PART NINE -DISORDERS OF THE RESPIRATORY SYSTEM

SECTION 1 -DIAGNOSIS

249. APPROACH TO THE PATIENT WITH DISEASE OF THE RESPIRATORY SYSTEM - *Jeffrey M. Drazen*, *Steven E. Weinberger*

Patients with disease of the respiratory system generally present because of symptoms, an abnormality on a chest radiograph, or both. A set of diagnostic possibilities is often suggested by the initial problems at presentation, including the particular symptom(s) and the appearance of any radiographic abnormalities. The differential diagnosis is then refined on the basis of additional information gleaned from physical examination, pulmonary function testing, additional imaging studies, and bronchoscopic examination. This**chapter**will consider the approach to the patient based on the major patterns of presentation, focusing on the history, the physical examination, and the chest radiograph.**For further discussion of pulmonary function testing, see Chap. 250, and of other diagnostic studies, see Chap. 251.*

CLINICAL PRESENTATION

HISTORY

Dyspnea (shortness of breath) and cough are the primary presenting symptoms for patients with respiratory system disease. Less common symptoms include hemoptysis (the coughing up of blood) and chest pain, often with a pleuritic quality.

Dyspnea (See alsoChap. 32) When evaluating a patient with shortness of breath, one should first determine the time course over which the symptom has become manifest. Patients who were well previously and developed *acute* shortness of breath (over a period of hours to days) can have acute disease affecting the airways (an acute attack of asthma), the pulmonary parenchyma (acute pulmonary edema or an acute infectious process such as a bacterial pneumonia), the pleural space (a pneumothorax), or the pulmonary vasculature (a pulmonary embolus). A *subacute* presentation (over days to weeks) can suggest an exacerbation of preexisting airways disease (asthma or chronic bronchitis), a parenchymal infection or a noninfectious inflammatory process that proceeds at a relatively slow pace (*Pneumocystis carinii* pneumonia in a patient with AIDS, mycobacterial or fungal pneumonia, Wegener's granulomatosis, eosinophilic pneumonia, bronchiolitis obliterans with organizing pneumonia, and many others), neuromuscular disease (Guillain-Barre syndrome, myasthenia gravis), pleural disease (pleural effusion from a variety of possible causes), or chronic cardiac disease (congestive heart failure). A *chronic* presentation (over months to years) often indicates chronic obstructive lung disease, chronic interstitial lung disease, or chronic cardiac disease. Chronic diseases of airways (not only chronic obstructive lung disease but also asthma) are characterized by exacerbations and remissions. Patients often have periods when they are severely limited by shortness of breath, but these may be interspersed with periods in which symptoms are minimal or absent. In contrast, many of the diseases of pulmonary parenchyma are characterized by a slow but inexorable progression.

Other Respiratory Symptoms *Cough* (Chap. 33) may indicate the presence of lung disease, but cough per se is not useful for the differential diagnosis. The presence of sputum accompanying the cough often suggests airway disease and may be seen in asthma, chronic bronchitis, or bronchiectasis.

Hemoptysis (Chap. 33) can originate from disease of the airways, the pulmonary parenchyma, or the vasculature. Diseases of the airways can be inflammatory (acute or chronic bronchitis, bronchiectasis, or cystic fibrosis) or neoplastic (bronchogenic carcinoma or bronchial carcinoid tumors). Parenchymal diseases causing hemoptysis may be either localized (pneumonia, lung abscess, tuberculosis, or infection with *Aspergillus*) or diffuse (Goodpasture's syndrome, idiopathic pulmonary hemosiderosis). Vascular diseases potentially associated with hemoptysis include pulmonary thromboembolic disease and pulmonary arteriovenous malformations.

Chest pain (Chap. 13) caused by diseases of the respiratory system usually originates from involvement of the parietal pleura. As a result, the pain is accentuated by respiratory motion and is often referred to as *pleuritic*. Common examples include primary pleural disorders, such as neoplasm or inflammatory disorders involving the pleura, or pulmonary parenchymal disorders that extend to the pleural surface, such as pneumonia or pulmonary infarction.

Additional Historic Information Information about risk factors for lung disease should be explicitly explored to assure a complete basis of historic data. A history of current and past smoking, especially of cigarettes, should be sought from all patients. The smoking history should include the number of years of smoking, the intensity (i.e., number of packs per day), and, if the patient no longer smokes, the interval since smoking cessation. The risk of lung cancer falls progressively with the interval following discontinuation of smoking, and loss of lung function above the expected age-related decline ceases with the discontinuation of smoking. Even though chronic obstructive lung disease and neoplasia are the two most important respiratory complications of smoking, other respiratory disorders (e.g., spontaneous pneumothorax, respiratory bronchiolitis-interstitial lung disease, eosinophilic granuloma of the lung, and pulmonary hemorrhage with Goodpasture's syndrome) are also associated with smoking. A history of significant secondhand (passive) exposure to smoke, whether in the home or at the workplace, should also be sought as it may be a risk factor for neoplasia or an exacerbating factor for airways disease.

The patient may have been exposed to other inhaled agents associated with lung disease, which act either via direct toxicity or through immune mechanisms (Chaps. 253 and254). Such exposures can be either occupational or avocational, indicating the importance of detailed occupational and personal histories, the latter stressing exposures related to hobbies or the home environment. Important agents include the inorganic dusts associated with pneumoconiosis (especially asbestos and silica dusts) and organic antigens associated with hypersensitivity pneumonitis (especially antigens from molds and animal proteins). Asthma, which is more common in women than men, is often exacerbated by exposure to environmental allergens (dust mites, pet dander, or cockroach allergens in the home or allergens in the outdoor environment such as pollen and ragweed) or may be caused by occupational exposures (diisocyanates). Exposure to particular infectious agents can be suggested by contacts with individuals with known

respiratory infections (especially tuberculosis) or by residence in an area with endemic pathogens (histoplasmosis, coccidioidomycosis, blastomycosis).

A history of coexisting nonrespiratory disease or of risk factors for or previous treatment of such diseases should be sought, as they may predispose a patient to both infectious and noninfectious respiratory system complications. Common examples include systemic rheumatic diseases that are associated with pleural or parenchymal lung disease (Chap. 312), metastatic neoplastic disease in the lung, or impaired host defense mechanisms and secondary infection, which occur in the case of hematologic and lymph node malignancies. Risk factors for AIDS should be sought, as the lungs are not only the most common site of AIDS-defining infection but also can be involved by nonfectious complications of AIDS (Chap. 309). Treatment of nonrespiratory disease can be associated with respiratory complications, either because of effects on host defense mechanisms (immunosuppressive agents, cancer chemotherapy) with resulting infection or because of direct effects on the pulmonary parenchyma (cancer chemotherapy, radiation therapy, or treatment with other agents, such as amiodarone) or on the airways (beta-blocking agents causing airflow obstruction, angiotensin-converting enzyme inhibitors causing cough) (Chap. 253).

Family history is important for evaluating diseases that have a genetic component. These include disorders such as cystic fibrosis,a_1-antitrypsin deficiency, and asthma.

PHYSICAL EXAMINATION

The general principles of inspection, palpation, percussion, and auscultation apply to the examination of the respiratory system. However, the physical examination should be directed not only toward ascertaining abnormalities of the lungs and thorax but also toward recognizing other findings that may reflect underlying lung disease.

On *inspection*, the rate and pattern of breathing as well as the depth and symmetry of lung expansion are observed. Breathing that is unusually rapid, labored, or associated with the use of accessory muscles of respiration generally indicates either augmented respiratory demands or an increased work of breathing. Asymmetric expansion of the chest is usually due to an asymmetric process affecting the lungs, such as endobronchial obstruction of a large airway, unilateral parenchymal or pleural disease, or unilateral phrenic nerve paralysis. Visible abnormalities of the thoracic cage include kyphoscoliosis and ankylosing spondylitis, either of which can alter compliance of the thorax, increase the work of breathing, and cause dyspnea.

On *palpation*, the symmetry of lung expansion can be assessed, generally confirming the findings observed by inspection. Vibration produced by spoken sounds is transmitted to the chest wall and is assessed by the presence or absence and symmetry of tactile fremitus. Transmission of vibration is decreased or absent if pleural liquid is interposed between the lung and the chest wall or if an endobronchial obstruction alters sound transmission. In contrast, transmitted vibration may increase over an area of underlying pulmonary consolidation.

The relative resonance or dullness of the tissue underlying the chest wall is assessed by *percussion*. The normal sound of underlying air-containing lung is resonant. In contrast,

consolidated lung or a pleural effusion sounds dull, while emphysema or air in the pleural space results in a hyperresonant percussion note.

On *auscultation* of the lungs, the examiner listens for both the quality and intensity of the breath sounds and for the presence of extra, or adventitious, sounds. Normal breath sounds heard through the stethoscope at the periphery of the lung are described as *vesicular breath sounds*, in which inspiration is louder and longer than expiration. If sound transmission is impaired by endobronchial obstruction or by air or liquid in the pleural space, breath sounds are diminished in intensity or absent. When sound transmission is improved through consolidated lung, the resulting *bronchial breath sounds* have a more tubular quality and a more pronounced expiratory phase. Sound transmission can also be assessed by listening to spoken or whispered sounds; when these are transmitted through consolidated lung, *bronchophony* and *whispered pectoriloquy*, respectively, are present. The sound of a spoken E becomes more like an A, though with a nasal or bleating quality, a finding that is termed *egophony*.

The primary adventitious (abnormal) sounds that can be heard include crackles (rales), wheezes, and rhonchi. *Crackles* represent the typically inspiratory sound created when alveoli and small airways open and close with respiration, and they are often associated with interstitial lung disease, microatelectasis, or filling of alveoli by liquid. *Wheezes*, which are generally more prominent during expiration than inspiration, reflect the oscillation of airway walls that occurs when there is airflow limitation, as may be produced by bronchospasm, airway edema or collapse, or intraluminal obstruction by neoplasm or secretions. *Rhonchi* is the term applied to the sounds created when there is free liquid in the airway lumen; the viscous interaction between the free liquid and the moving air creates a low-pitched vibratory sound. Other adventitious sounds include pleural friction rubs and stridor. The gritty sound of a *pleural friction rub* indicates inflamed pleural surfaces rubbing against each other, often during both inspiratory and expiratory phases of the respiratory cycle. *Stridor*, which occurs primarily during inspiration, represents flow through a narrowed upper airway, as occurs in an infant with croup.

A summary of the patterns of physical findings on pulmonary examination in common types of respiratory system disease is shown in Table 249-1.

A meticulous *general physical examination* is mandatory in patients with disorders of the respiratory system. Enlarged lymph nodes in the cervical and supraclavicular regions should be sought. Disturbances of mentation or even coma can occur in patients with acute carbon dioxide retention and hypoxemia. Telltale stains on the fingers point to heavy cigarette smoking; infected teeth and gums may occur in patients with aspiration pneumonitis and lung abscess.

Clubbing of the digits can be found in lung cancer, interstitial lung disease, and chronic infections in the thorax, such as bronchiectasis, lung abscess, and empyema. Clubbing can also be seen with congenital heart disease associated with right-to-left shunting and with a variety of chronic inflammatory or infectious diseases, such as inflammatory bowel disease and endocarditis. A number of systemic diseases, such as systemic lupus erythematosus, scleroderma, and rheumatoid arthritis, may be associated with pulmonary complications, even though their primary clinical manifestations and physical

findings are not primarily related to the lungs. Conversely, other diseases that most commonly affect the respiratory system, such as sarcoidosis, can have findings on physical examination not related to the respiratory system, including ocular findings (uveitis, conjunctival granulomas) and skin findings (erythema nodosum, cutaneous granulomas).

CHEST RADIOGRAPHY

Chest radiography is often the initial diagnostic study performed to evaluate patients with respiratory symptoms, but it can also provide the initial evidence of disease in patients who are free of symptoms. Perhaps the most common example of the latter situation is the finding of one or more nodules or masses when the radiograph is performed for a reason other than evaluation of respiratory symptoms.

A number of diagnostic possibilities are often suggested by the radiographic pattern (Figs. 249-1 and249-2). A localized region of opacification involving the pulmonary parenchyma can be described as a nodule (usually <6 cm in diameter), a mass (usually ^{3} 6 cm in diameter), or an infiltrate. Diffuse disease with increased opacification is usually characterized as having an alveolar, an interstitial, or a nodular pattern. In contrast, increased radiolucency can be localized, as seen with a cyst or bulla, or generalized, as occurs with emphysema. The chest radiograph is also particularly useful for the detection of pleural disease, especially if manifested by the presence of air or liquid in the pleural space. An abnormal appearance of the hila and/or the mediastinum can suggest a mass or enlargement of lymph nodes.

A summary of representative diagnoses suggested by these common radiographic patterns is presented inTable 249-2.

Additional Diagnostic Evaluation Further information for clarification of radiographic abnormalities is frequently obtained with computed tomographic scanning of the chest (Chap. 251; seeFig. 265-2). This technique is more sensitive than plain radiography in detecting subtle abnormalities and can suggest specific diagnoses based on the pattern of abnormality.**For further discussion of the use of other imaging studies, including magnetic resonance imaging, scintigraphic studies, ultrasound, and angiography, see Chap. 251.*

Alteration in the function of the lungs as a result of respiratory system disease is assessed objectively by pulmonary function tests, and effects on gas exchange are evaluated by measurement of arterial blood gases or by oximetry (Chap. 250). As part of pulmonary function testing, quantitation of forced expiratory flow assesses the presence of obstructive physiology, which is consistent with diseases affecting the structure or function of the airways, such as asthma and chronic obstructive lung disease. Measurement of lung volumes assesses the presence of restrictive disorders, seen with diseases of the pulmonary parenchyma or respiratory pump and with space-occupying processes within the pleura.

Bronchoscopy is useful in some settings for visualizing abnormalities of the airways and for obtaining a variety of samples from either the airway or the pulmonary parenchyma (Chap. 251).

INTEGRATION OF THE PRESENTING CLINICAL PATTERN AND DIAGNOSTIC STUDIES

Patients with respiratory symptoms but a normal chest radiograph most commonly have diseases affecting the airways, such as asthma or chronic obstructive pulmonary disease. However, the latter diagnosis is also commonly associated with radiographic abnormalities, such as diaphragmatic flattening and attenuation of vascular markings. Other disorders of the respiratory system for which the chest radiograph is normal include disorders of the respiratory pump (either the chest wall or the neuromuscular apparatus controlling the chest wall) or pulmonary circulation and occasionally interstitial lung disease. Chest examination and pulmonary function tests are generally helpful in sorting out these diagnostic possibilities. Obstructive diseases associated with a normal or relatively normal chest radiograph are often characterized by findings on physical examination and pulmonary function testing that are typical for these conditions. Similarly, diseases of the respiratory pump or interstitial diseases may also be suggested by findings on physical examination or by particular patterns of restrictive disease seen on pulmonary function testing.

When respiratory symptoms are accompanied by radiographic abnormalities, diseases of the pulmonary parenchyma or the pleura are usually present. Either diffuse or localized parenchymal lung disease is generally visualized well on the radiograph, and both air and liquid in the pleural space (pneumothorax and pleural effusion, respectively) are usually readily detected by radiography.

Radiographic findings in the absence of respiratory symptoms often indicate localized disease affecting the airways or the pulmonary parenchyma. One or more nodules or masses can suggest intrathoracic malignancy, but they also can be the manifestation of a current or previous infectious process. Patients with diffuse parenchymal lung disease on radiographic examination may be free of symptoms, as is sometimes the case with pulmonary sarcoidosis.

In approaching the patient with pulmonary disease, consideration must be given to the observation that substantial changes in the relative incidence of diseases affecting the respiratory system have taken place in the United States during the past four decades. The prevalence of chronic infectious disorders such as lung abscess and bronchiectasis has decreased. Tuberculosis declined only to undergo resurgence when two susceptible populations, patients with AIDS and immigrants from Southeast Asia, increased in number. Patients with chronic bronchitis and with emphysema now survive longer and form an increasing fraction of patients with chronic respiratory disease, as do patients with environmental lung disease and with drug-induced pulmonary disease. Modern intercontinental travel has increased the appearance in the western world of parasitic infestations of the lung. Also, the reduction of immune competence that occurs in patients with AIDS and in those with diabetes as well as in patients being treated for a variety of malignancies and those receiving immunosuppressive drugs has led to an increasing incidence of opportunistic infections of the lungs with a variety of microorganisms that were rarely pathogenic in the past.

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250. DISTURBANCES OF RESPIRATORY FUNCTION - *Steven E. Weinberger, Jeffrey M. Drazen*

The respiratory system includes the lungs, the central nervous system (CNS), the chest wall (with the diaphragm and intercostal muscles), and the pulmonary circulation. The CNS controls the activity of the muscles of the chest wall, which constitute the pump of the respiratory system. Because these components of the respiratory system act in concert to achieve gas exchange, malfunction of an individual component or alteration of the relationships among components can lead to disturbances in function. In this **chapter** we consider three major aspects of disturbed respiratory function: (1) disturbances in ventilatory function, (2) disturbances in the pulmonary circulation, and (3) disturbances in gas exchange. **For further discussion of disorders relating to CNS control of ventilation, see Chap. 263.*

DISTURBANCES IN VENTILATORY FUNCTION

Ventilation is the process whereby the lungs replenish the gas in the alveoli. Measurements of ventilatory function in common diagnostic use consist of quantification of the gas volume contained in the lungs under certain circumstances and the rate at which gas can be expelled from the lungs. Two measurements of lung volume commonly used for respiratory diagnosis are total lung capacity (TLC) and residual volume (RV). The former is the volume of gas contained in the lungs after a maximal inspiration, whereas the latter is the volume of gas remaining in the lungs at the end of a maximal expiration. The volume of gas that is exhaled from the lungs in going from TLC to RV is called the *vital capacity* (VC) (Fig. 250-1).

Common clinical measurements of airflow are obtained from maneuvers in which the subject inspires to TLC and then forcibly exhales to RV. Three measurements are commonly made from a recording of exhaled volume versus time -- i.e., a spirogram -- obtained during such a forced expiratory maneuver: (1) the volume of gas exhaled during the first second of expiration [forced expiratory volume (FEV) in 1 s, or FEV_1], (2) the total volume exhaled [forced vital capacity (FVC)], and (3) the average expiratory flow rate during the middle 50% of the VC [forced expiratory flow (FEF) between 25 and 75% of the VC, or $FEF_{25-75\%}$, also called the maximal midexpiratory flow rate (MMFR)] (Fig. 250-2).

PHYSIOLOGIC FEATURES

The lungs are elastic structures, containing collagen and elastic fibers that resist expansion. For normal lungs to contain air, they must be distended either by a positive internal pressure -- i.e., by a pressure in the airways and alveolar spaces -- or by a negative external pressure -- i.e., by a pressure outside the lung. The relationship between the volume of gas contained in the lungs and the distending pressure (the *transpulmonary pressure*, or P_{TP}, defined as internal pressure minus external pressure) is described by the pressure-volume curve of the lungs (Fig. 250-3*A*).

The chest wall is also an elastic structure, with properties similar to those of an expandable and compressible spring. The relationship between the volume enclosed by the chest wall and the distending pressure for the chest wall is described by the

pressure-volume curve of the chest wall (Fig. 250-3*B*). For the chest wall to assume a volume different from its resting volume, the internal or external pressures acting on it must be altered.

At functional residual capacity (FRC), defined as the volume of gas in the lungs at the end of a normal exhalation, the lungs are partially inflated, so their elastic recoil exerts a force tending to empty the lungs. At the same time, chest wall volume is such that its elastic recoil promotes outward expansion. FRC occurs at the lung volume at which the tendency of the lungs to contract is opposed by the equal and opposite tendency of the chest wall to expand (Fig. 250-3*C*).

For the lungs and the chest wall to achieve a volume other than the resting volume (FRC), either the pressures acting on them must be changed passively -- e.g., by a mechanical ventilator that delivers positive pressure to the airways and alveoli -- or the respiratory muscles must actively oppose the tendency of the lungs and the chest wall to return to FRC. During inhalation to volumes above FRC, the inspiratory muscles actively overcome the tendency of the respiratory system to decrease volume back to FRC. During active exhalation to volumes below FRC, expiratory muscle activity must overcome the tendency of the respiratory system to increase volume back to FRC.

AtTLC, the maximal force applied by the inspiratory muscles to expand the lungs is opposed mainly by the inward recoil of the lungs. As a consequence, the major determinants of TLC are the stiffness of the lungs and inspiratory muscle strength. If the lungs become stiffer -- i.e., less compliant -- TLC is decreased. If the lungs become less stiff (more compliant), TLC is increased. If the inspiratory muscles are significantly weakened, they are less able to overcome the inward elastic recoil of the lungs, and TLC is lowered.

AtRV, the force exerted by the expiratory muscles to decrease lung volume further is balanced by the outward recoil of the chest wall, which becomes extremely stiff at low lung volumes. Two factors influence the volume of gas contained in the lungs at RV. The first is the ability of the subject to exert a prolonged expiratory effort, which is related to muscle strength and the ability to overcome sensory stimuli from the chest wall. The second is the ability of the lungs to empty to a small volume. In normal lungs, as P_{TP} is lowered, lung volume decreases. In lungs with diseased airways, as P_{TP} is lowered, flow limitation or airway closure may limit the amount of gas that can be expired. Consequently, either weak expiratory muscles or intrinsic airways disease can result in an elevation in measured RV.

Dynamic measurements of ventilatory function are made by having the subject inhale toTLC and then perform a forced expiration toRV. If a subject performs a series of such expiratory maneuvers using increasing muscular intensity, expiratory flow rates will increase until a certain level of effort is reached. Beyond this level, additional effort at any given lung volume will not increase the forced expiratory flow rate; this phenomenon is known as the *effort independence* of forced expiratory flow. The physiologic mechanisms determining the flow rates during this effort-independent phase of FEF have been shown to be the elastic recoil of the lung, the airflow resistance of the airways between the alveolar zone and the physical site of flow limitation, and the airway wall compliance at the site of flow limitation. Physical processes that decrease

elastic recoil, increase airflow resistance, or increase airway wall compliance decrease the flow rate that can be achieved at any given lung volume. Conversely, processes that increase elastic recoil, decrease resistance, or stiffen airway walls increase the flow rate that can be achieved at any given lung volume.

MEASUREMENT OF VENTILATORY FUNCTION

Ventilatory function is measured under static conditions for determination of lung volumes and under dynamic conditions for determination of forced expiratory flow rates.VC, expiratory reserve volume (ERV), and inspiratory capacity (IC) (Fig. 250-1) are measured by having the patient breathe into and out of a spirometer, a device capable of measuring expired or inspired gas volume while plotting volume as a function of time. Other volumes -- specifically,RV,FRC, andTLC -- cannot be measured in this way because they include the volume of gas present in the lungs even after a maximal expiration. Two techniques are commonly used to measure these volumes: helium dilution and body plethysmography. In the helium dilution method, the subject repeatedly breathes in and out from a reservoir with a known volume of gas containing a trace amount of helium. The helium is diluted by the gas previously present in the lungs and very little is absorbed into the pulmonary circulation. From knowledge of the reservoir volume and the initial and final helium concentrations, the volume of gas present in the lungs can be calculated. The helium dilution method may underestimate the volume of gas in the lungs if there are slowly communicating airspaces, such as bullae. In this situation, lung volumes can be measured more accurately with a body plethysmograph, a sealed box in which the patient sits while panting against a closed mouthpiece. Because there is no airflow into or out of the plethysmograph, the pressure changes in the thorax during panting cause compression and rarefaction of gas in the lungs and simultaneous rarefaction and compression of gas in the plethysmograph. By measuring the pressure changes in the plethysmograph and at the mouthpiece, the volume of gas in the thorax can be calculated using Boyle's law.

Lung volumes and measurements made during forced expiration are interpreted by comparing the values measured with the values expected given the age, height, sex, and race of the patient (Appendix A). Regression curves have been constructed on the basis of data obtained from large numbers of normal, nonsmoking individuals without evidence of lung disease. Predicted values for a given patient can then be obtained by using the patient's age and height in the appropriate regression equation; different equations are used depending on the patient's race and gender. Because there is some variability among normal individuals, values between 80 and 120% of the predicted value have traditionally been considered normal. Increasingly, calculated percentiles are used in determining normality. Specifically, values of individual measurements falling below the fifth percentile are considered to be below normal.

The normal value for the ratioFEV_1/FVCis approximately 0.75 to 0.80, although this value does fall somewhat with advancing age. The$FEF_{25-75\%}$is often considered a more sensitive measurement of early airflow obstruction, particularly in small airways. However, this measurement must be interpreted cautiously in patients with abnormally small lungs (lowTLC andVC). These patients exhale less air during forced expiration, and the $FEF_{25-75\%}$may appear abnormal relative to the usual predicted value, even though it is normal relative to the size of the patient's lungs.

It is also a common practice to plot expiratory flow rates against lung volume (rather than against time); the close linkage of flow rates to lung volumes produces a typical *flow-volume curve* (Fig. 250-4). In addition, the spirometric values mentioned above can be calculated from the flow-volume curve. Commonly, flow rates during a maximal inspiratory effort performed as rapidly as possible are plotted as well, making the flow-volume curve into a *flow-volume loop*. AtTLC, before expiratory flow starts, the flow rate is zero; once forced expiration has begun, a high peak flow rate is rapidly achieved. As expiration continues and lung volume approachesRV, the flow rate falls progressively, in a nearly linear fashion as a function of lung volume for a person with normal lung function. During maximal inspiration from RV to TLC, inspiratory flow is most rapid at the midpoint of inspiration, so the inspiratory portion of the loop is U-shaped or saddle-shaped. The flow rates achieved during maximal expiration can be analyzed quantitatively by comparing the flow rates at specified lung volumes with the predicted values or qualitatively by analyzing the shape of the descending limb of the expiratory curve.

Assessing the strength of respiratory muscles is an additional part of the overall evaluation of some patients with respiratory dysfunction. When a patient exhales completely toRV and then tries to inspire maximally against an occluded airway, the pressure that can be generated is called the *maximal inspiratory pressure* (MIP). On the other hand, when a patient inhales toTLC and then tries to expire maximally against an occluded airway, the pressure generated is called the *maximal expiratory pressure* (MEP). In the proper clinical setting, these studies may provide useful information regarding the cause of abnormal lung volumes and the possibility that respiratory muscle weakness may be causally related to the lung volume abnormalities.

PATTERNS OF ABNORMAL FUNCTION

The two major patterns of abnormal ventilatory function, as measured by static lung volumes and spirometry, are restrictive and obstructive patterns. In the *obstructive pattern*, the hallmark is a decrease in expiratory flow rates. With fully established disease, the ratioFEV_1/FVCis decreased, as is the$FEF_{25-75\%}$(Fig. 250-2, line *B*). The expiratory portion of the flow-volume loop demonstrates decreased flow rates for any given lung volume. Nonuniform emptying of airways is reflected by a coved (concave upward) configuration of the curve (Fig. 250-4). With early obstructive disease, which originates in the small airways, FEV_1/FVC may be normal; the only abnormalities noted on routine testing of pulmonary function may be a depression in $FEF_{25-75\%}$and an abnormal, i.e., coved, configuration in the terminal portion of the forced expiratory flow-volume curve.

In *obstructive* disease, theTLC is normal or increased. When helium equilibration tests are used to measure lung volumes, the measured volume may be less than the actual volume if helium was not well distributed to all regions of the lung. Residual volume is elevated as a result of airway closure during expiration, and the ratioRV/TLC is increased.VC is frequently decreased in obstructive disease because of the striking elevations in RV with only minor changes in TLC.

A *restrictive pattern* can be broadly divided into two subgroups, depending on the

location of the pathology: pulmonary parenchymal and extraparenchymal. For extraparenchymal disease, dysfunction can be predominantly in inspiration or in both inspiration and expiration (Table 250-1). The hallmark of a restrictive pattern, found in all these subcategories, is a decrease in lung volumes, primarilyTLC andVC. In pulmonary parenchymal disease,RV is also generally decreased, and forced expiratory flow rates are preserved. In fact, when$FEV_1$is considered as a percentage of theFVC, the flow rates are often supranormal, i.e., disproportionately high relative to the size of the lungs (Fig. 250-2, line *C*). The flow-volume curve may graphically demonstrate this disproportionate relationship between flow rates and lung volumes, since the expiratory portion of the curve appears relatively tall (preserved flow rates) but narrow (decreased lung volumes), as shown inFig. 250-4.

In the extraparenchymal pattern characterized by *inspiratory dysfunction*, caused by either inspiratory muscle weakness or a stiff chest wall, inadequate distending forces are exerted on an otherwise normal lung. As a result,TLCvalues are less than predicted,RV is often not significantly affected, and expiratory flow rates are preserved. If inspiratory muscle weakness is the cause of this pattern, thenMIP is decreased. In the extraparenchymal pattern characterized by *inspiratory and expiratory dysfunction*, the ability to expire to a normal RV is also limited, because of either expiratory muscle weakness or a deformed chest wall that is abnormally rigid at volumes belowFRC. Consequently, RV is often elevated, unlike the pattern observed in the other restrictive subcategories. The ratioFEV_1/FVCis variable and depends on expiratory muscle strength. If expiratory muscle strength is significantly decreased, thenMEP is decreased, the ability to expire rapidly is impaired, and FEV_1/FVC may be decreased even though there is no airflow obstruction. If expiratory muscle strength is normal but the chest wall is abnormally stiff below FRC, then FEV_1/FVC is normal or increased.

CLINICAL CORRELATIONS

Table 250-1 summarizes the expected alterations in ventilatory function as indicated by pulmonary function testing. One reason to establish a ventilatory diagnosis is to categorize the functional disorder. This information can be useful in diagnosis, as outlined inTable 250-2. Note that lung disease such as pulmonary vascular disease or lung nodules can be present without abnormal ventilatory function, but the presence of specific diagnostic findings is an aid in differential diagnosis.

DISTURBANCES IN THE PULMONARY CIRCULATION

PHYSIOLOGIC FEATURES

The pulmonary vasculature must handle the entire output of the right ventricle, approximately 5 L/min in a normal adult at rest. The comparatively thin-walled vessels of the pulmonary arterial system provide relatively little resistance to flow and are capable of handling this large volume of blood at perfusion pressures that are low compared with those of the systemic circulation. The normal mean pulmonary artery pressure is 15 mmHg, as compared to approximately 95 mmHg for the normal mean aortic pressure. Regional blood flow in the lung is dependent on hydrostatic forces. In an upright person, pulmonary arterial pressure (PAP) is lowest at the apex of the lung and highest at the lung base. As a result, in the upright position, perfusion is least at the apex and greatest

at the base. When cardiac output increases, as occurs during exercise, the pulmonary vasculature is capable of recruiting previously unperfused vessels and distending underperfused vessels, thus responding to the increase in flow with a decrease in pulmonary vascular resistance. In consequence, the increase in mean PAP, even with a three- to fourfold increase in cardiac output, is small.

METHODS OF MEASUREMENT

Assessment of circulatory function in the pulmonary vasculature depends on measuring pulmonary vascular pressures and cardiac output. Clinically, these measurements are commonly made in intensive care units capable of invasive monitoring and in cardiac catheterization laboratories. With a flow-directed pulmonary arterial (Swan-Ganz) catheter,PAP and pulmonary capillary wedge pressure can be measured directly, and cardiac output can be obtained by the thermodilution method. Pulmonary vascular resistance (PVR) can then be calculated according to the equation

where PVR= pulmonary vascular resistance (dyn×s/cm^5); PAP = mean pulmonary arterial pressure (mmHg); PCW= pulmonary capillary wedge pressure (mmHg); and CO= cardiac output (L/min).

The normal value for pulmonary vascular resistance is approximately 50 to 150 dyn×s/cm^5.

MECHANISMS OF ABNORMAL FUNCTION (See alsoChap. 260)

PVRmay increase by a variety of mechanisms. Pulmonary arterial and arteriolar vasoconstriction is a prominent response to alveolar hypoxia. PVR also increases if intraluminal thrombi or proliferation of smooth muscle in vessel walls diminishes the luminal cross-sectional area. If small pulmonary vessels are destroyed, either by scarring or by loss of alveolar walls, the total cross-sectional area of the pulmonary vascular bed diminishes, and PVR increases. When PVR is elevated, eitherPAPrises to maintain normal cardiac output or cardiac output falls if PAP does not increase.

CLINICAL CORRELATIONS

Disturbances in the function of the pulmonary vasculature as a result of primary cardiac disease, either congenital heart disease or conditions that elevate left atrial pressure, such as mitral stenosis, are beyond the scope of this**chapter**and are discussed in Chaps. 234 and236, respectively. Instead, the focus will be on the pulmonary vasculature as its function is affected by diseases primarily involving the respiratory system, including the pulmonary vessels themselves.

All diseases of the respiratory system causing hypoxemia are potentially capable of increasingPVR, since alveolar hypoxia is a very potent stimulus for pulmonary vasoconstriction. The more prolonged and intense the hypoxic stimulus, the more likely it is that a significant increase in PVR producing pulmonary hypertension will result. In practice, patients with hypoxemia caused by chronic obstructive lung disease, interstitial

lung disease, chest wall disease, and the obesity hypoventilation-sleep apnea syndrome are particularly prone to developing pulmonary hypertension. If there are additional structural changes in the pulmonary vasculature secondary to the underlying process, these will increase the likelihood of developing pulmonary hypertension.

With diseases directly affecting the pulmonary vessels, a decrease in the cross-sectional area of the pulmonary vascular bed is primarily responsible for increasedPVR, while hypoxemia generally plays a lesser role. In the case of recurrent pulmonary emboli, parts of the pulmonary arterial system are occluded by intraluminal thrombi originating in the systemic venous system. With primary pulmonary hypertension (Chap. 260) or with pulmonary vascular disease secondary to scleroderma, the small pulmonary arteries and arterioles are affected by a generalized obliterative process that narrows and occludes these vessels. PVR increases, and significant pulmonary hypertension often results.

DISTURBANCES IN GAS EXCHANGE

PHYSIOLOGIC FEATURES

The primary functions of the respiratory system are to remove the appropriate amount of CO_2 from blood entering the pulmonary circulation and to provide adequate O_2 to blood leaving the pulmonary circulation. For these functions to be carried out properly, there must be adequate provision of fresh air to the alveoli for delivery of O_2 and removal of CO_2(ventilation), adequate circulation of blood through the pulmonary vasculature (perfusion), adequate movement of gas between alveoli and pulmonary capillaries (diffusion), and appropriate contact between alveolar gas and pulmonary capillary blood (ventilation-perfusion matching).

A normal individual at rest inspires approximately 12 to 16 times per minute, each breath having a tidal volume of approximately 500 mL. A portion (approximately 30%) of the fresh air inspired with each breath does not reach the alveoli but remains in the conducting airways of the lung. This component of each breath, which is not generally available for gas exchange, is called the *anatomic dead space component*. The remaining 70% reaches the alveolar zone, mixes rapidly with the gas already there, and can participate in gas exchange. In this example, the total ventilation each minute is approximately 7 L, composed of 2 L/min of dead space ventilation and 5 L/min of alveolar ventilation. In certain diseases, some alveoli are ventilated but not perfused, so that some ventilation in addition to the anatomic dead space component is wasted. If total dead space ventilation is increased but total minute ventilation is unchanged, then alveolar ventilation must fall correspondingly.

Gas exchange is dependent on alveolar ventilation rather than total minute ventilation, as outlined below. The partial pressure of CO_2 in arterial blood (Pa_{CO_2}) is directly proportional to the amount of CO_2produced per minute ($_{CO_2}$) and inversely proportional to alveolar ventilation (A), according to the relationship

where$_{CO_2}$ is expressed in mL/min, A in L/min, and Pa_{CO_2} in mmHg. At fixed$_{CO_2}$, when

alveolar ventilation increases, Pa_{CO_2} falls, and when alveolar ventilation decreases, Pa_{CO_2} rises. Maintaining a normal level of O_2 in the alveoli (and consequently in arterial blood) also depends on provision of adequate alveolar ventilation to replenish alveolar O_2. This principle will become more apparent from consideration of the alveolar gas equation below.

Diffusion of O_2 and CO_2 Both O_2 and CO_2 diffuse readily down their respective concentration gradients through the alveolar wall and pulmonary capillary endothelium. Under normal circumstances, this process is rapid, and equilibration of both gases is complete within one-third of the transit time of erythrocytes through the pulmonary capillary bed. Even in disease states in which diffusion of gases is impaired, the impairment is unlikely to be severe enough to prevent equilibration of CO_2 and O_2. Consequently, a diffusion abnormality rarely results in arterial hypoxemia at rest. If erythrocyte transit time in the pulmonary circulation is shortened, as occurs with exercise, and diffusion is impaired, then diffusion limitation may contribute to hypoxemia. Exercise testing can often demonstrate such physiologically significant abnormalities due to impaired diffusion. Even though diffusion limitation rarely makes a clinically significant contribution to resting hypoxemia, clinical measurements of what is known as *diffusing capacity* (see below) can be a useful measure of the integrity of the alveolar-capillary membrane.

Ventilation-Perfusion Matching In addition to the absolute levels of alveolar ventilation and perfusion, gas exchange depends critically on the proper matching of ventilation and perfusion. The spectrum of possible ventilation-perfusion (/) ratios in an alveolar-capillary unit ranges from zero, in which ventilation is totally absent and the unit behaves as a shunt, to infinity, in which perfusion is totally absent and the unit behaves as dead space. The P_{O_2} and P_{CO_2} of blood leaving each alveolar-capillary unit depend on the gas tension (of blood and air) entering that unit and on the particular / ratio of the unit. At one extreme, when an alveolar-capillary unit has a / ratio of 0 and behaves as a shunt, blood leaving the unit has the composition of mixed venous blood entering the pulmonary capillaries, i.e., P_{O_2}» 40 mmHg and P_{CO_2}» 46 mmHg. At the other extreme, when an alveolar-capillary unit has a high / ratio, it behaves almost like dead space, and the small amount of blood leaving the unit has partial pressures of O_2 and CO_2 (P_{O_2}» 150 mmHg, P_{CO_2}» 0 mmHg while breathing room air) approaching the composition of inspired gas.

In the ideal situation, all alveolar-capillary units have equal matching of ventilation and perfusion, i.e., a ratio of approximately 1 when each is expressed in L/min. However, even in the normal individual, some / mismatching is present, since there is normally a gradient of blood flow from the apices to the bases of the lungs. There is a similar gradient of ventilation from the apices to the bases, but it is less marked than the perfusion gradient. As a result, ventilation-perfusion ratios are higher at the lung apices than at the lung bases. Therefore, blood coming from the apices has a higher P_{O_2} and lower P_{CO_2} than blood coming from the bases. The net P_{O_2} and P_{CO_2} of the blood mixture coming from all areas of the lung is a flow-weighted average of the individual components, which reflects both the relative amount of blood from each unit and the O_2 and CO_2 *content* of the blood coming from each unit. Because of the sigmoid shape of the oxyhemoglobin dissociation curve (see Fig. 106-2), it is important to distinguish between the partial pressure and the content of O_2 in blood. Hemoglobin is almost fully

(~90%) saturated at a P_{O_2} of 60 mmHg, and little additional O_2 is carried by hemoglobin even with a substantial elevation of P_{O_2}above 60 mmHg. On the other hand, significant O_2desaturation of hemoglobin occurs once P_{O_2}falls below 60 mmHg and onto the steep descending limb of the curve. As a result, blood coming from regions of the lung with a high / ratio and a high P_{O_2} has only a small elevation in O_2content and cannot compensate for blood coming from regions with a low / ratio and a low P_{O_2}, which has a significantly decreased O_2content. Although / mismatching can influence P_{CO_2}, this effect is less marked and is often overcome by an increase in overall minute ventilation.

MEASUREMENT OF GAS EXCHANGE

Arterial Blood Gases The most commonly used measures of gas exchange are the partial pressures of O_2 and CO_2 in arterial blood, i.e., Pa_{O_2} and Pa_{CO_2}, respectively. These partial pressures do not measure directly the quantity of O_2 and CO_2 in blood but rather the driving pressure for the gas in blood. The actual quantity or content of a gas in blood also depends on the solubility of the gas in plasma and the ability of any component of blood to react with or bind the gas of interest. Since hemoglobin is capable of binding large amounts of O_2, oxygenated hemoglobin is the primary form in which O_2 is transported in blood. The actual content of O_2 in blood therefore depends both on the hemoglobin concentration and on the Pa_{O_2}. The Pa_{O_2}determines what percentage of hemoglobin is saturated with O_2, based on the position on the oxyhemoglobin dissociation curve. Oxygen content in normal blood (at 37°C, pH 7.4) can be determined by adding the amount of O_2dissolved in plasma to the amount bound to hemoglobin, according to the equation

since each gram of hemoglobin is capable of carrying 1.34 mL O_2 when fully saturated, and the amount of O_2 that can be dissolved in plasma is proportional to the P_{O_2}, with 0.0031 mL O_2dissolved per deciliter of blood per mmHg P_{O_2}. In arterial blood, the amount of O_2transported dissolved in plasma (approximately 0.3 mL O_2 per deciliter of blood) is trivial compared with the amount bound to hemoglobin (approximately 20 mL O_2 per deciliter of blood).

Most commonly, P_{O_2} is the measurement used to assess the effect of respiratory disease on the oxygenation of arterial blood. Direct measurement of O_2saturation in arterial blood by oximetry is also important in selected clinical conditions. For example, in patients with carbon monoxide intoxication, carbon monoxide preferentially displaces O_2 from hemoglobin, essentially making a portion of hemoglobin unavailable for binding to O_2. In this circumstance, carbon monoxide saturation is high and O_2saturation is low, even though the driving pressure for O_2 to bind to hemoglobin, reflected by P_{O_2}, is normal. Measurement of O_2saturation is also important for the determination of O_2content when mixed venous blood is sampled from a pulmonary arterial catheter to calculate cardiac output by the Fick technique. In mixed venous blood, the P_{O_2} is normally about 40 mmHg, but small changes in P_{O_2} may reflect relatively large changes in O_2saturation.

A useful calculation in the assessment of oxygenation is the alveolar-arterial O_2difference (PA_{O_2}-Pa_{O_2}), commonly called the *alveolar-arterial O_2gradient* (or A - a

gradient). This calculation takes into account the fact that alveolar and, hence, arterial P_{O_2} can be expected to change depending on the level of alveolar ventilation, reflected by the arterial P_{CO_2}. When a patient hyperventilates and has a low P_{CO_2} in arterial blood and alveolar gas, alveolar and arterial P_{O_2} will rise; conversely, hypoventilation and a high P_{CO_2} are accompanied by a decrease in alveolar and arterial P_{O_2}. These changes in arterial P_{O_2} are independent of abnormalities in O_2transfer at the alveolar-capillary level and reflect only the dependence of alveolar P_{O_2} on the level of alveolar ventilation.

In order to determine the alveolar-arterial O_2difference, the alveolar P_{O_2}(PA_{O_2}) must first be calculated. The equation most commonly used for this purpose, a simplified form of the alveolar gas equation, is

where FI_{O_2}= fractional concentration of inspired O_2(»0.21 when breathing room air); P_B= barometric pressure (approximately 760 mmHg at sea level); P_{H_2O}= water vapor pressure (47 mmHg when air is fully saturated at 37°C); and R= respiratory quotient (the ratio of CO_2production to O_2consumption, usually assumed to be 0.8). If the preceding values are substituted into the equation for the patient breathing air at sea level, the equation becomes

The alveolar-arterial O_2difference can then be calculated by subtracting measured $Pa_{O_2}$from calculated PA_{O_2}. In a healthy young person breathing room air, the PA_{O_2}-Pa_{O_2} is normally less than 15 mmHg; this value increases with age and may be as high as 30 mmHg in elderly patients.

The adequacy of CO_2elimination is measured by the partial pressure of CO_2 in arterial blood, i.e., Pa_{CO_2}. A more complete understanding of the mechanisms and chronicity of abnormal levels of P_{CO_2}also requires measurement of pH and/or bicarbonate (HCO_3^-), since P_{CO_2} and the patient's acid-base status are so closely intertwined (Chap. 50).

Pulse Oximetry Because measurement of Pa_{O_2}requires arterial puncture, it is not ideal either for office use or for routine or frequent measurement in the inpatient setting. Additionally, because it provides intermittent rather than continuous data about the patient's oxygenation, it is not ideal for close monitoring of unstable patients. Pulse oximetry, an alternative method for assessing oxygenation, is readily available in many clinical settings. Using a probe usually clipped over a patient's finger, the pulse oximeter calculates oxygen saturation (rather than Pa_{O_2}) based on measurements of absorption of two wavelengths of light by hemoglobin in pulsatile, cutaneous arterial blood. Because of differential absorption of the two wavelengths of light by oxygenated and nonoxygenated hemoglobin, the percentage of hemoglobin that is saturated with oxygen, i.e., the Sa_{O_2}, can be calculated and displayed instantaneously.

Although the pulse oximeter has been a major advance in the noninvasive, continuous monitoring of oxygenation, there are several issues and potential problems concerning its use. First, the clinician must be aware of the relationship between oxygen saturation and tension as shown by the oxyhemoglobin dissociation curve (Fig. 106-2). Because

the curve becomes relatively flat above an arterial P_{O_2} of 60 mmHg (corresponding to Sa_{O_2}= 90%), the oximeter is relatively insensitive to changes in Pa_{O_2}above this level. In addition, the position of the curve and therefore the specific relationship between Pa_{O_2} and Sa_{O_2} may change depending on factors such as temperature, pH, and the erythrocyte concentration of 2,3-diphosphoglycerate. Second, when cutaneous perfusion is decreased, e.g., owing to low cardiac output or the use of vasoconstrictors, the signal from the oximeter may be less reliable or even unobtainable. Third, other forms of hemoglobin, such as carboxyhemoglobin and methemoglobin, are not distinguishable from oxyhemoglobin when only two wavelengths of light are used. The Sa_{O_2}values reported by the pulse oximeter are not reliable in the presence of significant amounts of either of these forms of hemoglobin. In contrast, the device used to measure oxygen saturation in samples of arterial blood, called the CO-oximeter, uses at least four wavelengths of light and is capable of distinguishing oxyhemoglobin, deoxygenated hemoglobin, carboxyhemoglobin, and methemoglobin. Finally, the clinician must remember that the often-used goal of Sa_{O_2}[3] 90% does not indicate anything about CO_2elimination and therefore does not ensure a clinically acceptable P_{CO_2}.

Diffusing Capacity The ability of gas to diffuse across the alveolar-capillary membrane is ordinarily assessed by the diffusing capacity of the lung for carbon monoxide (DL_{CO}). In this test, a small concentration of carbon monoxide (0.3%) is inhaled, usually in a single breath that is held for approximately 10 s. The carbon monoxide is diluted by the gas already present in the alveoli and is also taken up by hemoglobin as the erythrocytes course through the pulmonary capillary system. The concentration of carbon monoxide in exhaled gas is measured, and DL_{CO} is calculated as the quantity of carbon monoxide absorbed per minute per mmHg pressure gradient from the alveoli to the pulmonary capillaries. The value obtained for DL_{CO}depends on the alveolar-capillary surface area available for gas exchange and on the pulmonary capillary blood volume. In addition, the thickness of the alveolar-capillary membrane, the degree of / mismatching, and the patient's hemoglobin level will affect the measurement. Because of this effect of hemoglobin levels on DL_{CO}, the measured DL_{CO} is frequently corrected to take the patient's hemoglobin level into account. The value for DL_{CO}, ideally corrected for hemoglobin, can then be compared with a predicted value, based either on age, height, and gender or on the alveolar volume (VA) at which the value was obtained. Alternatively, the DL_{CO} can be divided by VA and the resulting value for DL_{CO}/VA compared with a predicted value.

Approach to the Patient

Arterial Blood Gases Hypoxemia is a common manifestation of a variety of diseases affecting the lungs or other parts of the respiratory system. The broad clinical problem of hypoxemia is often best characterized according to the underlying mechanism. The four basic, and not mutually exclusive, mechanisms of hypoxemia are (1) a decrease in inspired P_{O_2}, (2) hypoventilation, (3) shunting, and (4) / mismatching. Hypoxemia due to decreased diffusion occurs only under selected clinical circumstances and is not usually included among the general categories of hypoxemia. Determining the underlying mechanism for hypoxemia depends on measurement of the Pa_{CO_2}, calculation of PA_{O_2}-Pa_{O_2}, and knowledge of the response to supplemental O_2. A flowchart summarizing the approach to the hypoxemic patient is given inFig. 250-5.

A decrease in the inspired P_{O_2} and hypoventilation both cause hypoxemia by lowering $P_{A_{O_2}}$ and therefore $P_{a_{O_2}}$. In each case, gas exchange at the alveolar-capillary level occurs normally, and $P_{A_{O_2}}$-$P_{a_{O_2}}$ is not elevated. Hypoxemia due to decreased inspired P_{O_2} can be diagnosed from knowledge of the clinical situation. Inspired P_{O_2} is lowered either because the patient is at a high altitude, where barometric pressure is low, or, much less commonly, because the patient is breathing a gas mixture containing less than 21% O_2. The hallmark of hypoventilation as a cause of hypoxemia is an elevation in $P_{a_{CO_2}}$. This is associated with an increase in $P_{A_{CO_2}}$and a fall in $P_{A_{O_2}}$. When hypoxemia is due purely to a low inspired P_{O_2} or to alveolar hypoventilation, $P_{A_{O_2}}$-$P_{a_{O_2}}$ is normal. If $P_{A_{O_2}}$-$P_{a_{O_2}}$ and $P_{a_{CO_2}}$are both elevated, then an additional mechanism, such as / mismatching or shunting, is contributing to hypoxemia.

Shunting is a cause of hypoxemia when desaturated blood effectively bypasses oxygenation at the alveolar-capillary level. This situation occurs either because a structural problem allows desaturated blood to bypass the normal site of gas exchange or because perfused alveoli are not ventilated. Shunting is associated with an elevation in the $P_{A_{O_2}}$-$P_{a_{O_2}}$value. When shunting is an important contributing factor to hypoxemia, the lowered $P_{a_{O_2}}$ is relatively refractory to improvement by supplemental O_2.

Finally, the largest clinical category of hypoxemia is / mismatching. With / mismatching, regions with low / ratios contribute blood with a low P_{O_2} and a low O_2content. Corresponding regions with high / ratios contribute blood with a high P_{O_2}. However, because blood is already almost fully saturated at a normal P_{O_2}, elevation of the P_{O_2} to a high value does not significantly increase O_2saturation or content and therefore cannot compensate for the reduction of O_2saturation and content in blood coming from regions with a low / ratio. When / mismatch is the primary cause of hypoxemia, $P_{A_{O_2}}$-$P_{a_{O_2}}$ is elevated, and P_{CO_2}generally is normal. Supplemental O_2corrects the hypoxemia by raising the P_{O_2} in blood coming from regions with a low / ratio; this response distinguishes hypoxemia due to / mismatching from that due to true shunt.

The essential mechanism underlying all cases of hypercapnia is alveolar ventilation that is inadequate for the amount of CO_2produced. It is conceptually useful to characterize CO_2retention further, based on a more detailed examination of the potential contributing factors. These include (1) increased CO_2production; (2) decreased ventilatory drive ("won't breathe"); (3) malfunction of the respiratory pump or increased airways resistance, which makes it more difficult to sustain adequate ventilation ("can't breathe"); and (4) inefficiency of gas exchange (increased dead space or / mismatch) necessitating a compensatory increase in overall minute ventilation. In practice, more than one of these mechanisms is commonly responsible for hypercapnia, since increased minute ventilation is capable of compensating for increased CO_2production and for inefficiencies of gas exchange.

Diffusing Capacity Although abnormalities in diffusion are rarely responsible for hypoxemia, clinical measurement of diffusing capacity is frequently used to assess the functional integrity of the alveolar-capillary membrane, which includes the pulmonary capillary bed. Diseases that affect solely the airways generally do not lower DL_{CO}, whereas diseases that affect the alveolar walls or the pulmonary capillary bed will have an effect on DL_{CO}. Even though DL_{CO} is a useful marker for assessing whether disease affecting the alveolar-capillary bed is present, an abnormal DL_{CO}does not necessarily

imply that diffusion limitation is responsible for hypoxemia in a particular patient.

CLINICAL CORRELATIONS

Useful clinical correlations can be made with the mechanisms underlying hypoxemia (Fig. 250-5). A lowered inspired P_{O_2} contributes to hypoxemia if either the patient is at high altitude or if the concentration of inspired O_2 is less than 21%. The latter problem occurs if a patient receiving anesthesia or ventilatory support is inadvertently given a gas mixture to breathe containing less than 21% O_2 or if O_2 is consumed from the ambient gas, as can occur during smoke inhalation from a fire. The primary feature of hypoventilation as a cause of hypoxemia is an elevation in arterial P_{CO_2}. *For further discussion of the clinical correlations with hypoventilation, see Chap. 263.*

Shunting as a cause of hypoxemia can reflect transfer of blood from the right to the left side of the heart without passage through the pulmonary circulation, as occurs with an intracardiac shunt. This problem is most common in the setting of cyanotic congenital heart disease, when an interatrial or interventricular septal defect is associated with pulmonary hypertension so that shunting is in the right-to-left rather than the left-to-right direction. Shunting of blood through the pulmonary parenchyma is most frequently due to disease causing absence of ventilation to perfused alveoli. This can occur if the alveoli are atelectatic or if they are filled with fluid, as in pulmonary edema (both cardiogenic and noncardiogenic), or with extensive intraalveolar exudation of fluid due to pneumonia. Less commonly, vascular anomalies with arteriovenous shunting in the lung can cause hypoxemia. These anomalies can be hereditary, as found with hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber syndrome), or acquired, as in pulmonary vascular malformations secondary to hepatic cirrhosis, which are similar to the commonly recognized cutaneous vascular malformations ("spider hemangiomas").

Ventilation-perfusion mismatch is the most common cause of hypoxemia clinically. Most of the processes affecting either the airways or the pulmonary parenchyma are distributed unevenly throughout the lungs and do not necessarily affect ventilation and perfusion equally. Some areas of lung may have good perfusion and poor ventilation, whereas others may have poor perfusion and relatively good ventilation. Important examples of airways diseases in which / mismatch causes hypoxemia are asthma and chronic obstructive lung disease. Parenchymal lung diseases causing / mismatch and hypoxemia include interstitial lung disease and pneumonia.

Clinically important alterations in CO_2 elimination range from excessive ventilation and hypocapnia to inadequate CO_2 elimination and hypercapnia. *For further discussion of these clinical problems, see Chap. 263.*

Diffusing Capacity Measurement of DL_{CO} may be useful for assessing disease affecting the alveolar-capillary bed or the pulmonary vasculature. In practice, three main categories of disease are associated with lowered DL_{CO}: interstitial lung disease, emphysema, and pulmonary vascular disease. With interstitial lung disease, scarring of alveolar-capillary units diminishes the area of the alveolar-capillary bed as well as pulmonary blood volume. With emphysema, alveolar walls are destroyed, so the surface area of the alveolar-capillary bed is again diminished. In patients with disease causing a decrease in the cross-sectional area and volume of the pulmonary vascular bed, such

as recurrent pulmonary emboli or primary pulmonary hypertension, DL_{CO} is commonly diminished.

Diffusing capacity may be elevated if pulmonary blood volume is increased, as may be seen in congestive heart failure. However, once interstitial and alveolar edema ensue, the net DL_{CO}depends on the opposing influences of increased pulmonary capillary blood volume elevating DL_{CO} and pulmonary edema decreasing it. Finding an elevated DL_{CO} may be useful in the diagnosis of alveolar hemorrhage, as in Goodpasture's syndrome. Hemoglobin contained in erythrocytes in the alveolar lumen is capable of binding carbon monoxide, so the exhaled carbon monoxide concentration is diminished and the measured DL_{CO} is increased.

(Bibliography omitted in Palm version)

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251. DIAGNOSTIC PROCEDURES IN RESPIRATORY DISEASE - *Steven E. Weinberger*, *Jeffrey M. Drazen*

The diagnostic modalities available for assessing the patient with suspected or known respiratory system disease include imaging studies and techniques for acquiring biologic specimens, some of which involve direct visualization of part of the respiratory system.*Methods used to characterize the functional changes developing as a result of disease, including pulmonary function tests and measurements of gas exchange, are discussed in Chap. 250.*

IMAGING STUDIES

ROUTINE RADIOGRAPHY

Routine chest radiography, which generally includes both posteroanterior and lateral views, is an integral part of the diagnostic evaluation of diseases involving the pulmonary parenchyma, the pleura, and, to a lesser extent, the airways and the mediastinum (see Figs. 249-1 and249-2). Lateral decubitus views are often useful for determining whether pleural abnormalities represent freely flowing fluid, whereas apical lordotic views can often visualize disease at the lung apices better than the standard posteroanterior view. Portable equipment, which is often used for acutely ill patients who either cannot be transported to a radiology suite or cannot stand up for posteroanterior and lateral views, generally yields just a single radiograph taken in the anteroposterior direction.**Common radiographic patterns and their clinical correlates are reviewed in Chap. 249.*

COMPUTED TOMOGRAPHY

Computed tomography (CT) offers several advantages over routine chest radiography. First, the use of cross-sectional images often makes it possible to distinguish between densities that would be superimposed on plain radiographs. Second, CT is far better than routine radiographic studies at characterizing tissue density, distinguishing subtle differences in density between adjacent structures, and providing accurate size assessment of lesions. As a result, CT is particularly valuable in assessing hilar and mediastinal disease (which is often poorly characterized by plain radiography), in identifying and characterizing disease adjacent to the chest wall or spine (including pleural disease), and in identifying areas of fat density or calcification in pulmonary nodules (Fig. 251-1). Its utility in the assessment of mediastinal disease has made CT an important tool in the staging of lung cancer (Chap. 88), as an assessment of tumor involvement of mediastinal lymph nodes is critical to proper staging. With the additional use of contrast material, CT also makes it possible to distinguish vascular from nonvascular structures, which is particularly important in distinguishing lymph nodes and masses from vascular structures.

HelicalCTscanning allows the collection of continuous data over a larger volume of lung during a single breath-holding maneuver than is possible with conventional CT. With CT angiography, in which intravenous contrast is administered and images are acquired rapidly by helical scanning, pulmonary emboli can be detected in segmental and larger pulmonary arteries. With high-resolution CT (HRCT), the thickness of individual

cross-sectional images is approximately 1 to 2 mm, rather than the usual 10 mm, and the images are reconstructed with high-spatial-resolution algorithms. The detail that can be seen on HRCT scans allows better recognition of subtle parenchymal and airway disease, such as bronchiectasis, emphysema, and diffuse parenchymal disease (Fig. 251-2). Certain nearly pathognomonic patterns have now been recognized for many of the interstitial lung diseases, such as lymphangitic carcinoma, idiopathic pulmonary fibrosis, sarcoidosis, and eosinophilic granuloma; at present it is not yet clear in what settings these patterns will obviate the need for obtaining lung tissue.

MAGNETIC RESONANCE IMAGING

The role of magnetic resonance imaging (MRI) in the evaluation of respiratory system disease is less well defined than that ofCT. Because MRI generally provides a less detailed view of the pulmonary parenchyma as well as poorer spatial resolution, its usefulness in the evaluation of parenchymal lung disease is limited at present. However, MRI has advantages over CT in certain clinical settings. Because its images can be reconstructed in sagittal and coronal as well as transverse planes, MRI may be better for imaging abnormalities near the lung apex, the spine, and the thoracoabdominal junction. In addition, vascular structures can be distinguished from nonvascular structures without the need for contrast. Flowing blood does not produce a signal on MRI, so vessels appear as hollow tubular structures. This feature can be useful in determining whether abnormal hilar or mediastinal densities are vascular in origin and in defining aortic lesions such as aneurysms or dissection.

SCINTIGRAPHIC IMAGING

Radioactive isotopes, administered by either intravenous or inhaled routes, allow the lungs to be imaged with a gamma camera. The most common use of such imaging is ventilation-perfusion lung scanning performed for evaluation of pulmonary embolism. When injected intravenously, albumin macroaggregates labeled with technetium 99m become lodged in pulmonary capillaries; therefore, the distribution of the trapped radioisotope follows the distribution of blood flow. When inhaled, radiolabeled xenon gas can be used to demonstrate the distribution of ventilation. For example, pulmonary thromboembolism usually produces one or more regions of ventilation-perfusion mismatch -- that is, regions in which there is a defect in perfusion that follows the distribution of a vessel and that is not accompanied by a corresponding defect in ventilation (Chap. 261). Another common use of such radioisotope scans is in a patient with impaired lung function who is being considered for lung resection. The distribution of the isotope(s) can be used to assess the regional distribution of blood flow and ventilation, allowing the physician to estimate the level of postoperative lung function.

Another scintigraphic imaging technique, gallium imaging, has been of diagnostic value in patients with *Pneumocystis carinii* pneumonia and other opportunistic infections. Use of gallium imaging may provide clues to sort out the differential diagnosis of pulmonary infiltrates in immunosuppressed patients, especially patients with AIDS.

PULMONARY ANGIOGRAPHY

The pulmonary arterial system can be visualized by pulmonary angiography, in which

radiopaque contrast medium is injected through a catheter previously threaded into the pulmonary artery. When performed in cases of pulmonary embolism, pulmonary angiography demonstrates the consequences of an intravascular clot -- either a defect in the lumen of a vessel (a "filling defect") or an abrupt termination ("cutoff") of the vessel. Other, less common indications for pulmonary angiography include visualization of a suspected pulmonary arteriovenous malformation and assessment of pulmonary arterial invasion by a neoplasm.

ULTRASOUND

Because ultrasound energy is rapidly dissipated in air, ultrasound imaging is not useful for evaluation of the pulmonary parenchyma. However, it is helpful in the detection and localization of pleural abnormalities and is often used as a guide to placement of a needle for sampling of pleural liquid (i.e., for thoracentesis).

TECHNIQUES FOR OBTAINING BIOLOGIC SPECIMENS

COLLECTION OF SPUTUM

Sputum can be collected either by spontaneous expectoration or after inhalation of an irritating aerosol, such as hypertonic saline. The latter method, called *sputum induction*, is commonly used to obtain sputum for diagnostic studies, either because sputum is not spontaneously being produced or because of an expected higher yield of certain types of findings. Knowledge of the appearance and quality of the sputum specimen obtained is especially important when one is interested in Gram's staining and culture. Because sputum consists mainly of secretions from the tracheobronchial tree rather than the upper airway, the finding of alveolar macrophages and other inflammatory cells is consistent with a lower respiratory tract origin of the sample, whereas the presence of squamous epithelial cells in a "sputum" sample indicates contamination by secretions from the upper airways.

Besides processing for routine bacterial pathogens by Gram's staining and culture, sputum can be processed for a variety of other pathogens, including staining and culture for mycobacteria or fungi, culture for viruses, and staining for *P. carinii*. In the specific case of sputum obtained for evaluation of *P. carinii* pneumonia in a patient infected with HIV, for example, sputum should be collected by induction, rather than spontaneous expectoration, and an immunofluorescent stain should be used to detect the organisms. Cytologic staining of sputum for malignant cells, using the traditional Papanicolaou method, allows noninvasive evaluation for suspected lung cancer. Traditional stains and cultures are now also being supplemented in some cases by immunologic techniques and by molecular biologic methods, including the use of polymerase chain reaction amplification and DNA probes.

PERCUTANEOUS NEEDLE ASPIRATION

A needle can be inserted through the chest wall into a pulmonary lesion for the purpose of aspirating material for analysis by cytologic or microbiologic techniques. The procedure is usually carried out underCTguidance, which assists in the positioning of the needle and assures that it is localized in the lesion. Although the potential risks of

this procedure include intrapulmonary bleeding and creation of a pneumothorax with collapse of the underlying lung, the low risk of complication in experienced hands is usually worth the information obtained. However, a limitation of the technique is sampling error due to the small amount of material obtained. Thus, findings other than a specific cytologic or microbiologic diagnosis are of limited clinical value.

THORACENTESIS

Sampling of pleural liquid by thoracentesis is commonly performed for diagnostic purposes or, in the case of a large effusion, for palliation of dyspnea. Diagnostic sampling, either by blind needle aspiration or after localization by ultrasound, allows the collection of liquid for microbiologic and cytologic studies. Analysis of the fluid obtained for its cellular composition and chemical constituents, including glucose, protein, and lactate dehydrogenase, allows the effusion to be classified as either exudative or transudative (Chap. 262). In some cases, particularly in the setting of possible tuberculous involvement of the pleura (tuberculous pleuritis), closed biopsy of the parietal pleura is also performed, using a cutting needle (either an Abrams or a Cope biopsy needle) to sample tissue for histopathologic examination and culture.

BRONCHOSCOPY

Bronchoscopy is the process of direct visualization of the tracheobronchial tree. Bronchoscopy with a rigid bronchoscope is generally performed in an operating room on a patient under general anesthesia. The development of a flexible fiberoptic bronchoscope has revolutionized the diagnostic use of bronchoscopy. Although bronchoscopy is now performed almost exclusively with fiberoptic instruments, rigid bronchoscopes still have a role in selected circumstances, primarily because of their larger suction channel and the fact that the patient can be ventilated through the bronchoscope channel. These situations include the retrieval of a foreign body and the suctioning of a massive hemorrhage, for which the small suction channel of the bronchoscope may be insufficient.

Flexible Fiberoptic Bronchoscopy This is an outpatient procedure that is usually performed in an awake but sedated patient. The bronchoscope is passed through either the mouth or the nose, between the vocal cords, and into the trachea. The ability to flex the scope makes it possible to visualize virtually all airways to the level of subsegmental bronchi. The bronchoscopist is able to identify endobronchial pathology, including tumors, granulomas, bronchitis, foreign bodies, and sites of bleeding. Samples from airway lesions can be taken by several methods, including washing, brushing, and biopsy. Washing involves instillation of sterile saline through a channel of the bronchoscope and onto the surface of a lesion. A portion of the liquid is collected by suctioning through the bronchoscope, and the recovered material can be analyzed for cells (cytology) or organisms (by standard stains and cultures). Brushing or biopsy of the surface of the lesion, using a small brush or biopsy forceps at the end of a long cable inserted through a channel of the bronchoscope, allows recovery of cellular material or tissue for analysis by standard cytologic and histopathologic methods.

The bronchoscope can be used to sample material not only from the regions that can be directly visualized (i.e., the airways) but also from the more distal pulmonary

parenchyma. With the bronchoscope wedged into a subsegmental airway, aliquots of sterile saline can be instilled through the scope, allowing sampling of cells and organisms even from alveolar spaces. This procedure, called *bronchoalveolar lavage*, has been particularly useful for the recovery of organisms such as *P. carinii* in patients with HIV infection.

Brushing and biopsy of the distal lung parenchyma can also be performed with the same instruments that are used for endobronchial sampling. These instruments can be passed through the scope into small airways, where they penetrate the airway wall, allowing biopsy of peribronchial alveolar tissue. This procedure, called *transbronchial biopsy*, is used when there is either relatively diffuse disease or a localized lesion of adequate size. With the aid of fluoroscopic imaging, the bronchoscopist is able to determine not only whether and when the instrument is in the area of abnormality, but also the proximity of the instrument to the pleural surface. If the forceps are too close to the pleural surface, there is a risk of violating the visceral pleura and creating a pneumothorax; the other potential complication of transbronchial biopsy is pulmonary hemorrhage. The incidence of these complications is less than several percent.

Another procedure involves use of a hollow-bore needle passed through the bronchoscope for sampling of tissue adjacent to the trachea or a large bronchus. The needle is passed through the airway wall, and cellular material can be aspirated from mass lesions or enlarged lymph nodes, generally in a search for malignant cells. This procedure can facilitate the staging of lung cancer by identifying mediastinal lymph node involvement and in some cases obviates the need for a more invasive procedure.

The bronchoscope may provide the opportunity for treatment as well as diagnosis. For example, an aspirated foreign body may be retrieved with an instrument passed through the scope, and bleeding may be controlled with a balloon catheter similarly introduced. Newer interventional techniques performed through a bronchoscope include methods for achieving and maintaining patency of airways that are partially or completely occluded, especially by tumors. These techniques include laser therapy, cryotherapy, electrocautery, and stent placement.

VIDEO-ASSISTED THORACIC SURGERY

Recent advances in video technology have allowed the development of thoracoscopy, or video-assisted thoracic surgery (VATS), for the diagnosis and management of pleural as well as parenchymal lung disease. This procedure, done under general anesthesia, involves the passage of a rigid scope with a distal lens through a trocar inserted into the pleura. A high-quality image is shown on a monitor screen, allowing the operator to manipulate instruments passed into the pleural space through separate small intercostal incisions. With these instruments, the operator can biopsy lesions of the pleura under direct vision, which provides an obvious advantage over closed pleural biopsy. In addition, this procedure is now used commonly to biopsy peripheral lung tissue or to remove peripheral nodules, for both diagnostic and therapeutic purposes. Because this procedure is much less invasive than the traditional thoracotomy performed for lung biopsy, it has largely supplanted "open lung biopsy."

THORACOTOMY

Although frequently replaced byVATS, thoracotomy remains an option for the diagnostic sampling of lung tissue. It provides the largest amount of material, and it can be used to biopsy and/or excise lesions that are too deep or too close to vital structures for removal by VATS. The choice between VATS and thoracotomy needs to be made on a case-by-case basis, and the relative indications for each are still evolving as more experience is being gained with VATS.

MEDIASTINOSCOPY AND MEDIASTINOTOMY

Tissue biopsy is often critical for the diagnosis of mediastinal masses or enlarged mediastinal lymph nodes. AlthoughCT is useful for determining the size of mediastinal lymph nodes as part of the staging of lung cancer, confirmation that enlarged lymph nodes are actually involved with tumor generally requires biopsy and histopathologic examination. The two major procedures used to obtain specimens from masses or nodes in the mediastinum are mediastinoscopy (via a suprasternal approach) and mediastinotomy (via a parasternal approach). Both procedures are performed under general anesthesia by a qualified surgeon. In the case of suprasternal mediastinoscopy, a rigid mediastinoscope is inserted at the suprasternal notch and passed into the mediastinum along a pathway just anterior to the trachea. Tissue can be obtained with biopsy forceps passed through the scope, sampling masses or nodes that are in a paratracheal or pretracheal position. Left paratracheal and aortopulmonary lymph nodes are not accessible by this route and thus are commonly sampled by parasternal mediastinotomy (the Chamberlain procedure). This approach involves either a right or left parasternal incision and dissection directly down to a mass or node that requires biopsy.

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SECTION 2 -DISEASES OF THE RESPIRATORY SYSTEM

252. ASTHMA - *E. R. McFadden, Jr.*

DEFINITION

Asthma is defined as a chronic inflammatory disease of airways that is characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli. It is manifested physiologically by a widespread narrowing of the air passages, which may be relieved spontaneously or as a result of therapy, and clinically by paroxysms of dyspnea, cough, and wheezing. Asthma is an episodic disease, with acute exacerbations interspersed with symptom-free periods. Typically, most attacks are short-lived, lasting minutes to hours, and clinically the patient seems to recover completely after an attack. However, there can be a phase in which the patient experiences some degree of airway obstruction daily. This phase can be mild, with or without superimposed severe episodes, or much more serious, with severe obstruction persisting for days or weeks; the latter condition is known as *status asthmaticus*. In unusual circumstances, acute episodes can cause death.

PREVALENCE AND ETIOLOGY

Asthma is very common; it is estimated that 4 to 5% of the population of the United States is affected. Similar figures have been reported from other countries. Bronchial asthma occurs at all ages but predominantly in early life. About one-half of cases develop before age 10, and another third occur before age 40. In childhood, there is a 2:1 male/female preponderance, but the sex ratio equalizes by age 30.

From an etiologic standpoint, asthma is a heterogeneous disease. It is useful for epidemiologic and clinical purposes to classify asthma by the principal stimuli that incite or are associated with acute episodes. However, it is important to emphasize that this distinction may often be artificial, and the response of a given subclassification usually can be initiated by more than one type of stimulus. Furthermore, the application of molecular and cell biologic techniques to asthma pathogenesis is also beginning to blur this type of classification. With these reservations in mind, one can describe two broad types of asthma: allergic and idiosyncratic.

Atopy is the single largest risk factor for the development of asthma. *Allergic asthma* is often associated with a personal and/or family history of allergic diseases such as rhinitis, urticaria, and eczema, with positive wheal-and-flare skin reactions to intradermal injection of extracts of airborne antigens, with increased levels of IgE in the serum, and/or with a positive response to provocation tests involving the inhalation of specific antigen.

A significant fraction of patients with asthma present with no personal or family history of allergy, with negative skin tests, and with normal serum levels of IgE, and therefore have disease that cannot be classified on the basis of defined immunologic mechanisms. These patients are said to have *idiosyncratic asthma*. Many develop a typical symptom complex on contracting an upper respiratory illness. The initial insult may be little more than a common cold, but after several days the patient begins to

develop paroxysms of wheezing and dyspnea that can last for days to months. These individuals should not be confused with persons in whom the symptoms of bronchospasm are superimposed on chronic bronchitis or bronchiectasis (Chaps. 256 and258).

Many patients have disease that does not fit clearly into either of the preceding categories but instead falls into a mixed group with features of each. In general, asthma that has its onset in early life tends to have a strong allergic component, whereas asthma that develops late tends to be nonallergic or to have a mixed etiology.

PATHOGENESIS OF ASTHMA

The common denominator underlying the asthmatic diathesis is a nonspecific hyperirritability of the tracheobronchial tree. When airway reactivity is high, symptoms are more severe and persistent, and the amount of therapy required to control the patient's complaints is greater. In addition, the magnitude of diurnal fluctuations in lung function is greater, and the patient tends to awaken at night or in the early morning with breathlessness.

In both normal and asthmatic individuals, airway reactivity rises after viral infections of the respiratory tract and exposure to oxidant air pollutants such as ozone and nitrogen dioxide (but not sulfur dioxide). Viral infections have more profound consequences, and airway responsiveness may remain elevated for many weeks after a seemingly trivial upper respiratory tract infection. In contrast, airway reactivity remains high for only a few days after exposure to ozone. Allergens can cause airway responsiveness to rise within minutes and to remain elevated for weeks. If the dose of antigen is high enough, acute episodes of obstruction may occur daily for a prolonged period after a single exposure.

The most popular hypothesis at present for the pathogenesis of asthma is that it derives from a state of persistent subacute inflammation of the airways. An active inflammatory process is frequently observed in endobronchial biopsy specimens even from asymptomatic patients. The airways can be edematous and infiltrated with eosinophils, neutrophils, and lymphocytes, with or without an increase in the collagen content of the epithelial basement membrane. There may also be glandular hypertrophy. The most ubiquitous finding is a generalized increase in cellularity associated with an elevated capillary density. Occasionally, denudation of the epithelium may also be observed.

Although the translation of these histologic observations into a disease process is still incomplete, it is widely believed that the physiologic and clinical features of asthma derive from an interaction among the resident and infiltrating inflammatory cells in the airway surface epithelium, inflammatory mediators, and cytokines. The cells thought to play important parts in the inflammatory response are mast cells, eosinophils, lymphocytes, and epithelial cells. The roles of neutrophils and macrophages are less well defined. Each of these cell types can contribute mediators and cytokines to initiate and amplify both acute inflammation and the long-term pathologic changes described above. The mediators released -- histamine; bradykinin; the leukotrienes C, D, and E; platelet-activating factor; and prostaglandins (PGs) E_2, F_2a, and D_2 -- produce an intense, immediate inflammatory reaction involving bronchoconstriction, vascular congestion, and edema formation. In addition to their ability to evoke prolonged

contraction of airway smooth muscle and mucosal edema, the leukotrienes may also account for some of the other pathophysiologic features of asthma, such as increased mucus production and impaired mucociliary transport. This intense local event can then be followed by a more chronic one. The chemotactic factors elaborated (eosinophil and neutrophil chemotactic factors of anaphylaxis and leukotriene B_4) bring eosinophils, platelets, and polymorphonuclear leukocytes to the site of the reaction. These infiltrating cells as well as resident macrophages and the airway epithelium itself potentially are an additional source of mediators to enhance both the immediate and the cellular phase. The airway epithelium is both the target of, and a contributor to, the inflammatory cascade. These cells amplify bronchoconstriction by elaborating endothelin-1 and promoting vasodilatation through the release of nitric oxide,PG$E_2$and the 15-hydroxyeicosatetraenoic acid (15-HETE) products of arachidonic acid metabolism. They also generate cytokines such as granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin (IL)8, Rantes, and eotaxin.

Like the mast cell in the early reaction, the eosinophil appears to play an important part in the infiltrative component. The granular proteins in this cell (major basic protein and eosinophilic cationic protein) and oxygen-derived free radical are capable of destroying the airway epithelium, which then is sloughed into the bronchial lumen in the form of Creola bodies. Besides resulting in a loss of barrier and secretory function, such damage elicits the production of chemotactic cytokines, leading to further inflammation. In theory, it also can expose sensory nerve endings, thus initiating neurogenic inflammatory pathways. That, in turn, could convert a primary local event into a generalized reaction via a reflex mechanism.

T lymphocytes also appear to be important in the inflammatory response. These cells are present in increased numbers in asthmatic airways and produce cytokines that activate cell-mediated immunity, as well as humoral (IgE) immune responses. Activated T cells recovered from the lungs of persons with asthma express messenger RNA for the cytokines known to play a part in the recruitment and activation of mast cells and eosinophils. Furthermore, the T_H1 and T_H2 lymphocyte subtypes have functions that may influence the asthmatic response. The T_H1 cytokinesIL-2 and interferon (IFN) g can promote the growth and differentiation of B cells and the activation of macrophages, respectively. The T_H2 cytokines IL-4 and IL-5 stimulate B-cell growth and immunoglobulin secretion, and IL-5 promotes eosinophil proliferation, differentiation, and activation. It can also facilitate granule release from basophils.

Cytokine production is another central component of the inflammation of asthma. Cytokines are synthesized and released from many of the inflammatory cells mentioned above, as well as from epithelial cells, fibroblasts, endothelial cells, and airway smooth muscle. Cytokines activate specific cell-surface receptors that are coupled to signal transduction pathways, which often result in alterations of gene regulation and enzyme production. The cytokines that are particularly relevant to asthma are secreted by T lymphocytes and includeIL-3 enhanced (mast cell survival), IL-4 and IL-13 (switching of B lymphocytes to IgE production and expression of adhesion molecules), and IL-5 (differentiation and enhanced survival of eosinophils). Other cytokines, such as IL-1B, IL-6, IL-11, tumor necrosis factor a(TNF-a) andGM-CSF, are proinflammatory and may amplify the inflammatory response.

The relative roles of each of the above elements in the production of heightened airway reactivity and clinical asthma have yet to be determined. Although inflammation is clearly important, recent evidence indicates that the intensity of the cellular infiltrate in the airways is not related either to the severity of the disease state or to the level of airway reactivity. Furthermore, it is unlikely that any one cell type or mediator accounts for every feature. For example, mast cell-derived mediators cannot explain the whole picture, for they have been found in the blood of individuals with mast cell-related diseases such as cold-induced and cholinergic-induced urticaria and in the airways of atopic individuals without asthma. Since these individuals had no lower respiratory illness or complaints, these alleged mediators of asthma would appear to need a unique background from which to exhibit their effects. Similarly, the inflammatory cells believed to be relevant to asthma are also found in the airways of atopic individuals without asthma, raising the possibility that they are merely nonspecific markers of atopy rather than specific indexes of asthma. Finally, the therapeutic administration ofIL-2 andGM-CSFto patients with cancer results in eosinophilia with cell activation but not in asthma.

GENETIC CONSIDERATIONS

Although there is little doubt that asthma has a strong familial component, the identification of the genetic mechanisms underlying the illness has proven difficult for multiple reasons, including such fundamental issues as a lack of uniform agreement on the definition of the disease, the inability to define a single phenotype, non-Mendelian modes of inheritance, and an incomplete understanding of how environmental factors modify genetic expression. Screening families for candidate genes has identified multiple chromosomal regions that relate to atopy, elevated IgE levels, and airway hyperresponsiveness. Evidence for genetic linkage of high total serum IgE levels and atopy has been observed on chromosomes 5q, 11q, and 12q in a number of populations scattered throughout the world. Regions of the genome demonstrating evidence for linkage to bronchial hyperreactivity also typically show evidence for linkage to elevated total serum IgE levels. Excellent candidate genes exist for specific abnormalities in asthma within the regions that were identified in the linkage studies. For example, chromosome 5q contains cytokine clusters includingIL-4, IL-5, IL-9, and IL-13. Other regions on chromosome 5q also contain the beta-adrenergic receptors and the glucocorticoid receptors. Chromosome 6p contains regions that are important in antigen presentation and mediation of the inflammatory response. Chromosome 12q contains two genes that could influence atopy and airway hyperresponsiveness, including nitric oxide synthase.

The stimuli that interact with airway responsiveness and incite acute episodes of asthma can be grouped into seven major categories: allergenic, pharmacologic, environmental, occupational, infectious, exercise-related, and emotional.

Allergens Allergic asthma is dependent on an IgE response controlled by T and B lymphocytes and activated by the interaction of antigen with mast cell-bound IgE molecules. The airway epithelium and submucosa contain dendritic cells that capture and process antigen. After taking up an immunogen, these cells migrate to the local lymph nodes where they present the material to T cell receptors. In the appropriate genetic setting, the interaction of antigen with a naive T cell T_H0 in the presence of IL-4

leads to the differentiation of the cell to a T_H2 subset. This process not only helps facilitate the inflammation of asthma but also causes B lymphocytes to switch their antibody production from IgG and IgM to IgE. Most of the allergens that provoke asthma are airborne, and to induce a state of sensitivity they must be reasonably abundant for considerable periods of time. Once sensitization has occurred, however, the patient can exhibit exquisite responsivity, so that minute amounts of the offending agent can produce significant exacerbations of the disease. Immune mechanisms appear to be causally related to the development of asthma in 25 to 35% of all cases and to be contributory in perhaps another third. Higher prevalences have been suggested, but it is difficult to know how to interpret the data because of confounding factors. Allergic asthma is frequently seasonal, and it is most often observed in children and young adults. A nonseasonal form may result from allergy to feathers, animal danders, dust mites, molds, and other antigens that are present continuously in the environment. Exposure to antigen typically produces an immediate response in which airway obstruction develops in minutes and then resolves. In 30 to 50% of patients, a second wave of bronchoconstriction, the so-called late reaction, develops 6 to 10 h later. In a minority, only a late reaction occurs. It was formerly thought that the late reaction was essential to the development of the increase in airway reactivity that follows antigen exposure. Recent data show that not to be the case.

The mechanism by which an inhaled allergen provokes an acute episode of asthma depends in part on antigen-antibody interactions on the surface of pulmonary mast cells, with the subsequent generation and release of the mediators of immediate hypersensitivity. Current hypotheses hold that very small antigenic particles penetrate the lung's defenses and come in contact with mast cells that interdigitate with the epithelium at the luminal surface of the central airways. The subsequent elaboration of mediators and cytokines then produces the sequence outlined above.

Pharmacologic Stimuli The drugs most commonly associated with the induction of acute episodes of asthma are aspirin, coloring agents such as tartrazine,b-adrenergic antagonists, and sulfiting agents. It is important to recognize drug-induced bronchial narrowing because its presence is often associated with great morbidity. Furthermore, death sometimes has followed the ingestion of aspirin (or other nonsteroidal anti-inflammatory agents) orb-adrenergic antagonists. The typical aspirin-sensitive respiratory syndrome primarily affects adults, although the condition may occur in childhood. This problem usually begins with perennial vasomotor rhinitis that is followed by a hyperplastic rhinosinusitis with nasal polyps. Progressive asthma then appears. On exposure to even very small quantities of aspirin, affected individuals typically develop ocular and nasal congestion and acute, often severe episodes of airways obstruction. The prevalence of aspirin sensitivity in patients with asthma varies from study to study, but many authorities feel that 10% is a reasonable figure. There is a great deal of cross reactivity between aspirin and other nonsteroidal anti-inflammatory compounds that inhibit prostaglandin G/H synthase 1 (cyclooxygenase type 1). Indomethacin, fenoprofen, naproxen, zomepirac sodium, ibuprofen, mefenamic acid, and phenylbutazone are particularly important in this regard. However, acetaminophen, sodium salicylate, choline salicylate, salicylamide, and propoxyphene are well tolerated. The exact frequency of cross reactivity to tartrazine and other dyes in aspirin-sensitive individuals with asthma is also controversial; again, 10% is the commonly accepted figure. This peculiar complication of aspirin-sensitive asthma is particularly insidious,

however, in that tartrazine and other potentially troublesome dyes are widely present in the environment and may be unknowingly ingested by sensitive patients.

Patients with aspirin sensitivity can be desensitized by daily administration of the drug. After this form of therapy, cross tolerance also develops to other nonsteroidal anti-inflammatory agents. The mechanism by which aspirin and other such drugs produce bronchospasm appears to be a chronic overexcretion of cysteinyl leukotrienes, which activate mast cells. The adverse reaction to aspirin can be inhibited with the use of leukotriene synthesis blockers or receptor antagonists.

Beta-adrenergic antagonists regularly obstruct the airways in individuals with asthma as well as in others with heightened airway reactivity and should be avoided by such individuals. Even the selective $beta_1$agents have this propensity, particularly at higher doses. In fact, the local use of $beta_1$blockers in the eye for the treatment of glaucoma has been associated with worsening asthma.

Sulfiting agents, such as potassium metabisulfite, potassium and sodium bisulfite, sodium sulfite, and sulfur dioxide, which are widely used in the food and pharmaceutical industries as sanitizing and preserving agents, also can produce acute airway obstruction in sensitive individuals. Exposure usually follows ingestion of food or beverages containing these compounds, e.g., salads, fresh fruit, potatoes, shellfish, and wine. Exacerbation of asthma has been reported after the use of sulfite-containing topical ophthalmic solutions, intravenous glucocorticoids, and some inhalational bronchodilator solutions. The incidence and mechanism of action of this phenomenon are unknown. When suspected, the diagnosis can be confirmed by either oral or inhalational provocations.

Environment and Air Pollution (See also Chap. 254) Environmental causes of asthma are usually related to climatic conditions that promote the concentration of atmospheric pollutants and antigens. These conditions tend to develop in heavily industrial or densely populated urban areas and are frequently associated with thermal inversions or other situations creating stagnant air masses. In these circumstances, although the general population can develop respiratory symptoms, patients with asthma and other respiratory diseases tend to be more severely affected. The air pollutants known to have this effect are ozone, nitrogen dioxide, and sulfur dioxide. Sulfur dioxide needs to be present in high concentrations and produces its greatest effects during periods of high ventilation. In some regions of North America, seasonal concentrations of airborne antigens such as pollen can rise high enough to result in epidemics of asthma admissions to hospitals and an increase in the death rate. These events may be ameliorated by treating patients prophylactically with anti-inflammatory drugs before the allergy season begins.

Occupational Factors (See alsoChap. 254) Occupation-related asthma is a significant health problem, and acute and chronic airway obstruction has been reported to follow exposure to a large number of compounds used in many types of industrial processes. Bronchoconstriction can result from working with or being exposed to *metal salts* (e.g., platinum, chrome, and nickel), *wood and vegetable dusts* (e.g., those of oak, western red cedar, grain, flour, castor bean, green coffee bean, mako, gum acacia, karay gum, and tragacanth), *pharmaceutical agents* (e.g., antibiotics, piperazine, and cimetidine),

industrial chemicals and plastics (e.g., toluene diisocyanate, phthalic acid anhydride, trimellitic anhydride, persulfates, ethylenediamine, *p*-phenylenediamine, and various dyes), *biologic enzymes* (e.g., laundry detergents and pancreatic enzymes), and *animal and insect dusts, serums, and secretions*. It is important to recognize that exposure to sensitizing chemicals, particularly those used in paints, solvents, and plastics, also can occur during leisure or non-work-related activities.

There seem to be three underlying mechanisms for this airway obstruction: (1) In some cases, the offending agent results in the formation of a specific IgE, and the cause seems immunologic (the immunologic reaction can be immediate, late, or dual); (2) in other cases, the substance causes a direct liberation of bronchoconstrictor substances; and (3) in other instances, the substance causes direct or reflex stimulation of the airways of individuals with either latent or frank asthma. If the occupational agent causes an immediate or dual immunologic reaction, the history is similar to that which occurs with exposure to other antigens. Often, however, patients will give a characteristic cyclic history. They are well when they arrive at work, and symptoms develop toward the end of the shift, progress after the work site is left, and then regress. Absence from work during weekends or vacations brings about remission. Frequently, there are similar symptoms in fellow employees.

Infections Respiratory infections are the most common of the stimuli that evoke acute exacerbations of asthma. Well-controlled investigations have demonstrated that respiratory viruses and not bacteria or allergy to microorganisms are the major etiologic factors. In young children, the most important infectious agents are respiratory syncytial virus and parainfluenza virus. In older children and adults, rhinovirus and influenza virus predominate as pathogens. Simple colonization of the tracheobronchial tree is insufficient to evoke acute episodes of bronchospasm, and attacks of asthma occur only when symptoms of an ongoing respiratory tract infection are, or have been, present. Viral infections can actively and chronically destabilize asthma, and they are perhaps the only stimuli that can produce constant symptoms for weeks. The mechanism by which viruses induce exacerbations of asthma may be related to the production of T cell-derived cytokines that potentiate the infiltration of inflammatory cells into already susceptible airways.

Exercise Exercise is a very common precipitant of acute episodes of asthma. This stimulus differs from other naturally occurring provocations, such as antigens, viral infections, and air pollutants, in that it does not evoke any long-term sequelae, nor does it increase airway reactivity. Exercise can be made to provoke bronchospasm in every patient with asthma, and in some it is the only trigger that produces symptoms. When such patients are followed for sufficient periods, however, they often develop recurring episodes of airway obstruction independent of exercise; thus, the onset of this problem frequently is the first manifestation of the full-blown asthmatic syndrome. The critical variables that determine the severity of the postexertional airway obstruction are the levels of ventilation achieved and the temperature and humidity of the inspired air. The higher the ventilation and the lower the heat content of the air, the greater the response. For the same inspired air conditions, running produces a more severe attack of asthma than walking. Conversely, for a given task, the inhalation of cold air markedly enhances the response, while warm, humid air blunts or abolishes it. Consequently, activities such as ice hockey, cross-country skiing, and ice skating are more provocative than is

swimming in an indoor, heated pool. The mechanism by which exercise produces obstruction may be related to a thermally produced hyperemia and engorgement of the microvasculature of the bronchial wall and does not appear to involve smooth-muscle contraction.

Emotional Stress Abundant objective data demonstrate that psychological factors can interact with the asthmatic diathesis to worsen or ameliorate the disease process. The pathways and nature of the interactions are complex but are operational to some extent in almost half the patients studied. Changes in airway caliber seem to be mediated through modification of vagal efferent activity, but endorphins also may play a role. The most frequently studied variable has been that of suggestion, and the weight of current evidence indicates that it can be quite important in selected individuals with asthma. When psychically responsive individuals are given the appropriate suggestion, they can actually decrease or increase the pharmacologic effects of adrenergic and cholinergic stimuli on their airways. The extent to which psychological factors participate in the induction and/or continuation of any given acute exacerbation is not established but probably varies from patient to patient and in the same patient from episode to episode.

PATHOLOGY

In a patient who has died of acute asthma, the most striking feature of the lungs at necropsy is their gross overdistention and failure to collapse when the pleural cavities are opened. When the lungs are cut, numerous gelatinous plugs of exudate are found in most of the bronchial branches down to the terminal bronchioles. Histologic examination shows hypertrophy of the bronchial smooth muscle, hyperplasia of mucosal and submucosal vessels, mucosal edema, denudation of the surface epithelium, pronounced thickening of the basement membrane, and eosinophilic infiltrates in the bronchial wall. There is an absence of any of the well-recognized forms of destructive emphysema.

PATHOPHYSIOLOGY

The pathophysiologic hallmark of asthma is a reduction in airway diameter brought about by contraction of smooth muscle, vascular congestion, edema of the bronchial wall, and thick, tenacious secretions. The net result is an increase in airway resistance, a decrease in forced expiratory volumes and flow rates, hyperinflation of the lungs and thorax, increased work of breathing, alterations in respiratory muscle function, changes in elastic recoil, abnormal distribution of both ventilation and pulmonary blood flow with mismatched ratios, and altered arterial blood gas concentrations. Thus, although asthma is considered to be primarily a disease of airways, virtually all aspects of pulmonary function are compromised during an acute attack. In addition, in very symptomatic patients there frequently is electrocardiographic evidence of right ventricular hypertrophy and pulmonary hypertension. When a patient presents for therapy, his or her forced vital capacity tends to be £50% of normal. The 1-s forced expiratory volume (FEV_1) averages 30% or less of predicted, while the maximum and minimum midexpiratory flow rates are reduced to 20% or less of expected. In keeping with the alterations in mechanics, the associated air trapping is substantial. In acutely ill patients, residual volume (RV) frequently approaches 400% of normal, while functional residual capacity doubles. The patient tends to report that the attack has ended clinically

when the RV has fallen to 200% of its predicted value and the FEV_1 reaches 50% of the predicted level.

Hypoxia is a universal finding during acute exacerbations, but frank ventilatory failure is relatively uncommon, being observed in 10 to 15% of patients presenting for therapy. Most individuals with asthma have hypocapnia and a respiratory alkalosis. In acutely ill patients, the finding of a normal arterial carbon dioxide tension tends to be associated with quite severe levels of obstruction. Consequently, when found in a symptomatic individual, it should be viewed as representing impending respiratory failure, and the patient should be treated accordingly. Equally, the presence of metabolic acidosis in the setting of acute asthma signifies severe obstruction. Usually, there are no clinical counterparts to the derangements in blood gases. Cyanosis is a very late sign. Hence, a dangerous level of hypoxia can go undetected. Likewise, signs attributable to carbon dioxide retention, such as sweating, tachycardia, and wide pulse pressure, or to acidosis, such as tachypnea, tend not to be of great value in predicting the presence of hypercapnia or hydrogen ion excess in individual patients, because they are too frequently seen in anxious patients with more moderate disease. Trying to judge the state of an acutely ill patient's ventilatory status on clinical grounds alone can be extremely hazardous, and clinical indicators should not be relied on with any confidence. Therefore, in patients with suspected alveolar hypoventilation, arterial blood gas tensions must be measured.

CLINICAL FEATURES

The symptoms of asthma consist of a triad of dyspnea, cough, and wheezing, the last often being regarded as the *sine qua non*. In its most typical form, asthma is an episodic disease, and all three symptoms coexist. At the onset of an attack, patients experience a sense of constriction in the chest, often with a nonproductive cough. Respiration becomes audibly harsh, wheezing in both phases of respiration becomes prominent, expiration becomes prolonged, and patients frequently have tachypnea, tachycardia, and mild systolic hypertension. The lungs rapidly become overinflated, and the anteroposterior diameter of the thorax increases. If the attack is severe or prolonged, there may be a loss of adventitial breath sounds, and wheezing becomes very high pitched. Furthermore, the accessory muscles become visibly active, and a paradoxical pulse often develops. These two signs are extremely valuable in indicating the severity of the obstruction. In the presence of either, pulmonary function tends to be significantly more impaired than in their absence. It is important to note that the development of a paradoxical pulse depends on the generation of large negative intrathoracic pressures. Thus, if the patient's breathing is shallow, this sign and/or the use of accessory muscles could be absent even though obstruction is quite severe. The other signs and symptoms of asthma only imperfectly reflect the physiologic alterations that are present. Indeed, if the disappearance of subjective complaints or even of wheezing is used as the end point at which therapy for an acute attack is terminated, an enormous reservoir of residual disease will be missed.

The end of an episode is frequently marked by a cough that produces thick, stringy mucus, which often takes the form of casts of the distal airways (Curschmann's spirals) and, when examined microscopically, often shows eosinophils and Charcot-Leyden crystals. In extreme situations, wheezing may lessen markedly or even disappear,

cough may become extremely ineffective, and the patient may begin a gasping type of respiratory pattern. These findings imply extensive mucus plugging and impending suffocation. Ventilatory assistance by mechanical means may be required. Atelectasis due to inspissated secretions occasionally occurs with asthmatic attacks. Spontaneous pneumothorax and/or pneumomediastinum occur but are rare.

Less typically, a patient with asthma may complain of intermittent episodes of nonproductive cough or exertional dyspnea. Unlike other individuals with asthma, when these patients are examined during symptomatic periods, they tend to have normal breath sounds but may wheeze after repeated forced exhalations and/or may show ventilatory impairments when tested in the laboratory. In the absence of both these signs, a bronchoprovocation test may be required to make the diagnosis.

DIFFERENTIAL DIAGNOSIS

The differentiation of asthma from other diseases associated with dyspnea and wheezing is usually not difficult, particularly if the patient is seen during an acute episode. The physical findings and symptoms listed above and the history of periodic attacks are quite characteristic. A personal or family history of allergic diseases such as eczema, rhinitis, or urticaria is valuable contributory evidence. An extremely common feature of asthma is nocturnal awakening with dyspnea and/or wheezing. In fact, this phenomenon is so prevalent that its absence raises doubt about the diagnosis. *Upper airway obstruction by tumor* or *laryngeal edema* can occasionally be confused with asthma. Typically, a patient with such a condition will present with stridor, and the harsh respiratory sounds can be localized to the area of the trachea. Diffuse wheezing throughout both lung fields is usually absent. However, differentiation can sometimes be difficult, and indirect laryngoscopy or bronchoscopy may be required. Asthma-like symptoms have been described in patients with glottic dysfunction. These individuals narrow their glottis during inspiration and expiration, producing episodic attacks of severe airway obstruction. Occasionally, carbon dioxide retention develops. However, unlike asthma, the arterial oxygen tension is well preserved, and the alveolar-arterial gradient for oxygen narrows during the episode, instead of widening as with lower airway obstruction. To establish the diagnosis of glottic dysfunction, the glottis should be examined when the patient is symptomatic. Normal findings at such a time exclude the diagnosis; normal findings during asymptomatic periods do not.

Persistent wheezing localized to one area of the chest in association with paroxysms of coughing indicates *endobronchial disease* such as foreign-body aspiration, a neoplasm, or bronchial stenosis.

The signs and symptoms of *acute left ventricular failure* occasionally mimic asthma, but the findings of moist basilar rales, gallop rhythms, blood-tinged sputum, and other signs of heart failure (Chap. 232) allow the appropriate diagnosis to be reached.

Recurrent episodes of bronchospasm can occur with *carcinoid tumors* (Chap. 93), *recurrent pulmonary emboli* (Chap. 261), and *chronic bronchitis* (Chap. 258). In chronic bronchitis there are no true symptom-free periods, and one can usually obtain a history of chronic cough and sputum production as a background on which acute attacks of wheezing are superimposed. Recurrent emboli can be very difficult to separate from

asthma. Frequently, patients with this condition present with episodes of breathlessness, particularly on exertion, and they sometimes wheeze. Pulmonary function studies may show evidence of peripheral airway obstruction (Chap. 250); when these changes are present, lung scans also may be abnormal. The therapeutic response to bronchodilators and to the institution of anticoagulant therapy may be helpful, but pulmonary angiography may be necessary to establish the correct diagnosis.

Eosinophilic pneumonias (Chap. 253) are often associated with asthmatic symptoms, as are various chemical pneumonias and exposures to insecticides and cholinergic drugs. Bronchospasm occasionally is a manifestation of *systemic vasculitis* with pulmonary involvement.

DIAGNOSIS

The diagnosis of asthma is established by demonstrating reversible airway obstruction. *Reversibility* is traditionally defined as a 15% or greater increase in FEV_1after two puffs of a b-adrenergic agonist. When the spirometry results are normal at presentation, the diagnosis can be made by showing heightened airway responsiveness to challenges with histamine, methacholine, or isocapnic hyperventilation of cold air. Once the diagnosis is confirmed, the course of the illness and the effectiveness of therapy can be followed by measuring peak expiratory flow rates (PEFRs) at home and/or the FEV_1 in the laboratory. Positive wheal-and-flare reactions to skin tests can be demonstrated to various allergens, but such findings do not necessarily correlate with the intrapulmonary events. Sputum and blood eosinophilia and measurement of serum IgE levels are also helpful but are not specific for asthma. Chest roentgenograms showing hyperinflation are also nondiagnostic.

TREATMENT

Elimination of the causative agent(s) from the environment of an allergic individual with asthma is the most successful means available for treating this condition (for details on avoidance, see Chap. 310). Desensitization or immunotherapy with extracts of the suspected allergens has enjoyed widespread favor, but controlled studies are limited and have not proved it to be highly effective.

Drug Treatment The available agents for treating asthma can be divided into two general categories: drugs that inhibit smooth muscle contraction, i.e., the so-called "quick relief medications" (beta-adrenergic agonists, methylxanthines, and anticholinergics) and agents that prevent and/or reverse inflammation, i.e., the "long-term control medications" (glucocorticoids, leukotriene inhibitors and receptor antagonists, and mast cell-stabilizing agents).

Adrenergic Stimulants The drugs in this category consist of the catecholamines, resorcinols, and saligenins. These agents are analogues and produce airway dilation through stimulation of beta-adrenergic receptors and activation of G proteins with the resultant formation of cyclic adenosine monophosphate (AMP). They also decrease release of mediators and improve mucociliary transport. The catecholamines available for clinical use are epinephrine, isoproterenol, and isoetharine. As a group, these

compounds are short-acting (30 to 90 min) and are effective only when administered by inhalational or parenteral routes. Epinephrine and isoproterenol are notb_2-selective and have considerable chronotropic and inotropic cardiac effects. Epinephrine also has substantial alpha-stimulating effects. The usual dose is 0.3 to 0.5 mL of a 1:1000 solution administered subcutaneously. Isoproterenol is devoid of alpha activity and is the most potent agent of this group. It is usually administered in a 1:200 solution by inhalation. Isoetharine is the mostb_2-selective compound of this class, but it is a relatively weak bronchodilator. It is employed as an aerosol and supplied as a 1% solution. The use of these agents in treating asthma has been superceded by longer acting selective$b_2$agonists.

The commonly used resorcinols are metaproterenol, terbutaline, and fenoterol, and the most widely known saligenin is albuterol (salbutamol). With the exception of metaproterenol, these drugs are highly selective for the respiratory tract and virtually devoid of significant cardiac effects except at high doses. Their major side effect is tremor. They are active by all routes of administration, and because their chemical structures allow them to bypass the metabolic processes used to degrade the catecholamines, their effects are relatively long-lasting (4 to 6 h). Differences in potency and duration among agents can be eliminated by adjusting doses and/or administration schedules.

Inhalation is the preferred route of administration because it allows maximal bronchodilation with fewer side effects. In the past it was fashionable to treat episodes of severe asthma with intravenous sympathomimetics such as isoproterenol. This approach no longer appears justifiable. Isoproterenol infusions clearly can induce myocardial damage, and even for theb_2-selective agents such as terbutaline and albuterol, intravenous administration offers no advantages over the inhaled route.

Salmeterol is a very long-lasting (9 to 12 h) congener of albuterol. When given every 12 h, it is effective in providing sustained symptomatic relief. It is particularly helpful for conditions such as nocturnal and exercise-induced asthma. It is not recommended for the treatment of acute episodes because of its relatively slow onset of action (approximately 30 min), nor is it intended as a rescue drug for breakthrough symptoms. In addition, its long half-life means that administration of extra doses can cause cumulative side effects.

Methylxanthines Theophylline and its various salts are medium-potency bronchodilators that work by increasing cyclicAMP by the inhibition of phosphodiesterase. The therapeutic plasma concentrations of theophylline traditionally have been thought to lie between 10 and 20 ug/mL. Some sources, however, recommend a lower target range between 5 and 15 ug/mL to avoid toxicity. The dose required to achieve the desired level varies widely from patient to patient owing to differences in the metabolism of the drug. Theophylline clearance, and thus the dosage requirement, is decreased substantially in neonates and the elderly and those with acute and chronic hepatic dysfunction, cardiac decompensation, and cor pulmonale. Clearance is also decreased during febrile illnesses. Clearance is increased in children. In addition, a number of important drug interactions can alter theophylline metabolism. Clearance falls with the concurrent use of erythromycin and other macrolide antibiotics, the quinolone antibiotics, and troleandomycin, allopurinol, cimetidine, and propranolol. It

rises with use of cigarettes, marijuana, phenobarbital, phenytoin, or any other drug that is capable of inducing hepatic microsomal enzymes.

For maintenance therapy, long-acting theophylline compounds are available and are usually given once or twice daily. The dose is adjusted on the basis of the clinical response with the aid of serum theophylline measurements. Single-dose administration in the evening reduces nocturnal symptoms and helps keep the patient complaint-free during the day. Aminophylline and theophylline are available for intravenous use. The recommendations for intravenous therapy in children aged 9 to 16 and in young adult smokers not currently receiving theophylline products are a loading dose of 6 mg/kg followed by an infusion of 1 mg/kg per hour for the next 12 h and then 0.8 mg/kg per hour thereafter. In nonsmoking adults, older patients, and those with cor pulmonale, congestive heart failure, and liver disease, the loading dose remains the same, but the maintenance dose is reduced to between 0.1 and 0.5 mg/kg per hour. In patients already receiving theophylline, the loading dose is frequently withheld or, in extreme situations, reduced to 0.5 mg/kg.

The most common side effects of theophylline are nervousness, nausea, vomiting, anorexia, and headache. At plasma levels greater than 30 ug/mL there is a risk of seizures and cardiac arrhythmias.

Anticholinergics Anticholinergic drugs such as atropine sulfate produce bronchodilation in patients with asthma, but their use is limited by systemic side effects. Nonabsorbable quaternary ammonium congeners (atropine methylnitrate and ipratropium bromide) have been found to be both effective and free of untoward effects. They may be of particular benefit for patients with coexistent heart disease, in whom the use of methylxanthines andb-adrenergic stimulants may be dangerous. The major disadvantages of the anticholinergics are that they are slow to act (60 to 90 min may be required before peak bronchodilation is achieved) and they are only of modest potency.

Glucocorticoids Glucocorticoids are the most potent and most effective anti-inflammatory medications available. Systemic or oral steroids are most beneficial in acute illness when severe airway obstruction is not resolving or is worsening despite intense optimal bronchodilator therapy, and in chronic disease when there has been failure of a previously optimal regimen with frequent recurrences of symptoms of increasing severity. Inhaled glucocorticoids are used in the long-term control of asthma.

Glucocorticoids are not bronchodilators and the correct dose to use in acute situations is a matter of debate. The available data indicate that very high doses do not offer any advantage over more conventional amounts. In the United States, a usual starting dose is 40 to 60 mg of methylprednisolone intravenously every 6 h. Since intravenous and oral administration produce the same effects, prednisone, 60 mg every 6 h, can be substituted. Clinical impressions suggest that smaller quantities may work as effectively, but there are no confirmatory data. In the United Kingdom and elsewhere, acute asthma both in and out of hospital is frequently treated with doses of prednisolone ranging from 30 to 40 mg given once daily. It should be emphasized that the effects of steroids in acute asthma are not immediate and may not be seen for 6 h or more after the initial administration. Consequently, it is mandatory to continue vigorous bronchodilator therapy during this interval. Irrespective of the regimen chosen, it is important to

appreciate that rapid tapering of glucocorticoids frequently results in recurrent obstruction. Most authorities recommend reducing the dose by one-half every third to fifth day after an acute episode. In situations in which it appears that continued steroid therapy will be needed, an alternate-day schedule should be instituted to minimize side effects. This is particularly important in children, since continuous glucocorticoid administration interrupts growth. Long-acting preparations such as dexamethasone should not be used in this approach, for they defeat the purpose of alternate-day schedules by causing prolonged suppression of the pituitary-adrenal axis. The availability of inhaled agents has all but eliminated the need for this form of therapy.

INHALED GLUCOCORTICOIDS These drugs are indicated in patients with persistent symptoms. The agents currently available in the United States are beclomethasone, budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide. Each has relative advantages and disadvantages, and they are not absolutely interchangeable on either a microgram or a per puff basis. However, all of these drugs share the ability to control inflammation, facilitate the long-term prevention of symptoms, and reduce the need for oral glucocorticoids.

There is no fixed dose of inhaled steroid that works for all patients. Requirements are dictated by the response of the individual and wax and wane in concert with progression of the disease. Generally, the worse the patient's condition, the more inhaled steroid is needed to gain control. Once achieved, however, remission can often be maintained with quantities as low as one or two puffs/day. Inhaled steroids can take up to a week or more to produce improvements; consequently, in rapidly deteriorating situations, it is best to prescribe oral preparations and initiate inhaled drugs as the dose of the former is reduced. In less emergent circumstances, the quantity of inhaled drug can be increased up to 2 to 2.5 times the recommended starting doses. It is critical to remember that the side effects increase in proportion to the dose-time product. In addition to thrush and dysphonia, the increased systemic absorption that accompanies larger doses of inhaled steroids has been reported to produce adrenal suppression, cataract formation, decreased growth in children, interference with bone metabolism, and purpura. As is the case with oral agents, suppression of inflammation, per se, cannot be relied upon to provide optimal results. It is essential to continue adrenergic or methylxanthine bronchodilators if the patient's disease is unstable.

Mast Cell-Stabilizing Agents Cromolyn sodium and nedocromil sodium do not influence airway tone. Their major therapeutic effect is to inhibit the degranulation of mast cells, thereby preventing the release of the chemical mediators of anaphylaxis.

Cromolyn sodium and nedocromil, like the inhaled steroids, improve lung function, reduce symptoms, and lower airway reactivity in persons with asthma. They are most effective in atopic patients who have either seasonal disease or perennial airway stimulation. A therapeutic trial of two puffs four times daily for 4 to 6 weeks frequently is necessary before the beneficial effects of the drug appear. Unlike steroids, nedocromil and cromolyn sodium, when given prophylactically, block the acute obstructive effects of exposure to antigen, industrial chemicals, exercise, or cold air. With antigen, the late response is also abolished. Therefore, a patient who has intermittent exposure to either antigenic or nonantigenic stimuli that provoke acute episodes of asthma need not use these drugs continuously but instead can obtain protection by taking the drug only 15 to

20 min before contact with the precipitant.

Leukotriene Modifiers As mentioned earlier, the cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4) produce many of the critical elements of asthma, and drugs have been developed to either reduce the synthesis of all of the leukotrienes by inhibiting 5-lipoxygenase (5-LO), the enzyme involved in their production, or competitively antagonizing the principal moiety (LTD_4). Zileuton is the only 5-lipoxygenase synthesis inhibitor that is available in the United States. It is a modest bronchodilator that reduces asthma morbidity, provides protection against exercise-induced asthma, and diminishes nocturnal symptoms, but it has limited effectiveness against allergens. Hepatic enzyme levels can be elevated after its use, and there are significant interactions with other drugs metabolized in the liver. The LTD_4receptor antagonists (zafirlukast and montelukast) have therapeutic and toxicologic profiles similar to that of zileuton but are long acting and permit twice to single daily dose schedules.

This class of drugs does not appear to be uniformly effective in all patients with asthma. Although precise figures are lacking, most authorities put the number of positive responders at less than 50%. As yet, there is no way of determining prospectively who will benefit, so clinical trials are required. Typically, if there is no improvement after one month, treatment can be discontinued.

Miscellaneous Agents It has been suggested that steroid-dependent patients might benefit from the use of immunosuppressant agents such as methotrexate or gold salts. The effects of these agents on steroid dosage and disease activity are minor, and side effects can be considerable. Consequently, this form of treatment can be viewed only as experimental. Opiates, sedatives, and tranquilizers should be absolutely avoided in the acutely ill patient with asthma because the risk of depressing alveolar ventilation is great, and respiratory arrest has been reported to occur shortly after their use. Admittedly, most individuals are anxious and frightened, but experience has shown that they can be calmed equally well by the physician's presence and reassurances. b-Adrenergic blockers and parasympathetic agonists are contraindicated because they can cause marked deterioration in lung function.

Expectorants and mucolytic agents have enjoyed great vogue in the past, but they do not add significantly to the treatment of the acute or chronic phases of this disease. Mucolytic agents such as acetylcysteine may actually produce bronchospasm when administered to susceptible patients with asthma. This effect can be overcome by aerosolizing them in solution with a b-adrenergic agent. The use of intravenous fluids in the treatment of acute asthma also has been advocated. There is little evidence that this adjunct hastens recovery. Nonstandard bronchodilators, such as intravenous magnesium sulfate, for the treatment of acute asthma attacks are not yet warranted in clinical practice because of the controversy surrounding their efficacy.

Special Instructions The treatment of patients with asthma who have coexisting conditions such as heart disease or pregnancy does not differ materially from that outlined above. Therapy with inhaledb_2-selective and anti-inflammatory agents is the mainstay. The lowest doses of adrenergics that produce the desired effects should be used.

FRAMEWORK FOR MANAGEMENT

Emergency Situations The most effective treatment for acute episodes of asthma requires a systematic approach based on the aggressive use of sympathomimetic agents and serial monitoring of key indices of improvement. Reliance on empirism and subjective assessment is no longer acceptable. Multiple inhalations of a short-acting sympathomimetic, such as albuterol, are the cornerstone of most regimens. These drugs provide three to four times more relief than does intravenous aminophylline. Anticholinergic drugs are not first-line therapy because of their long lag time to onset (~ 30 to 40 min) and their relatively modest bronchodilator properties. In emergency situations,$b_2$agonists can be given every 20 min by handheld nebulizer for 2 to 3 doses. The optimum cumulative dose of albuterol appears to lie between 5 and 10 mg. It does not matter how the adrenergic agonists are inhaled. Treatment with albuterol administered by jet nebulizer, metered dose inhaler, or dry powder inhaler all provide equal resolution in acute situations. Aminophylline or ipratropium can be added to the regimen after the first hour in an attempt to speed resolution. Recent studies in a large series of patients demonstrate that$b_2$agonists alone terminate attacks in approximately two-thirds of patients, and that another 5 to 10% benefit from a methylxanthine or ipratropium in combination with a sympathomimetic. The remainder have a poor acute response to all forms of therapy.

Acute episodes of bronchial asthma are one of the most common respiratory emergencies seen in the practice of medicine, and it is essential that the physician recognize which episodes of airway obstruction are life-threatening and which patients demand what level of care. These distinctions can be made readily by assessing selected clinical parameters in combination with measures of expiratory flow and gas exchange. The presence of a paradoxical pulse, use of accessory muscles, and marked hyperinflation of the thorax signify severe airways obstruction, and failure of these signs to remit promptly after aggressive therapy mandates objective monitoring of the patient with measurements of arterial blood gases and the peak expiratory flow rate (PEFR) or FEV_1.

In general, there is a correlation between the severity of the obstruction with which the patient presents and the time it takes to resolve it. Those individuals with the most impairment typically require the most extensive therapy for resolution. If thePEFR or FEV_1 is equal to or less than 20% of predicted on presentation and does not double within an hour of receiving the preceding therapy, the patient is likely to require extensive treatment including glucocorticoids before the obstruction dissipates. This group represents approximately 20% of all the patients who present for acute care. They generally require 3 to 4 days of inpatient treatment before becoming asymptomatic. In such individuals, if the clinical signs of a paradoxical pulse and accessory muscle use are diminishing, and/or if PEFR is increasing, there is no need to change medications or doses; the patient need only be followed. However, if the PEFR falls by more than 20% of its previous value or if the magnitude of the pulsus paradoxicus is increasing, serial measures of arterial blood gases are required, as well as a reconsideration of the therapeutic modalities being employed. If the patient has hypocarbia, one can afford to continue the current approaches a while longer. On the other hand, if the Pa_{CO_2} is within the normal range or is elevated, the patient should be monitored in an intensive care setting, and therapy should be intensified to reverse or

arrest the patient's respiratory failure.

Chronic Treatment The goal of chronic therapy is to achieve a stable, asymptomatic state with the best pulmonary function possible using the least amount of medication. The first step is to educate patients to function as partners in their management. The severity of the illness needs to be assessed and monitored with objective measures of lung function. Asthma triggers should be avoided or controlled, and plans should be made for both chronic management and treatment of exacerbations. Regular follow-up care is mandatory. With respect to pharmacologic interventions, in general, the simplest approach works best. Infrequent symptoms require only the use of an inhaled sympathomimetic on an "as needed" basis. When the disease worsens, as manifested by nocturnal awakenings and daytime symptoms, inhaled steroids and/or mast cell-stabilizing agents should be added. If symptoms do not abate, the dose of inhaled steroids can be increased. An upper limit has not yet been established, but side effects of glucocorticoid excess begin to appear more frequently when the dose exceeds 2.0 mg/d. Persistent asthma complaints can be treated with long-acting inhaled$b_2$agonists, sustained-release theophylline, and/or parasympatholytics. In patients with recurrent or perennial symptoms and unstable lung function, oral steroids in a single daily dose are added to the regimen. Once control is reached and sustained for several weeks, a step-down reduction in therapy should be undertaken, beginning with the most toxic drug, to find the minimum amount of medication required to keep the patient well. During this process, thePEFRshould be monitored and medication adjustments should be based on objective changes in lung function as well as on the patient's symptoms.

PROGNOSIS AND CLINICAL COURSE

The mortality rate from asthma is small. The most recent figures indicate fewer than 5000 deaths per year out of a population of approximately 10 million patients at risk. Death rates, however, appear to be rising in inner-city areas where there is limited availability of health care.

Information on the clinical course of asthma suggests a good prognosis particularly for those whose disease is mild and develops in childhood. The number of children who still have asthma 7 to 10 years after the initial diagnosis varies from 26 to 78%, averaging 46%; however, the percentage who continue to have severe disease is relatively low (6 to 19%).

Although there are reports of patients with asthma developing irreversible changes in lung function, these individuals frequently have comorbid stimuli such as cigarette smoking that could account for these findings. Even when untreated, individuals with asthma do not continuously move from mild to severe disease with time. Rather, their clinical course is characterized by exacerbations and remissions. Some studies suggest that spontaneous remissions occur in approximately 20% of those who develop the disease as adults and that 40% or so can be expected to experience improvement, with less frequent and severe attacks, as they grow older.

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253. HYPERSENSITIVITY PNEUMONITIS AND PULMONARY INFILTRATES WITH EOSINOPHILIA - *Joel N. Kline*, *Gary W. Hunninghake*

HYPERSENSITIVITY PNEUMONITIS

Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is an immunologically induced inflammatory disorder of the lung parenchyma, involving alveolar walls and terminal airways, secondary to repeated inhalation of a variety of organic agents by a susceptible host. Causes of HP are typically designated with colorful names denoting the occupational or avocational risk associated with the disease; "farmer's lung" is the term most commonly used for HP due to inhalation of antigens present in moldy hay, such as thermophilic actinomyces, *Micropolyspora faeni*, and *Aspergillus* species. The prevalence of HP is unknown but varies with the environmental exposure and the specific antigen involved. The prevalence of farmer's lung among Wisconsin dairy farmers has been reported as 4.2 per 1000. The diagnosis of HP requires a constellation of clinical, radiographic, physiologic, pathologic, and immunologic criteria, each of which is rarely pathognomonic alone; and the preferred treatment is avoidance of the causative antigen when practical.

ETIOLOGY

Agents implicated as causes ofHPinclude those listed in Table 253-1. Many cases of HP occurring in various occupations involve exposure to similar agents, particularly the thermophilic actinomycetes. In the United States, the most common types of HP are farmer's lung, bird fancier's lung, and chemical worker's lung. In *farmer's lung*, inhalation of proteins such as thermophilic bacteria and fungal spores that are present in moldy bedding and feed are most commonly responsible for the development of HP. These antigens are probably also responsible for the etiology of *mushroom worker's disease* (moldy composted growth medium is the source of the proteins) and *bagassosis* (moldy sugar cane is the source). *Bird fancier's lung* (and the related disorders of duck fever, turkey handler's lung, and dove pillow's lung) is a response to inhalation of bird proteins from feathers and droppings. *Chemical worker's lung* is an example of how simple chemicals, such as isocyanates, may also cause immune-mediated diseases. In this case, antihapten antibodies may be responsible for the development of HP.

PATHOGENESIS

The finding that precipitating antibodies against extracts of moldy hay were demonstrable in most patients with farmer's lung led to the early conclusion that HPwas an immune-complex-mediated reaction. Subsequent investigations of HP in humans and animal models provided evidence for the importance of cell-mediated hypersensitivity. The very early (acute) reaction is characterized by an increase in polymorphonuclear leukocytes in the alveoli and small airways. This early lesion is followed by an influx of mononuclear cells into the lung and the formation of granulomas that appear to be the result of a classic delayed (T cell mediated) hypersensitivity reaction to repeated inhalation of antigen and adjuvant-active materials. Recent studies in animal models suggest that the disease is mediated as a classic T_H1 cell-mediated immune response to antigen.

Bronchoalveolar lavage in patients with HPconsistently demonstrates an increase in the number of T lymphocytes in lavage fluid (a finding that is also observed in patients with other granulomatous lung disorders). Patients with recent or continual exposure to antigen may have an increase in the number of polymorphonuclear leukocytes in lavage fluid. Increased numbers of mast cells have also been reported. In most patients examined during recovery from acute disease, the T lymphocytes in lavage fluid are predominantly the CD8+ T cell subset. In patients with very recent exposure to antigen, however, the numbers of CD4+ T cells may increase in lavage fluid. Similar findings may be present in similarly exposed, asymptomatic individuals. These observations and others in animal models suggest that there is an active modulation of granuloma formation in the lung by immunoregulatory T cells and associated cytokines in this disorder.

CLINICAL PRESENTATION

The clinical picture is that of an interstitial pneumonitis, although it varies from patient to patient and seems related to the frequency and intensity of exposure to the causative antigen and perhaps other host factors. The presentation can be *acute, subacute*, or *chronic*. In the *acute form*, symptoms such as cough, fever, chills, malaise, and dyspnea may occur 6 to 8 h after exposure to the antigen and usually clear within a few days if there is no further exposure to antigen. The *subacute form* often appears insidiously over a period of weeks marked by cough and dyspnea and may progress to cyanosis and severe dyspnea requiring hospitalization. In some patients, a subacute form of the disease may persist after an acute presentation of the disorder, especially if there is continued exposure to antigen. In most patients with the acute or subacute form ofHP, the symptoms, signs, and other manifestations of HP disappear within days, weeks, or months if the causative agent is no longer inhaled. Transformation to a chronic form of the disease may occur in patients with continued antigen exposure, but the frequency of such progression is uncertain. The *chronic form* of HP may be clinically indistinguishable from pulmonary fibrosis due to a wide variety of causes. Physical examination may reveal clubbing. This stage may progressively worsen, resulting in dependence on supplemental O_2, pulmonary hypertension, and death from respiratory failure. An indolent gradually progressive form of the disease can be associated with cough and exertional dyspnea without a prior history consistent with acute or subacute manifestations. Such a gradual onset frequently occurs with low-dose exposure to the antigen.

Because strict definitions of acute, subacute, and chronic stages ofHP have not been generally agreed on, interpretation of epidemiologic and clinical studies can be difficult. Therefore, it has been proposed that HP be described as recently diagnosed, recurrent or progressive, or residual disease. For these categories, required diagnostic criteria include the presence of an appropriate exposure; exertional dyspnea; inspiratory crackles; and, if performed, lymphocytic alveolitis on bronchoalveolar lavage. Supportive criteria include recurrent febrile episodes, radiographic infiltrates, diminished pulmonary diffusing capacity, precipitating antibodies to appropriate antigens, histopathologic demonstration of granulomas, and improvement in symptoms with avoidance of exposure.

DIAGNOSIS

After acute exposure to antigen, neutrophilia and lymphopenia are frequently present. Eosinophilia is not a feature. All forms of the disease may be associated with elevations in erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and serum immunoglobulins. Antinuclear antibodies are rarely present and appear to have no pathogenic role. Examination for *serum precipitins* against suspected antigens, such as those listed inTable 253-1, is an important part of the diagnostic workup and should be performed on any patient with interstitial lung disease, especially if a suggestive exposure history is elicited. If found, precipitins indicate sufficient exposure to the causative agent for generation of an immunologic response. The diagnosis ofHP is not established solely by the presence of precipitins, however, as precipitins are found in sera of many individuals exposed to appropriate antigens who demonstrate no other evidence of HP. False-negative results may occur because of poor-quality antigens or an inappropriate choice of antigens. Extraction of antigens from the suspected source may at times be helpful.

No specific or distinctive *chest roentgenogram* occurs inHP. It can be normal even in symptomatic patients. The acute or subacute phase may be associated with poorly defined, patchy, or diffuse infiltrates or with discrete, nodular infiltrates (Fig. 253-1). In the chronic phase, the chest x-ray usually shows a diffuse reticulonodular infiltrate. Honeycombing may eventually develop as the condition progresses. Apical sparing is common, suggesting that disease severity correlates with inhaled antigen load, but no particular distribution or pattern is classic for HP. Abnormalities rarely seen in HP include pleural effusion or thickening, and hilar adenopathy. High-resolution chest computed tomography (CT) has been reported to show a characteristic constellation of abnormalities, including (1) global lung involvement with increased lung density, (2) prominence of medium-sized bronchial walls, (3) patchy air space opacification with reticular and nodular patterns and midzone prominence, and (4) absence of hilar lymph node enlargement. No pathognomonic CT features of HP have been described (Fig. 253-2).

Pulmonary function studies in all forms ofHP may show a restrictive or obstructive pattern with loss of lung volumes, impaired diffusion capacity, decreased compliance, and an exercise-induced hypoxemia. Resting hypoxemia may also be found. Bronchospasm and bronchial hyperreactivity are sometimes found in acute HP. With antigen avoidance, the pulmonary function abnormalities are usually reversible, but they may gradually increase in severity or may occur rapidly after acute or subacute exposure to antigen.

Bronchoalveolar lavage is used in some centers to aid in diagnostic evaluation. A marked lymphocytic alveolitis on bronchoalveolar lavage is almost universal, although not pathognomonic. Lymphocytes typically have a decreased helper/suppressor ratio and are activated. Alveolar neutrophilia is also prominent acutely but tends to fade in the absence of recurrent exposure. Bronchoalveolar mastocytosis may correlate with disease activity. *Lung biopsy*, obtained through flexible bronchoscopy, open-lung procedures, or thoracoscopy, may be diagnostic. Although the histopathology is distinctive, it may not be pathognomonic ofHP. When the biopsy is taken during the active phase of disease, typical findings include an interstitial alveolar infiltrate consisting of plasma cells, lymphocytes, and occasional eosinophils and neutrophils,

usually with accompanying granulomas. Interstitial fibrosis may be present but most often is mild in earlier stages of the disease. Some degree of bronchiolitis is found in about half the cases, whereas vasculitis is not a feature of the disorder. The triad of mononuclear bronchiolitis; interstitial infiltrates of lymphocytes and plasma cells; and single, nonnecrotizing, and randomly scattered parenchymal granulomas without mural vascular involvement is consistent with but not specific for HP.

Inhalation challenge studies have been described as useful to differentiate betweenHP and other interstitial lung diseases. These tests should be performed in a center that specializes in provocation testing for reasons of both safety and accuracy. Moveover, because the antigens used for provocation testing are not standardized, interpretation of these tests is difficult. In general, these tests may be used to support a diagnosis of HP, but they are not sufficiently accepted to either confirm or deny the diagnosis. The lack of standardized, nonirritating antigens and of proven controlled protocols makes *skin testing* useful only for research purposes. Similarly, in vitro tests of cell-mediated (delayed) hypersensitivity have not consistently been shown to correlate with clinical HP and have no place in the routine diagnostic workup.

In summary, the diagnosis in most cases is established by (1) consistent history, physical findings, pulmonary function tests, and chest x-ray; (2) exposure to a recognized antigen; and (3) finding an antibody to that antigen. In a few circumstances, bronchoalveolar lavage and/or lung biopsy may be needed. Provocation tests may be useful but are not essential for the diagnosis.

DIFFERENTIAL DIAGNOSIS

ChronicHP may often be difficult to distinguish from a number of other interstitial lung disorders such as idiopathic pulmonary fibrosis, sarcoidosis, interstitial lung disease associated with a collagen vascular disorder, and drug-induced lung diseases. A negative history for use of relevant drugs and no evidence of a systemic disorder usually exclude the presence of drug-induced lung disease or a collagen vascular disorder. Bronchoalveolar lavage often shows predominance of neutrophils in idiopathic pulmonary fibrosis and a predominance of CD4+ lymphocytes in sarcoidosis. Hilar/paratracheal lymphadenopathy or evidence of multisystem involvement also favors the diagnosis of sarcoidosis. In some patients, a lung biopsy may be required to differentiate chronic HP from other interstitial diseases. The lung disease associated with acute or subacute HP may clinically resemble other disorders that present with systemic symptoms and recurrent pulmonary infiltrates, including the allergic bronchopulmonary mycoses and other eosinophilic pneumonias.

Eosinophilic pneumonia is often associated with asthma and is typified by peripheral eosinophilia; neither of these is a feature ofHP. Allergic bronchopulmonary aspergillosis (ABPA) is the most common example of the allergic bronchopulmonary mycoses and is sometimes confused with HP because of the presence of precipitating antibodies to *A. fumigatus*. ABPA is associated with allergic (atopic) asthma. Acute HP may be confused with *organic dust toxic syndrome* (ODTS), a condition that is more common than HP. ODTS follows heavy exposure to organic dusts and is characterized by transient fever and muscle aches, with or without dyspnea and cough. Serum precipitins are absent, and the chest x-ray is usually normal. Studies have shown no immunologic basis for

ODTS, and endotoxin is suspected to be involved in its pathogenesis. This distinction is important, as ODTS is a self-limited disorder without significant long-term sequellae, whereas continued antigen exposure in HP can result in permanent disability. Massive exposure to moldy silage may result in a syndrome termed *pulmonary mycotoxicosis*, or *atypical farmer's lung*, with fever, chills, and cough and the presence of pulmonary infiltrates within a few hours of exposure. No previous sensitization is required, and precipitins are absent to *Aspergillus*, the suspected causative agent.

TREATMENT

Because effective treatment depends largely on avoiding the antigen, identification of the causative agent and its source is essential. This identification is usually possible if the physician takes a careful environmental and occupational history or, if necessary, visits the patient's environment. The simplest way to avoid the incriminated agent is to remove the patient from the environment or the source of the agent from the patient's environment. This recommendation cannot be taken lightly when it completely changes the life-style or livelihood of the patient. In many cases, however, the source of exposure (birds, humidifiers) can easily be removed. If occupational exposure is involved, an initial attempt can be made at antigen avoidance maneuvers that are least disruptive to the patient's livelihood, which usually means avoiding areas associated with heavy exposure and wearing an appropriate mask. This will not protect against small-molecular-weight agents such as isocyanates, which require more elaborate respiratory systems. Pollen masks, personal dust respirators, airstream helmets, and ventilated helmets with a supply of fresh air are increasingly efficient means of purifying inhaled air. If symptoms recur or physiologic abnormalities progress in spite of these measures, then more effective measures to avoid antigen exposure must be pursued. Compromises with environmental control pertain primarily to the acute, recurrent, transient clinical form ofHP and must be accompanied by careful follow-up. Subacute forms are ordinarily the result of a heavy, sustained exposure. The chronic form typically results from low-grade or recurrent exposure over many months or years, and the lung disease may already be partially irreversible. These patients are usually advised to avoid completely all possible contact with the offending agent, although follow-up studies of individuals with farmer's lung and bird fancier's lung have found resolution of the disease despite continued exposure in some patients.

Patients with the *acute*, recurrent form ofHPusually recover without need for glucocorticoids. *Subacute* HP may be associated with severe symptoms and marked physiologic impairment and may continue to progress for several days despite hospitalization. Urgent establishment of the diagnosis and prompt institution of glucocorticoid treatment are indicated in such patients. Such therapy may also hasten recovery in patients with lesser involvement. Prednisone at a dosage of 1 mg/kg per day or its equivalent is continued for 7 to 14 days and then tapered over the ensuing 2 to 6 weeks at a rate that depends on the patient's clinical status. Patients with *chronic* HP may gradually recover without therapy after the institution of environmental control. In many patients, however, a trial of prednisone may be useful to obtain maximal reversibility of the lung disease. After initial prednisone therapy (1 mg/kg per day for 2 to 4 weeks), the drug is tapered to the lowest dosage that will maintain the functional status of the patient. Many patients will not require or benefit from long-term therapy if there is no further exposure to antigen. Available studies report no effect of

glucocorticoid therapy on long-term prognosis of farmer's lung.

PULMONARY INFILTRATES WITH EOSINOPHILIA

Pulmonary infiltrates with eosinophilia (PIE, eosinophilic pneumonias) include distinct individual syndromes characterized by eosinophilic pulmonary infiltrates and, commonly, peripheral blood eosinophilia. Since Loeffler's initial description of a transient, benign syndrome of migratory pulmonary infiltrates and peripheral blood eosinophilia of unknown cause, this group of disorders has been enlarged to include several diseases of both known and unknown etiology (Table 253-2). These diseases may be considered as putative hypersensitivity lung diseases but are not to be confused withHP(extrinsic allergic alveolitis), in which eosinophilia is not a feature. When an eosinophilic pneumonia is associated with bronchial asthma, it is important to determine if the patient has atopic asthma and has wheal-and-flare skin reactivity to *Aspergillus* or other relevant fungal antigens. If so, other criteria should be sought for diagnosis ofABPA(Table 253-3) or other, rarer examples of allergic bronchopulmonary mycosis such as those caused by *Penicillium*, *Candida*, *Curvularia*, or *Helminthosporium* spp. *A. fumigatus* is the most common cause of ABPA, although other *Aspergillus* species have also been implicated. ABPA has been reported to complicate cystic fibrosis. The chest roentgenogram in ABPA may show transient, recurrent infiltrates or may suggest the presence of proximal bronchiectasis. High-resolution chestCT is a sensitive, noninvasive technique for the recognition of proximal bronchiectasis. The bronchial asthma of ABPA likely involves an IgE-mediated hypersensitivity, whereas the bronchiectasis associated with this disorder is thought to result from a deposition of immune complexes in proximal airways. Treatment usually requires the long-term use of systemic glucocorticoids.

Tropical eosinophilia is usually caused by filarial infection; however, eosinophilic pneumonias also occur with other parasites such as *Ascaris*, *Ancyclostoma* sp., *Toxocara* sp., and *Strongyloides stercoralis*. Tropical eosinophilia due to *Wuchereria bancrofti* or *W. malayi* occurs most commonly in southern Asia, Africa, and South America, and is treated successfully with diethylcarbamazine.

Drug-induced eosinophilic pneumonias are exemplified by acute reactions to nitrofurantoin, which may begin 2 h to 10 days after nitrofurantoin is started, with symptoms of dry cough, fever, chills, and dyspnea; an eosinophilic pleural effusion accompanying patchy or diffuse pulmonary infiltrates may also occur. Other drugs associated with eosinophilic pneumonias include sulfonamides, penicillin, chlorpropamide, thiazides, tricyclic antidepressants, hydralazine, mephenesin, mecamylamine, nickel carbonyl vapor, gold salts, isoniazid, para-aminosalicylic acid, and others. Treatment consists of withdrawal of the incriminated drugs and the use of glucocorticoids, if necessary. The eosinophilia-myalgia syndrome, caused by dietary supplements of L-tryptophan, is occasionally associated with pulmonary infiltrates.

The group of idiopathic eosinophilic pneumonias consists of diseases of varying severity. *Loeffler's syndrome* was originally reported as a benign, acute eosinophilic pneumonia of unknown cause characterized by migrating pulmonary infiltrates and minimal clinical manifestations. In some patients, these clinical characteristics may prove to be secondary to parasites or drugs. *Acute eosinophilic pneumonia* has been

described recently as an idiopathic acute febrile illness lasting less than 7 days with severe hypoxemia, pulmonary infiltrates, and no history of asthma. *Chronic eosinophilic pneumonia* presents with significant systemic symptoms including fever, chills, night sweats, cough, anorexia, and weight loss lasting for several weeks to months. The chest x-ray classically shows peripheral infiltrates resembling a photographic negative of pulmonary edema. Some patients also have bronchial asthma of the intrinsic or nonallergic type. Dramatic clearing of symptoms and chest x-rays is often noted within 48 h after initiation of glucocorticoid therapy.

Allergic angiitis and granulomatosis of Churg and Strauss is a multisystem vasculitic disorder that frequently involves the skin, kidney, and nervous system in addition to the lung. The disorder may occur at any age and favors persons with a history of bronchial asthma. The asthma often is progressive until the onset of fever and exaggerated eosinophilia, at which time the symptoms of asthma may ease. The illness may be fulminating and the prognosis grave unless treated aggressively with glucocorticoids and, at times, immunosuppressive therapy. The recent introduction of leukotriene-modifying agents (zafirlukast, zyleuton, and montelukast) has unmasked a number of cases of unrecognized Churg-Strauss syndrome when individuals with asthma have been weaned from glucocorticoids with the use of these antigens.

The *hypereosinophilic syndrome* is characterized by the presence of more than 1500 eosinophils per microliter of peripheral blood for 6 months or longer; lack of evidence for parasitic, allergic, or other known causes of eosinophilia; and signs or symptoms of multisystem organ dysfunction. Consistent features are blood and bone marrow eosinophilia with tissue infiltration by relatively mature eosinophils. The heart may be involved with tricuspid valve abnormalities or endomyocardial fibrosis and a restrictive, biventricular cardiomyopathy. Other organs affected typically include the lungs, liver, spleen, skin, and nervous system. Treatment consists of glucocorticoids and/or hydroxyurea, plus treatment as needed for cardiac dysfunction, which is frequently responsible for much of the morbidity and mortality in this syndrome.

(Bibliography omitted in Palm version)

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254. ENVIRONMENTAL LUNG DISEASES - *Frank E. Speizer*

This**chapter**provides perspectives on ways to assess pulmonary diseases for which environmental causes are suspected. This assessment is important because removal of the patient from a harmful environment is often the only intervention that might prevent further significant deterioration or lead to improvement in a patient's condition. Furthermore, the identification of an environment-associated disease in a single patient may lead to primary preventive strategies affecting other similarly exposed people who have not yet developed disease.

The exact magnitude of the problem is unknown, but there is no question that large numbers of people are at risk for developing serious respiratory disease as a result of occupational or environmental exposures. For example, recent estimates suggest that approximately 2.4 million workers in the United States have been exposed to crystalline silica or asbestos dust in mining and nonmining industries. Even if only 5% of these workers (a conservative estimate) are to suffer from respiratory disease as a result of their exposure, this figure represents more than 100,000 individuals.

Although industries are required to spend substantial amounts of capital in efforts to protect their workers, occupationally related respiratory diseases continue to occur. These diseases are often attributed to exposures in the past, at a time when we were not aware of the risk incurred and the need for worker protection to the degree that we are today.

HISTORY AND PHYSICAL EXAMINATION

The patient's history is of paramount importance in assessing any potential occupational or environmental exposure, and the physician must ask the patient to describe a suspected environmental exposure in detail.

Inquiry into specific work practices should include questions about specific contaminants involved, the availability and use of personal respiratory protection devices, the size and ventilation of workspaces, and whether coworkers have similar complaints. In addition, the patient must be questioned about alternative sources for potentially toxic exposures, including hobbies or other environmental exposures at home. Short-term exposures to potential toxic agents in the distant past must also be considered (Chap. 391).

Many people are aware of the potential hazards in their workplaces, and many states require that employees be informed about potentially hazardous exposures. These requirements include the provision of specific educational materials (including Material Safety Data Sheets), personal protective equipment and instructions in its use, and information on environmental control procedures. Reminders posted in the workplace may warn workers about hazardous substances. Protective clothing, lockers, and shower facilities may be considered necessary parts of the job. However, even in these more progressive industries, the introduction of new processes, particularly when related to the use of new chemical compounds, may change exposure significantly, and often only the employee on the production line is aware of the change. For the physician who regularly sees patients from a particular industry, a visit to the work site can be very instructive. Alternatively, physicians can request inspections by appropriate federal

and/or state authorities.

The physical examination of patients with environment-related lung diseases may help to determine the nature and severity of the pulmonary condition. Unfortunately, the pulmonary response to most injurious agents is the development of a limited number of nonspecific physical signs. These findings do not point to the specific causative agent, and other types of information must be used to arrive at an etiologic diagnosis.

PULMONARY FUNCTION TESTS AND CHEST RADIOGRAPHY

Many mineral dusts produce characteristic alterations in the mechanics of breathing and lung volumes that clearly indicate a restrictive pattern (Chaps. 250 and259). Exposures to a number of organic dusts or chemical agents capable of producing occupational asthma result in pronounced obstructive patterns of pulmonary dysfunction that may be reversible (Chap. 252). Measurement of change in forced expiratory volume (FEV_1) before and after a working shift can be used to detect an acute inflammatory or bronchoconstrictive response. An acute decrement of FEV_1over the first work shift of the week is a characteristic feature of cotton textile workers with byssinosis.

The chest radiograph is useful in detecting and monitoring the pulmonary response to mineral dusts. The International Labour Organization (ILO) International Classification of Radiographs of Pneumoconioses classifies chest radiographs according to the nature and size of opacities seen and the extent of involvement of the parenchyma. In general, opacities may be round or irregular, small (<10 mm in diameter) or large. They may be few in number, with visible normal lung markings, partially obscure normal markings, or totally obscure normal markings. Although useful for screening large numbers of workers, the ILO system lacks specificity and may over- or underestimate the functional impact of pneumoconiosis. With dusts causing rounded, regular opacities like those evident in coal worker's pneumoconiosis, the degree of involvement on the chest radiograph may be extensive, while pulmonary function may be only minimally impaired.

In contrast, in pneumoconiosis causing linear, irregular opacities like those seen in asbestosis, the radiograph may lead to underestimation of the severity of the impairment. It is possible for a patient to have a history of exposure, a moderately reduced forced vital capacity (FVC), and a reduced diffusion capacity in asbestosis with a relatively normal chest radiograph. The radiographic findings of irregular or linear opacities are simply more difficult to separate from normal markings until relatively late in the disease. When shadows become large, as shown in Fig. 254-1, the condition is termed *complicated pneumoconiosis*, sometimes called progressive massive fibrosis (PMF). For the individual patient with a history of exposure, conventional computed tomography (CT) and high-resolution computed tomography (HRCT) have improved the sensitivity of identifying diffuse parenchymal abnormalities of the lung. The procedures have been shown to provide earlier detection of silicosis and asbestosis.

Other diagnostic procedures of use in identifying environment-induced lung disease include evaluation of heavy metal concentrations in urine (arsenic in smelter workers, cadmium in battery plant workers); bacteriologic studies (tuberculosis in medical care personnel, anthrax in wool sorters); fungal studies (coccidioidomycosis in southwestern farm workers, histoplasmosis in poultry or pigeon handlers); and serologic studies

(psittacosis in pet shop workers or owners of sick birds, Q fever in tanners or slaughterhouse workers). Ultimately, a lung biopsy may be required both for morphologic diagnosis of the underlying pulmonary disease and for attempted identification of the specific etiologic agent.

MEASUREMENT OF EXPOSURE

If reliable environmental sampling data are available, this information should be used in assessing a patient's exposure. Since many of the chronic diseases result from exposure over many years, current environmental measurements should be combined with work histories to arrive at estimates of past exposure. Even in acute conditions, when monitoring of exposure may be possible, little may be known about the actual dose received by the lung. Most of the research on health effects of air pollutants (discussed later in this**chapter**) has relied on fixed-station monitoring of outdoor air, often at locations somewhat distant from the residences of the people being studied. In addition, most people spend less than 20% of their time outdoors. Therefore, outdoor measurements can be used only in a relative sense, and they cannot be relied on to estimate actual dose.

In situations where individual exposure to specific agents -- either in a work setting or via ambient air pollutants -- has been determined, transport of these agents through the airways may be an important factor affecting dose. Highly soluble gases such as sulfur dioxide are absorbed in the upper airway and presumably produce their effects by reflex response of sensitive neural fibrils in the trachea or larger airways. In contrast, nitrogen dioxide, which is less soluble, may reach the bronchioles and alveoli in sufficient quantities to result in an acute life-threatening disease in farmers exposed even briefly to the gas evolved from moldy hay in silos (silo-filler's disease).

Particle size and chemistry of air contaminants also must be considered. Particles above 10 to 15 um in diameter, because of their settling velocities in air, do not penetrate beyond the upper airways. These larger particles are often referred to as "fugitive dusts" and include pollens, other windblown dusts, and dusts resulting from mechanical industrial processes. They have little or no role in chronic respiratory disease except perhaps as related to cancer (see below).

Particles below 10 um in size are created by the burning of fossil fuels or high-temperature industrial processes resulting in condensation products from gases, fumes, or vapors. These particles are divided into two size fractions on the basis of their chemical characteristics. Particles of approximately 2.5 to 10 um (coarse-mode fraction) contain crustal elements, such as silica, aluminum, and iron. These particles mostly deposit relatively high in the tracheobronchial tree. Although the total mass of an ambient sample is dominated by these larger respirable particles, the number of particles, and therefore the surface area on which potential toxic agents can deposit and be carried to the lower airways, is dominated by particles smaller than 2.5 um (fine-mode fraction or accumulation mode). The smallest particles, those less than 0.1 um in size, remain in the airstream and deposit in the lung only on a random basis as they come into contact with the alveolar walls.

Besides the size characteristics of particles and the solubility of gases, the actual

chemical composition, mechanical properties, and immunogenicity or infectivity of inhaled material determine in large part the nature of the diseases found among exposed persons. Few studies to date have directly measured those characteristics. However, they are of increasing concern as management strategies for environmental and occupational exposures are developed.

OCCUPATIONAL EXPOSURES AND PULMONARY DISEASE

ASBESTOSIS

Except in localized regions with single industrial exposures, such as coal-mining or granite-quarrying regions, the most frequent inorganic dust-related chronic pulmonary diseases are associated with industries using *asbestiform fibers*. *Asbestos* is a generic term for several different mineral silicates, including chrysolite, amosite, anthophyllite, and crocidolite. Besides workers involved in the mining, milling, and manufacturing of asbestos products, workers in the building trades, including pipe fitters and boilermakers, were exposed to asbestos, which was widely used in construction because of its exceptional thermal and electric insulation properties. In addition, asbestos was used in the manufacture of fire-smothering blankets and safety garments, as filler for plastic materials, in cement and floor tiles, and in friction materials, such as brake and clutch linings.

Exposure to asbestos is not limited to persons who directly handle the material. Cases of asbestos-related diseases have been encountered in individuals with only moderate exposure, such as the painter or electrician who works alongside the insulation worker in a shipyard or the housewife who does no more than shake out and wash her husband's work clothes. Community exposure has probably resulted from the use of asbestos-containing material sprayed on steel girders in many large buildings as a safety feature to prevent buckling in case of fire.

Asbestos was first used extensively in the 1940s. Starting in 1975 it was mostly replaced with synthetic mineral fibers, such as fiberglass or slag wool. However, asbestos is still used in the manufacture of brake linings and remains as pipe and boiler insulation in hundreds of thousands of workplaces and homes. Despite current regulations mandating adequate training for any worker potentially exposed to asbestos, exposure probably continues among inexperienced demolition workers. The major health effects from exposure to asbestos are pulmonary fibrosis (asbestosis) and cancers of the respiratory tract, the pleura, and (in rare cases) the peritoneum.

Asbestosis is a diffuse interstitial fibrosing disease of the lung that is directly related to the intensity and duration of exposure. Except for its association with a history of exposure to asbestos (generally in a work setting), asbestosis resembles the other forms of diffuse interstitial fibrosis (Chap. 259). Usually, moderate to severe exposure has taken place for at least 10 years before the disease becomes manifest.

Physiologic studies reveal a restrictive pattern with a decrease in lung volumes. Flow rates are commonly reduced less than would be predicted on the basis of the volume reduction. An early sign of severe disease may be a reduction in diffusing capacity.

Pulmonary fibrosis may occur following sufficient exposure to any of the asbestiform fiber types. The fibrotic lesions do not appear to relate to either shape or chemical composition of any fiber type. During phagocytosis of the asbestos fiber, the membrane of the macrophage is damaged and this damage results in the release of lysosomes containing enzymes that may act to damage the lung parenchyma. The clinical manifestations are typical of those physical findings in any patient with pulmonary fibrosis (Chap. 259).

Diagnosis The chest radiograph can be used to detect a number of manifestations of asbestos exposure as well as to identify specific lesions. Past exposure is specifically indicated by pleural plaques, which are characterized by either thickening or calcification along the parietal pleura, particularly along the lower lung fields, the diaphragm, and the cardiac border. Without additional manifestations, pleural plaques imply only exposure, not pulmonary impairment. Benign pleural effusions may occur, particularly in patients with asbestosis, but are not necessarily restricted to those with overt disease. The fluid is sterile but may be a serous or blood-stained exudate and may occur bilaterally. The effusion may be slowly progressive or may resolve spontaneously.

The radiographic diagnosis of asbestosis depends on the presence of irregular or linear opacities, usually first noted in the lower lung fields and spreading into the middle and upper lung fields as the disease progresses. An indistinct heart border or a "ground glass" appearance in the lung fields is seen in some cases. As the fibrotic changes in the parenchyma begin to coalesce, the patient develops obliteration of entire acinar units, with eventual formation of the classical honeycombed lung, which appears on chest radiographs as coarse infiltrates with small (about 7- to 10-um) air spaces. In cases in which the x-ray changes are less obvious,HRCT may show distinct changes of subpleural curvilinear lines 5 to 10 cm in length that appear to be parallel to the pleural surface; these alterations increase the positive predictive value of radiographic evidence from approximately 85% to about 100%.

In general, newly diagnosed cases will have resulted from exposure levels that were present many years before and, in spite of the patients' having left the industry, are attributable to that former exposure. Since the patient may be eligible for compensation within a specific time frame after the diagnosis of an asbestos-related disease is made, the physician making the diagnosis should be certain to inform the patient promptly. On occasion, the physician may have reason to suspect ongoing exposure from a patient's current job description or actual monitoring data. In such cases, federal or state health authorities may need to be notified. Present-day occupational safety and health regulations, if followed properly, protect workers from exposure.

Casual, nonoccupational exposure to undisturbed sources of asbestos-containing materials -- e.g., in walls of schools or other buildings -- represents little if any hazard to people who inhabit or work in such buildings. Because the association of smoking and asbestos exposure increases the risk of developing lung cancer (see below), it is extremely important to advise patients with a history of exposure to asbestos to stop smoking. No specific therapy is available in the management of patients with asbestosis. The supportive care is the same as that given to any patient with diffuse interstitial fibrosis from any cause.

Lung cancer (Chap. 88), either squamous cell carcinoma or adenocarcinoma, is the most frequent cancer associated with asbestos exposure. The excess frequency of lung cancer in asbestos workers is associated with a minimum lapse of 15 to 19 years between first exposure and development of the disease. Persons with more exposure are at greater risk of disease. In addition, there appears to be a significant multiplicative effect that leads to a far greater risk of lung cancer in persons who are cigarette smokers and have asbestos exposure than would be expected from the additive risk of each factor. To date, efforts to consider these high-risk individuals for special surveillance studies, including sputum cytologic examinations and repeated chest x-rays as frequently as every 4 to 6 months, have resulted in neither significant early detection nor prolonged survival once the lung cancer is found.

Mesotheliomas (Chap. 262), both pleural and peritoneal, are also associated with asbestos exposure. In contrast to lung cancers, these tumors do not appear to be associated with smoking. Relatively short-term asbestos exposures of 1 to 2 years or less occurring some 20 to 25 years in the past have been associated with the development of mesotheliomas (an observation that emphasizes the importance of obtaining a complete environmental exposure history). The risk for this type of tumor peaks 30 to 35 years after initial exposure. Since maximum exposure took place in the United States between 1930 and 1960, peak incidence of disease in men occurred in 1997, with a total of 2300 cases. Incidence is expected to decline over the next 30+ years to about 500 cases per year.

Although approximately 50% of mesotheliomas metastasize, the tumor generally is locally invasive, and death usually results from local extension. Most patients present with effusions that may obscure the underlying pleural tumor. In contrast to the findings in effusion due to other causes, because of the restriction placed on the chest wall, no shift of mediastinal structures toward the opposite side of the chest will be seen. The major diagnostic problem is differentiation from peripherally spreading pulmonary adenocarcinoma or from adenocarcinoma metastasized to pleura from an extrathoracic primary site. Although a needle biopsy may be diagnostic, an open biopsy is often necessary, and even the latter procedure may not provide a definitive diagnosis of the origin of the tumor.

Since epidemiologic studies have shown that more than 80% of mesotheliomas may be associated with asbestos exposure, documented mesothelioma in a worker with occupational exposure to asbestos may be compensable in many parts of the United States.

SILICOSIS

In spite of the technical adequacy of existing protective equipment, *free silica* (SiO_2), or crystalline quartz, is still a major occupational hazard. In the United States, estimates of potential numbers of exposed workers range between 1.2 and 3 million people. The major occupational exposures include: mining; stonecutting; employment in abrasive industries, such as stone, clay, glass, and cement manufacturing; foundry work; packing of silica flour; and quarrying, particularly of granite. Most often, progressive pulmonary fibrosis (silicosis) occurs in a dose-response fashion after many years of exposure.

Workers exposed through sandblasting in confined spaces, tunneling through rock with high quartz content (15 to 25%), or the manufacture of abrasive soaps may develop acute silicosis with as little as 10 months' exposure. The disease may be rapidly fatal in less than 2 years, despite the discontinuation of exposure. A radiographic picture of profuse miliary infiltration or consolidation is characteristic of acute silicosis.

In long-term, less intense exposure, small rounded opacities in the upper lobes, with retraction and hilar adenopathy, classically appear on the radiograph after 15 to 20 years. Calcification of hilar nodes may occur in as many as 20% of cases and produces the characteristic "eggshell" pattern. These changes may be preceded by or associated with a reticular pattern of irregular densities that are uniformly present throughout the upper lung zones.

The nodular fibrosis may be progressive in the absence of further exposure, with coalescence and formation of nonsegmental conglomerates of irregular masses in excess of 1 cm in diameter. These masses become quite large and are characteristic ofPMF(Figure 254-1). Significant functional impairment with both restrictive and obstructive components may be associated with this form of silicosis. In the late stages of the disease, ventilatory failure may develop. In more subtle cases,CT may be helpful both in identifying nodules, which are preferentially located in the posterior aspect of the upper lobes, as well as in identifying larger opacities and more coalescence than might be noted on regular chest x-rays. Patients with silicosis are at greater risk of acquiring *Mycobacterium tuberculosis* infections (silicotuberculosis) and atypical mycobacterial infections. Because the frequency with which tuberculosis has been found at autopsy in patients with PMF exceeds considerably the frequency of premorbid diagnosis, treatment for tuberculosis is indicated in any patient with silicosis and a positive tuberculin test.

Other less hazardous silicates include Fuller's earth, kaolin, mica, diatomaceous earths, silica gel, soapstone, carbonate dusts, and cement dusts. The production of fibrosis in workers exposed to these agents is believed to be related either to the free silica content of these dusts or, for substances that contain no free silica, to the potentially large dust loads to which these workers may be exposed.

Other silicates, including *talc dusts*, may be contaminated with asbestos and/or free silica. Accidental exposure to significant quantities of talc may result in an acute syndrome with cough, cyanosis, and labored breathing (acute talcosis). Severe progressive fibrosis with respiratory failure may ensue within a few years. Far more common is the fibrosis and/or pleural or lung cancer associated with chronic exposure in rubber workers who use commercial talc as a lubricant in tire molds. Pure talc does not produce fibrosis; thus, it is difficult to sort out whether the effects are due to the contamination of commercial talc by asbestos or by free silica.

COAL WORKER'S PNEUMOCONIOSIS (CWP)

Coal dust is associated with CWP, which has enormous social, economic, and medical significance in every nation in which coal mining is an important industry. Simple radiographically identified CWP is seen in 12% of all miners and in as many as 50% of anthracite miners with more than 20 years' work on the coal face. The prevalence of

disease is lower in workers in bituminous coal mines. Since much western U.S. coal is bituminous, CWP is less prevalent in that region.

Much of the symptomatology associated with simpleCWPappears to be similar and additive to the effects of cigarette smoking on the development of chronic bronchitis and obstructive lung disease (Chap. 258). In the early stages of simple CWP, radiographic abnormalities consist of small, irregular opacities (reticular pattern). With prolonged exposure, one sees small, rounded, regular opacities, 1 to 5 mm in diameter (nodular pattern). Calcification is generally not seen, although approximately 10% of older anthracite miners have calcified nodules.

ComplicatedCWP is manifested by the appearance on the chest radiograph of nodules ranging from 1 cm in diameter to the size of an entire lobe, generally confined to the upper half of the lungs. This condition, considered a form ofPMF, is accompanied by a significant reduction in diffusing capacity and is associated with premature mortality. In contrast to patients with silicosis, underground miners with simple CWP develop PMF at a rate of only 5 to 15%, depending on the type of coal.

The mechanism whereby PMFoccurs inCWP is not fully understood. Several hypotheses have been proposed, including: (1) sufficient free silica is present in the dust; (2) normal clearance mechanisms are unable to clear the excessive dust loads; and (3) atypical reactions to *M. tuberculosis* occur. As previously described, PMF in silicosis is associated with prolonged duration and high intensity of exposure to free silica. Heavy exposure to carbon particles free of silica occurs in carbon black, graphite, and charcoal workers. The prolonged exposure of these workers may result in sufficient accumulation of carbon in the lung to produce PMF. The mechanism appears to relate to a breakdown of the clearance capacity of the airways.

Caplan's syndrome (Chap. 312), first described in coal miners but subsequently found in patients with a variety of pneumoconioses, includes seropositive rheumatoid arthritis with characteristicPMF. The syndrome suggests an immunopathologic mechanism. Over the last decade, the mechanisms by which the chronic inhalation of mineral dusts produce an increase in inflammatory cells (including macrophages and neutrophils), which in turn causes PMF, have been explored. Coal dust can: (1) be a source of reactive oxygen species causing lung injury; (2) result in stimulation of macrophages to produce cytokines and enhance production of (anti)fibrogenic factors such as TNF-a; (3) increase protease activity; and (4) increase inactivation of a_1-antitrypsin and leukocyte elastase activity. The final pathologic pathway may be fibrosis resulting from the interactions of a variety of these mechanisms.

BERYLLIOSIS

Beryllium may produce an acute pneumonitis or, far more commonly, a chronic interstitial pneumonitis. Unless one inquires specifically about occupational exposures to beryllium in the manufacture of alloys, ceramics, high-technology electronics, and (before the 1950s) the production of fluorescent lights, one may miss entirely the etiologic relationship to an occupational exposure. Nonspecific pulmonary function tests may be normal or may indicate evidence of restrictive disease. Between 2 and 15 years of exposure, depending on its intensity, are required for the disease to become

manifest. On open lung biopsy, granulomatous formation similar to that seen in sarcoidosis (Chap. 318) may make differentiation impossible unless tissue levels of beryllium are measured.

Other hard metals, including aluminum powders, chromium, cobalt, titanium dioxide, and tungsten, may produce an interstitial pneumonitis, but this is rare.

OTHER INORGANIC DUSTS

Other dusts are considered *nuisance dusts* because their major environmental and health effects seem to be reduction in visibility and irritation of eyes, ears, nasal passages, and other mucous membranes, respectively. If they penetrate to the lower airways, these dusts do not affect the architecture of the terminal bronchioles or acinar spaces nor do they destroy collagen. Generally, clinical effects are reversible. Pulmonary function tests are usually normal unless another disease process coexists. If the dusts are radiodense, macular collections may produce striking radiographic pictures that are so characteristic that patients with a history of significant exposure are easily diagnosed as having the condition that bears the name reflecting the nature of the dust. Examples of radiodense dusts include iron and iron oxides from welding or silver finishing (*siderosis*); tin oxide used in metallurgy, color stabilization, printing, and the manufacture of porcelain, glass, and fabric (*stannosis*); and barium sulfate used as a catalyst for organic reactions, drilling mud components, and electroplating (*baritosis*). Other metal dusts producing similar radiodense pictures include *cerium dioxide* and *antimony salts*.

Most of the inorganic dusts discussed thus far are associated with the production of either dust macules or interstitial fibrotic changes in the lung. Another set of dusts (Table 254-1), along with some of the dusts previously discussed, is associated with chronic mucous hypersecretion (chronic bronchitis), with or without reduction of expiratory flow rates. These conditions are caused by cigarette smoking, and any effort to attribute some component of the disease to occupational and environmental exposures must take cigarette smoking into account. Most studies suggest an additive effect of dust exposure and smoking. The pattern of the effect is similar to that of cigarette smoking, suggesting that small airway inflammation may be the initial site of pathologic response in those cases associated with the development of obstructive lung disease. Cigarette smoke is usually the more noxious agent, and dust effects may be discernible only in nonsmokers.

ORGANIC DUSTS

Some of the specific diseases associated with organic dusts are discussed in detail in the chapters on asthma (Chap. 252) and hypersensitivity pneumonitis (Chap. 253). Many of these diseases are named for the specific setting in which they are found, e.g., farmer's lung, malt worker's disease, or mushroom worker's disease. Occupational and other environmental exposures must be sought when these conditions are suspected. Often the temporal relation of symptoms to exposure furnishes the best evidence for the diagnosis. Three occupational groups are singled out for discussion because they represent the largest proportion of people affected by the diseases resulting from organic dusts.

Cotton Dust (Byssinosis) Estimates of the number of exposed persons in the United States vary, but probably over 800,000 persons are exposed occupationally to cotton, flax, or hemp in the production of yarns for cotton, linen, and rope making. Although this discussion focuses on cotton, the same syndrome -- albeit somewhat less severe -- has been reported in association with exposure to flax, hemp, and jute.

Exposure occurs throughout the manufacturing process but is most pronounced in those portions of the factory involved with the treatment of the cotton prior to spinning -- i.e., blowing, mixing, and carding (straightening of fibers). Attempts to control dust levels by use of exhaust hoods, general increases in ventilation, and wetting procedures in some settings have been highly successful. However, respiratory protective equipment appears to be required during certain operations to prevent workers from being exposed to levels of dust that exceed the current U.S. cotton dust standard.

Byssinosis is characterized clinically as occasional (early stage) and then regular (late stage) chest tightness toward the end of the first day of the workweek ("Monday chest tightness"). In epidemiologic studies, depending on the level of exposure via the carding room air, up to 80% of employees may show a significant drop in theirFEV_1over the course of a Monday shift.

Initially the symptoms do not recur on subsequent days of the week. However, in 10 to 25% of workers, the disease may be progressive, with chest tightness recurring or persisting throughout the workweek. After more than 10 years of exposure, workers with recurrent symptoms are more likely to have an obstructive pattern on pulmonary function testing. These higher grades of impairment are seen in workers exposed both to high levels of dust and for greater durations. There is an additive effect of cotton dust exposure plus cigarette smoking. The highest grades of impairment are generally seen in smokers.

Treatment in the early stages of the disease is directed toward reversing the bronchospasm with bronchodilators; however, the chest tightness appears to relate, at least in part, to histamine release, and antihistamines have been shown to lessen the anticipated fall in$FEV_1$the first day of the week. Clearly, reduction of dust exposure is of primary importance. All workers with persistent symptoms or significantly reduced levels of pulmonary function should be moved to areas of lower risk of exposure. Regular surveillance of pulmonary function in the industry has made it easier to identify affected persons. Persons with reduced pulmonary function, a personal history of respiratory allergy, and a history of continued cigarette smoking should be considered at increased risk of developing byssinosis in association with work in the cotton industry.

Grain Dust Although the exact number of workers at risk in the United States is not known, at least 500,000 people work in grain elevators, and over 2 million farmers are potentially exposed to grain dust. The presentation of disease in grain elevator employees or in workers in flour or feed mills is virtually identical to the characteristic findings in cigarette smokers, i.e., persistent cough, mucous hypersecretion, wheeze and dyspnea on exertion, and reduced$FEV_1$and FEV_1/FVCratio (Chap. 250).

Dust concentrations in grain elevators vary greatly but appear to be in excess of 10,000

ug/m3; approximately one-third of the particles, by weight, are in the respirable range. The effect of grain dust exposure is additive to that of cigarette smoking, with approximately 50% of workers who smoke having symptoms. Among nonsmoking grain elevator operators, approximately one-quarter have mucous hypersecretion, about five times the number that would be expected in unexposed nonsmokers. However, evidence of obstruction on pulmonary function studies is observed only in workers who smoke. It is not clear whether the reason is an enhancement of the cigarette smoking effect in exposed workers or a greater susceptibility of smokers to the effects of grain dust.

Farmer's Lung This condition results from exposure to moldy hay containing spores of thermophilic actinomycetes that produce a hypersensitivity pneumonitis (Chap. 253). There are few good population-based estimates of the frequency of occurrence of this condition in the United States. However, among farmers in Great Britain, the rate of disease ranges from approximately 10 to 50 per 1000. The prevalence of disease varies in association with rainfall, which determines the amount of fungal growth, and with differences in agricultural practices related to turning and stacking hay.

The patient with acute farmer's lung presents 4 to 8 h after exposure with fever, chills, malaise, cough, and dyspnea without wheezing. The history of exposure is obviously essential to distinguish this disease from influenza or pneumonia with similar symptoms. In the chronic form of the disease, the history of repeated attacks after similar exposure is important in differentiating this syndrome from other causes of patchy fibrosis (e.g., sarcoidosis).

A wide variety of other organic dusts are associated with the occurrence of hypersensitivity pneumonitis (Chap. 253). For those patients who present with hypersensitivity pneumonitis, specific and careful inquiry about occupations, hobbies, or other home environmental exposures will, in most cases, reveal the source of the etiologic agent.

ASSESSMENT OF DISABILITY

Significant reduction of dust levels in coal mines has resulted from federal legislation, enacted in the United States in 1969, that requires that respirable dust levels in underground mines be reduced to less than 2000 ug/m3. This same legislation authorizes payment to coal miners (or their survivors) totally disabled byCWP. The criteria for disability from CWP remain unclear and arbitrary. It is critical that physicians involved in occupational lung disease claim cases be aware of detailed exposure histories of their patients, in terms of both occupational exposures and other environmental exposures (cigarette smoking). To assess disability properly may require input not only from physicians but also from experts in ergonomics and vocational rehabilitation, lawyers, and employer and employee representatives.

Most commonly, the patient presents with asthma, and it is the physician's task to decide whether the asthma is occupation-induced or work-aggravated asthma. The distinction is important not only because of the implications for disability compensation but also because the longer one is exposed to an inciting agent, the worse the prognosis for recovery from occupation-induced asthma. The clinical evaluation of such

a patient requires adherence to a prescribed protocol that may include not only the components of the evaluation previously described but also rechallenge of the patient in a controlled setting or under a carefully monitored program in a work setting.

TOXIC CHEMICALS

Exposure to toxic chemicals affecting the lung generally involves gases and vapors. A common accident is one in which the victim is trapped in a confined space where the chemicals have accumulated to toxic levels. In addition to the specific toxic effects of the chemical, the victim will often sustain considerable anoxia, which can play a dominant role in determining whether the individual survives.

Table 254-2 lists a variety of toxic agents that can produce acute and sometimes life-threatening reactions in the lung. All these agents in sufficient concentrations have been demonstrated, at least in animal studies, to affect the lower airways and disrupt alveolar architecture, either acutely or as a result of chronic exposure. Some of these agents may be generated acutely in the environment. For example, when plastics burn, a number of compounds, including hydrogen cyanide and hydrochloric acid, may be formed and released.**The effects and treatment of exposure to these toxic gases are discussed in Chap. 391.*

Firefighters and fire victims are at risk of *smoke inhalation*, a numerically important cause of acute cardiorespiratory failure. Smoke inhalation kills more fire victims than does thermal injury. Carbon monoxide poisoning with resulting significant hypoxemia can be life-threatening (Chap. 396). Firefighters may inappropriately use the "blackness" of the smoke to indicate the degree of incomplete combustion and thus of carbon monoxide elevation. The use of synthetic materials (plastic, polyurethanes), which, when burned, may release a variety of other toxic agents, must be considered when evaluating smoke inhalation victims. Exposed victims may suffer some degree of lower respiratory tract inflammation, similar to that seen with exposure to other irritant gases (e.g., chlorine). Severe cases may include pulmonary edema.

Firefighters and victims also may be exposed to large quantities of particulate smoke. Significant long-term effects are not clearly associated with this particulate exposure except as related to the production of irritating effects on the upper airways; however, increased airway responsiveness in firefighters with repeated episodes of smoke inhalation has been demonstrated.

Some agents used in the manufacture of synthetic materials such as plastics, polyurethanes, and other polymers have resulted in some workers' being sensitized to extremely low levels of *isocyanates*, *aromatic amines*, or *aldehydes*. Repeated exposure to these agents causes some workers to develop chronic cough and sputum production, asthma, or episodes of low-grade fever and malaise.

Exposure occurs by an unusual route in *polymer fume fever*. Polymers, notably fluorocarbons, which at normal temperatures produce no reaction, may be transmitted from a worker's hands to his or her cigarettes. As the cigarette burns, the polymer is volatilized, and the inhaled agent causes a characteristic syndrome of fever, chills, malaise, and occasionally mild wheezing. The same scenario applies when workers are

exposed to heated polymers without cigarette use -- *meat wrappers' asthma*. A similar self-limited, influenza-like syndrome -- *metal fume fever* -- results from acute exposure to fumes or smoke of zinc, copper, magnesium, and other volatilized metals. The syndrome may begin several hours after work and resolves within 24 h, only to return on repeated exposure. A proper occupational history should make the diagnosis evident.

ENVIRONMENTAL RESPIRATORY CARCINOGENS

Historically, it has been the astute clinician who has recognized a higher incidence of malignant tumors associated with certain environmental exposures. When these observations are linked to an occupational setting, they must be pursued by epidemiologic studies of relatively large groups of both current and former workers. Often the concentration and/or exact nature of the substances involved in the putative exposures cannot be determined. Rarely, the possibility that a substance can play an etiologic role in cancer is supported by observing that a few cases of a very rare tumor in a particular group represent "an epidemic." Examples are nasal sinus and lung cancer in nickel workers, angiosarcomas of the liver in vinyl chloride workers, and adenocarcinomas of the nose in woodworkers.

Only in those few cases in which animal studies have been carried out can one confirm that a given suspected agent is really a carcinogen. For example, bis(chloromethyl)ether (BCME) has been shown to produce tumors in animals and oat cell cancer of the lung in humans. In this particular case, BCME, used as a chemical intermediary in the manufacture of a number of organic compounds, was found to produce tumors in animals at about the same time as the substance was introduced into industry.

In addition to asbestos exposures, other occupational exposures associated with either proven or suspected respiratory carcinogens include those to acrylonitrile, arsenic compounds, beryllium (animal studies only),BCME, chromium, polycyclic hydrocarbons (through coke oven emissions), iron oxide, isopropyl oil (nasal sinuses), mustard gas, the various ores used to produce pure nickel, talc (possible asbestos contamination in both mining and milling), vinyl chloride, welding materials, wood used in woodworking (nasal cancer only), and uranium. The occurrence of excess cancers in uranium miners raises the possibility that a large number of workers are at risk by virtue of exposure to similar radiation hazards. This number includes not only workers involved in processing uranium but also workers exposed in underground mining operations where radon daughters may be emitted from rock formations.

GENERAL ENVIRONMENTAL EXPOSURES

AIR POLLUTION

Dramatic and disastrous episodes of air pollution inversion have been documented in many industrialized centers in the world. Each of these episodes has been associated with excess acute mortality in the very old, the very young, and those with chronic cardiopulmonary diseases. The most dramatic event was the London fog of 1952, in which approximately 4000 excess deaths occurred over a 2-week period following 5 days of severe cold and dense fog. Similar episodes in the United States, although less dramatic in terms of total deaths, occurred in Donora, Pennsylvania, in 1948 and in New

York City in the 1960s. In these episodes, which were generally associated with cold temperature and air stagnation, patients with underlying cardiopulmonary disease were most severely affected.

In addition to significant excess mortality during these episodes, a large number of people required medical care for cardiorespiratory complaints. Subsequent follow-up studies failed to implicate these episodic disasters in the etiology of chronic respiratory disease in adults. On the other hand, many epidemiologic studies of both international and regional differences in the prevalences of chronic respiratory disease suggest that long-term exposures in polluted areas in the early to middle part of the twentieth century were associated with excess chronic respiratory disease.

In 1970, the U.S. government established air quality standards for several pollutants believed to be responsible for excess cardiorespiratory diseases. Primary standards regulated by the Environmental Protection Agency (EPA) designed to protect the public health with an adequate margin of safety exist for sulfur dioxide, particulates <10 um in size, nitrogen dioxide, ozone, lead, and carbon monoxide. Standards for each of these pollutants are updated regularly through an extensive review process conducted by the EPA. In 1997, a new standard was added for particles less than 2.5 um; however, the standard does not become effective until year 2002.

Pollutants are generated from both stationary sources (power plants and industrial complexes) and mobile sources (automobiles), and none of the pollutants occurs in isolation. Thus, except for the change in carboxyhemoglobin from carbon monoxide exposure, it becomes extremely difficult to relate any specific health effect to any single pollutant. Furthermore, pollutants may be changed by chemical reactions after being emitted. For example, reducing agents, such as sulfur dioxide and particulate matter from a power plant stack, may react in air to produce acid sulfates and aerosols, the precursors of acid rain, which can be transported long distances in the atmosphere. Oxidizing substances, such as oxides of nitrogen and oxidants from automobile exhaust, may react with sunlight to produce ozone. Although originally a problem confined to the southwestern part of the United States, in recent years, at least during the summertime, elevated ozone and acid aerosol levels have been documented throughout the United States. Both acute and chronic effects of these exposures are currently under investigation.

The symptoms and diseases associated with air pollution are the same as the nononcogenic conditions commonly associated with cigarette smoking. In addition, respiratory illness in early childhood has been associated with chronic exposure to only modestly elevated levels of SO_2 and respirable particles. Recent population-based studies comparing cities that have relatively high levels of particulate exposures with less polluted communities suggest excess morbidity and mortality from cardiorespiratory conditions in long-term residents of the former communities. This finding, in part, has led to greater emphasis on publicizing pollution alert levels. One can only advise individuals with significant cardiopulmonary impairment to stay indoors during periods when pollution exceeds current standards.

INDOOR EXPOSURE

Because of increased concern about energy costs, efforts to become energy efficient have led to reduced air-exchange rates in indoor environments. The unintentional effect of these efforts has been to increase exposures to a variety of air contaminants heretofore not considered important.

Until relatively recently, little attention was given to the effects of *passive cigarette smoking* (Chap. 390). Several studies have shown that the respirable particulate load in any household is directly proportional to the number of cigarette smokers living in the home. Increases in prevalence of respiratory illnesses and reduced levels of pulmonary function measured with simple spirometry have been found in children of smoking parents in a number of studies.

Evidence from numerous case-control and cohort studies shows modest excess disease associations for cardiopulmonary diseases and lung cancer. Because most of these excess relative risks appear to be below 50%, it is virtually impossible for any one of the studies to be considered definitive. Thus, the techniques of meta-analysis have been used effectively to combine data from the best of these studies. The most recent meta-analyses for lung cancer, cardiac disease, and respiratory disease in terms of excess mortality suggest an approximately 25% increase for each condition, even after adjustment for major potential confounders. According to measures of plasma cotinine, a metabolite of nicotine, a nonsmoker living with a smoker is exposed to approximately 1% of the level of tobacco smoke to which a smoker of 20 cigarettes a day is exposed. In spite of some prominent detractors, these combined relative risks appear to be consistent with the estimated exposure levels and suggest a consensus that the associations are causal.

Radon gas is believed to be a risk factor for lung cancer. The main radon product (radon 222) is a gas that results from the decay series of uranium 238, with the immediate precursor being radium 226. The amount of radium in earth materials determines how much radon gas will be emitted. Outdoors, the concentrations are trivial. Indoors, levels are dependent on the ventilation rate and the size of the space into which the gas is emitted. Levels associated with excess lung cancer risk may be present in as many as 10% of the houses in the United States. When smokers reside in the household, the problem is potentially greater, since the molecular size of radon particles allows them to readily attach to smoke particles that are inhaled. Fortunately, technology is available for assessing and reducing the level of exposure.

Other indoor exposures associated with an increased risk of atopy and asthma include those to such specific recognized putative biologic agents as cockroach antigen, dust mites, and pet danders. Other indoor chemical agents include formaldehyde, perfumes, and latex particles. Of recent interest are the nonspecific responses associated with "tight-building syndrome," in which no particular agent has been implicated; the affected individuals suffer from a wide variety of complaints, including respiratory symptoms, that are relieved only by avoiding exposure in the building in question. The degree to which "smells" or other sensory stimuli are involved in the triggering of potentially incapacitating psychological or physical responses has yet to be determined, and the long-term consequences of such environmental exposures are as yet unknown.

PORTAL OF ENTRY

The lung is a primary point of entry into the body for a number of toxic agents that affect other organ systems. For example, the lung is a route of entry for benzene (bone marrow), carbon disulfide (cardiovascular and nervous systems), cadmium (kidney), and metallic mercury (kidney, central nervous system). Thus, in any disease state of obscure origin, it is important to consider the possibility of inhaled environmental agents. Such consideration can sometimes furnish the clue needed to identify a specific external cause for a disorder that might otherwise be labeled "idiopathic."

(Bibliography omitted in Palm version)

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255. PNEUMONIA, INCLUDING NECROTIZING PULMONARY INFECTIONS (LUNG ABSCESS) - *Matthew E. Levison*

Pneumonia is an infection of the pulmonary parenchyma that can be caused by various bacterial species, including mycoplasmas, chlamydiae, and rickettsiae; viruses; fungi; and parasites (Table 255-1). Thus pneumonia is not a single disease but a group of specific infections, each with a different epidemiology, pathogenesis, clinical presentation, and clinical course. Identification of the etiologic microorganism is of primary importance, since this is the key to appropriate antimicrobial therapy. However, because of the serious nature of the infection, antimicrobial therapy generally needs to be started immediately, often before laboratory confirmation of the causative agent. The specific microbial etiology remains elusive in more than one-third of cases -- e.g., when no sputum is available for examination, blood cultures are sterile, and there is no pleural fluid. Serologic confirmation requires weeks because of the late formation of specific antibody.

Thus initial antimicrobial therapy is often empirical and is based on the setting in which the infection was acquired, the clinical presentation, patterns of abnormality on chest radiography, results of staining of sputum or other infected body fluids, and current patterns of susceptibility of the suspected pathogens to antimicrobial agents. After the etiologic agent is identified, specific antimicrobial therapy can be chosen.

DEFENSE MECHANISMS

The lung is a complex structure composed of aggregates of units that are formed by the progressive branching of the airways. Approximately 80% of the cells lining the central airways are ciliated, pseudostratified, columnar epithelial cells; the percentage decreases in the peripheral airways. Each ciliated cell contains about 200 cilia that beat in coordinated waves ~1000 times per minute, with a fast forward stroke and a slower backward recovery. Ciliary motion is also coordinated between adjacent cells so that each wave is propagated toward the oropharynx. The cilia are covered by a liquid film that is ~5 to 10 um thick and is composed of two layers. The outer, or gel, layer is viscous and traps deposited particles. The cilia beat in the less viscous inner, or sol, layer. During the forward stroke, the tips of the cilia just touch the viscous gel and propel it toward the oropharynx. During recovery, the cilia move entirely within the low-resistance sol layer. Ciliated cells are interspersed with mucus-secreting cells in the trachea and bronchi but not in the bronchioles.

The alveolar walls, from blood to air, consist of the endothelium that lines the network of anastomotic capillaries, the capillary basement membrane, the interstitial tissue, the alveolar basement membrane, the alveolar lining epithelial cells (which are either flattened type I pneumocytes that cover 95% of the alveolar surface or rounded, granular, surfactant-producing type II pneumocytes), and epithelial lining fluid. The epithelial lining fluid contains surfactant, fibronectin, and immunoglobulin, which may opsonize or -- in the presence of complement -- lyse microbial pathogens deposited on the alveolar surface. Loosely attached to the lining cells or lying free within the lumen are the alveolar macrophages, lymphocytes, and a few polymorphonuclear leukocytes.

The lower respiratory tract is normally sterile, despite being adjacent to enormous

numbers of microorganisms that reside in the oropharynx and being exposed to environmental microorganisms in inhaled air. This sterility is the result of efficient filtering and clearance mechanisms.

Infectious particles deposited on the squamous epithelium of distal nasal surfaces normally are removed by sneezing, while those deposited on the more proximal ciliated surfaces are swept posteriorly in the mucus lining into the nasopharynx, where they are swallowed or expectorated. Reflex closure of the glottis and cough protect the lower respiratory tract. Those particles deposited on the tracheobronchial surface are swept by ciliary motion toward the oropharynx. Infectious particles that bypass defenses in the airways and are deposited on the alveolar surface are cleared by phagocytic cells and humoral factors. Alveolar macrophages are the major phagocytes in the lower respiratory tract. Some phagocytosed microorganisms are killed by the phagocyte's oxygen-dependent systems, lysosomal enzymes, and cationic proteins. Other microorganisms can evade microbicidal mechanisms and persist within the macrophage. For example, *Mycobacterium tuberculosis* persists within the lysosome, while *Legionella* resides within intracellular inclusions that fail to fuse with lysosomes. Intracellular pathogens can then be transported to the ciliated surfaces and into the oropharynx or via the lymphatics to regional lymph nodes. The alveolar macrophages process and present microbial antigens to the lymphocyte and also secrete cytokines (e.g., tumor necrosis factor and interleukin 1) that modulate the immune process in T and B lymphocytes. Cytokines facilitate the generation of an inflammatory response, activate alveolar macrophages, and recruit additional phagocytes and other immunologic factors from plasma. The inflammatory exudate is responsible for many of the local signs of pulmonary consolidation and for the systemic manifestations of pneumonia, such as fever, chills, myalgias, and malaise.

TRANSMISSION

Microbial pathogens may enter the lung by one of several routes.

Aspiration of Organisms That Colonize the Oropharynx Most pulmonary pathogens originate in the oropharyngeal flora. Aspiration of these pathogens is the most common mechanism for the production of pneumonia. At various times during the year, healthy individuals transiently carry common pulmonary pathogens in the nasopharynx; these pathogens include *Streptococcus pneumoniae*, *S. pyogenes*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The sources of anaerobic pulmonary pathogens, such as *Porphyromonas gingivalis*, *Prevotella melaninogenica*, *Fusobacterium nucleatum*, *Actinomyces* spp., spirochetes, and anaerobic streptococci, are the gingival crevice and dental plaque, which contain more than 10^{11}colony-forming units (CFU) of microorganisms per gram. The frequency of aerobic gram-negative bacillary colonization of the oropharyngeal mucosa, which is unusual in healthy persons (<2%), increases with hospitalization, worsening debility, severe underlying illness, alcoholism, diabetes, and advanced age. This change may be a consequence of increased salivary proteolytic activity, which destroys fibronectin, a glycoprotein coating the surface of the mucosa. Fibronectin is the receptor for the normal gram-positive flora of the oropharynx. Loss of fibronectin exposes the receptors for aerobic gram-negative bacilli on the epithelial cell surface. The source of aerobic gram-negative bacilli may be the patient's own stomach (which can become colonized with these organisms as the

result of an increase in gastric pH with atrophic gastritis or after the use of H_2-blocking agents or antacids), contaminated respiratory equipment, hands of health care workers, or contaminated food and water. Nasogastric tubes can facilitate the transfer of gastric bacteria to the pharynx.

About 50% of healthy adults aspirate oropharyngeal secretions into the lower respiratory tract during sleep. Aspiration occurs more frequently and may be more pronounced in individuals with an impaired level of consciousness (e.g., alcoholics; drug abusers; and patients who have had seizures, strokes, or general anesthesia), neurologic dysfunction of the oropharynx, and swallowing disorders or mechanical impediments (e.g., nasogastric or endotracheal tubes). Pneumonia due to anaerobes is an especially likely outcome if the aspirated material is large in volume or contains virulent components of the anaerobic microbial flora or foreign bodies, such as aspirated food or necrotic tissue. Impairment of the cough reflex increases the risk of pneumonia, as does mucociliary or alveolar macrophage dysfunction.

Inhalation of Infectious Aerosols Deposition of inhaled particles within the respiratory tract is determined primarily by particle size. Particles>10 um in diameter are deposited mostly in the nose and upper airways. Particles <5 um in diameter (also called *airborne droplet nuclei*) and containing one or perhaps two microorganisms fail to settle out by gravity but rather remain suspended in the atmosphere for long periods unless removed by ventilation or by filtration in the lungs of the individual breathing the contaminated air. Transmission of an infectious agent in the form of an aerosol is particularly efficient. These infectious aerosols are small enough to bypass host defenses in the upper respiratory tract and airways. A greater percentage of particles are deposited in small bronchioles and alveoli as particle size decreases below 5 um. One inhaled particle of appropriate size may be sufficient to reach the alveolus and initiate infection. The etiologies of pneumonia typically acquired by inhalation of infectious aerosols include tuberculosis, influenza, legionellosis, psittacosis, histoplasmosis, Q fever, and hantavirus pulmonary syndrome (HPS).

Hematogenous Dissemination from an Extrapulmonary Site Infection, usually with *Staphylococcus aureus*, disseminates hematogenously to the lungs in patients (such as intravenous drug users) who have either right- or left-sided bacterial endocarditis and in patients with intravenous catheter infections. *Fusobacterium* infections of the retropharyngeal tissues (Lemierre's syndrome -- i.e., retropharyngeal abscess and jugular venous thrombophlebitis) also disseminate hematogenously to the lungs.

Direct Inoculation and Contiguous Spread Two additional routes of transmission of bacteria to the lungs are direct inoculation (as a result of either tracheal intubation or stab wounds to the chest) and contiguous spread from an adjacent site of infection.

PATHOLOGY

The pneumonic process may involve primarily the interstitium or the alveoli. Involvement of an entire lobe is called *lobar pneumonia*. When the process is restricted to alveoli contiguous to bronchi, it is called *bronchopneumonia*. Confluent bronchopneumonia may be indistinguishable from lobar pneumonia. Cavities develop when necrotic lung tissue is discharged into communicating airways, resulting in either necrotizing

pneumonia (multiple small cavities, each <2 cm in diameter, in one or more bronchopulmonary segments or lobes) or lung abscess (one or more cavities>2 cm in diameter). The classification of pneumonia is best based upon the causative microorganism rather than upon these anatomic characteristics (the criteria used in the past).

EPIDEMIOLOGY

The patient's living circumstances, occupation, travel history, pet or animal exposure history, and contacts with other ill individuals as well as the physician's knowledge of the epidemic curve of community outbreaks provide clues to the microbial etiology of a given case of pneumonia (Table 255-1). The relative frequency of various pulmonary pathogens varies with the setting in which the infection was acquired -- e.g., community, nursing home, or hospital. In patients hospitalized with community-acquired pneumonia, the most frequent pathogens are *S. pneumoniae*, *H. influenzae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*. *C. pneumoniae* is often found in association with other pathogens, including *S. pneumoniae*, and the associated pathogen appears to influence the course of the pneumonia. *M. pneumoniae*, which usually causes mild illness, is common among outpatients with community-acquired pneumonia, but may also be an underappreciated cause in all age groups of severe pneumonia that requires hospitalization. In contrast, enteric aerobic gram-negative bacilli and *Pseudomonas aeruginosa*, uncommon causes of community-acquired pneumonia, are estimated to account for>50% of cases of hospital-acquired pneumonia, while *S. aureus* is responsible for >10%. The relative frequencies of pathogens in pneumonia acquired in nursing homes fall somewhere between those of community- and hospital-acquired pneumonia. Enteric aerobic gram-negative bacilli and *P. aeruginosa* are more common among nursing home residents than among patients who acquire pneumonia in noninstitutional settings.

The season of the year and the geographic location are other predictors of etiology. The frequency of influenza virus as a cause of both community-acquired and institutionally acquired pneumonia increases during the winter months. Moreover, influenza virus infection causes an increase in the frequency of secondary bacterial pneumonia due to *S. pneumoniae*, *S. aureus*, and *H. influenzae*. Outbreaks of influenza in a community tend to be explosive and widespread, with many secondary cases resulting from the short incubation period of several days and the high degree of communicability. *Legionella* colonizes hot-water storage systems that provide favorable conditions for its proliferation, such as warm temperature, stagnation, and sediment accumulation. Acquisition of *Legionella* pneumonia requires exposure to aerosols generated from these contaminated water supplies -- e.g., during an overnight stay in a hotel with a faulty air-handling system or after repair of domestic plumbing in buildings with contaminated water supplies. Legionellosis also occurs in explosive outbreaks when large numbers of susceptible people are exposed to an infectious aerosol; however, no secondary cases occur because of the low level of communicability of *L. pneumophila*. *Mycoplasma* causes outbreaks, usually in relatively closed populations such as those at military bases, at colleges, or in households; however, because of its long incubation period (2 to 3 weeks) and its relatively low degree of communicability, *Mycoplasma* infection moves through the community slowly, affecting another person as the first is recovering. In communities where infection with HIV type 1 is endemic, *Pneumocystis*

carinii and *M. tuberculosis* are more prominent causes of community-acquired pneumonia. *Chlamydia psittaci* produces illness in bird handlers. Histoplasmosis, blastomycosis, and coccidioidomycosis are causes of pneumonia that have specific geographic distributions.

HPSis a newly described, frequently fatal disease caused by one of several hantaviruses. Most cases in the United States have been reported from the Four Corners area (New Mexico, Arizona, Utah, and Colorado), where the pathogen is the Sin Nombre virus. The primary hosts are rodents, which apparently remain healthy but excrete the virus in urine, feces, and saliva. Hantavirus infection is acquired by inhalation of infectious aerosols when rodent nests are disturbed by human domestic, occupational, or recreational activities. The appearance of HPS in the southwestern United States is thought to have occurred because of increased rainfall in the region, which increased the rodent food supply and thus the rodent population. No person-to-person transmission of HPS is thought to have taken place, except perhaps in an outbreak in southern Argentina in 1996.

AGE AND COMORBIDITY

Age is an important predictor of the infecting agent in pneumonia. *Chlamydia trachomatis* and respiratory syncytial virus are common among infants< 6 months of age; *H. influenzae* among children 6 months to 5 years of age; *M. pneumoniae*, *C. pneumoniae,* and hantavirus among young adults; *H. influenzae* and *M. catarrhalis* among elderly individuals with chronic lung disease; and *L. pneumophila* among elderly persons, smokers, and persons with compromised cell-mediated immunity (e.g., transplant recipients), renal or hepatic failure, diabetes, or systemic malignancy.

Oral anaerobes, frequently in combination with aerobic bacterial components of the human flora (e.g., viridans streptococci), are causes of community-acquired pneumonia and anaerobic lung abscess in patients who are prone to aspiration. Edentulous persons, who have lower numbers of oral anaerobes, are less likely to develop pneumonia due to anaerobes. When the etiology of community-acquired pneumonia in unselected hospitalized patients has been studied by methods that entail strict anaerobic bacteriology and that avoid contamination of lower respiratory tract secretions by the oral flora, anaerobic bacteria have been found to account for as many as 20 to 30% of cases. In hospital-acquired pneumonia, anaerobes are the pathogens -- with or without aerobic copathogens -- in about one-third of cases. However, the aerobic copathogens in hospital-acquired pneumonia are frequently virulent microorganisms in their own right (e.g., enteric aerobic gram-negative bacilli, *P. aeruginosa*, and *S. aureus*).

The patient's underlying disease may be characterized by specific immunologic or inflammatory defects that predispose to pneumonia due to specific pathogens (Table 255-2). For example, immunoglobulin deficiencies -- especially those involving IgG subtypes 2 and 4, which are important in the immune response to encapsulated organisms (e.g., *S. pneumoniae* and *H. influenzae*) -- may be associated with recurrent sinopulmonary infections. Immunoglobulin deficiencies may be inherited, or they may be acquired (i.e., as a result of either decreased production, as in lymphoproliferative malignancies, or excessive protein loss, as in nephrosis or protein-losing enteropathy).

Inherited immunoglobulin deficiencies may be global or selective. Patients with recurrent sinopulmonary infections and a selective deficiency of IgG2 and/or IgG4 may have a total plasma IgG level within the normal range, as these particular IgG subtypes constitute only 25% of total IgG. HIV-infected patients may also exhibit ineffective antibody formation, which predisposes to infection with these encapsulated bacteria. Severe neutropenia (<500 neutrophils/uL) increases the risk of infections due to *P. aeruginosa*, Enterobacteriaceae, *S. aureus*, and (if neutropenia is prolonged) *Aspergillus*. The risk is unusually high for infections due to *M. tuberculosis* among HIV-infected patients with circulating CD4+ lymphocyte counts of<500/uL; for infections due to *P. carinii*, *Histoplasma capsulatum*, and *Cryptococcus neoformans* among those with CD4+ counts of<200/uL; and for infections due to *M. avium-intracellulare* and cytomegalovirus among those with counts of<50/uL. Long-term glucocorticoid therapy increases the risk of tuberculosis and nocardiosis.

CLINICAL MANIFESTATIONS

Community-Acquired Pneumonia Community-acquired pneumonia has traditionally been thought to present as either of two syndromes: the typical presentation or the atypical presentation. Although current data suggest that these two syndromes may be less distinct than was once thought, the characteristics of the clinical presentation may nevertheless have some diagnostic value.

The "typical" pneumonia syndrome is characterized by the sudden onset of fever, cough productive of purulent sputum, shortness of breath, and (in some cases) pleuritic chest pain; signs of pulmonary consolidation (dullness, increased fremitus, egophony, bronchial breath sounds, and rales) may be found on physical examination in areas of radiographic abnormality. The typical pneumonia syndrome is usually caused by the most common bacterial pathogen in community-acquired pneumonia, *S. pneumoniae*, but can also be due to other bacterial pathogens, such as *H. influenzae* and mixed anaerobic and aerobic components of the oral flora.

The "atypical" pneumonia syndrome is characterized by a more gradual onset, a dry cough, shortness of breath, a prominence of extrapulmonary symptoms (such as headache, myalgias, fatigue, sore throat, nausea, vomiting, and diarrhea), and abnormalities on chest radiographs despite minimal signs of pulmonary involvement (other than rales) on physical examination. Atypical pneumonia is classically produced by *M. pneumoniae* but can also be caused by *L. pneumophila*, *C. pneumoniae*, oral anaerobes, and *P. carinii* as well as by *S. pneumoniae* and the less frequently encountered pathogens *C. psittaci*, *Coxiella burnetii*, *Francisella tularensis*, *H. capsulatum*, and *Coccidioides immitis*. *Mycoplasma* pneumonia (Chap. 178) may be complicated by erythema multiforme, hemolytic anemia, bullous myringitis, encephalitis, and transverse myelitis. *Legionella* pneumonia (Chap. 151) is frequently associated with deterioration in mental status, renal and hepatic abnormalities, and marked hyponatremia; pneumonia due to *H. capsulatum* (Chap. 201) or *C. immitis* (Chap. 202) is often accompanied by erythema nodosum. In *C. pneumoniae* pneumonia (Chap. 179), sore throat, hoarseness, and wheezing are relatively common. The atypical pneumonia syndrome in patients whose behavioral history places them at risk of HIV infection suggests *Pneumocystis* infection. These patients may have concurrent infections caused by other opportunistic pathogens, such as pulmonary (and frequently

extrapulmonary) tuberculosis, oral thrush due to *Candida albicans*, or extensive perineal ulcers due to herpes simplex virus.

Certain viruses also produce pneumonia that is usually characterized by an atypical presentation -- i.e., chills, fever, shortness of breath, dry nonproductive cough, and predominance of extrapulmonary symptoms. Primary viral pneumonia can be caused by influenza virus (usually as part of a community outbreak in winter), by respiratory syncytial virus (in children and immunosuppressed individuals), by measles or varicella-zoster virus (accompanied by the characteristic rash), and by cytomegalovirus (in patients immunocompromised by HIV infection or by therapy given in association with organ transplantation). Hantavirus causes an initial nonspecific febrile prodrome, after which the patient develops rapidly progressive respiratory failure and diffuse pulmonary infiltrates on chest radiographs as a result of exudation into the pulmonary interstitium and alveoli, with thrombocytopenia, neutrophilic leukocytosis, circulating immunoblasts, and laboratory evidence of hemoconcentration. In addition, influenza and measles can predispose to secondary bacterial pneumonia as a result of the destruction of the mucociliary barrier of the airways. Secondary bacterial infection may either follow the viral infection without interruption or be separated from the viral infection by several days of transient relief of symptoms. Bacterial infection may be heralded by sudden worsening of the patient's clinical condition, with persisting or renewed chills, fever, and cough productive of purulent sputum, possibly accompanied by pleuritic chest pain.

Patients with hematogenous *S. aureus* pneumonia may present with fever and dyspnea only. In these cases the inflammatory response is initially confined to the pulmonary interstitium. Cough, sputum production, and signs of pulmonary consolidation develop only after the infection extends into the bronchi. These patients are usually gravely ill, with intravascular infection as well as pneumonia, and may have signs of endocarditis (Chap. 126).

Nocardiosis (Chap. 165) is frequently complicated by metastasis of lesions to the skin and central nervous system. Signs of pulmonary consolidation, cough, and sputum production may be lacking in patients who are unable to mount an inflammatory response, such as those with agranulocytosis. The major manifestations in these patients may be limited to fever, tachypnea, agitation, and altered mental status. Elderly or severely ill patients may fail to develop fever.

Tuberculosis also produces an atypical presentation that is characterized by fever, night sweats, cough, and shortness of breath and sometimes by pleuritic chest pain and blood-streaked sputum. Several weeks usually elapse before the patient seeks medical attention because of the gradual worsening of these symptoms, by which time he or she will have lost considerable weight.

Nosocomial Pneumonia Patients with nosocomial pneumonia often pose a diagnostic challenge. The differential diagnosis of acute respiratory disease in critically ill, hospitalized patients is diverse and includes noninfectious entities, such as congestive heart failure, acute respiratory distress syndrome, preexisting lung disease, atelectasis, and oxygen- or drug-related toxicities, that may be difficult to distinguish clinically or radiologically from pneumonia. The usual criteria for nosocomial pneumonia, which include new or progressive pulmonary infiltrates, purulent tracheobronchial secretions,

fever, and leukocytosis, are frequently unreliable in these patients, who often have preexisting pulmonary disease, endotracheal tubes that irritate the tracheal mucosa and may elicit an inflammatory exudate in respiratory secretions, or multiple other problems likely to produce fever and leukocytosis. Patients with nosocomial pneumonia complicating an underlying illness associated with significant neutropenia often have no purulent respiratory tract secretions or pulmonary infiltrates, and patients with nosocomial pneumonia complicating uremia or cirrhosis often remain afebrile. In addition, the patients at greatest risk for nosocomial pneumonia are most likely to be heavily colonized with potential pulmonary pathogens in the oropharyngeal or tracheobronchial mucosa; thus the presence of these organisms in gram-stained preparations or cultures of respiratory tract secretions does not necessarily confirm the diagnosis of pneumonia.

Aspiration Pneumonia and Anaerobic Lung Abscess Aspiration of a sufficient volume of gastric acid produces a chemical pneumonitis characterized by acute dyspnea and wheezing with hypoxemia and infiltrates on chest radiographs in one or both lower lobes. Clinical findings following aspiration of particulate matter depend on the extent of endobronchial obstruction and range from acute apnea to persistent cough with or without recurrent infection. Although the aspiration of oral anaerobes can initially lead to an infiltrative process, it ultimately results in putrid sputum, tissue necrosis, and pulmonary cavities. In about three-quarters of cases, the clinical course of an abscess of anaerobic polymicrobial etiology is indolent and mimics that of pulmonary tuberculosis, with cough, shortness of breath, chills, fever, night sweats, weight loss, pleuritic chest pain, and blood-streaked sputum lasting for several weeks or more. In other patients the disease may present more acutely. Patients with anaerobic abscesses are usually prone to aspiration of oropharyngeal contents and have periodontal disease. One genus of oral anaerobes, *Actinomyces*, produces a chronic fibrotic necrotizing process that crosses tissue planes and may involve the pleural space, ribs, vertebrae, and subcutaneous tissue, with eventual discharge of sulfur granules (macroscopic bacterial masses) through the skin (empyema necessitatis).

DIAGNOSIS

Radiography Chest radiography is more sensitive than physical examination for detection of pulmonary infiltrates. Indeed, *P. carinii* pneumonia (PCP) is the only relatively common form of pneumonia associated with false-negative chest radiographs; up to 30% of patients with PCP have false-negative results. Chest radiographs can confirm the presence and location of the pulmonary infiltrate; assess the extent of the pulmonary infection; detect pleural involvement, pulmonary cavitation, or hilar lymphadenopathy; and gauge the response to antimicrobial therapy. However, chest radiographs may be normal when the patient is unable to mount an inflammatory response (e.g., in agranulocytosis) or is in the early stage of an infiltrative process (e.g., in hematogenous *S. aureus* pneumonia or PCP associated with AIDS). High-resolution computed tomography of the lungs can improve the accuracy of diagnosis of pneumonia, especially when the process involves lung obscured by the diaphragm, liver, ribs and clavicles, or heart.

The anatomic localization of the inflammatory process, as visualized in chest radiographs, occasionally has diagnostic implications. Most pulmonary pathogens

produce focal lesions. A multicentric distribution suggests hematogenous infection, in which case the remote location of the primary infection (e.g., endocarditis or thrombophlebitis) should be sought. Hematogenous pneumonia, which results from septic embolization in patients with thrombophlebitis or right-sided endocarditis and from bacteremia in patients with left-sided endocarditis, appears on the chest radiograph as multiple areas of pulmonary infiltration that subsequently may cavitate. A diffuse distribution suggests the involvement of *P. carinii*, cytomegalovirus, hantavirus, measles virus, or herpes zoster virus (with pneumonia due to the last two pathogens diagnosed by the characteristic accompanying rash). Pleurisy and hilar nodal enlargement are unusual with PCPand cytomegalovirus pneumonia; their presence suggests another etiology. Diffuse lesions in immunocompromised patients also suggest legionellosis, tuberculosis, histoplasmosis, *Mycoplasma* infection, or disseminated strongyloidiasis.

Oral anaerobes, *S. aureus, S. pneumoniae* serotype III, aerobic gram-negative bacilli, *M. tuberculosis*, and fungi as well as certain noninfectious conditions can produce tissue necrosis and pulmonary cavities (Table 255-3). In contrast, *H. influenzae*, *M. pneumoniae*, viruses, and most other serotypes of *S. pneumoniae* almost never cause cavities. Apical disease, with or without cavities, suggests reactivation tuberculosis. Anaerobic abscesses are located in dependent, poorly ventilated, and poorly draining bronchopulmonary segments and characteristically have air-fluid levels, unlike the well-ventilated, well-drained upper-lobe cavities caused by *M. tuberculosis*, an obligate aerobe. Air-fluid levels may also be present in cavities due to pulmonary necrosis of other infectious etiologies, such as *S. aureus* and aerobic gram-negative bacilli. *Mucor* and *Aspergillus* invade blood vessels and cause pleural-based, wedge-shaped areas of pulmonary infarction; these infarcts may subsequently cavitate.

In the patient with an uncomplicated course, chest radiographs need not be repeated before discharge, since the resolution of infiltrates may take up to 6 weeks after initial presentation. However, patients who do not respond clinically, who have a pleural effusion on admission, who may have postobstructive pneumonia, or who are infected with certain pathogens (e.g., *S. aureus*, aerobic gram-negative bacilli, or oral anaerobes) need more intensive surveillance. At times, computed tomography may be especially helpful in distinguishing different processes -- e.g., pleural effusion versus underlying pulmonary consolidation, hilar adenopathy versus pulmonary mass, and pulmonary abscess versus empyema with an air-fluid level.

Sputum Examination Examination of the sputum remains the mainstay of the evaluation of a patient with acute bacterial pneumonia. Unfortunately, expectorated material is frequently contaminated by potentially pathogenic bacteria that colonize the upper respiratory tract (and sometimes the lower respiratory tract) without actually causing disease. This contamination reduces the diagnostic specificity of any lower respiratory tract specimen. In addition, it has been estimated that the usual laboratory processing methods detect the pulmonary pathogen in fewer than 50% of expectorated sputum samples from patients with bacteremic *S. pneumoniae* pneumonia. This low sensitivity may be due to misidentification of the a-hemolytic colonies of *S. pneumoniae* as nonpathogenic a-hemolytic streptococci ("normal flora"), overgrowth of the cultures by hardier colonizing organisms, or loss of more fastidious organisms due to slow transport or improper processing. In addition, certain common pulmonary pathogens, such as anaerobes, mycoplasmas, chlamydiae, *Pneumocystis*, mycobacteria, fungi, and

legionellae, cannot be cultured by routine methods.

Since expectorated material is routinely contaminated by oral anaerobes, the diagnosis of anaerobic pulmonary infection is frequently inferred. Confirmation of such a diagnosis requires the culture of anaerobes from pulmonary secretions that are uncontaminated by oropharyngeal secretions, which in turn requires the collection of pulmonary secretions by special techniques, such as transtracheal aspiration (TTA), transthoracic lung puncture, and protected brush via bronchoscopy. These procedures are invasive and are usually not used unless the patient fails to respond to empirical therapy.

Gram's staining of sputum specimens, screened initially under low-power magnification (10´ objective and 10´ eyepiece) to determine the degree of contamination with squamous epithelial cells, is of utmost diagnostic importance. In patients with the typical pneumonia syndrome who produce purulent sputum, the sensitivity and specificity of Gram's staining of sputum minimally contaminated by upper respiratory tract secretions (>25 polymorphonuclear leukocytes and<10 epithelial cells per low-power field) in identifying the pathogen as *S. pneumoniae* are 62 and 85%, respectively. Gram's staining in this case is more specific and probably more sensitive than the accompanying sputum culture. The finding of mixed flora on Gram's staining of an uncontaminated sputum specimen suggests an anaerobic infection. Acid-fast staining of sputum should be undertaken when mycobacterial infection is suspected. Examination by an experienced pathologist of Giemsa-stained expectorated respiratory secretions from patients with AIDS has given satisfactory results in the diagnosis ofPCP. The sensitivity of sputum examination is enhanced by the use of monoclonal antibodies to *Pneumocystis* and is diminished by prior prophylactic use of inhaled pentamidine. Blastomycosis can be diagnosed by the examination of wet preparations of sputum. Sputum stained directly with fluorescent antibody can be examined for *Legionella*, but this test yields false-negative results relatively often. Thus sputum should also be cultured for *Legionella* on special media.

Expectorated sputum usually is easily collected from patients with a vigorous cough but may be scant in patients with an atypical syndrome, in the elderly, and in persons with altered mental status. If the patient is not producing sputum and can cooperate, respiratory secretions should be induced with ultrasonic nebulization of 3% saline. An attempt to obtain lower respiratory secretions by passage of a catheter through the nose or mouth rarely achieves the desired results in an alert patient and is discouraged; usually the catheter can be found coiled in the oropharynx.

In some cases that do not require the patient's hospitalization (see "Decision to Hospitalize," below), an accurate microbial diagnosis may not be crucial, and empirical therapy can be started on the basis of clinical and epidemiologic evidence alone. This approach may also be appropriate for hospitalized patients who are not severely ill and who are unable to produce an induced sputum specimen. Use of invasive procedures to establish a microbial diagnosis carries risks that must be weighed against potential benefits. However, the decision to initiate empirical therapy without an evaluation of induced sputum should be undertaken with caution and, in the case of hospitalized patients, should always be accompanied by the culture of several blood samples. The ability to understand the cause of a poor response to empirical antimicrobial therapy (Table 255-4) may be compromised by the lack of initial sputum and blood cultures.

Establishing a specific microbial etiology in the individual patient is important, for it allows institution of specific pathogen-directed antimicrobial therapy and reduces the use of broad-spectrum combination regimens to cover multiple possible pathogens. Use of a single narrow-spectrum antimicrobial agent exposes the patient to fewer potential adverse drug reactions and reduces the pressure for selection of antimicrobial resistance. Emergence of antimicrobial resistance is a type of adverse drug reaction unlike others, because it is "contagious." In addition, establishing a microbial diagnosis can help define local community outbreaks and antimicrobial resistance patterns.

Invasive Procedures The sensitivities and specificities of the invasive procedures described below for obtaining pulmonary material vary with the type of immunocompromised patient, the type of pulmonary lesion, and the degree of prior exposure to therapeutic or prophylactic antimicrobial agents.

Transtracheal Aspiration Popular several decades ago,TTA is rarely performed today. Although the sensitivity of the procedure is high (approaching 90%), the specificity is low. The material obtained by TTA (from a catheter inserted through the cricothyroid cartilage and advanced toward the carina) is not contaminated by upper respiratory tract secretions but can contain organisms that colonize the tracheobronchial tree without necessarily causing pneumonia. Significant morbidity and even death have attended the use of TTA. Contraindicated in patients with a bleeding diathesis, TTA may cause infection at the puncture site and may lead to severe subcutaneous and mediastinal emphysema in patients who are coughing vigorously.

Percutaneous Transthoracic Lung Puncture This procedure employs a skinny (small-gauge) needle that is advanced into the area of pulmonary consolidation with computed tomographic guidance. It requires that the patient cooperate, have good hemostasis, and be able to tolerate a possible associated pulmonary hemorrhage or pneumothorax. Patients on mechanical ventilation cannot undergo lung puncture because of the high incidence of complicating pneumothorax.

Fiberoptic Bronchoscopy Fiberoptic bronchoscopy is safe and relatively well tolerated and has become the standard invasive procedure used to obtain lower respiratory tract secretions from seriously ill or immunocompromised patients with complex or progressive pneumonia. This technique provides a direct view of the lower airways. Specimens obtained by bronchoscopy should be subjected to Gram's, acid-fast, *Legionella*direct fluorescent antibody, and Gomori's methenamine silver staining and should be cultured for routine aerobic and anaerobic bacteria, legionellae, mycobacteria, and fungi. Samples are collected with a protected double-sheathed brush (PSB), by bronchoalveolar lavage (BAL), or by transbronchial biopsy (TBB) at the site of pulmonary consolidation. The PSB sample is usually contaminated by oropharyngeal flora; quantitative cultures of the 1 mL of sterile culture medium into which the brush is placed after withdrawal from the inner catheter must be performed to differentiate contamination (<1000CFU/mL) from infection (³1000 CFU/mL). The results of PSB are highly specific and highly sensitive, especially when the patient has not received antibiotics before culture. BAL is usually performed with 150 to 200 mL of sterile, nonbacteriostatic saline. When used to facilitate endoscopy, local anesthetic agents with antibacterial activity can lower the sensitivity of culture results. Quantitative bacteriologic evaluation of BAL fluid has given results similar to those obtained with the PSB

technique. Gram's staining of the cytocentrifuged BAL fluid specimen can serve as an immediate guide in the selection of antimicrobial therapy to be administered while culture results are awaited.

Open-Lung Biopsy This procedure is most commonly needed when specimens obtained bronchoscopically from an immunocompromised patient with progressive pneumonia have been unrevealing. Limitations on the performance of an open-lung biopsy include hypoxemia and a bleeding diathesis, which may supervene while the physician is deciding whether to undertake this procedure. Results of an open-lung biopsy are considered diagnostic because of the large size of the tissue sample. The diagnostic yield of this procedure is greatest in focal lesions, whereas bronchoscopic evaluation is most useful in diffuse lesions.

Other Diagnostic Tests In the initial evaluation of a patient with pneumonia, at least two blood samples for culture should be obtained from different venipuncture sites; if empyema is a clinical consideration, diagnostic thoracentesis is indicated. Positive blood or pleural fluid culture is generally considered diagnostic of the etiology of pneumonia. However, bacteremia and empyema each occur in fewer than 10 to 30% of patients with pneumonia.

Serologic studies are sometimes helpful in defining the etiology of certain types of pneumonia, although serologic diagnosis -- because it is often delayed by the need to demonstrate at least a fourfold rise in convalescent-phase antibody titer -- is usually retrospective. A single IgM antibody titer of >1:16, a single IgG antibody titer of >1:128, or a fourfold or greater rise in the IgG titer obtained by indirect immunofluorescence is diagnostic of *M. pneumoniae* infection. A single IgM antibody titer of³1:20, a single IgG antibody titer of³1:128, or a fourfold or greater rise in the IgG titer obtained by micro-indirect immunofluorescence is diagnostic of *C. pneumoniae* infection. A single *Legionella* antibody titer of³1:256 or a fourfold rise to a titer of³1:128 suggests acute legionellosis. A highly sensitive and specific urinary antigen test is available to detect *L. pneumophila* serogroup 1 in patients with pneumonia; this organism accounts for ~70% of *L. pneumophila* infections. The diagnosis of hantavirus infection is confirmed by detection of IgM serum antibodies, a rising titer of IgG serum antibodies, hantavirus-specific RNA by polymerase chain reaction in clinical specimens, and hantavirus-specific antigen by immunohistochemistry.

DECISION TO HOSPITALIZE

Approximately 20% of patients with community-acquired pneumonia are hospitalized, some perhaps unnecessarily. Use of inpatient hospital services is costly and at times poses risks to the patient (e.g., the risk of nosocomial infections). Thus hospitalization must be justified by anticipation of a poor outcome if the case is managed in an outpatient setting.

The Pneumonia Patient Outcomes Research Team (PORT) has attempted to quantify the risk of death and other adverse outcomes of community-acquired pneumonia by assignment of points to 19 variables (Fig. 255-1), with stratification of patients into five classes based on cumulative point score. This prediction rule was derived and validated in a large number of patients. On the basis of their observations, the PORT investigators

suggest that outpatient management is appropriate for many patients in classes I and II, in whom the risks of subsequent hospitalization (£8.2%) and of death (<0.6%) are low. They suggest outpatient management after a short hospital stay for patients in class III, whose risk of subsequent hospitalization if initially treated at home is 16.7% but whose risk of admission to the intensive care unit (ICU) is 5.9% -- similar to that for patients in classes I and II. The PORT investigators further suggest that patients in classes IV and V (risk of death, 8.2 and 29.2%, respectively; risk of ICU admission, 11.4 and 17.3%, respectively) should receive traditional inpatient care. An expert panel from the Infectious Diseases Society of America (IDSA) endorses the PORT recommendations.

Other characteristics that favor a decision to hospitalize the patient include the known presence of certain etiologic microorganisms (e.g., *S. aureus*) that are associated with a poor prognosis, multilobe pulmonary involvement, suppurative complications (e.g., empyema or septic arthritis), evidence of poor functional status (e.g., hypotension or hypoxemia on presentation in patients otherwise in classes I, II, and III), evidence of a patient's inability to comply with treatment recommendations, anticipated difficulty in assessing the response to outpatient treatment, and an inadequate home support system that may compromise outpatient care. Discharge from the hospital should be guided by similar considerations.

TREATMENT

Community-Acquired Pneumonia: Outpatient Management Most cases of community-acquired pneumonia in otherwise-healthy adults do not require hospitalization. Although desirable, it is often impractical in the outpatient setting to obtain a chest radiograph and sputum Gram's stain and culture in order to confirm the clinical diagnosis of pneumonia and its microbial etiology before starting antimicrobial therapy. Consequently, the oral antimicrobial treatment administered in the outpatient setting is frequently empirical (Table 255-5). The pathogen in such a situation is likely to be *M. pneumoniae*, *S. pneumoniae*, or *C. pneumoniae*. In older patients with underlying chronic respiratory disease, *L. pneumophila*, *H. influenzae*, or *M. catarrhalis* should also be considered. In patients at risk of aspiration, oral anaerobes may be involved. Few oral antimicrobial drugs have a reliable spectrum encompassing all of these pathogens (Table 255-5). Whatever regimen is chosen, its antimicrobial activity should encompass *S. pneumoniae*, the most common cause of pneumonia. Increasing resistance among pneumococci to all the available oral antimicrobial agents precludes the designation of any one agent as the clear drug of choice.

Strains of *S. pneumoniae* for which the minimal inhibitory concentration (MIC) of penicillin (as determined by the broth dilution method) is 0.1 to 1.0 ug/mL are considered to have intermediate-level resistance, while strains whose MIC is>1.0 ug/mL are considered to have high-level resistance. The current, less time-consuming method to screen for penicillin resistance is the use of a 1-ug oxacillin disk in a disk diffusion assay. Penicillin resistance (i.e., an MIC ³0.1 ug/mL) is indicated by a zone of growth inhibition of£19 mm. Antimicrobial gradient paper strips (the E-test), which yield the exact MIC, are as accurate as the broth dilution technique, can be performed as rapidly as the oxacillin disk diffusion assay, and have replaced the oxacillin disk test in many institutions.

The resistance of *S. pneumoniae* to penicillin varies greatly with the source of the clinical sample tested (e.g., strains isolated from middle-ear fluid are most often resistant), the age of the patient (e.g., resistance is more frequent among children than among adults), the setting (e.g., resistance is more common in day-care centers), the patient's socioeconomic status (the frequency of resistance is highest in samples from suburban and white patients), and the geographic region in which the specimen was collected. Caution must be exercised in the interpretation of surveys of antimicrobial resistance among pneumococci in the United States, which can be strongly affected by these types of sampling bias. In a national survey of clinical isolates from normally sterile body sites that was conducted in 1997 in various surveillance areas throughout the United States by the Centers for Disease Control and Prevention (CDC), 11% (range, 6 to 19%) of 3110 isolates of *S. pneumoniae* exhibited intermediate-level resistance to penicillin, and 14% (range, 8 to 26%) displayed high-level resistance. However, in another national survey of the antimicrobial susceptibility of clinical isolates obtained from respiratory tract sites between February and June 1997 at 27 U.S. medical centers (SENTRY surveillance program), 28% of 845 isolates (with a range of 11 to 52% at the various medical centers) displayed intermediate-level penicillin resistance, and an additional 16% (with a range of 0 to 33%) displayed high-level penicillin resistance.

As a consequence of the production of altered penicillin-binding proteins with decreasedb-lactam affinity, penicillin-resistant *S. pneumoniae* exhibits at least some degree of cross-resistance to allb-lactams, including the extended-spectrum third- and fourth-generation cephalosporins. Since the mechanism of penicillin resistance does not involve b-lactamase production,b-lactam/b-lactamase inhibitor combinations (e.g., amoxicillin/clavulanate) offer no advantage. Indeed, theMICs of penicillin and amoxicillin are nearly identical, but the serum levels after equivalent doses are much higher for amoxicillin than for penicillin, a difference that may reflect a therapeutic advantage of amoxicillin. Among the oral cephalosporins, cefaclor, cefadroxil, and cephalexin have variable activity against penicillin-sensitive strains; cefuroxime and cefpodoxime have activity against penicillin-susceptible strains but variable activity against penicillin-intermediate strains and no activity against highly penicillin-resistant strains.

Resistance to other antimicrobial agents, such as the macrolides (erythromycin, clarithromycin, and azithromycin), clindamycin, tetracycline and doxycycline, and trimethoprim-sulfamethoxazole (TMP-SMZ), is also more common among penicillin-intermediate strains than among penicillin-susceptible strains, and it is most common among highly penicillin-resistant strains. Overall rates of resistance among *S. pneumoniae* strains are ~14% for the macrolides, 4% for clindamycin, up to 10% for tetracyclines, and 20 to 30% for TMP-SMZ. Rates of resistance to the newer fluoroquinolones levofloxacin, gatifloxacin, moxifloxacin, and sparfloxacin are <4%, regardless of penicillin susceptibility. At best, the older fluoroquinolones (e.g., ciprofloxacin) have borderline activity, as judged by serum levels in relation to MICsof these drugs against the pneumococcus.

Optimally, the choice of antimicrobial drugs for empirical therapy should be guided by local resistance patterns, if known. Options for empirical antimicrobial therapy should be modified in light of continually evolving antimicrobial resistance patterns resulting from the introduction of new resistant clones into the community from other regions or the

emergence of resistant mutants under the selective pressure of local patterns of antimicrobial use. TheIDSA has published guidelines for the treatment of community-acquired pneumonia. These guidelines emphasize the need for a chest radiograph when pneumonia is suspected and for the establishment of a microbial diagnosis (e.g., by sputum Gram's stain with or without culture) whenever possible. Doxycycline and the newer fluoroquinolones are recommended alternatives for initial empirical oral therapy, especially when penicillin-resistant pneumococci are suspected. The utility of the macrolides and amoxicillin depends on susceptibility of pneumococci in the local community.

The regimen should be modified for patients with particular epidemiologic factors or comorbidities related to specific pathogens\em\e.g., structural lung disease or suspected aspiration. Aspiration pneumonia can be treated with amoxicillin/clavulanate, clindamycin, or amoxicillin plus metronidazole because these regimens are active against oral anaerobes. Metronidazole alone has inadequate activity against microaerophilic gram-positive cocci and must be supplemented with a b-lactam agent that compensates for this defect in spectrum. If macrolides are used and *H. influenzae* is suspected, azithromycin or clarithromycin is preferred because of erythromycin's poor activity against this organism. Alternative agents for *H. influenzae* include amoxicillin/clavulanate, doxycycline, or a fluoroquinolone. Theb-lactams are not active against pathogens causing atypical pneumonia (e.g., *Mycoplasma*, *C. pneumoniae*, or *Legionella*), in which case doxycycline, a macrolide, or a fluoroquinolone is preferred.

TheIDSAguidelines recommend that pneumococcal pneumonia be treated for 7 to 10 days or until the patient has been afebrile for 72 h. Pneumonia caused by *Legionella, C. pneumoniae*, or *Mycoplasma* should be treated for 2 to 3 weeks unless azithromycin is used, in which case a 5-day course is acceptable because of the drug's prolonged half-life in tissues.

Community-Acquired Pneumonia: Inpatient Management Patients who have community-acquired pneumonia and are ill enough to be hospitalized (Fig. 255-1) must have a chest radiograph to establish the diagnosis of pneumonia, must undergo prompt microbiologic evaluation (including Gram's staining and culture of sputum and culture of two blood samples drawn by separate venipuncture), and must receive empirical antimicrobial therapy based on Gram's staining of sputum and knowledge of the current antimicrobial sensitivities of the pulmonary pathogens in the local geographic area (Tables 255-6 and255-7). Antimicrobial therapy should be initiated promptly (e.g., within 8 h of admission). Parenteral antimicrobial therapy in the hospitalized patient is usually mandatory. A lack of sputum production, an atypical clinical presentation, the presence of diffuse radiographic infiltrates, a rapidly progressive downhill course, and a poor response to prior empirical therapy are among the indications for the use of invasive procedures to detect the pulmonary pathogen, especially in the immunocompromised patient. Although broad-spectrum antibacterial therapy should be started during a full evaluation in severely ill patients with rapidly progressing illness, these empirical regimens cannot encompass all the possible pathogens without producing unnecessary toxicity and expense. Indeed, in immunocompromised patients (including those with neutropenia or HIV infection), the number of microbial and noninfectious causes of pulmonary disease is large and increasing. Since failure to provide specific treatment can prove rapidly fatal, a diagnosis should be sought aggressively so that optimal

therapy can be started promptly.

Penicillin or ampicillin remains the drug of choice for infection due to penicillin-susceptible pneumococci. Studies suggest that high-dose intravenous penicillin G (e.g., 10 to 20 million units daily), ampicillin (2 g every 6 h), ceftriaxone (1 or 2 g every 24 h), or cefotaxime (1 to 2 g every 6 h) constitutes adequate therapy for pneumonia due to strains exhibiting intermediate resistance to penicillin (MIC, 0.1 to 1 ug/mL). The effectiveness of high-dose intravenous penicillin against pneumonia due to highly resistant pneumococcal strains is unknown, but MICs of cefotaxime and ceftriaxone for these strains are usually lower than those of penicillin or ampicillin and most other b-lactam antibiotics. Ceftriaxone or cefotaxime may be effective when the MIC of penicillin is ³1 ug/mL and those of ceftriaxone and cefotaxime are £2 ug/mL. However, highly cephalosporin-resistant strains have become a problem in certain geographic areas. Since all penicillin-resistant strains are sensitive to vancomycin, initial empirical therapy should include this antibiotic (1 g intravenously every 12 h) when the patient with pneumococcal pneumonia is severely ill, has significant comorbidity, and lives in a region where highly penicillin- or cephalosporin-resistant strains have become common.

If the result of Gram's staining of sputum is not interpretable or not available, then theIDSAguidelines recommend empirical therapy for patients hospitalized on a general medical unit with a b-lactam (e.g., ceftriaxone, cefotaxime) or ab-lactam/b-lactamase inhibitor combination, with or without a macrolide, or with one of the fluoroquinolones alone. Seriously ill patients who are hospitalized in theICUshould always receive a macrolide or a newer fluoroquinolone in addition to theb-lactam to cover *Legionella*. The therapeutic regimens should be modified further in the following situations: structural disease of the lung (e.g., bronchiectasis) requires treatment with an anti-*Pseudomonas* b-lactam plus a macrolide or with a newer fluoroquinolone plus an aminoglycoside; penicillin allergy requires treatment with a newer fluoroquinolone, with or without clindamycin; and suspected aspiration requires treatment with a newer fluoroquinolone plus either clindamycin or metronidazole or with ab-lactam/b-lactamase inhibitor combination alone. A recent study of almost 13,000 elderly hospitalized patients with pneumonia, which controlled for severity of illness, baseline differences in patient characteristics, and processes of care, documented 30-day mortality that was 26 to 36% lower among those treated initially with a fluoroquinolone alone or a macrolide combined with a second- or nonpseudomonal third-generation cephalosporin than among those initially given a nonpseudomonal third-generation cephalosporin alone. This result may reflect the importance of pathogens such as *Mycoplasma*, *Legionella*, and *C. pneumoniae* in these patients.

Therapy can be switched from intravenous to oral agents within 3 days to complete a 7- to 10-day course if the patient's clinical condition improves rapidly and if antimicrobial agents that are readily absorbed after oral administration and that reach tissue levels above theMIC are available. The presence of *S. aureus* or aerobic gram-negative bacilli or the development of suppurative complications requires a more prolonged course of therapy. Pneumonia caused by *Legionella*, *C. pneumoniae*, or *Mycoplasma* should be treated for 2 to 3 weeks unless azithromycin is used. Anaerobic lung abscess should be treated with the regimens suggested for aspiration pneumonia until a chest radiograph (with radiography performed at 2-week intervals) is clear or shows only a small stable

scar. Therapy is prolonged for ³6 weeks to prevent relapse, although shorter courses are probably sufficient for many patients. Surgery is rarely required for lung abscess; indications for surgery include massive hemoptysis and suspected neoplasm. Supportive measures include the administration of supplemental oxygen and intravenous fluids, assistance in clearing secretions, fiberoptic bronchoscopy, and (if necessary) ventilatory support. Caution should be exercised in bronchoscopic drainage of large, fluid-filled lung abscesses because of the potential for sudden massive spillage of large collections of pus into the airways.

Patients with risk factors for HIV infection and an atypical pneumonia syndrome should be evaluated forPCPbecause of its frequency as an index diagnosis in HIV infection and its potential severity. Tuberculosis and other causes of atypical pneumonia must be excluded as part of the evaluation of these patients. Empirical therapy can consist of eitherTMP-SMZ(15 to 20 mg of trimethoprim per kg, given daily in four divided doses intravenously or by mouth) or pentamidine (3 to 4 mg/kg daily, given intravenously), and therapy is continued for 3 weeks in confirmed cases of PCP. Although some data suggest that TMP-SMZ is more effective than pentamidine, further studies directly comparing the two agents are needed. The frequency and severity of the adverse effects of the two drugs are generally thought to be equivalent. The addition of glucocorticoids (prednisone, 40 mg twice daily, with subsequent tapering of the dose) early in the course of PCP in patients with an arterial P_{O2} of<70 mmHg decreases the need for mechanical ventilation and improves the patient's chances of survival and functional status. Prophylaxis for recurrent PCP must be started at the end of therapy.

Institutionally Acquired Pneumonia Pneumonia acquired in institutions such as nursing homes or hospitals is frequently caused by enteric aerobic gram-negative bacilli, *P. aeruginosa*, or *S. aureus*, with or without oral anaerobes. Again, the selection of empirical antimicrobial therapy should be guided by Gram's staining of sputum (Tables 255-7 and255-8) and knowledge of the prevalent nosocomial pathogens and their current in vitro antimicrobial sensitivity patterns in the institution involved. An aggressive diagnostic approach is needed in some circumstances, especially for the immunocompromised patient (as outlined above).

S. aureus acquired in some institutions is frequently methicillin resistant. Such strains are resistant to all b-lactam antibiotics and may also be resistant to clindamycin, erythromycin, and the fluoroquinolones. Only vancomycin is predictably active against these organisms, and this drug should be added to the empirical regimen when methicillin-resistant organisms may be involved in pneumonia.

When multiantibiotic resistance is a problem, pneumonia due to gram-negative bacilli in the institutionalized patient can be treated initially with a b-lactam active against *P. aeruginosa* (ceftazidime, cefepime, piperacillin/tazobactam, ticarcillin/clavulanate, aztreonam, or imipenem) or with a parenterally administered fluoroquinolone (ciprofloxacin, ofloxacin, gatifloxacin, or levofloxacin). Among the fluoroquinolones, ciprofloxacin remains the most potent antipseudomonal agent. Ticarcillin/clavulanate and piperacillin/tazobactam are preferred over other penicillins with activity against *P. aeruginosa* (e.g., ticarcillin or piperacillin alone), which are not sufficiently active against *Klebsiella pneumoniae*, a relatively common pathogen. However, for infection suspected to be due to *P. aeruginosa*, the higher dose recommended by the package insert is

required; a lower dose contains less piperacillin or ticarcillin than is needed to be effective against this organism. Ampicillin/sulbactam, the other parenterally administeredb-lactam/b-lactamase inhibitor combination, is not active against many nosocomial pathogens, such as *P. aeruginosa*, *Enterobacter* spp., and *Serratia* spp., and therefore is inappropriate as empirical therapy for nosocomial pneumonia.

In seriously ill patients, especially those infected with organisms in which resistance frequently emerges during therapy (e.g., *P. aeruginosa*), use of ab-lactam/aminoglycoside orb-lactam/fluoroquinolone combination is prudent. Combinations of a b-lactam plus an aminoglycoside are used for bactericidal synergy. Combinations of ab-lactam or an aminoglycoside with a fluoroquinolone are not expected to enhance the already-rapid bactericidal activity of the fluoroquinolone alone. However, such combinations are also used to broaden the spectrum of antibacterial activity, to cover the possibility of infection with resistant pathogens, to treat polymicrobial infection, and to prevent the emergence of antimicrobial resistance.

Pneumonia due to possible coinfection with aerobic gram-negative bacilli and anaerobes, as reflected by a polymicrobial flora on Gram's staining of sputum, can usually be treated with any of the following regimens: (1) cefepime or ceftazidime plus metronidazole or clindamycin, (2) aztreonam or a fluoroquinolone plus clindamycin, or (3) imipenem, piperacillin/tazobactam, or ticarcillin/clavulanate. The regimens should include double coverage for *P. aeruginosa* when this organism is suspected (Table 255-8).

The production of chromosomally encoded, inducibleb-lactamases by some aerobic gram-negative bacilli, including *Serratia marcescens*, *Enterobacter cloacae*, *Citrobacter freundii*, *Morganella morganii*, *P. aeruginosa*, and *Acinetobacter calcoaceticus*, has important implications for the treatment of nosocomial pneumonia in institutions where these organisms are common nosocomial pathogens. Antibiotic resistance in these pathogens has been attributed to two related mechanisms: inducible production of chromosomally encoded b-lactamases and selection of mutants that have lost the genes that control expression ofb-lactamase production. The control genes repressb-lactamase production in the absence of ab-lactam agent and allowb-lactamase production in the presence of ab-lactam agent. This group of organisms has a relatively high mutation rate for loss of these control genes, and their loss results in continuous production of large amounts ofb-lactamase (*stable derepression*). The derepressed mutants are resistant to third-generation cephalosporins, aztreonam, and broad-spectrum penicillins. These chromosomally encoded, inducibleb-lactamases are not inhibited by clavulanic acid, tazobactam, or sulbactam.

Selection by theb-lactam antibiotic of the derepressed mutants present in the dense bacterial populations of infected pulmonary tissue at the initiation of antibiotic therapy apparently accounts for the emergence of resistance during therapy, which is especially problematic in severely compromised patients whose defective host defenses are unable to control the growth of a few resistant mutants. The only b-lactam agents that maintain activity against the derepressed mutants are the fourth-generation cephalosporin cefepime and the carbapenem imipenem. The fluoroquinolones and aminoglycosides may also retain activity against these mutants.TMP-SMZmay remain

active against all of these gram-negative bacilli except *P. aeruginosa*, which is inherently resistant to this agent. Some clinicians have questioned the efficacy of aminoglycosides alone for the treatment of gram-negative bacillary pneumonia. The poor clinical efficacy of aminoglycosides has been attributed to the low drug levels attained in bronchial secretions and to a loss of antimicrobial activity due to the relative acidity of purulent secretions, the anaerobic conditions in infected lung, and (in the case of *P. aeruginosa*) the divalent cations calcium and magnesium. The nephrotoxicity and ototoxicity of aminoglycosides frequently lead to underdosing with these agents. These problems are compounded by unpredictable pharmacokinetics that necessitate measurement of serum levels of aminoglycosides. If multiantibiotic-resistant nosocomial organisms are likely to be the pathogens infecting severely compromised patients, reliable empirical agents may be fluoroquinolones, cefepime, and imipenem -- unless resistance to these drugs is also endemic in the institution. Some strains of *K. pneumoniae* and *Escherichia coli* have acquired a plasmid encoding the production of an extended-spectrumb-lactamase that can be detected as in vitro resistance to ceftazidime or aztreonam. The presence of an extended-spectrumb-lactamase confers resistance to all third-generation cephalosporins and aztreonam. Some of these strains may also be resistant to piperacillin/tazobactam and cefepime, and many are also resistant to the fluoroquinolones. The only reliable agents are the carbapenems, such as imipenem. Up-to-date knowledge of the antimicrobial sensitivities of an institution's nosocomial pathogens and use of various preventive practices are mandatory.

Amantadine (200 mg/d for most adults and 100 mg/d for persons >65 years of age) is effective for the prevention of influenza A virus infection in the unimmunized patient during an influenza A outbreak and for the treatment (for 5 to 7 days) of early influenza A virus infection. Ribavirin is effective for respiratory syncytial virus infection. Intravenous acyclovir (5 to 10 mg/kg every 8 h for 7 to 14 days) is appropriate for varicella pneumonia. Treatment of cytomegalovirus pneumonia has yielded unsatisfactory results, but intravenous immunoglobulin combined with ganciclovir may be effective in some instances. Therapy for hantavirus pulmonary syndrome is supportive, and overall mortality has been 55%.

PREVENTION

The prevention of pneumonia involves either (1) decreasing the likelihood of encountering the pathogen or (2) strengthening the host's response once the pathogen is encountered. The first approach can include measures such as hand washing and glove use by persons who care for patients infected with contact-transmitted pathogens (e.g., aerobic gram-negative bacilli); use of face masks or negative-pressure isolation rooms for patients with pneumonia due to pathogens spread by the aerosol route (e.g., *M. tuberculosis*); prompt institution of effective chemotherapy for patients with contagious illnesses; and correction of conditions that facilitate aspiration. The second approach includes the use of chemoprophylaxis or immunization for patients at risk. Chemoprophylaxis may be administered to patients who have encountered or are likely to encounter the pathogen before they become symptomatic (e.g., amantadine during a community outbreak of influenza A, as mentioned above; isoniazid for tuberculosis; orTMP-SMZfor pneumocystosis) or to patients who are likely to have a recurrence following recovery from a symptomatic episode (e.g., TMP-SMZ for pneumocystosis in patients with HIV infection). The prevention of nosocomial pneumonia requires good

infection control practices, judicious use of broad-spectrum antimicrobial agents, and maintenance of patients' gastric acidity -- a major factor that prevents colonization of the gastrointestinal tract by nosocomial gram-negative bacillary pathogens. To prevent stress ulceration, it is preferable to use sucralfate, which maintains gastric acidity, rather than H_2-blocking agents. To prevent ventilator-associated nosocomial pneumonia, the following strategies have been proposed: use of the semirecumbent position, of endotracheal tubes that allow continuous aspiration of secretions accumulating above the cuff, and of heat and moisture exchangers that reduce the formation of condensate within the tubing circuitry. Vaccines (Chaps. 122,138,149,190, and194) are available for immunization against *S. pneumoniae*, *H. influenzae* type b, influenza viruses A and B, and measles virus. Influenza vaccine is strongly recommended for individuals > 55 years old and pneumococcal vaccine for those > 65 years old; these vaccines should be administered to persons of any age who are at risk of adverse consequences of influenza or pneumonia because of underlying conditions. Pneumococcal, *Haemophilus*, and influenza vaccines are recommended for HIV-infected patients who are still capable of responding to a vaccine challenge. The currently available 23-valent pneumococcal vaccine covers 88% of the serotypes causing systemic disease as well as 8% of related serotypes. The increasing prevalence of multiantibiotic resistance among pneumococci makes pneumococcal immunization of high-risk individuals of utmost importance. Immune serum globulin is available for intravenous replacement therapy in those patients with congenital or acquired hypogammaglobulinemia. Some patients who have selective IgG2 subtype deficiency and recurrent sinopulmonary infections and who are immunologically unresponsive to capsular polysaccharide vaccines may nevertheless have an antibody response to the capsular polysaccharide that is covalently linked to a protein, as it is in the conjugate *H. influenzae* type b vaccine and a similar experimental conjugate pneumococcal vaccine.

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256. BRONCHIECTASIS - *Steven E. Weinberger*

DEFINITION

Bronchiectasis is an abnormal and permanent dilatation of bronchi. It may be either focal, involving airways supplying a limited region of pulmonary parenchyma, or diffuse, involving airways in a more widespread distribution. Although this definition is based on pathologic changes in the bronchi, diagnosis is often suggested by the clinical consequences of chronic or recurrent infection in the dilated airways and the associated secretions that pool within these airways.

PATHOLOGY

The bronchial dilatation of bronchiectasis is associated with destructive and inflammatory changes in the walls of medium-sized airways, often at the level of segmental or subsegmental bronchi. The normal structural components of the wall, including cartilage, muscle, and elastic tissue, are destroyed and may be replaced by fibrous tissue. The dilated airways frequently contain pools of thick, purulent material, while more peripheral airways are often occluded by secretions or obliterated and replaced by fibrous tissue. Additional microscopic features include bronchial and peribronchial inflammation and fibrosis, ulceration of the bronchial wall, squamous metaplasia, and mucous gland hyperplasia. The parenchyma normally supplied by the affected airways is abnormal, containing varying combinations of fibrosis, emphysema, bronchopneumonia, and atelectasis. As a result of the inflammation, vascularity of the bronchial wall increases, with associated enlargement of the bronchial arteries and anastomoses between the bronchial and pulmonary arterial circulations.

Three different patterns of bronchiectasis were described by Reid in 1950. In *cylindrical bronchiectasis* the bronchi appear as uniformly dilated tubes that end abruptly at the point that smaller airways are obstructed by secretions. In *varicose bronchiectasis* the affected bronchi have an irregular or beaded pattern of dilatation resembling varicose veins. In *saccular (cystic) bronchiectasis* the bronchi have a ballooned appearance at the periphery, ending in blind sacs without recognizable bronchial structures distal to the sacs.

ETIOLOGY AND PATHOGENESIS

Bronchiectasis is a consequence of inflammation and destruction of the structural components of the bronchial wall. Infection is the usual cause of the inflammation; microorganisms such as *Pseudomonas aeruginosa* and *Haemophilus influenzae* produce pigments, proteases, and other toxins that injure the respiratory epithelium and impair mucociliary clearance. The host inflammatory response induces epithelial injury, largely as a result of mediators released from neutrophils. As protection against infection is compromised, the dilated airways become more susceptible to colonization and growth of bacteria. Thus, a reinforcing cycle can result, with inflammation producing airway damage, impaired clearance of microorganisms, and further infection, which then completes the cycle by inciting more inflammation.

Infectious Causes Adenovirus and influenza virus are the main viruses that cause

bronchiectasis in association with lower respiratory tract involvement. Virulent bacterial infections, especially with potentially necrotizing organisms such as *Staphylococcus aureus*, *Klebsiella*, and anaerobes, remain important causes of bronchiectasis when antibiotic treatment of a pneumonia is not given or is significantly delayed. Bronchiectasis has been reported in patients with HIV infection, perhaps at least partly due to recurrent bacterial infection. Tuberculosis can produce bronchiectasis by a necrotizing effect on pulmonary parenchyma and airways and indirectly as a consequence of airway obstruction from bronchostenosis or extrinsic compression by lymph nodes. Nontuberculous mycobacteria are frequently cultured from patients with bronchiectasis, often as secondary infections or colonizing organisms. However, it has now also been recognized that these organisms, especially those of the *Mycobacterium avium* complex, can serve as primary pathogens associated with the development and/or progression of bronchiectasis. Mycoplasmal and necrotizing fungal infections are rare causes of bronchiectasis.

Impaired host defense mechanisms are often involved in the predisposition to recurrent infections. The major cause of localized impairment of host defenses is endobronchial obstruction. Bacteria and secretions cannot be cleared adequately from the obstructed airway, which develops recurrent or chronic infection. Slowly growing endobronchial neoplasms such as carcinoid tumors may be associated with bronchiectasis. Foreign-body aspiration is another important cause of endobronchial obstruction, particularly in children. Airway obstruction can also result from bronchostenosis, from impacted secretions, or from extrinsic compression by enlarged lymph nodes.

Generalized impairment of pulmonary defense mechanisms occurs with immunoglobulin deficiency, primary ciliary disorders, or cystic fibrosis. Infections and bronchiectasis are therefore often more diffuse. With panhypogammaglobulinemia, the best described of the immunoglobulin disorders associated with recurrent infection and bronchiectasis, patients often also have a history of sinus or skin infections. Selective deficiency of an IgG subclass, especially IgG2, has also been described in a small number of patients with bronchiectasis.

The primary disorders associated with ciliary dysfunction, termed *primary ciliary dyskinesia*, are responsible for 5 to 10% of cases of bronchiectasis. Numerous defects are encompassed under this category, including structural abnormalities of the dynein arms, radial spokes, and microtubules. The cilia become dyskinetic; their coordinated, propulsive action is diminished, and bacterial clearance is impaired. The clinical effects include recurrent upper and lower respiratory tract infections, such as sinusitis, otitis media, and bronchiectasis. Because normal sperm motility also depends on proper ciliary function, males are generally infertile (Chap. 335). Approximately half of patients with primary ciliary dyskinesia fall into the subgroup of *Kartagener's syndrome*, in which situs inversus accompanies bronchiectasis and sinusitis.

In cystic fibrosis (Chap. 257), the tenacious secretions in the bronchi are associated with impaired bacterial clearance, resulting in colonization and recurrent infection with a variety of organisms, particularly mucoid strains of *P. aeruginosa* but also *S. aureus*, *H. influenzae*, *Escherichia coli*, and *Burkholderia cepacia*.

Noninfectious Causes Some cases of bronchiectasis are associated with exposure to

a toxic substance that incites a severe inflammatory response. Examples include inhalation of a toxic gas such as ammonia or aspiration of acidic gastric contents, though the latter problem is often also complicated by aspiration of bacteria. An immune response in the airway may also trigger inflammation, destructive changes, and bronchial dilatation. This mechanism is presumably responsible at least in part for bronchiectasis with allergic bronchopulmonary aspergillosis (ABPA), which is due to an immune response to *Aspergillus* organisms that have colonized the airway (Chap. 253). Bronchiectasis accompanying ABPA often involves proximal airways and is associated with mucoid impaction. Bronchiectasis also occurs rarely in ulcerative colitis, rheumatoid arthritis, and Sjogren's syndrome, but it is not known whether an immune response triggers airway inflammation in these patients.

In α_1-antitrypsin deficiency, the usual respiratory complication is the early development of panacinar emphysema, but affected individuals may occasionally have bronchiectasis. In the *yellow nail syndrome*, which is due to hypoplastic lymphatics, the triad of lymphedema, pleural effusion, and yellow discoloration of the nails is accompanied by bronchiectasis in approximately 40% of patients.

CLINICAL MANIFESTATIONS

Patients typically present with persistent or recurrent cough and purulent sputum production. Hemoptysis occurs in 50 to 70% of cases and can be due to bleeding from friable, inflamed airway mucosa. More significant, even massive bleeding is often a consequence of bleeding from hypertrophied bronchial arteries.

When a specific infectious episode initiates bronchiectasis, patients may describe a severe pneumonia followed by chronic cough and sputum production. Alternatively, patients without a dramatic initiating event often describe the insidious onset of symptoms. In some cases, patients are either asymptomatic or have a nonproductive cough, often associated with "dry" bronchiectasis in an upper lobe. Dyspnea or wheezing generally reflects either widespread bronchiectasis or underlying chronic obstructive pulmonary disease. With exacerbations of infection, the amount of sputum increases, it becomes more purulent and often more bloody, and patients may become febrile. Such episodes may be due solely to exacerbations of the airway infection, but associated parenchymal infiltrates sometimes reflect an adjacent pneumonia.

Physical examination of the chest overlying an area of bronchiectasis is quite variable. Any combination of crackles, rhonchi, and wheezes may be heard, all of which reflect the damaged airways containing significant secretions. As with other types of chronic intrathoracic infection, clubbing may be present. Patients with severe, diffuse disease, particularly those with chronic hypoxemia, may have associated cor pulmonale and right ventricular failure. Amyloidosis can result from chronic infection and inflammation but is now seldom seen.

RADIOGRAPHIC AND LABORATORY FINDINGS

Though the chest radiograph is important in the evaluation of suspected bronchiectasis, the findings are often nonspecific. At one extreme, the radiograph may be normal with mild disease. Alternatively, patients with saccular bronchiectasis may have prominent

cystic spaces, either with or without air-liquid levels, corresponding to the dilated airways. These may be difficult to distinguish from enlarged airspaces due to bullous emphysema or from regions of honeycombing in patients with severe interstitial lung disease. Other findings are due to dilated airways with thickened walls, which result from peribronchial inflammation. Because of decreased aeration and atelectasis of the associated pulmonary parenchyma, these dilated airways are often crowded together in parallel. When seen longitudinally, the airways appear as "tram tracks"; when seen in cross-section, they produce "ring shadows." Because the dilated airways may be filled with secretions, the lumen may appear dense rather than radiolucent, producing an opaque tubular or branched tubular structure.

Bronchography, which involves coating the airways with a radiopaque, iodinated lipid dye instilled through a catheter or bronchoscope, can provide excellent visualization of bronchiectatic airways. However, this technique has now been replaced by computed tomography (CT), which also provides an excellent view of dilated airways as seen in cross-sectional images (Fig. 256-1). With the advent of high-resolution CT scanning, in which the images are 1.0 to 1.5 mm thick, the sensitivity for detecting bronchiectasis has improved even further. Other features on high-resolution CT scanning can suggest a specific etiology of the bronchiectasis. For example, bronchiectasis of relatively proximal airways suggestsABPA, whereas the presence of multiple small pulmonary nodules (nodular bronchiectasis) suggests infection with *M. avium* complex.

Examination of sputum often reveals an abundance of neutrophils and colonization or infection with a variety of possible organisms. Appropriate staining and culturing of sputum often provide a guide to antibiotic therapy.

Additional evaluation is aimed at diagnosing the cause for the bronchiectasis. When bronchiectasis is focal, fiberoptic bronchoscopy may reveal an underlying endobronchial obstruction. In other cases, upper lobe involvement may be suggestive of either tuberculosis orABPA. With more widespread disease, measurement of sweat chloride levels for cystic fibrosis, structural or functional assessment of nasal or bronchial cilia or sperm for primary ciliary dyskinesia, and quantitative assessment of immunoglobulins may explain recurrent airway infection. In an asthmatic person with proximal bronchiectasis or other historical features to suggest ABPA, skin testing, serology, and sputum culture for *Aspergillus* are helpful in confirming the diagnosis.

Pulmonary function tests may demonstrate airflow obstruction as a consequence of diffuse bronchiectasis or associated chronic obstructive lung disease. Bronchial hyperreactivity, e.g., to methacholine challenge, and some reversibility of the airflow obstruction with inhaled bronchodilators are relatively common.

TREATMENT

Therapy has four major goals: (1) elimination of an identifiable underlying problem; (2) improved clearance of tracheobronchial secretions; (3) control of infection, particularly during acute exacerbations; and (4) reversal of airflow obstruction. Appropriate treatment should be instituted when a treatable cause is found, for example, treatment of hypogammaglobulinemia with immunoglobulin replacement, tuberculosis with antituberculous agents, andABPAwith glucocorticoids.

Secretions are typically copious and thick and contribute to the symptoms. Chest physical therapy with vibration, percussion, and postural drainage frequently helps patients with copious secretions. Mucolytic agents to thin secretions and allow better clearance are controversial. Aerosolized recombinant DNase, which decreases viscosity of sputum by breaking down DNA released from neutrophils, has been shown to improve pulmonary function in cystic fibrosis, but similar benefits have not been found with bronchiectasis due to other etiologies.

Antibiotics have an important role in management. For patients with infrequent exacerbations characterized by an increase in quantity and purulence of the sputum, antibiotics are commonly used only during acute episodes. Although choice of an antibiotic may be guided by Gram's stain and culture of sputum, empiric coverage (e.g., with ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, or cefaclor) is often given initially. When *P. aeruginosa* is present, oral therapy with a quinolone or parenteral therapy with an aminoglycoside or third-generation cephalosporin may be appropriate. In patients with chronic purulent sputum despite short courses of antibiotics, more prolonged courses, e.g., with oral amoxicillin or inhaled aminoglycosides, or intermittent but regular courses of single or rotating antibiotics have been used.

Bronchodilators to improve obstruction and aid clearance of secretions are particularly useful in patients with airway hyperreactivity and reversible airflow obstruction. Although surgical therapy was common in the past, more effective antibiotic and supportive therapy has largely replaced surgery. However, when bronchiectasis is localized and the morbidity is substantial despite adequate medical therapy, surgical resection of the involved region of lung should be considered.

When massive hemoptysis, often originating from the hypertrophied bronchial circulation, does not resolve with conservative therapy, including rest and antibiotics, therapeutic options are either surgical resection or bronchial arterial embolization (Chap. 33). Although resection may be successful if disease is localized, embolization is preferable with widespread disease. In patients with extensive disease, chronic hypoxemia and cor pulmonale may indicate the need for long-term supplemental oxygen. For selected patients who are disabled despite maximal therapy, lung transplantation is a therapeutic option.

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257. CYSTIC FIBROSIS - *Richard C. Boucher*

Cystic fibrosis (CF) is a monogenetic disorder that presents as a multisystem disease. The first signs and symptoms typically occur in childhood, but about 7% of patients in the United States are diagnosed as adults. Due to improvements in therapy, more than 36% of patients are now adults³18 years of age and 12% are past the age of 30. The median survival is over 32 years for males and 29 years for females with CF. Thus, CF is no longer only a pediatric disease, and internists must be prepared to recognize and treat its many complications. This disease is characterized by chronic airways infection that ultimately leads to bronchiectasis and bronchiolectasis, exocrine pancreatic insufficiency and intestinal dysfunction, abnormal sweat gland function, and urogenital dysfunction.

PATHOGENESIS

GENETIC CONSIDERATIONS

CFis an autosomal recessive disease resulting from mutations in a gene located on chromosome 7. The prevalence of CF varies with the ethnic origin of a population. CF is detected in approximately 1 in 3000 live births in the Caucasian population of North America and northern Europe, 1 in 17,000 live births of African-Americans, and 1 in 90,000 live births of the Asian population of Hawaii. The most common mutation in the CF gene (~70% of CF chromosomes) is a 3-bp deletion that results in an absence of phenylalanine at amino acid position 508 (DF_{508}) of the CF gene protein product, known as the CF transmembrane regulator (CFTR). The large number (>800) of relatively uncommon (<2%) mutations identified in the CF gene makes it difficult to use DNA diagnostic technologies for identifying heterozygotes in populations at large, and no simple physiologic measurements allow heterozygote detection.

CFTRPROTEIN

TheCFTRprotein is a single polypeptide chain containing 1480 amino acids that appears to function both as a cyclic AMP-regulated Cl^- channel and, as its name implies, a regulator of other ion channels. The fully processed form of CFTR is found in the plasma membrane in normal epithelia (Fig. 257-1). Biochemical studies indicate that theDF_{508}mutation leads to improper processing and intracellular degradation of the CFTR protein. Thus, absence of CFTR at appropriate cellular sites is often part of the pathophysiology ofCF. However, other mutations in the CF gene produce CFTR proteins that are fully processed but are nonfunctional or only partially functional at the appropriate cellular sites.

EPITHELIAL DYSFUNCTION

The epithelia affected byCFexhibit different functions in their native state; i.e., some are volume-absorbing (airways and distal intestinal epithelia), some are salt-absorbing but not volume absorbing (sweat duct), and others are volume-secretory (proximal intestine and pancreas). Given this diverse array of native activities, it should not be surprising that CF produces very different effects on patterns of electrolyte and water transport. However, the unifying concept is that all affected tissues express abnormal ion transport

function.

ORGAN-SPECIFIC PATHOPHYSIOLOGY

Lung The diagnostic biophysical hallmark ofCF is the raised transepithelial electric potential difference (PD) detected in airway epithelia. The transepithelial PD reflects components of both the rate of active ion transport and the resistance to ion flow of the superficial epithelium. CF airway epithelia exhibit both raised transport rates (Na^+) and decreased Cl^-permeability (Fig. 257-2). The Cl^- permeability defect reflects at least in part the absence of cyclic AMP-dependent kinase and protein kinase C-regulated Cl^- transport that is mediated by the Cl^-channel functions ofCFTR. An important observation is that there is an alternative Cl^- channel expressed in airway epithelia. This "alternative" Cl^- channel (Cl_{a^-}) is different from CFTR and is regulated by intracellular Ca^{2+}levels. This channel can substitute for CFTR with regard to net Cl^- transport and may be a potential therapeutic target.

Raised Na^+absorption is a routine feature ofCFairway epithelia. Na^+transport abnormalities in CF are not a widespread feature of the CF epithelial phenotype and appear confined to volume-absorbing epithelia. Recent studies demonstrate that the increased Na^+transport reflects the absence ofCFTR's tonic inhibitory regulatory function on Na^+channel activity. It appears that CFTR inhibits Na^+channel activity as a part of its general function to act as a "switch" that coordinates the balance between Na^+absorption and Cl^-secretion.

The central hypothesis ofCFairways pathophysiology has been that an abnormally high rate of Na^+absorption and low rate of Cl^- secretion reduce the salt and water content of mucus and deplete the volume of the perciliary liquid (PCL). Both the thickening of mucins and the depletion of the PCL lead to a failure to clear mucus normally from the airways by either ciliary or airflow-dependent (cough) mechanisms. An alternative hypothesis suggests that the central defect in CF airways is raised salt concentration in secretions that inhibits the function of antimicrobial substances. Direct measurements of salt concentration *in vivo* have, however, provided no evidence that there are differences in salt concentration in CF versus normal airway secretions.

The unique predisposition ofCFairways to chronic infection by *Staphylococcus aureus* and *Pseudomonas aeruginosa* raises the issue that other as yet undefined abnormalities in airway surface liquids also may contribute to the failure of lung defense. However, it may be that *Pseudomonas* is selected by its propensity to grow in biofilm colonies on the surfaces of thickened, retained mucus plaques in CF airways.

Gastrointestinal Tract The gastrointestinal effects ofCF are diverse. In the exocrine pancreas, the absence of theCFTRCl^- channel in the apical membrane of pancreatic ductal epithelia limits the function of an apical membrane Cl^--HCO_3^-exchanger to secrete $HCO_3^-$and Na^+(by a passive process) into the duct. The failure to secrete Na^+-$HCO_3^-$and water leads to retention of enzymes in the pancreas and ultimately destruction of virtually all pancreatic tissue. The CF intestinal epithelium, because of the lack of Cl^- and water secretion, fails to flush the secreted mucins and other macromolecules from intestinal crypts. The diminished CFTR-mediated secretion of liquid may be exacerbated by excessive absorption of liquid in the distal intestine,

reflecting abnormalities of CFTR-mediated regulation of Na^+absorption (both mediated by Na^+channels and possibly other Na^+transporters, e.g., Na^+-H^+exchangers). Both dysfunctions lead to dessicated intraluminal contents and obstruction of both the small and large intestines. In the hepatobiliary system, defective hepatic ductal Cl^- and water secretion causes retention of biliary secretions and focal biliary cirrhosis and bile duct proliferation in approximately 25 to 30% of patients with CF. The inability of the CF gallbladder epithelium to secrete salt and water can lead to both chronic cholecystitis and cholelithiasis.

Sweat Gland Patients with CFsecrete nearly normal volumes of sweat in the sweat acinus. However, they are not able to absorb NaCl from sweat as it moves through the sweat duct due to the inability to absorb Cl^- across the ductal epithelial cells.

CLINICAL FEATURES

Most patients withCFpresent with signs and symptoms of the disease in childhood. Approximately 15% of patients present within the first 24 h of life with gastrointestinal obstruction, termed *meconium ileus*. Other common presentations within the first year or two of life include respiratory tract symptoms, most prominently cough and/or recurrent pulmonary infiltrates, and failure to thrive. A significant proportion of patients (~7%), however, are diagnosed after age 18.

RESPIRATORY TRACT

Upper respiratory tract disease is almost universal in patients withCF. Chronic sinusitis is common in childhood and leads to nasal obstruction and rhinorrhea. The occurrence of nasal polyps approaches 25% and often requires surgery.

In the lower respiratory tract, the first symptom ofCF is cough. With time, the cough becomes persistent and produces viscous, purulent, often greenish colored sputum. Inevitably, periods of clinical stability are interrupted by "exacerbations," defined by increased cough, weight loss, increased sputum volume, and decrements in pulmonary function. These exacerbations require aggressive therapy, including frequent postural drainage and oral antibiotics, and often intravenous antibiotics (see below), with the goal being recovery of lung function. Over the course of years, the exacerbations become more frequent and the recovery of lost lung function incomplete, leading to respiratory failure.

Patients withCFexhibit a characteristic sputum microbiology. *Haemophilus influenzae* and *S. aureus* are often the first organisms recovered from samples of lung secretions in newly diagnosed patients with CF. *P. aeruginosa* is typically cultured from lower respiratory tract secretions thereafter. After repetitive antibiotic exposure, *P. aeruginosa*, often in a mucoid form, is usually the predominant organism recovered from sputum and may be present as several strains with different antibiotic sensitivities. *Burkholderia* (formerly *Pseudomonas*) *cepacia* has been recovered from CF sputum and is pathogenic. Patient-to-patient spread of certain strains of this organism indicates that infection control in the hospital should be practiced. Other gram-negative rods recovered from CF sputum include *Xanthomonas zylosoxida* and *P. gladioli*, and occasionally, mucoid forms of *Proteus*, *Escherichia coli*, and *Klebsiella*. Up to 50% of

patients with CF have *Aspergillus fumigatus* in their sputum, and up to 10% of these patients exhibit the syndrome of allergic bronchopulmonary aspergillosis. *Mycobacterium tuberculosis* is rare in patients with CF. However, 10 to 20% of adult patients with CF have sputum cultures positive for nontuberculous mycobacteria, and in some patients these microorganisms are associated with disease.

The first lung function abnormalities observed in children withCF, increased ratios of residual volume to total lung capacity, suggest that small airways disease is the first functional lung abnormality in CF. As the disease progresses, both reversible and irreversible changes in forced vital capacity and forced expiratory volume in 1 s are noted. The reversible component reflects the accumulation of intraluminal secretions and/or airway reactivity, which occurs in 40 to 60% of patients with CF. The irreversible component reflects chronic destruction of the airway wall and bronchiolitis.

The earliest chest x-ray change in CFlungs is hyperinflation, reflecting small airways obstruction. Later, signs of luminal mucus impaction, bronchial cuffing, and finally, bronchiectasis, e.g., ring shadows, are noted. For reasons that are still unknown, the right upper lobe displays the earliest and most severe changes. Neither CT nor MRI scanning is routinely performed on patients with CF.

CFpulmonary disease is associated with many intermittent complications. Pneumothorax is common (>10% of patients). The production of small amounts of blood in sputum is common in CF patients with advanced pulmonary disease and appears to be associated with lung infection. Massive hemoptysis is life-threatening and difficult to localize bronchoscopically. With advanced lung disease, digital clubbing becomes evident in virtually all patients with CF. As late events, respiratory failure and cor pulmonale are prominent features of CF.

GASTROINTESTINAL TRACT

The syndrome of meconium ileus in infants presents with abdominal distention, failure to pass stool, and emesis. The abdominal flat plate can be diagnostic with small intestinal air fluid levels, a granular appearance representing meconium, and a small colon. In children and young adults, a syndrome termed *meconium ileus equivalent* or distal intestinal obstruction occurs. The syndrome presents with right lower quadrant pain, loss of appetite, occasional emesis, and often a palpable mass. The syndrome can be confused with appendicitis, which occurs frequently in patients withCF. The characteristic intestinal abnormalities are complicated by exocrine pancreatic insufficiency in more than 90% of patients with CF. Insufficient pancreatic enzyme release yields the typical pattern of protein and fat malabsorption, with frequent, bulky, foul-smelling stools. Signs and symptoms of malabsorption of fat-soluble vitamins, including vitamins E and K, are also noted. Pancreatic beta cells are typically spared, but function decreases with age, causing hyperglycemia and increasing requirements for insulin in older patients with CF.

GENITOURINARY SYSTEM

Late onset of puberty is common in both males and females withCF. The delayed maturational pattern is likely secondary to the effects of chronic lung disease and

inadequate nutrition on reproductive endocrine function. More than 95% of male patients with CF are azoospermic, reflecting obliteration of the vas deferens that probably reflects defective liquid secretion. Twenty percent of women with CF are infertile due to effects of chronic lung disease on the menstrual cycle; thick, tenacious cervical mucus that blocks sperm migration; and possibly fallopian tube/uterine wall abnormalities in liquid transport. More than 90% of completed pregnancies produce viable infants, and women with CF are generally able to breast-feed infants normally.

DIAGNOSIS

Because of the large number ofCFmutations, DNA analysis is not used for primary diagnosis. The primary diagnosis of CF rests on a combination of clinical criteria and analyses of sweat Cl^- values. The values for the Na^+ and Cl^- concentration in sweat vary with age, but typically in adults a Cl^- concentration of>70 mEq/L discriminates between patients with CF and patients with other lung diseases.

DNA analyses are being performed increasingly in patients withCF. Comprehensive genotype-phenotype relationships have not yet been established sufficiently for prognosis. A relationship betweenDF_{508}homozygosity and pancreatic insufficiency has been established, but no predictive relationship holds forDF_{508}homozygosity and lung disease.

Between 1 and 2% of patients with the clinical syndrome ofCF have normal sweat Cl^-values. In most of these patients, the nasal transepithelialPD is raised into the diagnostic range for CF, and sweat acini do not secrete in response to injected beta-adrenergic agonists. A single mutation of theCFTRgene, 3849 + 10 kb C ® T, is associated with approximately 50% of CF patients with normal sweat Cl^-values.

TREATMENT

The major objectives of therapy forCF are to promote clearance of secretions and control infection in the lung, provide adequate nutrition, and prevent intestinal obstruction. Ultimately, gene therapy may become the treatment of choice.

Lung Disease The principal techniques for clearing pulmonary secretions are breathing exercises, flutter valves, and chest percussion. Regular use of these maneuvers is effective in preserving lung function. There is increasing interest in the use of hypertonic saline (3 to 7%) aerosols to augment the clearance of secretions.

More than 95% of patients withCF die of complications resulting from lung infection. Antibiotics are the principal agents available for treating lung infection, and their use should be guided by sputum culture results. Early intervention with antibiotics is useful, and long courses of treatment are the rule. Because of increased total-body clearance and volume of distribution of antibiotics in patients with CF, the required doses are higher for patients with CF than for patients with similar chest infections who do not have CF.

Increased cough and mucus production are treated with antibiotics given orally. Typical oral agents used to treat *Staphylococcus* include a semisynthetic penicillin or a

cephalosporin. Oral ciprofloxacin may reduce pseudomonal bacterial counts and control symptoms. However, its clinical usefulness may be limited by rapid emergence of resistant organisms, and accordingly, courses should be intermittent (2 to 3 weeks) and not chronic. More severe exacerbations, or exacerbations associated with bacteria resistant to oral antibiotics, require intravenous antibiotics. Traditionally, intravenous therapy has been given in the hospital, but outpatient intravenous antibiotic administration has gained widespread acceptance. Usually, two drugs, often one of them an aminoglycoside, are used to treat *P. aeruginosa* to hinder emergence of resistant organisms. Drug dosage should be monitored so that levels for gentamicin or tobramycin peak at ranges of ~10 ug/mL and exhibit troughs of<2 ug/mL. Usually, a cephalosporin, e.g., ceftazadime, and/or a penicillin derivative is used as the second drug. Antibiotics directed at *Staphylococcus* and/or *H. influenzae* are added depending on the results of the culture. Aerosolization of antibiotics also may have an important role in treatingCF lung infection. Large doses of aminoglycosides, e.g., 600 mg tobramycin twice daily, via aerosol may be effective at delaying exacerbations. Aerosol administration also permits the use of other drugs, e.g., colistin, that are relatively ineffective by the intravenous route.

A number of pharmacologic agents for promoting mucus clearance are in use. *N*-acetyl-cysteine, which solubilizes mucus glycoproteins, has not been shown to have clinically significant effects on mucus clearance and/or lung function. Recombinant human DNAse, however, degrades the concentrated DNA inCFsputum, decreases sputum viscosity, and increases airflow during short-term administration. Long-term (6 months) DNAse treatment increases the time between pulmonary exacerbations. Most patients receive a therapeutic trial of DNAse to test for efficacy, and a sizeable minority appear to demonstrate persistent objective benefits. Clinical trials of experimental drugs aimed at restoring salt and water content of secretions are underway. The most promising may be long-acting nucleotide (UTP)-based compounds that appear active in inducing liquid secretion in CF airways.

Inhaledb-adrenergic agonists can be useful to control airways constriction. They achieve a short-term increase in airflow, but long-term benefit has not been shown. Inhaled anticholinergics provide an alternative. Oral steroids are not first-line agents for controlling airways constriction and are of no use in improving the nonreversible component of lung function. Steroids may be useful for treating allergic bronchopulmonary aspergillosis.

The chronic damage to airway walls reflects to some extent the destructive activities of inflammatory enzymes generated in part by inflammatory cells. To date, specific therapies with antiproteases have not been successfully developed. However, a subset of adolescents withCFappears to benefit from long-term, high-dose non-steroidal (ibuprofen) therapy.

A number of pulmonary complications require acute interventions. Atelectasis is best treated with chest physiotherapy and antibiotic therapy. Pneumothoraces involving 10% or less of the lung can be observed without intervention. The use of chest tubes to expand collapsed, diseased lung often requires long periods of time, and sclerosing agents should be used with caution because of possible limitations for subsequent lung transplantation. Small-volume hemoptysis requires no specific therapy other than

treatment of lung infection and assessment of coagulation and vitamin K status. If massive hemoptysis occurs, bronchial artery embolization can be successful. The most ominous complications ofCF are respiratory failure and cor pulmonale. The most effective conventional therapy for these conditions is vigorous medical management of the lung disease and O_2supplementation. Noninvasive positive pressure ventilation through a face mask may be an effective adjunctive therapy. Ultimately, the only effective treatment for respiratory failure in CF is lung transplantation (Chap. 267). The 2-year survival for lung transplantation exceeds 60%, and deaths in transplant patients result principally from graft rejection, often involving obliterative bronchiolitis. The transplanted lungs do not develop a CF-specific phenotype.

Gastrointestinal Disease Maintenance of adequate nutrition is critical for the health of the patient withCF. Most (>90%) of patients with CF benefit from pancreatic enzyme replacement. Capsules generally contain between 4000 and 29,000 units of lipase. The dose of enzymes (typically no more than 20,000 units/kg per meal) should be adjusted on the basis of weight gain, abdominal symptomatology, and character of stools. Replacement of fat-soluble vitamins, particularly vitamins E and K, is usually required. Hyperglycemia most often becomes manifest in the adult and typically requires insulin treatment.

For treatment of acute obstruction due to meconium ileus equivalent, megalodiatrizoate or other hypertonic radiocontrast materials delivered by enema to the terminal ileum are utilized. For control of symptoms, adjustment of pancreatic enzymes and the supplementation of intake by salt solutions containing osmotically active agents, e.g., propyleneglycol or lactulose, are utilized. Persistent symptoms may indicate a diagnosis of gastrointestinal malignancy, which is increased in incidence in patients withCF. Hepatic and gallbladder complications are treated as for patients without CF. End-stage liver disease can be treated by transplantation, which has a 2-year survival rate exceeding 50%.

Psychosocial Factors CFimposes a tremendous burden on patients. Health insurance, career options, family planning, and life expectancy become major issues. Thus, assisting patients with the psychosocial adjustments required by CF is critical.

(Bibliography omitted in Palm version)

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258. CHRONIC BRONCHITIS, EMPHYSEMA, AND AIRWAYS OBSTRUCTION - *Eric G. Honig*, *Roland H. Ingram, Jr.*

DEFINITION

Chronic obstructive pulmonary disease (COPD) is the name of a group of chronic and slowly progressive respiratory disorders characterized by reduced maximal expiratory flow during forced exhalation. Most of the airflow obstruction is fixed, but a variable degree of reversibility and bronchial hyperreactivity may be seen. COPD may coexist with asthma and, when abnormal airway reactivity is present, differentiation between these disorders can be challenging. COPD comprises emphysema and chronic bronchitis, two distinct processes, although most often present in combination. The definition excludes other causes of chronic airflow obstruction such as cystic fibrosis (Chap. 257), bronchiolitis obliterans (Chap. 259), and bronchiectasis (Chap. 256).

Emphysema is defined anatomically as a permanent and destructive enlargement of airspaces distal to the terminal bronchioles without obvious fibrosis and with loss of normal architecture. *Chronic bronchitis* is defined clinically as the presence of a cough productive of sputum not attributable to other causes on most days for at least 3 months over 2 consecutive years. Chronic bronchitis may be present in the absence of airflow limitation, butCOPDalways involves clinically significant airflow limitation.

EPIDEMIOLOGY

COPDis a common medical problem affecting an estimated 16 million Americans. Males are more frequently affected than females, and Caucasians more frequently than African Americans. There is a higher prevalence of COPD among persons with a lower socioeconomic status and in those with a history of low birth weight. COPD is the fourth leading cause of death in the United States and is the only one of the 10 leading causes of death for which mortality rates are still rising. Prevalence peaks in the seventh and eighth decades, then levels off, largely due to mortality.

DISEASE MECHANISMS

PATHOGENESIS

COPDevolves from an inflammatory process involving the airways and distal airspaces. Increased activity of oxidants combined with decreased activity of antioxidants, termed *oxidative stress*, have been implicated in the development of inflammation and COPD. Cigarette smoke produces high concentrations of oxygen free radicals including superoxide, hydrogen peroxide, and hypochlorous acid. Cigarette smoke is an independent source of Fe^{2+}, releases $Fe^{2+}$from ferritin, and catalyzes the formation of the highly active hydroxyl radical from $O_2^-$and $H_2O_2$by eosinophils, neutrophils, and alveolar macrophages. Cigarette tar contains nitric oxide and induces nitric oxide synthase. In the presence of oxidants, NO is metabolized to cytotoxic peroxynitrates. In order for elastase to degrade elastin,$a_1$antitrypsin (a_1AT) must be inactivated. Cigarette smoke, oxidants, activated neutrophils, and type II alveolar pneumocytes are all capable of inactivating a_1AT as well as matrix metalloproteinase inhibitors. Oxidant stress is also capable of inducing mucus hypersecretion. Cigarette smoke also acts as a

chemoattractant and upregulates adhesion molecules. Smoke increases neutrophil transit time through the pulmonary circulation, increases adhesion, and decreases deformability. Smoke and elastase both increase the expression of the proinflammatory nuclear transcription factor kB (NfkB) as well as interleukin 8, a chemokine found to be elevated in COPD patients, that recruits neutrophils, basophils, eosinophils, and T lymphocytes.

The submucosa of the small airway in patients withCOPD has increased numbers of CD8 lymphocytes and eosinophils, macrophages, and mast cells. Neutrophils are increased in smokers, but their numbers do not correlate with the presence of airflow obstruction. Patients with chronic airflow obstruction show higher levels of myeloperoxidase and eosinophilic cationic protein than do patients with normal airflow. Macrophages and mast cells produce transforming growth factor b(TGF-b), a peptide related to fibrogenesis. Patients with chronic airflow obstruction show a twofold elevation of TGF-b in lavage liquid; the amount of TGF-b shows a significant negative correlation with FEV_1(the forced expiratory volume in 1 s). Smoke also leads to lipid peroxidation and to DNA damage. Widespread point mutations of the p53 gene locus have been identified in patients with lung cancer and precancerous dysplasia. These may predispose to the development of lung cancer.

RISK FACTORS

COPDis characterized by a reducedFEV$_1$and an accelerated rate of decline of FEV_1. The reduction in FEV_1 can occur by any of three pathways: (1) impaired childhood growth and development, with a lower peak in early adulthood and a normal rate of decline with aging (e.g., early childhood infection and passive smoke exposure); (2) normal growth and development with a premature peak but normal subsequent decline (e.g., asthma and passive smoking); and (3) normal growth and development and peak with accelerated decline (e.g., active smoking and, to a lesser degree, environmental exposures).

Smoking Cigarette smoking is the most commonly identified correlate with both chronic bronchitis during life and extent of emphysema at postmortem. The prevalence ofCOPDshows a dose-response relationship with the number of pack-years of tobacco consumed. Some 90% of all COPD patients are current or former tobacco smokers. Experimental studies have shown that prolonged cigarette smoking impairs respiratory epithelial ciliary movement, inhibits function of alveolar macrophages, and leads to hypertrophy and hyperplasia of mucus-secreting glands; massive exposure in dogs can produce emphysematous changes. Cigarette smoke also inhibits antiproteases and causes polymorphonuclear leukocytes to release proteolytic enzymes acutely. Cigarette smoke can produce an acute increase in airways resistance due to vagally mediated smooth-muscle constriction by stimulating submucosal irritant receptors. Increased airways responsiveness is associated with more rapid progression in patients with chronic airways obstruction. Obstruction of small airways is the earliest demonstrable mechanical defect in young cigarette smokers and may disappear completely after cessation of smoking.

Although smoking cessation does not result in complete reversal of more pronounced obstruction, there is a significant slowing of the decline in lung function in all smokers

who give up cigarettes. Passive exposure to tobacco smoke correlates with respiratory symptoms such as cough, wheeze, and sputum production. Not only is cigarette smoking the most common single factor leading to chronic airways obstruction, it also adds to the effects of every other contributory factor to be discussed below.

Air Pollution The incidence and mortality rates of both chronic bronchitis and emphysema may be higher in heavily industrialized urban areas. Exacerbations of bronchitis are clearly related to periods of heavy pollution with sulfur dioxide (SO_2) and particulate matter. While nitrogen dioxide (NO_2) can produce small-airways obstruction (bronchiolitis) in experimental animals exposed to high concentrations, there are no data convincingly implicating NO_2, at even the highest pollutant levels, in the pathogenesis or worsening of airways obstruction in humans (Chap. 254).

Occupation Chronic bronchitis is more prevalent in workers who engage in occupations exposing them to either inorganic or organic dusts or to noxious gases. Epidemiologic surveys have succeeded in demonstrating an accelerated decline in lung function in many such workers -- e.g., workers in plastics plants exposed to toluene diisocyanate, and carding room workers in cotton mills (Chap. 254) -- suggesting that their occupational exposure contributes to their future disability.

Infection Morbidity, mortality, and frequency of acute respiratory illnesses are higher in patients with chronic bronchitis. Many attempts have been made to relate these illnesses to infection with viruses, mycoplasmas, and bacteria. However, only the rhinovirus is found more often during exacerbations; that is to say, pathogenic bacteria, mycoplasmas, and viruses other than rhinovirus are found just as often between as during exacerbations. Epidemiologic studies, however, implicate acute respiratory illness as one of the major factors associated with the etiology as well as the progression of chronic airways obstruction. Cigarette smokers may either transitorily develop or worsen small-airways obstruction in association with even mild viral respiratory infections. There is also some evidence that severe viral pneumonia early in life may lead to chronic obstruction, predominantly in small airways.

GENETIC CONSIDERATIONS

Despite the strong etiologic association between smoking and COPD, only 15 to 20% of smokers lose FEV_1 at a rate fast enough to manifest COPD. Epidemiologic evidence of familial clustering of COPD cases is strong and repeated, suggesting that susceptibility to the effects of tobacco smoke has genetic determinants. Twin studies show that even after controlling for active and passive smoking, FEV_1 correlated more closely in monozygotic than dizygotic twins and more than in other family members with a lesser percentage of shared genotype. In first-degree relatives of a cohort of COPD patients with normal α_1AT levels, FEV_1 was reduced compared to controls but only among current or ex-smokers. Smoking and nonsmoking relatives of control subjects both had normal FEV_1. These data suggest genetic risk factors that are expressed in response to smoking.

α_1Antitrypsin Deficiency Thus far, deficiency of α_1AT is the only genetic abnormality that has been specifically linked to COPD. α_1AT is a 394-amino acid serine proteinase inhibitor whose synthesis is governed by a 12.2-kB 7-exon gene located at

14q32.1.a_1AT synthesis is expressed primarily in the liver and to a lesser degree in neutrophils and monocytes. Hepatica_1AT escapes into the general circulation, where it counteracts neutrophil elastase. Normal levels ofa_1AT are 20 to 48 umol/L; levels above 11 umol/L (35% of normal) are considered protective. There are 75 known alleles ofa_1AT, which are inherited in an autosomal codominant manner and are generally classified as normal (MM), deficient, null, or dysfunctional. The most common deficient allele, termed ZZ (or Pi_{ZZ}phenotype), results from a single amino acid substitution$_{342}$Glu® Lys, which causes spontaneous polymerization of the polypeptide, markedly impeding its release into the circulation from the liver. What does escape is vulnerable to oxidation and spontaneous polymerization, further impeding its function. The retained material is associated with hepatic cirrhosis (Chap. 299), while diminished circulating levels (2.5 to 7 umol/L, averaging 16% of normal) lead to antiprotease deficiency. Pi_{ZZ}, the most common disease-relateda_1AT abnormality, occurs in 1:2000 to 1:7000 persons of European descent and is rare in those of Oriental and African lineage. Pi_{SS}phenotypes are associated witha_1AT levels of 15 to 33 umol (mean 52% of normal). Pi_{null}have no detectable antiprotease levels. Heterozygotes have intermediate levels of antiprotease.

Clinically significant deficiency ofa_1AT, with levels below 11 umol/L, has been associated with homozygous Pi_{ZZ}, $Pi_{nullnull}$, or $Pi_{nullZ}$and the premature development of severe emphysema, chronic bronchitis, or bronchiectasis.a_1AT deficiency accounts for 2% of observed cases of emphysema. Rare below age 25, the disease usually presents as dyspnea and cough in patients in their fourth decade. Although not a true population-based study, a large national registry of 1129 severea_1AT-deficiency cases indicated that the typical patient was in the mid-forties, with an$FEV_1$and a pulmonary diffusing capacity at or below 50% of the predicted levels. Most had exertional dyspnea and wheezing, but fewer than half reported a chronic cough. Nearly 80% had a positive family history of lung disease, and 25% reported a positive family history for liver disease. The average rate of decline of FEV_1 is reported to be 100 to 130 mL per year for smokers and 50 to 80 mL per year for ex-smokers or lifetime nonsmokers witha_1AT deficiency.

Pathologically, panacinar emphysema predominates, and radiographically, changes are more marked in the lower lobes. It is becoming increasingly apparent that tobacco smoking is an extremely important cofactor for the development of disease ina_1AT-deficient individuals. Only a few lifetime nonsmokers with Pi_{ZZ}develop emphysema. Most never have symptoms, have a normal rate of decline ofFEV_1, and live a normal life span. Many cases are discovered only as a consequence of family screening of emphysema patients. Because the total number of Pi_{ZZ}individuals is unknown, the risk of disease for smokers is difficult to ascertain accurately. The risk of disease is lower still for heterozygotes with one M or S allele. Smoking is again an important cofactor.

PATHOLOGY

The pathologic changes ofCOPDinvolve large and small airways and the terminal respiratory unit. Airway narrowing is seen in large and small airways and is caused by changes in their normal constituents in response to persistent inflammation.

The airway epithelium is characterized by squamous metaplasia, atrophy of ciliated cells, and hypertrophy of mucus glands. The remodeled epithelium actively produces cytokines that amplify and sustain the inflammatory process. The small airways are the major site of airflow limitation. Small airways show a variety of lesions narrowing their lumina, including goblet cell hyperplasia, mucosal and submucosal inflammatory cells, edema, peribronchial fibrosis, intraluminal mucus plugs, and increased smooth muscle. CD8+ T lymphocytes and B lymphocytes characterize the inflammatory infiltrate. The marked thickening of the subepithelial lamina reticularis, characteristic of asthma, is absent inCOPD.

In the central airways, subepithelial inflammation is present with increased numbers of eosinophils and CD8+ T lymphocytes. Unlike asthma, the eosinophils are not activated and do not degranulate. Neutrophils are present in the epithelium but not in the subepithelial layers. In larger cartilaginous airways, chronic bronchitis is associated with hypertrophy of submucosal mucus-producing glands. Quantitation of this anatomic change, known as the *Reid index*, is based on the ratio of the thickness of the submucosal glands to that of the bronchial wall. In persons without a history of chronic bronchitis, the mean ratio is 0.44 ± 0.09, whereas in those with such a history, the mean ratio is 0.52 ± 0.08. Although a low index is rarely associated with symptoms and a high index is commonly associated with symptoms during life, there is a great deal of overlap. Therefore, many persons will have morphologic changes in large airways without having had chronic bronchitis.

Emphysema begins as an increase in the number and size of alveolar fenestrae and results in the eventual destruction of alveolar septae and their attachments to terminal and respiratory bronchioles. Emphysema is classified according to the pattern of involvement of the gas-exchanging units (acini) of the lung distal to the terminal bronchiole. With *centriacinar emphysema*, the distention and destruction are mainly limited to the respiratory bronchioles with relatively less change peripherally in the acinus. Because of the large functional reserve in the lung, many units must be involved in order for overall dysfunction to be detectable. The centrally destroyed regions of the acinus have a high ventilation/perfusion ratio because the capillaries are missing, yet ventilation continues. This results in a deficit of perfusion relative to ventilation, while the peripheral portions of the acinus have crowded and small alveoli with intact, perfused capillaries giving a low ventilation/perfusion ratio. This results in a deficit of ventilation relative to blood flow, giving a high alveolar-arterial P_{O_2}difference (PA_{O_2}-Pa_{O_2}) (Chap. 250).

During normal aging, airspaces enlarge and alveolar ducts increase in diameter. These changes are extremely common in lungs from persons over age 50 and may be misidentified as emphysema.

Panacinar emphysema involves both the central and peripheral portions of the acinus, which results, if the process is extensive, in a reduction of the alveolar-capillary gas exchange surface and loss of elastic recoil properties. When emphysema is severe, it may be difficult to distinguish between the two types, which most often coexist in the same lung.

PATHOPHYSIOLOGY

Airflow Limitation Although both chronic bronchitis and emphysema can exist without evidence of obstruction, by the time a patient begins to experience dyspnea as a result of these processes, obstruction is always demonstrable. Airflow limitation and increased airways resistance may be caused by loss of elastic recoil driving passive exhalation due to emphysema, by increased collapsibility of small airways through loss of radial traction on airways, or to increased resistance due to intrinsic narrowing of small airways.

In addition to providing radial support to airways during quiet breathing, the elastic recoil properties of the lung serve as a major determinant of maximal expiratory flow rates. The static recoil pressure of the lung is the difference between alveolar and intrapleural pressure. During forced exhalations, when alveolar and intrapleural pressures are high, there are points in the airway at which bronchial pressure equals pleural pressure. Flow does not increase with higher pleural pressure after these points become fixed, so that the effective driving pressure between alveoli and such points is the elastic recoil pressure of the lung (Fig. 258-1). Hence maximal expiratory flow rates represent a complex and dynamic interplay among airways caliber, elastic recoil pressures, and collapsibility of airways. Correlative studies of structure and function suggest that small-airway narrowing is the most important correlate of airflow obstruction, followed by loss of elastic recoil. Collapsibility is probably a less important factor. As a direct consequence of the altered pressure-airflow relationships, the work of breathing is increased in bronchitis and emphysema. Since flow-resistive work is flow rate-dependent, there is a disproportionate increase in the work of breathing when ventilation must be increased, as in exercise.

Hyperinflation The designated subdivisions of the lung volume outlined inChap. 250 are abnormal to varying degrees in both bronchitis and emphysema. The residual volume and functional residual capacity (FRC) are almost always higher than normal. Since the normal FRC is the volume at which the inward recoil of the lung is balanced by the outward recoil of the chest wall, loss of elastic recoil of the lung results in a higher FRC. In addition, prolongation of expiration in association with obstruction would lead to a dynamic increase in FRC (dynamic hyperinflation) if inspiration is initiated before the respiratory system reaches its static balance point. Dynamic hyperinflation contributes additionally to the discomfort associated with airflow obstruction by flattening the diaphragm and placing it at a mechanical disadvantage due to shortened diaphragmatic fiber length and a perpendicular insertion with the lower ribs. The exertional increase in end-expiratory lung volume and consequent decrease in inspiratory capacity have been strongly associated with the degree of dyspnea. Elevations of total lung capacity (TLC) are frequent. The exact cause is uncertain, but increases in total lung capacity are often found in association with decreases in the elastic recoil of the lung. Although the vital capacity is frequently reduced, significant airways obstruction can be present with a normal to near-normal vital capacity.

Impaired Gas Exchange Maldistribution of inspired gas and blood flow is always present to some extent. When the mismatching is severe, impairment of gas exchange is reflected in abnormalities of arterial blood gases. Small-airway narrowing causes a decrease in ventilation of their distal alveolar acini. When alveolar capillaries remain intact, this results in mismatching of ventilation and blood flow, reduced

ventilation-perfusion ratios, and mild to moderate hypoxemia. With emphysema, destruction of alveolar walls may decrease alveolar capillary perfusion as well, better preserving ventilation-perfusion matching, and Pa_{O_2}. Shunt hypoxemia is unusual. There are regions of the lung with a deficit of perfusion in relation to ventilation that increase the wasted ventilation ratio (i.e., V_d/V_t; Chap. 250). At a normal resting CO_2 production, the net effective alveolar ventilation, as reflected by the arterial P_{CO_2}, may be excessive, normal, or insufficient, depending on the relationship of the overall minute volume to the wasted ventilation ratio.

The severity of gas exchange disturbances and, in large part, the clinical manifestations depend on the ventilatory response to the disordered lung function. Some patients, at the cost of extremely high effort of breathing and chronic dyspnea, maintain a strikingly increased minute volume, which results both in a normal to low arterial P_{CO_2}, despite the high V_d/V_t, and a relatively high arterial P_{O_2}, despite the high difference, PA_{O_2}-Pa_{O_2}. Other patients with only modest increases in effort of breathing and less dyspnea maintain a normal to only moderately elevated minute volume at the cost of accepting a high arterial P_{CO_2} and a severely depressed arterial P_{O_2}.

Factors that account for clear differences in ventilatory responses among patients have been studied and debated for years. The bulk of available evidence suggests that those patients who maintain relatively normal or low arterial P_{CO_2} levels are those with an increased ventilatory drive relative to their blood gas values, and those who chronically maintain high arterial P_{CO_2} and lower P_{O_2} levels have a diminished ventilatory drive in relation to their more severely deranged blood gas values. It is not at all certain whether individual differences are accounted for by variations in peripheral or central chemoreceptor sensitivity or through other afferent pathways.

Pulmonary Circulation The pulmonary circulation malfunctions not only in terms of regional distribution of blood flow but also in terms of abnormal overall pressure-flow relationships. In advanced disease, there is often mild to severe pulmonary hypertension at rest, with further increases disproportionate to cardiac output elevations during exercise. A reduction in the total cross-sectional area of the pulmonary vascular bed can be attributed to thickening of medium and large muscular pulmonary arteries, to enhanced contraction of vascular smooth muscle in pulmonary arteries and arterioles, as well as to destruction of alveolar septa with loss of capillaries. Rarely does loss of capillaries alone lead to severe pulmonary hypertension with cor pulmonale, except as a near-terminal event (Chap. 237). Of more importance is the constriction of pulmonary vessels in response to alveolar hypoxia. The pulmonary arteries of patients with severe hypoxemia COPD have been shown to exhibit increased contractility and impaired relaxation in response to pharmacologic stimuli in vitro. These differences between the pulmonary arteries of COPD patients and normal individuals are abolished by inhibition of NO synthase, suggesting that patients develop an endothelial defect in NO synthesis. The constriction is somewhat reversible by an increase in alveolar P_{O_2} with therapy.

There is a synergism between hypoxia and acidosis that assumes importance during episodes of acute or chronic respiratory insufficiency. Chronic hypoxia, especially in concert with carboxyhemoglobinemia, often seen with heavy cigarette smoking, leads not only to pulmonary vascular constriction but also to secondary erythrocytosis. The latter, although not proved to be a significant contributor to pulmonary hypertension,

could add to pulmonary vascular resistance. As discussed inChap. 237, chronic afterload on the right ventricle leads to hypertrophy and, in association with disordered blood gases, ultimately to failure. Hypoventilation may occur during rapid eye movement sleep and lead to desaturation, which may be severe. Repeated desaturation may cause pulmonary hypertension.

Renal and Hormonal Dysfunction Chronic hypoxemia and hypercapnia have been shown to cause increased circulating levels of norepinephrine, renin, and aldosterone and decreased levels of antidiuretic hormone. Renal arterial endothelium inCOPDpatients exhibits defects similar to those seen in the pulmonary arteries, shifting renal blood flow from the cortex to the medulla and impairing renal functional reserve. The combination of hemodynamic and hormonal disturbances leads to defective excretion of salt and water loads and, together with right ventricular dysfunction, to the plethoric and cyanotic manifestations of some patients with COPD.

Cachexia Weight loss sometimes occurs in patients with advancedCOPD. A body-mass index (BMI) < 25 kg/m_2 is associated with increased frequency of exacerbations and with significantly reduced survival. Cachexia has been attributed to caloric intake failing to keep pace with energy expenditures associated with increased work of breathing, but more recent evidence suggests that a biochemical basis is more likely. Hypoxemia leads to increased circulating levels of tumor necrosis factora (TNF-a), and weight loss has now been correlated with levels of the latter.

Peripheral Muscle Dysfunction Protein and muscle are lost as part of wasting in advancedCOPD. Skeletal muscle bulk is lost with proportional reductions in strength. Proximal limb girdle muscles of the upper and lower extremities are particularly affected, contributing to dyspnea with activities of daily living. Fiber composition in skeletal muscle changes, favoring endurance over strength. These changes occur in parallel with$FEV_1$and independently of glucocorticoid use, which can also cause myopathy and muscle weakness.

Osteoporosis Loss of bone density is common in advanced disease. Over half ofCOPDpatients lose more than 1 SD of bony density, and more than one-third have values more than 2 SDs below normal. Vertebral fractures are especially common. These changes are even more severe in patients receiving chronic glucocorticoid therapy.

NATURAL HISTORY

COPDis identified by the presence of an abnormalFEV_1in middle age, usually early in the fifth decade, and is characterized by an accelerated decline of $FEV_1$with aging. In normal individuals, FEV_1normally reaches a lifetime peak at age 25 and undergoes a linear decline of about 35 mL per year thereafter. Annual loss of FEV_1among susceptible individuals who develop COPD is between 50 and 100 mL per year. Greater rates of decline have been associated with mucus hypersecretion, especially in men, and with bronchial hyperreactivity. Acute exacerbations do not alter the rate of decline. Dyspnea and impairment of physical work capacity are characteristic only of moderately severe to severe airways obstruction. There is considerable variation among individual patients. The majority of patients usually experience exertional dyspnea when FEV_1falls

below 40% of predicted and have dyspnea at rest when the FEV_1<25% of predicted. In addition to dyspnea at rest, CO_2retention and cor pulmonale frequently occur when the FEV_1falls to 25% of predicted. With a respiratory infection, small changes in the degree of obstruction can make a large difference in symptoms and gas exchange. Thus small therapeutic gains may have rewarding results.

Exacerbation The clinical course ofCOPD can be characterized as one of slow progression and relative stability punctuated by episodic exacerbations occurring, on average, a little more than once per year. Exacerbations are generally described as a worsening of previously stable disease characterized by increased dyspnea, wheeze, and cough and sputum volume, tenacity, and purulence, with variable degrees of water retention and with worsening gas exchange and ventilation-perfusion relationships. Hyperinflation and work of breathing are increased. To the extent that diaphragmatic function and neuromuscular drive can compensate for the increased work, Pa_{CO_2}will not rise, but when work demands exceed respiratory pump capacity, hypercapnia and respiratory acidemia ensue. Cardiac output often does not increase sufficiently to compensate for the increased oxygen consumption from respiratory muscles, thereby compounding the hypoxemia due to / mismatching and hypercapnia.

MostCOPDexacerbations are thought to be a consequence of acute tracheobronchitis, usually infectious. Most infections are primarily bacterial or the consequence of bacterial superinfection of a primary viral process. Exacerbations may also be triggered by, and must be distinguished from, left ventricular failure, cardiac arrhythmias, pneumothorax, pneumonia, and pulmonary thromboembolism. Upper airway obstruction, aspiration, rhinitis or sinusitis, asthma, or gastroesophageal reflux should be excluded. Although COPD exacerbations are individually serious and potentially life-threatening, they do not cause accelerated declines ofFEV_1over time.

CLINICAL MANIFESTATIONS

HISTORY

Patients withCOPD are most often tobacco smokers with a history of at least one pack per day for at least 20 years. The disease is only rarely seen in nonsmokers. Onset is typically in the fifth decade and often comes to attention as a productive cough or acute chest illness. Exertional dyspnea is usually not encountered until the sixth or seventh decade. The patient's perception of dyspnea correlates poorly with physiologic measurements, especially among older patients. A morning "smoker's cough" is frequent, usually mucoid in character but becoming purulent during exacerbations, which in early disease are intermittent and infrequent. Volume is generally small. Production of more than 60 mL/d should prompt investigation for bronchiectasis. The frequency and severity of cough generally do not correlate with the degree of functional impairment. Wheezing may be present but does not indicate severity of illness. As COPD progresses, exacerbations become more severe and more frequent. Gas exchange disturbances, worsen and dyspnea becomes progressive. Exercise tolerance becomes progressively limited. With worsening hypoxemia, erythrocytosis and cyanosis may occur. The development of morning headache may indicate the onset of significant CO_2retention. In advanced disease, weight loss is frequent and correlates with an adverse prognosis. When blood gas derangements are severe, cor pulmonale may

manifest itself by peripheral edema and water retention. Anxiety, depression, and sleep disturbances are not infrequent.

PHYSICAL FINDINGS

The physical examination has poor sensitivity and variable reproducibility inCOPD. Findings may be minimal or even normal in mild disease, requiring objective laboratory data for confirmation. In early disease, the only abnormal findings may be wheezes on forced expiration and a forced expiratory time prolonged beyond 6 s. With progressive disease, findings of hyperinflation become more apparent. These include an increased anteroposterior diameter of the chest, inspiratory retraction of the lower rib margins (Hoover's sign), decreased cardiac dullness, and distant heart and breath sounds. Coarse inspiratory crackles and rhonchi may be heard, especially at the bases. To gain better mechanical advantage for their compromised respiratory muscles, patients with severe airflow obstruction may adopt a characteristic tripod sitting posture with the neck angled forward and the upper torso supported on the elbows and arms. Breathing through pursed lips prolongs expiratory time and may help reduce dynamic hyperinflation.

Cor pulmonale and right heart failure may be evidenced by dependent edema and an enlarged, tender liver (Chap. 237). With pulmonary hypertension, a loud pulmonic component of the second heart sound may be audible, along with a right ventricular heave and a murmur of tricuspid regurgitation; these findings may be obscured by hyperinflation. If right-sided pressures are sufficiently high, neck veins may elevate instead of collapse with inspiration (Kussmaul's sign). Cyanosis is a somewhat unreliable manifestation of severe hypoxemia and is seen when severe hypoxemia and erythrocytosis are present.

Radiographic Findings A posteroanterior and lateral chest film should be obtained primarily to exclude competing diagnoses. They may be entirely normal in mild disease. AsCOPDprogresses, abnormalities reflect emphysema, hyperinflation, and pulmonary hypertension. Emphysema is manifested by an increased lucency of the lungs. In smokers, these changes are more prominent in the upper lobes, while ina_1ATdeficiency, they are more likely in basal zones. Local radiolucencies>1 cm in diameter and surrounded by hairline arcuate shadows indicate the presence of bullae and are highly specific for emphysema. With hyperinflation, the chest becomes vertically elongated with low flattened diaphragms. The heart shadow is also vertical and narrow. The retrosternal airspace is increased on the lateral view, and the sternal-diaphragmatic angle exceeds 90°. In the presence of pulmonary hypertension, the pulmonary arteries become enlarged and taper rapidly. The right heart border may become prominent and impinge on the retrosternal airspace. The presence of "dirty lung fields" may reflect the presence of bronchiolitis.

Computed tomography has greater sensitivity and specificity for emphysema than the plain film but is rarely necessary except for the diagnosis of bronchiectasis and evaluation of bullous disease. Nonhomogeneous distribution of emphysema is thought by some to be an indicator of suitability for lung volume reduction surgery (LVRS).

PULMONARY FUNCTION TESTING (See alsoChap. 250)

Because of the imprecision of clinical findings, objective evaluation of the presence, severity, and reversibility of airflow obstruction is essential in the diagnostic evaluation ofCOPD. A normalFEV$_1$essentially excludes the diagnosis. The spirogram in COPD shows decreased volume changes with time and a failure to reach a plateau after 3 to 5 s. Continued airflow may be evident for 10 s or more on forced exhalation. The flow-volume curve shows diminished expiratory flow at all lung volumes. Expiratory flow is concave to the volume axis. When flow is plotted against absolute lung volume, the entire curve is shifted to higher volumes, reflecting hyperinflation. Serial spirometry is important in assessing the rate of decline of FEV$_1$.

Reversibility is assessed by spirometry before and after administration of an inhaled bronchodilator, most often a short-actingb$_2$-adrenergic agonist. Testing should be performed when the patient is clinically stable. Short-acting bronchodilators should be withheld for 6 h, long-acting dilators for 12 h, and theophylline for 24 h prior to testing. A significant response is an increase of at least 12% and 200 mL in eitherFEV$_1$or forced vital capacity (FVC). Postbronchodilator FEV$_1$ is useful for prognostication. Although only one-third ofCOPDpatients show a significant response to an inhaled bronchodilator in the pulmonary function laboratory on any one day, two-thirds will show a significant response when tested with different bronchodilators on several different occasions. The degree of bronchodilator response at any one testing session does not predict the degree of clinical benefit to the patient. Therefore, bronchodilators are given irrespective of the acute response obtained in the pulmonary function laboratory. The American Thoracic Society recommends staging COPD by FEV$_1$. Stage I, mild disease, is defined as FEV$_1$[3] 50% predicted; stage II, moderate disease, 35 to 49% predicted; and stage III, severe disease,<35% predicted.

Lung volumes are useful for the assessment of hyperinflation. Transfer factor for carbon monoxide (DL$_{CO}$) correlates negatively with the degree of emphysema but is not specific and may miss mild disease. Neither test is indicated routinely, but DL$_{CO}$ may help distinguish chronic asthma from emphysema.

Measurements for arterial blood gas are not needed for mild disease, but they should be assessed routinely for stage II or stage IIICOPD. Patients with pulmonary hypertension or cor pulmonale with normal daytime blood gases should be evaluated for nocturnal desaturation by overnight oximetry. Polysomnography to exclude concurrent sleep apnea should be obtained for patients who also complain of excessive daytime somnolence or who have a history of snoring.

a$_1$ATlevels are not needed routinely but should be obtained for chronic airflow obstruction or chronic bronchitis in nonsmokers, as well as inCOPDpatients with bronchiectasis, cirrhosis without apparent risks, premature emphysema, or basilar emphysema; in patients under age 50 with unremitting asthma; and in individuals with a family history ofa$_1$AT deficiency.

TREATMENT

Treatment of COPDis based on the principles of prevention of further evolution of disease, preservation of airflow, preservation and enhancement of functional capacity,

management of physiologic complications, and avoidance of exacerbations.

Smoking Cessation (See also Chap. 390) The Lung Health Study has demonstrated that elimination of tobacco smoking confers significant survival benefit to patients with COPD. Prolonged survival is associated with reduced rates of malignancy and cardiovascular disease as well as with a significant increment in FEV_1 in the first year after smoking cessation. The rate of decline of FEV_1 reverts back to that of a nonsmoker. Although bronchodilator therapy produces similar first-year gains in FEV_1, pharmacotherapy alone does not modify the decline of airflow over time. Even unsuccessful quitters show significant benefits when compared to continuing smokers.

Despite the demonstrated benefits of smoking cessation, sustained quitting is difficult to achieve. Overall, only 6% of smokers succeed in quitting long term, and 70 to 80% of short-term quitters start smoking again. Successful quitting requires concerted active and continuing intervention by the physician. The physician should address the issue in regular patient visits, assess the patient's readiness to quit, advise the patient as to the best methods for smoking cessation, provide emotional and pharmacologic support, and arrange close follow-up of the patient's efforts. The concept of "lung age" may be helpful in promoting smoking cessation by determining the age at which the observed FEV_1 would be a normal finding. Lungs of 50- to 60-year-old smokers may be "normal" for a 70- to 80-year-old individual. Nicotine patches and nicotine polacrilex gum improve quit rates, especially among nicotine-dependent smokers. The addition of oral bupropion at 150 mg twice daily produces significant additional benefit, with a 1-year sustained abstinence rate of 22.5% compared to 6% for placebo. Smoking cessation is typically associated with weight gain of 3 to 4 kg. To minimize weight gain, reluctance to quit, and relapse, prospective quitters should be counseled to reduce caloric intake and to increase physical activity.

Bronchodilators These drugs improve dyspnea and exercise tolerance by improving airflow and by reducing end-expiratory lung volume and air-trapping. Although airflow limitation is relatively fixed, some degree of response to bronchodilator medication is usually present. Bronchodilator medication is available in metered-dose inhaler (and some dry-powder inhalers) and in nebulizable and oral forms. Inhalers deliver medications directly to the airways and have limited systemic absorption and side effects. Proper use requires timing and coordination of inspiration and inhaler actuation and presents frequent difficulties for chronic lung patients. These problems can usually be overcome with education and with the use of holding chambers. Aerosol nebulizers have no pharmacologic advantage over metered-dose inhalers. Their use should be limited to patients who remain unable to master metered dose inhalers adequately. Oral medication is associated with higher rates of adherence than inhalers but shows higher rates of systemic side effects without superior bronchodilation.

Three major classes of bronchodilators are commonly employed in the treatment of patients with COPD: short- and long-acting β_2-adrenergic agonists, anticholinergics, and theophylline derivatives. Short-acting β_2-agonists (albuterol, pirbuterol, terbutaline, metaproterenol) are relatively bronchoselective with minimal effects on heart rate and blood pressure. They produce significant bronchodilation at 5 to 15 min and remain effective for 4 to 6 h. Long-acting β_2-agonists (oral sustained-release albuterol and inhaled salmeterol) have an onset of action of 15 to 30 min and a 12-h duration of

action. Anticholinergic agents (ipratropium bromide) have a 30- to 60-min onset of action and a 4- to 6-h duration. Theophyllines are generally administered orally in 12- or 24-h preparations. Recommended bronchodilator regimens are shown in Table 258-1.

Regular use of ipratropium may lead to improvements in baseline FEV_1 when compared with short-acting β_2-agonists. When used together, ipratropium and short-acting β_2-agents show greater clinical efficacy than either agent alone, without an increase in side effects. Salmeterol as a single agent produces longer lasting bronchodilation than ipratropium, improves baseline FEV_1 over time, and is not associated with loss of efficacy over a period of several months. Salmeterol, however, has not yet been evaluated as a component of combination therapy.

Theophylline is a weak bronchodilator with a narrow therapeutic window. Much of its clinical benefit derives from effects other than bronchodilation; therapeutic doses of theophylline increase ventilatory drive, enhance diaphragmatic contractility, and increase cardiac output. About 20% of COPD patients respond to theophylline with improved airflow, exercise tolerance, and quality of life. Theophylline produces additional benefits in exercise capacity and quality of life when used in combination with short-acting β_2-adrenergic agonists. The therapeutic range for theophylline is commonly given as 10 to 20 ug/mL, with greater efficacy but greater toxicity seen at higher serum levels. The risk of toxicity is greater in older patients and in those with heart and kidney disease. Optimal dosing must balance the competing considerations of risk and benefit for each individual patient.

Glucocorticoids Because COPD, like asthma, is a disease associated with airway inflammation, glucocorticoids are an intuitively attractive therapeutic modality. Nevertheless, results of clinical trials of glucocorticoid therapy in COPD patients have shown less impressive benefits when compared to patients with asthma. The degree of response to glucocorticoids appears to correlate with the presence of asthmatic features, but data supporting their use is limited. Only 10% more patients show subjective benefit and increase their FEV_1 or forced vital capacity by at least 20% when compared to those on placebo. Responders cannot be reliably identified on clinical grounds, although response to an inhaled β_2-agonist is commonly used as a predictor. The benefits of a 10- to 14-day trial of 30 to 40 mg/d of prednisone for patients with stage III disease who have not responded adequately to mixed bronchodilator therapy remain to be proven. Long-term systemic glucocorticoid use is associated with multiple side effects. In particular, they have been associated with worsened osteoporosis and increased risk of vertebral fracture. If systemic steroids are used, the lowest effective dose should be employed and alternate-day dosing used whenever possible. The use of inhaled glucocorticoids ameliorates systemic side effects. Three large clinical trials have shown that inhaled glucocorticoids do not alter the rate of decline of FEV_1. While an inhaled glucocorticoid does not decrease the number or frequency of COPD exacerbations, it may decrease their severity and reduce the need for hospitalization. Symptoms and exercise tolerance improve on inhaled glucocorticoids.

Management of α_1AT Deficiency Given the central role of smoking in the pathogenesis of disease, smoking cessation is an important cornerstone in the management of α_1AT deficiency. Exogenous α_1AT derived from pooled human plasma administered intravenously in a weekly dose of 60 mg/kg has been shown to induce protective levels

ofa1AT in deficient individuals. Because of the expense and inconvenience of the treatment, replacement ofa1AT is used only for patients over age 18 witha1AT levels below 11 umol/L who have stopped smoking and who have airflow obstruction. A recently published large nonrandomized trial showed that augmentation therapy significantly decreased 5-year mortality (RR 0.64) for patients receiving replacement. The rate of decline ofFEV1also decreased with augmentation therapy. In both instances, benefit was largely restricted to those patients with FEV1 35 to 49% of predicted. These findings require confirmation in randomized controlled trials.

Oxygen Severe and progressive hypoxemia is often seen in advancedCOPD and may result in cellular hypoxia with deleterious physiologic consequences. The establishment of adequate systemic oxygen transport is essential to the prevention of tissue hypoxia and requires attention to cardiac output and hemoglobin concentration as well as to arterial O2saturation (SaO2). Long-term O2therapy has been shown to reverse secondary polycythemia; improve body weight; ameliorate cor pulmonale; and enhance neuropsychiatric function, exercise tolerance, and activities of daily living. Two major studies, one in the United States and one in the United Kingdom, established a survival benefit for long-term O2therapy that increased with the number of hours per day that O2 was used. The mechanism for this benefit has not been conclusively elucidated, but it appears to be related to the stabilization of pulmonary hemodynamics.

The need for long-term O2therapy should be documented with measurement of arterial blood gases obtained at rest and confirmed by a separate determination of resting arterial blood gases during a period of medical stability after 30 to 90 days of optimum medical therapy. Once the need for O2 has been demonstrated in a stable patient, the requirement is generally for the duration of the patient's life. Patients with a PaO2£ 55 mmHg or SaO2£ 88% should be provided with oxygen titrated to raise SaO2 to³90%. Oxygen is likewise indicated for patients who have a PaO2 of 56 to 59 mmHg with SaO2³ 89% when hematocrit is >55% or when cor pulmonale or other objective evidence of pulmonary hypertension is present. Oxygen may be appropriate for patients whose resting awake PaO2³60 mmHg with SaO2³ 90% if they become hypoxic during exercise or sleep. Once oxygen is prescribed, the dose should be titrated to maintain SaO2³ 90% during sleep and normal walking, as well as at rest, and it should be used for a minimum of 15 h a day to realize a survival benefit.

Oxygen is most frequently delivered through a nasal cannula at rates of 2 to 5 L/min. Oxygen-sparing cannulae are available. Transtracheal administration provides further O2-sparing benefits but requires scrupulous attention to catheter maintenance and hygiene and is not suitable for all patients. Oxygen is packaged as compressed gas or compressed liquid or can be delivered from an O2concentrator, a molecular sieve that enriches O2 by removing nitrogen from ambient air. O2should be prescribed from sources that are appropriate to the individual patient's life-style and needs. It is customary to provide a stationary O2source, either an O2concentrator, which is dependent on a reliable source of electricity, or 100-kg (200-lb) H cylinders of compressed O2. Flow resistance imposes a 15-m (50-ft) practical limit to the length of tubing connecting the O2source to the patient's cannula. For patients whose activities of daily living require ambulation beyond this limit, ambulatory or portable systems should be provided. Ambulatory O2 needs may be met with rolling 10-kg (22-lb) E cylinders of compressed O2, or with portable 2-kg (4.5-lb) aluminum cylinders or 3-kg (6.6-lb) liquid

oxygen packs. The duration of O_2availability from an O_2concentrator is unlimited. For compressed gas and liquid sources, the amount of available oxygen is determined by the size of the system and the patient's liter flow needs. Portable systems generally provide 4 to 5 h of O_2flow.

Oxygen therapy is generally safe. Cylinders should be secured to prevent tipping over or potentially explosive disconnection of the regulator valve. Oxygen should be stored away from open flames or other source of heat, and patients and family members should be educated to be especially scrupulous about avoiding smoking in the presence of flowing O_2.

Prophylaxis No evidence supports the prophylactic use of antibiotics in stableCOPD. Yearly influenza vaccination is recommended for all patients with chronic cardiopulmonary disease, although objective benefit has not been conclusively demonstrated. Pneumococcal vaccination with 23-valent polysaccharide is also recommended. Amantadine should be used for unvaccinated patients who are placed at risk by an outbreak of influenza A.

Rehabilitation Airflow limitation, dyspnea, and muscle loss and deconditioning all compromise cardiopulmonary fitness and contribute to a progressively constrained daily life and unsatisfactory quality of life. Pulmonary rehabilitation is a multidisciplinary program of care for patients with chronic respiratory impairments that is individually tailored and designed to optimize physical and social performance. A pulmonary rehabilitation program consists of exercise training, patient education, psychosocial and behavioral intervention, and regular assessment of outcomes and is designed to minimize the disability and handicap imposed by the physiologic impairments consequent toCOPD. Rehabilitation in COPD should be considered for patients with persistent symptoms and disability despite optimal medical management. Spirometric criteria should not be the primary basis for referral into rehabilitation programs. Exercise consists of 20 to 30 min of upper and lower extremity exercise at 60 to 75% maximumO_2 or heart rate two to five times a week. Both strength and endurance exercises are provided. Education covers pursed lip and other breathing strategies to minimize dyspnea, energy-conservation skills, principles of medications and proper use of metered-dose inhalers, nutrition, and end-of-life decision-making. Behavioral interventions focus on dyspnea, depression, and self-sufficiency and on issues of control, coping, and role function. Dyspnea, exercise tolerance, activity level, and quality of life are followed at regular intervals. Pulmonary rehabilitation programs have been shown to improve endurance time for submaximal exercise by 38 to 80% and 6-min walking distance by 80 to 113 m. Clinically meaningful reduction in dyspnea and improvement of quality of life have been reported. No clinical trials have been adequately designed to address the issue of survival benefit. Reductions in costs of care and resource consumption have not reached statistical significance.

Despite maximal medical therapy, whenCOPDprogresses to stage III and is complicated by hypercapnia or pulmonary hypertension, surgical approaches to treatment may be considered.

Transplantation (See alsoChap. 267) Owing to its frequency in the general population, emphysema is the most common indication for lung transplantation. Transplantation

should be actively considered for end-stage COPD patients when the prognosis from the disease is worse than the survival statistics for the surgery. Lung transplantation should be considered for COPD patients who, despite maximal medical therapy, have an FEV_1 < 25% predicted and with pulmonary hypertension or cor pulmonale. Precedence is given to those patients with a Pa_{CO2} of 55 mmHg and progressive deterioration. Asthma and other reversible airflow limitation must be excluded. Rehabilitation and long-term O_2 therapy, where appropriate, should be provided prior to transplant evaluation.

Lung Volume Reduction Surgery LVRS, or pneumectomy, is designed to relieve dyspnea and improve exercise function in severely disabled patients with stage III emphysema. At operation, severely emphysematous lung tissue is resected, leading to improvement in elastic recoil in the remaining pulmonary parenchyma. This decreases hyperinflation and enhances diaphragmatic function, with consequent 25 to 50% improvement of airflow and exercise capacity. In early uncontrolled studies, hospital mortality for LVRS ranged from 5 to 18% and hospital stays averaged 9 to 18 days, with frequent significant air leaks. Cost of LVRS was $33,000 to $70,000 per case. Because of the large number of potential candidates, the high cost involved, and unanswered questions about the benefits of the operation, use of LVRS in the United States has been restricted to a multicenter randomized controlled trial, the National Emphysema Treatment Trial (NETT), comparing LVRS with best medical therapy. Stage III emphysema patients accepted for evaluation into NETT are under age 75, are severely hyperinflated, and have severe dyspnea despite optimal medical therapy. Contraindications to LVRS are similar to those for lung transplantation, including active smoking, marked obesity or cachexia, and inability to undertake pulmonary rehabilitation successfully. There has been little consensus regarding features identifying ideal and suboptimal candidates for the surgery. Radiographic heterogeneity of disease and the absence of significant intrinsic airway disease have been suggested characteristics of patients likely to benefit. Results from the NETT suggest that physiologic benefits from LVRS may begin to be lost as early as 1 year after surgery. Accelerated declines of FEV_1 have been reported, averaging 100 mL per year and particularly marked in those patients with the greatest postoperative gains in airflow. Improvements in dyspnea and exercise tolerance may be sustained for as long as 3 years but may decline thereafter. Until these issues are satisfactorily resolved, LVRS will remain an experimental procedure.

Treatment of Exacerbations

Triage The initial decision in the management of an exacerbation of COPD is whether hospitalization is necessary. Rapidity of evolution of symptoms and response to initial therapy, level of consciousness, presence or absence of respiratory distress, severity of gas exchange disturbance, and arterial blood gas deviation from the patient's stable baseline should influence the decision to hospitalize. The patient's ability to manage at home and the resources available for home care should weigh heavily in the decision-making process.

Home Therapy For patients with mild exacerbations for whom outpatient therapy is appropriate, a combination of anticholinergic and short-acting b_2-adrenergic agonist bronchodilators should be prescribed. Although b_2-agonists may be given as frequently as once an hour, there is no advantage to administering anticholinergic bronchodilators

more frequently than every 4 to 6 h. Metered-dose inhalers should be used with spacers. There is no evidence that the use of nebulizers provides any improvement in outcome.

The presence of increased sputum volume or purulence suggest an infectious cause of an exacerbation. With either of these features is present in conjunction with increased breathlessness or when both are present, antibiotics should be prescribed. The organisms most frequently associated with mildCOPDexacerbations include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Trimethoprim/sulfamethoxazole, doxycycline, or amoxicillin is an appropriate management option, although choices may be modified by local antibiotic sensitivity data.

There is a need for well-controlled studies on the utility of glucocorticoids in the outpatient management ofCOPDexacerbations. Oral glucocorticoids may be continued in patients already receiving such treatment or given to patients who do not show a satisfactory response to bronchodilator therapy. The usual dose is 20 to 40 mg daily for 7 to 10 days. Short-term glucocorticoid therapy lasting less than 3 weeks may be discontinued without the use of a tapering dose.

Hospital Management For patients with exacerbations of sufficient severity to warrant hospitalization, improvement of airflow, gas exchange, and acid-base status are of central importance. Hospitalized patients should receive bronchodilators, antibiotics, oral glucocorticoids, and sufficient O_2 to keep the Sa_{O2}³ 90%.b_2-agonists and anticholinergic agents should be given together every 4 to 6 h. The frequency of sympathomimetic bronchodilator administration may be increased as needed to as often as every 20 min. Because high doses ofb_2-agonists may cause hypokalemia, serum potassium levels and heart rate should be monitored closely for patients receiving frequent doses of these agents. Data are contradictory regarding the addition of theophylline to the bronchodilator regiment of patients showing an inadequate initial response, yet the current American and British Thoracic Societies' guidelines recommend consideration of its use to produce plasma theophylline levels between 10 and 20 ug/mL. Oral glucocorticoids have been shown to produce modest improvements in$FEV_1$and in the duration of hospitalization forCOPDexacerbations. Recent data indicate that more severe COPD exacerbations are associated with the recovery of enterobacteriaciae in respiratory secretions. For this reason, a second- or third-generation cephalosporin, a fluoroquinolone, a second-generation macrolide, or an extended-spectrum penicillin is now recommended as initial therapy. Attempts to obtain diagnostically adequate sputum should be made, and, when available, sputum results should be used to individualize therapy in the light of local microbial sensitivity spectra. Oxygen therapy is an important component of the management of a severe exacerbation of COPD. It is important to maintain the Sa_{O2}> 90% and Pa_{O2}between 60 and 65 mmHg for most patients. In many cases, administration of O_2 will result in worsening hypercapnia, although rarely to a clinically significant degree if the O_2 is used only in amounts to achieve the minimal goals. The elevation of Pa_{CO2} is multifactorial, resulting from increased dead space due to reduced tidal volume as well as from the Haldane effect, i.e., a right wave shift of the CO_2dissociation curve in the presence of increased saturated hemoglobin. The lower the initial Pa_{O2} and the greater the increase, the larger the increase in Pa_{CO2}observed. Patients whose pH on presentation is below

7.25 and with Pa_{O_2}< 50 mmHg are at particular risk and should be observed closely.

For patients at increased risk of hypercapnia, administration of controlled concentrations of O_2through a Venturi mask is reasonable. Inspired O_2concentrations (FI_{O_2}) of 0.24 to 0.28 are usually sufficient to keep Sa_{O_2}³90%.

*MECHANICAL VENTILATION (See also*Chap. 266*)* Patients with impaired consciousness, respiratory distress evidenced by tachypnea with a respiratory rate greater than 35 breaths per minute and/or abdominal paradox, severe hypoxemia, or significant respiratory acidosis with pH< 7.25 and who deteriorate despite treatment are candidates for immediate ventilatory support using either noninvasive (mask) or invasive (intubation) approaches. The goals are to buy time for medical treatments to take effect, to rest the respiratory muscles, and to improve gas exchange abnormalities while avoiding the major complications of mechanical ventilatory support.

Noninvasive positive-pressure ventilation (NIPPV) delivered by nasal mask should be considered in units that have experience with the technique for patients who remain alert and cooperative, who are not heavily sedated, who are hemodynamically stable, and who are able to clear their airways by coughing up secretions. In these circumstances, NIPPV has been shown to be successful in avoiding the need for endotracheal intubation in up to 70% of cases. Success, as evidenced by improved $Pa_{CO_2}$and pH, should be evident within the first 60 min. Part-time NIPPV for 6 to 8 h per day may afford sufficient respiratory muscle rest to avert the need for invasive conventional ventilation. Failed attempts at NIPPV can be followed by intubation and conventional ventilation and do not appear to carry a worse prognosis. Successful application of NIPPV has been associated with a decrease in intensive care and hospital stays, incidence of nosocomial pneumonia, and costs.

Before committing to endotracheal intubation and conventional ventilatory support, the patient's wishes for such support, the patient's quality of life, and the benefits and costs of care should be thoroughly reviewed. Where the patient's wishes cannot be clearly ascertained or there is uncertainty about the appropriateness of the intervention, intubation and ventilation should proceed. If mechanical ventilatory support is subsequently determined to be inappropriate, support may then be withdrawn.

Once intubation is accomplished, the patient can be ventilated in the controlled ventilation, assist-control, intermittent mandatory ventilation, or pressure support modes. FI_{O_2}should be sufficient to obtain Sa_{O_2}³ 90% and Pa_{O_2} of 60 to 65 mmHg. An FI_{O_2} of 0.24 to 0.40 is usually adequate for the purpose. Minute volume should be adequate to keep pH ³ 7.25, but one should not strive to achieve a "normal" Pa_{CO_2}. It is important to try to avoid overventilation and hyperinflation in ventilatedCOPDpatients. Because the time constant for exhalation is abnormally prolonged, it is essential to allow adequate expiratory time to permit as complete emptying of each breath as possible, preferably at least 3 to 4 s. This is best accomplished by minimizing tidal volume and respiratory rate. Lesser gains in expiratory (E) time can be obtained by high inspiratory (I) flow rates and I:E ratios of 1:2 or higher. Inadequate expiratory time leads to dynamic hyperinflation and in turn to the development of intrinsic positive end-expiratory pressure (PEEPi). PEEPi is just as capable of producing hypotension as extrinsically applied PEEP. When a mechanically ventilated patient with obstructive lung disease abruptly develops

hypotension, PEEPi should be excluded, either by direct measurement or by disconnecting the patient from the ventilator for 30 to 60 s. PEEPi and dynamic hyperinflation increase the work of breathing, place the diaphragm at mechanical disadvantage, and contribute significantly to difficulties in weaning from ventilatory support. Over a period of days, as the underlying precipitants of the exacerbation are controlled, airway obstruction gradually remits and gas exchange improves and it becomes appropriate to consider removal from mechanical ventilatory support.

The principles of weaning from mechanical ventilation are discussed in detail in Chap. 266.

Prognosis after Exacerbation The hospital mortality rate for an episode of respiratory failure in COPD ranges from 11 to 25% and depends on the severity of the episode, the patient's chronic health and nutritional status, and the presence of cor pulmonale or congestive heart failure. Data regarding subsequent course may be helpful in educating COPD patients and in guiding their subsequent management decisions. Among survivors of mechanical ventilation, the 6-month mortality rate is approximately 40%. Two-thirds of survivors have frequent recurrences of exacerbations, and functional status thereafter is often poor.

(Bibliography omitted in Palm version)

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259. INTERSTITIAL LUNG DISEASES - *Talmadge E. King, Jr.*

The interstitial lung diseases (ILDs) represent a large number of conditions that involve the parenchyma of the lung -- the alveoli, the alveolar epithelium, the capillary endothelium, and the spaces between these structures, as well as the perivascular and lymphatic tissues. This heterogeneous group of disorders is classified together because of similar clinical, roentgenographic, physiologic, or pathologic manifestations. These disorders are often associated with considerable morbidity and mortality, and there is little consensus regarding the best management of most of them.

ILDshave been difficult to classify because more than 200 known individual diseases are characterized by diffuse parenchymal lung involvement, either as the primary condition or as a significant part of a multiorgan process, as may occur in the connective tissue diseases (CTDs). One useful approach to classification is to separate the ILDs into two groups, those of known and those of unknown causes (Table 259-1). Each of these groups can be subdivided into subgroups according to the presence or absence of histologic evidence of granulomas in interstitial or vascular areas. For each ILD there may be an acute phase, and there is usually a chronic one as well. Rarely, some are recurrent, with intervals of subclinical disease.

Sarcoidosis (Chap. 318), idiopathic pulmonary fibrosis (IPF), and pulmonary fibrosis associated withCTDs(Chaps. 311 to 317) are the most commonILDs of unknown etiology. Among the ILDs of known cause, the largest group comprises occupational and environmental exposures, especially the inhalation of inorganic dusts, organic dusts, and various fumes or gases (Chaps. 253 and254). A clinical diagnosis is possible for many forms of ILD, especially if an occupational and environmental history is aggressively pursued. For other forms, tissue examination, usually obtained by thoracoscopic or open lung biopsy is critical to confirmation of the diagnosis. High-resolution computed tomography (HRCT) scanning promises to improve diagnostic accuracy further as histologic-image correlation is perfected.

PATHOGENESIS

TheILDs are nonmalignant disorders and are not caused by identified infectious agents. The precise pathway(s) leading from injury to fibrosis is not known. Although there are multiple initiating agent(s) of injury, the immunopathogenic responses of lung tissue are limited, and the mechanisms of repair have common features. Two major histopathologic patterns are found in patients with ILD: a granulomatous pattern (Fig. 259-1) and a pattern in which inflammation and fibrosis predominate.

GRANULOMATOUS LUNG DISEASE

This process is characterized by an accumulation of T lymphocytes, macrophages, and epithelioid cells organized into discrete structures (granulomas) in the lung parenchyma. The granulomatous lesions can progress to fibrosis. Many patients with granulomatous lung disease remain free of severe impairment of lung function, or, when symptomatic, they improve after treatment. The main differential diagnosis is between sarcoidosis (Chap. 318) and hypersensitivity pneumonitis (Chap. 253).

INFLAMMATION AND FIBROSIS

The initial insult is an injury to the epithelial surface causing inflammation in the air spaces and alveolar walls. If the disease becomes chronic, inflammation spreads to adjacent portions of the interstitium and vasculature and eventually causes interstitial fibrosis. Other important histopathologic patterns inILDsinclude diffuse alveolar damage (acute or organizing), desquamative interstitial pneumonia, respiratory bronchiolitis, lymphocytic interstitial pneumonia, and an organizing pneumonia [bronchiolitis obliterans with organizing pneumonia (BOOP) pattern]. The development of irreversible scarring (fibrosis) of alveolar walls, airways, or vasculature is the most feared outcome in all of these conditions because it is often progressive and leads to significant derangement of ventilatory function and gas exchange.

INITIAL EVALUATION

Patients withILDscome to medical attention mainly because of the onset of progressive exertional dyspnea or a persistent, nonproductive cough. Hemoptysis, wheezing, and chest pain may be present. Often, the identification of interstitial opacities on chest x-ray focuses the diagnostic approach toward one of the ILDs.

HISTORY

Duration of Illness *Acute presentation* (days to weeks), while unusual, occurs with allergy (drugs, fungi, helminths), acute idiopathic interstitial pneumonia, eosinophilic pneumonia, and hypersensitivity pneumonitis. These conditions may be confused with atypical pneumonias because of diffuse alveolar opacities on chest x-ray. *Subacute presentation* (weeks to months) may occur in all ILDs but is seen especially in sarcoidosis, drug-induced ILDs, the alveolar hemorrhage syndromes, cryptogenic organizing pneumonia (COP), and the acute immunologic pneumonia that complicates systemic lupus erythematosus (SLE) or polymyositis. In most ILDs the symptoms and signs are *chronic* (months to years). Examples includeIPF, sarcoidosis, pulmonary Langerhans cell histiocytosis (PLCH) (also known as Langerhans cell granulomatosis, eosinophilic granuloma, and histiocytosis X), pneumoconioses, andCTDs. *Episodic presentations* are unusual and include eosinophilic pneumonia, hypersensitivity pneumonitis, cryptogenic organizing pneumonia, vasculitides, pulmonary hemorrhage, and Churg-Strauss syndrome.

Age Most patients with sarcoidosis,ILDassociated withCTD, lymphangioleiomyomatosis (LAM),PLCH, inherited forms of ILD (familialIPF, Gaucher's disease, Hermansky-Pudlak syndrome) present between the ages of 20 and 40 years. Most patients with IPF are older than 50 years.

Gender LAM and pulmonary involvement in tuberous sclerosis occur exclusively in premenopausal women. Also,ILD in Hermansky-Pudlak syndrome and in theCTDs is more common in women; an exception is ILD in rheumatoid arthritis, which is more common in men. Because of occupational exposures, pneumoconioses also occur more frequently in men.

Family History Family history is occasionally helpful because familial associations (with

an autosomal dominant pattern) have been identified in tuberous sclerosis and neurofibromatosis. An autosomal recessive pattern of inheritance occurs in Niemann-Pick disease, Gaucher's disease, and the Hermansky-Pudlak syndrome. Familial clustering has been increasingly identified in sarcoidosis and familial pulmonary fibrosis, a process similar toIPF.

Smoking History Patients withPLCH, desquamative interstitial pneumonia (DIP), Goodpasture's syndrome, and respiratory bronchiolitis are almost always current or former smokers. Two-thirds to 75% of patients withIPF have a history of smoking.

Occupation and Environmental History A strict chronological listing of the patient's lifelong employment must be sought, including specific duties and known exposures. In hypersensitivity pneumonitis (Fig. 259-1), respiratory symptoms, fever, chills, and an abnormal chest roentgenogram are often temporally related to a hobby (pigeon breeder's disease) or to the workplace (Farmer's lung) (Chap. 253). Symptoms may diminish or disappear after the patient leaves the site of exposure for several days; similarly, symptoms may reappear on returning to the exposure site.

Other Important Past History Parasitic infections may cause pulmonary eosinophilia, and therefore a travel history should be taken in patients with known or suspectedILD. History of risk factors for HIV infection should be elicited from all patients with ILD because several processes may occur at the time of initial presentation or during the clinical course, e.g., HIV infection,BOOP, acute interstitial pneumonia, lymphocytic interstitial pneumonitis, or diffuse alveolar hemorrhage.

RESPIRATORY SYMPTOMS AND SIGNS

Dyspnea is a common and prominent complaint in patients withILD, especially the idiopathic interstitial pneumonias, hypersensitivity pneumonitis,COP, sarcoidosis, eosinophilic pneumonias, andPLCH. Some patients, especially patients with sarcoidosis, silicosis, PLCH, hypersensitivity pneumonitis, lipoid pneumonia, or lymphangitis carcinomatosis may have extensive parenchymal lung disease on chest x-ray without significant dyspnea, especially early in the course of the illness. Wheezing is an uncommon manifestation of ILD but has been described in patients with chronic eosinophilic pneumonia, Churg-Strauss syndrome, respiratory bronchiolitis, and sarcoidosis. Clinically significant chest pain is uncommon in most ILDs. However, substernal discomfort is common in sarcoidosis. Sudden worsening of dyspnea, especially if associated with acute chest pain, may indicate a spontaneous pneumothorax, which occurs in PLCH, tuberous sclerosis,LAM, and neurofibromatosis. Frank hemoptysis and blood-streaked sputum are rarely presenting manifestations of ILD but can be seen in the diffuse alveolar hemorrhage syndromes (DAHs), LAM, tuberous sclerosis, and the granulomatous vasculitides. Fatigue and weight loss are common in all ILDs.

PHYSICAL EXAMINATION

The findings are usually not specific. Most commonly, physical examination reveals tachypnea, and bibasilar end-inspiratory dry crackles, which are common in most forms ofILDassociated with inflammation but are less likely to be heard in the granulomatous

lung diseases. Crackles may be present in the absence of radiographic abnormalities on the chest radiograph. Scattered late inspiratory high-pitched rhonchi -- so-called inspiratory squeaks -- are heard in patients with bronchiolitis. The cardiac examination is usually normal except in the mid or late stages of the disease when findings of pulmonary hypertension and cor pulmonale may become evident (Chap. 237). Cyanosis and clubbing of the digits occurs in some patients with advanced disease.

LABORATORY

Antinuclear antibodies, anti-immunoglobulin antibodies (rheumatoid factors), and circulating immune complexes are identified in some patients, even in the absence of a definedCTD. A raised LDH is a nonspecific finding common to ILDs. Elevation of the serum angiotensin-converting enzyme level is common in sarcoidosis. Serum precipitins confirm exposure when hypersensitivity pneumonitis is suspected, although they are not diagnostic of the process. Antineutrophil cytoplasmic or anti-basement membrane antibodies are useful if vasculitis is suspected. The electrocardiogram is usually normal unless pulmonary hypertension is present; then it demonstrates right-axis deviation or right ventricular hypertrophy. Echocardiography also reveals right ventricular dilatation and/or hypertrophy in the presence of pulmonary hypertension.

CHEST IMAGING STUDIES

Chest X-ray ILD may be first suspected on the basis of an abnormal chest radiograph, which most commonly reveals a bibasilar reticular pattern. A nodular or mixed pattern of alveolar filling and increased reticular markings may also be present (seeFig. 249-1). A subgroup of ILDs exhibit nodular opacities with a predilection for the upper lung zones [sarcoidosis,PLCH, chronic hypersensitivity pneumonitis, silicosis, berylliosis, rheumatoid arthritis (necrobiotic nodular form), ankylosing spondylitis]. The chest x-ray correlates poorly with the clinical or histopathologic stage of the disease. The radiographic finding of honeycombing correlates with pathologic findings of small cystic spaces and progressive fibrosis; when present, it portends a poor prognosis. In most cases, the chest radiograph is nonspecific and usually does not allow a specific diagnosis.

Computed Tomography HRCT is superior to the plain chest x-ray for early detection and confirmation of suspectedILD. Also, HRCT allows better assessment of the extent and distribution of disease, and it is especially useful in the investigation of patients with a normal chest radiograph. Coexisting disease is often best recognized on HRCT scanning, e.g., mediastinal adenopathy, carcinoma, or emphysema. In the appropriate clinical setting HRCT may be sufficiently characteristic to preclude the need for lung biopsy inIPF, sarcoidosis, hypersensitivity pneumonitis, asbestosis, lymphangitic carcinoma, andPLCH. When a lung biopsy is required, HRCT scanning is useful for determining the most appropriate area from which biopsy samples should be taken.

Radionuclide Scanning Gallium-67 lung scanning is of limited value in evaluating the inflammatory component ofILD. An accelerated clearance from the lung of soluble aerosolized hydrophilic radionuclides such as^{99m}Tc-diethylenetriamene pentaacetate (DTPA) is an index of pulmonary epithelial permeability that results from inflammation. This test may provide a means of assessing the activity of ILD. Normal^{99m}Tc-DTPA

clearance inIPFpredicts stable disease, while rapid clearance identifies patients at risk for deterioration.

PULMONARY FUNCTION TESTING

Spirometry and Lung Volumes Measurement of lung function is important in assessing the extent of pulmonary involvement in patients withILD. Most forms of ILD produce a restrictive defect with reduced total lung capacity (TLC), functional residual capacity, and residual volume (Chap. 250). Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) are reduced, but these changes are related to the decreased TLC. The FEV_1/FVC ratio is usually normal or increased. Reductions in lung volumes increase as lung stiffness worsens with disease progression. A few disorders (uncommon in sarcoidosis and hypersensitivity pneumonitis, while common in tuberous sclerosis and LAM) produce interstitial opacities on chest x-ray and obstructive airflow limitation on lung function testing.

Diffusing Capacity A reduction in the diffusing capacity of the lung for carbon monoxide D_{LCO} is a common but nonspecific finding in mostILDs. This decrease is due, in part, to effacement of the alveolar capillary units but, more importantly, to mismatching of ventilation and perfusion (/). Lung regions with reduced compliance due to either fibrosis or cellular infiltration may be poorly ventilated but may still maintain adequate blood flow and / in these regions act like true venous admixture. The severity of the reduction in D_{LCO}does not correlate with disease stage.

Arterial Blood Gas The resting arterial blood gas may be normal or reveal hypoxemia (secondary to a mismatching of ventilation to perfusion) and respiratory alkalosis. A normal arterial O_2tension (or saturation by oximetry) at rest does not rule out significant hypoxemia during exercise or sleep. CO_2retention is rare and is usually a manifestation of end-stage disease.

Cardiopulmonary Exercise Testing Because hypoxemia at rest is not always present and because severe exercise-induced hypoxemia may go undetected, it is useful to perform exercise testing with measurement of arterial blood gases to detect abnormalities of gas exchange. Arterial oxygen desaturation, a failure to decrease dead space appropriately with exercise [i.e., a high V_D/V_Tratio (Chap. 250)], and an excessive increase in respiratory rate with a lower-than-expected recruitment of tidal volume provide useful information about physiologic abnormalities and extent of disease. Serial assessment of resting and exercise gas exchange is an excellent method for following disease activity and responsiveness to treatment, especially in patients withIPF.

FIBEROPTIC BRONCHOSCOPY AND BRONCHOALVEOLAR LAVAGE (BAL)

In selected diseases (e.g., sarcoidosis, hypersensitivity pneumonitis,DAHs, cancer, pulmonary alveolar proteinosis), cellular analysis of BAL fluid may be useful in narrowing the differential diagnostic possibilities among various types ofILD. The role for BAL in defining the stage of disease and assessment of disease progression or response to therapy remains poorly understood, and the usefulness of BAL in the clinical assessment and management remains to be established.

TISSUE AND CELLULAR EXAMINATION

Lung biopsy is the most effective method for confirming the diagnosis and assessing disease activity. The findings may identify a more treatable process than originally suspected, particularly chronic hypersensitivity pneumonitis,COP, respiratory bronchiolitis-associatedILD, or sarcoidosis. Biopsy should be obtained before initiation of treatment. A definitive diagnosis avoids confusion and anxiety later in the clinical course if the patient does not respond to therapy or suffers serious side effects from it.

Fiberoptic bronchoscopy with multiple transbronchial lung biopsies (4 to 8 biopsy samples) is often the initial procedure of choice, especially when sarcoidosis, lymphangitic carcinomatosis, eosinophilic pneumonia, Goodpasture's syndrome, or infection are suspected. If a specific diagnosis is not made by transbronchial biopsy, then surgical lung biopsy by video-assisted thoracic surgery or open thoracotomy is indicated. Adequate-sized biopsies from multiple sites, usually from two lobes, should be obtained. Relative contraindications to lung biopsy include serious cardiovascular disease, "honeycombing" and other roentgenographic evidence of diffuse end-stage disease, severe pulmonary dysfunction, or other major operative risks, especially in the elderly.

TREATMENT

Although the course ofILD is variable, progression is common and often insidious. All treatable possibilities should be carefully considered. Since therapy does not reverse fibrosis, the major goals of treatment are permanent removal of the offending agent when known and early identification and aggressive suppression of the acute and chronic inflammatory process, thereby reducing further lung damage.

Hypoxemia (PaO_2<55 mmHg) at rest and/or with exercise should be managed by supplemental oxygen. If cor pulmonale develops, diuretic therapy and phlebotomy may occasionally be required (Chap. 237).

Drug Therapy Glucocorticoids are the mainstay of therapy for suppression of the alveolitis present inILD, but the success rate is low. There have been no placebo-controlled trials of glucocorticoids in ILD, so there is no direct evidence that steroids improve survival in many of the diseases for which they are commonly used. Glucocorticoid therapy is recommended for symptomatic ILD patients with idiopathic interstitial pneumonias, eosinophilic pneumonias,COP,CTD, sarcoidosis, acute inorganic dust exposures, acute radiation pneumonitis,DAH, and drug-induced ILD. In organic dust disease, glucocorticoids are recommended for both the acute and chronic stages.

The optimal dose and proper length of therapy with glucocorticoids in the treatment of mostILDs is not known. A common starting dose is prednisone, 0.5 to 1 mg/kg in a once-daily oral dose (based on the patient's lean body weight). This dose is continued for 4 to 12 weeks, at which time the patient is reevaluated. If the patient is stable or improved, the dose is tapered to 0.25 to 0.5 mg/kg and is maintained at this level for an additional 4 to 12 weeks depending on the course. Rapid tapering or a shortened course of glucocorticoid treatment can result in recurrence. If the patient's condition

continues to decline while on glucocorticoids, a second agent (see below) is often added and the prednisone dose is lowered to or maintained at 0.25 mg/kg per day.

Cyclophosphamide and azathioprine (1 to 2 mg/kg lean body weight per day) with or without glucocorticoids, have been tried with variable success inIPF, vasculitis, and otherILDs. An objective response usually requires at least 8 to 12 weeks to occur. In situations in which these drugs have failed or could not be tolerated, other agents, including methotrexate, colchicine, penicillamine, and cyclosporine, have been tried. However, their role in the treatment of ILDs remains to be determined.

Many cases ofILD are chronic and irreversible despite the therapy discussed above, and lung transplantation may then be considered (Chap. 267).

INDIVIDUAL FORMS OF ILD

IDIOPATHIC PULMONARY FIBROSIS

Several risk factors appear to be associated with the development ofIPF, a commonILD of unknown etiology. These include cigarette smoking; exposure to antidepressants; a history of chronic aspiration secondary to gastroesophageal reflux; and exposures to metal dust, wood dust, and solvents. Numerous viruses have been implicated in the pathogenesis of IPF, but no clear evidence for a viral etiology has been confirmed. The most compelling evidence for participation of genetic factors is the description fo familial cases of pulmonary fibrosis, which is transmitted as an autosomal dominant trait with variable penetrance. An association has been reported between IPF and a, antitrypsin inhibition (Pi) alleles on chromosome 14.

Clinical Manifestations Exertional dyspnea, a nonproductive cough, and inspiratory crackles with or without digital clubbing may be present on physical examination. The chest roentgenogram andHRCTtypically show patchy, predominantly peripheral, subpleural, reticular opacities in the lower lung zones. There may also be a ground-glass opacity usually associated with traction bronchiectasis and bronchiolectasis or subpleural honeycombing. Pulmonary function tests often reveal a restrictive pattern, a reduced D_{LCO}, and arterial hypoxemia that is exaggerated or elicited by exercise.

Histologic Findings Confirmation of the presence of the usual interstitial pneumonia (UIP) pattern on histologic examination is essential to confirm this diagnosis (Fig. 259-2). Transbronchial biopsies are not helpful in making the diagnosis of UIP, and surgical biopsy is usually required. The histologic hallmark and chief diagnostic criterion of UIP is a heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb changes. The latter are composed of cystic fibrotic air spaces that are frequently lined by bronchiolar epithelium and filled with mucin. Smooth muscle hyperplasia is commonly present in areas of fibrosis and honeycomb change. Biopsies taken from patients during an accelerated phase of their illness may show a combination of UIP and diffuse alveolar damage. These histologic abnormalities affect the peripheral, subpleural parenchyma most severely. The interstitial inflammation is usually patchy and consists of a lymphoplasmacytic infiltrate in the alveolar septa, associated with hyperplasia of type 2

pneumocytes. The fibrotic zones are composed mainly of dense collagen, although scattered foci of proliferating fibroblasts are a consistent finding. The extent of fibroblastic proliferation is predictive of disease progression. A UIP-like pattern can also be seen withCTDs, pneumoconioses (e.g., asbestosis), radiation injury, certain drug-induced lung diseases (e.g., nitrofurantoin), and chronic aspiration. Also, a fibrotic pattern may be found in the chronic stage of several specific disorders such as sarcoidosis, chronic hypersensitivity pneumonitis, organized chronic eosinophilic pneumonia, andPLCH. Since other histopathologic features are frequently present in these syndromes, the term UIP is used for those patients in whom the lesion is idiopathic and not associated with another condition.

TREATMENT

The clinical course is variable with a 5-year survival rate of 30 to 50% after diagnosis. Treatment options include glucocorticoids, cytotoxic agents (e.g., azathioprine, cyclophosphamide), and antifibrotic agents (e.g., colchicine, perfenidone, or interferon gamma-1b), alone or in combination with glucocorticoids. However, there is no firm evidence that any of these treatment approaches improves survival or the quality of life. Because of the poor prognosis in untreated patients, a therapeutic trial may be tried. If therapy is recommended, it should be started at the first identification of clinical or physiologic evidence of impairment of lung function. Lung transplantation should be considered for those patients who experience progressive deterioration despite optimal medical management and who meet the established criteria (Chap. 267).

DESQUAMATIVE INTERSTITIAL PNEUMONIA

DIPis a rare but distinct clinical and pathologic entity found exclusively in cigarette smokers. The histologic hallmark is the extensive accumulation of macrophages in intraalveolar spaces with minimal interstitial fibrosis. The peak incidence is in the fourth and fifth decades. Most patients present with dyspnea. Lung function testing shows a restrictive pattern with reduced DL_{CO} and arterial hypoxemia. The chest x-ray usually shows diffuse hazy opacities. Clinical recognition of DIP is important because the process is associated with a better prognosis (10-year survival rate is ~70%) and a better response to smoking cessation and systemic glucocorticoids than the more commonIPF. Respiratory bronchiolitis-associatedILD is considered to be a subset of DIP and is characterized by the accumulation of macrophages in peribronchical alveoli.

ACUTE INTERSTITIAL PNEUMONIA (AIP) (HAMMAN-RICH SYNDROME)

This is a rare, fulminant form of lung injury characterized by diffuse alveolar damage on lung biopsy. Most patients are older than 40 years. AIP is similar in presentation to the acute respiratory distress syndrome (ARDS) (Chap. 265) and probably corresponds to the subset of cases of idiopathic ARDS. The onset is usually abrupt in a previously healthy individual. A prodromal illness, usually lasting 7 to 14 days before presentation, is common. Fever, cough, and dyspnea are frequent manifestations at presentation. Diffuse, bilateral, air-space opacification is present on chest radiograph. HRCT scans show bilateral, patchy, symmetric areas of ground-glass attenuation. Bilateral areas of air-space consolidation may also be present. A predominantly subpleural distribution may be seen. The diagnosis of AIP requires the presence of a clinical syndrome of

idiopathic ARDS and pathologic confirmation of organizing diffuse alveolar damage. Therefore, lung biopsy is required to confirm the diagnosis. Most patients have moderate to severe hypoxemia and develop respiratory failure. Mechanical ventilation is often required. The mortality rate is high (>60%), with most patients dying within 6 months of presentation. Recurrences have been reported. However, those who recover often have substantial improvement in lung function. The main treatment is supportive. It is not clear that glucocorticoid therapy is effective.

NONSPECIFIC INTERSTITIAL PNEUMONIA (NSIP)

This condition defines a subgroup of the idiopathic interstitial pneumonias that can be distinguished clinically and pathologically fromUIP,DIP,AIP, and idiopathicBOOP. Lung biopsy shows varying proportions of chronic interstitial inflammation and fibrosis. NSIP is a subacute restrictive process that usually occurs at a younger age than UIP. It is often associated with a febrile illness, relative lack of clubbing, andHRCTfindings that show ground-glass opacities and areas of consolidation. Unlike patients withIPF, most patients with NSIP have a good prognosis, and most show improvement after treatment with glucocorticoids.

ILDASSOCIATED WITH CONNECTIVE TISSUE DISORDERS

Clinical findings suggestive of aCTD(musculoskeletal pain, weakness, fatigue, fever, joint pains or swelling, photosensitivity, Raynaud's phenomenon, pleuritis, dry eyes, dry mouth) should be sought in any patient withILD. The CTDs may be difficult to rule out since the pulmonary manifestations occasionally precede the more typical systemic manifestations by months or years. The most common form of pulmonary involvement is a chronic interstitial pattern similar to that in patients withIPF. However, determining the precise nature of lung involvement in most of the CTDs is difficult due to the high incidence of lung involvement caused by disease-associated complications of esophageal dysfunction (predisposing to aspiration and secondary infections), respiratory muscle weakness (atelectasis and secondary infections), complications of therapy (opportunistic infections), and associated malignancies.

Progressive Systemic Sclerosis (PSS) (See alsoChap. 313) Clinical evidence ofILD is present in about one-half of patients with progressive systemic sclerosis, and pathologic evidence in three-quarters. Pulmonary function tests show a restrictive pattern and impaired diffusing capacity, often before any clinical or radiographic evidence of lung disease appears. Pulmonary vascular disease alone or in association with pulmonary fibrosis, pleuritis, or recurrent aspiration pneumonitis is strikingly resistant to current modes of therapy.

Rheumatoid Arthritis (RA) (See alsoChap. 312) ILDassociated with rheumatoid arthritis is more common in men. Pulmonary manifestations of rheumatoid arthritis include pleurisy with or without effusion, ILD in up to 20% of cases, necrobiotic nodules (nonpneumoconiotic intrapulmonary rheumatoid nodules) with or without cavities, Caplan's syndrome (rheumatoid pneumoconiosis), pulmonary hypertension secondary to rheumatoid pulmonary vasculitis,BOOP, and upper airway obstruction due to arytenoid arthritis.

Systemic Lupus Erythematosus (See also Chap. 311) Lung disease is a common complication inSLE. Pleuritis with or without effusion is the most common pulmonary manifestation. Other lung manifestations include the following: atelectasis, diaphragmatic dysfunction with loss of lung volumes, pulmonary vascular disease, pulmonary hemorrhage, uremic pulmonary edema, infectious pneumonia, andBOOP. Acute lupus pneumonitis characterized by pulmonary capillaritis leading to alveolar hemorrhage is common. Chronic, progressiveILD is uncommon. It is important to exclude pulmonary infection. Although pleuropulmonary involvement may not be evident clinically, pulmonary function testing, particularly D_{LCO}reveals abnormalities in many patients with SLE.

Polymyositis and Dermatomyositis (PM/DM) (See also Chap. 382) ILDoccurs in ~10% of patients with polymyositis and dermatomyositis, and the clinical features are similar to those ofIPF. Diffuse reticular or nodular opacities with or without an alveolar component occur radiographically, with a predilection for the lung bases. ILD occurs more commonly in the subgroup of patients with an anti-Jo-1 antibody that is directed to histidyl tRNA synthetase. Weakness of respiratory muscles contributing to aspiration pneumonia may be present. A rapidly progressive illness characterized by diffuse alveolar damage may cause respiratory failure.

Sjogren's Syndrome (See alsoChap. 314) General dryness and lack of airways secretion cause the major problems of hoarseness, cough, and bronchitis. Lymphocytic interstitial pneumonitis, lymphoma, pseudolymphoma, bronchiolitis, and bronchiolitis obliterans are associated with this condition. Lung biopsy is frequently required to establish a precise pulmonary diagnosis. Glucocorticoids have been used in the management ofILDassociated with Sjogren's syndrome with some degree of clinical success.

DRUG-INDUCED ILD (See alsoChap. 71)

Many classes of drugs have the potential to induce diffuseILD, which is manifest most commonly as exertional dyspnea and nonproductive cough. A detailed history of the medications taken by the patient is needed to identify drug-induced disease, including over-the-counter medications, oily nose drops, or petroleum products (mineral oil). In most cases, the pathogenesis is unknown, although a combination of direct toxic effects of the drug (or its metabolite) and indirect inflammatory and immunologic events is likely. The onset of the illness may be abrupt and fulminant, or it may be insidious, extending over weeks to months. The drug may have been taken for several years before a reaction develops (e.g., amiodarone), or the lung disease may occur weeks to years after the drug has been discontinued (e.g., carmustine). The extent and severity of disease are usually dose related. Treatment consists of discontinuation of any possible offending drug and supportive care.

CRYPTOGENIC ORGANIZING PNEUMONIA (COP)

Also known as idiopathicBOOP,COP is a clinicopathologic syndrome of unknown etiology. The onset is usually in the fifth and sixth decades. The presentation may be of a flu-like illness with cough, fever, malaise, fatigue, and weight loss. Inspiratory crackles are frequently present on examination. Pulmonary function is usually impaired, with a

restrictive defect and arterial hypoxemia being most common. The roentgenographic manifestations are distinctive, revealing bilateral, patchy, or diffuse alveolar opacities in the presence of normal lung volume. Recurrent and migratory pulmonary opacities are common.HRCTshows areas of air-space consolidation, ground-glass opacities, small nodular opacities and bronchial wall thickening and dilation. These changes occur more frequently in the periphery of the lung and in the lower lung zone. Lung biopsy shows granulation tissue within small airways, alveolar ducts, and airspaces, with chronic inflammation in the surrounding alveoli. Glucocorticoid therapy induces clinical recovery in two-thirds of patients. A few patients have rapidly progressive courses with fatal outcomes despite glucocorticoids.

Foci of organizing pneumonia (i.e., a "BOOPpattern") is a nonspecific reaction to lung injury found adjacent to other pathologic processes or as a component of other primary pulmonary disorders (e.g., cryptococcosis, Wegener's granulomatosis, lymphoma, hypersensitivity pneumonitis, and eosinophilic pneumonia). Consequently, the clinician must carefully reevaluate any patient found to have this histopathologic lesion to rule out these possibilities.

EOSINOPHILIC PNEUMONIA See Chap. 253

PULMONARY ALVEOLAR PROTEINOSIS

Although not strictly anILD, pulmonary alveolar proteinosis (PAP) resembles and is therefore considered with these conditions. It has been proposed that a defect in macrophage function, more specifically an impaired ability to process surfactant, may play a role in the pathogenesis of PAP. This diffuse disease is characterized by the accumulation of an amorphous, periodic acid-Schiff-positive lipoproteinaceous material in the distal air spaces. There is little or no lung inflammation, and the underlying lung architecture is preserved. Mutant mice lacking the gene for granulocyte-macrophage colony stimulating factor (GM-CSF) have a similar accumulation of surfactant and surfactant apoprotein in the alveolar spaces. Moreover, reconstitution of the respiratory epithelium of GM-CSF knockout mice with the GM-CSF gene completely corrects the alveolar proteinosis. Data from BAL studies in patients suggest that PAP is an autoimmune disease with neutralizing antibody of immunoglobulin G isotype against GM-CSF. These findings suggest that neutralization of GM-CSF bioactivity by the antibody causes dysfunction of alveolar macrophages, which results in reduced surfactant clearance.

The typical age of presentation is 30 to 50 years, and males predominate. The clinical presentation is usually insidious and manifested by progressive exertional dyspnea, fatigue, weight loss, and low-grade fever. A nonproductive cough is common, but occasionally expectoration of "chunky" gelatinous material may occur. Polycythemia, hypergammaglobulinemia, and increased LDH levels are frequent. Markedly elevated serum levels of lung surfactant proteins A and D have been found in PAP. Radiographically, bilateral symmetrical alveolar opacities located centrally in mid and lower lung zones result in a "bat-wing" distribution.HRCTshows a ground-glass opacification and thickened intralobular structures and interlobular septa. Whole lung lavage(s) through a double-lumen endotracheal tube provides relief to many patients with dyspnea or progressive hypoxemia and also may provide long-term benefit.

PULMONARY LYMPHANGIOLEIOMYOMATOSIS

PulmonaryLAM is a rare condition that afflicts premenopausal women and should be suspected in young women with emphysema, recurrent pneumothorax, or chylous pleural effusion. It is often misdiagnosed as asthma or chronic obstructive pulmonary disease. Pathologically, LAM is characterized by the proliferation of atypical pulmonary interstitial smooth muscle and cyst formation. The immature-appearing smooth-muscle cells react with monoclonal antibody HMB45, which recognizes a 100-kDa glycoprotein (gp100) originally found in human melanoma cells. Caucasians are affected much more commonly than members of other racial groups. The disease accelerates during pregnancy and abates after oopherectomy. Common complaints at presentation are dyspnea, cough, and chest pain. Hemoptysis may be life threatening. Spontaneous pneumothorax occurs in 50% of patients; it may be bilateral and necessitate pleurodesis. Chylothorax, chyloperitonium (chylous ascites), chyluria, and chylopericardium are other complications. Pulmonary function testing usually reveals an obstructive or mixed obstructive-restrictive pattern, and gas exchange is often abnormal.HRCTshows thin-walled cysts surrounded by normal lung without zonal predominance. Progression is common, with a median survival of 8 to 10 years from diagnosis. Oophorectomy, progesterone (10 mg/d), and, more recently, tamoxifen and luteinizing hormone-releasing hormone analogs have been used. Lung transplantation offers the only hope for cure despite reports of recurrent disease in the transplanted lung.

SYNDROMES OF ILD WITH DIFFUSE ALVEOLAR HEMORRHAGE

Injury to arterioles, venules, and the alveolar septal (alveolar wall or interstitial) capillaries can result in hemoptysis secondary to disruption of the alveolar-capillary basement membrane. This results in bleeding into the alveolar spaces, which characterizesDAH. Pulmonary capillaritis, characterized by a neutrophilic infiltration of the alveolar septae, may lead to necrosis of these structures, loss of capillary structural integrity, and the pouring of red blood cells into the alveolar space. Fibrinoid necrosis of the interstitium and red blood cells within the interstitial space are sometimes seen. Bland pulmonary hemorrhage (i.e., DAH without inflammation of the alveolar structures) may also occur.

The clinical onset is often abrupt, with cough, fever, and dyspnea. Severe respiratory distress requiring ventilatory support may be evident at initial presentation. Although hemoptysis is expected, it can be absent at the time of presentation in one-third of the cases. For patients without hemoptysis, new alveolar opacities, a falling hemoglobin level, and hemorrhagicBALfluid point to the diagnosis. The chest radiograph is nonspecific and most commonly shows new patchy or diffuse alveolar opacities. Recurrent episodes ofDAH may lead to pulmonary fibrosis, resulting in interstitial opacities on the chest radiograph. An elevated white blood cell count and falling hematocrit are frequent. Evidence for impaired renal function caused by focal segmental necrotizing glomerulonephritis, usually with crescent formation, may also be present.

Varying degrees of hypoxemia may occur and often are severe enough to require ventilatory support. TheD_{LCO}may be increased, resulting from the increased hemoglobin

within the alveoli compartment. Evaluation of either lung or renal tissue by immunofluorescent techniques indicates an absence of immune complexes (pauci-immune) in Wegener's granulomatosis, microscopic polyangiitis pauci-immune glomerulonephritis, and isolated pulmonary capillaritis. A granular pattern is found in theCTDs, particularlySLE, and a characteristic linear deposition is found in Goodpasture's syndrome. Granular deposition of IgA-containing immune complexes are present in Henoch-Schonlein purpura.

The mainstay of therapy for theDAHassociated with systemic vasculitis,CTD, Goodpasture's syndrome, and isolated pulmonary capillaritis is intravenous methylprenisolone, 0.5 to 2.0 g daily in divided doses for up to 5 days, followed by a gradual tapering, and then maintenance on an oral preparation. Prompt initiation of therapy is important, particularly in the face of renal insufficiency, since early initiation of therapy has the best chance of preserving renal function. The decision to start other immunosuppressive therapy (cyclophosphamide or azathioprine) acutely depends on the severity of illness.

Goodpasture's Syndrome Pulmonary hemorrhage and glomerulonephritis are features in most patients with this disease (Chap. 275). Autoantibodies to renal glomerular and lung alveolar basement membranes are present. This syndrome can present and recur asDAHwithout an associated glomerulonephritis. In such case, circulating anti-basement membrane antibody is often absent, and the only way to establish the diagnosis is by demonstrating linear immunofluorescence in lung tissue. The underlying histology may be bland hemorrhage or DAH associated with capillaritis. Plasmapheresis has been recommended as adjunctive treatment.

Idiopathic Pulmonary Hemosiderosis This condition is a diagnosis of exclusion. Only 20% of reported cases occur in adults. In children, the condition is associated with celiac disease, and elevated IgA levels are found in 50% of patients. These associations are lacking in most adults. A lung biopsy is usually necessary to document the lack of inflammatory injury in the lung tissues and to exclude other diseases with confidence.

INHERITED DISORDERS ASSOCIATED WITH ILD

Pulmonary opacities and respiratory symptoms typical ofILD can develop in related family members and in several inherited diseases. These include the phakomatoses, tuberous sclerosis and neurofibromatosis (Chap. 370), and the lysosomal storage diseases, Niemann-Pick disease and Gaucher's disease (Chap. 349). The Hermansky-Pudlak syndrome (Chap. 116) is an autosomal recessive disorder in which granulomatous colitis and ILD may occur. It is characterized by oculocutaneous albinism, bleeding diathesis secondary to platelet dysfunction, and the accumulation of a chromolipid, lipofuscin material in cells of the reticuloendothelial system. The pulmonary fibrosis is similar toIPF, but the alveolar macrophages may contain cytoplasmic ceroid-like inclusions.

ILD WITH A GRANULOMATOUS RESPONSE IN LUNG TISSUE OR VASCULAR STRUCTURES

Inhalation of organic dusts, which cause hypersensitivity pneumonitis, or of inorganic

dust, such as silica, which elicits a granulomatous inflammatory reaction leading toILD, produces diseases of known etiology (Table 259-1) that are discussed inChaps. 253 and254. Sarcoidosis (Chap. 318) is prominent among granulomatous diseases of unknown cause in which ILD is an important feature.

Pulmonary Langerhans Cell Histiocytosis (PLCH, Pulmonary Histiocytosis X, Langerhans Cell Granulomatosis, or Eosinophilic Granuloma PLCH is a rare, smoking-related, diffuse lung disease that primarily affects men between the ages of 20 and 40 years. The clinical presentation varies from an asymptomatic state to a rapidly progressive condition. The most common clinical manifestations at presentation are cough, dyspnea, chest pain, weight loss, and fever. Pneumothorax occurs in about 25% of patients. Hemoptysis and diabetes insipidus are rare manifestations. The radiographic features vary with the stage of the disease. The combination of ill-defined or stellate nodules (2 to 10 mm in diameter), reticular or nodular opacities, bizarre-shaped upper zone cysts, preservation of lung volume, and sparing of the costophrenic angles are characteristics of PLCH.HRCTthat reveals a combination of nodules and thin-walled cysts is virtually diagnostic of PLCH. The most frequent pulmonary function abnormality is a markedly reducedD_{LCO}, although varying degrees of restrictive disease, airflow limitation, and diminished exercise capacity may occur. Discontinuance of smoking is the key treatment, resulting in clinical improvement in one-third of patients. Most patients with PLCH suffer persistent or progressive disease. Death due to respiratory failure occurs in ~10% of patients.

Granulomatous Vasculitides (See also Chap. 317) The granulomatous vasculitides are characterized by pulmonary angiitis (i.e., inflammation and necrosis of blood vessels) with associated granuloma formation (i.e., infiltrates of lymphocytes, plasma cells, epithelioid cells, or histiocytes, with or without the presence of multinucleated giant cells, sometimes with tissue necrosis). The lungs are almost always involved, although any organ system may be affected. Wegener's granulomatosis and allergic angiitis and granulomatosis (Churg-Strauss syndrome) primarily affect the lung but are associated with a systemic vasculitis as well. The granulomatous vasculitides generally limited to the lung include necrotizing sarcoid granulomatosis and benign lymphocytic angiitis and granulomatosis. Granulomatous infection and pulmonary angiitis due to irritating embolic material (e.g., talc) are important known causes of pulmonary vasculitis.

LYMPHOCYTIC INFILTRATIVE DISORDERS

This group of disorders features lymphocyte and plasma cell infiltration of the lung parenchyma. The disorders either are benign or can behave as low-grade lymphomas. Included are angioimmunoblastic lymphadenopathy with dysproteinemia, a rare lymphoproliferative disorder characterized by diffuse lymphadenopathy, fever, hepatosplenomegaly, and hemolytic anemia, withILD in some cases.

Lymphocytic Interstitial Pneumonitis This rare form ofILDoccurs in adults, some of whom have an autoimmune disease or dysproteinemia. It has been reported in patients with Sjogren's syndrome and HIV infection.

Lymphomatoid Granulomatosis This multisystem disorder of unknown etiology is an angiocentric malignant (T cell) lymphoma characterized by a polymorphic lymphoid

infiltrate, an angiitis, and granulomatosis. Although it may affect virtually any organ, it is most frequently characterized by pulmonary, skin, and central nervous system involvement.

BRONCHOCENTRIC GRANULOMATOSIS

Rather than a specific clinical entity, bronchocentric granulomatosis (BG) is a descriptive histologic term that describes an uncommon and nonspecific pathologic response to a variety of airway injuries. There is evidence that BG is caused by a hypersensitivity reaction to *Aspergillus* or other fungi in patients with asthma. About half of the patients described have chronic asthma with severe wheezing and peripheral blood eosinophilia. In patients with asthma, BG probably represents one pathologic manifestation of allergic bronchopulmonary aspergillosis, or another allergic mycosis. In patients without asthma, BG has been associated with rheumatoid arthritis and a variety of infections, including tuberculosis, echinococcosis, histoplasmosis, coccidiodomycosis, and nocardiosis. The chest roentgenogram reveals irregularly shaped nodular or mass lesions with ill-defined margins, which are usually unilateral and solitary, with an upper-lobe predominance. Glucocorticoids are the treatment of choice, often with excellent outcome, although recurrences may occur as therapy is tapered or stopped.

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260. PRIMARY PULMONARY HYPERTENSION - *Stuart Rich*

Primary pulmonary hypertension is an uncommon disease characterized by increased pulmonary artery pressure and pulmonary vascular resistance. The incidence has been estimated at approximately 2 cases per million. There is a female-to-male preponderance (1.7:1), with patients most commonly presenting in the third and fourth decades, although the age range is from infancy to greater than 60 years. Because the predominant symptom of primary pulmonary hypertension is dyspnea, which can have an insidious onset in an otherwise healthy person, the disease is typically diagnosed late in its course. By that time, the clinical and laboratory findings of severe pulmonary hypertension are usually present.

PATHOLOGY

The histopathology of primary pulmonary hypertension is not pathognomonic for the disease but represents a pulmonary arteriopathy that is observed in pulmonary hypertension from a variety of causes. A wide spectrum of vascular abnormalities involving the endothelium, smooth muscle cells, and extracellular matrix is present. Heterogeneity with respect to these abnormalities is often seen from patient to patient, and within patients. The most common features noted are medial hypertrophy, concentric and eccentric intimal fibrosis, recanalized thrombi appearing as fibrous webs, and plexiform lesions. In most patients, varying degrees of these abnormalities can be found. Rare variant forms of primary pulmonary hypertension also exist.

Pulmonary venoocclusive disease is a rare and distinct pathologic entity, found in fewer than 10% of patients with primary pulmonary hypertension. Histologically, it is manifest by widespread intimal proliferation and fibrosis of the intrapulmonary veins and venules, occasionally extending to the arteriolar bed. The pulmonary venous obstruction explains the increased pulmonary capillary wedge pressure observed in patients with advanced disease. These patients may develop orthopnea that can mimic left ventricular failure.

Pulmonary capillary hemangiomatosis is also a very rare form of primary pulmonary hypertension. Histologically, it is characterized by infiltrating thin-walled blood vessels that are widespread throughout the pulmonary interstitium and walls of the pulmonary arteries and veins. These patients often have hemoptysis as a clinical feature.

ETIOLOGY

It is likely that there are several pathobiologic processes that result in pulmonary hypertension as a final common pathway. These include inhibition of the voltage-regulated (Kv) potassium channel producing vasoconstriction secondary to contraction of the pulmonary artery smooth muscle cells, an imbalance in vasocontricting and vasodilating mediators that are involved in the control of pulmonary vascular tone (including prostacyclin and thromboxane), reduced expression of nitric oxide synthase in the endothelium of the pulmonary arterial bed, inflammation, thrombosis in situ of the pulmonary vascular bed from a procoagulant state, and persistent matrix protein synthesis in the pulmonary arteries. The types of abnormalities that occur are likely influenced by the patient's genotype and exposure to risk factors that serve to trigger these processes. Risk factors that have been linked to the

development of pulmonary hypertension include anorexigens, collagen vascular diseases, congenital systemic to pulmonary shunts, portal hypertension, and HIV infection.

Recently, a marked increase in the incidence of primary pulmonary hypertension occurred in Europe and the United States as a result of the widespread use of the fenfluramine appetite suppressants. The clinical and pathologic features of these cases were identical to patients with primary pulmonary hypertension who were unexposed. Atlhough very limited exposure to the fenfluramines can cause primary pulmonary hypertension, the risk increased dramatically with prolonged use. Like the experience with aminorex, an anorexigen that produced a similar epidemic in the 1960s, the incidence of primary pulmonary hypertension fell when the drugs were withdrawn from the market. The mechanism by which these agents produce pulmonary hypertension is unknown.

GENETIC CONSIDERATIONS

The locus of a gene linked to familial primary pulmonary hypertension has been identified on chromosome 2q31-32. Familial primary pulmonary hypertension occurs in approximately 6 to 12% of cases and is characterized by autosomal dominant inheritance, variable age of onset, and incomplete penetrance. The clinical and pathologic features of familial and sporadic primary pulmonary hypertension are virtually identical. Genetic anticipation, which relates to offspring of subsequent generations manifesting the disease at younger ages or with greater severity, is also a feature. Trinucleotide repeat expansion, originally described in several neurologic disorders, remains the only biologic explanation for genetic anticipation and raises the possibility that the pathogenesis of familial primary pulmonary hypertension may have a neurologic basis. Patients who present with sporadic disease probably possess a genetic predisposition that becomes expressed following exposure to an external trigger or risk factor.

PATHOPHYSIOLOGY

The underlying hemodynamic derangement in primary pulmonary hypertension is an increased resistance to pulmonary blood flow. Early in the disease there is a marked elevation in pulmonary artery pressure with relatively normal cardiac function. Over time the cardiac output becomes progressively reduced rather than the pulmonary artery pressure becoming progressively increased. Initially, the pulmonary arteries may respond to vasodilators, but as the disease progresses, the elevated pulmonary vascular resistance becomes fixed. The pulmonary capillary wedge pressure remains normal until the late stages, when it tends to rise in response to impaired diastolic filling of the left ventricle due to the altered configuration of the intraventricular septum. Eventually, as the right ventricle fails, the right atrial and right ventricular end-diastolic pressures rise in an attempt to compensate for the myocardial depression that has developed in response to chronic severe right ventricular pressure overload.

Pulmonary function is usually normal in primary pulmonary hypertension, although a mild restrictive pattern (Chap. 250) is sometimes seen. Hypoxemia is common and is believed to be due to a mismatch between pulmonary ventilation and perfusion,

magnified by a low cardiac output. Occasional patients with a patent foramen ovale may develop right-to-left shunting, which can also contribute to systemic arterial desaturation.

DIAGNOSIS

Primary pulmonary hypertension refers to pulmonary arterial hypertension wihtout an identifiable risk factor. Clinically, primary pulmonary arterial hypertension should be distinguished from pulmonary venous hypertension, pulmonary hypertension associated with disorders of the respiratory system and/or hypoxema, and pulmonary hypertension due to chronic thrombotic and/or embolic disease (Chap. 261).

A thorough diagnostic evaluation to look for all potential causes should be undertaken (Fig. 260-1). The history usually reveals the gradual onset of shortness of breath with effort, progressing until the patient is dyspneic with minimal activity. The average duration from symptom onset until diagnosis is 2.5 years. Other common symptoms are fatigue, angina pectoris that likely represents right ventricular ischemia, syncope, near syncope, and peripheral edema.

The physical examination is characteristic. Increased jugular venous pressure, a reduced carotid pulse, and an easily palpable right ventricular lift are typical. Most patients have an increased pulmonic component of the second heart sound and right-sided third and fourth heart sounds. Tricuspid regurgitation is a clinical feature of right ventricular failure. Peripheral cyanosis and/or edema tend to occur in later stages of the disease. Clubbing is not a feature.

The chest x-ray generally shows enlarged central pulmonary arteries and clear lung fields. The electrocardiogram usually reveals right axis deviation and right ventricular hypertrophy. The echocardiogram demonstrates right ventricular enlargement, a reduction in left ventricular cavity size, and abnormal septal configuration consistent with right ventricular pressure overload. Doppler studies have revealed a marked dependence on atrial systole for ventricular filling. Hypoxemia, hypocapnia, and an abnormal diffusing capacity for carbon monoxide are almost invariable findings. A mild restrictive pattern on pulmonary function is sometimes observed, but evidence of airways obstruction suggests a secondary etiology for the pulmonary hypertension. The presence of significant restrictive changes on pulmonary function testing (Chap. 250) should prompt a high-resolution computed tomographic scan to look for interstitial lung disease, which may otherwise not be obvious. A perfusion lung scan may be normal or abnormal with multiple diffuse patchy filling defects of a nonsegmental nature and not suggestive of pulmonary thromboembolism. If the lung scan reveals perfusion defects of a segmental or subsegmental nature, a pulmonary angiogram must be done. Severe pulmonary hypertension in a patient with a high-probability lung scan should suggest a chronic process and *not* acute pulmonary embolism, since the nonconditioned right ventricle is unable to generate high systolic pressures acutely in the face of pulmonary thromboembolism. Chronic thromboembolic obstruction of the large pulmonary arteries (Chap. 261) can mimic primary pulmonary hypertension but can be amenable to treatment with surgical thromboendarterectomy.

There is risk in performing pulmonary angiography in patients with primary pulmonary

hypertension, and it is recommended that selective or subselective injections with small amounts of low-osmolar, nonionic contrast material be made following the pretreatment with 1 mg atropine to prevent vagally mediated bradycardia.

Cardiac catheterization is mandatory to characterize the disease and exclude an underlying cardiac shunt as the cause. The use of balloon-flotation catheters, especially those with removable guidewires, can facilitate right heart catheterization. A right-to-left shunt might be attributable to a patent foramen ovale, but any left-to-right shunting implies the presence of a congenital defect. Although it may be difficult to obtain, the pulmonary capillary wedge pressure is normal. If it is increased, left heart catheterization should also be performed to exclude mitral stenosis or increased left ventricular end-diastolic pressures as the cause of the pulmonary hypertension. Although the diagnostic evaluation of these patients can be hazardous, experience from a national multicenter study revealed no mortality or serious morbidity in more than 300 patients whose evaluation included pulmonary angiography and cardiac catheterization. It is not necessary to perform an open lung biopsy in these patients to make an accurate diagnosis. Laboratory tests should also be performed, including antinuclear antibody and HIV testing.

On occasion, a patient may have marked elevations in pulmonary artery pressure in association with mild obstructive or interstitial lung disease, essential hypertension, ischemic heart disease, or valvular heart disease. Although it may appear that the pulmonary hypertension is out of proportion to the underlying associated condition, it likely represents a pulmonary vasoconstrictive response to the associated condition, which is serving as a trigger of pulmonary arterial hypertension. Thus severe pulmonary hypertension can coexist with mild chronic obstructive pulmonary disease, small intracardiac shunts, mild mitral stenosis, and even ischemic heart disease. The distinction is important because the treatment of pulmonary hypertension should always include treating the underlying associated cause.

NATURAL HISTORY

The natural history of primary pulmonary hypertension is unknown because initially the disease is largely asymptomatic. Several older series have reported a mean survival of 2 to 3 years for patients from the time of diagnosis. Functional class is a strong predictor of survival, since patients who are New York Heart Association functional classes II and III have a mean survival of 3.5 years compared with those who are functional class IV, in whom the mean survival is 6 months. The cause of death is usually right ventricular failure or sudden death; sudden death appears to be a late feature of the disease. Increased right atrial pressure above 15 mmHg and reduced cardiac index below 2 (L/min)/$m^2$are hemodynamic predictors of a poor prognosis.

TREATMENT

Because the pulmonary vascular resistance increases dramatically with exercise, patients should be cautioned against participating in activities that demand increased physical stress. Digoxin may increase cardiac output and lower circulating levels of norepinephrine. Diuretic therapy relieves dyspnea and peripheral edema and may be useful in reducing right ventricular volume overload in the presence of tricuspid

regurgitation.

It is recommended that all patients in whom primary pulmonary hypertension is confirmed undergo acute drug testing with short-acting pulmonary vasodilators to determine the extent of pulmonary vasodilator reserve or reactivity (Fig. 260-2). Intravenous adenosine, inhaled nitric oxide, and intravenous prostacyclin all appear to have similar effects in reducing pulmonary vascular resistance acutely with little effect on the systemic vascular bed. Adenosine is given as a constant infusion in doses of 50 (ug/kg)/min and increased every 2 min until side effects develop. Similarly, prostacyclin is given in doses of 2 (ng/kg)/min and increased every 30 min until side effects develop. Maximal physiologic effectiveness of the therapy is determined at the highest tolerated dose. Nitric oxide is generally administered via inhalation in 5 to 10 parts per million and increased every few minutes until no further effectiveness is obtained.

Calcium Channel Antagonists Patients who have substantial reductions in pulmonary vascular resistance from the short-acting vasodilators may be candidates to receive oral calcium channel blockers. These drugs should be administered under direct hemodynamic guidance in order to determine effectiveness and safety. Typically, patients will require high doses (e.g., nifedipine, 120 to 240 mg/d, or diltiazem, 540 to 900 mg/d).*

*These agents have not been approved for the treatment of primary pulmonary hypertension by the U.S. Food and Drug Administration.

Patients who manifest significant reductions in mean pulmonary artery pressure and pulmonary vascular resistance should demonstrate improved symptoms, regression of right ventricular hypertrophy, and improved survival with chronic therapy. However, fewer than half the patients who are responsive to the short-acting vasodilators will respond to this regimen. It is unknown whether the response to calcium blockers depends on the histologic subtype, but the therapy appears to be more successful in patients who are diagnosed early and have less advanced disease.

Prostacyclin This agent has been approved as a treatment of primary pulmonary hypertension for patients who are functional class III or IV and unresponsive to conventional therapy. Clinical trials have demonstrated that patients realize an improvement in symptoms and exercise tolerance and reduction in mortality, even if no acute hemodynamic response to drug challenge occurs. The drug can only be administered intravenously and requires placement of a permanent central venous catheter and continuous dose titration, as tolerance develops in all patients over a short period of time. The optimal dose has not been determined. Patients may deteriorate clinically from too much or too little drug. The side effects of prostacyclin, which include flushing, jaw pain, and diarrhea, are generally tolerated by most patients. The major problems with this therapy have been infections related to the venous catheter, which requires close monitoring and diligence on behalf of the patient. Recent data suggest that prostacyclin, in addition to its vasodilator and antithrombotic properties, may lead to reversal of the vascular remodeling that occurs in primary pulmonary hypertension. Long-term use of prostacyclin has been associated with adverse effects such as severe thrombocytopenia and severe foot pain, which can be disabling. The basis for these conditions is unknown. Because of the complexity involved in managing patients on

prostacyclin, it has been recommended that they be referred to centers with expertise in managing primary pulmonary hypertension for initiation of therapy.

Adverse Effects The administration of vasodilators can have serious acute and chronic adverse effects. The most common response is a reduction in pulmonary vascular resistance, manifest by an increased cardiac output, without a reduction in the mean pulmonary artery pressure. This results in increased stroke work of the right ventricle, which can result in worsening of ventricular function and precipitate right ventricular failure over time. In addition, maintenance of adequate systemic blood pressure is crucial, since right ventricular coronary blood flow is already compromised due to the loss of the normal gradient for myocardial perfusion between the aorta and right ventricle. Vasodilator drugs can provoke acute right ventricular ischemia, and deaths have been reported. For these reasons, the pharmacologic evaluation of primary pulmonary hypertension should always be undertaken with direct monitoring of systemic and pulmonary arterial pressures and cardiac output.

Anticoagulant therapy has also been advocated based on the evidence that thrombosis in situ is common. One retrospective study and one prospective study have demonstrated that the anticoagulant warfarin increases the survival of patients with primary pulmonary hypertension, and thus consideration for its use should be given to all patients. The dose of warfarin is generally titrated to achieve an increase in INR of 2.0 to 2.5 of control. Anticoagulants should not be expected to cause regression of the disease and result in any substantial change in symptoms.

Transplantation Because of the dramatic effects that prostacyclin has had in stabilizing the clinical course of patients with advanced disease, transplantation should be considered for patients on prostacyclin who develop or continue to manifest right heart failure. Acceptable results have been achieved with heart-lung, bilateral lung, and single lung transplant (Chap. 267). The availability of donor organs often influences the choice of procedure. The operation is best reserved for patients who are in the advanced stages of the disease in spite of medical therapy, or in whom medical therapy is not tolerated. Recurrence of disease has not been reported in any patient with primary pulmonary hypertension who has undergone single lung or heart-lung transplantation.

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261. PULMONARY THROMBOEMBOLISM - *Samuel Z. Goldhaber*

GENETIC CONSIDERATIONS

Rudolf Virchow postulated more than a century ago that three potentially overlapping factors predisposed to venous thrombosis: (1) local trauma to the vessel wall; (2) hypercoagulability; and (3) stasis. We now believe that many patients who suffer pulmonary thromboembolism (PTE) have an underlying inherited predisposition that remains clinically silent until an acquired stressor occurs such as surgery, obesity, or pregnancy (Table 261-1). When PTE is identified, a detailed family history for venous thromboembolism should be obtained.

Factor V Leiden The most frequent inherited predisposition to hypercoagulability is resistance to the endogenous anticoagulant protein, activated protein C. The phenotype of activated protein C resistance is associated with a single point mutation, designated *factor V Leiden*, in the factor V gene. This missense mutation -- a single nucleotide substitution of adenine for guanine 1691 -- causes an amino acid substitution of glutamine for arginine at position 506.

The prevalence of the heterozygous state was about 6% in healthy American male physicians participating in the Physicians' Health Study and was three times higher among those physicians who subsequently developed venous thrombosis. Furthermore, after anticoagulation (for at least 3 months) was completed and discontinued, those participants with factor V Leiden had a much higher rate of recurrent venous thrombosis than those without. A single-point mutation in the 3¢untranslated region of the prothrombin gene (G-to-A transition at nucleotide position 20210) appears to be associated with increased levels of prothrombin (factor II), the precursor of thrombin. In the Physicians' Health Study, the prevalence of the prothrombin gene mutation among control subjects was 3.9%. The G20210A mutation conferred an approximate doubling of the risk of venous thrombosis. Nevertheless, factor V Leiden is more common than all other (identified) inherited hypercoagulable states, including the prothrombin gene mutation, deficiencies in protein C, protein S, antithrombin III, and disorders of plasminogen (Chap. 117).

PATHOPHYSIOLOGY

EMBOLIZATION

When venous thrombi become dislodged from their site of formation, they embolize to the pulmonary arterial circulation or, paradoxically, to the arterial circulation through a patent foramen ovale or atrial septal defect. About half of patients with pelvic vein thrombosis or proximal leg deep venous thrombosis (DVT) havePTE, which is usually asymptomatic. Isolated calf vein or upper extremity venous thromboses also pose a risk (albeit lower) of PTE. Isolated calf vein thrombi are the most common source of paradoxical embolism.

PHYSIOLOGY

Pulmonary embolism can have the following effects:

1. *Increased pulmonary vascular resistance* due to vascular obstruction or neurohumoral agents including serotonin

2. *Impaired gas exchange* due to increased alveolar dead space from vascular obstruction and hypoxemia from alveolar hypoventilation in the nonobstructed lung, right-to-left shunting, and impaired carbon monoxide transfer due to loss of gas exchange surface

3. *Alveolar hyperventilation* due to reflex stimulation of irritant receptors

4. *Increased airway resistance* due to bronchoconstriction

5. *Decreased pulmonary compliance* due to lung edema, lung hemorrhage, or loss of surfactant

Right Ventricular Dysfunction Progressive right heart failure is the usual cause of death fromPTE. In the International Cooperative Pulmonary Embolism Registry (ICOPER), the presence of right ventricular dysfunction on baseline echocardiography of PTE patients was associated with a doubling of the 3-month mortality rate. As pulmonary vascular resistance increases, right ventricular wall tension rises and perpetuates further right ventricular dilatation and dysfunction. Consequently, the interventricular septum bulges into and compresses an intrinsically normal left ventricle. Increased right ventricular wall tension also compresses the right coronary artery and may precipitate myocardial ischemia and right ventricular infarction. Underfilling of the left ventricle may lead to a fall in left ventricular output and systemic arterial pressure, thereby provoking myocardial ischemia due to compromised coronary artery perfusion. Eventually, circulatory collapse and death may ensue.

DIAGNOSIS

The clinical setting can be immensely helpful in suggesting the diagnosis ofPTE. Patients with prior venous thromboembolism are at increased risk of recurrence (Table 261-1).

CLINICAL SYNDROMES

Patients with *massivePTE*present with systemic arterial hypotension and usually have anatomically widespread thromboembolism. Primary therapy with thrombolysis or embolectomy offers the greatest chance of survival. Those with *moderate to large PTE* have right ventricular hypokinesis on echocardiography but normal systemic arterial pressure. Optimal management is controversial; such patients may benefit from primary therapy to prevent recurrent embolism. Patients with *small to moderate PTE* have both normal right heart function and normal systemic arterial pressure. They have a good prognosis with either adequate anticoagulation or an inferior vena caval filter. The presence of *pulmonary infarction* usually indicates a small PTE, but one that is exquisitely painful, because it lodges near the innervation of pleural nerves.

Nonthrombotic pulmonary embolism may be easily overlooked. Possible etiologies

include fat embolism after blunt trauma and long bone fractures, tumor embolism, or air embolism. Intravenous drug users may inject themselves with a wide array of substances, such as hair, talc, or cotton. *Amniotic fluid embolism* occurs when fetal membranes leak or tear at the placental margin. The pulmonary edema seen in this syndrome is probably due primarily to alveolar capillary leakage.

SYMPTOMS AND SIGNS

Dyspnea is the most frequent symptom of PTE, and tachypnea is its most frequent sign. Whereas dyspnea, syncope, hypotension, or cyanosis indicate a massive PTE, pleuritic pain, cough, or hemoptysis often suggest a small embolism located distally near the pleura. On *physical examination*, young and previously healthy individuals may simply appear anxious but otherwise seem deceptively well, even with an anatomically large PTE. They need not have "classic" signs such as tachycardia, low-grade fever, neck vein distention, or an accentuated pulmonic component of the second heart sound. Sometimes, a paradoxical bradycardia occurs.

In older patients who complain of vague chest discomfort, the diagnosis ofPTE may not be apparent unless signs of right heart failure are present. Unfortunately, because acute coronary ischemic syndromes are so common, one may overlook the possibility of life-threatening PTE and may inadvertently discharge these patients from the hospital after the exclusion of myocardial infarction with serial cardiac enzyme measurements and electrocardiograms.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis ofPTE is broad (Table 261-2). Although PTE is known as "the great masquerader," quite often another illness simulates PTE. For example, when the proposed diagnosis of PTE is supposedly confirmed with a combination of dyspnea, chest pain, and an abnormal lung scan, the correct diagnosis of pneumonia might become apparent 12 h later when an infiltrate blossoms on chest x-ray, purulent sputum is first produced, and high fever and shaking chills develop.

Some patients havePTE and a coexisting illness such as pneumonia or heart failure. In such circumstances, clinical improvement will often fail to occur despite standard medical treatment of the concomitant illness. This situation can serve as a clinical clue to the possible coexistence of PTE.

NONIMAGING DIAGNOSTIC MODALITIES

These are generally safer, less expensive, but also less specific than diagnostic modalities that employ imaging.

Blood Tests The quantitative *plasma D*-dimer *enzyme-linked immunosorbent assay (ELISA)* level is elevated (>500 ng/mL) in more than 90% of patients withPTE, reflecting plasmin's breakdown of fibrin and indicating endogenous (though clinically ineffective) thrombolysis. A qualitative latex agglutination D-dimer assay, which is more readily available and less expensive than an ELISA, can be obtained initially; if elevated, the ELISA will also be elevated. However, if the latex agglutination is normal, a D-dimer

ELISA should be obtained, because the ELISA is much more sensitive than the latex agglutination D-dimer assay, which cannot be used to exclude PTE. The plasma D-dimer ELISA has a high negative predictive value and can be used to help exclude PTE. However, neither D-dimer assay is specific. Levels increase in patients with myocardial infarction, sepsis, or almost any systemic illness.

Data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) indicate that, contrary to classic teaching, *arterial blood gases* lack diagnostic utility forPTE. Among patients suspected of PTE, neither the room air arterial P_{O2} nor calculation of the alveolar-arterial oxygen gradient can reliably differentiate or triage patients who actually have PTE at angiography.

Electrocardiogram Classic abnormalities include sinus tachycardia; new-onset atrial fibrillation or flutter; and an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III (Chap. 226). Often, the QRS axis is greater than 90°. T-wave inversion in leads V_1 to V_4reflects right ventricular strain.

NONINVASIVE IMAGING MODALITIES

Chest Roentgenography A normal or near-normal chest x-ray in a dyspneic patient suggestsPTE. Well-established abnormalities include focal oligemia (Westermark's sign), a peripheral wedged-shaped density above the diaphragm (Hampton's hump), or an enlarged right descending pulmonary artery (Palla's sign).

Venous Ultrasonography ConfirmedDVT is usually an adequate surrogate forPTE. Ultrasonography of the deep venous system relies upon loss of vein compressibility as the primary criterion for DVT. About one-third of patients with PTE have no imaging evidence of DVT. In these situations, the clot may have already embolized to the lung or is in the pelvic veins, where ultrasonography is usually inadequate. Therefore, the workup for PTE should continue if there is high clinical suspicion, despite a normal ultrasound examination.

Lung Scanning (See alsoChap. 251) Lung scanning is the principal imaging test for the diagnosis ofPTE. Small particulate aggregates of albumin labeled with a gamma-emitting radionuclide are injected intravenously and are trapped in the pulmonary capillary bed. A perfusion scan defect indicates absent or decreased blood flow, possibly due to PTE. Ventilation scans, obtained with radiolabeled inhaled gases such as xenon or krypton, improve the specificity of the perfusion scan. Abnormal ventilation scans indicate abnormal nonventilated lung, thereby providing possible explanations for perfusion defects other than acute PTE. A high probability scan for PTE is defined as having two or more segmental perfusion defects in the presence of normal ventilation (Fig. 261-1).

Lung scanning is particularly useful if the results are normal or near-normal, or if there is a high probability forPTE. The diagnosis of PTE is very unlikely in patients with normal and near-normal scans but, in contrast, is about 90% certain in patients with high-probability scans. Unfortunately, fewer than half of patients with angiographically confirmed PTE have a high-probability scan. Importantly, as many as 40% of patients with high clinical suspicion for PTE and "low-probability" scans do, in fact, have PTE at

angiography.

Chest CT Computed tomography (CT) of the chest with intravenous contrast effectively diagnoses large, centralPTE but may fail to detect more peripherally located thrombi that are clinically important. In a comparison with standard contrast pulmonary angiography at Massachusetts General Hospital, the sensitivity of chest CT for PTE was only 60%.

Echocardiography This technique is useful for rapid triage of acutely ill patients who may havePTE. Bedside echocardiography can usually reliably differentiate among illnesses that have radically different treatment, including acute myocardial infarction, pericardial tamponade, dissection of the aorta, and PTE complicated by right heart failure. Detection of right ventricular dysfunction due to PTE helps to stratify the risk, delineate the prognosis, and plan optimal management.

INVASIVE DIAGNOSTIC MODALITIES

Pulmonary Angiography Selective pulmonary angiography is the most specific examination available for establishing the definitive diagnosis ofPTE and can detect emboli as small as 1 to 2 mm. A definitive diagnosis of PTE depends upon visualization of an intraluminal filling defect in more than one projection. Secondary signs of PTE include abrupt occlusion ("cut-off") of vessels; segmental oligemia or avascularity; a prolonged arterial phase with slow filling; or tortuous, tapering peripheral vessels.

Pulmonary angiography can be carried out safely among properly selected patients at hospitals that perform at least several studies per month. InPIOPED, the procedure resulted in death in five patients (0.5%), two of whom had severe heart failure prior to the procedure. Angiography is most useful when the clinical likelihood ofPTEdiffers substantially from the lung scan result or when the lung scan is of intermediate probability for PTE.

Contrast Phlebography This technique has been mostly replaced by ultrasonography. Venography is costly, uncomfortable, and occasionally results in contrast allergy or contrast-induced phlebitis. Contrast phlebography is worthwhile when there is a discrepancy between the clinical suspicion and the ultrasound result. Phlebography is also useful for diagnosing isolated calf vein thrombosis or recurrentDVT. A recently approved nuclear medicine test utilizing a synthetic peptide that binds preferentially to the glycoprotein IIb/IIIa receptors on activated platelets may eventually replace contrast phlebography in clinical practice. This radiopharmaceutical permits scintigraphic imaging of acute DVT and may be especially useful for differentiating acute from chronic DVT.

INTEGRATED DIAGNOSTIC APPROACH

We advocate an integrated diagnostic approach to streamline the workup ofPTE(Fig. 261-2). This strategy combines the clinical likelihood of PTE with the results of noninvasive testing especially D-dimerELISA, venous ultrasonography, and lung scanning to determine whether pulmonary angiography is warranted.

TREATMENT

ConsensusGuidelinesfrom the American College of Chest Physicians are summarized as follows.

Primary versus Secondary Therapy Primary therapy consists of clot dissolution with thrombolysis or removal ofPTE by embolectomy. Anticoagulation with heparin and warfarin or placement of an inferior vena caval filter constitutes secondary prevention of recurrent PTE rather than primary therapy.

Primary therapy should be reserved for patients at high risk of an adverse clinical outcome. When right ventricular function remains normal, patients typically have good clinical outcomes with anticoagulation alone (Fig. 261-3).

Adjunctive Therapy Important adjunctive measures include pain relief (especially with nonsteroidal anti-inflammatory agents), supplemental oxygenation, and psychological support. Dobutamine -- ab-adrenergic agonist with positive inotropic and pulmonary vasolidating effects -- may successfully treat right heart failure and cardiogenic shock. Volume loading should be undertaken cautiously because increased right ventricular dilatation can lead to even further reductions in left ventricular forward output.

Heparin Heparin binds to and accelerates the activity of antithrombin III, an enzyme that inhibits the coagulation factors thrombin (factor IIa), Xa, IXa, XIa, and XIIa. Heparin thus prevents additional thrombus formation and permits endogenous fibrinolytic mechanisms to lyse clot that has already formed. After 5 to 7 days of heparin, residual thrombus begins to stabilize in the endothelium of the vein or pulmonary artery. However, heparin does *not* directly dissolve thrombus that already exists.

Low-Molecular-Weight Heparins These fragments of unfractionated heparin exhibit less binding to plasma proteins and endothelial cells and consequently have greater bioavailability, a more predictable dose response, and a longer half-life than unfractionated heparin. No laboratory monitoring or dose adjustment is needed unless the patient is markedly obese or has renal insufficiency. Therefore, low-molecular-weight heparins are far more convenient to use than unfractionated heparin.

A meta-analysis of more than 3,500 acuteDVTpatients showed that those treated with low-molecular-weight heparin had an overall 29% reduction in mortality and major bleeding compared with the unfractionated heparin group. *Enoxaparin*, originally approved for prophylaxis, has recently received Food and Drug Administration approval for treatment ofPTE in the presence of DVT with a once-daily dose of 1.5 mg/kg subcutaneously. However, it is almost always administered as 1 mg/kg twice daily. *Dalteparin* is approved for prophylaxis but not for treatment of venous thromboembolism.

Dosing For unfractionated heparin, a typical bolus is 5000 to 10,000 units followed by a continuous infusion of 1000 to 1500 units/h. An activated partial thromboplastin time that is at least twice the control value should provide a therapeutic level of heparin. Nomograms based upon a patient's weight may assist in adjusting the infusion rate of heparin.

Complications The most important adverse effect of heparin is hemorrhage. For life-threatening or intracranial hemorrhage, protamine sulfate can be administered. Heparin-associated thrombocytopenia and osteopenia are far less common with low-molecular-weight heparins than with unfractionated heparin. Heparin-associated elevations in transaminase levels occur commonly but are rarely associated with clinical toxicity.

Warfarin This vitamin K antagonist prevents g carboxylation activation of coagulation factors II, VII, IX, and X. The full effect of warfarin often requires 5 days, even if the prothrombin time, used for monitoring, becomes elevated more rapidly. When warfarin is initiated during an active thrombotic state, the levels of protein C and S decline, thus creating a thrombogenic potential. By overlapping heparin and warfarin for 5 days, the procoagulant effect of unopposed warfarin can be counteracted. Thus, heparin acts as a "bridge" until the full anticoagulant effect of warfarin is obtained.

Dosing In an average-sized adult, warfarin is usually initiated in a dose of 5 mg. Doses of 7.5 or 10 mg can be used in obese or large framed young patients who are otherwise healthy. Patients who are malnourished or who have received prolonged courses of antibiotics are probably deficient in vitamin K and should receive smaller initial doses of warfarin, such as 2.5 mg. The prothrombin time is standardized by using the International Normalized Ratio (INR) to assess the anticoagulant effect of warfarin (Chap. 118). The target INR should be approximately 2.5-3.0.

Complications As with heparin, bleeding is the most important and common complication associated with warfarin administration. Life-threatening bleeding can be treated with cryoprecipitate or fresh frozen plasma (usually 2 units) to achieve immediate hemostasis. For less serious bleeding, or an excessively highINR in the absence of bleeding, vitamin K may be administered. An initial dose of 5 to 10 mg subcutaneously will help lower the INR toward the upper portion of the therapeutic range within about 6 h. Reversing excessive INRs with oral rather than subcutaneous vitamin K will facilitate re-establishing a stable dose of warfarin.

Warfarin-induced skin necrosis is a rare complication that may be related to warfarin-induced reduction of protein C. It is usually associated with administration of a high initial dose of warfarin during an acute thrombotic state in which heparin is withheld. During pregnancy, warfarin should be avoided if possible because of warfarin embryopathy, which is most common with exposure during the sixth through twelfth weeks of gestation. However, women can take warfarin postpartum and breast feed safely.

Duration of Anticoagulation After discontinuation of anticoagulation, the risk of recurrentPTE is surprisingly high. Nevertheless, the optimal duration of anticoagulation remains unknown. Schulman and colleagues found that after a 6-month course of anticoagulation, 14% of PTE patients suffered a recurrent venous thromboembolism within the ensuing 2 years. The recurrence rate was twice as high among patients who received only 6 weeks of anticoagulation. It is reasonable to anticoagulate the first episode of PTE for at least 6 months.

Inferior Vena Caval Filters When anticoagulation cannot be undertaken because of active bleeding, insertion of an inferior vena caval filter is usually necessary. Other indications include recurrent venous thrombosis despite adequate anticoagulation, prevention of recurrentPTE in patients with right heart failure who are not candidates for thrombolysis, or prophylaxis of extremely high risk patients. The Bird's Nest filter infrarenally or, if necessary, a Greenfield filter suprarenally are recommended.

Thrombolysis Thrombolytic therapy may rapidly reverse right heart failure and thus lead to a lower rate of death and recurrentPTE. Thrombolysis usually achieves the following: (1) dissolves much of the anatomically obstructing pulmonary arterial thrombus; (2) prevents the continued release of serotonin and other neurohumoral factors that might otherwise exacerbate pulmonary hypertension; and (3) dissolves much of the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent PTE.

The preferred thrombolytic regimen is 100 mg of recombinant tissue plasminogen activator administered as a continuous peripheral intravenous infusion over 2 h. Patients appear to respond to thrombolysis for up to 14 days after thePTEoccurred.

Contraindications to thrombolysis include intracranial disease, recent surgery, or trauma. There is about a 1% risk of intracranial hemorrhage. Careful screening of patients for contraindications to thrombolysis is the best way to minimize bleeding risk.

Pulmonary Thromboendarterectomy Patients who develop chronic pulmonary hypertension due to priorPTE may become severely dyspneic at rest or with minimal exertion. They should be considered for pulmonary thromboendarterectomy which, if successful, can markedly reduce and at times even cure pulmonary hypertension.

Prevention Prevention ofPTE is of paramount importance because it is both difficult to recognize and expensive to treat. Fortunately, effective mechanical and pharmacologic prophylaxis modalities are widely available and usually effective (Table 261-3).

(Bibliography omitted in Palm version)

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