and pleura, making thoracoscopic removal difficult or impossible and increasing the incidence of complications, such as retained collections, persistent pleural drainage, or air leaks (28). Therefore, the optimal time to remove the clotted blood appears to be between 48 and 96 hours (29).

The optimal method for removal of the clotted blood appears to be VATS (22,28,29). Villavicencio et al. (22) reviewed eight reports with a total of 99 patients who were subjected to VATS for retained hemothoraces. Evacuation of the retained hemothorax was successful in 89 (90%) of the cases. An alternative approach to the patient with a retained hemothorax is to insert a second chest tube. A randomized study in which 24 patients received a second chest tube and 15 patients underwent VATS demonstrated that hospitalizations were significantly shorter (5.4 vs. 8.1 days) and the hospital costs were significantly less in the group that received VATS (30). Of the 24 patients who received a second chest tube, 10 (42%) eventually required thoracoscopy or thoracotomy (30).

Some authors have recommended the intrapleural injection of fibrinolytic agents for the treatment of retained hemothorax (31). Inci et al. (31) treated 24 patients with either 250,000 IU streptokinase or 100,000 IU urokinase, and each patient received a mean of five doses. Although complete response was demonstrated in 62.5% of the patients, this treatment is not recommended because it is more expensive than thoracoscopy owing to the expense of the fibrinolytic agents and the longer hospitalizations (31,32). In addition, there has been one case in which hypoxemic respiratory failure developed after the intrapleural administration of fibrinolytics (33). Nevertheless, if VATS is not readily available, consideration can be given to intrapleural fibrinolytics or thoracotomy.

Posttraumatic Empyema

The second complication following hemothorax is empyema, occurring in 3% to 4% of cases (34). This complication can be minimized by using meticulously sterile technique while inserting thoracostomy tubes and by ensuring good apposition of the pleural surfaces so that no space remains for the accumulation of fluid or blood. The risk of empyema increases with the presence of persistent bronchopleural fistula, pulmonary contusions, and residual clotted hemothoraces. As mentioned in the preceding text, the administration of antibiotics to patients with hemothorax who are treated with tube thoracostomy significantly reduces the subsequent development of empyema and possibly pneumonia (24). Patients who are admitted in shock are more likely to develop empyema, as are those with gross contamination of the pleural space at the time of the original injury. Empyema is also more common with associated abdominal injuries (13) and with prolonged pleural drainage (14). At times, the pathogenesis of the empyema is rupture of a pulmonary abscess (35). The treatment of empyema complicating hemothorax is similar to that of any bacterial infection of the pleural space (see Chapter 12).

Pleural Effusion

The third complication of hemothorax is the occurrence of a pleural effusion when the chest tubes are removed. In the series reported by Wilson et al. (15), 37 of 290 patients (13%) with no residual hemothorax developed pleural effusions after removal of the chest tubes, and 40 of 118 patients (34%) with residual hemothorax had pleural effusions at the time of discharge from the hospital. Of these 77 patients with a pleural effusion after tube thoracostomy, 20 (26%) had empyema, but the pleural effusions resolved in the other 57, leaving no or minimum residual disease (15). This series indicates that pleural effusions are common after tube thoracostomy for hemothorax. When such effusions occur, a diagnostic thoracentesis should be performed to rule out the possibility of a pleural infection. If no pleural infection is present, the pleural effusion usually clears by itself and leaves no residual disease.

Fibrothorax

The fourth complication of hemothorax is the development of diffuse pleural thickening producing a fibrothorax weeks to months after the hemothorax. This complication occurs in less than 1% of patients, even if residual blood is not removed by exploratory thoracotomy (15). Fibrothorax appears to be more common with hemopneumothorax or when pleural infection is present in addition to the hemothorax. The definitive treatment for fibrothorax is decortication of the lung (see Chapter 27). Decortication should be postponed for several months following the injury in most cases because the pleural thickening frequently diminishes with time.

IATROGENIC HEMOTHORAX

When a hemothorax is discovered, the possibility of iatrogenic origin should be considered. The most common causes of iatrogenic hemothorax are the perforation of a central vein by a percutaneously inserted catheter (16,17,36) or leakage from the aorta after translumbar aortographic study (37). Iatrogenic hemothorax can also follow thoracentesis or pleural biopsy. Insertion of a Swan-Ganz catheter is occasionally associated with rupture of the pulmonary artery with a resulting hemothorax, and, in such instances, an immediate thoracotomy is necessary if the patient is going to survive (38). Iatrogenic hemothoraces have also been reported after many other procedures, including percutaneous lung aspiration or biopsy, transbronchial biopsy, and sclerotherapy for esophageal varices (39). In the intensive care unit, hemothorax is more common in patients after invasive procedures if they have chronic renal failure (40). Patients with iatrogenic hemothorax should be managed with chest tubes for the same reasons as are patients with traumatic hemothorax.

NONTRAUMATIC HEMOTHORAX

Nontraumatic hemothoraces are distinctly uncommon. The most common cause, not associated with pneumothorax, is metastatic malignant pleural disease (41). The most common tumors are schwanommas of von Recklinghausen disease and soft tissue tumors such as sarcomas, angiosarcomas, and hepatocellular carcinomas. The second most common cause is a complication of anticoagulant therapy for pulmonary emboli (42), and the third leading cause is probably catamenial hemothorax (43). Other causes of spontaneous hemothorax include a complication of a bleeding disorder such as hemophilia or thrombocytopenia (44), a complication of spontaneous pneumothorax (see the discussion on spontaneous hemopneumothorax later in this chapter), ruptured thoracic aorta, pancreatic pseudocyst (45), rupture of a patent ductus arteriosus (46), rupture of a coarctation of the aorta (46), rupture of a splenic artery aneurysm through the diaphragm (47), rupture of a pulmonary arteriovenous fistula (48), hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber syndrome) (49), intrathoracic extramedullary hematopoiesis (50), chickenpox pneumonia (51), osteochondroma of the rib (52), and bronchopulmonary sequestration (53). In some patients, the cause of the hemothorax remains unknown despite exploratory thoracotomy (44,49).

Diagnosis and Treatment

When bloody-appearing pleural fluid is obtained during a diagnostic thoracentesis, the hematocrit of the pleural fluid should be determined. If the hematocrit of the pleural fluid is greater than 50% that of the peripheral blood, the patient has a hemothorax. Regardless of how bloody the pleural fluid looks, a hematocrit should be obtained because pleural fluid with a hematocrit of less than 5% may appear to be blood. If a hematocrit is not available, a pleural fluid RBC count that is more than 50% of the peripheral RBC count indicates that the patient has a hemothorax. A chest tube should be inserted into patients with a spontaneous hemothorax to evacuate the blood and to assess the rate of continued bleeding. Thoracotomy or VATS should be considered if brisk bleeding (>100 mL/hour) persists. If the bleeding is from an intercostal artery, it may be controlled with selective angiographic embolization (54).

Hemothorax Complicating Anticoagulant Therapy

Twenty cases of hemothorax complicating anticoagulant therapy had been reported by 2008. (55). The anticoagulation was for pulmonary embolism in 18 or the 20 cases (55). Usually, the hemothorax becomes apparent 4 to 7 days after anticoagulant therapy is initiated, but it may occur only after several months (55). Most of the patients were receiving heparin and warfarin and the coagulation parameters were supratherapeutic in six (55). Hemothoraces have also been observed with enoxaparin therapy (56) and systemic therapy with thrombolytics (57). The spontaneous hemothorax is almost always on the side of the original

pulmonary embolus (58). The treatment for spontaneous hemothorax complicating anticoagulant therapy is immediate discontinuation of the anticoagulant therapy and insertion of chest tubes in an attempt to remove all the blood in the pleural space (58).

Catamenial Hemothorax

Catamenial hemothorax is a hemothorax that occurs in conjunction with menstruation and it is unusual. By 1993, there had only been 16 cases reported (43). Most patients with catamenial hemothorax have associated pelvic and abdominal endometriosis. The right hemithorax is almost always involved, and diaphragmatic fenestrations with communication of pleural and peritoneal spaces have been documented in some of the patients. Most patients with catamenial hemothorax have endometriosis of the pleura upon close examination of the pleura. Catamenial hemothorax can be treated by suppressing ovulation using oral contraceptives or progesterone or suppression of gonadotropins using danazol or gonadotropin-releasing hormone (59). However, hormonal therapy frequently fails. In such instances, chemical pleurodesis can be performed, and if this measure fails, total hysterectomy with bilateral oophorectomy can be done (43).

Spontaneous Hemopneumothorax

Probably the most common nontraumatic hemothorax is the spontaneous hemopneumothorax. Hwong et al. (60) reviewed 793 patients admitted to their hospital for spontaneous pneumothorax and found that 30 (3.8%) had spontaneous hemopneumothorax. Wu et al. (61) reviewed 363 patients with spontaneous pneumothorax and reported that 24 (6.6%) had spontaneous hemopneumothorax. The extent of bleeding can be significant as attested by the fact that 15 of the 54 patients (28%) in the two studies mentioned in the preceding text were hypotensive (60,61). Most of the patients in these two series had a primary spontaneous pneumothorax, as the mean age was 25 years.

When a patient is found to have a spontaneous hemopneumothorax, surgery should be performed if the bleeding persists at a rate of more than 100 mL/hour or if the patient is hypotensive (62). It appears that most patients can be managed with VATS (60,61). VATS was performed in 49 of the 54 patients in the two series. In each case, it was the definitive procedure. A source of the bleeding was found in most patients and included aberrant vessels, torn parietal pleura, torn vascular adhesion band from the parietal pleura, and vascular blebs.

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chapter 26

Chylothorax and Pseudochylothorax

At times, pleural fluid is milky or at least turbid. When the milkiness or turbidity persists after centrifugation, it is almost always due to a high lipid content of the pleural fluid. High levels of lipid accumulate in the pleural fluid in two situations. First, when the thoracic duct is disrupted, chyle can enter the pleural space to produce a chylous pleural effusion. In this situation, the patient is said to have a chylothorax (1). Second, in long-standing pleural effusions, large amounts of cholesterol or lecithin–globulin complexes can accumulate in the pleural fluid to produce a chyliform pleural effusion. The patient is then said to have a pseudochylothorax. It is important to differentiate these two conditions because their prognosis and management are completely different.

CHYLOTHORAX

A chylothorax is formed when the thoracic duct is disrupted and chyle enters the pleural space.

Pathophysiologic Features

Dietary fats in the form of long-chain triglycerides are transformed into chylomicra and very-low-density lipoproteins. These are secreted into the intestinal lacteals and lymphatics and are then conveyed to the cisterna chyli, which overlies the anterior surface of the second lumbar vertebra, posterior to and to the right of the aorta. Usually, one major lymphatic vessel, the thoracic duct, leaves the cisterna chyli and passes through the esophageal hiatus of the diaphragm into the thoracic cavity. The thoracic duct ascends extrapleurally in the posterior mediastinum along the right side of the anterior surface of the vertebral column and lies between the azygos vein and the descending aorta in close proximity to the esophagus and the pericardium. At the level of the fourth to sixth thoracic vertebrae, the duct crosses to the left of the vertebral column and continues cephalad to enter the superior mediastinum between the aortic arch and the subclavian artery and the left side of the esophagus.

Once the thoracic duct passes the thoracic inlet, it arches 3 to 5 cm above the clavicle and passes anterior to the subclavian artery, vertebral artery, and thyrocervical trunk to terminate in the region of the left jugular and subclavian veins. Wide anatomic variations may exist in all portions of the thoracic duct. More than one thoracic duct may leave the cisterna chyli. The duct may continue on the right side of the vertebral column to enter the veins in the right subclavian region. Multiple anastomoses usually exist between various lymphatic channels, and direct lymphaticovenous communications with the azygos vein may be present (2,3).

The drainage from the thoracic duct is called *chyle*. Chyle appears grossly as a milky, opalescent fluid that usually separates into three layers upon standing: a creamy uppermost layer containing chylomicrons, a milky intermediate layer, and a dependent layer containing cellular elements, most of which are small lymphocytes (4). If the patient has not eaten, however, chyle may be only slightly turbid because its lipid content will be reduced. Chyle is bacteriostatic and does not become infected even when it stands at room temperature for several weeks (5). Lampson (5) reported that *Escherichia coli* and *Staphylococcus aureus* were unable to grow in 100% chyle. Chyle that is extravasated into the pleural cavity is not irritating and usually does not evoke the formation of a pleural peel or a fibroelastic membrane.

Each day, between 1,500 and 2,500 mL of chyle normally empties into the venous system (6). The ingestion of fat can increase the flow of lymph in the thoracic duct by 2 to 10 times the resting level for several hours (7). Ingestion of liquid also increases the chyle flow, whereas the ingestion of protein or carbohydrates has little effect on the lymph flow (7). The protein content of chyle is usually above 3 g/dL, and the electrolyte composition of chyle is similar to that of serum (7).

The primary cell in chyle is the small lymphocyte, and lymphocyte counts range from 400 to 6,800/mm^3 (4). Prolonged drainage of a chylous pleural effusion can result in profound T-lymphocyte depletion. Breaux and Marks (8) reported that the total peripheral lymphocyte count fell from 1,665 to 264/mm^3 with 14 days of chest tube drainage in one patient with a chylothorax. Almost all the lymphocytes in the pleural fluid were T lymphocytes.

A chylothorax results when the lymphatic duct becomes disrupted. Ligation of the thoracic duct at any point in its course does not produce a chylothorax in experimental animals (6), presumably as a result of the many collateral vessels and lymphaticovenous anastomoses. Ligation of the superior vena cava produces chylothorax approximately half the time in experimental animals. In the experimental animal, laceration or transection of the thoracic duct does not always produce a chylothorax. Hodges et al. (9) produced a 2.5-cm longitudinal laceration of the thoracic duct in three dogs at the level of T9 and transected the thoracic duct at this level in three other dogs. They reported that all animals developed a pleural effusion but that the effusion ceased to form after 2 to 5 days in the animals with lacerations and after 4 to 10 days in the animals with transections (9). Lymphangiograms demonstrated that there was no continuity of the thoracic duct in animals with transections and researchers concluded that lymph was being conveyed by collaterals (9).

Etiologic Factors

The causes of 143 chylothoraces from five separate earlier series (6,7,10–12) are tabulated in Table 26.1. The causes of 203 chylothoraces seen at the Mayo Clinic between January 1980 and December 2000 were as follows: surgery or trauma, 101 patients (49.8%); malignancy, 34 (16.7%); congenital or acquired lymphatic disorders, 19 (9.4%); chylous ascites, 16 (7.9%); miscellaneous medical causes, 20 (10%); and no identifiable cause, 13 (6.4%) (13).

TABLE 26.1 ■ Causes of 143 Chylothoraces from Five Separate Series

Cause		Number	Percentage
Tumor	—	76	54
Lymphoma	57	—	—
Other	19	—	—
Trauma	—	36	25
Surgical	31	—	—
Other	5	—	—
Idiopathic	—	22	15
Congenital	8	—	—
Other	14	—	—
Miscellaneous	—	9	6

The differences in the distribution of the diagnoses in this latter study compared with the former studies may be due in part to the fact that the Mayo Clinic is a tertiary referral center and that the distribution of diagnoses is changing with time.

For convenience, the causes of chylothorax can be grouped into four different categories, namely, trauma, tumor, miscellaneous, and idiopathic (14). Trauma is the leading cause of chylothorax. This trauma is usually a cardiovascular, pulmonary, or esophageal surgical procedure. Chylothorax appears particularly frequently following operations in which the left subclavian artery is mobilized (15). The incidence of chylothorax after most thoracic surgeries is less than 1.0%. The incidence of chylothorax was 0.5% in one series of 2,660 cardiovascular operations (16), whereas it was 2.4% in a series of 1,110 lobectomies and pneumonectomies with systematic mediastinal lymph node dissection (17). The incidence of chylothorax is relatively high in children undergoing cardiothoracic surgery. In one series of 1,257 surgeries, there were 48 cases of chylothorax (3.8%) (18). The incidence exceeded 10% in patients undergoing the Fontan procedure, heart transplantation, and repair of the Tetralogy of Fallot (18). The incidence of chylothorax following esophageal resection is relatively high; it was 3.8% in one series of 892 cases (19). Dougenis et al. (20) reported that the incidence of chylothorax following esophageal surgery was significantly higher when the main thoracic duct was not ligated at the time of the resection. A subsequent study (21) randomized 653 patients undergoing esophageal resection to undergo or not undergo thoracic duct ligation. They reported that the incidence of chylothorax in the treatment group (0.3%) was significantly less than in the control group (2.1%) (21).

Chylothorax has also been reported as a complication of coronary artery bypass surgery when the internal mammary artery is harvested (22), heart transplant (23), high translumbar aortography (24), sclerotherapy for esophageal varices (25), thoracolumbar fusion for correction of kyphosis (26), and cervical node dissection (27).

Of course, penetrating trauma to the chest or neck such as gunshot or knife wounds can also sever the thoracic duct and may lead to chylothorax. Trauma in which the spine is hyperextended or a vertebra is fractured is most likely to cause chylothorax, particularly if the injury occurs after the recent ingestion of a fatty meal (27). A chylothorax secondary to closed trauma is usually on the right side, and the site of rupture is most commonly in the region of the 9th or 10th thoracic vertebra (27). Such trauma includes falls from a height, motor vehicle accidents, compression injuries to the trunk, heavy blows to the back or stomach, and childbirth (28). The injury may be less impressive, and chylothoraces have been attributed to coughing, vomiting, and weight lifting. In one well-documented case report, an episode of vigorous stretching while yawning was followed by swelling in the left supraclavicular fossa and the development of bilateral chylothoraces (29).

Another leading cause of chylothorax is malignancy. The most common malignancy to cause a chylothorax is a lymphoma, and lymphomas accounted for 75% of the chylothoraces due to malignancies are listed in Table 26.1. In the series from the Mayo Clinic (13), lymphomas (20 non–Hodgkin lymphoma and 3 Hodgkin disease) accounted for 68% of the chylothoraces due to malignancy. Other malignancies producing a chylothorax in the Mayo Clinic series included chronic lymphocytic leukemia 5, metastatic disease 5, and lung cancer 1 (13). Chylothorax may be the presenting symptom of lymphoma (7,11,15). Therefore, a nontraumatic chylothorax is an indication for a diligent search for a lymphoma. In the series of Roy et al. (11) before the availability of computed tomographic (CT) scans, the diagnosis of lymphoma was not established until 6 to 12 months after the appearance of the chylothorax in four patients.

The third category of chylothorax is the miscellaneous category. Thrombosis of the superior vena cava or the subclavian vein is becoming one of the more common causes of chylothorax. Berman et al. (30) reviewed the case histories of 37 infants and children with thrombosis of their superior vena cava in a newborn and pediatric intensive care unit and reported that 9 (24%) had a chylothorax. We reviewed cases of the superior vena caval syndrome at my previous hospital over a 6-year period and found that chylothorax complicated 4 of 76 cases (31). Chylothorax can also complicate innominate vein (32) or left subclavian vein thrombosis (33). Cirrhosis is a relatively common cause of chylothorax. Romero et al. (34) analyzed 24 cases of chylothorax occurring at their institution and reported that 5 (21%) were secondary to cirrhosis. Interestingly, the mean protein level in these five chylothoraces was only 1.7 g/dL (compared with 4.1 g/dL in the other chylous effusions), the mean lactate dehydrogenase (LDH) level was only 96 IU/L (compared with 351 IU/L in the other chylous effusions) and ascites was present in three of the five patients (34). On rare occasions, a chylothorax is associated with heart failure or the nephrotic syndrome and the effusion is also a transudate in these instances (35). In most patients with the nephrotic syndrome and a chylothorax, the chylothorax is secondary to chylous ascites, but on occasions, it can be secondary to superior vena caval thrombosis (36).

Many other causes of chylothorax have been reported, but even when all are grouped together, they account for only a small percentage of chylothoraces. The most interesting of these is pulmonary lymphangioleiomyomatosis (LAM), which has associated interstitial parenchymal infiltrates, and is discussed later in this chapter. Other causes include Gorham syndrome (37) (also discussed later in this chapter), Kaposi sarcoma in patients with acquired immunodeficiency syndrome (AIDS) (38,39), the yellow nail syndrome (14), filariasis, paragonimiasis (40), giant lymph node hyperplasia (Castleman disease) (41), lymphangiomatosis (42), familial lymphedema (43), lymphangitis of the thoracic duct, obstruction of the superior vena cava secondary to Behçet syndrome (44,45), tuberculosis (46), sarcoidosis involving the intrathoracic lymph nodes (47), aneurysms of the thoracic aorta that erode the duct, abnormalities of the lymphatic vessels such as intestinal lymphangiectasis (48) or reticular hyperplasia (12,49), radiation-induced mediastinal fibrosis (50), and hypothyroidism (51).

The fourth category of chylothorax is idiopathic, including most cases of congenital chylothorax. One should exclude lymphoma as a cause of the chylothorax before it is labeled idiopathic. Most cases of idiopathic chylothorax in the adult are probably due to minor trauma, such as coughing or hiccupping, after the ingestion of fatty meals.

Chylothorax is the most common form of pleural effusion encountered in the first few days of life (52). The fetal pleural effusion discussed in Chapter 20 is probably also a chylothorax. Neonatal chylothorax is relatively uncommon; during a 22-year period, 12 cases were diagnosed at the Hospital for Sick Children, which is a large pediatric tertiary care center (53). The babies are usually born at full term after normal labor and delivery. The etiology of congenital chylothorax is unknown (54). Abnormalities of the thoracic duct have not been found in most babies who have undergone exploratory thoracotomy (52). Several cases of generalized pleural oozing have been described during surgery (53). It is possible that birth trauma may result in a tear of a major lymphatic channel in at least some individuals. Most neonatal chylothoraces represent pleural effusions that had been present antenatally. In some cases, a congenital chylothorax is associated with Turner's syndrome, Noonan's syndrome, or Down's syndrome (54). Congenital chylothorax is also more common in infants who are hydropic or who have polyhydramnios (53).

Interestingly, mice that lack the integrin $\alpha_9\beta_1$ appear normal at birth but then develop respiratory failure and die between 6 and 12 days of age (55). The respiratory failure is caused by bilateral chylothoraces. Although the thoracic duct appears normal grossly, microscopic examination reveals edema and lymphocytic infiltration in the chest wall (55). Members of the integrin family of adhesion receptors mediate both cell–cell and cell–matrix interactions and have been shown to play vital roles in embryonic development, wound healing, and other biologic processes. It has been postulated that integrin $\alpha_9\beta_1$ deficiency could be one cause of congenital chylothorax (55).

Clinical Manifestations

The initial symptoms of chylothorax are usually related to the presence of the space-occupying fluid in the thoracic cavity, and, therefore, patients have dyspnea. On rare occasions, the patient can develop a tension chylothorax with compromise of the systemic circulation (56). Pleuritic chest pain and fever are rare because chyle is not irritating to the pleural surface. With traumatic chylothorax, a latent period of 2 to 10 days usually occurs between the trauma and the onset of the pleural effusion (27). There is one case report in which the latent period was 11 weeks (57). Lymph collects extrapleurally in the mediastinum after the initial thoracic duct disruption, forms a chyloma, and produces a posterior mediastinal mass (3). The mediastinal pleura eventually ruptures, chyle gains access to the pleural space, and dyspnea is produced by the chyle compressing the lung. At times, hypotension, cyanosis, and extreme dyspnea occur when the chyloma ruptures into the pleural space. The ruptured chyloma is no longer visible radiographically.

With nontraumatic chylothorax, the onset of symptoms is usually gradual. In congenital chylothorax, the infant develops respiratory distress in the first few days of life; 50% of patients have symptoms within the first 24 hours, whereas 75% have symptoms by the end of the first week (52). The chyle production in a neonate may exceed 250 mL/day (54).

The main threat to life from chylothorax is malnutrition and a compromised immunologic status. Because the thoracic duct carries 2,500 mL of fluid daily that contains substantial amounts of protein, fats, electrolytes, and lymphocytes, the patient can become cachectic rapidly if this amount of chyle is removed daily through chest tubes or repeated thoracentesis. In addition, the patients develop lymphopenia and a compromised immunologic status because of the removal of large numbers of lymphocytes with the chyle (58). In one case report, one patient had more than 35 L of fluid withdrawn over a 14-day period that contained 2.3 kg of fat and 0.7 kg of protein. During this period, the peripheral lymphocyte count dropped from 1,665 to 264/mm^3 (8). Indeed, until Lampson initially described successful ligation of the thoracic duct in 1948 (5), the mortality rate from chylothorax was 50%. When managing a patient with chylothorax, one should abandon conservative treatment before the patient becomes too malnourished and immunocompromised.

Diagnosis

The diagnosis of chylothorax is usually not difficult because chyle typically has a distinctive white, odorless, milky appearance. When such fluid is found, the main differentiation is between chylothorax, empyema, and a pseudochylothorax. The milkiness with empyema is caused by the suspended white blood cells (WBCs) and debris, and if such fluid is centrifuged, the supernatant is clear. The cloudiness of the chyliform pleural effusion from a pseudochylothorax is also caused by high lipid levels and either cholesterol or lecithin–globulin complexes. Chylous and chyliform pleural fluids remain opaque after centrifugation.

If cholesterol crystals are responsible for the turbidity, they may be easily demonstrated by examination of the pleural fluid sediment (Fig. 26.1). If the turbidity is

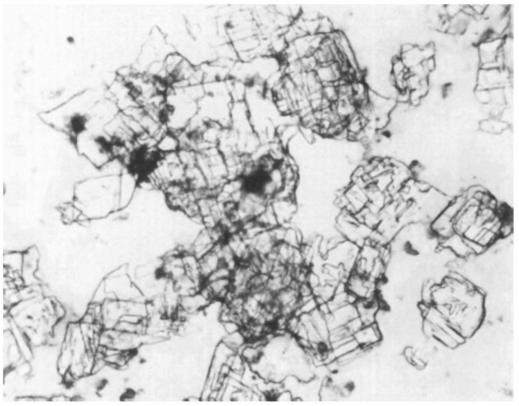

FIGURE 26.1 ■ Cholesterol crystals. Typical large polyhedric crystals from a patient with a cholesterol pleural effusion. This patient had a rheumatoid pleural effusion.

due to high levels of cholesterol, the turbidity will clear when 1 to 2 mL of ethyl ether is added to a test tube containing the fluid; if the turbidity is due to chylomicrons or lecithin complexes, the turbidity does not clear (59).

Not all chylous pleural effusions have the typical, milky appearance. With congenital chylothorax, the pleural fluid is initially serous and turns chylous only when milk feedings are started (52). Because congenital chylothorax is the most common cause of pleural effusion in the newborn (52), pleural fluid triglyceride and lipoprotein analyses should be performed in all newborns with pleural effusion. In adults, the pleural fluid does not always look like typical chyle. Maldonado et al. (60) reported that the pleural fluid appeared milky in only 44% of 74 chylothoraces, whereas Romero et al. (34) reported that 10 of 24 (42%) patients with chylothorax had nonmilky pleural fluid. In this study of 809 patients with pleural effusions, 24 (3%) had chylothorax (34). This study suggests that lipid measurements might be indicated in all patients with pleural effusions of unknown etiology in order to rule out the diagnosis of chylothorax.

The pleural fluid with chylothorax usually meets exudative criteria. However, Diaz-Guzman et al. (61) summarized the world's literature on chylothoraces that met transudative criteria. They were able to find 15 such instances and 14 were due to cirrhosis, nephrosis, or congestive heart failure.

Triglyceride Measurement

The best way to establish the diagnosis of chylothorax is by measuring the triglyceride and cholesterol levels in the pleural fluid (Fig. 7.8). If the pleural fluid triglyceride level is above 110 mg/dL and the ratio of the pleural fluid to serum cholesterol is less than 1.0, the diagnosis of chylothorax is established. The cholesterol ratio is used to exclude pseudochylothorax because some patients with chyliform pleural effusions also have triglyceride levels above 110 mg/dL, but their pleural fluid to serum cholesterol ratio will exceed 1.0 (34). Although it has been suggested that to establish the diagnosis of chylothorax the pleural fluid triglyceride level should be more than the serum triglyceride level (34), this criterion appears to be unnecessary because there is no relationship between the pleural fluid and the serum triglyceride levels in patients not having a chylothorax (62). The only other situation in which the pleural fluid triglyceride is above 110 mg/dL is when intravenous fluid containing high levels of triglycerides leaks from a central vein into the pleural space (63). One should usually be able to differentiate chylothorax and pseudochylothorax by the clinical course. A chylothorax has an acute onset with normal pleural surfaces, whereas a pseudochylothorax occurs in a patient with a long-standing pleural effusion with thickened pleura (64). If any doubt exists, the pleural fluid should be analyzed for chylomicrons by lipoprotein analysis. The demonstration of chylomicrons in the pleural fluid by lipoprotein analysis establishes the diagnosis of chylothorax (10).

Lipophilic Dye Ingestion

Another test for the diagnosis of chylothorax is ingestion of a fatty meal with a lipophilic dye, followed by a thoracentesis 30 to 60 minutes later, to ascertain whether the pleural fluid has changed in color (65). The most commonly used dye is Drug and Cosmetic Green No. 6, a coal-tar dye. One gram of this dye is mixed thoroughly with 0.25 lb of butter, and the mixture is spread on a slice of bread. The patient eats the bread, and a thoracentesis performed 30 to 60 minutes later should yield green fluid if a chylothorax is present. I have attempted this test in approximately six different patients. The greatest problem I encountered was in maintaining a straight face when I asked the patient to eat the disgusting green mess. Because the diagnosis is usually easily established with triglyceride and lipoprotein analysis, I no longer ask my patients with suspected chylothorax to eat dark green sandwiches.

Imaging of the thoracic duct

At times, one would like to demonstrate the location of the disruption of the thoracic duct. In other

patients, visualization of the thoracic duct is desired in patients with chylothorax for which there is no ready explanation. In the past, this has most commonly been done by injecting a dye in the dorsum of the feet, which is subsequently absorbed in the lymphatics. When the dye is conveyed to the chest, the thoracic duct can be visualized. However, most medical centers no longer perform lymphangiograms.

There have been two recent reports that have demonstrated that imaging of the thoracic duct can be performed by lymphoscintigraphy (66,67). With this procedure, Technetium-99m human serum albumin is injected into the dorsum of the foot or hand and subsequently the thoracic duct is imaged in nuclear medicine. There is one paper that reported the successful imaging of the thoracic duct after the oral ingestion of iodine-123-labeled 15-(4-iodophenyl)-3-(*R*,*S*)-methyl-pentadecanoic acid (I-123 BMIPP) (68). The thoracic duct can be imaged approximately 80 minutes after the ingestion of this tracer (68). The advantage of this procedure is that it does not require the difficult injections into the foot.

Treatment

The main danger to patients with chylothorax is that they become malnourished and immunocompromised because of the removal of large amounts of protein, fat, electrolytes, and lymphocytes from the body with repeated thoracentesis or chest tube drainage. In the past, the mortality rate from chylothorax approached 50%. When managing a patient with chylothorax, one must treat the chylothorax definitively, such as with thoracic duct ligation or pleuroperitoneal shunt implantation, before the patient becomes too cachectic to tolerate the operation. Because the management of chylothorax differs for traumatic, nontraumatic, and congenital chylothoraces, treatment regimens are described separately.

Traumatic Chylothorax

The general aims in treating the patient with traumatic chylothorax are relief of dyspnea by removal of the chyle, prevention of dehydration, maintenance of nutrition, and a reduction in the rate of chyle formation. When a postoperative chylothorax is discovered, tube thoracostomy should be performed to remove the chyle and relieve the dyspnea. In this situation, consideration should be given to recycling the chyle to prevent malnutrition and immunosuppression. Thomson and Simms (69) reported one case in which the chyle was reinfused directly from the chest tube into the subclavian vein for a total of 18 days. There have been no large series evaluating this procedure. In the first half of the last century, a couple of patients died from "anaphylaxis" soon after chyle infusion was started (69).

When a postoperative chylothorax is managed initially with tube thoracostomy, efforts should be made to decrease the flow of chyle through dietary manipulation. The flow of chyle is minimized if all nourishment by mouth is halted and if the patient's gastrointestinal tract is maintained as empty as possible by constant gastric suction (70). The patient's nutritional status can be maintained with intravenous hyperalimentation (71). In the past, attempts have been made to decrease the lymph flow by providing the fat calories in the diet with medium-chain triglycerides (71). These triglycerides have 10 or fewer carbon atoms and are absorbed directly into the portal vein and thereby gain entrance to the circulatory system without ever entering the thoracic duct (72). Because they are relatively unpalatable and hyperalimentation decreases the flow of chyle much more, hyperalimentation rather than medium-chain triglycerides is recommended when one wishes to reduce the flow of chyle. The flow of chyle is also decreased if the patient stays in bed because any lower extremity movement increases the flow of lymph (72). There is one report in which the flow of chyle was reduced markedly with inhaled nitrous oxide in a 41-week-old infant with a postoperative chylothorax (73). The reduction in the flow of chyle was thought to be due to alleviation of the central venous hypertension (73). One must question the efficacy of this approach as there have been no subsequent articles on this subject.

The defect in the thoracic duct frequently closes spontaneously in traumatic chylothorax. If the thoracic duct is transected in dogs, chyle ceases to enter the pleural space within 10 days as collateral lymphatic channels are formed (9). In one series of 22 children with postoperative chylothorax, 19 (86.4%) closed spontaneously when the patients were treated concomitantly with total parenteral nutrition or low-fat enteral diets (74). The average duration of drainage of these 19 patients was 13.7 days, with a range of 7 to 30 days (74). In another series of 47 adults with postoperative chylothorax from the Mayo Clinic (75), the leak closed spontaneously in 7 of 36 patients (19%) who received central hyperalimentation and in 6 of 11 patients (55%) who were treated with medium-chain triglyceride diets (75).

Chylothoraces that occur after pulmonary resections are usually small and resolve with medical

therapy (76). In one series, 20 of 26 cases resolved with only medical therapy (76). The probable explanation for these excellent results is that the injury is usually to a tributary of the thoracic duct and not to the thoracic duct itself (17,76).

If large amounts of chyle continue to drain for more than several days postoperatively, a procedure should be performed to treat the chylothorax definitively. The alternatives at this juncture are (a) to administer somatostatin or its analogue octreotide, (b) to insert a pleuroperitoneal shunt, (c) to percutaneously embolize the thoracic duct using a transabdominal approach, (d) to attempt to create a pleurodesis to obliterate the pleural space through tube thoracostomy, (e) to perform thoracoscopy with pleural abrasion or partial pleurectomy to create a pleurodesis, (f) to perform thoracoscopy with attempted ligation of the thoracic duct, or (g) to perform a thoracotomy with ligation of the thoracic duct.

Somatostatin (Octreotide)

In the last decade, there have been numerous reports on treating chylothoraces with somatostatin or octreotide. These agents have been used for congenital chylothoraces (77,78), postoperative chylothoraces in both children (79–85) and adults (86–88), spontaneous chylothoraces (88), chylothorax due to the yellow nail syndrome (89), or non–Hodgkin lymphoma (90).

Octreotide is a somatostatin analog and offers the advantage of subcutaneous administration whereas somatostatin requires continuous intravenous infusion (91). The mechanism of action of octreotide is unknown. Its administration decreases lymphatic flow and triglyceride absorption in dogs (92) presumably by decreasing the blood flow in the splanchnic circulation and by decreasing gastrointestinal motility (91). Alternatively, the lymphatic vessels may have somatostatin receptors and their stimulation could result in decreased lymphatic flow (84). The primary side effects are related to suppressive actions of gastrointestinal motility and secretion and include loose stools, malabsorption, nausea, and flatulence. The usual starting dose of somatostatin is 3.5 μg/kg/hour, which can be increased to 10 μg/kg/hour. The usual dose for octreotide in the adult is 50 mg q 8 hours (91). The usual dose for octreotide in children has ranged from 0.3 to 1.0 μg/kg/hour (77,81).

The actual efficacy of somatostatin or octreotide in the management of chylothorax is difficult to evaluate. There are no controlled studies comparing the efficacy of octreotide with anything. Most cited reports are of one or two cases. Sometimes the results are impressive as the chyle seems to cease entering the chest soon after the medication is started. In other cases, the chylothorax resolves but the relationship between the administration of the drug and the resolution of the chylothorax is unclear. Some patients do not respond at all (18,88,93). Until better data are available, it seems prudent to use octreotide in persistent chylothoraces before proceeding to more invasive procedures (91). If there is no large decrease in the lymphatic flow within a few days, then one should proceed to a more invasive procedure.

The side effects of octreotide are usually mild and transient. The most serious side effect was necrotizing enterocolitis in an infant treated with intravenous octreotide for postoperative chylothorax (94). One case of hypothyroidism was attributed to somatostatin administration (95).

Pleuroperitoneal Shunt

A good method to remove the chyle and alleviate the dyspnea with chylothorax appears to be the insertion of a pleuroperitoneal shunt (96–98) (see the discussion on pleuroperitoneal shunt in Chapter 10). The primary advantage of the pleuroperitoneal shunt is that the lymph is not removed from the body, and, therefore, the patient does not become malnourished or immunocompromised. When the chyle is shunted to the peritoneal cavity, it is absorbed without creating significant ascites (96). A second advantage is that the pleuroperitoneal shunt can be inserted with local anesthesia as opposed to general anesthesia, which is required for thoracic duct ligation. When a pleuroperitoneal shunt is implanted, the defect closes spontaneously in most cases and the shunt can be removed 30 to 90 days after its insertion (99). When the chyle ceases to enter the pleural space, the shunt is removed. The shunt should not be inserted if chylous ascites is present. Little et al. (96) inserted pleuroperitoneal shunts in two patients with chylothoraces postoperatively and reported that the patients had complete resolution of their effusions with subsequent removal of the shunts. In the largest series using the pleuroperitoneal shunt, 16 infants were treated with the shunt and excellent results were obtained in 12 (97). The only patients who did not have favorable outcomes were those whose chylothoraces were due to central venous thrombosis (97). Murphy et al. (97) recommend placing the shunt if the drainage persists beyond 5 days. An alternative approach to patients with postoperative chylothorax is to insert the pleuroperitoneal shunt as

soon as the diagnosis is made without ever resorting to tube thoracostomy. It is not known how important it is to slow the flow of lymph if a pleuroperitoneal shunt is inserted. At present, I place no dietary restrictions on my patients who have chylothoraces and who are being treated with pleuroperitoneal shunts. It should be noted that since the pleuroperitoneal shunt is being used less for malignant pleural effusions, it is also being used less commonly to treat chylothorax.

Percutaneous Transabdominal Thoracic Duct Blockage

This is a new technique that has been described in the past few years that appears to be minimally invasive and relatively effective in the management of chylothorax. With this technique that was developed by Cope and Kaiser, pedal lymphography is initially performed to opacify large retroperitoneal lymph channels. If there is extravasation of the dye, then a suitable duct (one that is more than 2 mm in diameter) is punctured transabdominally to allow catheterization and embolization of the thoracic duct under fluoroscopic guidance. The embolization is performed using platinum microcoils or microparticles. In more recent patients, glue has been used singly or in combination with coils and this has been a more efficient way to prevent recanalization.

There has been an absence of catheterizable retroperitoneal lymph ducts in approximately 30% of the patients because of previous abdominal surgery, obstructed diseased lymph nodes, or developmental anomalies. In these cases, attempts have been made to occlude small lymphatic collaterals feeding the thoracic duct fistula by needle disruption using rotary and back-and-forth motions.

The preceding technique was attempted in 106 patients at the University of Pennsylvania (100). Embolization was performed in 71 patients and the chylothorax resolved in 64 (90%) (100). Needle interruption of the thoracic duct was successful in 13 of 18 patients (72%). In another series (101), 37 patients with chylothoraces post thoracic surgery had lymphangiography which was successful in 36 patients. Extravasation of the dye was demonstrated in only 20 patients. Lymphangiographically directed percutaneous interventions were performed in 20 patients (101). Four of these 20 patients required further surgical intervention (101). This technique has also been used to treat infants with postoperative chylothoraces (102). Although one might expect numerous complications from this procedure, complications have been rare. In a review of 78 patients receiving this procedure with a mean follow-up of 34 months, four patients had chronic leg swelling and six had chronic diarrhea (103). There was a report of one patient who developed chylous ascites (104). This procedure appears to be the best available option in those facilities where it is available.

Pleurodesis through a Chest Tube

There are a limited number of reports in which pleurodesis has been attempted by injecting a sclerosing agent through a chest tube. Shimizu et al. (105) reported that six of seven patients (86%) with postoperative chylothorax had a successful pleurodesis after the intrapleural administration of OK-432 one to five times. OK-432 is an immunostimulating agent that is used extensively in Japan for pleurodesis, but the drug is not available in the United States. Adler and Levinsky reported the successful treatment of one patient with a postoperative chylothorax with 10 g talc slurry (106). Akaogi et al. (107) reported that two patients with postoperative chylothorax were successfully managed with fibrin glue injected through the chest tube. Others have had a less satisfactory experience with tetracycline (108), nitrogen mustard, or quinacrine (109). Tetracycline was ineffective in three patients on whom I attempted pleurodesis. Huang and Lee (110) did report the successful treatment of three adult patients with a continuous infusion of lidocaine and minocycline. In view of these experiences, pleurodesis by injecting a material through the chest tube is not generally recommended for patients with chylothorax.

Thoracoscopy with Talc Insufflation

There are at least three reports in which more than five patients were treated with talc insufflation at the time of thoracoscopy for chylothorax. Weisssberg and Ben-Zeev (111) reported that the intrapleural insufflation of 2 g talc controlled the chylothorax in seven of nine patients. Vargas et al. (112) reported the successful treatment of five patients with 2 g insufflated talc at the time of thoracoscopy. Graham et al. (113) insufflated talc in eight patients with chylothorax and reported that the treatment was successful in all. Although four of the patients experienced a prolonged course of high output from their chest tubes with relatively slow resolution of the effusions, all had completely resolved by 12 days after the procedure. Therefore, thoracoscopy with the insufflation of talc appears to be an effective treatment for chylothorax.

It is not recommended, however, because the intrapleural administration of talc can lead to the development of the acute respiratory distress syndrome (see Chapter 10). An alternative to thoracoscopy with talc insufflation is thoracoscopy with pleural abrasion (114) or partial parietal pleurectomy. However, if one is going to perform thoracoscopy, ligation of the thoracic duct is a better procedure.

Ligation of the Thoracic Duct through Thoracotomy

A definitive treatment for postoperative chylothorax is ligation of the thoracic duct. Lampson first demonstrated that a chylothorax could be controlled by ligation of the thoracic duct (5). Ligation of the thoracic duct causes no ill effects, probably on account of the multiple anastomoses among various lymphatic channels and direct lymphaticovenous communications (6,7). In one recent series (115), ligation of the thoracic duct controlled the chylothorax in 21 of 22 cases of chylothorax following surgery in adults (95%). Nath et al. (116) performed thoracic duct ligation in 20 pediatric patients with chylothorax after cardiothoracic surgery. They reported that the procedure was successful in 16 patients (80%), but noted that patients with thrombosis of upper body venous vessels or prolonged chest tube drainage were more likely to fail and/or die (116). These researchers recommend thoracic duct ligation within 2 weeks of recognizing the chylothorax (116). Usually, the side of the chylothorax is ipsilateral to the original surgery, and reoperation can be performed through the original thoracotomy incision (75). If the chylothorax is unilateral, the thoracotomy should be performed on the side of the fluid (70). If the chylothorax is bilateral, a right thoracotomy should be performed because the duct is more readily approached from that side (70). An alternative approach has been suggested by Mason et al. (117), who recommend that the thoracic duct be ligated just below the diaphragm through an intraabdominal approach.

It has been recommended that a preoperative lymphangiogram be obtained in every case of chylothorax that does not respond to nonoperative management because the site of leak or obstruction can usually be demonstrated by this technique (75). At the time of operation, one should attempt to find the actual point of leakage from the duct and ligate the duct on both sides of the leak (70). In many instances, however, the leak cannot be located, and, therefore, the thoracic duct should be ligated. Several aids for identifying the thoracic duct intraoperatively have been suggested. Probably, the best method is to inject Evans blue dye at a dose of 0.7 to 0.8 mg/kg, the total dose not exceeding 25 mg, into the subcutaneous tissue of the leg. Within 5 minutes, the chyle will be stained blue (70). The patient may also be given butter or cream to eat 3 to 4 hours preoperatively. The objection to this method is that the stomach may not be empty before the induction of anesthesia, although stomach contents may be removed by nasogastric suction (70). It is probably preferable to place a tube in the duodenum and inject the cream in this location (118). If for some reason the thoracic duct cannot be successfully ligated at thoracotomy, a parietal pleurectomy should be performed to obliterate the pleural space (7).

If the chylous drainage from the chest tubes persists and the nutritional status of the patient is deteriorating, one must not delay thoracotomy too long. In one series, all three patients with traumatic chylothorax who underwent thoracotomy died in the postoperative period (11). These deaths were attributed to the debilitation of the patients by the time the operation was performed.

Ligation of the Thoracic Duct through Thoracoscopy

With the advent of video-assisted thoracic surgery (VATS), one would expect that ligation of the thoracic duct would be tried with the videothoracoscope. Thoracoscopy permits the entire pleural space to be visualized, as well as allowing direct suture of a lymphatic leak. Fahimi et al. (119) performed VATS on six adult patients with postoperative chylothorax and reported that the site of the thoracic duct injury could be identified and treated in four patients. In the remaining two patients, the site of injury could not be identified and either fibrin glue or talc insufflation was performed. The chylothoraces were cured in all six patients (119). Wurnig et al. (120) reported the successful use of VATS with ligation of the thoracic duct immediately above the diaphragm in four cases of adults with chylothoraces of varying etiology. None of the patients had pleural drainage for more than 7 days postoperatively (120). Similar results were reported by Christodoulou et al. (121). Pego-Fernandez et al. (122) performed thoracic duct ligation via VATS in 14 children with chylothorax post cardiac surgery and reported that it was successful in 12 (86%).

Nontraumatic Chylothorax

In general, the goals of management of nontraumatic chylothorax are the same as for traumatic chylothorax.

With nontraumatic chylothorax, however, one must also attempt to establish a cause. If the characteristics of the chyle are transudative, that is, there is a low protein and a low LDH, then the three most likely etiologies are cirrhosis, congestive heart failure, and the nephrotic syndrome (34).

The possibility of lymphoma should be considered in all patients with a nontraumatic chylothorax because it is the most common cause of nontraumatic chylothorax (Table 26.1). Frequently, the patient with lymphoma and chylothorax has no evidence of lymphoma outside the thorax. CT studies of the mediastinum should be performed in all patients with nontraumatic chylothorax to ascertain whether mediastinal lymphadenopathy is present. In women with chylothorax and parenchymal infiltrates, another possibility is pulmonary LAM (see the section later in this chapter).

Another test that should be obtained on all patients with nontraumatic chylothoraces is a lymphangiogram (123). With the lymphangiogram, a total or partial obstruction of lymph flow and the position of the obstacle can be demonstrated. In addition, the lymphangiogram can demonstrate the presence of enlarged lymph nodes or lymphangiectasis that may give a clue as to the etiology of the chylothorax. However, as mentioned previously, lymphangiograms are not available in many medical centers.

The initial management of a patient with a nontraumatic chylothorax should be similar to that of a patient with a traumatic chylothorax. In most cases, a pleuroperitoneal shunt should be inserted. If tube thoracostomy is performed, the gastrointestinal tract should be put at rest and the patient's nutritional status should be maintained by parenteral hyperalimentation. If the chylothorax is due to minor trauma, these measures are usually curative within 1 week. If CT examination of the mediastinum reveals no lymphadenopathy or other masses and the chylothorax is controlled, no further treatment is indicated. In one series of 35 patients with chylothorax due to tumors, none were successfully managed with chest tubes or repeated pleural aspiration (11). If the chylothorax is not controlled with the pleuroperitoneal shunt, or if the CT study of the mediastinum is positive, the patient should undergo a videothoracoscopy or an exploratory thoracotomy. The mediastinum should then be carefully examined for masses, with lymphoma in mind. In addition, the thoracic duct should be ligated.

If the patient is known to have lymphoma or metastatic carcinoma, then radiation should be given to the mediastinum or chemotherapy should be administered. Roy et al. (11) reported that radiation therapy to the mediastinum adequately controlled the chylothorax for the remainder of the patient's life in 68% of those with lymphoma and in 50% of those with metastatic carcinoma. If radiotherapy or chemotherapy does not control the chylothorax in patients with known lymphoma or metastatic carcinoma, exploratory thoracotomy is probably not indicated in view of these patients' dismal prognosis (11). If these patients are symptomatic from the chylothorax, however, one should insert a pleuroperitoneal shunt unless the patient also has ascites. An alternative to the pleuroperitoneal shunt is medical thoracoscopy with the instillation of talc. Mares and Mathur (124) reported their experience with this procedure for 24 hemithoraces in 19 patients with lymphoma-related chylothorax in whom chemotherapy or radiation therapy had failed. They reported that none of their patients had a recurrence of their chylothorax during the 90-day follow-up period. Other alternatives are VATS with ligation of the thoracic duct or the implantation of an indwelling catheter (125). I am hesitant to insert an indwelling catheter because of the risk of malnutrition and immunosuppression.

There are special aspects to the treatment of chylothorax associated with some entities. Because patients with chylothorax secondary to the nephrotic syndrome are likely to have chylous ascites, it is important not to place a pleuroperitoneal shunt or ligate the thoracic duct until this possibility is evaluated (126). The chylothorax associated with sarcoidosis is likely to disappear if the patient is treated with corticosteroids (99). The chylothorax associated with thrombosis of the superior vena cava resolved in one case with the use of thrombolytic therapy and placement of a self-expanding metallic stent (127). The chylothorax associated with cirrhosis has been successfully treated by a transjugular intrahepatic portosystemic shunt (128).

Congenital Chylothorax

As mentioned earlier in this chapter, chylothorax is the most common type of pleural effusion in infants. Chylothorax in infancy can be fatal. The mortality rate was 30% in an earlier series of 10 patients with congenital chylothorax (129). The three deaths in this series were all ascribed to malnutrition and secondary infection, and the babies who died were the only ones in the series who were subjected to more than 14 thoracenteses. On the other hand, five of the babies (50%) had no recurrence of their chylothorax after one to three thoracenteses, and all seven babies who survived were apparently normal (129). In a more

recent study of 19 infants with congenital chylothorax, the mortality was zero (130). In this latter series, polyhydramnios was present in 10 of the pregnancies (130). All 19 patients had respiratory distress, 15 at birth, and the others at a subsequent time. In this series, 16 of the patients required mechanical ventilation (130).

The recommended management of congenital chylothorax is as follows. Initially, the baby should be treated conservatively with repeated thoracenteses. In addition, the nutrition for the infant should be provided by total parenteral nutrition (131). An alternative to TPN is to feed the baby with its mother's fat-free milk (132). If the chylothorax recurs after the third pleural aspiration, a trial of octreotide should be given. Although there are no randomized controlled trials of octreotide, a review (133) of the literature in 2010 found 19 case reports of 20 neonates and this treatment was successful in 14 (70%). However, Horvers et al. (134) treated 7 infants with octreotide and concluded that no clear and consistent effect of octreotide was identified. If the infant does not respond to the octreotide, a pleuroperitoneal shunt should be inserted (135). Milson et al. (135) implanted pleuroperitoneal shunts in seven infants, one of whom was 7 days old, and reported that the shunt cured the chylothorax in six of the seven patients. Thoracic duct ligation is indicated if the pleuroperitoneal shunting fails. The advantage of the shunt over the thoracic duct ligation is that it is a much simpler procedure.

PULMONARY LYMPHANGOLEIOMYOMATOSIS

Pulmonary LAM is a rare condition characterized by widespread proliferation of immature smooth muscle throughout the peribronchial, perivascular, and perilymphatic regions of the lung (136,137). The lymph nodes in the mediastinum and retroperitoneal space may be infiltrated with immature smooth muscle cells impairing lymphatic flow. The thoracic duct may be either obliterated or dilated (138). The perilymphatic proliferation of smooth muscle results in lymphatic obstruction. The preceding three factors result in a significant incidence of chylothorax with LAM. When two recent series with a total of 104 patients are combined, chylothorax occurred in 28 of the patients (27%) (136,137). However, only 8 of 79 patients (10.1%) seen at the Mayo Clinic with LAM between 1976 and 2000 had chylothoraces (139). These eight patients represented 3.5% of all patients with chylothorax at the Mayo clinic during this time (139). In a series of 50 patients with LAM from the United Kingdom, 11 (22%) had a chylothorax (140).

The proliferation of smooth muscle in the perivascular spaces may obstruct the pulmonary venules and may produce pulmonary hemorrhage, hemoptysis, and pulmonary hemosiderosis. The proliferation of peribronchial smooth muscles can partially or completely obstruct the airways to cause air trapping, cyst and bullae formation, and a high incidence of pneumothorax (141). Approximately one third of patients have renal angiomyolipoma, which is a benign mesenchymal tumor (136). Usually, the renal angiomyolipoma is discovered before the diagnosis of LAM is made.

It should be noted that there is now an International LAM Registry (lamregistry.org) (142). There is also a LAM foundation in the United States (http://www.thelamfoundation.org). (143). The telephone number for the LAM Foundation is 1-877-CURELAM.

Clinical Manifestations

LAM occurs almost exclusively in women of reproductive age (136). In one series of 69 patients, however, 5 patients were postmenopausal at disease onset (136) and there is a case report of LAM occurring in a 3-year-old girl (144). The onset of symptoms can occur from age 3 to 70, but most patients are between the ages of 25 and 50. Most patients have increasing shortness of breath and/or cough, but hemoptysis, pneumothorax, or an incidentally discovered chylothorax can be the presenting manifestation. During the course of their disease, almost all patients have parenchymal infiltrates, 15% to 30% have chylothorax, and approximately 70% have pneumothorax (136,137).

Pulmonary LAM is at times part of the syndrome of pulmonary tuberous sclerosis (TSC). TSC is an uncommon, genetically transmitted disease with the classic triad of seizures, adenoma sebaceum, and mental retardation. In one study from the Mayo Clinic, 20 of 76 patients (26%) with TSC had evidence of LAM (145). The radiographic and pathologic findings in the lung are similar in both disorders. Lymph nodes are less commonly involved, and chylothorax occurs less commonly with pulmonary TSC, however (138,146).

Spontaneous LAM and the LAM associated with TSC are linked genetically (147). TSC patients have germline mutations in the *TSC* genes whereas patients with spontaneous LAM do not have germline mutations in the *TSC* genes, but rather have

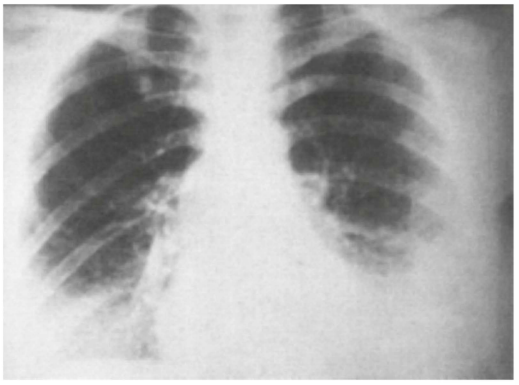

FIGURE 26.2 ■ Posteroanterior radiograph from a 37-year-old woman with pulmonary lymphangioleiomyomatosis. Note the reticulonodular pattern and the wide distance between the ribs suggesting hyperinflation. The pleural effusion on the left was a chylothorax. *(Courtesy of Dr. Harry Sassoon.)*

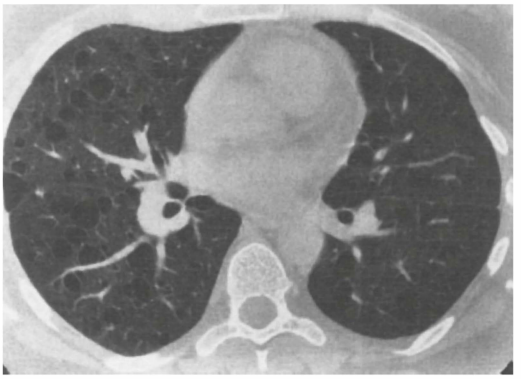

FIGURE 26.3 ■ High-resolution computed tomographic scan of 48-year-old woman with lymphangioleiomyomatosis. Note the numerous thin-walled cysts, rounded and uniform in shape, with normal intervening lung parenchyma.

mutations in the lymph nodes and abnormal lung tissue. The available data strongly suggest that spontaneous LAM is caused by mutations in the *TSC2* gene that cause defects or deficiency in tuberin (147).

The chest radiograph usually suggests the diagnosis of LAM (Fig. 26.2). A coarse bilateral reticular pattern similar to that of fibrosing alveolitis is seen; however, the lung volumes in LAM are usually increased rather than decreased as in fibrosing alveolitis and almost every other cause of interstitial lung disease (148). The interstitial lung infiltrates vary in extent, and their distribution may be primarily basal or diffuse. Pleural effusion from the chylothorax may be unilateral or bilateral and is typically large and recurrent. All have been chylous on direct examination. The high-resolution CT scan of patients with LAM is very characteristic (Fig. 26.3) in that there are numerous air-filled cysts surrounded by normal lung parenchyma. The only other disease that has similar findings on the high-resolution CT scan is Langerhans cell histiocytosis. In the latter disease, lung bases are relatively spared and frequently there are nodules (148). Serial CT scans may be useful in assessing the response to therapy.

Pulmonary function tests in the patient with LAM reveal a normal or reduced vital capacity but an increased total lung capacity (TLC). Evidence of moderate to severe obstructive ventilatory dysfunction usually exists, and the diffusing capacity for carbon monoxide is usually reduced (148). Arterial blood gases reveal hypoxia and hypocapnia.

Diagnosis

The diagnosis of pulmonary LAM is frequently delayed. In the series of 32 patients from Stanford and the Mayo Clinic, the diagnosis was delayed by an average of 44 months after the initial manifestation of the disease. Only one patient was given a diagnosis of LAM during her initial medical evaluation (149). This diagnosis should be suspected in any woman between the ages of 25 and 50 with a chylothorax, particularly if interstitial infiltrates and increased lung volumes are also present.

Although the diagnosis is strongly suggested by the findings on the high-resolution CT scan, a definitive diagnosis requires tissue confirmation. The tissue can be obtained by transbronchial biopsy, thoracoscopy, or open thoracotomy (136). The diagnosis of LAM is established by the demonstration of the typical histologic pattern of widespread proliferation of immature smooth muscle. This perilymphatic smooth muscle proliferation is generally regarded as a hamartomatous rather than a neoplastic process (138). Characteristically, clefts or spaces between the smooth muscle bundles are lined by endothelium. Microscopic changes in involved lymph nodes are similar to those in the lung: interlacing bundles of smooth muscle proliferation demarcated by endothelial-lined clefts (138).

It has been shown that the demonstration of the presence of smooth muscle cells that have specific immunoreactivity for the monoclonal antibody HMB45 is specific and highly sensitive for LAM (150). HMB45

is a monoclonal antibody with specific immunoreactivity for malignant melanoma (150). LAM cell clusters can also be demonstrated in pleural fluid and they stain positively with HMB45 (151). The availability of this test will probably facilitate the use of transbronchial biopsy in making the diagnosis of LAM (152).

Measurement of the serum vascular endothelial growth factor-D (VEGF-D) appears useful in the diagnosis of LAM. Young et al. (153) measured the VEGF-D levels in 56 patients with LAM and 44 patients with other cystic lung diseases and reported that the serum VEGF-D levels in the patients with LAM were (median 1,175 [interquartile range (IQR): 780–2,013] pg/mL) were significantly higher than those in the other patients (median 281 [IQR 203–351] pg/ml). Patients with TSC-LAM had significantly higher levels than patients with TSC only (153). These results were confirmed in a subsequent study (154), but in the second study VEGF-D levels were not increased in patients that had LAM involving only the lung.

Treatment

In the past, it was believed that the prognosis of women with pulmonary LAM was dismal because most patients died within 10 years of the onset of symptoms (146). More recent reports suggest that the prognosis may be better to some extent. In a study from France, the Kaplan-Meier plot showed survival probabilities of 91% after 5 years, 79% after 10 years, and 71% after 15 years of disease duration (136). Patients die primarily of progressive respiratory insufficiency (152). Characteristics associated with a poor prognosis include a reduced forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), an increased TLC, and a predominantly cystic type of histology as opposed to a predominantly smooth muscle type of histology (155).

Several researchers have suggested that hormonal manipulation may be of value in treating this disease (136). The almost exclusive occurrence of the disease in women of reproductive age has suggested that the smooth muscle proliferation may be hormonally dependent. The results, however, with hormonal manipulation have not been impressive. Johnson and Tattersfield (156) retrospectively analyzed the rate of decline in pulmonary function of 43 patients with LAM. They reported that the mean drop in FEV_1 and diffusing capacity was significantly less in patients receiving progesterone than in those not receiving progesterone, and in postmenopausal women as opposed to premenopausal women, although there was much overlap between the groups (156). Urban et al. (136) reported that hormonal therapy was administered in 57 patients but that only 4 had a greater than 15% improvement in their FEV_1. The most common treatment regimen is medroxyprogesterone acetate, 400 mg intramuscularly each month. However, doses this suprapharmacologic are probably not needed as the primary goal is to suppress serum estrogen production (147). Norethindrone acetate, 10 mg PO daily or twice a day is recommended (147). Estrogen-containing medications may have adverse effects and should be discontinued (147).

One therapy that should be considered for patients with LAM is sirolimus. The theory behind sirolimus is that it inhibits mammalian target of rapamycin (mTOR) which is upgraded due to mutations of the TSC1 and TSC2 gene and leads to abnormal cellular growth (157). Taveira-DaSilva et al. (157) treated 19 patients with rapidly progressing LAM with sirolimus and reported that the mean declines in the FEV_1 and DLCO were 2.8% and 4.8% per year, respectively, before treatment and both actually increased after treatment to 1.8% and 0.8% per year, respectively. In this study, 11 patients had a chylothorax for at least 1.5 years before therapy with sirolimus and the chylothorax disappeared completely in 9 with sirolimus. This study suggests that sirolimus should be considered in patients with LAM with chylothorax.

One possible therapy for LAM is lung transplantation. In 2009, Benden et al. (158) reviewed 61 patients who received lung transplantation for LAM at 30 centers in Europe between 1997 and 2007. Prior to surgery, the mean FEV_1 and FVC were 27% and 52% of the predicted, respectively. They reported that the actuarial Kaplan-Meier survival was 79% at 1 year and 73% at 3 years post-transplant (158). Recurrence of LAM occurred in 4 recipients (158). The results of Benden et al. (158) are better than those reported by Boehler et al. (158a) in 1996 in which actuarial survival calculated by the Kaplan-Meier method was 69% after 1 year and 58% after 2 years. Given the relatively good prognosis of the patients in the study by Urban et al. (136), lung transplantation is not recommended until the patient becomes debilitated from her disease.

The chylothorax associated with LAM should be managed as are chylothoraces secondary to other medical conditions. If the chylothorax is small and is asymptomatic, it need not be treated. If it is larger, it is probably best treated with thoracoscopic ligation of the thoracic duct or the implantation of a pleuroperitoneal shunt.

GORHAM'S SYNDROME

Gorham's syndrome is a rare disease that can occur at any age but is most often recognized in children or young adults. There is no sex predilection and no inheritance pattern. Other names for Gorham's syndrome include hemangiomatosis, disappearing bone disease, and massive osteolysis. The characteristic lesion of Gorham's syndrome is an intraosseous proliferation of vascular or lymphatic channels that leads to the disappearance of bones. There is a propensity for involvement of the maxilla, shoulder girdle, and pelvis (37).

Patients with Gorham's syndrome have a high incidence of chylothorax. Chylothorax was present in 25 of the 146 cases (17%) of Gorham's syndrome in the literature until 1994 (37). All the patients with Gorham's syndrome and chylothorax had a rib, scapular, clavicular, or thoracic vertebral bony involvement. Patients with Gorham's syndrome and chylothorax should be treated with a pleuroperitoneal shunt or thoracic duct ligation (37).

CHYLIFORM PLEURAL EFFUSIONS AND PSEUDOCHYLOTHORAX

A chyliform pleural effusion resulting in a pseudochylothorax is a pleural effusion that is turbid or milky from high lipid content not resulting from disruption of the thoracic duct. Some authors have separated pseudochylothoraces into those with cholesterol crystals, designated *pseudochylous effusions*, and those without cholesterol crystals, designated *chyliform pleural effusions* (59). Because no practical reason exists for making this distinction, I designate all high-lipid nonchylous effusions as *chyliform pleural effusions*. Pseudochylothoraces with their associated chyliform pleural fluid are uncommon. Until 1999, only 174 cases had been reported in the international literature (159). Pseudochylothoraces are much less common than chylothoraces. In a series of 53 nontraumatic high-lipid effusions, only 6 (11%) were chyliform pleural effusions (11).

Pathogenesis

The precise pathogenesis of chyliform pleural effusions is not known (160). Most patients with chyliform pleural effusions have long-standing pleural effusions (mean >5 years) and have thickened and sometimes calcified pleura. Most of the cholesterol in chyliform pleural effusions is associated with high-density lipoproteins in contrast to the cholesterol in acute exudates that is mostly bound to low-density lipoproteins (160). It has been hypothesized that the cholesterol that enters the pleural space with acute pleural inflammation becomes trapped in the pleural space and undergoes a change in lipoprotein-binding characteristics (160). The diseased pleura may result in an abnormally slow transfer of cholesterol and other lipids out of the pleural space and may lead to the accumulation of cholesterol in the pleural fluid (64). The origin of the cholesterol and other lipids is not definitely known, but one possibility is from degenerating red blood cells and WBCs in the pleural fluid (64). Most patients with chyliform pleural effusions do not appear to have disturbed cholesterol metabolism because the serum cholesterol levels are usually within normal limits and the patients have no signs of altered cholesterol metabolism such as xanthomas.

Some chyliform pleural effusions contain cholesterol crystals. The factors that dictate whether cholesterol crystals will be present are unknown. Cholesterol crystals have been seen in pleural fluid with cholesterol levels below 150 mg/dL, whereas other pleural fluids with cholesterol levels above 800 mg/dL have had none (64). The cholesterol crystals can be miscounted by automated cell counters as WBCs giving falsely high pleural fluid WBC counts (161).

Clinical Manifestations

Chyliform pleural effusions are usually seen in patients with long-standing pleural effusions (64). The mean duration of the effusion is 5 years before it turns chyliform, but some chyliform effusions have developed within 1 year of onset. The two most common causes of the effusion initially are rheumatoid pleuritis and tuberculosis (64,162,163). Wrightson et al. (164) reported six patients with chyliform pleural effusions secondary to rheumatoid arthritis whose effusions had been present for less than 2 years and who did not have pleural thickening. Patients who have had artificial pneumothoraces for pulmonary tuberculosis and in whom the lung remains atelectatic with a resultant pleural effusion are particularly prone to chyliform pleural effusions (163). In many patients, the etiology of the original pleural effusion remains undetermined. Many pleural effusions secondary to paragonimiasis contain cholesterol crystals (165).

Many patients with chyliform pleural effusions are asymptomatic, or at least are no more symptomatic than when they initially developed the pleural effusion.

Because the visceral pleura is usually thickened, the underlying lung contributes minimally to the total ventilation, and the patient may have dyspnea on exertion. Chyliform pleural effusions are usually unilateral.

Diagnosis

The diagnosis of chyliform pleural effusion is not usually difficult. When a patient with a long-standing pleural effusion is found to have turbid or milky pleural fluid, the two other diagnostic possibilities are empyema and chylothorax. In an empyema, centrifugation results in a clear supernatant. The differentiation between chylothorax and pseudochylothorax is not usually difficult; the patient with chylothorax has an acute pleural effusion and normal pleural surfaces, whereas the patient with pseudochylothorax has a chronic pleural effusion and a thickened or calcified pleura (166). On occasion, fat-fluid or fat-calcium levels can be seen on the CT scan in patients with a pseudochylothorax (166).

Analysis of the pleural fluid is useful in the differentiation of chylothorax and pseudochylothorax. If cholesterol crystals are seen on smears of the sediment, the patient has a chyliform pleural effusion. The cholesterol crystals give a distinct, satin-like sheen to the pleural fluid. Microscopically, the cholesterol crystals present a typical rhomboid configuration (Fig. 26.1). If no cholesterol crystals are seen, the patient may still have a chyliform effusion. Pleural fluid cholesterol levels above 200 mg/dL strongly suggest a chyliform effusion (160). The cholesterol levels in the pleural fluid are elevated in high-lipid pleural effusions owing to high numbers of cholesterol crystals or lecithin–globulin complexes (59), but cholesterol levels may also be elevated in chylous pleural effusions (10). Lipoprotein analysis should be performed if any doubt exists as to whether the fluid is chylous or pseudochylous because only chylous pleural fluid contains chylomicrons (10,64). Some chyliform effusions have high (>250 mg/dL) triglyceride levels (64), so this finding is not diagnostic of chylothorax.

Treatment

When a patient is diagnosed as having a chyliform pleural effusion, the possibility of tuberculosis should always be entertained. If the patient has a history of tuberculosis and has never been treated with antituberculous therapy, isoniazid and rifampin should be given for at least 9 months. Similarly, if the patient has a positive purified protein derivative test, he or she should be treated with these drugs unless he or she has been treated previously or has received the bacille Calmette-Guérin vaccine.

If the patient's exercise capacity is limited by shortness of breath, a therapeutic thoracentesis should be performed. Hillerdal reported that the removal of several hundred milliliters of pleural fluid from patients with pseudochylothorax resulted in a markedly improved exercise tolerance (163). Decortication should be considered if the patient is symptomatic and the underlying lung is believed to be functional (167). The decortication may result in a markedly improved functional status for the patient (167).

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chapter 27

Other Pleural Diseases

PATHOGENESIS OF PLEURAL FIBROSIS

Most of the diseases discussed in this chapter deal with pleural fibrosis. It is therefore appropriate to start this chapter with a brief discussion of the pathogenesis of pleural fibrosis. It should be noted that the process that leads to a pleurodesis after the injection of a sclerosing agent is probably very similar to that which leads to fibrosis. The reader is referred to Chapter 4 and Chapter 10 for discussions on the mechanisms of pleurodesis.

The initial step in the production of pleural fibrosis is almost always an inflammatory response in the pleura, whether it is in response to infection, an immunological process, asbestos, or other inflammatory processes. Subsequent interactions among resident and inflammatory cells, cytokines, growth factors, and blood-derived products are important in determining whether the inflammatory process will resolve or fibrosis will result. The balance between the procoagulant system and the fibrinolytic system is important in determining the outcome of an inflammatory insult to the pleura. If the procoagulant system dominates, then pleural fibrosis will develop whereas, if the fibrinolytic system dominates, no pleural fibrosis will result (1). Another important factor in the production of pleural fibrosis is angiogenesis. If vascular endothelial growth factor (VEGF) inhibitors are administered after the pleura is injured, the fibrosis is markedly reduced (2). The reader is referred to review articles (1,3) for a more in-depth discussion of the pathogenesis of pleural fibrosis.

PLEURAL DISEASE DUE TO ASBESTOS EXPOSURE

Exposure to asbestos can cause several different types of pleural disease (4). First, it can lead to a diffuse malignant mesothelioma, as described in Chapter 11; second, it can lead to a benign pleural effusion, as described in Chapter 23; third, it can bring about the development of pleural plaques or calcification; fourth, it can lead to massive pleural fibrosis; and fifth, it can produce a localized pleural abnormality called *rounded atelectasis*, which is easily confused with a parenchymal tumor. Pleural plaques, massive pleural fibrosis, and rounded atelectasis are discussed in this chapter.

PLEURAL PLAQUES

These hyalinized fibrous tissue collections are located predominantly in the parietal pleura at the lateral and posterior intercostal spaces; over the mediastinal pleura, particularly at the pericardium; and over the dome of the diaphragm. These locations generally correspond to areas involved in the clearance of particles from the pleural space by the lymphatics (5). Pleural plaques are one of the earliest and most common manifestations of asbestos exposure and can serve as a marker for clinically relevant asbestos exposure. Although malignant transformation has never been demonstrated in a pleural plaque, the presence of large plaques (>4 cm) has been associated with an increased risk of developing mesothelioma (5). The large plaques serve as an indication of heavy exposure, but it is believed that these plaques do not undergo a malignant transformation.

Prevalence

The prevalence of pleural plaques is somewhat dependent on the population studied. Hillerdal (6) reviewed the chest radiographs of a sizable proportion of the residents of Uppsala, Sweden, and found that the prevalence of pleural plaques in those individuals older than 40 had increased from 0.2% in 1965 to 2.7% in 1985.

The prevalence of pleural plaques was 22% in 91 elevator construction workers who probably had been exposed to low levels of asbestos in their work (7). The incidence of pleural plaques at autopsy has varied from 0.5% to 58% (8,9). When 16 separate studies with a total of 7,085 routine autopsies were combined, the prevalence of pleural plaques was 12.2% (8). The standard chest radiograph identifies between 50% and 80% of the pleural plaques that are actually present (8).

Pleural plaques slowly develop in patients exposed to asbestos. Epler et al. (10) reviewed the chest radiographs of 1,135 patients who had been exposed to asbestos and reported that none of the patients developed pleural plaques during the 10 years after the initial exposure, and the incidence was still only approximately 10% 20 years after the initial exposure (10). Forty years after the initial exposure, however, more than 50% of the patients had radiologically visible pleural plaques. The mean duration between the initial exposure to asbestos and the development of pleural plaques was 33 years in the series of Hillerdal (6). These plaques usually calcify within several years of becoming evident radiologically. Calcification of the pleural plaques rarely occurs within the first 20 years of initial exposure to asbestos, but by 40 years, more than one third of these individuals have calcified pleural plaques (10).

Pleural plaques can also develop in individuals who are not occupationally exposed to asbestos. Kilburn et al. (11) reported that the prevalence of pleural abnormalities was 5.4% in the chest radiographs of 280 wives of asbestos workers who were initially exposed to asbestos at least 20 years previously. Churg and DePaoli (12) reported four cases of pleural plaques found at autopsy in individuals who resided in or near the chrysotile mining town of Thetford Mines, Quebec, but who did not work with asbestos. Mineral analysis of the lungs revealed that the individuals with pleural plaques had higher levels of tremolite but comparable levels of chrysotile than did the lungs of nine control subjects without pleural plaques. Constantopoulos et al. (13) reported that the prevalence of pleural calcification was 47% in 688 inhabitants of the Metsovo area in northwest Greece, an area where a solution containing tremolite was used to whitewash the houses.

Pathogenesis

Convincing evidence links pleural plaques to previous asbestos exposure. Kiviluoto (14) reviewed the place of residence of all individuals with bilateral pleural calcification in Finland and demonstrated that almost all such subjects lived near open asbestos pits. Hillerdal (6) reported that 88% of 1,596 adults older than 40 with pleural plaques had an occupational exposure to asbestos. Many patients who have pleural plaques at autopsy have a work history in which asbestos exposure would be expected (15,16). Most pleural plaques contain many submicroscopic asbestos fibers that can be demonstrated by transmission electron microscopic examination, selective area electron diffraction, and microchemical analysis of particles (17,18). In a large study (19) from France, 5,545 patients with a history of asbestos exposure had a HRCT and 882 (16%) had pleural plaques. Patients who had pleural plaque had a longer time since their first exposure and a greater cumulative exposure.

Ferruginous bodies (asbestos bodies), long considered the histologic hallmark of exposure to asbestos (20), consist of fibers coated by complexes of hemosiderin and glycoproteins and are believed to be formed by macrophages that have phagocytized the particles. Although these bodies have been shown to form from foreign inorganic and organic fibers of many different types, ferruginous bodies in most human lungs have asbestos as a core and are commonly known as *asbestos bodies* (20). Patients with pleural plaques have higher numbers of asbestos bodies in their lungs than do patients without pleural plaques (15,21,22). Similarly, the higher the number of asbestos bodies in the lungs, the more likely the presence of pleural plaques (20,22). It should be noted, however, that the number of asbestos fibers that are uncoated or bare (and visible only on electron microscopy) exceeds the number of asbestos bodies, which are visible by light microscopy, by 5- to 10,000-fold (23).

It appears that the various types of asbestos fibers differ in their ability to induce pleural plaques. Exposure to crocidolite is most frequently associated with the production of pleural plaques. In North America, pleural plaques are more likely to result from tremolite than from chrysotile exposure. Churg et al. (24) correlated the presence of pleural plaques with the fiber type, fiber concentration, and fiber size as determined by analytic electron microscopy in 94 long-term chrysotile miners. They found that patients with pleural plaques had a significantly higher length–width ratio for the tremolite fibers than did those without plaques (24). It is believed by some that tremolite rather than chrysotile is responsible for pleural plaques in the asbestos miners in Canada (25).

Not all pleural plaques are due to asbestos exposure (26). Zeolite minerals are aluminum silicates that

are widespread in the earth's crust. Erionite is a zeolite that is found in old volcanic sites such as in Turkey, New Zealand, areas of Japan, and in southwestern United States. Erionite is also present in gravel pits in North Dakota, and pleural plaques were present in 3 of 15 gravel pit or road maintenance workers (20%) in one study (27). In a few villages in Turkey, the mineral has been used in buildings and for road construction, and a large percentage of the population has fiber-related pleural changes (28). One case of diffuse pleural thickening has been attributed to this fiber in Nevada (29). Wollastonite, a silicate that can be fibrous and is used in ceramics, has been reported to cause pleural plaques (30). Talc, another mineral that is a flaky silicate, has been reported to be associated with plaque formation, but this mineral is often contaminated with amphiboles, so the relationship remains to be proved (31). Pleural plaques, which may or may not be calcified, occur in other pneumoconioses including those caused by mica, Bakelite, calcimine, tin, barite, silica, and kaolin (26). They also occur after exposure to manmade vitreous fibers (26). However, concomitant exposure to asbestos is sometimes responsible for the pleural plaques seen with such diseases (17).

The mechanism by which asbestos fibers produce pleural plaques is unknown. Kiviluoto (14) proposed that pleural plaques are formed in response to inflammation of the parietal pleura. When an asbestos fiber is inhaled, it passes toward the periphery of the lung. Kiviluoto (14) suggested that the fiber pierces the visceral pleura and then rubs against and irritates the parietal pleura during respiratory movements. The resulting parietal pleural inflammation then gradually evolves into the hyaline plaque, which eventually calcifies. If this theory were correct, however, one would expect to find adhesions between the visceral and parietal pleura in the areas of pleural plaques, as well as long asbestos fibers in the parietal pleura.

Hillerdal (32) has suggested that the short submicroscopic fibers are primarily responsible for the pleural plaques because these fibers can be demonstrated in the plaques. He proposes that these short fibers reach the pleural space by penetrating the pulmonary parenchyma and the visceral pleura. These fibers are then removed from the pleural space, as is all particulate matter, by the lymphatic vessels that lie in the parietal pleura. Some fibers are caught in the lymphatic vessels, however, and the presence of the fiber, in conjunction with the appropriate inflammatory cell, causes pleural plaques to form over many years. One observation that does not support this hypothesis is the following: the location of black spots in the parietal pleura that represent areas where organic and inorganic material are sequestered in the pleural lymphatics do not correspond to locations where pleural plaques are found (33). A third hypothesis for the pathogenesis of pleural plaques is that the microfibrils embolize to the parietal pleura by either the parenchymal lymphatic plexus or through the costal vascular supply. Then once present in the parietal pleura, the fiber itself or agents carried by the fiber appear to be responsible for initiating and promoting the inflammatory response. Bernstein et al. (34) have demonstrated that in rats the inhalation of amosite asbestos for 5 days results in fibers penetrating the visceral pleural wall and within the parietal pleura within 7 days with a concomitant inflammatory response by 14 days. In contrast, no inflammatory response was found when chrysotile asbestos was inhaled (34).

If asbestos is injected intratracheally, it migrates to the pleura. In one study in rats, the asbestos fibers appeared in the pleural space within 3 days of intratracheal injection (35). Over a 30-day period, there were two peaks in the appearance of the asbestos fibers in the pleural space. The first peak occurred on day 7, at which time the mean length of the fiber was 1.2 μm. The second peak occurred on day 21 when the mean length of the fiber was only 0.3 μm (35).

The intrapleural injection of either crocidolite or chrysotile asbestos fibers leads to the development of a pleural effusion (36,37). Sahn and Antony (37) injected chrysotile asbestos fibers into normal rabbits, which developed exudative pleural effusions within 4 hours. Over the next 120 hours, there was increasing metabolic activity in the pleural fluid, as evidenced by a falling pH and an increasing P_{CO_2}. The animals developed pleural plaques that were evident by 7 days and developed completely by 1 month. Interestingly, if the rabbits were made neutropenic, they still developed the pleural effusion but subsequently developed marked pleural fibrosis and did not develop pleural plaques. The neutropenic rabbits did not have a macrophage influx as did the normal rabbits. These workers concluded that the pleural macrophage is important in localizing the asbestos fiber and in the ultimate formation of the pleural plaque. When a critical number of macrophages is not present, disorganization and widespread fibrosis occur (37).

Several studies have demonstrated that the exposure of mesothelial cells in cell culture to asbestos particles can induce the cells to produce substances associated with the development of fibrosis. If rat pleural mesothelial cells are exposed to crocidolite or chrysotile

asbestos fibers, the asbestos fibers are actively phagocytized and incorporated within the phagosomes. Both types of asbestos also stimulate the mesothelial cells to produce fibronectin, a substance with fibroblast chemoattractant activity (38). In contrast, quartz and carbonyl iron particles do not induce similar changes (38). After interaction with cells, asbestos fibers can also trigger a number of signaling cascades involving mitogen-activated protein kinases and nuclear factor κ-B (39). These signaling cascades can result in the production of various inflammatory mediators such as tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), IL-6, IL-8, and transforming growth factor β (TGF-β) (39). The induction of TGF-β is particularly noteworthy because it is one of the most fibrogenic agents ever discovered. Indeed, the intrapleural injection of TGF-β produces dense pleural fibrosis (40).

Pathologic Features

Macroscopically, pleural plaques appear as discrete, raised, irregularly shaped areas separated by normal or slightly thickened pleura (21). These plaques are always present on the parietal pleura and found most commonly on the posterior wall of the lower half of the pleural space. Pleural plaques on the costal pleura usually have an elliptical shape, running parallel to the ribs superiorly and inferiorly (21). Pleural plaques usually do not occur in the apices of the pleural cavities or in the costophrenic angles (21). The thinner plaques are only slightly raised above the pleural surface and are grayish white in color, whereas the thicker plaques are ivory or cream colored. The diameter of the plaques varies from a few millimeters to 10 cm (21). The pleural plaques are usually multiple, and the costal pleura can look like an archipelago of different-sized plaques (31). At thoracoscopy the striking smooth whiteness of the plaques has been likened to the appearance of icing on a cake (41).

Microscopically, the plaques consist of collagenous connective tissue containing few cells (18,21). The connective tissue is arranged in a coarse, basket-weave pattern and contains only a few capillaries. Normal mesothelium covers the plaques. The boundary between a plaque and the surrounding normal pleura is always sharply demarcated (21). Elastin stains show the continuity of the lamellae beneath the plaque with the surrounding normal parietal pleural connective tissue. Some calcium deposition is present in a high proportion of plaques (21). Although no asbestos fibers are visible by light microscopy, electron microscopic study demonstrates many submicroscopic fibers in almost all plaques (18).

Radiologic Features

Noncalcified pleural plaques are frequently not visible on the posteroanterior (PA) and lateral chest radiographs (15,16). The earliest radiologically visible change is a line of increased density adjacent to a rib (Fig. 27.1), usually the seventh or the eighth (17,18,32). As the plaque enlarges, it becomes elliptical and protuberant, with tapering superior and inferior margins typical of an extrapleural lesion. A plaque rarely extends vertically for more than four interspaces. The thickness of the plaque varies from 1 to more than 10 mm but is usually in the range of 1 to 5 mm. Involvement of the apices or the costophrenic angles by pleural plaques is rare. Pleural plaques are usually bilateral and are often symmetric. When the pleural plaques are unilateral, they are left sided approximately 75% of the time (42). In addition, if the disease is bilateral, there tends to be more disease on the left side (43). However, one recent study was unable to demonstrate a greater amount of plaque on the left. Gallego (44) recently performed computed tomography (CT) on 40 adults with asbestos exposure and reported that the average total plaque area on the right of 47.8 cm^2 was not significantly different from the average plaque area on the left of 45.3 cm^2.

On a standard chest radiograph, pleural plaques are most clearly defined when viewed tangentially, that is, in profile along their long axes. A routine PA

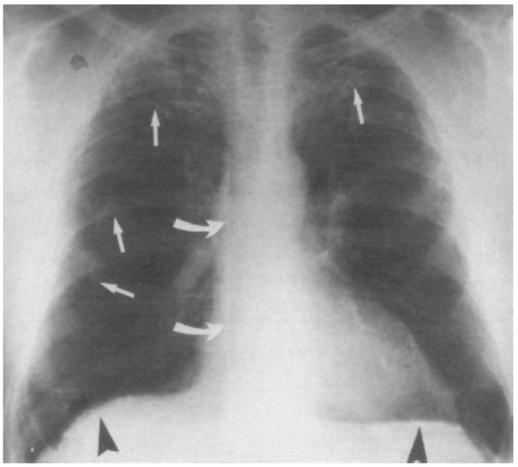

FIGURE 27.1 ■ Pleural plaques. Posteroanterior radiograph of a 62-year-old man with prior asbestos exposure and a 40-pack-a-year smoking history shows bilateral calcified pleural plaques (straight arrows) and diffuse calcification of the mediastinal (curved arrows) and diaphragmatic (arrowheads) pleura.

chest radiograph distinctly demonstrates a plaque located on the inner surface of the lateral chest wall because the x-ray beam passes through more of the plaque. Noncalcified pleural plaques are best visualized by radiography at 110 to 140 kV, whereas calcification within plaques is best demonstrated at 80 kV. When the x-ray beam is perpendicular to the plaque, the plaque is presented in a frontal or *en face* orientation. When viewed *en face*, small, noncalcified plaques are difficult to see and are perceived as ill-defined, irregular densities adjacent to the ribs. The *en face* plaque rarely appears uniformly rounded; rather, it shows a peripheral irregularity of contour that has been likened to the fringe of a map or a lily leaf (17). Because of its faintness in outline, the plaque is often overlooked or is dismissed as an artifact.

Conventional and high-resolution computed tomography (HRCT) scans are more sensitive at detecting pleural plaques than is the standard chest radiograph. In one study of 159 asbestos-exposed workers with a normal chest radiograph, pleural plaques were detected in 59 (37.1%) by CT scan. The conventional CT detected pleural plaques in 58 of the patients, whereas the HRCT detected the pleural plaques in only 48 cases (45). On CT, plaques appear as discrete soft tissue or calcified thickening of the pleural surface (Fig. 27.2). Focal plaques are commonly observed in the posterior and paraspinous regions of the thorax, areas that are poorly seen on chest radiographs.

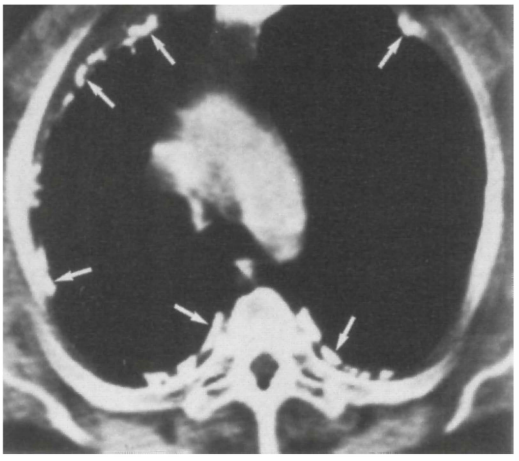

FIGURE 27.2 ■ Computed tomography scan of the patient in Fig. 27.1 after administration of intravenous contrast material shows numerous bilateral calcified pleural plaques *(arrows)*, characteristic of asbestos-related pleural disease.

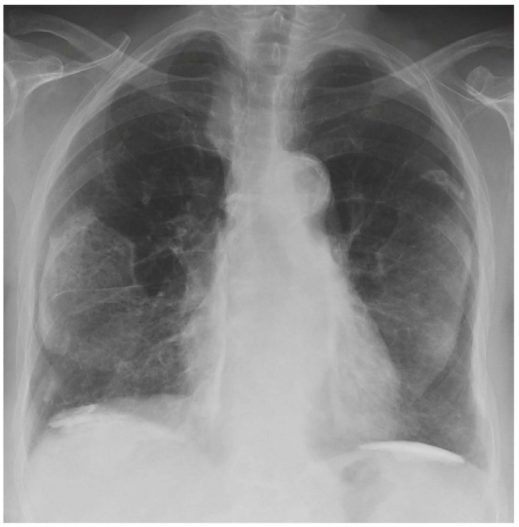

FIGURE 27.3 ■ "Soft tissue" image from dual-energy digital subtraction chest radiography of a man with a prior history of asbestos exposure demonstrating virtual absence of ribs and thickening of the pleura. (Courtesy of Dr. Robert C. Gilkeson.)

One of the most sensitive and inexpensive means to identify pleural plaques is dual-energy digital subtraction chest radiography (46). With this method, the chest is x-rayed at two different energy levels. Then the images are processed with a computer to give a "soft tissue" image (Fig. 27.3) and a "bone image" (Fig. 27.4). With the soft tissue image, the bones are essentially eliminated, which makes it easier to identify parenchymal lesions. With the bone image, calcium in the costal and diaphragmatic pleural plaques is readily identified.

Differential Radiologic Diagnosis

The greatest problem in the diagnosis of early plaque formation lies in distinguishing plaques from normal companion shadows of the chest wall. At autopsy, some degree of fat accumulation is almost always visible on gross examination along the chest wall in the reflections of the parietal pleura, oriented parallel to the long axes of the ribs on the subpleural osseous surfaces (47). Fat deposits that are more extensive tend to form pads and folds concentrated at the level of the midthoracic wall in the region of the fourth to eighth ribs. Subpleural fat and pleural plaques are frequently indistinguishable on standard chest radiographs (47). Patients with higher body mass indices

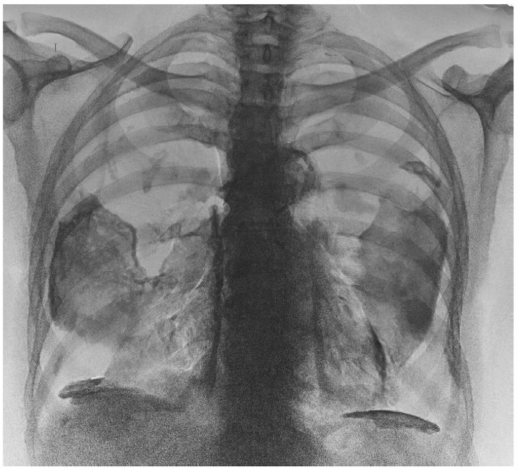

FIGURE 27.4 ■ "Bone" image from the same person in Figure 27.3 demonstrating marked calcification of the pleura, the diaphragmatic pleura and the pericardium. (Courtesy of Dr. Robert C. Gilkeson.)

are more likely to have thickening due to fat misdiagnosed as pleural thickening (48). The chest CT scan is efficient at distinguishing pleural plaques from subpleural fat. If a pleural abnormality is not calcified, a CT scan should probably be obtained to verify that the pleural abnormalities are indeed plaques, particularly if litigation is involved. When two series are combined (47,49), 87 patients were thought to have pleural plaques on their standard chest radiographs. When they underwent CT examination, however, only 48 of the patients (55%) had pleural plaques, whereas the remainder had fat pads.

On the normal PA chest radiograph, a vertical line of water density may parallel the medial surface of the first three or four ribs along the lateral thoracic wall (17). This line is formed by a combination of muscles, the areolar tissue of the endothoracic fascia, and fat, but it is distinguishable from pleural plaques because plaques rarely extend superior to the third rib and are most prominent at the level of the seventh and eighth ribs. Below the level of the fourth rib, 1 mm is generally considered the maximal acceptable thickness for this normal pleural shadow (18).

The costal slips of origin of the serratus anterior and external abdominal oblique muscles have been confused with pleural plaques because they produce a characteristic rhythmic sequence of shadows between successive intercostal spaces. These anatomic structures are most commonly visible over the eighth rib, but the fifth through the ninth ribs may be involved. These costal slips of muscular origin appear either as one or two distinct triangular shadows or a combination of two opacities superimposed, and they can usually be differentiated from pleural plaques in that the muscle shadow has one sharply defined border and elsewhere fades into the surrounding soft tissues.

The diaphragm is also a common site for pleural plaques. In the PA projection, the plaques usually affect the middle third of each diaphragm and rarely occur within 2.5 cm of the lateral chest wall. Most fibrous plaques are rounded or button-like and may easily be confused with the normal polycyclic outline of the diaphragm because of uneven muscle contraction.

Pleural Calcifications

As mentioned earlier in this chapter, pleural plaques often become calcified. Forty years after the initial exposure to asbestos, nearly 40% of individuals have radiologically demonstrable pleural calcification (10). In general, calcified plaques are more striking than uncalcified plaques on the radiograph. When the x-ray beam strikes a plaque tangentially, the calcification is seen as a dense white line, usually discontinuous, paralleling the chest wall, diaphragm, or cardiac border (Fig. 27.4). Because calcium is deposited near the center of the typical subpleural hyalinized plaque, it is separated from the inner surface of the rib by a line of water density. If the x-ray beam strikes the surface of the calcified plaque *en face*, it presents an irregular and unevenly dense pattern.

Differential Diagnosis

Asbestos exposure is not the only cause of localized pleural thickening or pleural calcification. Discrete, localized, noncalcified pleural thickening may occur with localized mesothelioma, metastatic disease, lymphoma, or myeloma (17). Pleural thickening from these diseases is usually unilateral. Localized pleural thickening and callus formation simulating asbestos pleural plaques may occur following rib fractures. The changes in such patients are usually unilateral, and the overlying rib deformity suggests the diagnosis (17).

The other main causes of diffuse pleural calcification are long-standing inflammatory diseases, particularly hemothorax, empyema, postpleurodesis, or repeated iatrogenic pneumothorax for tuberculosis therapy. In such instances, the pleural thickening is unilateral, and the calcification is often extensive and sheet-like. The thickening is usually on the visceral

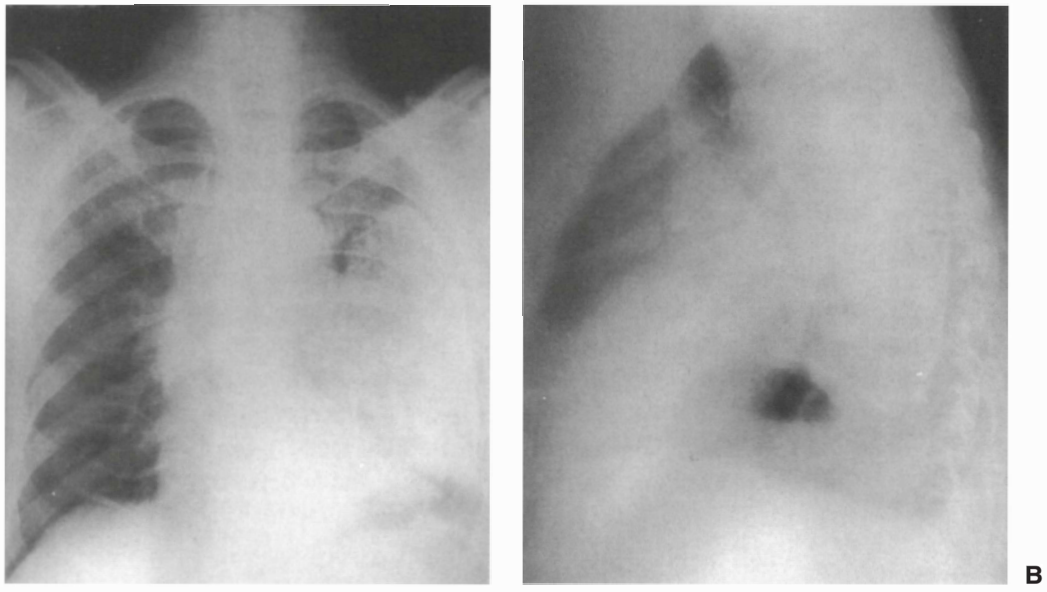

FIGURE 27.5 ■ Posteroanterior (PA) (A) and lateral (B) chest radiographs of a 69-year-old man who sustained a gunshot wound to the left chest 30 years previously show a large irregular dense opacity obscuring much of the left lung on the PA view and both lungs on the lateral view. On the lateral view, note the dense calcific opacity conforming to the outline of the pleural space.

pleura, and the calcification occurs in the inner aspect of the pleural thickening (Fig. 27.5).

Significance

Bilateral pleural plaques or calcifications are significant as an index of previous exposure to asbestos. It appears that the presence of pleural plaques is not associated with the development of pleural mesothelioma when the level and duration of exposure to asbestos are taken into consideration (50). It is controversial whether patients with pleural plaques have an increased risk of lung cancer when the level of smoking is taken into consideration (51). Weiss (52) reviewed the literature published in English in 1993 and concluded that the weight of evidence favors the conclusion that persons with asbestos-related pleural plaques do not have an increased risk of lung cancer in the absence of parenchymal asbestosis. In 1994, Hillerdal (53) reviewed the incidence of bronchial carcinoma and mesothelioma in 1,596 men with pleural plaques initially detected between 1963 and 1985. He found that 50 bronchial carcinomas occurred whereas 32.1 were expected, and that 9 mesotheliomas occurred whereas only 0.8 were expected. The risk of cancer and mesotheliomas is therefore probably increased in patients with pleural plaques to some extent, and they should be encouraged to stop smoking.

The presence of pleural plaques alone probably results in a small decrease in the pulmonary function test values when there is no parenchymal asbestosis and when smoking is taken into consideration. Schwartz et al. (54) performed spirometry on 1,211 sheet metal workers. They reported that the forced vital capacity (FVC) in the 258 individuals with circumscribed plaque was 3.75 L compared with an FVC of 4.09 in 877 workers without pleural plaques. In a subsequent study, this same group was able to demonstrate a significant relationship between the volume of the pleural fibrosis as computed from the three-dimensional reconstruction of the HRCT scan and the total lung capacity (TLC) (55). The mean TLC, however, of 24 patients with pleural fibrosis was 106% of that predicted (55). In a large study Clin et al. (56) reported that the mean TLC (98.1% predicted) and FVC (96.6% predicted) in 403 patients with pleural plaques and no parenchymal abnormalities were significantly lower than the mean TLC (101.2% predicted) and FVC (100.4% predicted) in 1,802 patients with asbestos exposure but normal CT scans. Certainly, the functional abnormalities produced by pleural plaques alone are not sufficient to produce symptoms. Shih et al. (57) demonstrated the

maximal work capacity to be 91.4% of that predicted in 20 patients with pleural plaques and no asbestosis of the lung on chest radiograph.

DIFFUSE THICKENING

In addition to the occurrence of parietal pleural plaques, exposure to asbestos may be followed by the development of diffuse pleural fibrosis. Although some authors consider this diffuse pleural fibrosis to be part of the spectrum of parenchymal asbestosis (18), it appears to be a distinct entity (6,58–60). In contrast to pleural plaques, diffuse pleural fibrosis commonly involves the costophrenic angles, is associated with involvement of the visceral pleura with pleural symphysis (Fig. 27.6), and sometimes involves a marked loss of pulmonary function that can lead to hypercapnic respiratory failure (58–61).

The incidence of diffuse pleural fibrosis is much lower than that of pleural plaques. Hillerdal (58), in surveying a group of asbestos workers, found 827 individuals with pleural plaques but only 27 with progressive pleural thickening. Schwartz et al. (54) reviewed the chest radiographs of 1,211 sheet metal workers and reported that 260 had circumscribed plaques, whereas 74 had diffuse thickening. The prevalence of diffuse pleural thickening is higher with longer durations of exposure and higher intensity of exposure (61). One report suggested that the development of pleural fibrosis was more common with human leukocyte antigen (HLA) phenotype DQ2 (62).

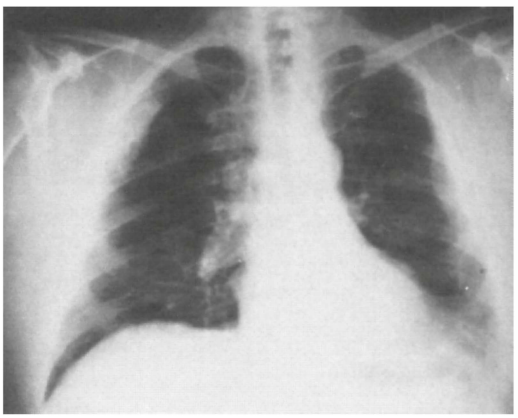

FIGURE 27.6 ■ Posteroanterior chest radiograph demonstrating diffuse pleural thickening and blunting of the left costophrenic angle from a patient with a history of asbestos exposure.

Although bromocriptine and asbestos exposure can each lead to the development of diffuse pleural fibrosis, it appears that the administration of bromocriptine and a history of asbestos exposure act synergistically to produce diffuse pleural fibrosis (63). Hillerdal et al. (63) reported on a series of 15 patients who had a history of asbestos exposure and who developed diffuse bilateral pleural thickening after taking bromocriptine for Parkinson's disease for 1 to 10 years. The patients complained of malaise, often associated with weight loss, dyspnea, and a disturbing cough. When the bromocriptine was withdrawn, the patients improved clinically. However, in most cases, the diffuse pleural fibrosis and the restrictive lung function defect persisted (63).

The pathogenesis of diffuse pleural thickening is unknown. However, its locale and strong association with interstitial fibrosis suggest that it may be a direct extension of parenchymal fibrosis to the visceral pleura (8). Subpleural interstitial fibrosis has been a constant feature in the limited studies using HRCT in subjects with diffuse pleural disease (64). This does not explain the observation that the diffuse pleural fibrosis associated with asbestos exposure frequently follows a benign asbestos pleural effusion (41) (see Chapter 23). Epler et al. (10) reviewed the chest radiographs of 1,135 asbestos workers and found that of the 44 patients with diffuse thickening greater than 5 mm, almost 50% had had a previous asbestos pleural effusion. Of the 35 workers with asbestos effusion, 54% had residual diffuse pleural thickening. Hillerdal (58) documented that the initiating event in 4 of 27 patients with progressive pleural thickening was a benign pleural effusion. Diffuse pleural thickening secondary to asbestos exposure almost always involves the costophrenic angle and invariably becomes bilateral, although it may be unilateral at first. This diffuse pleural thickening starts at the bases and progresses at a variable rate. Thickening of the pleural cap may be considerable (58). Although routine radiographs do not demonstrate pleural calcification in most patients, CT scanning often demonstrates pleural calcification (59). Many patients with diffuse pleural fibrosis have no evidence of intrapulmonary fibrosis on a CT scan (59).

Patients with diffuse pleural thickening tend to have symptoms from their pleural disease. In one study, 61 of 64 patients (95%) complained of significant breathlessness on exertion (65). In the same series, 56% of the patients complained of chest pain, which was more frequently precipitated by exertion than by deep inspiration. Six of the patients

complained of regular chest pain, which they found to be a constant problem (65).

Patients with diffuse pleural thickening have a significant decrease in the results of their pulmonary function testing (6,65). In one study of 64 patients with diffuse pleural thickening, the results for various pulmonary functions expressed as a percentage of those predicted were as follows: FEV_1 62%; FVC 77%; TLC 71%; Dl_{co} 74%; and K_{co} 104% (65). In this study, there was no accelerated decline in pulmonary function over a mean follow-up period of 9 years (65). The exercise capacity of some patients with diffuse pleural fibrosis is diminished (57,66). In one study of 12 patients with diffuse pleural thickening, the mean work capacity was 82.7% of that predicted. The intense dyspnea during exercise has been attributed to the rapid shallow breathing pattern that these patients exhibit during exercise. Oxygen desaturation does not occur, and there is no definite evidence that the patients develop respiratory muscle fatigue (67).

The diagnosis of diffuse pleural thickening secondary to asbestos exposure is usually based primarily on the history of exposure. Pleural plaques are present in most patients with diffuse pleural thickening secondary to asbestos exposure (68). In addition, the diffuse thickening secondary to asbestos exposure is usually bilateral and does not involve nodular invasion of the lung (68). One must worry about the possibility of mesothelioma in patients with diffuse thickening from asbestos exposure, particularly if the disease is not symmetric. Other features that suggest neoplasm are the presence of pleural nodularity or ring, parietal pleural thickening greater than 1 cm, or involvement of the mediastinal pleural surfaces (64).

The optimal management of patients with progressive pleural fibrosis due to asbestos exposure is unknown. Wright et al. (59) suggested that because these patients have an increased elastic recoil and a normal diffusing capacity when corrected for lung volume, they might benefit from decortication. Hillerdal (58), however, performed decortication on four patients and reported that only one of them improved subjectively. He attributed the lack of improvement to concomitant parenchymal fibrosis. Fielding et al. (69) subjected four patients with diffuse pleural thickening and opiate-resistant chest pain to thoracotomy and decortication and reported that the results were disappointing. Munoz et al. (70) reported one patient with hypercapnic respiratory failure who was treated successfully at home with noninvasive mechanical ventilation.

ROUNDED ATELECTASIS

Rounded atelectasis refers to atelectasis of the peripheral lung resulting from pleural adhesions and fibrosis. It is also known as Blevosky syndrome after an early author described the phenomena of "folded lung" (71). Rounded atelectasis can mimic a pulmonary neoplasm because it presents as a peripheral mass. Rounded atelectasis consists of a peripheral part of the lung that has become atelectatic secondary to the pleural inflammation (72). Rounded atelectasis may occur anywhere in the chest, but by far, the most common site is along the posterior surface of the lower lobe. Aerated lung is interposed between the mass and the diaphragm (72). It may be unilateral or bilateral. At thoracotomy, fibrous tissue can always be peeled off in several layers. After extensive dissection, the lung fully expands. The most probable explanation for rounded atelectasis is that an inflammatory reaction starts in the visceral pleura and leads to formation of fibrous tissue on the lung surface. This tissue consequently shrinks and causes atelectasis of the underlying lung (73).

Rounded atelectasis is usually due to asbestos exposure. Dernevik and Gatzinsky (73) reported pleural plaques in 29 of 37 cases (78%) of rounded atelectasis. Hillerdal and Ozesmi (74) reported that 6 of 60 patients (10%) with benign asbestos pleural effusion developed rounded atelectasis. Rounded atelectasis has also been reported in conjunction with tuberculosis, parapneumonic effusions, pulmonary embolization, Dressler's syndrome (75), uremia (76), and treatment with pergolide (77). It is likely that any disease that produces localized inflammation of the visceral pleura can lead to rounded atelectasis.

The main importance of rounded atelectasis is that it must be differentiated from a malignant lung lesion. The rounded atelectasis itself does not produce symptoms. The roentgenologic picture is often suggestive of the diagnosis, whereas a CT scan is frequently diagnostic (Fig. 27.7). On the standard chest radiograph, rounded atelectasis appears as a spherical, sharply marginated mass abutting the pleura. Pleural thickening is always present and is frequently thickest near the mass. A comet-tail sign is produced by the crowding together of bronchi and blood vessels that extend from the lower border of the mass to the hilum (Fig. 27.7C). Although these features may be appreciated on standard radiographs, CT shows the characteristic features to better advantage, including the associated pleural thickening and peripheral location of the mass (78). Positron emission tomographic (PET) scans of rounded atelectasis show minimal

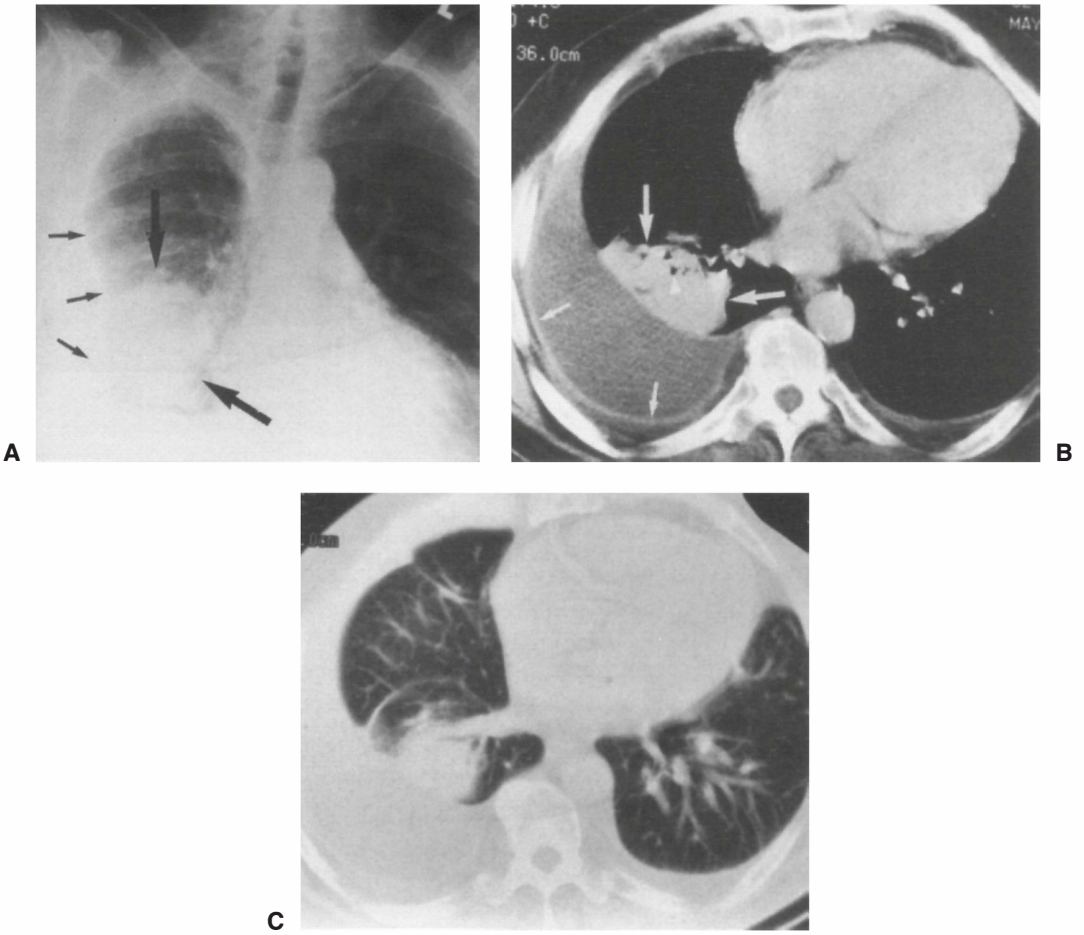

FIGURE 27.7 ■ Asbestos-related pleural disease and rounded atelectasis in a 62-year-old man with a 20-year history of asbestos exposure. **A**: PA chest radiograph shows a large right pleural effusion *(short arrows)* and a right lower lobe "mass" *(long arrows)*. **B**: Computed tomographic (CT) scan with intravenous contrast demonstrates enhancement of the parietal pleura *(short arrows)*, indicating a chronic pleural effusion. The parenchymal "mass" *(long arrows)*, in contact with the visceral pleural surface, represents collapsed lung. The atelectatic lung has a rounded shape owing to fibrous adhesions and infolding of the visceral pleura. Air bronchograms are seen within the collapsed lung *(arrowhead)*. **C**: CT scan (lung windows) shows the comet-tail sign or the vacuum cleaner effect, both descriptions of how the vessels leading toward the atelectatic lung diverge and arc around the undersurface of the atelectatic lung before merging with it.

metabolic activity (79). Fine-needle biopsy can be performed easily because the lesion is pleural based, but its utility is limited because malignancy cannot be excluded (75). Thoracotomy is definitive, but should rarely be necessary (31).

PLEURAL DISEASE RELATED TO MINERALS OTHER THAN ASBESTOS

On occasion, exposure to minerals other than asbestos can produce pleural changes. Orriols et al. (80) reviewed the chest radiographs of 765 coal miners without significant parenchymal abnormalities and reported that 45 (5.9%) had some pleural abnormality. Patients who had heavier exposures to silica were more likely to have pleural changes (80). The most common abnormality was obliteration of the costophrenic sinus (80). A second study assessed pleural changes in 110 individuals with a history of silica exposure, a CT scan in the 2 years before death and an autopsy (81). They reported that 28 of 62 patients (45.2%) with complicated silicosis and 10 of 48

patients (20.8%) with uncomplicated silicosis had a pleural effusion on the chest radiograph or CT scan (81). Alternative explanations for the pleural effusion were present in 26 patients, but there was no other explanation in 10 patients. Moreover, 37% of those with uncomplicated and 77% of those with complicated silicosis had pleural thickening at autopsy (81).

In another study of 1,008 workers using refractory ceramic fibers, pleural changes were found in 27 (2.7%) (82). In these workers, the changes were mainly pleural plaques (82). Pleural plaques have also been reported after exposure to pumice, an amorphous complex silicate (83), and talc (84). In the latter instance, the pleural changes may well have been due to concomitant exposure to asbestos (84).

DIFFUSE BILATERAL PLEURAL THICKENING UNRELATED TO ASBESTOS

Although asbestos exposure accounts for most cases of diffuse bilateral pleural thickening, there are other causes. These include drugs, particularly ergot alkaloid drugs such as bromocriptine (85) (see Chapter 22); collagen vascular disease (86) (see Chapter 21); and infectious diseases, which usually produce unilateral pleural thickening. Nevertheless, there are some cases for which no etiology is apparent. Buchanan et al. (87) described four patients with bilateral pleural effusions progressing to diffuse pleural thickening for which there was no evidence of an infective, embolic, or occupational cause. Histology showed that in all cases, both layers of the pleura were thickened by fibrous tissue and frequently the pleural space was obliterated. Interestingly, all four cases were HLA-B44 positive. Pleural decortication was successful in the three patients on whom this procedure was attempted (87). Pleural fibrosis can be familial. Azoulay et al. (88) reported three sisters with bilateral isolated apical pleural fibrosis that progressed to produce severe bilateral fibrosis. Two of the sisters died of respiratory failure, and the third received a lung transplant.

FIBROTHORAX

When pleural inflammation is intense, its resolution may be associated with the deposition of a thick layer of dense fibrous tissue on the visceral pleura. The patient is then said to have a fibrothorax. As a result of the marked pleural thickening, the hemithorax becomes contracted, and its mobility is reduced (89). As the fibrothorax progresses, the intercostal spaces may narrow, the size of the involved hemithorax may diminish, and the mediastinum may be displaced ipsilaterally. Radiologically, a peel of uniform thickness surrounds the lung. Calcification occurs frequently on the inner aspect of the peel (Fig. 27.5) and provides an indicator by which the thickness of the peel may be accurately measured (89). The three main causes of fibrothorax are hemothorax, tuberculosis, and bacterial lung infection (89); but pancreatitis (90), collagen vascular disease (91), and uremia (92) can also lead to fibrothorax. In a few instances, no etiology is ever discovered (93).

Clinical Manifestations

Pulmonary function is severely compromised in fibrothorax. The degree of functional abnormality is much greater than one would expect from the degree of pleural disease (94). Pleural thickening in the costophrenic angle can cause profound alterations in the ventilation of and blood flow to the entire lung. Routine pulmonary function testing reveals mild-to-severe restrictive ventilatory dysfunction. Surprisingly, the blood flow is reduced more than the ventilation of the affected side (95). In a study of 127 patients (95), the mean oxygen uptake on the affected side was 19% of the total, whereas the mean ventilation was 33% of the total. This finding is in contrast to parenchymal diseases, in which the oxygen uptake and ventilation are reduced to the same degree (95). In severe disease, there is no ventilation or perfusion to the affected side (95).

Treatment

The only treatment available for fibrothorax is decortication, which involves removing the fibrous peel from the visceral pleura. The functional improvement following decortication has been variable (89,94,95). The most important clinical factor is the extent of the disease in the underlying lung (94,95). The vital capacity may improve more than 50% following decortication if no underlying parenchymal disease is present, but the vital capacity may even decrease following decortication in patients with extensive parenchymal disease. Even in patients with long-standing fibrothorax, decortication can still lead to functional improvement. One case report noted a marked subjective improvement in a patient who had had a fibrothorax for 44 years (94).

Which patients should have decortication? Patients with recent hemothorax (see Chapter 25),

recent empyema in which the infection is controlled (see Chapter 12), or recent tuberculous pleuritis (see Chapter 13) should not have a decortication because the pleural thickening frequently resolves by itself over several months. Therefore, decortication should be considered only if the pleural thickening has been stable or progressive over at least a 6-month period. If the pleural thickening has been present for several months and if the patient's way of life is compromised by exertional dyspnea, decortication should probably be performed unless previous chest radiographs demonstrated extensive parenchymal disease. Decortication is a major surgical procedure and should not be performed on patients debilitated by other diseases. In one series of 141 patients, the mortality rate with decortication was 3.5% (73).

PLEUROPARENCHYMAL FIBROELASTOSIS

Pleuroparenchymal fibroelastosis is a rare condition characterized by predominantly upper lobe pleural and subjacent parenchymal fibrosis (96). The parenchymal fibrosis is intra-alveolar with accompanying elastosis of alveolar walls. There is also dense fibrous thickening of the visceral pleura. The intra-alveolar and pleural changes have a striking upper-zone predominance. Most cases are idiopathic, although a few cases are familial and some have been reported in association with previous bone marrow transplantation (96). Patients present frequently with shortness of breath and/or cough (96). In one series (96) of 12 patients, 3 (25%) developed a spontaneous pneumothorax. The etiology of this disease is unknown (96). The natural history of this disease is progression. In one series (96) of 10 patients, 5 patients died and the time between diagnosis and death ranged from 4 months to 2 years. There is no evidence that any treatment changes the course of the disease (96) with the exception of lung transplantation.

INTRATHORACIC SPLENOSIS

Splenosis is defined as the autotransplantation of splenic tissue, usually after rupture of the spleen. Most commonly, it is discovered as innumerable purple nodules coating the mesentery, omentum, and peritoneal surfaces of the abdominal cavity. When the diaphragm and spleen are lacerated simultaneously, seeding of the pleural cavities can occur.

Intrathoracic splenosis can present with solitary or multiple pleural-based nodules (97). The presentation may be 15 years or more after the spleen was injured. A clue to the diagnosis is the absence of Howell-Jolly bodies, pitted erythrocytes, and siderocytes in the peripheral blood of asplenic individuals. Normally asplenic individuals have these abnormalities in their peripheral blood smear. However, if there is functional splenic tissue elsewhere, such as in the chest, these cells will be absent. Technetium-99 labeled sulfur colloid radionuclide scanning can identify residual splenic tissue. However, it appears that scanning with heat-damaged red blood cells is more sensitive (98). The diagnosis can also be made by fine-needle aspiration (99), but this is usually unnecessary with the typical history and radiographic findings. If the patient is asymptomatic, no therapy is indicated.

THORACOLITHIASIS

Thoracolithiasis is a rare benign condition characterized by the presence of a calcified or noncalcified loose body in the pleural space. They are usually an incidental finding on imaging or at surgery (100) and do not require any treatment or intervention. Through 2009, only 22 cases had been reported in the literature (100). Seventeen of the 22 thoracoliths were on the left side. They may be related to degenerated lipomas, old tuberculosis, phagocytosis of dust, or dropping of pleural or pericardial fat into the pleural space. They frequently migrate from throughout the pleural space.

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chapter 28

Thoracentesis (Diagnostic and Therapeutic) and Pleural Biopsy

Thomsen et al. (1) have created an excellent video on performing a thoracentesis, and watching this video is recommended before one performs his or her first diagnostic or therapeutic thoracentesis.

DIAGNOSTIC THORACENTESIS

Indications

A diagnostic thoracentesis should be performed on almost every patient with a pleural effusion of unknown origin. Empirically, I have found it difficult to obtain fluid with a diagnostic thoracentesis if the thickness of the fluid on the decubitus chest radiograph or the CT scan is less than 10 mm, and I usually do not attempt thoracentesis in such patients. If thoracentesis is attempted with small amounts of fluid, the proper location can be identified using ultrasound (2).

Contraindications

The main contraindication to a diagnostic thoracentesis is a hemorrhagic diathesis. One should hesitate to perform a thoracentesis in a patient who is receiving anticoagulants, particularly thrombolytic agents. Depending on the urgency of the situation, however, diagnostic thoracentesis using a small (22-gauge) needle can be performed on almost any patient if one is careful. McVay et al. (3) demonstrated that there was no increased risk of bleeding if the prothrombin time or the partial thromboplastin time was not more than two times the normal value. Likewise, there was no increased risk of bleeding with low platelet counts ($<25{,}000/mm^3$). A more recent study reported similar results (4). Accordingly, these authors recommend that prophylactic blood product transfusions are not needed before thoracentesis in patients with mild coagulopathy and no clinical evidence of bleeding (3). These authors did note an increased risk of bleeding if the creatinine level was elevated above 6 mg/dL (3), presumably because of decreased platelet function in the setting of uremia.

It appears that thoracentesis can be safely performed on patients who are undergoing mechanical ventilation. In one study from Beth Israel Hospital in New York, 232 thoracenteses were performed in 211 patients receiving mechanical ventilation under ultrasound guidance (5). In this series, 95.6% of the patients were on positive end expiratory pressure (PEEP), 63% were receiving vasopressors, and 61% underwent therapeutic thoracenteses (5). Thoracentesis yielded fluid in 98.7% of the procedures and the incidence of pneumothorax was only 1.3% (5). It should be noted that the ultrasound in this series was performed by pulmonologists (5). When thoracentesis has been performed without ultrasound on patients receiving mechanical ventilation, the incidence of pneumothorax has been much higher. McCartney et al. (6) reported a series of 31 patients who underwent thoracentesis while they were receiving mechanical ventilation; 25 patients were receiving PEEP between 5 and 20 cm H_2O. All thoracenteses were performed with patients in the lateral decubitus position. Three of the patients (10%) developed a pneumothorax, and all were managed with a chest tube (6). In a second series, 2 of 32 patients (6%) developed a pneumothorax after undergoing a thoracentesis while on mechanical ventilation (7). A thoracentesis should not be attempted through an area affected by a local cutaneous condition such as pyoderma or herpes zoster infection.

Positioning of Patient

For a diagnostic thoracentesis, and particularly for a therapeutic thoracentesis, the patient and the operator must be comfortable. I find that the patient is most comfortable when he or she sits on the side of the bed with arms and head resting on one or more pillows on a bedside table (Fig. 28.1). A footstool is placed on the floor for the patient to have someplace to rest the feet. The bed is elevated so that the operator does not have to stoop over. The patient sits near the foot of the bed, with the side containing the fluid toward the foot of the bed. With the patient in this position, the operator does not have to reach across the entire bed, yet the foot of the bed can be covered with sterile drapes to provide a sterile area from which to work. The patient should be positioned with his back vertical so that the lowest part of his hemithorax is posterior. If the patient leans forward too far, the lowest part of the hemithorax may move anteriorly, and no fluid will remain posteriorly.

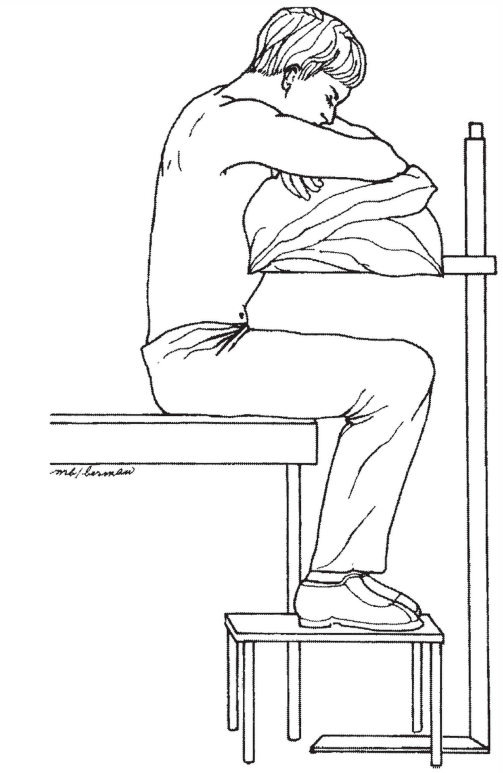

FIGURE 28.1 ■ Recommended position of the patient for diagnostic or therapeutic thoracentesis.

Some patients are too debilitated to assume a sitting position. The thoracentesis may then be performed with the patient lying on the side of the pleural effusion in the lateral decubitus position with his back near the edge of the operating table or bed. Alternately, the patient may sit in bed with the head of the bed maximally elevated. With the patient in this position, the thoracentesis is performed in the midaxillary line.

Selection of Site

The site for the attempted thoracentesis should be selected with care. Most thoracenteses that fail to yield fluid are performed too low (8). A review of the chest radiographs indicates an approximate location. The physical examination of the patient's chest is most important in determining the site, however. When fluid is present between the lung and the chest wall, tactile fremitus is lost, and the light percussion note becomes dull. Accordingly, thoracentesis should be attempted one interspace below the spot where tactile fremitus is lost and the percussion note becomes dull. Thoracentesis should usually be performed posteriorly several inches from the spine, where the ribs are easily palpated. The exact location for the thoracentesis attempt should be just superior to a rib. The rationale for this location is that the arteries, veins, and nerves run just inferior to the ribs (Fig. 28.2), so that if the needle is just superior to a rib, the danger of damage to these structures is minimized.

Ultrasound has been proposed as being superior to chest roentgenography in identifying pleural fluid and choosing the optimal site for thoracentesis (9). The usefulness of ultrasound in identifying the site was demonstrated in one study from South Africa (10). In this study, attempts were made by pulmonologists to identify the site for thoracentesis 255 times in 67 patients on the basis of physical examination and chest radiographs. A site was proposed in 172 cases (67%). Ultrasound demonstrated that 25 of the identified sites (15%) were inaccurate and in 17 (10%) a solid structure would have been punctured (10). Experienced operators did not perform better than physicians-in-training (9). An earlier study (11), however, was unable to demonstrate that it is cost effective to obtain ultrasound routinely before thoracentesis. Kohan et al. (11) randomly allocated 205 patients to undergo or not undergo chest ultrasonography before thoracentesis. They reported that the incidence of dry attempts was significantly higher without ultrasound (33%) than with ultrasound (10%) in patients with small effusions, but there was

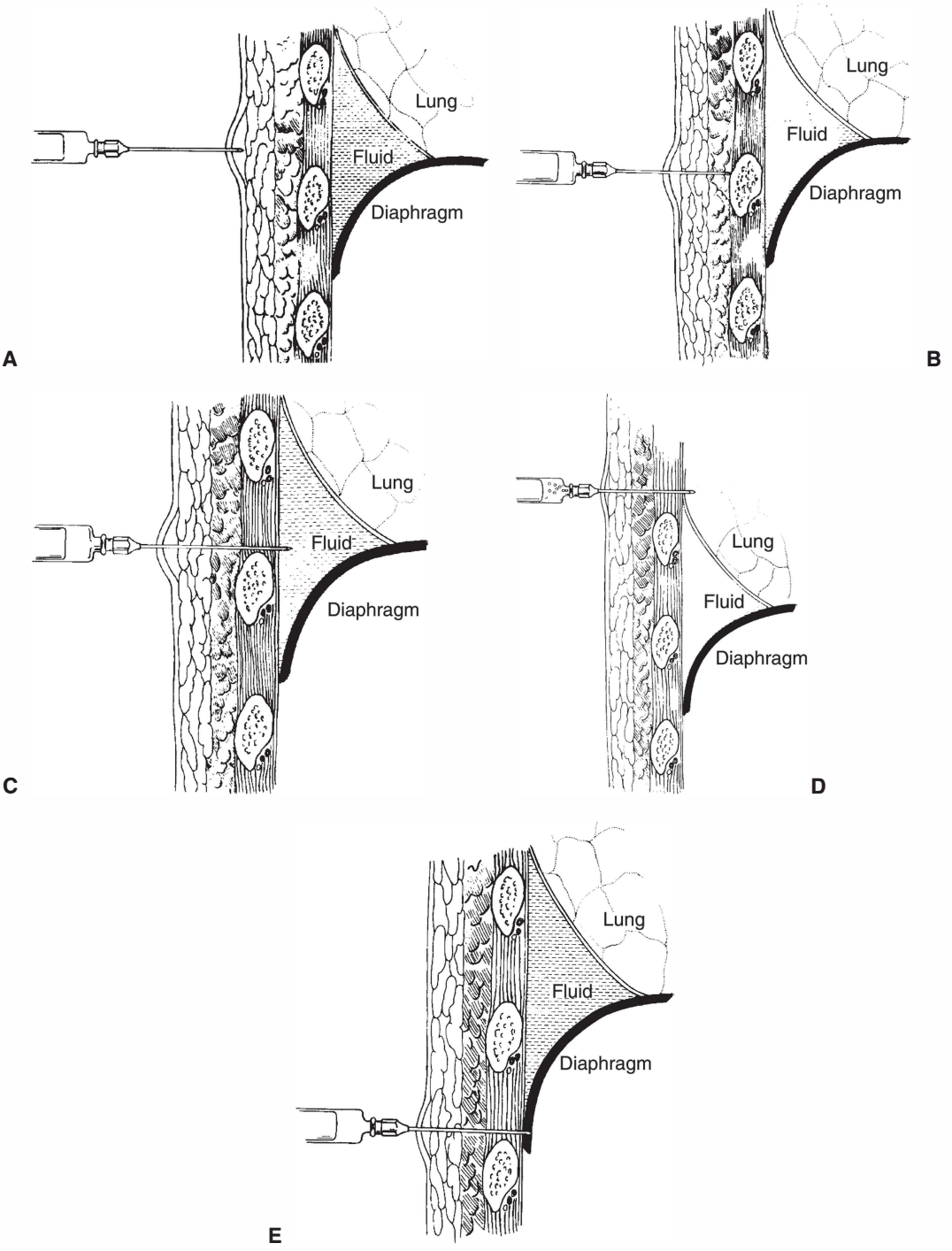

FIGURE 28.2 ■ Diagnostic thoracentesis. **A**: The skin is injected using a 25-gauge needle with a local anesthetic agent. **B**: The periosteum is injected with the local anesthetic. **C**: The pleural space is entered and pleural fluid is obtained. **D**: The thoracentesis attempt is too high, and air bubbles are obtained. **E**: The thoracentesis attempt is too low, and neither bubbles nor fluid is obtained.

no difference with large effusions. Moreover, the use of ultrasound did not lead to a lower rate of complications in patients with either small or large effusions (11). In a smaller study (12), the incidence of pneumothorax was much less (0/19) if the thoracentesis was done with ultrasound guidance than if it was done without ultrasound guidance (10/33) (12). In a recent study of 941 thoracenteses performed with ultrasound guidance, the incidence of pneumothorax was only 2.5% (13). On the basis of the preceding studies, it is recommended that thoracentesis be initially attempted with ultrasound unless the amount of pleural fluid is large. In patients with larger effusions, ultrasound should be utilized if no fluid is obtained after one or two attempts. The British Thoracic Society (14) has recommended that thoracic ultrasound be used for all thoracenteses.

Thoracentesis Kits

The materials required to perform diagnostic thoracentesis are listed in Table 28.1, and these materials should be assembled before the procedure is initiated. What is done more commonly, however, is to use a thoracentesis kit in which the materials have been preassembled. There are several thoracentesis kits available commercially including the Arrow-Clark™ Pleura-Seal® Thoracentesis Kit distributed by Arrow, and the Argyle™ Turkel™ Safety Thoracentesis System distributed by Kendall. When a thoracentesis kit is selected, it is important to select one with a needle-catheter system, particularly if a therapeutic thoracentesis is going to be performed. If one performs a therapeutic thoracentesis with a sharp needle, the needle is likely to lacerate the lung as it reexpands with the removal of pleural fluid and cause a pneumothorax.

One excellent thoracentesis kit is the Arrow-Clark™ Pleura-Seal® Thoracentesis Kit manufactured by Arrow International, Reading, Pennsylvania (www.arrowintl.com, 800-523-8446). The basic thoracentesis apparatus in this kit is an 8-F gauge catheter over an 18-gauge needle with a three-way stopcock and self-sealing valve. With this apparatus, one constantly aspirates as the catheter is advanced through the chest wall. Then, when a free flow of fluid is encountered, the catheter is advanced approximately 1 cm and the needle is withdrawn completely. One nice feature of this set is that there is a self-sealing valve so that air does not leak into the pleural space when the needle is withdrawn; however, the needle cannot be reinserted through the catheter. With this system, small amounts of fluid can be withdrawn by aspirating directly through the side port on the catheter. Another nice feature of this set is that one may easily withdraw large amounts of fluid either with a syringe or through vacuum bottles. If a syringe is used, aspiration is performed through a Y connector that has one-way valves so that no stopcocks need be turned with each aspiration. If vacuum bottles are used, vacuum bottle tubing is included, which attaches directly to the sideport of the catheter. There is also a roller clamp to control the flow of fluid into the vacuum bottles. The cost of this thoracentesis kit is approximately US$31.

Another excellent set is the Argyle™ Turkel™ Safety Thoracentesis System set manufactured by Kendall Company (St. Louis, MO, USA, www.kendallhq.com, 800-962-9888). This system incorporates a blunt, multiside fenestrated, spring-loaded inner cannula coaxially housed within a 16-gauge conventional sharp-beveled hollow needle. The advantage of this system is that as the needle and blunt cannula penetrate the chest wall, the blunt cannula is forced into the shaft of the needle. Then when the tip of the needle encounters low resistance, such as an area of pleural effusion within the pleural space, the spring-loaded cannula automatically extends beyond

TABLE 28.1 ■ Materials Needed for Diagnostic Thoracentesis

Basic materials
Lidocaine 1% or 2%
Aqueous heparin, 1,000 U/mL
Atropine
Antiseptic solution
Alcohol swabs
Sterile gloves
Six 4 × 4-in. gauze pads
Sterile drape with center hole
Sterile drape (to cover bed)
Adhesive tape
Two 5- to 10-mL syringes
One 50- to 60-mL syringe
One No. 25 needle, 5/8 in. long
Two No. 20 to No. 22 needles,1.5 in. long
Band-aids
Additional materials for therapeutic thoracentesis
Two No. 14 needles and catheters
One 3-way stopcock
One sterile container for pleural fluid
One 50-mL syringe (additional)
Additional materials for pleural biopsy
Pleural biopsy needle
Scalpel
Formalin

the bevel, thereby helping to protect the underlying tissue from further, inadvertent penetration. Another advantage of this system is an indicator in the needle housing that identifies the position of the blunt cannula; if resistance is being met such that the sharp end of the needle is exposed, then the indicator is red. In contrast, if no resistance is being met, then the indicator is green. Therefore, when the pleural space is entered, the indicator turns green. If a diagnostic thoracentesis is being performed, the pleural fluid can be withdrawn through the needle. If a therapeutic thoracentesis is being performed, the catheter assembly is advanced and then the needle assembly is withdrawn completely. There is a one-way valve such that there is no possibility of air leaking into the pleural space when the needle is withdrawn. There is a side port for fluid removal. The cost of these kits is approximately US$24.

When comparing the two kits described earlier, the Argyle Turkel kit has the advantage of the spring-loaded inner cannula, which should decrease the incidence of lung laceration. The advantage of the Arrow-Clark system is the ease with which a therapeutic thoracentesis can be performed either with a syringe or with vacuum bottles.

Technique

The procedure should be carefully explained to the patient, and a signed consent form should be obtained. Routine administration of atropine to prevent vasovagal reactions is not recommended as such reactions are very uncommon during thoracentesis (13). Atropine should be available, however, and 1.0 mg should be administered subcutaneously or intramuscularly at the first sign of such a reaction. Similarly, I do not administer an analgesic, a sedative, or a tranquilizer routinely before the procedure unless the patient shows excessive anxiety. If there is excessive anxiety, I administer intravenous midazolam (Versed) just before the procedure.

Once the site for thoracentesis is identified, it is marked by exerting pressure using the end of a ballpoint pen with the tip retracted. This leaves a small indentation that will not be removed by subsequent cleansing of the area. Then the skin surrounding the site is cleansed thoroughly with an antiseptic solution over an area extending at least 4 in. in all directions from the proposed thoracentesis site. The sterile drape with the center hole is then taped to the patient's back, and another sterile drape is placed on the bed.

The next step is to obtain local anesthesia. It is necessary to anesthetize the skin, the periosteum of the rib, and the parietal pleura. The skin is anesthetized using a short 25-gauge needle by injecting enough lidocaine, approximately 0.5 mL, to raise a small wheal (Fig. 28.2A). The small needle is then replaced by a 1.5-in.-long 22-gauge needle. This needle is inserted to the periosteum of the underlying rib and is moved up and over the rib with frequent injection of small amounts (0.1 to 0.2 mL) of lidocaine (Fig. 28.2B). Once this needle is superior to the rib, it is slowly advanced toward the pleural space with aspiration, followed by the injection of 0.1 to 0.2 mL of lidocaine every 1 to 2 mm (Fig. 28.2C). This frequent aspiration and the injection of lidocaine guarantee anesthesia of the parietal pleura. As soon as pleural fluid is aspirated through this needle into the syringe containing lidocaine, the needle should be withdrawn from the pleural space and reattached to a 50- to 60-mL syringe containing 1 mL of heparin. Heparin is added into the syringe to prevent clotting of the pleural fluid as it is difficult to obtain differential white blood cell counts or pH determinations if the pleural fluid is clotted. The same needle is reintroduced along the same tract slowly with constant aspiration until pleural fluid is obtained. Aspiration is then continued until the syringe is filled. The needle is then withdrawn, and the procedure is finished. The commercially available kits can be used to perform a diagnostic thoracentesis. The special needles that come with these kits, however, have few advantages over a syringe and a needle for a diagnostic thoracentesis. They do have significant advantages for therapeutic thoracentesis, and they should be used in this situation.

At times, no pleural fluid is obtained when the1.5-in. No. 22 needle is inserted all the way to its hub. In such a situation, the needle should be slowly withdrawn with constant aspiration. The rim of the pleural fluid is sometimes thin and may be missed as the needle is inserted. If no pleural fluid is obtained either as the needle is inserted or withdrawn, one of four possibilities exists: (a) the needle was too short; (b) placement of the needle was too far superior; (c) placement of the needle was too far inferior; or (d) no pleural fluid is present. If the patient is markedly muscular or obese and if no air is obtained on the initial attempt, the 1.5-in. needle should be replaced with a longer needle such as a spinal needle, which is used for performing lumbar puncture, and the attempt should be repeated. If no fluid is aspirated, but air bubbles are obtained on the initial attempt with

the local anesthetic, the lung parenchyma has been penetrated and the needle was inserted too far superiorly (Fig. 28.2D). Therefore, the procedure should be repeated one interspace inferiorly. Penetration of the lung with a small needle is not a catastrophe, and only occasionally does a pneumothorax result. If no fluid or air bubbles are obtained on the initial attempt, the needle was inserted too far inferiorly (Fig. 28.2E), and the procedure should be repeated one interspace superiorly. Pleural fluid is almost never too viscous to be aspirated through a No. 20 or a No. 22 needle. If no fluid is obtained after two or three attempts, ultrasound guidance for the thoracentesis is recommended.

Processing of Pleural Fluid

The main purpose of a diagnostic thoracentesis is to examine the pleural fluid. The recommended distribution of the pleural fluid to various laboratories is outlined in Table 28.2. For the cell count and differential, the fluid should be placed in ethylenediaminetetraacetic acid (EDTA)-treated tubes (purple top tubes) if the syringe was not initially heparinized. If the syringe was not initially heparinized and if fluid is placed in the tubes without anticoagulants that come with the thoracentesis trays, the cells are likely to clump or the fluid is likely to clot, giving inaccurate cell counts and differentials (15). For the determination of pleural fluid pH, the sample should be maintained anaerobically and the determination should be made with a blood gas machine (16,17), although it is not necessary to pack it in ice as long as the pH determination is performed within an hour (17,18). For the bacterial cultures, it is best to innoculate the pleural fluid directly into blood culture bottles at the bedside (19). Interpretation of the results of the various tests obtained in Table 28.2 is discussed in Chapters 7 and 8. If there is a good chance that the patient has a transudative pleural effusion, the most cost-effective approach is to measure only the lactate dehydrogenase (LDH) and protein in the pleural fluid. If these measurements demonstrate that the patient does not have a transudative pleural effusion (20), the remaining studies should be performed.

Complications

Three factors are important in reducing the risk of thoracentesis: ultrasonography, simulation and supervision (21–23). The most common complication of thoracentesis is pneumothorax. At the Mayo Clinic, the risk of pneumothorax following thoracentesis decreased from 8.6% to 1.1% after a program was instituted to restrict the number of physicians authorized to perform a thoracentesis to a subset of physicians who had specific training, used ultrasound, and performed the procedure on a regular basis (22). The incidence of pneumothorax following thoracentesis is reduced if experienced individuals such as pulmonary fellows or pulmonologists perform the procedure (24). The incidence of iatrogenic pneumothorax is lower if the procedure is performed under ultrasound guidance (21,25). In the largest study, the incidence

TABLE 28.2 ■ Laboratory Distribution of Pleural Fluid Obtained with Diagnostic Thoracentesis

Laboratory	Amount (mL)	Test Ordered
Chemistry (red top tube)	5	Protein Lactic acid dehydrogenase Glucose Adenosine deaminase (ADA)
Hematology (purple top tube)	5	White blood cell count Wright's stain for differential Hematocrit (if pleural fluid is bloody)
Bacteriology	10	Aerobic and anaerobic cultures Gram's stain
Tuberculosis and mycology	5	Tuberculosis and fungal cultures Acid-fast stain
Cytology	5–25	Cytologic examination
Blood gas (By blood gas machine)	5	pH P_{CO_2}

of pneumothorax was only 2.5% in 941 procedures performed under ultrasound guidance and only 0.8% of the patients received a chest tube (13). Raptopoulos et al. (26) reported that the incidence of pneumothorax was 18% for 154 thoracenteses performed with conventional techniques, whereas it was only 3% for 188 performed with ultrasound guidance. Patel et al. (25) reported that the incidence of pneumothorax in 8,824 patients who underwent thoracentesis with ultrasound (3.9%) was significantly lower than that in 10,510 patients who underwent the procedure without ultrasound (4.6%) in 2008. It is noteworthy that less than 50% of the patients had their thoracentesis with ultrasound.

It appears that the likelihood of the development of a pneumothorax may be higher in patients with chronic obstructive pulmonary disease (COPD). Brandstetter et al. (27) performed thoracentesis in 106 patients, of whom 36 had COPD. The incidence of pneumothorax was significantly higher (41.7%) in those patients with COPD than in those without COPD (18.5%) (27). Nine of the 106 patients were treated with chest tubes and 7 of them had COPD (27). The explanation of the very high incidence of pneumothorax in this series is not clear. In contrast, Raptopoulos et al. (26) were unable to find a relationship between the occurrence of a pneumothorax and the presence of underlying lung disease.

There are two different reasons that patients develop pneumothorax after a thoracentesis. First, air may flow from the atmosphere into the pleural space if the pleural space (with its negative pressure) communicates freely with the atmosphere. This most commonly happens when a syringe is removed from a needle or catheter and the air then flows from the atmosphere into the pleural space and produces a pneumothorax. This problem can be prevented if special needles with one-way valves (such as the Arrow-Clark™ Pharma-Seal® or Argyle™ Turkel™) are used during thoracentesis. It can also be prevented if the patient hums (producing positive pleural pressure) while the needle is being changed. Second, the needle for thoracentesis may lacerate the lung and permit air to enter the pleural space from the alveoli. This can be prevented if catheters, rather than sharp needles, are used to perform therapeutic thoracenteses.

Should chest radiographs be obtained routinely after diagnostic thoracentesis? It appears that routine chest radiographs are not indicated. Aleman et al. (24) reported that only 5 of 488 patients without symptoms after thoracentesis developed a pneumothorax and that only 1 of these 5 patients required a chest tube. Gervais et al. (28) reported that the incidence of iatrogenic pneumothorax was approximately 1% in nonintubated patients undergoing ultrasound-guided thoracentesis and concluded that routine postprocedure chest radiographs are not indicated in spontaneously breathing patients who undergo thoracentesis. Doyle et al. (29) reviewed their experience with 174 thoracentesis and concluded that postprocedure chest radiographs were indicated only when a pneumothorax is suspected (29). Jones et al. reported that only 3 of 907 patients (0.3%) who were asymptomatic after a thoracentesis procedure developed a pneumothorax and required a chest tube (13). In view of the series mentioned in the preceding text, I recommend postprocedure radiographs only when air is obtained during the thoracentesis, the patient develops symptoms, or when tactile fremitus is lost over the superior part of the aspirated hemithorax. The treatment of iatrogenic pneumothorax is discussed in Chapter 24.

Other common complications of thoracentesis are cough and chest pain (24). Cough most frequently complicates thoracentesis when it is performed for therapeutic reasons and usually occurs toward the end of the thoracentesis (24). Indeed if coughing occurs during a thoracentesis, it should serve as an indication to stop the procedure. The chest pain that complicates thoracentesis is of three types. First, the patient may experience sharp pain when the skin is anesthetized or when the parietal pleura is pierced. This pain should not be persistent if the parietal pleura is adequately anesthetized. Second, the patient may experience chest tightness or dull pain as fluid is removed during a therapeutic thoracentesis. This type of pain usually indicates that the patient's lung is not expanding rapidly and should serve as an indication to stop the procedure. Third, the patient may develop pleuritic chest pain after the procedure, which is usually because of the roughened pleural surfaces rubbing on each other after some of the fluid has been withdrawn. On auscultation, a pleural rub is often heard in these cases.

At times, a diagnostic thoracentesis provokes a vasovagal reflex characterized by bradycardia, a decreased stroke volume, and a resultant fall in cardiac output and blood pressure. This reaction is blocked by the intramuscular administration of 1 mg of atropine. A similar syndrome may be provoked by various noxious, emotional, and physical stimuli such as apprehension, pain, or the sight of blood and is characterized by the sudden loss of peripheral vascular resistance without significant bradycardia. The patient

develops hypotension, pallor, cold and clammy skin, and faintness. This syndrome is not blocked by atropine. The recommended treatment is termination of the procedure and the immediate placement of the patient in a reverse Trendelenberg position.

Another complication of thoracentesis is infection of the pleural space. Approximately 2% of all pleural infections are due to contamination of the pleural space at the time of thoracentesis. For this reason, sterile technique must be strictly followed during thoracentesis, and the skin must be thoroughly cleansed before the procedure is started. The treatment of pleural infections is discussed in Chapter 12.

Diagnostic thoracentesis can also produce a hemothorax if an intercostal artery is lacerated. This complication can usually be avoided if thoracentesis is performed just superior to a rib, as previously described. In older patients, however, the intercostal arteries may be tortuous, and a hemothorax can result even with proper technique (30). The treatment of iatrogenic hemothorax is described in Chapter 25. Other rare complications of diagnostic thoracentesis include splenic or hepatic laceration, soft tissue infection secondary to seeding of the needle tract with bacteria, seeding of the needle tract with tumor cells, and adverse reactions to the local anesthetic.

Another uncommon complication of which one should be aware is human immunodeficiency virus (HIV) infection with seroconversion. Oksenhendler et al. (31) reported an instance in which a nurse received a superficial self-inflicted needle stick injury to the finger while recapping a needle contaminated by the bloody pleural fluid of a patient with persistent generalized lymphadenopathy, pleural effusion, and seropositivity for HIV and hepatitis B surface antigen. Anicteric hepatitis developed 53 days later, and serum samples became HIV antibody positive by day 68. This case emphasizes the need for strict precautions regarding the handling of needles and body fluids from patients infected with HIV.

THERAPEUTIC THORACENTESIS

Indications

The three main indications for therapeutic thoracentesis are to remove the pleural fluid in patients with parapneumonic effusions or empyema, to relieve the symptom of dyspnea secondary to a pleural effusion, and to remove the pleural fluid so that the status of the lung underlying a pleural effusion can be evaluated. With the exception of patients with parapneumonic effusions or empyema (see Chapter 12), therapeutic thoracentesis provides symptomatic relief, but it is not the definitive therapy. Pleural fluid collects because the rate of pleural fluid formation has exceeded the rate of pleural fluid absorption. If nothing is done to change these two factors, then pleural fluid will reaccumulate after the therapeutic thoracentesis. The thoracentesis itself does not alter the basic condition that produced the pleural effusion. However, a therapeutic thoracentesis should always be performed in an acutely dyspneic patient with a large pleural effusion to alleviate the dyspnea.

Serial therapeutic thoracenteses can be performed in patients who are dyspneic from malignant pleural effusions with mediastinal shift toward the contralateral side in which a pleurodesis cannot be successfully performed. It is recommended, however, that such patients have an indwelling catheter or a pleuroperitoneal shunt placed. A therapeutic thoracentesis is also indicated in a patient with a malignant pleural effusion and dyspnea to determine whether the dyspnea can be relieved by the thoracentesis. This procedure should be performed before a chest tube is inserted and pleurodesis is attempted (see Chapter 10). The contraindications for therapeutic thoracentesis are the same as for diagnostic thoracentesis.

Technique

The positioning of the patient and the selection of the site for the thoracentesis are the same as for a diagnostic thoracentesis. The most important difference between a therapeutic and a diagnostic thoracentesis is that one must not use a sharp needle for the therapeutic thoracentesis. As the fluid is removed, the lung expands and can easily be lacerated if a sharp needle is present in the pleural space. Therefore, either a plastic catheter or a blunt pleural biopsy needle should be used for therapeutic thoracentesis. If a pleural biopsy is also indicated, the therapeutic thoracentesis can be performed through the pleural biopsy needle once the biopsy specimens have been obtained.

The additional materials required for the procedure are listed in Table 28.1. It is recommended that the Arrow-Clark™ Pleura-Seal® or the Argyle™ Turkel™ thoracentesis kits be used for therapeutic thoracentesis. Directions for their use come with the kits and additional information is available on the Internet. When these kits are used, it is important to make a large enough incision in the skin to allow easy passage for the needle with its overlying catheter. If the incision is too small, the catheter may be damaged

during the insertion. It is important to use a kit with a catheter over a needle, rather than one that only has a sharp needle. The Arrow-Clark™ Pleura-Seal® or the Argyle™ Turkel™ thoracentesis kits are recommended because they each contain the catheter and they each have a device that prevents air from entering the pleural space when the needle is withdrawn (see the discussion on these kits earlier in this chapter).

If these kits are not available, the procedure can be performed with a plastic catheter (Intracath) as outlined in Figure 28.3. When the fluid has been localized and identified by means of the lidocaine-filled syringe, as in diagnostic thoracentesis, a standard 16-gauge (Intracath) needle is attached to a plastic syringe. With gentle constant suction on the syringe, the needle is carefully and evenly advanced until pleural fluid is obtained. When the pleural fluid has been obtained, the syringe is disconnected from the needle, and the needle is temporarily occluded by a finger to prevent the development of a pneumothorax. Then, the 16-gauge (Intracath) catheter is inserted through the needle and is directed inferiorly

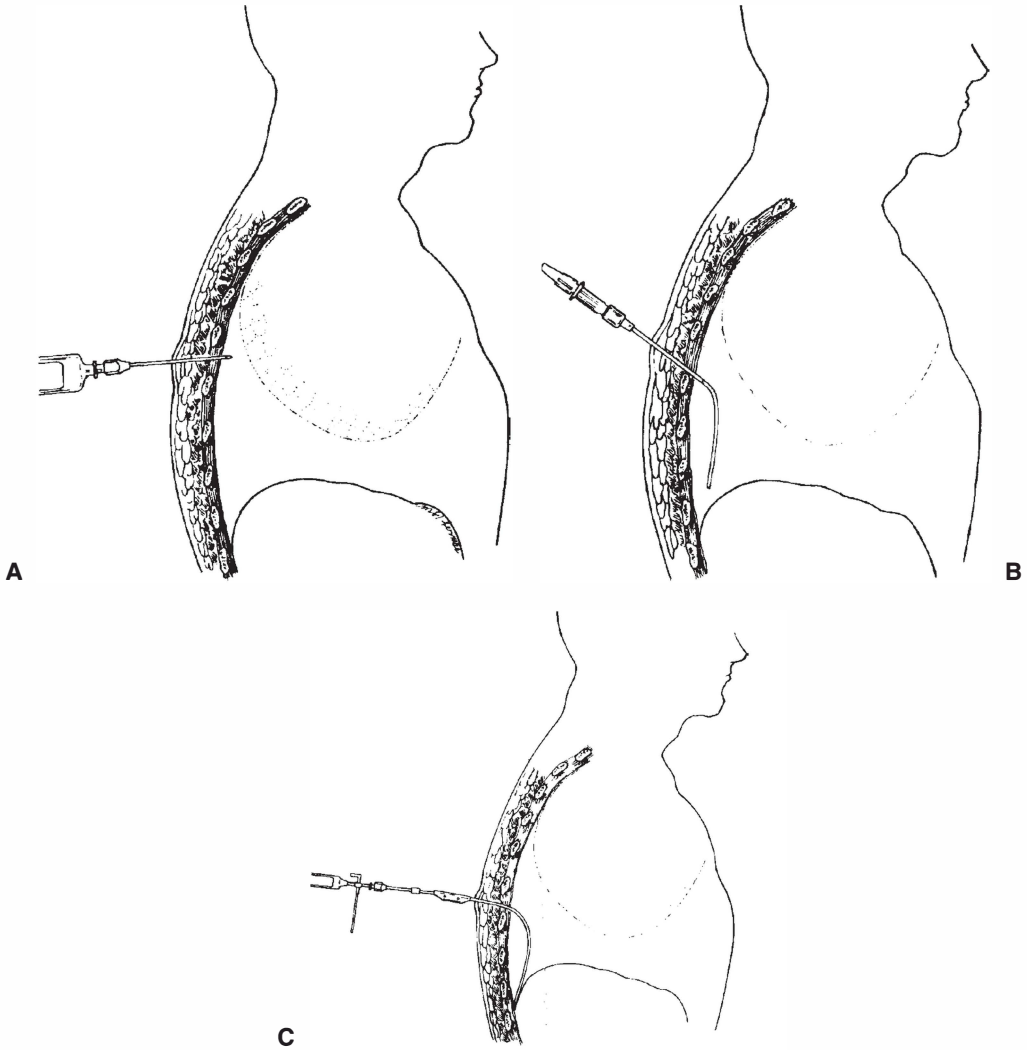

FIGURE 28.3 ■ Therapeutic thoracentesis. **A**: A standard 14-gauge needle attached to a syringe is introduced into the pleural space. **B**: A 14-gauge catheter is threaded through the needle and is directed down toward the costodiaphragmatic recess. **C**: The needle is withdrawn from the pleural space, and its end is covered immediately with the guard. Fluid can be withdrawn from the pleural space using the three-way stopcock and the syringe.

toward the costodiaphragmatic recess. The catheter should not be advanced against resistance or its end may become traumatized and occluded. When the catheter has been advanced all the way to the hilt of the needle or when resistance is encountered, the needle is withdrawn carefully from the chest and the plastic catheter is left in the pleural space.

Immediately after withdrawing the needle, one should place the guard over the end of the needle so that the needle does not shear off the end of the catheter. The catheter should not be pulled back through the needle because the needle's sharp point may cut off a portion of the catheter. Once the needle is withdrawn from the pleural space, the catheter should be taped to the patient's skin so that it is not inadvertently removed from the pleural space.

The advantage of the plastic catheter system for therapeutic thoracentesis is that no sharp needle is present in the pleural space to lacerate the lung as it reexpands. Moreover, the patient can be repositioned with the catheter in place to allow more complete pleural fluid removal. When the catheter has been positioned in the pleural space, the needle has been withdrawn, and the needle's end has been covered with the guard, a syringe with a three-way stopcock is attached to the end of the catheter, and the pleural fluid is withdrawn. Alternatively, the fluid can be drained by vacuum bottles. There are no studies comparing the side effects with syringe versus vacuum bottle drainage.

A chest radiograph is not routinely indicated after a therapeutic thoracentesis to rule out pneumothorax unless the patient has developed symptoms, air is obtained during the thoracentesis, or the tactile fremitus has disappeared over the superior aspect of the ipsilateral hemithorax. Nevertheless, a postprocedure chest radiograph is frequently indicated in patients with undiagnosed pleural effusions who undergo a therapeutic thoracentesis to assess the appearance of the lung in the absence of the fluid. If the therapeutic thoracentesis was performed mainly for diagnostic purposes, it is sometimes useful to obtain bilateral decubitus radiographs after the procedure to delineate the amount of fluid remaining and to distinguish the remaining fluid from parenchymal infiltrates or masses. Similarly, it may be useful to inject 200 to 400 mL air into the pleural space at the end of the procedure before obtaining the radiographs. By means of this intentional iatrogenic pneumothorax, the thickness of the visceral and parietal pleura can be determined.

How Much Pleural Fluid Can Be Withdrawn?

It is not clear how much fluid can be safely withdrawn during a therapeutic thoracentesis. Occasionally, reexpansion pulmonary edema (see subsequent section) may develop following therapeutic thoracentesis. Because the reexpansion pulmonary edema is at times fatal, it is important to prevent it.

It has been hypothesized that the development of reexpansion pulmonary edema is related to the development of negative pleural pressure during therapeutic thoracentesis (32). We have demonstrated that large volumes of pleural fluid can be removed safely if the pleural pressure is monitored during thoracentesis and if thoracentesis is terminated when the pleural pressure falls below -20 cm H_2O (32). Pleural pressure can be monitored by a U-shaped manometer, as illustrated in Figure 28.4. The pleural pressures can also be measured with the pressure transducers that are used to measure intravascular pressures (33). The change in the pleural pressure as fluid is withdrawn varies from patient to patient (Fig. 28.5). Frequently, neither the operator nor the patient is aware of the development of abnormally negative pleural pressure (33). In our series of 52 patients, 13 procedures (25%) were stopped because the patient's pleural pressures dropped below -20 cm H_2O. We have now

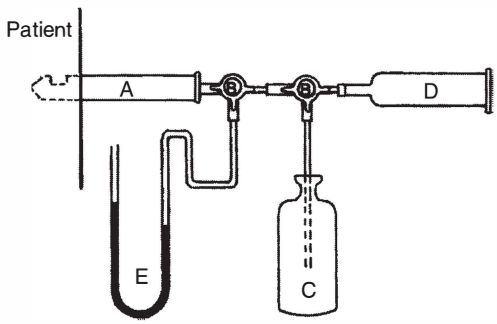

FIGURE 28.4 ■ Schematic diagram of apparatus used to measure pleural pressures and to aspirate pleural fluid. To measure the pleural pressure, the stopcock (B) adjacent to the Abram's needle (A) is turned so that the pleural space is in communication with the manometer (E). It is important while measuring the pressure not to let fluid enter the plastic catheter between the tube and the manometer. Bottle (C); 60-mL syringe (D). (From Light RW, Jenkinson SG, Minh V, et al. Observations on pleural pressures as fluid is withdrawn during thoracentesis. *Am Rev Respir Dis.* 1980;121:799–804, with permission.)

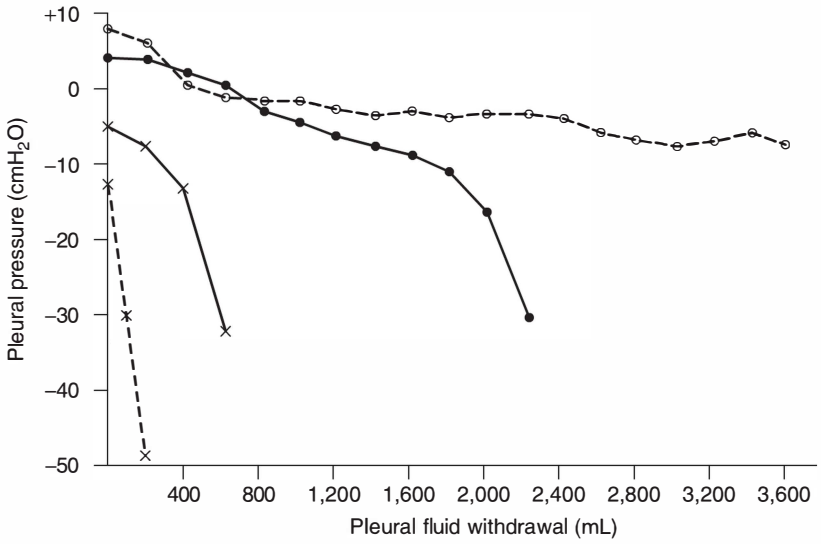

FIGURE 28.5 ■ Changes in pleural pressure as fluid is withdrawn during therapeutic thoracentesis in two patients with malignant pleural disease (*circles*) and in two patients with trapped lung ("*x*"s). Note how rapidly the pleural pressures fall in the patients with trapped lung. (From Light RW, Jenkinson SG, Minh V, et al. Observations on pleural pressures as fluid is withdrawn during thoracentesis. *Am Rev Respir Dis.* 1980;121:799–804, with permission.)

removed more than 4,000 mL pleural fluid in a single thoracentesis from each of eight separate patients with no adverse consequences. Villena et al. (34) confirmed these observations in a series of 57 patients. They removed more than 1,500 mL from 29 patients with pleural pressure monitoring and had no instances of reexpansion pulmonary edema (34). In their 57 patients, the thoracentesis was stopped in 16 (28%) due to excessively negative (<-20 cm H_2O) pleural pressure without any symptoms, in 29 patients (51%) due to the development of symptoms (chest pain, cough, or chest tightness), in 10 patients (18%) because no more fluid could be obtained, and in 2 patients (4%) because the physician considered that too much fluid had been evacuated. In another study, Jones et al. (13) performed 941 therapeutic thoracenteses without pressure monitoring. The procedure was terminated if the patient developed chest pain, more than minimal coughing, or shortness of breath, or if no more fluid could be obtained. In this series, reexpansion pulmonary edema only occurred in two patients from whom 1,000 and 1,200 mL pleural fluid had been withdrawn. In this series, more than 1,000 mL of fluid was removed with 201 procedures, more than 1,500 mL with 119 procedures, and more than 2,000 mL with 53 procedures (13). Feller-Kopman et al. (35) measured pleural pressures in 185 patients undergoing a thoracentesis of greater than 1,000 ml and reported that only five patients developed reexpansion pulmonary edema. The reexpansion pulmonary edema was not related to pleural pressure or pleural pressure changes. In view of these latter series, it is recommended that no limit be placed on the amount of pleural fluid withdrawn during a therapeutic thoracentesis. However, the procedure should be stopped if the patient develops more than minimal coughing, chest tightness, chest pain, or shortness of breath.

Complications

Therapeutic thoracentesis is associated with the same complications as diagnostic thoracentesis, including vasovagal reaction, pneumothorax, pleural infection, and hemothorax. In addition, reexpansion pulmonary edema and hypovolemia may complicate therapeutic thoracentesis, and, as mentioned earlier, these complications may be related to the development of abnormally negative pleural pressures. Pneumothorax is more common with therapeutic than with diagnostic thoracentesis for two reasons. First, if a sharp needle is used for therapeutic thoracentesis, the lung is likely to be lacerated as it reexpands, leading to a bronchopleural fistula and a pneumothorax. Second, because the pleural pressure

at times becomes quite negative during a therapeutic thoracentesis, air is more likely to enter the pleural space through faulty technique or even through the thoracentesis tract.

The treatment of iatrogenic pneumothorax is discussed in Chapter 24. A special situation exists in some patients with malignant pleural effusion who undergo therapeutic thoracentesis. In the series of Boland et al. (36), therapeutic thoracentesis was performed on 512 patients with malignant pleural effusion over a 3-year period. Pneumothoraces were documented in 40 patients (8%), and 29 were treated with tube thoracostomy. However, the pneumothorax in 17 of the 29 (59%) persisted despite the application of suction and the insertion of larger (28 to 36 F) chest tubes. After the drainage catheters were removed, the effusion completely reaccumulated in all patients. This study demonstrates that a small subgroup of patients with malignant pleural effusions who undergo therapeutic thoracentesis develop asymptomatic hydropneumothoraces due to poor lung compliance. If a chest tube is inserted in these patients, the lung will not reexpand and there will be no evidence of a bronchopleural fistula. In such a situation, the chest tube should be removed as soon as the situation is recognized.

REEXPANSION PULMONARY EDEMA

Reexpansion pulmonary edema is characterized by the development of unilateral pulmonary edema in a lung that has been rapidly reinflated following a variable period of collapse secondary to a pleural effusion or pneumothorax (37). Unilateral pulmonary edema is associated with a variable degree of hypoxia and hypotension, sometimes requiring intubation and mechanical ventilation, and occasionally leading to death (38,39).

Pathophysiologic Features

The exact mechanisms responsible for reexpansion pulmonary edema are not known. In the experimental animal, reexpansion pulmonary edema occurs only if the lung has been collapsed for several days and if negative pressure is applied to the pleural space. Miller et al. (40) studied monkeys in which a pneumothorax had been present for 1 hour or 3 days. These researchers found that reexpansion pulmonary edema occurred only when the pneumothorax had been present for 3 days and the lung was reexpanded with −10 mm Hg pleural pressure. No pulmonary edema developed if the lung was reexpanded by underwater-seal drainage after 3 days of collapse or if negative pressure was used in a lung that had been collapsed for only 1 hour.

In a study in rabbits, Pavlin and Cheney (41) found that reexpansion pulmonary edema was much more extensive in lungs that had been collapsed for 7 days than in those that had been collapsed for 3 days. Reexpansion with −20 mm Hg pleural pressure led to no more edema than did reexpansion with positive airway pressure, but reexpansion with −40 mm Hg or −100 mm Hg increased the amount of edema. In some of these animals, contralateral pulmonary edema also developed, but to a lesser extent than in the ipsilateral lung (41). Some cases of reexpansion pulmonary edema in humans, however, have occurred when no negative pressure was applied to the pleural space (42,43). Almost all cases of reexpansion pulmonary edema occur when the pneumothorax or pleural effusion has been present for at least 3 days.

Reexpansion pulmonary edema appears to be due to increased permeability of the pulmonary vasculature. In both humans (44) and rabbits (45), the edema fluid has a high protein content, suggesting that it is leakiness of the capillaries rather than an increased hydrostatic pressure gradient that leads to the edema. Pavlin et al. (46) have hypothesized that the mechanical stresses applied to the lung during reexpansion damage the capillaries and lead to the development of pulmonary edema. There is no evidence that the collapsed lung has increased permeability before reinflation (46).

An alternate hypothesis that has become popular is that reexpansion pulmonary edema is due to a reperfusion injury (47,48). With atelectasis, hypoxia of the atelectatic lung may be severe because oxygen delivery to the lung is reduced by absent ventilation and hypoperfusion. Then when the hypoxic areas are reperfused, oxygen-free radical formation is promoted and lung injury can result. If the lung is only partially collapsed, the reexpansion edema sometimes occurs only in the part of the lung that has been atelectatic (49). Mechanical stress is probably not the sole factor responsible for reexpansion pulmonary edema because the edema is associated with neutrophil influx into the lung in both animals (50) and humans (51), and the edema fluid contains interleukin-8 and leukotriene B_4. Neutrophils are not responsible for the reexpansion edema, however, because neutrophil depletion in the animal model does not prevent its occurrence (50). The reperfusion injury hypothesis is

supported by the observation that the administration of an increased Fio_2 (40%) for the duration of the pneumothorax prevents edema when lungs are reexpanded (52). Supplemental oxygen eliminates the systemic hypoxemia although the lung is collapsed. Additional support for this hypothesis is provided by the observation that the administration of antioxidants before reexpansion minimizes both the permeability edema and the degree of inflammation in rabbits (53).

Clinical Manifestations

Patients who develop reexpansion pulmonary edema typically develop pernicious coughing or chest tightness during or immediately following thoracentesis or chest tube placement. The cough sometimes is productive of copious amounts of frothy pink sputum. Other symptoms include dyspnea, tachypnea, tachycardia, fever, hypotension, nausea, vomiting, and cyanosis. The symptoms progress for 24 to 48 hours, and the chest radiograph reveals pulmonary edema throughout the ipsilateral lung. Pulmonary edema may also develop in the contralateral lung (42,54). If the patient does not die within the first 48 hours, recovery is usually complete. The seriousness of the syndrome is emphasized by reports that it has been responsible for the death of healthy, young individuals. In one review of the subject, the outcome was fatal in 11 of 53 reported cases (20%) (42). The overall mortality rate is probably much less than 20% because fatal cases are more likely to be reported than are nonfatal cases.

The incidence of reexpansion pulmonary edema is not known, but it is thought to be uncommon. Until 1988, a total of only 53 cases had been reported (53). With therapeutic thoracentesis, the incidence is very low. Jones et al. (13) reported that reexpansion pulmonary edema occurred after only 2 of 941 therapeutic thoracenteses. In this series, no pleural pressure monitoring was performed and 119 patients had more than 1,500 mL pleural fluid withdrawn. Milanez de Campos et al. (55) reported that reexpansion pulmonary edema occurred in 2% of 500 patients who underwent thoracoscopy and talc insufflation for treatment of recurrent pleural effusion. In the Veterans Administration (VA) cooperative study on spontaneous pneumothorax, there were no cases of reexpansion pulmonary edema among the 229 study subjects despite the use of suction in more than 80% of the cases (56). In another study of 320 patients treated with tube thoracostomy for spontaneous pneumothorax, the incidence of reexpansion pulmonary edema was 1% (57).

Prevention

The possibility of reexpansion pulmonary edema should be considered in patients with large pleural effusions or pneumothoraces of more than a few days' duration who are undergoing tube thoracostomy or thoracentesis. When tube thoracostomy is performed for spontaneous pneumothorax, the tubes should be connected to an underwater-seal drainage apparatus rather than to a negative pressure apparatus in view of the animal studies of Miller et al. (40) and Pavlin and Cheney (41). If underwater-seal drainage does not effect reexpansion of the underlying lung within 24 to 48 hours, then negative pressure can be applied to the pleural space.

When a therapeutic thoracentesis is performed, the procedure should be stopped if the patient develops chest tightness, chest pain, shortness of breath, or more than minimal coughing. However, as discussed in the preceding text, no firm limit needs to be set on the amount of fluid that is withdrawn.

Treatment

The treatment of reexpansion pulmonary edema is primarily supportive with intravenous fluids, oxygen, and morphine. Diuresis may be detrimental and should be avoided (57). Suggested escalating levels of treatment include no treatment for an abnormality on radiography alone; nasal supplemental oxygen for mild hypoxemia; continuous positive airway pressure through face mask for moderate hypoxemia (58), and intubation, mechanical ventilation, and PEEP for severe hypoxemia; and volume replacement and inotropic agents for hypotension with low cardiac output (37).

NEEDLE BIOPSY OF THE PLEURA

Training Requirements

The guidelines from the American College of Chest Physicians recommend that physicians who perform needle biopsy of the pleura should be competent in thoracentesis, familiar with the mechanisms and technique of the biopsy needle being used and competent to recognize and treat the common complications. Trainees should perform at least five procedures in a supervised setting to establish basic competency. Then to maintain competency, dedicated operators should perform at least five procedures per year (59).

Indications

With a needle biopsy of the pleura, a small piece of the parietal pleura is obtained for microscopic or microbiologic evaluation. The main diagnoses established with a needle biopsy of the pleura are tuberculous pleuritis and malignancy of the pleura. The biopsy can either be done blindly or it can be image guided. Currently, blind needle biopsy of the pleura is used less than in the past because the diagnosis of tuberculous pleuritis can be made by measuring the adenosine deaminase (ADA) or interferon-gamma level in the pleural fluid, the diagnosis of pleural malignancy is usually established by pleural fluid cytology or thoracoscopy (60) and image guided biopsies provide higher yields (61,62). At the University of Texas, Galveston, 174 biopsies of the pleura were performed between 1996 and 2006 including 103 (59%) blind, 38 (22%) image guided, and 33 (19%) thoracoscopically or at thoracotomy (61). The diagnostic yield with the three procedures was 42%, 79%, and 93%, respectively (61). The proportion of blind pleural biopsies declined from 78% in 1996 to 27% in 2006 (61).

A needle biopsy of the pleura is currently recommended when tuberculous pleuritis is suspected and the pleural fluid ADA or interferon-gamma levels are not definitive. A needle biopsy of the pleura is also recommended when malignancy is suspected but the pleural fluid cytology is negative. It is recommended that most needle biopsies be image guided.

Contraindications

The main contraindication to a pleural biopsy is a bleeding diathesis. A pleural biopsy should not be performed in patients who are taking anticoagulants or whose bleeding parameters are prolonged. If the platelet count is below 50,000/mm^3, platelet transfusion should be given before the procedure is attempted. If the patient has borderline respiratory failure, one should hesitate to perform a pleural biopsy because the production of a pneumothorax could precipitate respiratory failure.

Another contraindication to needle biopsies is the presence of an empyema. In one series, subcutaneous abscesses developed at the biopsy site in two of five patients with empyema in whom a pleural biopsy was attempted (63). Other contraindications include an uncooperative patient and local cutaneous lesions such as pyoderma or herpes zoster infection.

Technique

The materials necessary for pleural biopsy are listed in Table 28.1. Most frequently, one uses a thoracentesis kit plus the pleural biopsy needle. When there is a moderate or larger pleural effusion, the biopsy is usually done with no imaging. If the effusion is small or loculated, then either ultrasound or computed tomography (CT) can accurately identify the location of the fluid. Ultrasound is the preferred technique for guiding biopsy because it offers the advantage of a real-time approach to the biopsy and has the added advantages of the absence of ionizing radiation, portability, ready availability, and low expense. Because the patient can be imaged in the erect position, the depth of the fluid is maximized, thereby minimizing complications (64).

The patient is positioned, and the site is selected as for diagnostic thoracentesis (described earlier in this chapter). The skin is cleaned, and the local anesthetic is administered as for diagnostic thoracentesis. Liberal amounts of lidocaine should be injected once the rib is passed to ensure adequate anesthesia of the parietal pleura. In general, if no fluid is obtained with the local anesthetic, biopsy should not be attempted. When pleural fluid has been obtained with the lidocaine syringe and needle, a pleural biopsy can be performed with an Abram's or a Cope needle. A biopsy is sometimes attempted without free pleural fluid. If there is no fluid, the procedure should be performed with ultrasonic or CT guidance (64).

Abram's Needle

The Abram's needle (Fig. 28.6) consists of three parts: a large outer trocar, an inner cutting cannula, and an inner solid stylet. The end of the outer trocar is blunt so that the instrument will not lacerate the lung, but the bluntness of the instrument requires one to make a small scalpel incision in the anesthetized skin and subcutaneous tissue to permit insertion of the biopsy needle without undue force. This

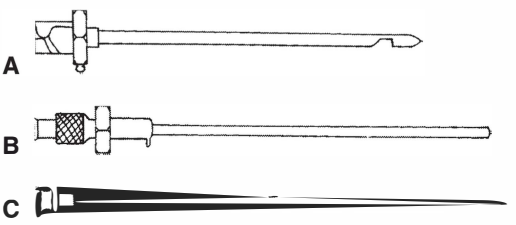

FIGURE 28.6 ■ **A**: Large outer trocar. **B**: Inner cutting cannula. **C**: Stylet.

incision should be made along the lines of cleavage to minimize postoperative scarring. The inner cutting cannula (Fig. 28.6B) fits tightly in the outer trocar (Fig. 28.6A) and can be locked in one of two positions: (a) a closed position in which the inner cannula obstructs the notch on the outer trocar to make the needle airtight and (b) an open position in which the inner cannula is slightly withdrawn so that the notch on the outer trocar is not occluded. An indicator knob in the hexagonal grip of the larger outer trocar indicates the position of the notch in the distal end of the trocar.

To insert the Abram's pleural biopsy needle, the stylet is placed in the inner cannula, which, in turn, is placed in the outer trocar. The inner cannula (Fig. 28.6B) is twisted clockwise to close the distal notch of the outer trocar. The needle is pushed into the pleural space by exerting firm pressure on the stylet. Because the needle has a large diameter and is blunt, a substantial amount of pressure is needed. Usually, a pop is heard as the needle enters the pleural space. The inability to pass the needle into the pleural space is usually because of an insufficiently large skin incision. At times, the ribs are too close together to allow the needle to pass. In such situations, rotation of the patient's arm and shoulder over his or her head frequently separates the ribs sufficiently.

Once the tip of the needle is thought to be in the pleural space, the inner stylet (Fig. 28.6C) is removed, and with the inner cannula in the closed position, a syringe is attached to the connection on the inner cannula. Then, the inner cannula is rotated counterclockwise in the outer trocar so that the distal notch is locked open (Fig. 28.7A). At this time, pleural fluid may be aspirated for diagnostic studies. When the desired fluid has been obtained, the inner cannula of the needle is rotated clockwise to occlude the distal notch so that the syringe can be changed without creating a pneumothorax. A 10- to 20-mL syringe is then attached to the needle, and the inner cannula is rotated to open the distal notch. The entire needle is then rotated so that the knob on the outer trocar is inferior. This is important so that the blood vessels and nerves that lie immediately below the rib will not be biopsied. The biopsy needle is then slowly withdrawn with constant aspiration until it hooks onto the pleura (Fig. 28.7B). When the needle hooks, one can be sure that parietal pleura is in the notch of the needle if pleural fluid can still be aspirated through the syringe. When the needle is hooked on the pleura, the outer trocar is held firmly with one hand while the inner cannula is rotated into the closed position with the other hand to cut off a small piece of parietal pleura (Fig. 28.7C). Usually, mild resistance is met immediately before the needle is completely closed, and this resistance is because the inner cannula is severing the entrapped pleura for the biopsy specimen.

Once the initial biopsy specimen is obtained, the needle can either be withdrawn from the pleural space in the closed position or reinserted into the pleural space. If the needle is withdrawn from the chest, the pleural biopsy specimen is found in the tip of the needle and can be closely examined, but the needle then has to be reinserted. Reinsertions of the needle are through the same tract, however, and are easier than the original insertion. If the needle is reinserted into the pleural space without a complete withdrawal, the tissue specimen can be aspirated through the syringe. The biopsy procedure can be repeated without

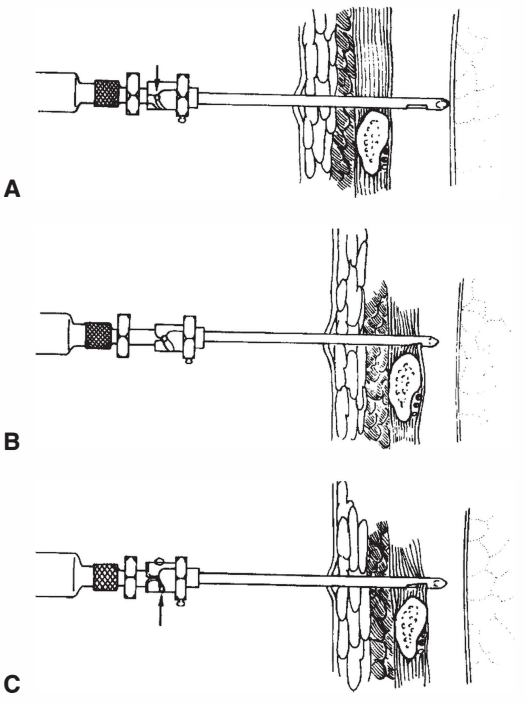

FIGURE 28.7 ■ **A**: Abram's needle in pleural space with notch open so that fluid can be aspirated. **B**: Abram's needle snagging the parietal pleura. **C**: The biopsy is obtained when the inner cutting cannula closes the notch in the outer trocar and shears off parietal pleura and anything else that remains in the notch. The *arrow* points to the pin on the inner cannula that locks into the outer trocar in either the open or the closed position.

removing the biopsy needle. The difficulty in not withdrawing the needle is that the biopsy specimen sometimes becomes lodged in the syringe or is confused with a pleural fluid clot. I prefer to remove the pleural biopsy needle after obtaining each biopsy specimen. Whenever the Abram's pleural biopsy needle is withdrawn from the pleural space, the biopsy tract should be occluded with a finger immediately after the needle is withdrawn to decrease the likelihood of a pneumothorax.

At least four separate biopsy specimens should be obtained. Three of the four should be placed in formalin and taken to the pathology laboratory, and the fourth should be placed in a saline-containing sterile tube and sent to the tuberculosis laboratory to be ground up and cultured for mycobacterium and fungus. If electron microscopy is indicated, for example, for suspected mesothelioma, an additional pleural biopsy should be placed in glutaraldehyde. Once the biopsy specimens are obtained, a therapeutic thoracentesis can be performed through the Abram's needle. The pleural fluid should be removed only after obtaining the biopsy specimens because the pleural fluid separates the parietal and visceral pleura, and increases the safety of the procedure.

When the Abram's needle is withdrawn for the last time, the biopsy site should be massaged for a short time to eradicate the needle tract. Then a small adhesive bandage should be placed over the biopsy incision in a crosswise manner to act as a butterfly-type dressing. Occasionally, pleural fluid exits or air enters through the biopsy tract after the procedure, particularly in patients who are debilitated and thin with poor tissue turgor. If this should happen, the biopsy site should be closed with a purse-string suture. Chest radiographs should be obtained on all patients after pleural biopsies.

Raja Needle

The Raja needle is very similar in design to the Abram's needle except that it has a self-opening stainless steel biopsy flap mounted on the inner tube (65,66). When the Raja needle is withdrawn from the pleural space, the biopsy flap catches the parietal pleura. In the hands of the inventor, the Raja needle provides larger biopsy specimens than the Abram's needle in the experimental situation (65). In addition, the developer has reported that there is a significantly higher diagnostic yield with the Raja needle compared with the Abram's needle (66). Until these findings are confirmed by investigators without a personal interest in the Raja needle, the Raja needle is not recommended.

Cope Needle

The Cope needle (Fig. 28.8) consists of four separate parts: (a) a large outer cannula with a square but sharp end; (b) a hollow, blunt-tipped, hooked biopsy trocar; (c) a hollow-beveled trocar; and (d) a solid thin obturator or stylet. To insert the outer cannula (Fig. 28.8A) into the pleural space, the stylet (Fig. 28.8D) is inserted into the hollow-beveled trocar (Fig. 28.8C), which, in turn, is placed in the large outer cannula. Then, this apparatus is inserted through a small skin incision into the pleural space. The stylet and the hollow-beveled trocar must then be removed from the outer cannula and replaced by the hollow, blunt-tipped, hooked biopsy trocar (Fig. 28.8B). This maneuver is performed at the end of a normal expiration while the patient is holding his breath, by removing the hollow-beveled trocar and the stylet, and by placing the operator's thumb over the end of the outer cannula to prevent a pneumothorax. A syringe may be attached to the outer cannula to obtain fluid for diagnostic studies at this time. Then, with the patient again holding his breath, the hooked biopsy trocar, to which a 10- or 20-mL syringe has been attached, is inserted through the large outer cannula into the pleural space. If a syringe is not attached to the hooked biopsy trocar, it should be occluded with a stopcock or the operator's thumb.

The right-angled projection on the proximal end of the hooked biopsy trocar indicates the direction of the distal biopsy hook. To obtain a biopsy, the apparatus is withdrawn with the hook directed inferiorly so as not to ensnare any nerves, veins, or arteries until the hooked biopsy trocar engages the parietal pleura (Fig. 28.9A). Then, with one hand, the engaged hook is held steady with a continual outward pulling motion, while the other hand advances the

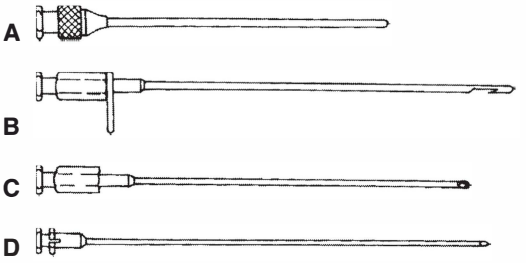

FIGURE 28.8 ■ Cope pleural biopsy needle. **A**: Outer cannula. **B**: Hollow, blunt-tipped, hooked biopsy trocar. **C**: Hollow-beveled trocar. **D**: Obturator or stylet.

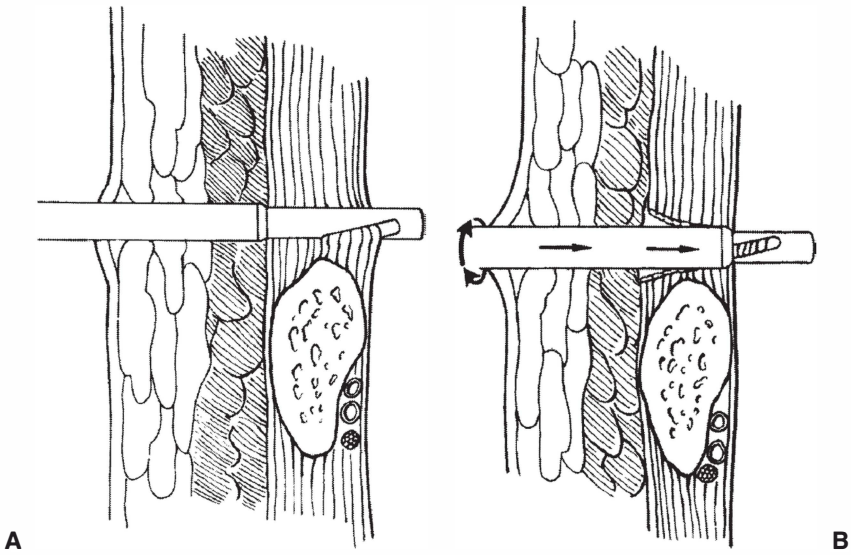

FIGURE 28.9 ■ A: The parietal pleura is hooked with the hollow, blunt-tipped biopsy trocar. **B**: The biopsy specimen is obtained by advancing the outer cannula with a rotary motion (*arrows*) to sever the engaged piece of pleura.

large outer cannula toward the pleural space using a rotary motion to sever the engaged piece of pleura (Fig. 28.9B). Then, the hooked biopsy trocar containing the tissue specimen is removed while the patient holds his breath, and the hooked trocar is replaced with the beveled trocar and obturator before the procedure is repeated for an additional biopsy specimen. Once the required biopsy specimens have been obtained, a therapeutic thoracentesis may be performed by attaching a large syringe and a three-way stopcock to the outer cannula.

The biopsy site and the biopsy specimens are handled identically with both Abram's and Cope pleural biopsy needles.

Abram's versus Cope Needles

The rate of success in obtaining a pleural biopsy specimen depends more on the skill of the operator than on the choice of instruments (67). Morrone et al. (68) obtained pleural biopsies simultaneously with the Abram's and Cope needles, and they reported that the diagnostic yields were virtually identical. The Abram's needle provided slightly larger specimens and was slightly superior in detecting mesothelial cells. The Cope needle provided larger specimens of intercostal muscle. The Abram's needle is generally preferred to the Cope needle, however, because it is easier to use, it is a closed system and hence the likelihood of a pneumothorax is decreased, it provides a larger biopsy specimen, and it is safer for concomitant therapeutic thoracentesis because the end of the outer cannula is blunt.

Image–Guided Needle Biopsy

The use of image-guided needle biopsy of the pleura has become much more widespread in the past decade. The reason for this is that it is more effective at establishing a diagnosis than is blind needle biopsy. The biopsy can be either CT (62,69) or ultrasound-guided (70) and either an Abram's needle (69,70) or a cutting-needle (62,70) can be used. Maskell et al. (62) randomly assigned 50 patients with unilateral pleural effusion and a clinical suspicion of malignancy to Abram's needle biopsy of the pleura or CT-guided cutting-needle biopsy. The CT-guided biopsy was made where the pleura was the most thickened, and, at most, two biopsies were performed. The Abram's needle biopsy was not necessarily aimed where the pleural thickening was greatest. The diagnosis of malignancy was made in 13 of 15 patients (87%) with the CT-guided biopsy but in only 8 of 17 patients (47%) with the Abram's needle (62). These results look very promising but it should be noted that 20 of the 27 patients with malignancy in this study had mesothelioma that is notoriously difficult to diagnose with Abram's needle biopsy of the pleura. Metintas et al. (71) earlier reported that they were

able to establish the diagnosis of malignant mesothelioma in 25 of 30 patients (83.3%) with CT-guided closed pleural needle biopsy using an Abram's pleural biopsy needle. Metintas et al. (69) subsequently randomized 124 patients suspected of having pleural malignancy to CT guided biopsy with an Abram's needle or thoracoscopy. They reported that the diagnostic sensitivity was 87.5% in the needle biopsy group and 94.1% in the thoracoscopy group which did not differ significantly (69). In the needle biopsy group the diagnostic sensitivity was 80% with malignant mesothelioma (12/15), 93% with malignant effusion due to lung cancer (14/15), 88% with malignancy from other organs (7/8), and 90% in tuberculous pleuritis (9/10) (69). Koegelenberg et al. (70) using ultrasound guidance performed four Abram's needle biopsies and four Tru-cut needle biopsies on 89 patients suspected of having tuberculous pleuritis. They reported that biopsies with the Abram's needle were more likely to contain pleural tissue (91%) than were the biopsies obtained with the Tru-cut needle (79%) and were more likely to establish the diagnosis of tuberculous pleuritis (82% vs. 65%) (70).

Complications

Pleural biopsy has the same complications as diagnostic thoracentesis. One might expect pneumothorax to be more common with pleural biopsy than with thoracentesis for two reasons. First, the atmosphere has much more opportunity to be in communication with the pleural space with the biopsy, particularly when the Cope needle is used. Second, when the biopsy specimen is obtained, the visceral pleura may be inadvertently incised, leaving a small bronchopleural fistula that can lead to a large pneumothorax. However, the incidence of pneumothorax and the requirement for tube thoracostomy are comparable after thoracentesis and pleural biopsy (72). This is probably because more experienced individuals usually perform the pleural biopsy.

The second major complication of pleural biopsy is bleeding. If an intercostal artery or vein is inadvertently biopsied, a hemothorax can result (63,73). There is one case report of an arteriovenous fistula from an intercostal artery to an intercostal vein developing after pleural biopsy (74). The fistula subsequently ruptured causing a hemothorax. The pleural biopsy needle can also be mistakenly inserted into the liver, spleen, or kidney. Although hepatic or kidney tissue may be demonstrated in the biopsy specimen, the patient usually suffers no significant adverse effects. Penetration of the spleen frequently requires splenectomy (75), however, and one should therefore be careful not to perform pleural biopsy or thoracentesis too far inferiorly on the left side.

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chapter 29

Chest Tubes

Chest tubes are frequently used in the practice of pulmonary medicine. Indeed, in 1995, it was estimated that 1,330,000 chest tubes were placed in the United States (1). However, it has been my impression that many medical personnel do not understand how the drainage system for chest tubes functions and how to troubleshoot problems with chest tubes. In this chapter, the various methods of inserting chest tubes are discussed, followed by a more in-depth discussion of the different drainage systems used with chest tubes, plus recommendations for troubleshooting-related problems. The indications for chest tube insertion with pneumothorax, hemothorax, empyema, and malignant pleural effusion are discussed in the respective chapters on these entities.

CHEST TUBE SIZE

In general, there has been a tendency over the past decade to use smaller (10–14 F) chest tubes (2–4). The advantages of the small-bore catheters are that they are easier to insert and there is less pain with their insertion and while they are in place. Small-bore chest tubes are recommended when pleurodesis is performed. Small-bore chest tubes are also recommended for the treatment of pneumothorax. However, patients on mechanical ventilation with barotrauma induced pneumothoraces are best managed with large-bore chest tubes (2). Small-bore catheters are also recommended for complicated parapneumonic effusions (5). When a small-bore chest tube is used to treat a complicated parapneumonic effusion, it should be flushed with 20 to 30 ml saline every 6 hours via a three-way stopcock (5). Patients with hemothorax are best managed with large-bore (>20 F) chest tubes because of blood clots and the high volume of pleural fluid (2). In the largest series (6) to date, 1,092 patients had (12 F) catheters inserted using guidewires. The percentages of successful cases were 93.8% of 324 malignant effusions, 93% of 399 pneumothoraces, 92.3% of 272 nonmalignant effusions, and 74.2% of 97 empyemas (6).

CHEST TUBE INSERTION

In general, chest tubes are inserted into the pleural space by four methods: tube thoracostomy with a guidewire and dilators, tube thoracostomy with a trocar, operative tube thoracostomy, and tube thoracoscopy through a single-port thoracoscope. There are no controlled studies comparing the efficacy of the different methods of placing chest tubes (2). It has been recommended that most chest tubes be placed in the "triangle of safety" which is the area bordered by the lateral edge of the latissimus dorsi and the lateral border of the pectoralis major and superior to the horizontal level of the fifth intercostal space (4). This position minimizes the risk to underlying structures and avoids damage to muscle and breast tissue.

Training Requirements

The guidelines from the American College of Chest Physicians recommend that trainees should perform at least 10 procedures in a supervised setting to establish basic competency. Then to maintain competency, dedicated operators should perform at least five procedures per year (7).

Guidewire Tube Thoracostomy

This is probably the easiest way to insert a chest tube. In many hospitals, chest tubes are inserted by a radiologist, who uses this technique with either ultrasound

or computed tomography (CT) guidance (8,9). Commercial kits are available for guidewire tube thoracostomy. This procedure uses the Seldinger technique with guidewires and dilators (10). In general, after the skin, periosteum, and parietal pleura are anesthetized as is done for pleural biopsy (see Chapter 28), an incision is made in the skin that is ample to permit passage of the chest tube of desired size (Fig. 29.1A). Then, an 18-gauge needle attached to a syringe is introduced into the pleural space. Fluid or air is aspirated to confirm the intrapleural position (Fig. 29.1B). The syringe is removed, and the "J" wire is threaded through the needle in the desired direction into the pleural space (Fig. 29.1C). The needle is then removed, and more local anesthetic is injected into the intercostal muscles surrounding the wire. The smallest dilator is inserted, and with a rotating movement, it is advanced into the pleural space over the guidewire (Fig. 29.1D). The wire should always project out beyond the end of the dilator or inserter. The first dilator is removed, leaving the wire in place. Then the next size dilator is advanced over the guidewire into the pleural space and removed. Finally, the chest tube containing the inserter is threaded over the guidewire (Fig. 29.1E). The tube should pass readily, following the path made by the dilators and guided by the wire (10). It is important to make certain that all of the side holes in the tube are in the pleural space.

Once the tube is in place, the inserter and the guidewire are withdrawn (Fig. 29.1F). The tube is then clamped until it is attached to the chest drainage system. The tube is anchored in place by means of a long suture through the skin and around the tube. The incision is sutured without tension to avoid necrosis of the skin next to the tube. The operative area is cleaned and is covered with plain 4 × 4 gauze pads.

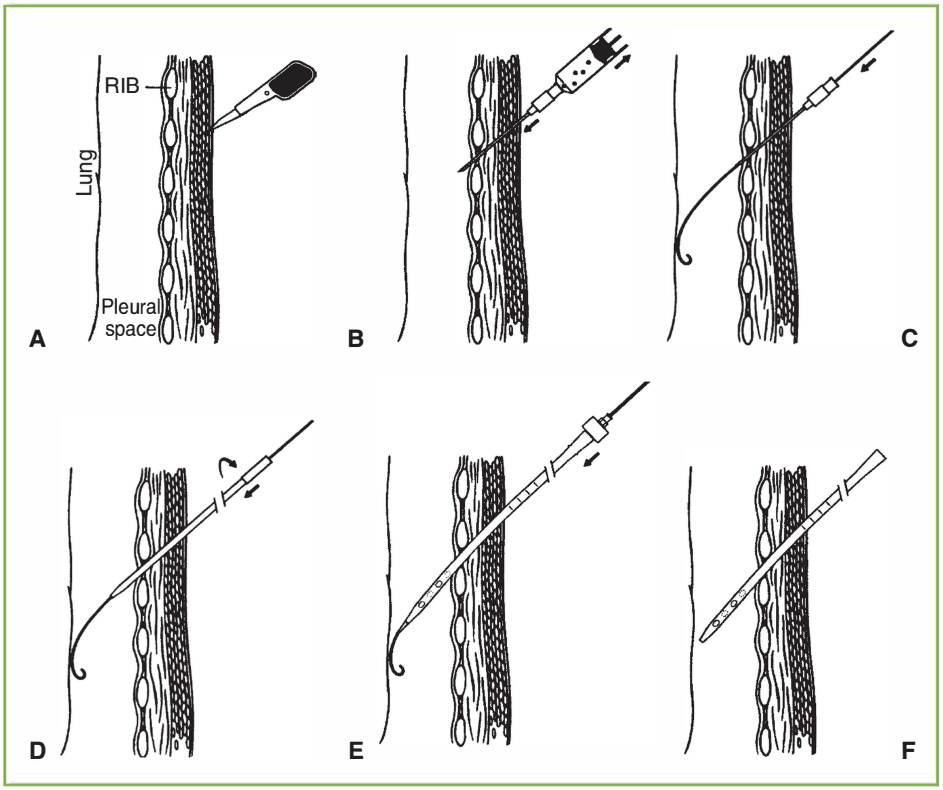

FIGURE 29.1 ■ Guidewire tube thoracostomy. **A**: Making a small skin incision slightly larger than the diameter of the chest tube. **B**: Introduction of 18-gauge needle into the pleural space. **C**: Insertion of wire with "J" end into the pleural space. **D**: With guidewire in place, the tract is enlarged by advancing progressively larger dilators over the wire guide. Introduction of the dilators is facilitated by rotating and advancing the dilators in the same plane of the wire guide. **E**: Introduction of the chest tube inserter or chest tube assembly over the guidewire. **F**: The guidewire and the chest tube inserter have been removed, leaving the chest tube positioned within the pleural space.

The gauze is then covered with tape, and additional fixation of the tube is obtained by the tape.

There are many different types of chest tubes that can be inserted with the technique mentioned in the preceding text. Kits are made so that chest tubes from 8.0 to 36.0 F can be inserted. The kits with the smaller chest tubes (<12.0 F) have no dilators. Some catheters have different characteristics. For example, with the Wayne Pneumothorax Set (Cook Medical Incorporated, Bloomington, IN), a 10.2 or 14.0 F size catheter is inserted over a 19-gauge needle; the catheter with this set is curved at the end like a pig's tail, and hence the name *pigtail catheter*. The Thal-Quick Chest Tube Sets come with chest tube sizes from 8.0 to 36.0 F (Cook Medical Incorporated, Bloomington, IN, 800-457-4500, www.cookcriticalcare.com).

Trocar Tube Thoracostomy

This method is similar to the guidewire tube thoracostomy, except that there is no guidewire or dilators. In general, it is not recommended because its use appears to be associated with more complications (1). This method initially requires a 2- to 4-cm incision parallel to the superior border of the rib through the skin and subcutaneous tissues after local anesthesia is obtained. The trocar can then be inserted between the ribs into the pleural cavity, with the flat edge of the stylet tip cephalad to prevent damage to the intercostal vessels (Fig. 29.2A). Because significant force is often required to insert the trocar, the hand not applying the force should be placed next to the patient's chest wall to control the depth of penetration. Once the trocar is in the pleural space, the stylet is removed. When the stylet is removed, the operator should immediately cover the trocar with the thumb to prevent a pneumothorax. Then, when the operator's thumb is removed, the chest tube, with its distal end clamped, is quickly inserted into the pleural space (Fig. 29.2B). The trocar is removed by sliding it back over the tube. When the trocar has been removed from the chest, the chest tube is clamped between the trocar and the chest wall so that the clamp on the distal end of the chest tube can be removed. The chest tube must remain clamped until it is attached to an underwater seal to prevent air from entering the pleural space.

An alternate trocar method uses a chest tube with a trocar positioned inside the tube. The procedure with this apparatus is similar to that already detailed. Once the pleural cavity is entered, the inner trocar is gradually removed from the chest tube. When the proximal end of the trocar clears the chest wall, a clamp is placed between the trocar and the chest wall until the trocar can be completely withdrawn and the tube attached to a water-seal drainage system.

Operative Tube Thoracostomy

Dev et al. (11) have created an excellent video on performing operative tube thoracostomy, and watching this video is recommended before one performs their first operative tube thoracostomy. With this method, an incision is made in the chest wall, and then after blunt dissection with a hemostat, the operator places his finger into the pleural space to break adhesions between the lung and chest wall and to ascertain the position of the chest tube. It is a more extensive procedure than guidewire tube thoracostomy or trocar tube thoracostomy, but it is probably safer. The most serious complications of tube thoracostomy are insertion of the tube ectopically, namely, into the lung, stomach, spleen, liver, or heart. These complications are more likely when a trocar chest tube is used. With the operative method, digital exploration of the insertion site delineates whether the tract leads into the pleural space and whether any tissue or organ is adherent to the parietal pleura at the planned site of tube insertion (12).

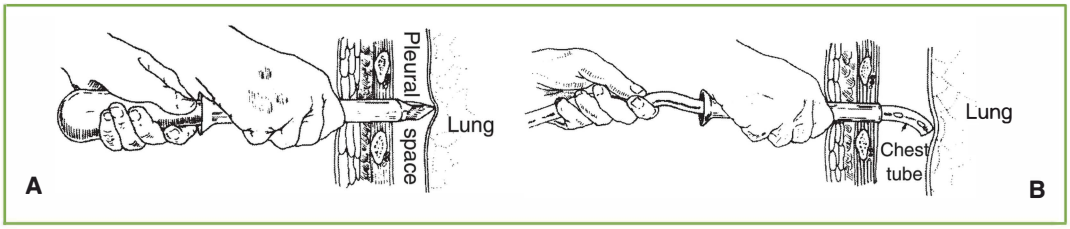

FIGURE 29.2 ■ Trocar tube thoracostomy. **A**: Insertion of trocar into the pleural space. Note the position of the hands, the position of the trocar relative to the ribs, and the cephalad position of the flat edge of the trocar. **B**: Insertion of chest tube through the trocar.

It is important to emphasize that operative tube thoracotomy can be very painful. Therefore, it is recommended that patients be given a narcotic or an anxiolytic medication 10 to 15 minutes before the procedure and that liberal doses of local anesthetic be used (13). To perform an operative tube thoracostomy, a 3- to 4-cm incision is made in the skin parallel to the chosen intercostal space. The incision should be made down to the fascia overlying the intercostal muscle. This fascia is then incised throughout the length of the incision, with care taken not to cut the muscle. Once the fascia has been incised, the muscle fibers are spread with a blunt-tipped hemostat until the intercostal interspace is identified. Then, an incision is made in the intercostal fascia just above the superior border of the inferior rib over which the tube will pass. The parietal pleura is then penetrated by pushing a blunt-tipped hemostat through it. The hole in the parietal pleura is then enlarged by means of the operator's index finger (Fig. 29.3A). At this time, the operator should palpate the adjacent pleural space to detect any adhesions. Then, the chest tube with its distal end clamped is inserted into the pleural space. A hemostat is used to guide the tube into the pleural space as the operator's finger is withdrawn (Fig. 29.3B). The last hole in the chest tube should be at least 2 cm inside the pleural space. The tube is sutured in place, and the incision is cleaned as in guidewire tube thoracostomy.

Single-Port Thoracoscopy

A novel means by which chest tubes can be inserted is through a single-port thoracoscopy. Zgoda et al. (14) placed a sterile Hopkins rod-lens telescope (Karl Storz-Endoskope, Tuttlingen, Germany) into the most proximal port of a 28-F chest tube (Fig. 29.4). Then under direct visualization, the chest tube was placed into the costodiaphragmatic gutter and the telescope was removed. It is important to use a rigid scope for this procedure. A flexible pleuroscope should not be used because of its larger diameter and potential for damage to the distal flexible portion of the scope when placed or removed from within the chest tube (14). It would be my guess that this procedure will be used more frequently for the insertion of chest tubes by individuals who are adept at thoracoscopy. The great advantage is the visualization of the place where the tube will be placed.

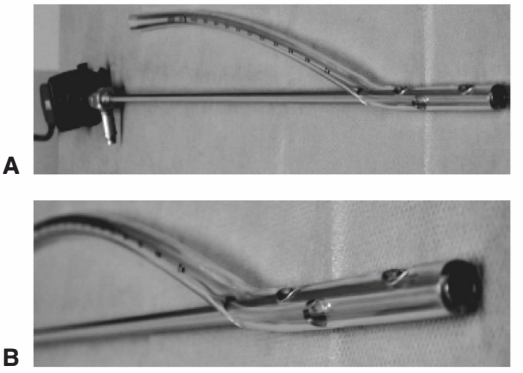

FIGURE 29.4 ■ A: Hopkins rod-lens telescope is loaded into the most proximal port of a 28 F chest tube. This allows for the direct visualization of chest tube placement. **B**: Close-up of Hopkins rod-lens telescope positioned through the most proximal port of the chest tube. *(From Zgoda MA, Lunn W, Ashiku S, et al. Direct visual guidance for chest tube placement through a single-port thoracoscopy: a novel technique.* Chest. *2005;127:1805–1807, with permission.)*

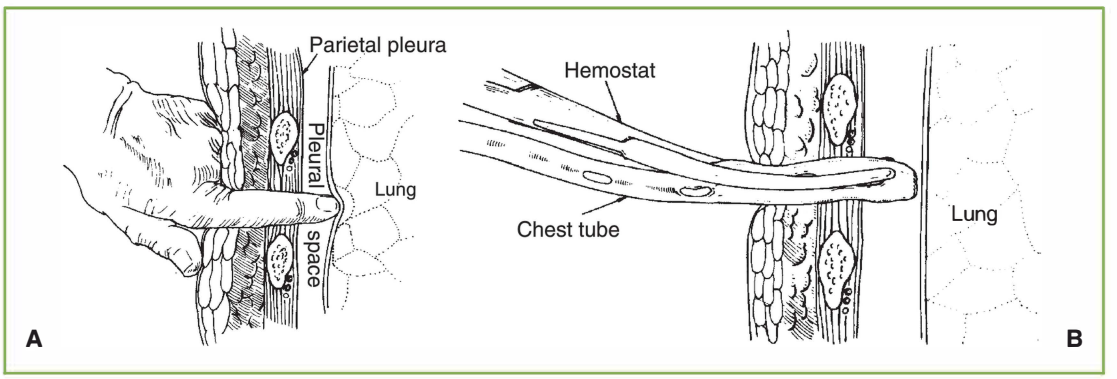

FIGURE 29.3 ■ Operative tube thoracostomy. **A**: The physician's index finger is used to enlarge the opening and to explore the pleural space. **B**: Placement of chest tube intrapleurally using a large hemostat.

Verification of Chest Tube Placement

After the chest tube has been inserted and connected to a drainage system, a chest radiograph should be obtained to verify the correctness of its position. Ideally, both a posteroanterior (PA) and a lateral view should be obtained because certain ectopic locations may not be apparent on the PA view alone (15). A CT scan should be obtained when the chest tube does not drain adequately and the chest radiograph is noncontributory (16). With CT, the tube can be visualized over its entire course with accurate location of its tip (16). If there are undrained locules of fluid, additional chest tubes can be inserted (8). Interestingly, chest tubes frequently end up in the fissures, even with operative tube thoracostomy. Curtin et al. (17) reviewed the PA and lateral chest radiographs in 50 patients who had 66 chest tubes placed in the emergency room for trauma. They reported that 38 of the 66 chest tubes (58%) were within a fissure. There was no evidence, however, that the presence of the tube within the fissure decreased its functional effectiveness (17). It is possible that some of the chest tubes were not in the fissures originally but became positioned in the fissures after the fluid was drained.

PLEURAL DRAINAGE SYSTEMS

Chest tubes are inserted into the pleural space to evacuate air or fluid. Because the pleural pressure is usually negative, at least during part of the respiratory cycle, various methods have been developed to prevent air from entering the pleural space when the pleural pressure is negative but to permit air or fluid, or both, to drain from the pleural space continuously. When managing patients with chest tubes, one must understand how these various drainage systems operate. In the past, the bottle system (described later) was used for pleural drainage. Commercially manufactured collection systems have subsequently replaced the bottle system. Nevertheless, the bottle system is described in detail because all the commercially manufactured systems are based on the same principles as is the bottle system.

One-Way (Heimlich) Valve

This drainage system is by far the simplest. The chest tube is attached to a one-way flutter valve assembly, which is constructed so that the flexible tubing is occluded whenever the pressure inside the tubing is less than atmospheric pressure and is patent whenever the pressure inside the tubing is above

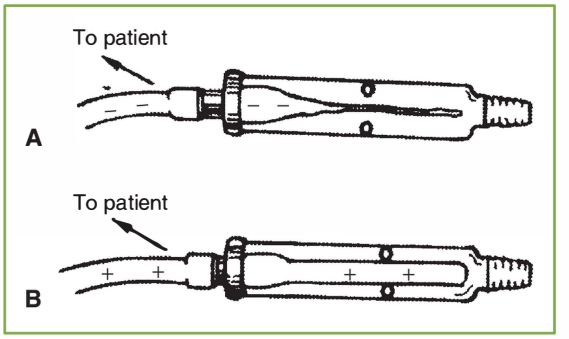

FIGURE 29.5 ■ Flutter valve. **A**: When the pleural pressure, and hence the intratube pressure, is negative (inspiration), the flexible tube is occluded because the pressure outside the tube is greater than the pressure inside the tube. **B**: When the pleural pressure is positive (expiration), the flexible tube is held open by the positive pressure, allowing the egress of air from the pleural space.

atmospheric pressure. Therefore, when the pleural pressure and hence the pressure in the tube are negative (Fig. 29.5A), the flutter valve is closed and no air enters the pleural space. When the pleural pressure becomes positive (Fig. 29.5B), however, the tube is patent and air or fluid can egress from the pleural space. This drainage system is most useful when the chest tube is placed for pneumothorax. If the chest tube is placed for a liquid, there is no good manner by which fluid, blood, or pus can be collected. The main advantages of the flutter valve are its simplicity and the freedom of the patient from a bulky drainage apparatus. Patients can be sent home with the flutter valve in place (18). The flutter valve is effective. In one study of patients with postoperative air leaks, it was shown that the pleural pressure was more negative when the flutter valve was used than when an underwater seal was used (19). When using the flutter valve, it is important to attach it with the correct orientation. Cases have been reported in which tension pneumothorax developed because the flutter valve was attached backwards (20).

One-Bottle Collection System

This system consists of one bottle that serves as both a collection container and a water seal (Fig. 29.6). The chest tube is connected to a rigid straw inserted through a stopper into a sterile bottle. Enough sterile saline solution is instilled into the bottle so that the tip of the rigid straw is approximately 2 cm below the surface of the saline solution. The bottle's stopper

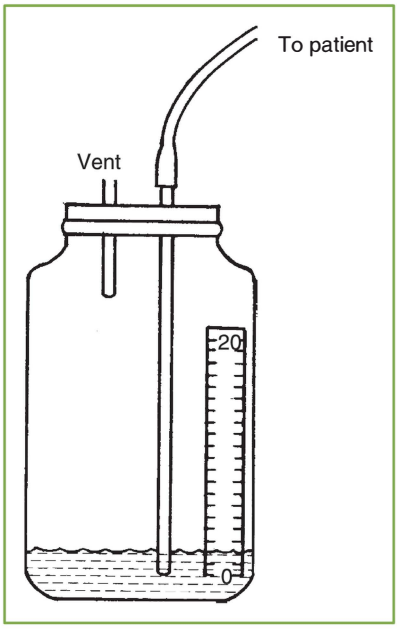

FIGURE 29.6 ■ One-bottle collection system.

must have a vent to prevent pressure from building up when air or fluid coming from the pleural space enters the bottle or a tension pneumothorax could result. The bottle usually is provided with a cap on the vent, and it is crucial to remove this cap before the system is connected to the patient.

This system works as follows. When the pleural pressure is positive, the pressure in the rigid straw becomes positive, and if the pressure inside the rigid straw is greater than the depth to which the straw is inserted into the saline solution, air (or liquid) will enter the bottle and air will be vented to the atmosphere and liquid will collect in the bottle. If the pleural pressure is negative, fluid will be drawn from the bottle into the rigid straw and no extra air will enter the system of the pleural space and the rigid straw. This system is called a *water seal* because the water in the bottle seals the pleural space from air or fluid from outside the body. Obviously, if the straw is above the fluid level in the bottle, the system will not operate and a large pneumothorax will develop.

This one-bottle system works well for uncomplicated pneumothorax. If substantial amounts of fluid are draining from the patient's pleural space, however, the level of fluid will rise in the one-bottle system,

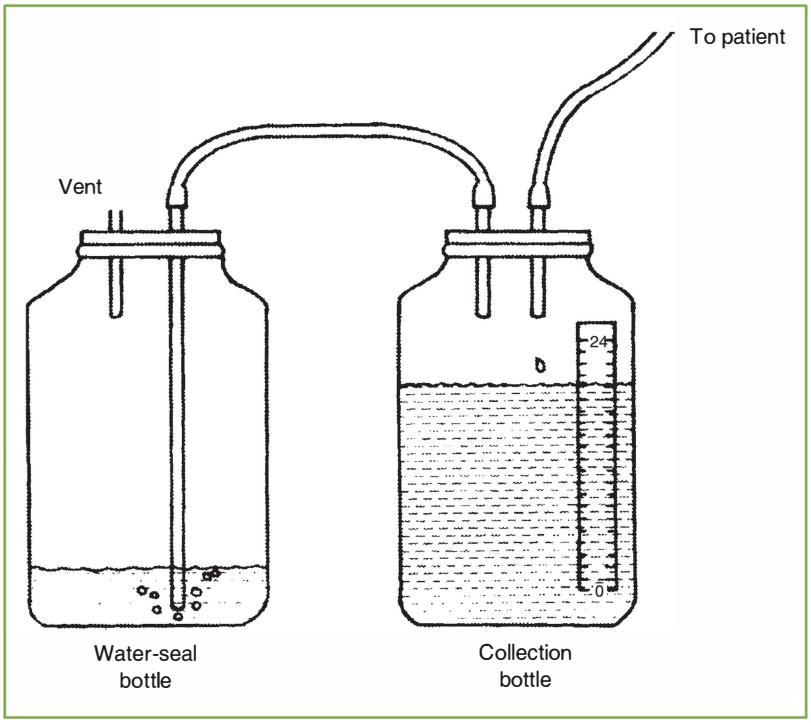

FIGURE 29.7 ■ Two-bottle collection system.

and therefore the pressure will have to be higher and higher in the rigid straw to allow additional air or fluid to exit from the pleural space. Another disadvantage of this system is that if the bottle is inadvertently placed above the level of the patient's chest, fluid can flow back into the pleural cavity.

Two-Bottle Collection System

This system (Fig. 29.7) is preferred to the one-bottle collection system when substantial amounts of liquid are draining from the pleural space. With this system, the bottle adjacent to the patient acts as a collection bottle for the drainage, and the second bottle provides the water seal and the air vent. Therefore, the degree of water seal does not increase as the drainage accumulates. The water-seal bottle functions identically in both the one- and two-bottle systems.

Suction and Three-Bottle Collection Systems

At times, it is desirable to apply negative pressure to the pleural space to facilitate reexpansion of the underlying lung or to expedite the removal of air or fluid from the pleural space. Suction at a fixed level, usually −15 to −20 cm H_2O, can be applied to the vent on a one- or two-bottle collection system with an Emerson pump. In many facilities, however, suction is provided by wall suction or other pumps in which the level of suction is not easily controlled. Because uncontrolled high levels of suction are considered dangerous, it is necessary to have some means of controlling the amount of suction.

Controlled amounts of suction can be readily applied to the system if a third bottle, the suction-control bottle, is added to the system, as illustrated in Figure 29.8. A vent on the suction-control bottle is connected to a vent on the water-seal bottle. The suction-control bottle has a rigid straw similar to that of the water-seal bottle. The suction is connected to a second vent on the suction-control bottle. When suction is applied to the suction-control bottle, air enters this bottle through its rigid straw if the pressure in the bottle is more negative than the depth to which the straw is submerged. Therefore, the amount of negative pressure in the system is equal to the depth to which the rigid straw in the suction-control bottle is submerged below the surface as long as bubbles are entering the suction-control bottle through its rigid straw. In the example in Figure 29.8, air enters the suction-control bottle from the atmosphere while its rigid straw is submerged at 20 cm H_2O. Therefore, the pressure in the suction-control bottle is −20 cm H_2O. The same pressure exists in the water-seal bottle because these two bottles are in

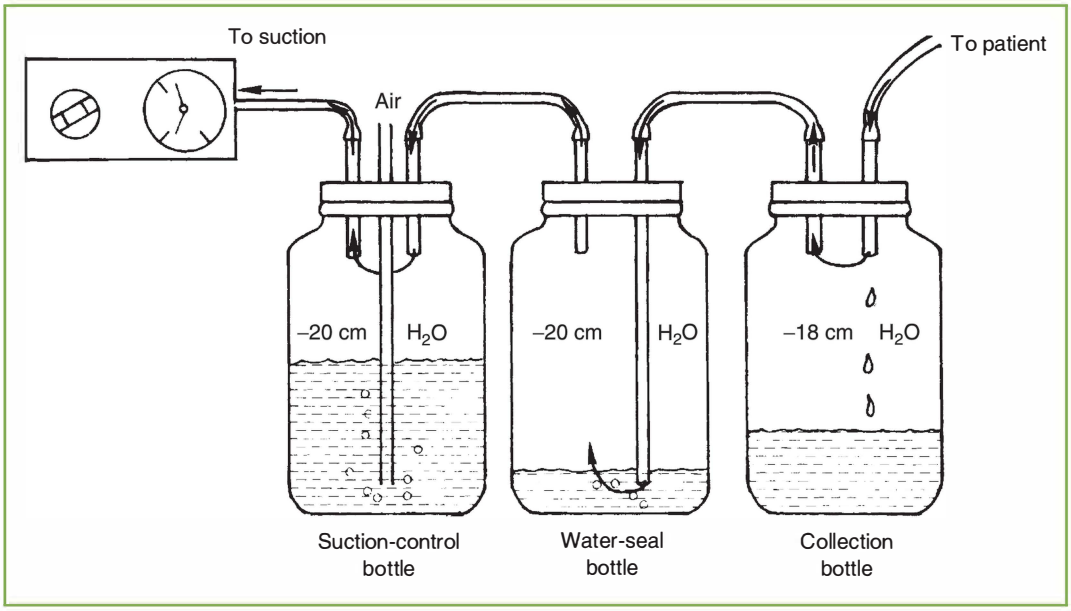

FIGURE 29.8 ■ Three-bottle collection system. The *arrows* describe the pathway for air to leave the pleural space.

direct communication. The pressure in the drainage collection bottle is less negative than that in the other bottles, however, on account of the intervening water seal. In this case, the depth of the water seal is 2 cm, so the pressure in the drainage collection bottle and the pleural space (if no liquid is present in the chest tube) is −18 cm H_2O.

The amount of negative pressure in the system can be changed by adjusting the position of the rigid straw in the suction-control bottle or by changing the depth of the water in the suction-control bottle. Bubbles must come continuously from the bottom of the suction-control straw if one is to obtain the expected degree of negative pressure. The bubbling does not need to be vigorous, just continuous; vigorous bubbling only creates more noise and hastens evaporation of the solution in the control bottle.

INTRINSIC NEGATIVE PRESSURE IN CHEST TUBES

The presence of liquid in the chest tubes can markedly influence the negative pressure that is applied to the pleural space, as illustrated in Figure 29.9. The liquid in the tube that runs from the patient to the floor produces the effects of a siphon (21,22). If the distance from the patient's chest to the top of the collection apparatus is 50 cm and the tube is filled with liquid, there will be a negative pressure of 50 cm H_2O in the pleural space if no suction is applied. The actual negative pressure applied to the pleural space from the entire system is the net vertical distance that the liquid occupies in the tube (A−B) minus the level of fluid in the water seal (C) plus the negative pressure applied through the suction (D). Of course, if there is no liquid in the tube, the actual applied pressure will be the suction pressure minus the depth of the water seal. In the clinical situation, the presence of fluid in a dependent loop will result in an increased pressure at the connection between the chest tube and the drainage system and will result in a decrease in the hourly drainage (23).

COMMERCIALLY AVAILABLE DRAINAGE SYSTEMS

As can be appreciated from Figure 29.8, three-bottle systems are unwieldy to set up and are cumbersome to move if the patient needs to be transported. However, a number of more compact and convenient chest drainage units are commercially available. The main disadvantage of these units is that they are more expensive than the older systems. The average cost is approximately US$75. Several different companies manufacture drainage systems including the Pleur-Evac systems (Teleflex Medical, www.teleflex-medical.com), the Atrium systems (Atrium Medical Corporation, www.atriummed.com, 603 880-1433), and the Argyle systems (Sherwood Medical, Tullamore, Ireland).

There are several types of drainage systems available. The suction control can be wet or dry, the water seal can be wet or dry, the amount of maximal suction varies, and the capacity of the collection chamber varies. In addition, some systems have a graduated leak monitor and some have an autotransfusion connection. The various models available are compared nicely in an article by Manzanet et al. (24).

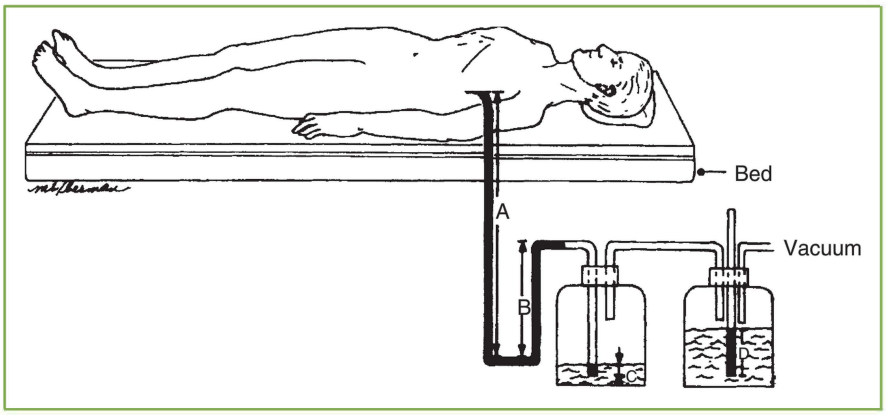

FIGURE 29.9 ■ The presence of liquid in the tube can affect the amount of negative pressure applied to the pleural space. The actual negative pressure in the chest = A − B − C + D.

An acceptable drainage system should have the following characteristics: (a) the water seal should be easily visualized, so one can determine whether the chest tube is patent and whether an air leak is present. Some systems have a one-way valve that does not contain water, but one can (and should, if dealing with a pneumothorax) fill the chamber with water to view the bubbling; (b) the system should be functional when no suction is applied; (c) the volume of the collection chamber should be adequate and the markings should be such that the drainage is easily quantitated; (d) there should be a pop-off valve to provide a safety factor if pressure builds up in the system. Neither of the single-chamber systems mentioned in the article by Manzanet et al. (24) have this capability and are not recommended. If the patient has a large amount of blood in the pleural space, consideration should be given to using a unit with autotransfusion capabilities.

The maximal amount of air that can be removed varies from one drainage system to another (24,25). Baumann et al. (25) measured the air flow at different levels of suction in eight commercially available pleural drainage units and reported that the maximal amount of air flow varied from 10.8 to 40.7 L/minute. However, the most important factor limiting air flow through chest tubes is probably the pleural drainage catheter. At 20 cm H_2O suction, the air flow through a 8.0 F catheter varies from 2.6 to 6.5 L/minute whereas the air flow through a 14.0-F catheter varies from 12.3 to 16.8 L/minute (25).

Pleur-Evac Unit

A typical drainage system (The Pleur-Evac system, Teleflex Medical, www.teleflexmedical.com) is depicted in Figure 29.10. The drainage system is a disposable,

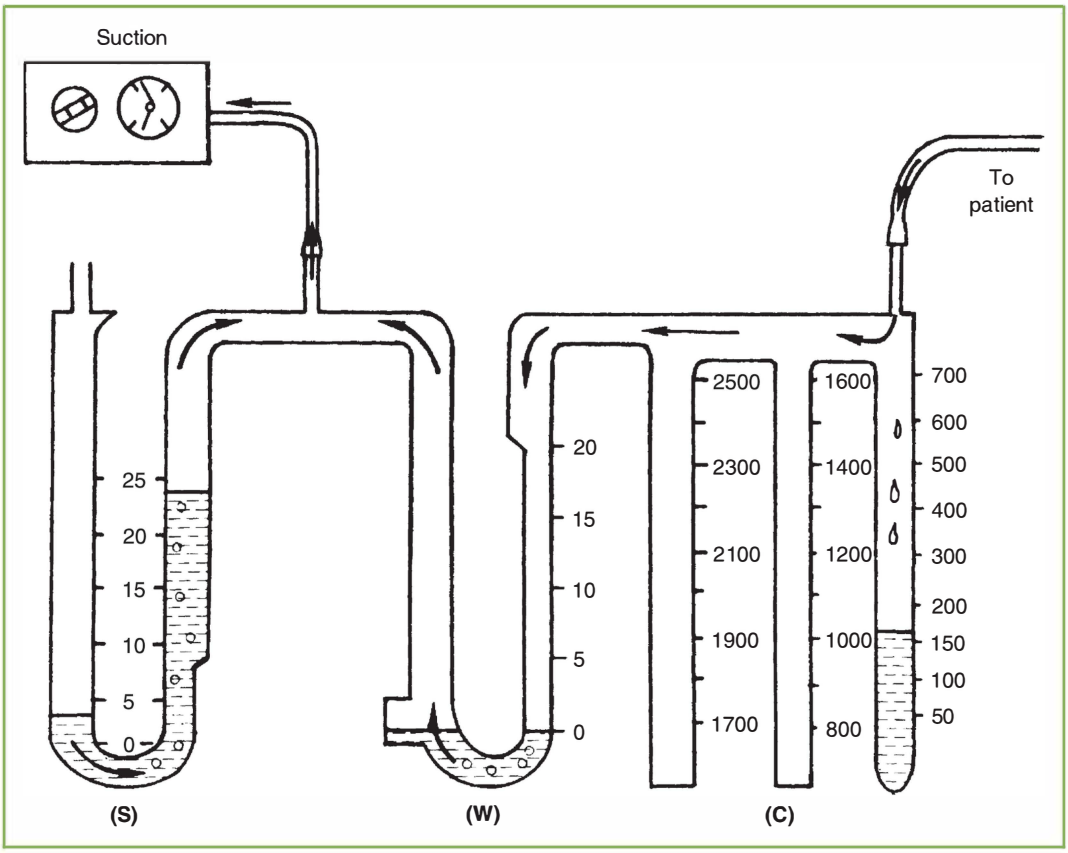

FIGURE 29.10 ■ Pleur-Evac collection system, which is analogous to a three-bottle collection system. The area labeled *C* is the calibrated collection system; *W* is the water-seal chamber; *S* is the suction-control chamber. *Arrows* demonstrate the pathway for air to leave the pleural space. If the suction vent is left open to atmospheric pressure, the Pleur-Evac system functions as a two-bottle collection system. When suction is applied, atmospheric air enters through *S* and leaves through the suction apparatus.

molded-plastic unit with three chambers duplicating the classic three-bottle system (Fig. 29.10). The chamber to the right side is equivalent to the drainage collection bottle, whereas the middle chamber is equivalent to the water-seal bottle, and the chamber on the left is equivalent to the suction-control bottle. The height of water in the suction-control chamber minus the height of water in the water-seal compartment again determines the amount of pressure applied to the pleural space when suction is being applied. A valve located in the water-seal portion of the Pleur-Evac unit also vents air whenever the pressure in the system is greater than +2 cm H_2O.

The advantages of the drainage systems compared with the three-bottle system are that it is simple to use, the amount of drainage can be easily measured, and the amount of negative pressure can be easily controlled. If a wet suction chamber is used and the negative pressure from the wall is set too high, the fluid will evaporate from the suction-control chamber and the system will be exceedingly noisy. Another problem that can happen if the bubbling rate is too high is that the negative pressure will be much higher than the height of the water column due to the resistance of pulling a large amount of air into the collection system (26). In one study, when there was a lot of bubbling the actual negative pressure was −40 cm H_2O in the collection system when the depth of the water was 20 cm H_2O (26). If suction levels more negative than –20 cm H_2O are desired, a drainage system with a dry suction-control chamber should be used. If no suction is applied and the suction port is vented to room air, the system functions as a two-bottle collection system. When the patient is not receiving suction, the patency of the chest tube can be assessed by observing oscillations in the water-seal chamber with respiratory movements. In addition, if the patient is not receiving suction, the pressure in the chest tube can be calculated as the difference in the level of water in the two arms of the water-seal chamber after taking into consideration the amount of fluid in the tubes.

INJECTION OF MATERIALS THROUGH CHEST TUBES

There are circumstances in which one would like to inject various materials through the chest tubes. For example, one might want to flush a chest tube with saline in a patient with a parapneumonic effusion, inject a fibrinolytic or DNAase in a patient with a loculated complicated parapneumonic effusion, or inject a tetracycline derivative or a different sclerosing agent through the chest tube in a patient with a malignant pleural effusion. This is usually done by taking the chest tube apart and injecting the material through a Toomey syringe. This procedure is less than ideal because the sterility of the system is compromised if the tubes are disconnected, and there is always the possibility of a pneumothorax if the tubes are not clamped properly.

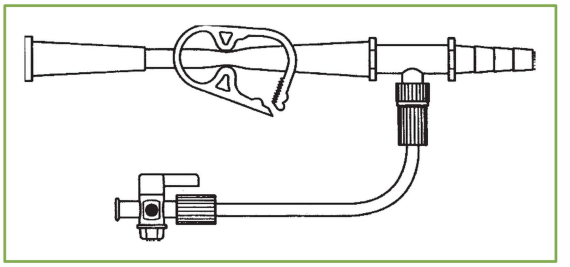

FIGURE 29.11 ■ Thal-Quick Chest Tube Adapter. This adapter provides an easy means by which materials can be injected into the pleural space through chest tubes.

If the patient has a small chest tube, a stopcock can be attached to the tube and the injection can take place via the stopcock. There is also a commercially available adapter called a *Thal-Quick Chest Tube Adapter* (Cook Medical Incorporated, Bloomington, IN, 800-457-4500, www.cookcriticalcare.com) that will fit into any chest tube. This unit (Fig. 29.11) consists of two adapters separated by flexible tubing with a clamp. On the proximal end, there is a sideport with a short segment of connecting tubing to which is attached a three-way stopcock. When one wishes to inject anything through the chest tube, the tube is clamped and the material is injected through the three-way stopcock. This system is recommended when a sclerosing agent is injected for pleurodesis or when a fibrinolytic agent is injected to break down loculi and the patient has a large chest tube.

CARE OF A CHEST TUBE

The following three questions should be answered each time a patient with a chest tube is evaluated:

1. Is there bubbling through the water-seal bottle or the water-seal chamber on the disposable unit?
2. Is the tube functioning?
3. What is the amount and type of drainage from the tube?

Bubbling through Water-Seal Chamber

If air bubbles are escaping through the water seal, it means that air is entering the chest tube between the pleural space and the water seal. If the patient is receiving water-seal drainage without suction, the presence of bubbling in the water seal usually indicates a persistent air leak from the lung into the pleural space. If no air bubbles are seen on the initial inspection of the water seal, the patient should be asked to cough, and the water seal should be observed for bubbling. The coughing maneuver increases the patient's pleural pressure and should demonstrate small air leaks into the pleural space. Cerfolio's (27) classification of air leaks is discussed in Chapter 24.

If the patient is receiving suction, disconnection or partial disconnection anywhere between the water seal and the patient will lead to bubbling through the water seal. For example, if the cap on the collection bottle in Figure 29.8 is not airtight, air will be pulled into the collection bottle by the negative pressure and will exit through the water-seal bottle producing bubbling. Leaks in the system may be detected by clamping the chest tube at the point where it exits from the chest. If bubbling through the water seal persists, the drainage system itself is responsible for the leak, and it should be examined thoroughly for leaks. If the bubbling stops when the chest tube is clamped, then the air is coming from the pleural space.

The presence of bubbling through the water seal does not necessarily indicate a communication between the lung and the pleural space. If the chest tube is not inserted far enough into the pleural space, one or more of the holes in the chest tube may lie outside the pleural space. Obviously, in such a situation, air enters the chest tube directly from the atmosphere if negative pressure is applied to the chest tube. The possibility is evaluated by inspecting the chest tube. At times, particularly in debilitated patients with poor tissue turgor, the negative pleural pressure will cause air to enter the pleural space around the chest tube at the insertion site. At times, it may be difficult to tell whether the air is leaking around the chest tube or whether it is due to a bronchopleural fistula. One may make this differentiation by measuring the level of P_{CO_2} in the air coming from the chest tube. The air from the chest tube is collected in a syringe and analyzed with the regular blood gas analyzer. Usually, a simple modification must be made on the analyzer so that it can analyze gas rather than liquid. If the air came from the lung through a bronchopleural fistula, then the P_{CO_2} should be greater than 20 mm Hg. Alternatively, if the air leaked around the chest tube, it will not have participated in gas exchange in the lung, and the P_{CO_2} should be less than 10 mm Hg. In such patients, additional sutures should be placed to make the chest tube insertion site airtight.

Bubbling through the water-seal chamber should not be confused with bubbling through the suction-control chamber. If suction is working properly, bubbling through the suction-control chamber or the suction-control bottle will always be present. When suction is being applied, the suction-control chamber should be checked to make certain that there is a continuous stream of small bubbles and that the liquid is at the desired height.

Is the Chest Tube Functioning?

Each time a patient with a chest tube is evaluated, the functional status of the chest tube itself should be evaluated. If the patient is not receiving suction, one should observe the level of the liquid in the water seal. If the chest tube is patent and in the pleural space, the level of the liquid should move higher on inspiration in the limb of the water seal proximal to the patient, indicating a more negative pleural pressure. Of course, if the patient is receiving mechanical ventilation, the level of liquid in the proximal limb will go down on inspiration because the pleural pressure becomes more positive. When no fluctuations are observed synchronous with respiratory movements, the patient should be asked to make a maximal inspiratory effort, and if still no movement is observed, it indicates that the chest tube is not functioning.

When the patient is receiving suction, it may be more difficult to ascertain chest tube function. If large bubbles of air are entering the suction-control chamber, the level of liquid in the water-seal chamber will fluctuate, depending on the number and size of bubbles in the chamber. These fluctuations should not be mistaken for evidence that the tube is functional. When the patient is receiving suction, the negative pressure in the suction-control chamber should be transmitted to the pleural space continuously to keep the pleural pressure constant.

Therefore, to detect changes in pleural pressures with respiration, the suction must be temporarily discontinued. When suction is discontinued, the volume of air and liquid between the water seal and the pleural space should not change, and therefore, the level of liquid in the water-seal chamber should rise to be equivalent to the suction previously applied. This initial rise occurs whether or not the chest tube is patent. After this initial rise, the level of the fluid in the water

seal should be observed for fluctuations with the respiratory cycle to verify patency of the chest tube.

If a chest tube is not functioning, its functional status should be restored, or it should be removed. Chest tubes can become obstructed with tissue around the holes or by clots within the tube. The simplest method for restoring patency is to flush the tube with 50 mL of saline. This frequently clears the tube by pushing the clot out of the tube or by pushing the tissue away from the holes in the tube. The patency of a chest tube obstructed by clots in the extrathoracic portion of the tube can frequently be restored by "stripping" the tube. The usual technique is to grip and stabilize the tubing adjacent to the chest with the thumb and index finger of one hand and then to slide the other hand toward the drainage unit to compress a section of the tubing. Then, the first hand is repositioned adjacent to the second hand, and the procedure is repeated until the entire length of the tubing is cleared. A special chest tube roller is sometimes used. Stripping may relieve the obstruction in the tube.

An alternate strategy is to instill a fibrinolytic into the chest tube. Although there are no studies to my knowledge assessing the efficacy of fibrinolytics for obstructed chest tubes, the utility of alteplase (tissue plasminogen inhibitor) in clearing obstructed peritoneal catheters has been documented. Zorzanello et al. (28) reported that alteplase was effective in relieving the obstruction in 24 of 29 instances of catheter obstruction. These researchers used 8 mg of alteplase rather than the 2 mg that are commonly used for obstructed intravascular catheters (28).

Chest tubes that are no longer patent and are no longer draining fluid should be removed because they serve as conduits for bacterial infection of the pleural space. Chest tubes frequently become colonized with bacteria. In one study (29), bacterial cultures of the fluid from the chest tubes were positive in 83% of 36 patients who had undergone lung resections. When a chest tube becomes obstructed with a clot, the clot may contain bacteria which can lead to pleural infection. At times, a chest tube does not fluctuate but continues to drain fluid. In such a situation, the chest tube need not be removed.

Amount and Type of Drainage

The amount and the character of the drainage from the chest tube should be recorded for each 24-hour period. The amount of drainage is most easily quantitated by marking the level of the liquid in the collection chamber each day. This record-keeping is important because many therapeutic decisions are based on the quantity of the drainage. The character of the drainage is best described by quantitating the percentage of solid drainage material. This quantitation is easily done by marking the level of the sediment in the collection chamber each day. If the increase in volume of the entire collection system is known and if the increase in volume of the solid sediment is known, it is simple to calculate what percentage of the daily drainage is solid.

COMPLICATIONS OF TUBE THORACOSTOMY

There are numerous complications of tube thoracostomy and some are serious or even fatal. Lamont et al. (30) reviewed safety reports from the National Patient Safety Agency in England and Wales between January 2005 and March 2008 and reported that there were 12 deaths and 15 cases of severe harm from chest tube insertion. They felt that the true rates were likely to be much higher (30). They attributed the complications to (a) poor selection of site for drain insertion and the lack of use of ultrasonography; (b) inadequate supervision of trainee doctors; (c) equipment problems including lack of familiarity with different kits and excessive length of available dilators; and (d) lack of awareness of national clinical guidelines (30). Harris et al. (31) subsequently sent questionnaires regarding harm from chest tube insertion between 2003 and 2008 to 148 acute hospitals in the UK from which they received 101 responses. Thirty-one cases of chest tube misplacement were reported with seven deaths. The chest tubes were placed in the liver (10), the peritoneal space (6), the heart (5), the spleen (5), subclavian vessels (2), colon (1), esophagus (1), and inferior vena cava (1). Forty-seven cases of serious lung or chest wall injuries with eight deaths were reported. Six chest tubes were placed on the wrong side with two deaths (31).

In order to minimize the risks of inserting chest tubes, Harris et al. (31) recommend the following with which I agree. (a) Chest tubes are only inserted by staff with relevant competencies and adequate supervision. (b) Ultrasound guidance is recommended when inserting a chest tube for fluid. (c) Clinical guidelines are followed and staff are made aware of risks. (d) Written informed consent is obtained when a chest tube is inserted.

One of the most common complications is misplacement of the chest tube. The incidence of this complication has varied markedly. In one study, the incidence of malpositioned chest tubes was 26% with the emergency insertion of 77 tubes (32). In contrast,

the incidence of chest tube malposition was only 1% in one series of 447 patients in whom the chest tubes were inserted through blunt dissection (33). A PA and lateral chest radiograph should always be obtained after a chest tube is inserted. It should be noted, however, that frequently the malposition is not diagnosed by these routine films. Accordingly, if a patient has an air or fluid collection that is not being drained adequately, a chest CT scan should be obtained to assess the position of the chest tube (and the presence of loculi). In one series, malpositioned chest tubes were diagnosed by supine chest radiographs in only 7 of 20 patients (35%) whereas the CT scan was necessary for diagnosis in the remaining 13 patients (32).

Another complication of chest tubes is that they fall out. In one study (34) from Oxford in which 100 12-F chest tubes were inserted by the Seldinger technique, 21% of the chest tubes fell out (34). The drain became blocked in an additional nine patients (34). There researchers recommended regular chest tube flushes to prevent blockage of the chest tube since only 1 of 58 chest tubes became obstructed when the tubes were flushed.

Pleural infection is another complication of tube thoracostomy. The administration of antibiotics to patients who have chest tubes for thoracic trauma may decrease the prevalence of empyema. Brunner et al. (35) randomly allocated 90 such patients to receive cefazolin or nothing immediately before and then every 6 hours until tube removal. They reported that there were six empyemas and three cases of pneumonia in the control group but only one case of pneumonia and no empyema in the antibiotic group (35). Two subsequent studies, which also evaluated trauma patients, reported similar results (36,37). A recently published meta-analysis (38) that included nearly 2,500 patients concluded that prophylactic antibiotics in patients receiving chest tubes for blunt or penetrating thoracic injuries had significantly less infections and empyemas than did patients who did not receive the antibiotics. In view of these studies, prophylactic antibiotics are recommended for all trauma patients who receive a chest tube. The antibiotic chosen should have activity against *Staphylococcus aureus* because this is the organism that causes the most infections (37). The utility of prophylactic antibiotics in other situations such as in postoperative patients, patients with spontaneous pneumothorax, and those with malignant effusions undergoing pleurodesis, is yet to be evaluated.

Another occasional complication of tube thoracostomy is the development of subcutaneous emphysema, which usually presents as soft tissue crepitus around the drain site but may rapidly spread to virtually any place in the body. The presence of subcutaneous emphysema in patients with tube thoracostomies indicates one of three possibilities (39): (a) a side-hole on the chest tube is lying outside the pleural space within the chest wall, allowing air to enter the tissue planes, (b) the chest tube is blocked, or (c) the drainage system cannot cope with the air leak. The latter situation is unusual and may be related to a chest tube that is too small or a massive air leak. Cerfolio et al. (40) reported that 6.3% of 4,023 patients undergoing lung resection for cancer developed subcutaneous emphysema. These workers (40) reported that they performed thoracoscopy on 64 of the patients and found that the lung was adhered to the part of the chest that had previously been opened. When the lung was removed from the opening and another chest tube was place, the subcutaneous emphysema resolved within 24 hours in all but one patient (40).

The insertion of a chest tube creates inflammation in the pleural space. Carvalho et al. (41) studied the pleural fluid characteristics of sheep with an experimental pleural effusion and an Argyle 32-Fr tube in the pleural space. The white blood cell count in the pleural effusion increased from 125 to more than 6,000/mm^3 within 6 hours. In this model, the pleural fluid protein level increased from 0 to 3.7 g/dL within 48 hours, and the pleural fluid lactate dehydrogenase level increased from 44 to 638 IU/L within 24 hours. There is one report of three patients (all with quadriplegia) who developed lung entrapment as a result of prolonged chest tube drainage. They could only be weaned off the ventilator after a decortication was performed (42).

AUTOTRANSFUSION

Autotransfusion involves the collection, filtration, and reinfusion of the patient's shed blood for repletion of intravascular volume and the diminution of transfusion requirements. Postoperative patients with chest tubes and patients with hemothorax should be considered as candidates for autotransfusion. Several autotransfusion systems are commercially available. Atrium Medical Corporation manufactures a system capable of continuous infusion.

CHEST TUBE REMOVALS

The indications for the discontinuation of the tube thoracostomy for various conditions are discussed in

the respective chapters on these conditions. In general, chest tubes for pneumothorax are removed when the lung has reexpanded and no air leaks are present. Chest tubes for hemothorax and empyema are removed when pleural drainage of blood or pus, respectively, has become minimal.

Before chest tube removal is attempted, the procedure should be explained to the patient. In addition, petrolatum-impregnated gauze and an occlusive bandage should be prepared for use in a sterile field. Then, the dressing covering the thoracostomy site is removed, and the suture restraining the chest tube is cut. Petrolatum-impregnated gauze is placed around the tube on the patient's chest wall so that it can be moved to cover the wound when the tube is removed. It is important that the pleural pressure be positive when the chest tube is removed so that air will not enter the pleural space. This can be accomplished by having the patient hum or perform a Valsalva maneuver. The chest tube is quickly pulled out of the chest, and the wound is covered immediately with the gauze. The wound usually closes sufficiently without using sutures. The procedure is completed by placing an occlusive dressing over the gauze.

An ultrasound (43) or a chest x-ray should be obtained after removal of the chest tube to assess for residual air. Ultrasound is probably more cost effective (43). Recurrent pneumothoraces following chest tube removal result more frequently from air entering the chest from the atmosphere during removal than from a leak in the lung parenchyma (39).

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chapter 30

Thoracoscopy

Although thoracoscopy has been a part of thoracic surgical practice for many years, the advent of video-assisted techniques has greatly expanded the indications and the uses of this procedure. In the past, thoracoscopy was performed mainly for diagnostic purposes. Presently, video-assisted thoracic surgery (VATS) has assumed a major role in the therapy of chest pathology. Indeed, in some institutions it is now the most commonly used operative approach in the general thoracic surgical practices (1). The primary advantage of VATS is that it produces less morbidity and mortality, and shorter duration of hospitalization than does thoracotomy. Presently, VATS is used for many surgical procedures in the chest other than those related to pleural disease including pulmonary nodule removal, lobectomy, lung biopsy, exploration of the mediastinum, myotomy for achalasia, sympathectomy, esophagectomy, and pericardial window creation. In this chapter, we discuss only those procedures that deal with pleural disease.

It is important to understand that there are two different techniques for thoracoscopy—VATS and medical thoracoscopy. VATS is performed in an operating room under general anesthesia with the patient selectively intubated to allow for single lung ventilation. Multiple puncture sites are made in the chest wall through which the thoracoscope and surgical instruments are introduced. Medical thoracoscopy differs from VATS in that the patient is usually not intubated and breathes spontaneously (2). The procedure is usually performed with conscious sedation and local anesthesia. Medical thoracoscopy primarily serves as a diagnostic tool rather than for intervention. It is usually performed by pulmonologists, whereas VATS is performed by thoracic surgeons (2). The primary advantages of medical thoracoscopy are that it can be performed in an endoscopy suite, it does not involve general anesthesia, and is less expensive than VATS (2). For diagnostic purposes, either VATS or medical thoracoscopy is appropriate and the choice of procedure depends primarily on its availability at one's institution. The number of centers performing medical thoracoscopy in the United States and the United Kingdom is gradually increasing. For example, between 1999 and 2004 the number of centers in the United Kingdom where medical thoracoscopy was performed increased from 11 to 17 (3).

HISTORY

Thoracoscopy was developed by Jacobaeus in the early 1900s because a method was needed to break down adhesions in patients with pulmonary tuberculosis so that an artificial pneumothorax could be produced (4). Thoracoscopy was used extensively for this purpose until 1945, at which time streptomycin was introduced for the treatment of tuberculosis (5). In one report, the results in 1,000 patients in whom thoracoscopy was used to break down adhesions were detailed (6). Jacobaeus also published an early report on the use of thoracoscopy to localize and diagnose benign and malignant lesions of the pleura and pulmonary parenchyma (7).

After 1950, thoracoscopy was rarely performed in the United States, although some physicians in Europe continued to perform the procedure (8). During this period, thoracoscopy was used primarily to assist in diagnosing pleural effusions, although pleurodesis was sometimes attempted with talc (9,10) or silver nitrate (11,12). A number of instruments were employed including rigid bronchoscopes, mediastinoscopes, flexible bronchoscopes, and specialized rigid fiber-optic

thoracoscopes (13). Two older books (14,15) provide state-of-the-art discussions on thoracoscopy before the advent of VATS, which has become available mainly since 1990.

The recent revival of thoracoscopy was made possible by the tremendous advances in endoscopic technology (16). The development of the charged coupling device and a silicon chip that is light sensitive led to the sufficient miniaturization of a video camera. When attached to a fiber-optic telescope, the video camera produces a well-defined, magnified image on a video monitor that allows the operating surgeon to work with an assistant. Previously, the surgeon had to hold the thoracoscope, and only he could look into it while working, which did not allow for the aid of an assistant and, therefore, limited the complexity of the procedures undertaken (13).

PROCEDURE

Medical Thoracoscopy

Training Requirements for Medical Thoracoscopy

The guidelines from the American College of Chest Physicians (ACCP) recommend that trainees should perform at least 20 procedures in a supervised setting to establish basic competency. Then to maintain competency, dedicated operators should perform at least 10 procedures per year (17).

There are two fundamental techniques by which medical thoracoscopy is performed, namely, single puncture and double puncture (18). Both techniques require a xenon light source, which satisfies the requirements for high-quality visual exploration and video documentation. For the single-puncture technique, a rigid thoracoscope with a 9-mm working channel is used. With the single-puncture technique, various instruments such as the biopsy forceps, needle biopsy, and suction catheter are used through the working channel, which also accommodates electrocautery. For the double-puncture technique, a smaller 7-mm rigid thoracoscope is used along with a second smaller 5-mm trocar that accommodates biopsy forceps, brushes, needles, and laser fibers. The single-puncture technique is the easiest method to learn and is commonly used by the chest physician (18).

Medical thoracoscopy can be done either under direct visual control through the endoscopic optic or indirectly by video transmission that allows a magnified view and demonstration to assistants and others, as well as appropriate documentation (18). For cauterization of adhesions and blebs, or in case of bleeding after biopsy, electrocoagulation or laser coagulation should be available.

Medical thoracoscopy is usually performed under local anesthesia, but some premedication (e.g., midazolam) should be routinely administered. Thoracoscopy is usually performed with the patient in the lateral decubitus position with the hemithorax to be studied facing upward.

The site for the introduction of the thoracoscope depends upon the location of radiographically detected abnormalities, while avoiding potentially hazardous areas such as that of the internal mammary artery, the axillary region with the lateral thoracic artery, and the infraclavicular region with the subclavian artery. It is important not to insert the thoracoscope too low because the diaphragm or spleen may be accidentally injured (18). The usual site for insertion of the thoracoscope is in the sixth or seventh intercostal space between the mid- and anterior-axillary lines.

Before the thoracoscope is introduced, a pneumothorax of several hundred cubic centimeters of air is usually induced (18). Thoracic ultrasound prior to thoracoscopy improves pleural access and predicts fibrous septation (19). Examination of the pleural space is only possible if the space between the lung and chest wall is sufficiently large to move the instruments around easily and to visualize all important areas of the thoracic cavity (15). After the trocar is introduced, the pleural fluid should be removed as completely as possible. Then the entire pleural cavity is inspected. Biopsies are obtained from suspicious areas. Biopsies from the visceral pleural are usually obtained only when the parietal pleura appears normal but the lung surface shows abnormal lesions. Following thoracoscopy, a chest tube should be introduced and connected to suction.

In the last few years, new instrumentation has been developed which may facilitate medical thoracoscopy. Tassi and Marchetti (20) reported their experience with a technique called *minithoracoscopy* in which two 3.8-mm trocars, one with a 3.3-mm telescope and the other with a 3.0-mm biopsy forceps were used for undiagnosed pleural effusion. They reported that the diagnostic yield with this procedure was 90% and concluded that it is most useful for assessment of small effusions not accessible to conventional medical thoracoscopy (20) and for patients with narrow intercostal spaces (21).

Ernst et al. (22) described their experience with a newly developed semirigid pleuroscope in the evaluation of the pleural space. This pleuroscope was

developed so that it interfaces with existing processors and light sources that are routinely employed for flexible bronchoscopy and are available in most endoscopy units. An additional benefit is that this pleuroscope operates much like a bronchoscope, and therefore it should be easier to use by the pulmonologist who is not trained in the use of rigid instruments (22,23).

Video-Assisted Thoracic Surgery

Most VATS procedures are performed under general anesthesia because with general anesthesia, endoscopic surgical manipulation can be accomplished safely and expeditiously (1). It is imperative that the anesthesia personnel be experienced in open thoracic procedures. In addition, they must be well versed with the principles of selective one-lung ventilation. Although most surgeons perform VATS with a double-lumen endotracheal tube, it can be performed with a single-lumen endotracheal tube if only a pleural effusion is to be drained and a biopsy obtained of the parietal pleura (24). Ventilation for the patient is provided through the contralateral lung. It is most convenient to work with two video monitors, one on each side, so that both the operator and the assistant may have an unobstructed view. VATS has also been performed with local anesthesia and sedation (25).

The patient is placed on the operating table, and the chest is prepared and draped as for a thoracotomy. After general anesthesia is induced, the thoracoscope is inserted and the ipsilateral lung is collapsed for unimpaired visibility of the intrathoracic structures. At this time, the thoracic cavity is systematically examined. After the initial thoracoscopic exploration of the pleural cavity is concluded, further intercostal access for VATS instrumentation is achieved under direct thoracoscopic vision. Usually, three incisions are made to create a triangular configuration, an arrangement that facilitates instrument placement and allows one to work in coordination with an assistant. The incisions are placed along a line appropriate for a thoracotomy incision so that if a subsequent thoracotomy is required, the incisions are simply joined. At the completion of the VATS procedure, a single chest tube is placed in the pleural space.

Instrumentation for VATS is slowly improving. Initially, instruments designed for laparoscopy were used but were less than ideal, particularly for grasping lung parenchyma, which has a tendency to tear. The most significant advance in instrumentation was the development of an endoscopic linear stapler, which simultaneously cuts while laying down parallel rows of staples that are both hemostatic and aerostatic (Endo-GIA, U.S. Surgical Corp., Norwalk, CT, USA).

The operative time for a patient with an undiagnosed pleural effusion is short. Cerfolio et al. (24) reported that when a single-lumen tube was used for undiagnosed pleural effusion, the mean operative time for pleural evaluation and pleural biopsy in a series of more than 200 patients was only 17 minutes.

Previous thoracoscopy has been considered a relative contraindication to a second thoracoscopy. However, Breen et al. (26) reported that they performed redo thoracoscopies in 29 patients and were able to induce a pneumothorax and complete the procedure in all patients although pleural adhesions were more common with the redo procedures. Most of their patients had malignant pleural effusions.

CONTRAINDICATIONS TO THORACOSCOPY

The two primary contraindications to thoracoscopy are the inability to tolerate one-lung ventilation and pleural adhesions of sufficient density to preclude entry into the chest (13,18). Of course, the patient must be able to tolerate general anesthesia and must not have bleeding abnormalities that would preclude other surgical procedures.

INDICATIONS AND RESULTS

Undiagnosed Pleural Effusion

On occasion, the etiology of a pleural effusion remains uncertain after the initial diagnostic workup, which includes a diagnostic thoracentesis with pleural fluid cytology, a pleural fluid marker for tuberculosis, and an evaluation for pulmonary embolus. Such patients are possible candidates for thoracoscopy to establish the etiology of the pleural effusion. It should be noted, however, that the only two diagnoses that are usually established with thoracoscopy are malignancy and tuberculosis. If the patient has a pleural effusion due to a different etiology, the diagnosis in all probability will not be established at thoracoscopy.

Thoracoscopy is an efficient way to establish the diagnosis of malignancy. In the early 1990s, two separate studies, each with 102 patients, were published that reported diagnostic yields of 93% (27) and 80% (28). However, when these two studies are examined in detail, one finds that the only diagnosis that was definitely established is malignancy. When the two studies mentioned in the preceding text are combined,

the diagnosis of malignancy was established in 99 of the 117 patients (85%) with malignancy, including 51 of 56 (91%) with mesothelioma. In a more recent study from Denmark, medical thoracoscopy established the diagnosis in 89 of 101 patients (88%) with malignancy (29). Preliminary results in one study suggest that the use of autofluorescence videothoracoscopy may help identify areas of the pleura with malignant involvement (30). Thoracoscopy can also establish the diagnosis of tuberculosis (31–33). In one study from South Africa, the diagnosis of tuberculosis was established with thoracoscopy in all 42 patients with tuberculous pleuritis (33).

Where is the rightful place of thoracoscopy in the management of the patient with an undiagnosed pleural effusion? Thoracoscopic procedures should be used only when the less invasive methods of diagnosis such as pleural aspiration for cytologic, bacteriologic, and chemical examinations have not yielded a diagnosis. In one series of 620 patients with pleural effusions, only 48 (8%) remained without a diagnosis and were subjected to thoracoscopy (34). In these 48 patients, a diagnosis of malignancy was established in 24 (50%), and in an additional 16 patients, the diagnosis of benign disease was established when the thoracoscopic and clinical findings were considered jointly. In the remaining eight patients (16%), no diagnosis was established at thoracoscopy, but six of them were subsequently diagnosed as having malignancy (34). Thoracoscopy is recommended for the patient with an undiagnosed pleural effusion in whom the diagnosis of malignancy or tuberculosis is suspected, and in whom at least one pleural fluid cytology and one pleural fluid marker for tuberculosis (adenosine deaminase or interferon) have been negative.

There are clinical findings that make it more likely that malignancy will be diagnosed at the time of thoracoscopy. Ferrer et al. (35) prospectively studied 93 patients referred for thoracoscopy at a tertiary hospital. They found that the following four variables were associated with pleural malignancy in a multivariate model: (a) a symptomatic period of more than 1 month, (b) absence of fever, (c) blood-tinged pleural fluid, and (d) chest computed tomography (CT) findings suggestive of malignancy (pulmonary or pleural masses, pulmonary atelectasis, or lymphadenopathy) (35). Twenty-eight patients had all four criteria and all had malignancy. Twenty-one patients had at most one criterion and none had malignancy.

When one performs thoracoscopy for diagnostic purposes, it is important to be prepared to perform a procedure to create a pleurodesis during surgery. Our preferred method is pleural abrasion with an alternative being the instillation of 100 mL of 2% iodopovidone (36). The efficacy of mechanical abrasion was documented in one study in which 87 patients with malignant effusions secondary to breast carcinoma were randomized to receive pleurodesis by mechanical abrasion in conjunction with thoracoscopy or by talc slurry (37). Pleurodesis with mechanical abrasion had a higher success rate (89%) than pleurodesis with talc slurry (74%) (37). Although talc insufflation was recommended in the earlier editions of this book, concerns about respiratory failure occurring after talc administration (see Chapter 10) have led to this different recommendation. If talc is used in this situation, only graded (large particle size) talc should be used. It should also be noted that the performance of thoracoscopy without any attempt to create a pleurodesis will result in a pleurodesis in more than 50% of patients with malignant pleural effusions (38,39).

How sensitive is thoracoscopy in making the diagnosis of malignancy? Davies et al. (40) performed medical thoracoscopy on 142 patients with undiagnosed pleural effusion and the diagnosis of malignancy was established in 89. Forty-four of the patients had nonspecific pleuritis at thoracoscopy and 5 of these (12%) were subsequently diagnosed with mesothelioma (40). Therefore, the sensitivity of medical thoracoscopy in making the diagnosis of malignancy was 94%.

Malignant Pleural Effusion

If a patient has a known malignancy, should thoracoscopy be performed to effect a pleurodesis? It appears that the success rates are comparable for pleurodesis with thoracoscopy and with tube thoracostomy. In one study, Dresler et al. (41) randomized 482 patients with malignant pleural effusions to have pleurodesis with talc slurry or insufflated talc and reported that the rate of successful 30-day outcomes did not differ significantly (78% success with talc insufflation and 71% success with talc slurry). In a smaller study, Yim et al. (42) randomized 55 patients to pleurodesis with thoracoscopy and talc insufflation or pleurodesis with tube thoracostomy and talc slurry and found that there was no significant difference in the results with the two treatment methods (42). Therefore, if a patient is known to have a malignant pleural effusion, it does not seem reasonable to subject him or her to general anesthesia and the extra expense of thoracoscopy when he or she could be managed just as effectively with tube thoracostomy and a tetracycline derivative intrapleurally (43).

There are certain situations in which thoracoscopy is indicated in patients with malignancy. Thoracoscopy should be considered if a patient has a malignant pleural effusion that is loculated because the loculations can be broken down and the pleural space cleared with thoracoscopy. Thoracoscopy should be considered in patients with ovarian carcinoma and pleural effusion because the amount of tumor present in the pleural space will dictate surgical therapy (44). In the patient with lung cancer and cytology negative pleural effusion, thoracoscopy is indicated to rule out tumor involvement of the pleura (23).

Parapneumonic Pleural Effusion

Thoracoscopy should be considered for the patient with a parapneumonic effusion that is not drained with either a therapeutic thoracentesis or tube thoracostomy. During thoracoscopy, the loculi in the pleural space can be disrupted, the pleural space can be completely drained, and the chest tube can be optimally placed. In addition, the pleural surfaces can be inspected to determine the necessity for further intervention such as decortication. Thoracoscopy should not be performed only for pleural thickening as such thickening resolves with time. A CT scan should be obtained before thoracoscopy to provide anatomic information about the size and extent of the empyema cavity and the thickness of the peel over the visceral pleura. If the fibropurulent material cannot be removed completely and if complete expansion of the lung cannot be obtained, the procedure should be converted to an open thoracotomy (45).

Incompletely drained parapneumonic effusions are treated very effectively with thoracoscopy. Most reports on thoracoscopy for complicated parapneumonic effusion have used VATS. When four series (46–49) from the late 1990s using VATS are combined, thoracoscopy was the definitive procedure in 178 of 232 patients (77%). The overall mortality was 3%. The median time for chest tube drainage after the procedure ranged from 3.3 to 7.1 days, and the median duration of hospital stay after thoracoscopy ranged from 5.3 to 12.3 days. Luh et al. (50) reviewed their experience with VATS in 234 patients with complicated parapneumonic effusions in 2005. Thoracoscopy was the definitive procedure in 194 patients (83%), whereas 40 patients required conversion to open thoracotomy or reoperation (50). The mortality rate within 30 days of surgery was 3%. Patients who required procedures in addition to thoracoscopy had a longer mean duration of mean preoperative hospital stay (18.4 ± 6.5 days) compared with those who did not require another procedure (11.4 ± 3.1 days) (50). Multiloculated empyema can also be treated with medical thoracoscopy. Brutsche et al. (51) reported their experience with 127 patients with multiloculated empyema subjected to medical thoracoscopy at three different centers. There were no mortalities and 62 of the patients (49%) received intrapleural fibrinolytic therapy for 3 to 5 days after thoracoscopy. The results in this retrospective study with medical thoracoscopy were excellent—115 patients (91%) needed no additional procedures (51). The median duration of chest tube drainage post medical thoracoscopy was 7 days, and there was no in-hospital mortality (51).

When faced with a patient with a complicated parapneumonic effusion that is not completely drained, there are basically four alternatives: (a) insert additional chest tubes, (b) instill fibrinolytics and DNAse intrapleurally, (c) perform thoracoscopy, or (d) perform thoracotomy. The insertion of additional chest tubes is not recommended because it is usually ineffective. A recent randomized double-blind study (52) demonstrated that the intrapleural instillation of 10-mg tissue plasminogen activator (tPA) plus 5-mg DNase twice a day for 3 days resulted in more clearing of the chest radiograph and a reduction in the need for additional surgery compared with either agent by themselves or placebo. Therefore, if fibrinolytic therapy is used, this is the preferred regimen. If fibrinolytics are used and drainage is incomplete after 3 to 5 days, thoracoscopy should be performed (53). Some have recommended not using the fibrinolytics and directly proceeding to thoracoscopy (54), and there are no controlled studies comparing intrapleural therapy with tPA and DNase with thoracoscopy. Thoracoscopy seems more effective if it is performed before fibrinolytics are administered (54). At the present time, I proceed directly to thoracoscopy if the patient is a good operative candidate because I believe that this will result in a shorter hospitalization. However, if the patient is not a good operative candidate, I will try tPA plus DNase initially. Thoracotomy is reserved for those cases in which thoracoscopy fails or in which thoracoscopy is indicated but is unavailable.

Postpneumonectomy Empyema

Thoracoscopy also appears to be useful in patients with postpneumonectomy empyemas. Gossot et al. (55) reported their experience using thoracoscopy in 11 patients with postpneumonectomy empyema. Thoracoscopy was performed to remove as much

infected material as possible, to check that there was no bronchopleural fistula, and to wash and drain the pleural cavity. Eight of the 11 patients were cured of their postpneumonectomy empyema within a mean drainage time of approximately 10 days postthoracoscopy (55). Hollaus et al. (56) reported that five patients with postpneumonectomy empyema without bronchopleural fistula, were cured with thoracoscopy followed by tube thoracostomy until the cultures were negative.

Pneumothorax

Thoracoscopy is effective in the treatment of spontaneous pneumothorax and the prevention of recurrent pneumothorax. With thoracoscopy, there are two primary objectives: (a) to treat the bullous disease responsible for the pneumothorax and (b) to create a pleurodesis. The most common means by which the bullae are treated presently is with an endoscopic stapling device. The primary disadvantage of the endostapler is cost, which is approximately US$1,000 per procedure (57). Previously, the bullae were treated with electrocoagulation, which was associated with a higher recurrence rate (58). An alternative method of dealing with the apical bullae is to ligate the bullae with a Roeder loop (59). However, Inderbitzi et al. (59) reported a relatively high recurrence rate after use of the loop and recommend that it be abandoned in favor of wedge resection with the endostapler. The best way to induce a pleurodesis appears to be with pleural abrasion. It is comparable in effectiveness to talc insufflation and does not carry the risk of inducing acute respiratory failure. It is also comparable in effectiveness to partial parietal pleurectomy but is easier to perform.

The effectiveness of VATS in conjunction with endostapling has been demonstrated in several large series. Cardillo et al. (60) used VATS to treat 432 patients with primary spontaneous pneumothorax between 1992 and 1998. They used subtotal pleurectomy to induce a pleurodesis in some patients and talc insufflation in others. In 2.3% of their 432 patients, conversion to an open procedure was necessary, usually because of extensive adhesions. The recurrence rate was 4.4%, with a mean follow-up period of 38 months (60). Yim and Liu (61) treated 483 patients with primary spontaneous pneumothorax creating a pleurodesis with mechanical abrasion. In this series, the mean postoperative stay was only 3 days and the recurrence rate was only 1.74%, with a mean follow-up period of 20 months (61). The best results with VATS were reported by Margolis et al. (62) who treated 156 young adults with primary spontaneous pneumothorax via VATS with stapling of blebs and pleural abrasion. In this uncontrolled study, there were no postoperative air leaks and the mean duration of hospital stay was only 2.4 days. There were no recurrences during the median follow-up period of 62 months (62). Thoracoscopy is also effective for treating secondary spontaneous pneumothorax (63,64).

Most series that have utilized thoracoscopy for the treatment of spontaneous pneumothorax have used VATS, but there are some proponents of medical thoracoscopy with the insufflation of talc (65,66). The effectiveness of talc insufflation at medical thoracoscopy was compared with chest tube drainage in a prospective randomized multicenter study of 108 patients with primary spontaneous pneumothorax, most of which were recurrent (65). Patients with bullae greater than 5 cm in diameter were excluded. In this study, the recurrence rate was 5% in the group that received talc and 34% in the group that received chest tubes. However, it should be noted that 10 of the 16 recurrences in the chest tube group occurred during the initial hospitalization, whereas only 1 recurrence occurred in the talc group during hospitalization. The recurrence rates after the initial hospitalization were 5% in the talc group and 13% in the chest tube group, although 10 of the 47 patients in the chest tube group also got talc during their initial hospitalization. In an uncontrolled study, Lee et al. (66) evaluated the effectiveness of medical thoracoscopy with the insufflation of talc in the treatment of secondary spontaneous pneumothorax in patients with advanced chronic obstructive pulmonary disease (COPD). They insufflated 3 g of talc in 41 patients with a mean age of 70.7 years and a mean FEV_1 of 0.88 L. The 30-day mortality in this group of patients was 10% and all the patients that died had an FEV_1 between 0.5 and 0.7 L. The recurrence rate in the survivors was 2 of 37 (5.4%) (66).

Which patients with spontaneous pneumothorax should be subjected to thoracoscopy? In some centers, all patients with spontaneous pneumothorax are subjected to thoracoscopy to evaluate the status of the underlying lung (67). This approach seems overly aggressive because approximately 50% of patients with their initial pneumothorax will never have a recurrence without any treatment. However, thoracoscopy is recommended for patients with primary pneumothorax in whom aspiration therapy has failed or who have a recurrent pneumothorax. The reason for this recommendation is that the duration of

hospital stays are comparable with thoracoscopy and tube thoracostomy, but the recurrence rates are much less after thoracoscopy. Because the recurrence of a pneumothorax is more life threatening in patients with secondary spontaneous pneumothorax, it is recommended that thoracoscopy be performed in most patients with secondary spontaneous pneumothorax after they are initially managed with tube thoracostomy (see Chapter 24). In general, it seems reasonable to hypothesize that VATS with the stapling of blebs and pleural abrasion would be superior to medical thoracoscopy with the insufflation of talc but there are no controlled studies comparing the two approaches.

The ACCP and the British Thoracic Society (BTS) have both published guidelines for the management of spontaneous pneumothorax in the last few years. The ACCP guidelines (68) stated that thoracoscopy was the preferred intervention for primary spontaneous pneumothorax and that it be performed after an ipsilateral recurrence. They recommended that patients with apical bullae should undergo intraoperative bullectomy. They also recommended that parietal pleural abrasion should be performed in most patients to induce a pleurodesis. The ACCP guidelines for patients with secondary spontaneous pneumothorax recommended an intervention to prevent pneumothorax recurrence after the first occurrence because of the potential lethality of secondary pneumothoraces (68). Otherwise, the recommendations for primary and secondary pneumothorax were very similar. The BTS (69) concluded that chemical pleurodesis can prevent recurrent pneumothorax, but it should be performed only if the patient is unwilling or unable to undergo surgery. The BTS gave the following indications for operative intervention: (a) second ipsilateral pneumothorax, (b) first contralateral pneumothorax, (c) bilateral spontaneous pneumothorax, (d) persistent air leak (>5–7 days of tube drainage; air leak or failure to completely reexpand), (e) professions at risk (e.g., pilots, divers). The BTS did not make a definitive statement about which surgical procedure is preferred for either primary or secondary spontaneous pneumothorax (69).

Hemothorax

Thoracoscopy may replace thoracotomy in some patients with traumatic hemothorax who otherwise would have been subjected to thoracotomy. However, thoracotomy rather than thoracoscopy should be performed if there is exsanguinating hemorrhage through the chest tubes (70,71). Villavicencio et al. (72) reviewed the literature in 1999 and reported that VATS was effective in controlling the bleeding in 33 of 40 (82%) of the patients on whom it was attempted. Thoracoscopy was effective in controlling the bleeding when it arose from intercostal vessels or from lung lacerations.

Approximately 10% of traumatic hemothoraces are complicated by retained clotted blood (73). If more than 30% of the hemithorax is occupied by clotted blood after tube thoracostomy, removal of the blood is usually recommended. Traditionally, the clotted blood has been removed with a thoracotomy. However, thoracoscopy now appears to be the optimal method for the removal of this clotted blood (72–75). Carrillo and Richardson (74) reviewed 25 patients with retained thoracic collections who underwent 26 VATS procedures for this problem. They reported that the procedure was successful in 19 of the 25 patients. If the procedure was performed within 7 days of the initial injury, it was more likely to be successful. Advantages of thoracoscopy over thoracotomy are a lower incidence of wound and pulmonary complications, a lower need for narcotics, a sooner return to normal activities, and a higher rate of return to a normal lifestyle (75). Oguzkaya et al. (73) showed that VATS was more effective in removing clotting blood than was the intrapleural administration of streptokinase.

Chylothorax

One of the options for the treatment of a chylothorax is ligation of the thoracic duct. It is possible to ligate the thoracic duct through thoracoscopy. Although thoracoscopy has not been widely employed for the control of chylothorax, there are now more than 14 reports of chylothorax being managed successfully with VATS in conjunction with either ligation or clipping of the thoracic duct (76). This intervention was successful in all the reported cases (76). It remains to be seen whether the endoscopic closure of chylous leaks is more successful or better tolerated than current open techniques (77).

Hepatic Hydrothorax

The management of hepatic hydrothorax is a difficult problem. The best treatment for this problem is insertion of a transjugular intrahepatic portal systemic (TIPS) shunt or liver transplantation. If neither of these is feasible, the best alternative treatment is probably VATS with closure of the diaphragmatic defects and pleurodesis. In one report, 18 patients were subjected

to 21 thoracoscopies with talc insufflation (3 patients were subjected to a second procedure after the first failed) (78). Diaphragmatic defects were detected and closed in 5 of the 18 patients (28%). The procedure was effective in 10 of 21 patients (48%). The median duration of hospital stay was 15 days. The precarious medical condition of patients with hepatothorax is reflected in the 30% mortality in the 3 months following the surgery (78). Mouroux et al. (79) performed VATS in eight patients. These workers found and closed diaphragmatic defects in six of the patients, and none had a recurrent pleural effusion. No defects were found in the remaining two patients, but after talc insufflation, the effusions occupied only the lower one third of the hemithorax. Ferrante et al. (80) could find no diaphragmatic defects in 15 patients with hepatic hydrothorax subjected to thoracoscopy and talc insufflation. In this series, the hepatic hydrothorax was controlled by the talc insufflation in 8 of the 15 (53%) patients (80). I do not recommend talc insufflation for the reasons discussed in Chapter 10, but instead would recommend pleural abrasion.

COMPLICATIONS OF THORACOSCOPY

Thoracoscopy has a relatively low rate of complications. Data collected on 1,820 patients from the VATS Study Group registry (81) in 1993 revealed that the overall mortality was 2%. Prolonged air leak was the most frequent complication and occurred in 3.2%; significant bleeding resulting in transfusion occurred in only 1%. Pneumonia and empyema occurred in 1.1% and 0.6%, respectively (81). Other researchers have reported comparable complication rates (82). Thoracoscopy is tolerated relatively well by the patient with COPD. In the study mentioned in the preceding text, there were 59 patients who had an FEV_1 below 1 L who underwent thoracoscopy. There was one death (1.7%), and the average postprocedure hospital stay was only 5.4 days (81). Jancovici et al. (83) reviewed 937 VATS procedures at four surgical institutions from June 1991 through May 1995. In this series, approximately half the procedures were performed for pleural problems. They reported that the in-hospital mortality rate was 0.5%, and death occurred principally in patients operated on for malignant pleural effusions. In their series, the overall incidence of postoperative complications was 10.9%; the most common complications were prolonged air leak (6.7%) and pleural effusion (0.7%). There have also been at least 21 instances of tumor seeding of VATS incisions reported by the VATS study group (84).

The complications of medical thoracoscopy are fewer than those of VATS (85). The mortality rate is less than 0.5%, and most deaths are thought to be unrelated to the procedure (85). The same type of complications occur with medical thoracoscopy as with VATS and include intrapleural bleeding, prolonged air leak, and empyema (18).

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