CHAPTER 23

RESPIRATORY DISORDERS

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INTRODUCTION

Lung disorders are common in the general population. Chronic bronchitis affects 10–25% of the USA population, asthma 5%, and emphysema about 3%. In 1992 these chronic obstructive pulmonary diseases were the fourth leading cause of mortality in the USA, accounting for more than 91,800 deaths.[1] Pneumonia is the sixth leading cause of death in the USA.[2] It has been estimated that 2–4 million cases of community-acquired pneumonia occur in the USA each year, and that as many as 20% of these require hospitalization. Occupational lung disease, cystic fibrosis, hypersensitivity pneumonitis and other respiratory disorders affect many others. Accordingly, life insurance applications from persons with a variety of respiratory disorders are frequently encountered, and the underwriter and medical consultant are called on with some regularity to render assessments of the mortality risk associated with various pulmonary impairments.

NORMAL PULMONARY FUNCTION

Although the lung serves many functions (mechanical filtration of blood, metabolic, immunologic etc.), the main function of the lung is to support

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cellular respiration, by providing an interface that will allow oxygen to move from ambient air into the vascular system in order that it may be delivered to the tissues, and to allow carbon dioxide, the by-product of cellular respiration, to be excreted back into the air.

Ventilation is the mechanical process by which ambient air is caused to move through the tracheo-bronchial tree into the alveolar spaces and back out again. The tracheo-bronchial tree is a system of branching airways which divide in an asymmetric and dichotomous manner. There are approximately 16 generations of airways from the trachea to the terminal bronchioles. The terminal bronchioles comprise the last generation of conducting airways leading to the terminal respiratory units. The terminal respiratory units, or acini, each consist of approximately three generations of respiratory bronchioles and alveolar ducts, which empty into alveolar sacs. No gas exchange occurs in the conducting airways. It is for this reason that these conducting airways are referred to as the 'anatomic dead space'. Beginning with the respiratory bronchioles, however, alveolar out-pouchings begin to appear from airway walls. The number of these alveolar out-pouchings increases with subsequent airway branching until the airway walls are composed entirely of alveolar openings. At this point the airways are called alveolar ducts. Thus respiratory bronchioles and alveolar ducts have the dual roles of air conduction and gas exchange. Alveolar ducts then open into alveolar sacs which consist of complex geometric clusterings of interconnected alveoli.

Each alveolus is surrounded by a network of capillaries. It is within these alveolar-capillary units that gas exchange occurs through the process of diffusion: oxygen moving down a concentration gradient from the alveolar spaces, across alveolar capillary membranes into the pulmonary capillaries; and carbon dioxide moving down a concentration gradient in the opposite direction.

Ventilation is under the control of the cerebral cortex, brainstem and peripheral chemoreceptors. Although ventilation can be volitionally modified to accommodate such activities as speech, it is also under autonomic control by the respiratory centers located in the pons and medulla. In addition, chemoreceptors located in the medulla and carotid bodies respond to changes in pH (medulla), and P_aCO_2 and P_aO_2 (carotid bodies). Even a slight decrease in pH or increase in P_aCO_2 above the normal range, or a reduction in P_aO_2 below 60 torr will markedly increase ventilation. Conversely, significant reductions in the P_aCO_2, provided pH and P_aO_2 remain normal, will result in a diminution (hypopnea) or pause (apnea) in ventilation until the P_aCO_2 is again normalized.

ARTERIAL BLOOD GASES ANALYSIS

Directly measured arterial blood gas parameters include measurements of arterial hydrogen ion concentration (pH), arterial carbon dioxide concentration (partial pressure of carbon dioxide in arterial blood or P_aCO_2) arterial oxygen concentration (partial pressure of oxygen in arterial blood or P_aO_2) and the degree to which hemoglobin is fully loaded or saturated with oxygen (S_aO_2).

Normal arterial pH is maintained within a narrow range (7.35–7.45) through a complex feedback loop involving ventilatory and metabolic adjustments that result in hyperventilation to lower P_aCO_2 and the retention of HCO_3 by the kidneys during periods of acidosis. Conversely alkalosis will result in hypoventilation and CO_2 retention and cause increased renal HCO_3 excretion.

Normal P_aCO_2 values fall within the range of 35–45 torr. An elevated P_aCO_2 level (hypercarbia) is the result of alveolar hypoventilation either because of a reduction in total ventilation or because of an increase in dead space ventilation at the expense of alveolar ventilation. Normal P_aO_2 values vary inversely with age. For normal subjects aged 20–80, P_aO_2 values determined while seated and breathing ambient air at 1 atmosphere pressure range from 100–80 torr.

The term hypoxia refers to the situation in which the P_aO_2 is below the normal range. Sometimes the term is also used to refer to tissue hypoxia, a condition in which cells are deprived of an adequate supply of oxygen, either because of low oxygen content in arterial blood, or because of cardiac or arterial insufficiency. It should be remembered that most oxygen in blood is bound to hemoglobin in the form of oxyhemoblobin and that only a small fraction is dissolved in the

plasma. However, the concentration of oxygen dissolved in plasma (P_aO_2) is one of the three factors that determines the amount of oxygen that can be bound by hemoglobin, the other factors being the binding affinity of hemoglobin for oxygen and the concentration of hemoglobin in blood. Hypoxemia is the term that refers to low arterial blood oxygen content either due to a low P_aO_2, a low hemoglobin-oxygen binding affinity or anemia.

It is sometimes useful to classify pulmonary insufficiency into two general types. In Type 1 or hypoxic pulmonary insufficiency, arterial P_aO_2 levels are reduced. If the degree of hypoxia is mild, ventilation may not increase and P_aCO_2 levels may be normal. However, reductions in P_aO_2 levels below 60 torr usually result in compensatory hyperventilation and a reduction in P_aCO_2. In Type 2 or hypercapnic-hypoxic respiratory insufficiency, alveolar hypoventilation produces elevated alveolar concentrations of carbon dioxide and reduced alveolar concentrations of oxygen which, in turn, result in the situation in which P_aCO2 is increased despite the presence of arterial hypoxemia. Although this classification is somewhat artificial due to the occurrence of mixed forms of respiratory insufficiency, it has proven useful in helping to identify the underlying disease process (*see* Table 23.1).

Risk selection

The relative mortality risk of persons with Type 1 respiratory insufficiency varies greatly, depending on the nature of the underlying disorder and the severity of hypoxemia. However, the presence of any degree of hypoxemia is a cause for concern and should prompt an investigation into the underlying etiology.

A severe degree of hypoxia ($P_aO_2 < 60$ torr) with or without any degree of hypercarbia ($P_aCO_2 > 45$ torr, Type 2 respiratory insufficiency) indicates the presence of a life-threatening disorder. In the 1970s, The British Medical Research Council sponsored randomized trials of the effect of supplementary oxygen therapy in hypoxemic patients ($P_2O_2 < 60$ torr) who has clinical evidence of pulmonary hypertension due to chronic obstructive pulmonary disease (COPD). The mean ages for men and women in these trials were 58 and 56 respectively. Patients receiving no supplementary oxygen had an annual death rate of 30%, compared with 18% for patients who received supplementary oxygen for 15 hours per day. In a complementary study in North America, the Nocturnal Oxygen Therapy Trial demonstrated that hypoxemic COPD patients (mean age 65) who received 12 hours of supplementary oxygen per day were found to have an annual death rate of

Table 23.1. Causes of respiratory insufficiency.

Type 1 (hypoxic)	Type 2 (hypoxic-hypercapneic)
Alveolar process	Neurologic
Pneumonia	Primary alveolar hypoventilation
Pulmonary edema	Sedation
Pulmonary hemorrhage	Cervical cord injury
Pulmonary alveolar proteinosis	Phrenic nerve injury
Atalectasis	Respiratory muscle weakness
Emphysema	Upper airway obstruction
Interstitial process	
Pulmonary fibrosis	
Pulmonary vascular process	
Thromboembolic	
Right-to-left shunt	

20%, compared with an annual death rate of about 11 per cent for patients who receive oxygen for at least 19 hours per day.[3]

Therefore, although supplemental oxygen therapy markedly improved survival in patients with COPD who were hypoxemic, even with supplemental oxygen their relative death rates were elevated several thousand-fold, compared with expected death rates. In more recent studies, subjects with COPD who require long-term oxygen therapy have been reported to have mortality rates of 18–22% over 18–24 months of follow-up.[4,5] Patients having hypoxia due to interstitial lung disease have even worse survival.[6]

PULMONARY FUNCTION TESTS

Pulmonary function testing is a valuable aid in determining the cause of such symptoms as cough and dyspnea, as well as gauging the severity of the pulmonary disease process and estimating prognosis. Many types of pulmonary function tests exist. These include tests designed to measure lung volume, airflow, gas exchange, respiratory muscle strength, ventilatory drive and ventilation-perfusion matching (*see* Table 23.2).

Lung volume measurements

Total lung volume, more properly referred to as total lung capacity (TLC), is the total amount of air contained within the tracheo-bronchial tree and alveolar units at the point of maximal inhalation. TLC can be further subdivided into four volumes and three other capacities (technically a capacity is the sum of one or more volumes (*see* Figure 23.1 and Table 23.3).

Disease processes that result in a reduction in TLC are termed restrictive diseases. In general, restrictive diseases are those that primarily affect the alveoli, interstitium, pleura, chest wall or the respiratory muscles (*see* Table 23.4). Since disease processes that result in reductions in TLC usually result in proportionate reductions in the other lung volume and capacity measurements, VC measurements are often used to substitute for TLC measurements. Thus a reduced vital capacity usually indicates the presence of a restrictive lung disease.

Table 23.2. Pulmonary function tests.

Parameter	Measurement
Lung volume	TLC by plethysmography, gas dilution, planimetry and static lung volume determinations
Airflow <	TTL > Volume-time curve (timed vital capacity), flow-volume curves
Bronchial reactivity	Specific or non-specific (histamine or methacholine) bronchial provocation challenges
Alveolar-capillary surface area	Carbon monoxide diffusion capacity by steady state ($DLCO_{ss}$) or single breath ($DLCO_{sb}$) methods
Respiratory muscle strength	
Maximum inspiratory and expiratory pressures	
Ventilatory drive	
Ventilatory response to induced hypercarbia and hypoxia	
Adequacy of ventilation	
Arterial carbon dioxide concentration ($PaCO_2$}	
Ventilation-perfusion matching	
Arterial oxygen concentration ($PaCO_2$), ventilation/perfusion pulmonary scintigraphy	

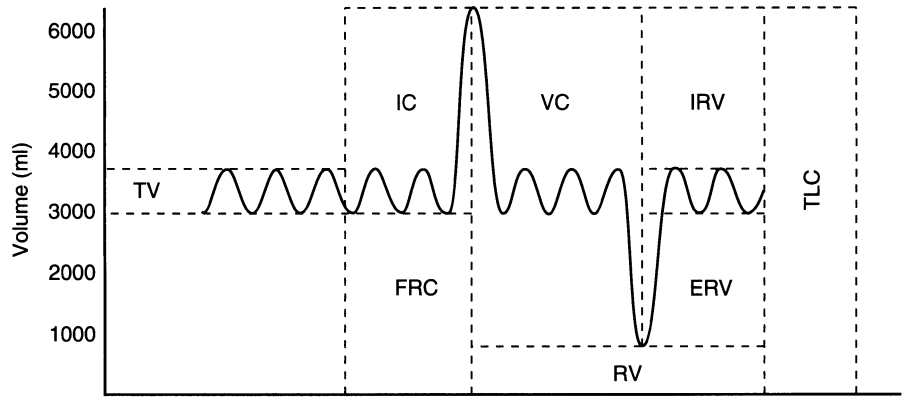

Figure 23.1. Lung volumes. (*See* Table 23.3 for key to abbreviations.)

Occasionally severe airflow obstruction may result in an exception to the rule that reductions in VC are paralled by proportionate reductions in TLC. Severe airflow obstruction may cause air to become trapped within the lung during exhalation. This may result in an increase in RV and a corresponding reduction in VC. In this situation, a reduced VC measurement alone might suggest the presence of restrictive lung disease. However, if TLC is measured, the true nature of the impairment will become clear: the reduction in VC will be seen to have occurred due to an increase in RV as a result of air trapping. At times, airflow obstruction and air trapping are sufficiently severe to cause a marked increase in RV and thereby an increase in TLC.

Table 23.3. Lung volumes.

Measurement	Abbreviation	Definition
Tidal volume	TV	Amount of air flowing in and out of the lung during quiet normal breathing
Residual volume	RV	Amount of air remaining in the lung after maximal exhalation
Expiratory reserve volume	ERV	Amount of air that can be maximally exhaled from the end of a normal tidal exhalation
Inspiratory reserve volume	IRV	Amount of air that can be maximally inhaled from the end of a normal tidal inhalation
Functional residual capacity	FRC	Sum of ERV and RV; this is the amount of air remaining in the lung at the end of a normal tidal exhalation
Inspiratory capacity	IC	Sum of TV and IRV; this is the amount of air that can be maximally inhaled from the end of a normal tidal exhalation
Vital capacity	VC	Amount of air than can be maximally exhaled following a maximal inhalation or, alter-natively, the amount of air that can be maximally inhaled from the end of a maximal exhalation. Also the sum of IC and ERV.
Total lung capacity	TLC	Sum of VC and RV; the total amount of air in the lungs at full inspiration; also the sum of IRV + TV + ERV + RV, or the sum of IC + FRC etc.

Table 23.4. Examples of restrictive lung diseases.

Interstitial lung disease	Disorders of the chest wall
Idiopathic pulmonary fibrosis	Rib fractures
Sarcoidosis	Kyphoscoliosis
Pneumoconioses	Spondylosis
Pulmonary edema	Obesity
Pleural disease	Neuromuscular disorders
Pneumothorax	Spinal cord injury
Pleural effusion	
Myasthenia gravis	
Empyema	
Myotonic distrophy	
Fibrothorax	
Anterior horn cell disease	

Airflow measurements

Dynamic spirometry, also called flow related spirometry, measure rates of airflow. Both inhalation and exhalation flow rates can be measured. Typically these tests are performed by asking the subject to inhale fully and then forcibly exhale until RV is reached, at which time the subject is asked to inhale again as rapidly and completely as possible. The volume of air inhaled and exhaled is recorded as a function of time and plotted as a volume-time curve, also known as timed vital capacity. Flow rates are then calculated by dividing the volume of air exhaled (or inhaled) by the time required for that exhalation (or inhalation) (*see* Figure 23.2).

The amount of air exhaled during the first second of a forced expiratory maneuver, the FEV_1, is the most commonly reported measurement of airflow. Another commonly reported measurement of airflow is the maximum mid-expiratory flow rate (MMEF). The MMEF has also been termed the mid-flow or the FEF_{25-75} (the forced expiratory flow between 25–75% of the vital capacity). This is the rate of airflow between the points at which 25–75% of the vital capacity are exhaled. It was previously thought that a reduction in the mid-flow in the presence of a normal or nearly normal FEV_1 was indicative of obstruction occurring in the small (mm diameter) airways. It is now believed that isolated reductions in mid-flow rates indicate mild airflow obstruction and are not specific for disease localized to the small airways.

The incorporation of microprocessors into spirometers has made it possible for instantaneous flow rates to be determined in real time during the forced VC maneuver and for these instantaneous flow rates to be plotted against lung volume. The resulting curve, termed a flow-volume loop, gives the same information contained in a volume-time curve but displayed in a manner that facilitates the

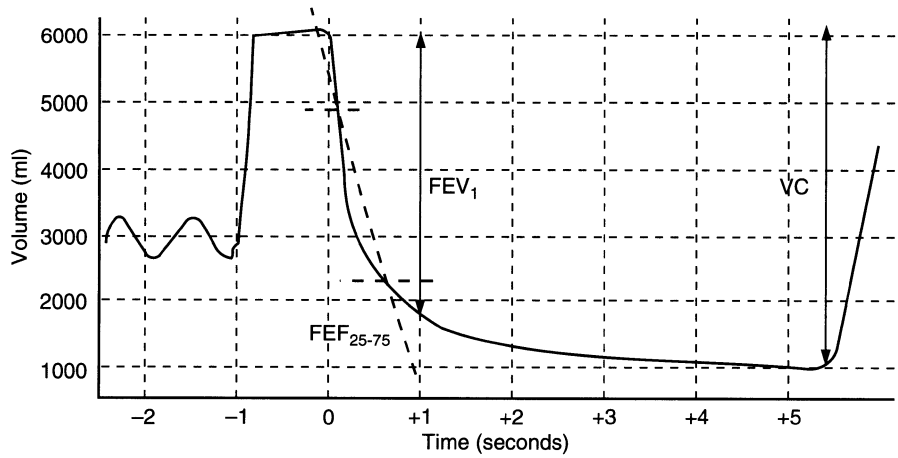

Figure 23.2. Normal volume-time curve (timed vital capacity curve).

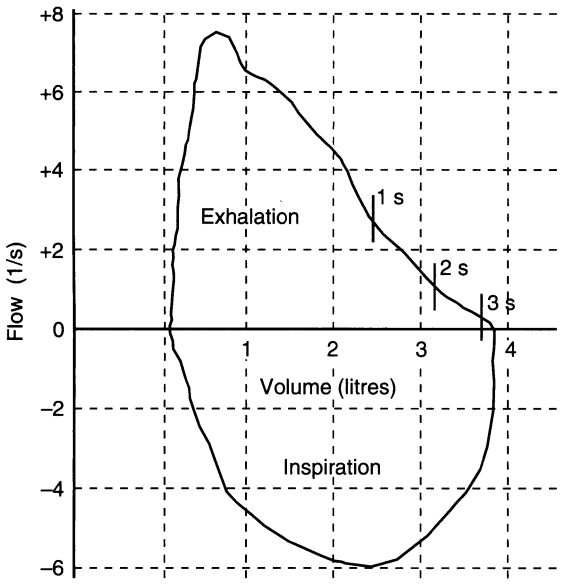

Figure 23.3. Normal flow-volume loop.

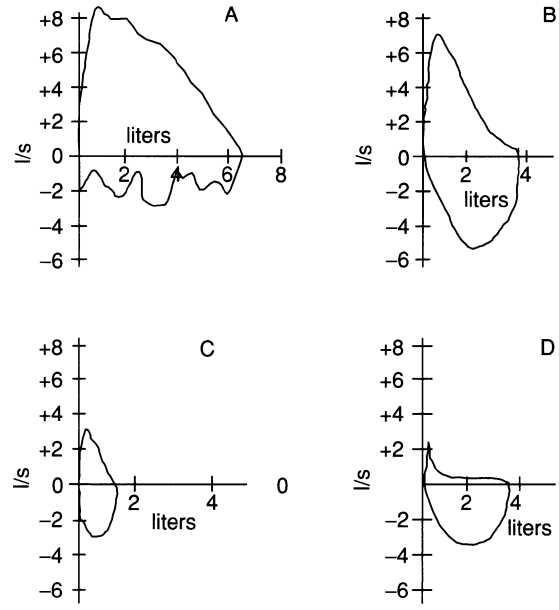

Figure 23.4. Examples of flow-volume loops in various disease states. A = upper airway obstruction; B = mild asthma; C = severe restrictive disease; D = severe COPD.

visual interpretation of the spirogram. Representative examples of flow-volume loops are shown in Figures 23.3 and 23.4.

It should be recognized that flow rates are dependent upon lung volume: as lung volume decreases so do flow rates. Therefore, impairments that cause a reduction in lung volume (restrictive disease) and impairments that produce a limitation in airflow (obstructive disease) will cause reductions in FEV_1. Accordingly, a reduction in FEV_1 is not sufficient in itself for determining whether the process responsible for that reduction is primarily restrictive or obstructive in nature. Rather, a restrictive process is indicated when the FEV_1 and FVC (or better, the TLC) are reduced to a similar degree. The presence of an obstructive process is indicated when the FEV_1 is reduced to a greater degree than the FVC. This is measured by the $FEV_{1/FVC}$ ratio, also known as the FEV_1 percent (*see* Table 23.5).

Interpretation

Reductions in flow rates and volumes are usually expressed in terms that compare a given subject's flows and volumes with the flows and volumes predicted for a normal individual of the same age, height and sex. Typical criteria used to categorize the degree of pulmonary impairment are shown in Table 23.6.[7]

Various sets of equations to predict normal pulmonary function exist. Most sets of equations predicting FEV_1 and FVC for normal men and women are linear functions of height and age and take the general form [(a × height−, (b × age) + c] where a, b and c are constants. The constants used in these equations have been derived empirically by studying populations presumed to consist of individuals having normal pulmonary function (*see* Tables 23.7–9). The degree to which these study populations represent individuals who truly have normal pulmonary function varies significantly. One of the earlier studies consisted of male patients in Veteran's Administration hospitals. Because cigarette smokers were included in this study, as well as for other reasons, the predicted values for FVC and FEV_1 derived from this study are substantially lower than those derived from other studies that excluded subjects

Table 23.5. Ventilatory defect patterns.

	TLC	FVC	FEV1	FEV1/FVC
Restrictive defect	Decreased	Decreased	Decreased	Normal or sometimes slightly increased
Obstructive defect	Normal or sometimes slightly increased	Normal or decreased[a]	Decreased	Decreased or normal[a]

[a]Severe airflow obstruction may produce air trapping and cause a reduction in the FVC and a corresponding preservation in the FEV1/FVC ratio.

Table 23.6. Classification of ventilatory impairment severity.

Degree of impairment	FVC		FEV1		FEV1/FVC
No impairment	≥ 80% predicted	and	≥ 80% predicted	and	≥ 70%
Mild impairment	60–79% predicted	or	60–79% predicted		
Moderate impairment	51–59% predicted	or	41–59% predicted		
Severe impairment	≤ 50% predicted	or	≤ 40% predicted		

Table 23.7. Studies used to derive equations predicting normal pulmonary function.

	Kory[8]	Morris[9]	Crapo[10]	Knudson[11]	Enright[12]
Year	1961	1971	1981	1982	1993
Number of subjects		988	251	901	288
% males	52%	50%	36%	39%	
Age range	Under 25	16%	7%		0%
	25–60	76%	66%		0%
	60–70	6%	14%		57%
	Over 70	2%	14%		43%
Population	Veterans	Mormons (55%) Seventh Day Adventists (24%)	Mormons (90%)		Elderly urban dwellers
Smokers exluded?	No	Yes	Yes	Regular smokers excluded	Yes
Methods used to exlude	Unknown	Questionnaire	Questionnaire Chest X-ray Physical exam	Questionnaire	Questionnaire
Height measured	Without shoes	Without shoes			
Spriometer	Stead-Wells	Water seal	Pneumotach ATS standards	Water seal ATS standards	ATS standards
Measurements	FEV_1, FVC,	FEV_1, FVC, $FEF_{200-1200}$ FEF_{25-75}	FEV_1, FVC, FEV_1/FVC FEF_{25-75}	FEV_1, FVC FEV_1/FVC FEF_{25-75} $\dot{V}_{50}$, $\dot{V}_{75}$	MIP, MEP

Table 23.8. Prediction equations for FEV_1. FEV_1 = H1 × Ht (in inches)-A_1 × age (in yr)-F_1.

Study	H1	A1	F1	SEE
Kory				
Males	0.0940	0.0280	1.5900	
Females	0.0711	0.0210	0.0870	
Morris				
Males	0.0920	0.0320	1.2600	0.550
Females	0.0890	0.0250	1.9320	0.470
Crapo				
Males	0.1052	0.0244	2.1900	0.486
Females	0.0869	0.0255	1.5780	0.326
Knudson				
Males	0.1689	0.0292	6.5147	
Females	0.0785	0.0201	1.4050	
Enright				
Males	0.0960	0.0271	1.7300	0.505
Females	0.0714	0.0325	0.0900	0.300

reporting any history of tobacco use, pulmonary disorders or current respiratory symptoms.

Because underwriting criteria for pulmonary function are often based on a percent reduction in FEV_1 and FVC compared with normal predicted values, it is desirable that the set of equations used to specify normal values for pulmonary function, or the tables constructed from these equations, be based on data that directly relate reductions in FEV_1 and FVC to mortality risk. If other sets of normal values are chosen, mortality experience may differ from expected unless underwriting actions are adjusted accordingly.

Table 23.9. Prediction equations for FVC FVC = H × Ht (in inches) – A × age (in yr) - F.

Study	H	A	F	SEE
Kory				
Males	0.1321	0.0220	3.6000	
Females	0.1041	0.0180	2.6900	
Morris				
Males	0.1480	0.0250	4.2410	0.740
Females	0.1150	0.0240	2.8250	0.520
Crapo				
Males	0.1524	0.0214	4.6500	0.644
Females	0.1247	0.0216	3.5900	0.395
Knudson				
Males	0.2144	0.0298	8.7818	
Females	0.1085	0.0174	2.9001	
Enright				
Males	0.1440	0.0206	4.3700	0.505
Females	0.0927	0.0330	0.7000	0.444

Risk selection

The spirometer was invented in 1846 by John Hutchinson, who believed that the maximum volume of air that a subject could exhale was a reliable indicator of the risk of subsequent death. Such was his confidence in this belief that he coined the term vital capacity for this measurement and offered his device to the insurance industry of London.[13] Numerous studies over the years have proven Dr Hutchinson's belief to be correct. However, it now appears that reductions in FEV_1 may be more predictive of subsequent mortality than reductions in VC or the ratio FEV_1/FVC.[14]

The Copenhagen City Heart Study followed 12,511 subjects for a mean of 6.5 years. Using a proportionate hazards model to predict the risk of cardiovascular death and fatal or non-fatal myocardial infarction (MI), the percent predicted FEV_1 and percent predicted FVC were shown to be significantly related to cardiovascular mortality and the risk of fatal MI. Subjects with a FEV_1 or a FVC < 60% of predicted, had a risk of death twice as great as those having values for FEV_1 or FVC > 80% of predicted.[15]

In a study of 2718 British men followed for 20–25 years, the ratio of FEV_1 to the cube of the standing height (FEV_1/H^3) measured at the time of entry into the study was shown to predict the risk of death from chronic obstructive lung disease, lung cancer, non-neoplastic respiratory causes, vascular disease and all-cause mortality.[16]

Data on 3133 men and women participating in the Framingham studies indicated that the ratio FEV_1/H^3 was inversely related to mortality in men and women under age 70 and in women older than age 70.[17]

In a 24-year follow-up study of 874 men enrolled in the Baltimore Longitudinal Study on

Aging, reductions inpercent predicted FEV_1 predicted mortality over 24 years of follow-up. After adjusting for the effect of age, smoking, education and race, the relative mortality risk for individuals having an FEV1 70–80% of predicted compared with individuals having an FEV_1 100–110% of predicted was 125%.[18] Individuals who had rapidly declining FEV_1 values had up to a fivefold increase risk of cardiac deaths, compared with those who had the lowest rate of FEV_1 decline.[19]

Reductions in FEV_1 have also been shown to predict deaths due to lung cancer. For men participating in the Multiple Risk Factor Intervention Trial (MRFIT), lung cancer death rates were increased sevenfold for persons having FEV_1 values in the lowest quintile ($\leq$ 2670 ml), compared with the highest quintile ($\geq$ 3749 ml) between the third and tenth years of follow-up. The authors report that this relationship was not weakened after adjustment for smoking history.[20]

In an insured lives study performed by Lincoln Re, excess death rates became significantly elevated even with what would be considered mild impairments in FEV_1 (FEV_1 between 60–79% of predicted).[21]

However, care should be taken when interpreting timed VC studies, to ensure that the reported results reliably reflect the subject's true pulmonary function status. Pulmonary function testing is fraught with potential for error, including errors resulting from faulty equipment, improper spirometer calibration, those introduced by inexperienced technicians and the failure of the subject to inhale to full lung capacity and to completely exhale with maximum force. The importance of this last point cannot be emphasized too strongly: performing a proper timed VC manoeuvre requires a skilled technician, and a capable, cooperative and highly motivated subject. Significant error will result if incorrect instructions are given to the subject, if technical errors are made or if the subject exerts less than maximum effort.

Reviewing the actual timed VC curves or flow-volume loop tracings will aid in identifying many sources of error. Fortunately most common errors (with the exception of calibration errors) tend to produce falsely low values for FVC and FEV_1. Accordingly, if errors other than calibration are suspected, it may be prudent to consider reported values for FVC and FEV_1 to represent the lower bound of what is likely to be the subject's true pulmonary function.

AIRWAYS DISORDERS

Airways disorders encompass the following diseases: asthma, asthmatic bronchitis, chronic bronchitis, emphysema, bronchiectasis, bronchiolitis and cystic fibrosis. Together, these comprise what has come to be called the chronic obstructive pulmonary diseases (COPD). Of these, asthma, emphysema and chronic bronchitis are the most common forms of COPD.

Asthma

Asthma is a disease characterized by airway inflammation and bronchospasm, which results in reversible airflow obstruction. Although our understanding of the pathophysiology of asthma is incomplete, it is clear that airway inflammation plays a central role in the pathogenesis and perpetuation of asthma, by causing the production and release of mediators and mitogens that produce structural remodeling of the lung. Over time, this remodeling may produce fixed airway narrowing and airway hyperresponsiveness that is refractory to treatment.[22] Accordingly, early and chronic treatment with inhaled anti-inflammatory agents (inhaled corticosteroids, chromolyn sodium or nedocromil) is now recommended for essentially all asthma patients, with perhaps the exception of those having only the mildest forms of asthma and those who can easily avoid exposure to identifiable allergens.[23,24]

In the past, asthma has been classified as intrinsic or extrinsic depending on whether airway hyperresponsiveness occurred in an atopic individual (i.e. an individual in whom an allergy to airborne substances could be demonstrated). Atopic individuals with bronchial hyperresponsiveness, elevated IgE levels and peripheral blood eosinophilia were said to have extrinsic asthma; those without atopic features were said to have intrinsic asthma.

No difference in histology or response to corticosteroids has been demonstrated between sub-

jects with intrinsic and extrinsic asthma, and these terms are used less commonly now than in the past. Indeed some investigators believe that if the cause stimuli were known for every patient, all cases of asthma would be extrinsic.[25]

Today, the causes of asthma are often discussed in terms of 'inducers' and 'triggers'. Inducers are those substances that cause airway inflammation. These include allergens, viral and mycoplasma infections, and exposure to noxious gases such as chlorine. Triggers are those stimuli that provoke bronchoconstriction and symptoms in asthmatics, but that do not cause airway inflammation. Examples of triggers include exercise, cold air, emotional upset, laughter and inhaled irritants such as perfumes, and second hand cigarette smoke. Long-term exposure to environmental tobacco smoke has also been suspected to be an inducer of inflammation in susceptible persons, such as young children.[26,27]

The prevalence of asthma has increased worldwide over the past 15 years, as have asthma death rates.[28,29] Data for the USA indicate that asthma mortality rates reached a nadir in 1977 but have progressively increased since then.[30] The reasons for this increase are uncertain, but rising levels of urban air pollution, indoor air pollution with second hand tobacco smoke, overuse of inhaled bronchodilators, changing social and economic factors and limited access to health care have all been proposed as possible causes.[31–34]

It is noteworthy, however, that the increase in asthma hospitalization rates and mortality rates have not been evenly distributed across all localities in the USA. Rather, there has been a disproportionate increase in asthma morbidity and mortality in specific counties, among specific social and ethnic groups, and in specific zip code areas within large cities such as New York and Boston.[35–37] Poverty, lower educational attainment, lack of treatment with inhaled corticosteroids, coexisting alcohol and substance abuse and genetic predisposition have all been postulated as factors to explain this pattern.[38]

Mortality studies

In a longitudinal study of 1075 asthmatics between the years 1974 and 1990, all-cause mortality was found to be increased to 240% (95% confidence intervals: 160–340%) compared with age- and sex-matched controls.[39] Multiple regression analysis revealed that age, a history of cigarette smoking, the presence of eosinophilia, percent predicted FEV_1 and the degree of reversible airway obstruction were all predictors of death. No association was found between previous hospital admissions for asthma and subsequent death (*see* Table 23.10).

In another long-term study of 2499 community residents with asthma living in Olmsted county, Minnesota, overall survival was found to be not significantly different than expected for the general population over a mean of 14 years of follow-up. Survival, however, was found to be less than expected for subjects who were 35 years of age or older when their asthma was diagnosed, and in those who had another coexisting lung disease.[40]

In contrast to the relatively favorable mortality rates reported in community studies of asthma, are those studies following persons with severe asthma. Marquette *et al.* followed 147 patients

Table 23.10. Risk factors for asthma deaths.[39]

Variable	RR death from asthma	95% CI
Age		
< 39	1.0	
40–69	2.5	0.8–8.1
> 70	8.5	2.2–33.7
Tobacco usage		
Lifelong non-smoker	1.0	
< 20 packs/year	2.6	1.0–6.8
> 20 packs/year	5.9	2.3–15.0
Blood eosinophils		
< 450/mm^3	1.0	
> 450/mm^3	7.4	2.8–19.7
FEV_1% predicted		
> 70%	1.0	
40–69%	4.9	2.0–11.8
< 40%	3.3	0.8–14.5
Reversibility		
15–24%	1.0	
25–49%	2.7	0.9–7.9
> 50%	7.0	2.4–21.0

with life-threatening asthma (defined as those requiring mechanical ventilation) for periods ranging from 1–75 months. In-hospital mortality was 16.5%. Among the 121 patients discharged from the intensive care unit (ICU), 18 subsequently died, 17 from a new asthma attack. Post-hospitalization mortality was 10.1%. Nearly 66% of these post-hospital deaths occurred within the year following discharge from the ICU. Smoking and age over 40 were associated with a higher risk of mortality.[41]

The *Medical Impairment Study 1983* included a relatively large number of insured lives with a history of asthma. In this study, 125,377 policies issued at standard or substandard rates to persons with asthma between the years 1952–76, were traced to 1977 policy anniversaries or death. Only policies on persons free from other impairments were included. Overall cumulative mortality ratios were found to be 118% for men and 183% for women. For men who were issued policies at standard rates, mortality ratios were 108% of expected. Comparable figures for women were 160% of expected. For men and women who were issued policies at substandard rates, mortality ratios were 211% for men and 281% for women. For men mortality ratios were somewhat lower for issue ages 30–39 (178%) and 40–49 (196%) compared with ages 15–29 (239%) or 50–69 (230–237%).[42]

In 1984, Swiss Re reported the results of an asthma mortality study in persons issued insurance between 1958 and 1982. Mortality ratios were 255% for men and women classified as having chronic, severe asthma and 105% for those classified as having occasional or seasonal asthma compared to standard insured lives expectations.[43]

In another insured lives study from Lincoln National, policyholders with asthma were found to have an overall mortality ratio of 194% compared to standard insured lives expectations.[44]

Selection of risks

Clinical criteria to classify asthma in terms of severity have been proposed (*see* Table 23.11).[45]

Data from recent studies indicated that mild asthma may be associated with relatively little excess mortality, especially if access to medical care is readily available, if therapy is directed toward ameliorating airway inflammation, and if there is good compliance with the prescribed treatment regimen. Certain subgroups of persons with asthma have a higher risk of death. These appear to include: women; persons with severe asthma; persons with a past episode of life-threatening asthma; those with other coexisting lung diseases; persons with psychiatric impairments;[46] and those with alcohol or substance abuse disorders.

Table 23.11. Clinical classification of asthma by severity (modified from Woolcock and Jenkins).[45]

Symptoms	Score	Bronchodilator use	Score	Steroid Use	Score	PF or FEV[1] Variability[a] %	Score
Life-threatening	4	< 6 ×/day	4	Daily oral for > 30 days per yr	4	> 50	4
Nocturnal symptoms or hospitalization or ER visit for asthma within the yr	3	4–6×/day	3	Daily oral < 30 days per yr	3	30–50	3
Symptomatic if not using bronchodilators	2	1–4×/day	2	Daily inhaled	2	20–30	2
Rare wheezing or cough-variant asthma of exercise-induced symptoms, only	1	< 1×/day	1	Occasionally inhaled			

Of these factors, a previous episode of life-threatening asthma, defined as a respiratory arrest or the need for tracheal intubation or mechanical ventilation, is particularly ominous. In a study of 147 patients requiring mechanical ventilation for asthma, hospital mortality was 16.5%. Among the 121 patients discharged from the intensive care unit, 18 subsequently died, 17 of those from a new asthma attack. The post hospitalization mortality was 10%. Nearly two-thirds of these post-hospital deaths occurred within the year following discharge.[47]

The use of inhaled steroids appears not to be a marker for an increased risk of asthma mortality. On the contrary, patients who regularly use inhaled steroids appear to have a significantly improved survival compared to those who do not.[48] The regular use of oral or parenteral coriticosteroids is a marker for asthma of at least moderate severity. The potential complications of chronic corticosteroid use should also be considered as part of total mortality risk.[49]

Chronic bronchitis and emphysema

Chronic bronchitis and emphysema are the two other common forms of COPD.

Chronic bronchitis has been defined on clinical grounds as the presence of a chronic productive cough on most days of the month for 3 months in each year for 2 consecutive years in an individual in whom other causes of cough (such as chronic infection, lung cancer and congestive heart failure) have been excluded. Most cases of chronic bronchitis are due to the chronic inhalation of tobacco smoke or, less commonly, other substances.

The histologic changes seen in chronic bronchitis consist of bronchial gland hyperplasia and hypertrophy, patchy areas of squamous metaplasia in bronchi and an increase in the amount of airway smooth muscle. Bronchioles, the small airways lacking cartilage, show varying degrees of inflammation, mucous plugging, smooth muscle hypertrophy and distortion. Bronchiolar distortion is related to airflow obstruction; however, not all cases of chronic bronchitis have significant degrees of airflow obstruction. Those cases without significant airflow limitation have been termed chronic simple bronchitis.

Emphysema is characterized by destruction of the terminal respiratory units or acini, the gas exchanging portions of the lung. Three general types of emphysema have been described, depending on which portions of the acini have been primarily affected: centriacinar, panacinar, and distal acinar (or paraseptal). Centriacinar emphysema affects primarily the proximal portions of the acini, just beyond the terminal bronchioles. This is the form of emphysema most commonly associated with cigarette smoking. Chronic dust inhalation can produce localized forms of centriacinar emphysema, also known as focal emphysema. In centriacinar emphysema the upper and posterior portions of the lung are most extensively affected.

Pan acinar emphysema involves destruction of the entire acinus. It most often involves the basal portions of the lung to a greater extent than the apices. The lung bases of cigarette smokers often have changes of panacinar emphysema, while the apices may show changes of centriacinar emphysema. A diffuse severe form of panacinar emphysema is seen in persons with alpha 1 antiprotease deficiency.

Distal acinar (or paraseptal) emphysema is a localized form of emphysema involving the subpleural airspaces and the airspaces adjacent to the interlobular septae. It is this form of emphysema that causes the apical bullae that result in spontaneous pneumothoraces often seen in young persons.

Although emphysema is primarily a disease of the acinus and alveolar capillary units, the destruction of elastic tissue causes a loss of pulmonary elastic recoil and results in airway collapse and airflow obstruction.

Emphysema, chronic bronchitis and asthma are often present together to varying degrees. However, although some degree of bronchial hyperreactivity is common in many cases of obstructive pulmonary disease, the term asthma should be reserved for cases where there is complete reversibility of airway obstruction (at least in the early stages of the disease) and that lack the other features of chronic bronchitis and emphysema (*see* Figure 23.5).

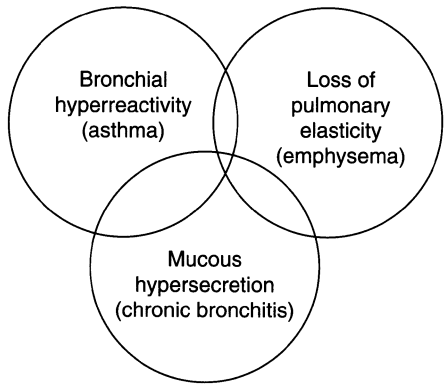

Figure 23.5. Relationship of various forms of COPD.

Relationship with tobacco smoke

In 1964 the first USA Surgeon General's Report on Smoking and Health established an association between cigarette smoking, symptoms of chronic cough and sputum production, and findings of impaired lung function in smokers over the age of 40.[50] Since then, cigarette smoking has been identified as the major cause of COPD in the USA.[51]

Tobacco smoke causes many pathologic changes in the lungs of smokers, including: loss of cilia; proliferation of goblet cells; mucous gland hyperplasia; squamous metaplasia of bronchial mucosa which may progress to bronchogenic carcinoma; inflammation, atrophy and mucous plugging of small airways; destruction of peribronchiolar alveoli; and activation of macrophages and neutrophiles.[52]

Epidemiologic studies have indicated that on average, lung function, as measured by the FEV_1, normally declines in non-smokers at an average rate of 20–30 ml per year beginning at about age 25. In smokers, FEV_1 may decline at a somewhat faster rate (25–80 ml per year).[53–56] Of smokers, 10–15% may be particularly susceptible to the effects of cigarette smoke and may lose lung function at a considerably faster rate (e.g. an annual FEV_1 loss on the order of 150 ml per year). At that rate, a susceptible smoker who began cigarette smoking at age 25 may have an FEV_1 under 1 liter before age 60. It has been suggested that a smoker who has an FEV_1 lower than 1 l below predicted after 20 years of smoking is a susceptible smoker.[57] Although smoking cessation does not result in any gain in lung function, the rate of loss appears to be reduced to rates comparable to non-smokers (20–50 ml per year).[52,56]

Some individuals appear to be genetically resistant to the detrimental effects of tobacco smoke. In fact, only 10–15% of smokers develop clinically significant COPD. Therefore it has been suggested that if lung function is normal in an individual over the age of 40, who has smoked for more than 20 years, the probability of that individual developing significant obstructive airways disease over the remainder of their lifetime is low.

In a study of 104 male smokers between the ages 45 and 55 years (mean age = 49.3 + 2.7 years, mean tobacco usage = 31.7 + 14.3 pack-years), 35 had normal pulmonary function, 37 had no airflow obstruction but had evidence of small airways disease by nitrogen washout studies, and 37 had obstructive airways disease. Fifty-six were studied again 13 years later. Those with initially normal pulmonary function continued to have normal pulmonary function – or at worst, mild airflow obstruction. Of those with small airways disease, about 33% developed airflow obstruction, which was mild in all but one case. Taken together, 79% of subjects with a normal FEV_1/FVC ratio at the beginning of the study still had a normal ratio at the end of the study.

Although this study provides evidence that middle aged male smokers having normal pulmonary function studies usually do not develop significant airflow obstruction even if they continue to smoke, they are still at risk for the other complications of smoking. In this study, 7 died from cancer, 3 from myocardial infarction and 3 from stroke.[58]

Although environmental tobacco smoke can trigger asthma in susceptible adults, its role in the development of other forms of COPD is uncertain. Several studies have demonstrated mild degrees of pulmonary function impairment in the children of parents who smoke, a higher incidence of respiratory illnesses, and have implicated environmental tobacco smoke in the development of childhood asthma.

The American Cancer Society's Cancer Prevention Studies I and II (CPS-I and CPS-II)

both demonstrated that cigarette smoking is associated with excess deaths in males and female from COPD as well as from all causes, coronary heart disease, stroke and cancer. CPS-I covered the years 1959–65 and involved 1,051,038 subjects in 25 states. CPS-II covered the years 1982–8 and involved 1,083,600 subjects in all 50 states, the District of Columbia, Puerto Rico and Guam. Age-adjusted death rates for smokers and non-smokers were calculated and compared to determine relative and excess death rates. Both studies demonstrated that deaths dues to COPD were increased markedly for male and female smokers compared to non-smokers. During the 23-year interval between studies, death rates due to COPD remained stable for non-smokers but increased by 1.5-fold for male smokers and 3.3-fold for female smokers.[59]

Alpha-1-protease inhibitor deficiency

Alpha-1-protease inhibitor (API) was formerly called alpha-1-antitrypsin. API is a protein, normally found in the serum, capable of inhibiting the action of several proteolytic enzymes including trypsin, chymotrypsin, elastase, neutrophilic elastase and collagenases. API is an acute-phase reactant which appears to play a role in inflammation.

The gene coding for API is located on chromosome 14 and is highly pleomorphic: 75 different alleles have been identified. Some alleles are associated with normal levels of normally functioning AP; other alleles are associated with low or absent amounts of API or abnormally functioning API. The amount and kind of API present in an individual is determined by the interaction of the two co-dominant alleles inherited from both parents. The normal API allele is termed M. Other common alleles and their corresponding genotypes and phenotypes are shown in Table 23.12.[60] A threshold protective effect of an API against emphysema in non-smokers is felt to occur at a serum concentration of 11 \mumol (80 mg/dl or 35% of normal).

It is postulated that API normally protects the lung from damage by neutrophilic elastase and other proteases liberated during inflammatory processes, and that an imbalance between proteolytic enzymes and antiproteolytic enzymes, such as occurs in hereditary API deficiency, can result in the destruction of lung tissue and lead to emphysema. It is also felt that cigarette smoking may cause a similar protease-antiprotease imbalance by producing chronic inflammation that leads to an increase in protease activity and to a simultaneous inactivation of API through the action of oxidants.

API deficiency is also associated with other disease states. PI-Z mutations result in aggregation of insoluble PI-Z protein in the endoplasm reticulum of hepatocytes, eventually producing cirrhosis. In addition, various forms of vasculitis may be seen in API deficiency states.[61]

Diagnosis

Chronic bronchitis and emphysema are diagnosed on the basis of history, physical examination and pulmonary function studies. Shortness of breath is the usual complaint in both chronic bronchitis and emphysema. Persons with emphysema may have few complaints other than the gradual and steady progression of shortness of breath over

Table 23.12. Protease inhibitor genotypes.[60]

Genotype	Serum API concentration	Risk of emphysema	
		Non-smokers	Smokers
PIMM	20–48 μmol (150–350 mg/dl)	Not increased	Increased
PIMZ	12–35 μmol (90–260 mg/dl)	Not increased	Increased
PISS	15–33 μmol (100–240 mg/dl)	Not increased	Increased
PISZ	8–19 μmol (60–140 mg/dl)	Slight increase	Increased
PIZZ	2.5–7 μmol (20–50 mg/dl)	Increased	Marked increase

many years. Chronic bronchitis is diagnosed clinically on the basis of the presence of a chronic cough and sputum production. Findings of lung hyperinflation, wheezing and prolonged exhalation may be present in asthma, chronic bronchitis and emphysema.

Cyanosis and signs of right heart failure may also be present in severe cases, but they are more common in chronic bronchitis.

Pulmonary function testing will show airflow obstruction in emphysema, most cases of chronic bronchitis and intermittently in asthma. For this reason, expiratory flow rates alone are not useful in distinguishing between these forms of obstructive airway disease. Because emphysema results in the destruction of alveolar-capillary units, whereas chronic bronchitis and asthma affect primarily the airways themselves, tests of carbon monoxide capacity, which measure the functioning alveolar-capillary surface area, are often used as an aid to distinguish emphysema from other obstructive airway diseases.

It should be emphasized that the finding of lung hyperinflation on a plain chest radiograph is not a sensitive or specific marker for obstructive airway disease. Lung hyperinflation can be seen in normal individuals, as well as in persons with a variety of types of obstructive airway diseases. Adding other radiographic criteria, such as rapid tapering of airways, paucity of vascular markings, peribronchial cuffing and bronchial wall thickening, may result in some increase in specificity. However, plain chest radiography is rarely useful in diagnosing any but the most severe cases of emphysema.[62]

Mortality studies on COPD

In 1987, Burrows reported the results of a 10-year follow-up study of 45 subjects having COPD and values for FEV_1 less than 65 percent predicted.[63] Butz compared the survival rates reported by Burrows to the 1975–9 Group Life tables and estimated excess death rates and relative mortality ratios. Over the interval, 0–5 years, the excess death rate was calculated to be 26 per 1000 per yr and the relative mortality ratio 215%. For the interval, 5–10 years, the corresponding figures were 67 per 1000 per year and 385%. Over the entire 10-year duration, the mean annual excess death rate was 46 per 1000 per year and the relative mortality ratio 280%.[64]

In a 13-year follow-up study of men having a FEV_1/FVC ratio between 65–75% of predicted, their relative mortality risk was almost twice that of men having a FEV_1/FVC ratio greater than 75% of predicted. For men having a FEV_1/FVC ratio less than 65% of predicted, the relative mortality risk was 250%.[65] In another study of 8,427 subjects between the ages of 25–74, the multivariate adjusted mortality risk for males over 9–12 years of follow-up was 167% (95% CI = 138% to 204%) for impairments in FEV_1, 137% (95% CI = 109–172%) for only cough or phlegm, and 158% (95% CI = 102–244%) for asthma. The corresponding figures for females were 222% (95% CI = 176–279%) for impairments in FEV_1, 98% (95% CI = 68–141%) for cough or phlegm, and 158% (95% CI = 104–240%) for asthma.[66]

One of the largest insured lives studies of the mortality risk associated with COPD is the *Medical Impairment Study 1983* covering the years 1962–77. Mortality was analyzed separately for chronic bronchitis and emphysema and for males and females. Males with chronic bronchitis who were offered policies at standard rates had a relative mortality ratio of 137% (standard mortality = 100% based on modified 1965–1970 Basic tables); those rated slightly substandard (up to 175%) had a mortality ratio of 239%; and those rated moderately substandard (180–250%) had a mortality ratio of 281%. The overall mortality ratio for substandard male issues was 240%. The overall mortality ratio for substandard females (235%) was similar to that for males. Males with emphysema who were offered policies at standard rates had a relative mortality ratio of 128%; those rated slightly substandard (up to 175%) had a mortality ratio of 309%; and those rated moderately substandard (180–250%) had a mortality ratio of 341%. The overall mortality ratio for substandard male issues was 323%, the second highest relative mortality in the *Medical Impairment Study 1983* after MI.

The number of policies issued on women with COPD were far fewer than the number issued on males. This precluded a detailed mortality analysis. For standard and substandard issues com-

bined, women having chronic bronchitis had a relative mortality ratio of 235%. The corresponding figures for women having emphysema was 252%.[67]

Brackenridge and Mills have reported that in a smaller intracompany study of COPD by the Swiss Reinsurance Company, the relative mortality ratio associated with chronic bronchitis compared with standard risks over the same period of observation (1958–82) was 210%. The corresponding figures for emphysema was 235%. When emphysema was combined with chronic bronchitis the relative mortality rose to 345%.[68] Brackenridge and Mills have also stated that this adverse effect of emphysema combined with chronic bronchitis was also seen in the study by the Prudential Assurance Company of London where, among insureds aged 39–49 at entry, the excess death rate was 13.5 per 1000 and the relative mortality ratio 323%. Among insureds aged 50 and older, the excess death rate was 20.3 per 1000 and the relative mortality ratio 196%.[69]

More recently, Fessel has reported a study of 1481 European males having emphysema and/or chronic bronchitis who were issued life policies between the years 1956 and 1985.[70] The average duration per policy issued was slightly more than 7.5 years. Overall, the mortality ratio of this cohort relative to standard insured lives over this duration was 230% with an annual average excess death rate of 6.7 per 1000 per year. Males issued policies between the ages 20–44 had a mortality ratio of 190%. The mortality ratio for policies issued between ages 45–54 was 235%, and for polices issued between ages 55–84 the mortality ratio was 265%.

Lung-volume reduction surgery (LVRS) as a treatment for end-stage emphysema was pioneered in 1957 by Brantigan, and was reintroduced by Cooper in 1995. LVRS removes damaged and nonfunctioning or poorly functioning lung tissue and improves the elasticity of the remaining tissue, since the remaining lung tissue must expand to fill the thoracic cavity. This increase in elasticity of the remaining tissue increases expiratory flow rates; reduces hyperinflation; improves respiratory muscle performance; decreases the work of breathing; improves ventilation-perfusion matching; and ameliorates symptoms. LVRS works particularly well if there are localized areas of lung destruction and over inflation as is commonly the case in bullous emphysema.

However, LVRS does not increase the alveolar-capillary area available for gas exchange as measured by carbon dioxide diffusing capacity. Only about half of patients requiring supplemental oxygen before LVRS are able to discontinue oxygen afterwards and 80% of patients initially able to discontinue oxygen require it again within 4 years following surgery.

Although survival is improved with LVRS, this surgery is usually performed in patients with severe emphysema and the mortality rate remains high. After the first year following surgery, the annual mortality rate averages 7–10%. Analysis of data from a recent 5-year follow-up study on patients undergoing LVRS for severe emphysema study demonstrated that the geometric annual average mortality ratio for years 1–5 was over 600% compared to the general population.[71,72]

Risk selection

Depending on the severity of airflow obstruction, excess mortality may range from mild to extreme. The results of pulmonary function testing are helpful in stratifying risk. Continuing tobacco use in the presence of obstructive airways disease is associated with continuing loss of lung function at an accelerated pace. The presence of hypoxemia, pulmonary hypertension and cor pulmonale are also adverse prognostic factors. LVRS is usually performed on patients having severe emphysema. Although symptoms and some aspects of pulmonary function are improved at least temporarily by this procedure, the excess mortality risk attributable to the underlying disease process remains high.

Bronchiectasis

Bronchiectasis is a condition in which the muscular, elastic and cartilaginous components of the walls of medium or large airways are damaged or destroyed. This results in an abnormal dilatation (ectasia) of the bronchus and impaired mucociliary clearance. Bronchiectasis may result from bronchial obstruction or infection, or be a complication of a systemic disorder (such as cystic

fibrosis, primary ciliary dyskinesia (Kartagener's syndrome), allergic bronchopulmonary aspergillosis, IgG deficiency, alpha-1 protease inhibitor deficiency or Marfan's syndrome).

If caused by bronchial obstruction or acute pneumonia, bronchiectasis may be localized to discrete areas of the lung. Some cases of localized bronchiectasis may even resolve. However, it is more common for bronchiectasis to be the result of a diffuse process, to be chronic, persistent, and involve multiple areas of the lungs or be generalized. Impaired mucociliary clearance results in secondary bacterial colonization, infection, and inflammation resulting in further bronchial damage and fibrosis.

Bronchiectasis may be asymptomatic or result in a chronic cough productive of copious amounts of muco-purulent sputum ('wet bronchiectasis'). If bronchiectasis is localized to the upper lobes of the lungs, good bronchial drainage may be preserved and cough may be non-productive ('dry bronchiectasis').

Common complications of bronchiectasis include recurrent pneumonia, lung abscess, pneumothorax and hemoptysis. Hemoptysis usually follows a mild respiratory infection. It is said to be more often a complication of dry bronchiectasis than of wet bronchiectasis. Usually the hemoptysis is mild and self-limited. However, because bronchial arteries contain blood under systemic pressure, hemoptysis may be massive. Despite this, it has been stated that patients with bronchiectasis rarely die from hemoptysis.[73]

Treatment for bronchiectasis includes the following components: controlling infection with antibiotics, promoting adequate mucociliary clearance, and identifying and treating any underlying disease processes (e.g. immunoglobulin administration for patients having IgG deficiency). Medical management is effective for most patients. Surgical resection should be reserved for patients with focal bronchiectasis who have life-threatening hemoptysis, uncontrollable infection, or who are unwilling or unable to take antibiotics. Double lung or heart-lung transplantation is being performed for patients with severe, generalized bronchiectasis, most often that associated with cystic fibrosis.

In the pre-antibiotic era, survival in patients with bronchiectasis was dismal and the quality of life poor. However, with the advent of antibiotics survival has improved dramatically.

The *Medical Impairment Study 1983* reported insured lives mortality experience on 5300 life insurance policies issued between 1952–77 on persons with a history of bronchiectasis. Most of the exposure occurred in males (n = 76) and in policies issued standard (n = 26) or mildly (n = 36) or moderately substandard (n = 18). There were 87 deaths in this cohort. For males the standardized mortality ratio compared with insured lives expectations was 132% for standard issues, 134% for mildly substandard issues, and 153% for moderately substandard issues. The mortality ratio was higher for males aged 40 or older the time of issue compared with younger males (167% versus 81%).

Risk selection

Mortality risk in patients with bronchiectasis is influenced by the extent of the disease; the presence of complications (such as life-threatening hemoptysis); pulmonary function; the coexistence of asthma, emphysema or chronic bronchitis; and the presence of underlying disease processes such as immune deficiency states and cystic fibrosis. Patients who have localized bronchiectasis, whose overall pulmonary function remains good, who have not had serious complications and who have no other pulmonary disease would be expected to have the best prognosis.

Bronchiolitis and bronchiolitis obliterans

Bronchiolitis is the term applied to inflammatory processes primarily affecting the small (< 2 mm diameter) non-cartilagenous airways. A wide variety of toxic, irritative, infectious, immunologic, and inflammatory processes can cause bronchiolitis. Infectious bronchiolitis occurs commonly in children. Respiratory syncitial virus, parainfluenza virus, adenovirus, influenza A and B viruses, Mycoplasma pneumonia, and Legionella pneumophila are common etiologic agents. Infectious bronchiolitis is uncommon in adults.

More often in adults, bronchiolitis is the result of inhaling toxic gases. Oxides of nitrogen (NO, NO_2, N_2O_4) produced by the anaerobic fermentation of silage is responsible for the bonchiolitis of Silo Filler's Disease. Fire Victims' Lung or Fire-Fighter's Lung results from the inhalation of a wide variety of toxic fumes liberated by combustion.

Depending on the degree of exposure, the resulting illness may be mild with minor cough and wheeze, or severe with resulting respiratory failure, pulmonary hemmorhage, adult respiratory distress syndrome and death. Fortunately most patients recover from acute bronchiolitis.

Bronchiolitis may also be caused by the inhalation of organic dusts. Bronchiolitis is a prominent histopathologic feature (along with the findings ofalveolitis, interstitial inflammation and fibrosis) of hypersensitivity pneumonitis.[74] Examples of hypersensitivity pneumonitis include farmer's lung disease, pigeon breeder's disease and bagassosis.

In some patients bronchiolitis may become chronic. Fibrous scarring of the small airways and exudative plugging of airway lumens may occur. This condition, termed bronchiolitis obliterans, has been reported to follow respiratory infection, toxic fume inhalation, as a result of medications, as a complication of transplantation or in association with a connective tissue disorder. If the exudative and inflammatory process extends into the alveoli, the condition is termed bronchiolitis obliterans with organizing pneumonia (BOOP).

Bronchiolitis obliterans begins insidiously with a non-productive cough and mild shortness of breath. Over time, it may progress to disabling dyspna and respiratory failure. Chest radiographs may be normal or show a nodular or reticulonodular pattern. BOOP is associated with patchy ground-glass infiltrates in the majority of cases.[75] Spirometry reveals an obstructive defect in pure bronchiolitis and a restrictive defect in BOOP, usually with an impairment in the carbon monoxide diffusion capacity.[76] Early treatment with corticosteroids or other immunosuppressants, such as azathioprine or cyclophosphamide, may suppress the inflammatory process and ameliorate or prevent severe obstruction. If severe obstruction and fibrosis are present, however, treatment is less likely to be effective.[77] Corticosteroid treatment appears to be effective in most cases of BOOP.

Risk selection

Acute infectious bronchiolitis may be fatal in children, especially those under the age of two. The most common sequela of acute bronchiolitis in children is the development of bronchial hyperreactivity, which may last for years after the initial infection.

There have been few long-term mortality studies on bronchiolitis obliterans. In one study of allogenic bone marrow transplant recipients, the 5-year survival rate of 35 patients with obstructive airways disease was approximately 18% compared with a 54% survival at 5 years for 412 concurrent patients with chronic graft-versus-host (GVHD) disease who survived more than 80 days after transplantation but who had normal pulmonary function.[78]

Cystic fibrosis (CF)

CF is a multisystem disorder caused by mutations of a gene, termed the cystic fibrosis transmembrane conductance regulator (CFTR), located on the long arm of chromosome 7. The major manifestations of CF are obstructive airways disease, recurrent pulmonary infection and exocrine pancreatic insufficiency. Other manifestations may include obstructive azoospermia, pansinusitis, mucoid appendiceal impaction, distal intestinal obstruction or intussusception in children and young adults, salty-tasting skin and hyponatremic dehydration.

CF is inherited in an autosomal recessive pattern. The prevalence of the carrier state is 2–5%. The homozygous state has been estimated to occur in 1 in 2500 live births in the Caucasian population. CF is much less prevalent in other populations and it is rare in Asians, native American Indians and black natives of Africa.

The CFTR regulates cAMP activated chloride conductance across membranes. Mutations of the CFTR gene result in the production of a defective CFTR protein and impairment in transmembrane

chloride ion conductance. This results in abnormalities in salt and water transport, leading to alterations in the composition of secretions of the lung, pancreas, gastrointestinal tract, sweat glands and other exocrine organs. Respiratory tract secretions become more viscous, and mucociliary transport becomes impaired, predisposing to bacterial colonization of airways with *Staphlococcus aureus, Hemophilis influenza* and *Pseudomonas aeruginosa*. Chronic infection leads to the development of a combination of bronchiectasis, bronchial hyperreactivity, airflow obstruction, cystic dilitation of airspaces and organizing pneumonitis.[79]

Over 500 mutations of the CFTR gene have been described.[80] The 70 most common mutations account for more than 90% of all cases.[81] All reported CFTR gene mutations are associated with elevated chloride concentrations in sweat. Many mutations (including the most common mutation, ΔF508, a three base pair deletion at position 508) are associated with pancreatic exocrine insufficiency. The relation between genotype and severity of pulmonary disease has not been as clearly defined. It has been suggested that this lack of tight correlation may be due to the other genetic and environmental influences and the lack of a good system for classifying pulmonary disease severity in CF.[82]

The standard screening test for CF remains the sweat chloride test, in which the concentration of chloride in sweat is measured by ion-selective electrodes or gravimetric methods. Chloride concentrations of 60 mmol/l and typical clinical manifestions are usually diagnostic of CF.[81]

Chest radiographs taken early in the course of the disease demonstrate broncial thickening, hyperinflation and segmental or subsegmental atalectasis. Later, evidence of bronchiectasis appears. In advanced cases, radiographs show nodular opacities, hyperinflation, cystic airspace dilitation, honeycombing and evidence of right heart failure.

Pulmonary complications of CF include pneumothorax, hemoptysis (which can be minor or life-threatening), respiratory failure, pulmonary hypertension and cor pulmonale.

Progressive pancreatic insufficiency occurs in 85–90% of cystic fibrosis patients. Inspissated secretions block pancreatic ducts resulting in cystic changes and inflammation. Eventually a shrunken, cystic and fatty pancreas results. Lack of pancreatic enzyme secretion leads to malabsorption of fat and protein resulting in malnutrition. Thirty to 40% of cystic fibrosis patients have glucose intolerance and 5% have diabetes.

Abnormalities of the intestinal glands results in absorptive defects and lack of water in intestinal contents. In the neonatal period this often leads to meconium ileus which usually results in acute intestinal obstruction within 48 hours of birth. In the past, meconium ileus was invariable fatal. Now, with surgery, a survival rate exceeding 90% is possible. Infants who survive beyond 6 months appear to have the same prognosis as those without meconium ileus. After the neonatal period, inspissated intestinal secretions may continue to cause distal intestinal obstructions, which can usually be treated successfully with pancreatic enzyme replacement, stool softeners, mucolytics such as N-acetylcysteine, and enemas.

Current treatment strategies are directed toward maintaining adequate nutrition, controlling respiratory tract infections, promoting mucus clearance and combating inflamation. Lung transplantation for end-stage pulmonary disease is being performed more often.[83,84] Investigative treatments include employing agents that modulate ion transport, gene therapy and direct introduction of normal CFTR proteins into lung epithelia.

The natural history of CF varies markedly, ranging from death during the neonatal period to relatively asymptomatic and prolonged survival well into the third, fourth and even fifth decades of life. A recent report from the Danish Cystic Fibrosis Center indicates that with aggressive treatment there is a 80.4% probability that a newborn child with CF will live until age 45 (confidence interval = 76.5–84.6%).[85]

Analysis of data published by the National Cystic Fibrosis foundation on 21,044 patients revealed that over the first 10 years following diagnosis, the annual geometric average mortality ratio compared to the general population was 500% for males and 600% for females. (geometric annual average edr = 3.6 per 1000 per yr and 3.8 per 1000 per yr for males and females, respect-

ively.). For durations 10–20 years following diagnosis, the annual geometric average mortality ratio was 2000% for males and 5500% for females (geometric annual average edr = 12.5 per 1000 per yr and 16.4 per 1000 per yr for males and females, respectively). The relative mortality risk of patients surviving 20 years or more and who continue to have normal or only mildly impaired pulmonary function is unknown.

INTERSTITIAL AND INFILTRATIVE LUNG DISEASE

Diffuse interstitial lung disease (ILD) is a generic term that encompasses a large number of unrelated conditions that nevertheless share the propensity to cause cough and/or shortness of breath, restricted lung-testing physiology, and to cause diffuse changes on chest radiographs or lung CT scans. The morbidity and mortality implications vary widely, and it behooves underwriters to try as establish as carefully as possible, from the medical records available, the underlying cause of an applicant's abnormality.

Broadly, the ILDs can be divided into four major categories:

1. ILD of known cause, such as drug-related lung disease or lung disease secondary to other primary diseases, most commonly collagen vascular diseases
2. granulomatous ILD, with the typical example being sarcoidosis
3. idiopathic interstitial pneumonias
4. all other causes of diffuse ILD not included into the first three categories fall into a final 'wastebasket' category, with such desperate causes of lung disease as lymphangioleiomatosis (LAM), pulmonary Langerhans' cell histiocytosis/histiocytosis X, and eosinophilic pneumonia.

Interstitial lung diseases of known cause

Many, and perhaps most, drugs have some incidence, albeit small, of causing lung toxicity. The more common offenders include nitrofurantoin,[86] bleomycin,[87]methotrexate,[88] and amiodarone.[89] If identified early, cessation of the drug may lead to complete resolution of the lung process, with no further morbidity or mortality implications assuming the drug is not resumed. A regularly updated list of drugs causing lung disease is available on the internet.[90] Connective tissue diseases are a heterogeneous group of immunologically mediated inflammatory diseases of poorly-understood cause. 'It is not surprising that, by virtue of their abundant connective tissue and blood supply, the lungs are frequently involved in these disorders.'[91] ILD complicating connective tissue diseases accounts for approximately 25% of the mortality seen in these diseases[92] and usually occurs as a nonspecific interstitial pneumonia rather than as a usual interstitial pneumonia.[93–95]

In striking contrast of the predilection of rheumatoid arthritis (RA) for women, RA associated with pulmonary disease is much more common in men (ratio of at least 3:1[96]) and occurs more commonly in late-onset RA and cigarette-smokers.[97] It has been estimated that the prognosis of RA patients with usual interstitial pneumonitis (UIP) is no different than patients with idiopathic pulmonary fibrosis (IPF),[98] with survival of patients with RA decreased by 3.5 to 4.9 years.[99,100] Less ominous lung and pleural changes associated with RA include rheumatoid nodules (which may cause hemoptysis from cavitation and/or pneumothorax from erosion into the pleural space)[101] and rheumatoid pleural effusion (the latter being the most common pulmonary complication of RA and generally not life-threatening).

Three pathologic patterns of ILD have been recognized in patients with systemic lupus erythematosus (SLE): acute lupus pneumonitis (acute interstitial pneumonia or diffuse alveolar damage), chronic interstitial pneumonia (nonspecific interstitial pneumonia), and lymphocytic interstitial pneumonia (LIP). The acute lupus pneumonitis is the most serious of the three, with a reported mortality rate of 50% acutely, and with residual disease in survivors.[102] Chronic interstitial pneumonia in SLE is much less common, occurs in older patients, and may actually represent an evolution from acute to chronic pneumonitis. Histologically, a cellular interstitial pneumonitis is far more prominent than is the fibrotic stage, even in autopsy studies.[103,104] A variety of lymphoid lesions have been reported in patients with

SLE, including LIP,[105] nodular lymphoid hyperplasia,[106] bronchus-associated lymphoid tissue (BALT) hyperplasia, and malignant lymphoma.[107] Other complicating lung problems in SLE include pulmonary hypertension (uncommon without ILD),[108] an acute reversible hypoxemia syndrome thought to be due to excessive complement activation in association with primed endothelial cells that induces leukocyte-endothelial cell adhesion and leuko-occlusive vasculopathy[109] and that usually responds to high-dose corticosteroids, and something called the 'shrinking lung syndrome' that is due primarily to diaphragmatic dysfunction.[110–112]

Progressive systemic sclerosis (PSS), or scleroderma, is one-fourth as common as SLE but is more common than either polymyositis or polyarteritis.[113] Although cutaneous involvement is the hallmark of scleroderma and the extent of skin involvement determines the classification of patients' disease, the cause of death in scleroderma is usually related to internal organ disease. The 10-year mortality rates for patients with diffuse cutaneous sclerosis range between 38 to 79%.[114] In contrast to other connective tissue diseases, diffuse ILD is the most common pulmonary manifestation of scleroderma[115] and is seen in up to 80% of patients.[116] The 5-year survival rate after lung involvement ranges from 38–45%[117] and appears to correlate with abnormal pulmonary function (5-year survival rate greater than 90% in those with normal pulmonary function), 58% in those with mild-to-moderate restriction, and a dismal 9% survival rate in those with a lung diffusion (DLCO) less than 40% of predicted.[118]

Pulmonary complications are important determinants of the clinical course of polymositis and dermatomyositis (PM/DM). In a Mayo Clinic series of 58 patients with PM/DM and ILD, the 5-year survival was 60%.[119] This survival is similar to that of patients with nonspecific interstitial pneumonitis (NSIP) and significantly better that that of patients with usual interstitial pneumonitis (UIP). Recently investigated serologic markers of disease activity have included KL-6, which is not unique to PM/DM but is 99% specific for the presence of ILD in rheumatologic disorders.[120,121]

There is no clear-cut definition of Sjögren's syndrome, but the triad of keratoconjunctivitis sicca (or dry eyes, with or without lacrimal gland enlargement), xerostomia (dry mouth, with or without salivary gland enlargement), and the presence of a connective tissue disease, usually RA, is generally used. Sjögren's syndrome is classified as 'primary' (a disease predominantly of postmenopausl women older than 40 years) or 'secondary' (if it occurs with a connective tissue disease). In addition to RA, Sjögren's syndrome is found in SLE, PSS, mixed connective tissue diseases, polymyositis, and polyarteritis nodosa.[122] Pulmonary manifestations occur frequently in Sjögren's syndrome[123] but because of the frequently associated connective tissue disease, it has been difficult to determine which of the pulmonary manifestations is the result of Sjögren's and not of the associated connective tissue disease (*see* Table 23.13).

Other examples of ILD with well-established causation include a host of occupationally-related diseases, with typical examples of inhaled inorganic dusts being silicosis, coal workers' pneumoconiosis, and asbestosis and asbestosis-induced pleural fibrosis. Inhaled organic dusts may cause

Table 23.13. Pleuropulmonary manifestations of Sjögren's syndrome.

Parenchymal lung disease
Nonspecific interstitial pneumonitis (NSIP)
Organizing pneumonia (OP)
Usual interstitial pneumonitis (UIP)
Lymphocytic interstitial pneumonits (LIP)
Amyloidosis
Recurrent bronchopneumonia
Airway disease: desiccation of the tracheobronchial tree
Atrophic rhinitis
Xerostomia (dry mouth)
Xerotrachea (chronic dry cough)
Chronic bronchitis with tenacious sputa
Atelectatis, middle-lobe collapse
Pulmonary vascular disease
Pulmonary vasculitis
Pulmonary hypertension
Pleural disease
Pleurisy with or without effusion

hypersensitivity pneumonitis, and include bagassosis (sugar cane), bird-breeder's lung (pigeons, parakeets, etc), chicken-handler's lung, and Farmer's lung.

OCCUPATIONAL LUNG DISEASE

Estimates of the rate of development of occupational lung disease in the USA range from 1.25–4/1000 workers. As most of these estimates come from physicians reporting of occupational illnesses, and as most states do not require such reporting, there is a general feeling by experts in the field that these estimates are conservative and that the real incidence may even be tenfold higher. For instance, a series of studies have provided support for the conclusion that up to 15% of adult-onset asthma is occupationally related.[124] NIOSH (National Institute for Occupational Safety and Health) estimates that in the USA, 3–9 million people are exposed to carcinogens in the workplace, and that 2–4% of all cancers are occupational in origin.[2]

Methods of assessing occupational lung disease include use of the chest radiograph and pulmonary function testing. Efforts to try and standardize interpretation of chest X-rays in occupational disease led to the adoption in 1980 of the International Labour Organization (ILO) Classification (*see* Table 23.14). In the USA, physicians who undergo training and accreditation for the ILO Classification are called 'A' readers if they have attended the course, and 'B' readers if they have taken and passed the very difficult certification test. Using the ILO system requires that readers have available to them the standard set of radiographs, which are fundamental to the interpretation.

Lung parenchymal abnormalities are classified into large (>1 cm) and small opacities. Small opacities are further defined by assigning letters for increasing size and shape: *p*, *q*, and *r* for small, rounded opacities, and *s*, *t*, and *u* for small, irregular opacities. There may be a combination of two designations, with the first indicating the most numerous change. A report of *s/t* in a patient with asbestosis, for instance, would indicate that the *s* was the primary opacity and *t* was the secondary small, irregular opacity noted.[124]

Table 23.14. Classification of occupational lung disorders.

I Interstitial lung disorders (pneumoconioses)
A Fibrogenic (e.g. silica, asbestos, silicates)
B Non-fibrogenic (e.g. tin, iron, barium)
II Airway disorders
A Upper respiratory tract irritation (e.g. formaldehyde)
B Industrial bronchitis (e.g. coal dust)
C Laryngeal edema (e.g. ammonia)
D Allergic occupational asthma (e.g. TDI, red cedar)
E Non-allergic occupational asthma (e.g. RADS or VCD)
F Bronchiolitis obliterans (e.g. nitrogen dioxide)
G Byssinosis, etc. (e.g. cotton, grain, flax dust)
III Alveolar disorders
A Adult respiratory distress syndrome (e.g. phosgene)
B Chemical pneumonitis (e.g. cadmium fumes)
C Granulomatous disorders (e.g. berylliosis, extrinsic allergi alveolitis)
D Organic dust toxic syndrome (e.g. fungal dust)
E Fume fever (e.g. metal or polymer fumes)
IV Pulmonary infectious disorders
A Indoor (e.g. Legionella, tuberculosis)
B Outdoor (e.g. histoplasmosis, anthrax)
V Lung cancer
A Bronchogenic (e.g. asbestos, bis-chloromethyl ether)
B Pleural (e.g. mesothelioma)

Spirometry is the major form of pulmonary function testing and is perfectly adequate for screening and for minor abnormalities. However, if there is question about significant abnormalities, full pulmonary function studies, usually available only in hospital laboratories, are necessary to measure actual lung and diffusion capacity.

'Pneumoconiosis' is derived from the Greek – pneumo (lung) and konis (dust) – and describes lung diseases resulting from the inhalation of mineral dusts. Over the course of time it has been adapted to indicate the nature of the dust (e.g. silicosis (silica), asbestosis (asbestos), stannosis (tin)); to indicate the occupational risk (e.g. coal workers' pneumoconiosis); and to include organic dusts (e.g. byssinosis).[125]

Asbestos lung and pleural disease

Asbestos is a term applied to mineral silicates with a 'fibrous habit' (i.e. they occur naturally in bundles of parallel, radiating or interlaced fibers that can be readily separated into javelin-like fibers. These fibers have in common a remarkable resistance to deterioration due to heat, cold, salt water or a variety of other influences, making them ideal insulating material. Their fibrous nature also allows them to be spun.

World use of asbestos increased exponentially between the two world wars, but then peaked in the late 1970s and 1980s in the USA and other developed countries, when the ill-health effects of exposure became known. Since asbestos is a cheap, durable material with remarkable insulating properties, its production and use have continued to increase in emerging markets.

It has been estimated that between the years 1940–79 roughly 19 million USA workers had significant occupational asbestos exposure. Of this number, it has been estimated that several hundred thousand deaths have already occurred, primarily due to lung cancer, and to a lesser extent to mesothelioma and other cancers.[126,127]

Asbestos fiber inhalation results in three major health consequences: (1) pleural disease; (2) development of fibrosis; and (3) development of malignancy.

Pleural disease

The pleura is the lining membrane of the chest wall (parietal pleura) and of the lung (visceral pleura). Presumably, the javelin-like asbestos fibers are inhaled lengthwise into the lung parenchyma, then migrate to the pleural surfaces. The resulting reaction causes pleural plaques; discrete areas of pleural thickening that may be evident on routine chest X-rays. Occasionally, benign pleural effusions may also be the presumed consequence of asbestos inhalation. Although there is no precise dose-response relationship between exposure to asbestos fibers and consequent pleural disease, there does appear to be a threshold below which no risk occurs, and above which there is an increase in proportion affected with increasing exposure. This threshold is thought to be the OSHA (Occupational Safety and Health Administration) standards for workplace exposure limits, but in reality the actual threshold for 'safe' exposure limits is unknown.

Asbestos-caused pleural plaques and benign pleural effusions, in and of themselves, are usually of no major concern for significant morbidity or mortality. However, workers with pleural plaques are more likely to develop asbestos-induced parenchymal fibrosis than similarly exposed workers without plaques. Also, there is an increased risk of lung cancer among similarly exposed workers who develop pleural disease. Thus, from an underwriting standpoint, a finding of pleural plaques (or benign pleural effusions) thought to be a consequence of asbestos exposure should serve as a 'red flag' for potential development of fibrotic lung disease or cancer.

Development of fibrosis

The development of fibrosis is termed asbestosis, and is most prominent in the lower lobes of the lungs and in the subpleural areas (in contrast to silicosis and coal workers' pneumoconiosis, which predominantly involve the upper lung zones). Microscopically, the fibrosis seen is indistinguishable from the fibrotic reaction to other fibrogenic dusts and idiopathic pulmonary fibrosis, except for the presence of the asbestos fibers. The actual fibers are invisible on routine light microscopy and require electron microscopy or phase contrast microscopy for identification. However, some of these fibers will be surrounded and 'coated' with alveolar macrophages and other inflammatory cells, which will stain for iron, and which are referred to as ferruginous bodies. Most commonly, there are hundreds or even thousands of uncoated fibers for every ferruginous body seen. It is a comment on the ubiquitous use of asbestos that autopsy studies of unexposed persons invariably reveal the presence of asbestos fibers, if a thorough search for them is performed.

The pulmonary fibrosis following asbestos exposure requires more than just the exposure history to confirm causality. There must be a minimum of at least 6 months of a moderate intensity of exposure, and at least 20 years from time of exposure to appearance of clinical and roentgenographic disease. In general, the grade of pulmonary fibrosis relates to the fiber burden

carried by the lungs. Radiologic asbestosis may remain static or progress, following cessation of exposure. Regression does not occur. Dreesen *et al.*, studying dust and disease in a South Carolina textile factory, concluded that the threshold for development of asbestosis occurred at dust levels above 5 million particles per ft^3 (probably equivalent to 15–30 fibers/ml).[128,129]

Asbestosis is most commonly heralded by shortness of breath (dyspnea). Cough is also commonly reported, and is often non-productive in non-smokers and productive in smokers. On physical examination, the most common finding is auscultatory crackles (rales) over the lung bases. Although the presence of 'small irregular opacities' of fine reticular or ground-glass appearance in the mid-and lower lung fields ('shaggy heart border') remains the *sine qua non* for pulmonary asbestosis, high-resolution computer tomography (HRCT) will reveal interstitial abnormality before it is visible by routine chest radiography.

Asbestosis is classically described as a restrictive lung process, with less-than-predicted lung volumes, decreased diffusing capacity and impaired gas exchange on pulmonary function testing. However, airway obstruction is also commonly seen, both because cigarette smoking is common in this population, and because asbestos fibers apparently cause airway obstruction even without the confounding influence of smoking.

Development of malignancy

Most commonly, the malignancy developed is lung cancer, but in fact there is an increased incidence of malignant tumor of any tissue site that may be impacted by the asbestos fiber, including the larynx, esophagus and stomach. There is a striking relationship between asbestos exposure and the development of a primary malignancy of the pleura, called malignant mesothelioma. Some federal courts have even judged the occurrence of this neoplasm to signal significant asbestos exposure, recognized or not. Epidemiologic studies of lung cancer mortality in exposed work forces have confirmed the excess risk of asbestosis and have shown it to be related to the intensity and duration of exposure, thus providing evidence for causality. The increased association of cancer with cigarette smoking and with asbestos exposure has been found to be multiplicative, not just additive. The increased risk of asbestos workers who smoke for developing lung cancer is estimated to be as high as 50–90 times that of non-smoking, non-asbestos-exposed persons.

Although human exposure to asbestos is probably universal, significant exposure sufficient to cause asbestosis or cancer is usually occupational. Recently in the USA, there has been concern about the risk of living or working in a building or home originally built with asbestos products (especially in some one-third of USA schools). The lifetime risk for premature cancer death from such exposure has been estimated at only 4–6 per million exposed.

Risk selection

The diagnosis of asbestos lung or pleural disease, either admitted on the application or incidentally found in the attending physician's statement (APS), should be significant and unequivocal. Litigious and compensation-related concerns have caused many workers exposed to asbestos to be 'diagnosed' as having asbestos disease, when in reality they may only have, at most, asbestos pleural disease or very early or mild fibrotic change. Certainly there remains some risk for development of malignancy in this cohort, especially among the smokers, but unless they have significant symptoms or chest X-ray changes, most will certainly remain insurable. Chest X-ray reports and, if available, pulmonary function studies should confirm either the absence of significant disease or the presence of mild dysfunction.

The presence of significant symptoms or chest X-ray signs of asbestos fibrotic disease, on the other hand, suggests significant morbidity and mortality concerns, especially with the observation that progressive disease may occur despite cessation of exposure to asbestos.

Finally, the presence or history of any asbestos-related malignancy is cause for the greatest concern and caution by underwriters. Many of these malignancies are not curable and occur in the setting of significant asbestosis.

Silicosis

Silicosis refers to lung disease caused by inhalation of silica (silicon dioxide) in crystalline

form, usually as quartz. Silica is the earth's most abundant mineral. Minerals with high amounts of free silica include quartz (also granite), flint, chert, opal, chalcedony and diatomite. Combined forms of silica (silicates) include, among others, asbestos, talc, mica and kaolin. Whenever the earth's crust is broken and silica-containing rock or sand is gathered, milled and processed, or used, there are potential risks for the men and women whose occupation(s) involve them in these processes.[130]

Silicosis is a disease defined by the chest X-ray. Simple silicosis appears as small (less than 10 mm in diameter) rounded opacities, usually in the upper lung fields, and often accompanied by enlarged and calcified hilar lymph nodes. Progressive massive fibrosis (PMF) is the result of coalescence of these small nodules into larger opacities, also typically in the upper lung fields. These disease processes require a lifetime of occupational exposure to develop. Rarely, in cases of massive exposure to dust with very high quartz content, an acute form of silicosis, silicoproteinosis, may be seen, with disease evolving over a time period of months to years.

There are three requirements for the diagnosis of silicosis: (1) a history of silica exposure; (2) the presence on chest X-ray of characteristic small rounded opacities in upper lung fields; and (3) the absence of other illnesses that might mimic silicosis, such as miliary tuberculosis or fungal disease. Usually exposure for 10–30 years is required before these chest radiographic changes are noted. Although host factors, such as genetics, smoking and underlying diseases, may play a part in the development of silicosis, the most important factors include silica dust in ambient air, duration of dust exposure, the polymorphic structure of the silica particles, the percentage of free silica and the particle size.[131]

Silicosis is incorrectly considered by many physicians to be a radiologic abnormality dissociated from impairment, disability or excessive mortality. In fact, survival may be reduced in persons with dyspnea, sputum production or abnormal breath sounds on physical exam, and a reduced vital capacity (reduced FVC % predicted) on spirometric testing. Spirometry more commonly indicates obstruction or combined obstruction and restriction, rather than just pure restriction, even in non-smokers. Up to one-half of cases of simple or conglomerate silicosis demonstrate progression on chest X-ray even after exposure has ceased. There is a questionable slight increased incidence of lung cancer in persons with more advanced silicosis. This association remains controversial, however, due to the difficulty in controlling for other carcinogenic exposures common to the population of workers exposed to silica, such as radon, asbestos and smoking. Also, it may be that the respiratory impairment in the more severe cases of silicosis results in premature deaths and masks the role of silica as a carcinogen in some of the negative studies.

The chest radiograph in silicosis is rather distinctive in that the infiltration of small rounded densities are usually confined to the upper lung zones, and the hilar lymph nodes calcify in a peculiar peripheral fashion, often referred to as 'eggshell calcification'. Conglomeration of the opacities into PMF, also usually confined to the upper lung zones, results in retraction of the hilar pulmonary vasculature into the upper lungs. Pleural plaques occur but are not a common feature of silicosis.

An interesting association exists between silicosis and tuberculosis. Rates for active tuberculosis in silicotic workers range from 5–43%, depending on whether radiologic or autopsy criteria are used, an increase of 2- to 30-fold more than in non-silicotic miners. The presence of cough, hemoptysis, and the systemic symptoms of weight loss and fever in a person with silicosis should always suggest the possibility of mycobacterial disease. The incidence of tuberculosis increases from simple silicosis to PMF, with the highest incidence occurring in acute silicosis (alveoloproteinosis) and commonly accounting for death in this setting.

Although silicosis is associated with increased prevalence of positive autoimmune serologies, antinuclear antibodies and elevated immunoglobulin levels have not correlated with the baseline profusion category of the chest radiograph, the rate of chest radiographic progression or the rate of lung function decline in sandblasters with silicosis. Rheumatoid nodules may appear in the upper lung zones of silica workers with rheuma-

toid arthritis, a coincidence termed Caplan's syndrome.

Risk selection

Once silicosis develops, the primary risks to the applicant are progression of disease and the development of mycobacterial infection. Simple silicosis is associated with little mortality significance. Conglomerate silicosis (PMF), especially when accompanied by significant symptoms and pulmonary function abnormalities, calls for much greater concern in underwriting. Acute silicoproteinosis is such a severe disease that it would be unlikely for anyone with this disorder to be an applicant for insurance.

Coal workers' pneumoconiosis (CWP)

Coal is the end result of a gradually formed sedimentary process beginning with decaying vegetable matter and evolving through peat, lignites, sub-bituminous and bituminous coals to anthracite through the application of heat and great pressure over time. The carbon content increases progressively from peat through various stages to anthracite, and as the percentage of carbon increases the amount of quartz and other minerals decreases. The degree of risk to which an applicant for insurance has been exposed therefore depends on the type of coal mined as well as the type of mining done (surface strip mining versus underground mining).

CWP is a distinct pathological entity resulting from the inhalation of coal dust into the lungs. As coal dust also contains a variable amount of silica, some degree of silicosis may also be found in many of these persons. The deposition of the dust in the distal airways and lung parenchyma results in two lesions. Deposition of dust in the distal airways and lung appears to cause bronchitis and emphysema, similar to that seen with cigarette smoking, with expiratory airflow obstruction and hyperinflation on pulmonary function testing. The dark pigment localizes in lung macrophages that coalesce at the level of respiratory bronchioles, causing scarring and destruction of adjacent alveolar walls and forming the characteristic dust macule that is considered pathognomonic of CWP.

With increasing dust deposition, the pigmented macule progressively enlarges, becoming solid and palpable. Coalescence of multiple dust macules results in the formation of nodular lesions, which may cause vascular damage to surrounding lung tissue.[132] Coalescence of many nodular lesions results in PMF and is referred to as complicated CWP. These lesions are greater than 1–2 cm in diameter and are usually seen in the upper portions of the lungs.

Almost all miners with complicated CWP also have severe bronchitis and emphysema. Coal dust appears to be far less fibrogenic than other bioactive dusts such as silica and asbestos.[133] Thus the total dust burden in the lung may be much higher in CWP than in other pneumoconiosis, yet with less consequence. Classic silicotic lesions are seen when lung dust residue contains 18% or more quartz.

There were still 175,000 miners working in the USA in 1986.[134] Although the number of coal miners is decreasing worldwide, the increased mechanization of mining is resulting in generation of finer dusts. This fact, along with the observation that there is a long latency period from exposure to the dust to evolution of lung pathology, means that insurance underwriters will continue to see applicants for insurance for several decades to come.

Overall, the life expectancy of coal miners appears to be comparable to that of the general population.[135] Survival rates for men with PMF are substantially reduced, and this disorder is also associated with increased morbidity, impairment of pulmonary function and disability.[136]Although current dust-control measures in mines have resulted in lower prevalence of CWP, the lifetime risk is still 1.4–14%.[137] Miners exposed to the current USA standard for respirable coal mine dust of 2 mg/m^3 or less over a working lifetime are at increased risk of death from pneumoconiosis, or from chronic bronchitis or emphysema.[138]

Risk selection

Miners and ex-miners with simple pneumoconiosis survive as well as those with no evidence of pneumoconiosis at all. PMF, the prevalence of which is now low, affects mortality in only a minority of subjects, most of whom have chronic

airflow obstruction related to smoking. The dust effects in miners who smoke cigarettes appear to be additive; no disproportionate effect of smoking has been identifiable.

Interstitial lung disease due to granulomatous infiltration

Diffuse granulomatous inflammation may be seen secondary to infectious (tuberculosis, fungal diseases) and non-infectious causes (sarcoidosis, beryllium disease).

Sarcoidosis

Sarcoidosis is systemic inflammatory disorder of unknown etiology. It can affect virtually every organ in the body including the lungs, brain, eyes, heart, liver, kidneys, lymph nodes, bone and skin.

The pathologic hallmark of the disorder is the non-caseating granuloma. However, the presence of non-caseating granulomas is not specific for sarcoidosis: they may be seen in: mycobacterial and fungal infections; extrinsic allergic alveolitis; bronchogenic carcinoma; leukemia; Hodgkin's and non-Hodgkin's lymphoma; Crohn's disease; Whipple's disease; and pneumoconiosis. They are also related to drugs and foreign bodies.[139]

Although many granulomas resolve over time, some undergo progressive fibrosis. There is abundant evidence that sarcoidosis is an immunologic process which begins by exposure to an as yet unidentified antigen or antigens and is mediated by cellular immune mechanisms, involving T cells, interleukins, macrophages, mast cells, neutrophils, natural killer cells and fibroblasts.

Sarcoidosis occurs worldwide. Although it can affect persons of all ages and races, it is more common in persons under the age of 40, blacks and those of Irish and Scandinavian decent. For unclear reasons, the incidence of sarcoidosis is higher in the winter and early spring.[140] Although there is evidence from family and twin studies that genetic predisposition plays a role in the development of sarcoidosis, it is unlikely to be due to a single gene mutation.

Sarcoid pulmonary disease has been described in terms of five stages. The International Congress on Sarcoid refers to Stages 0, 1, 2A, 2B and 3. Other investigators refer to Stages 0–4, designating Stage 2B as Stage 3, and Stage 3 as Stage 4. The International Congress staging system will be used here.

Stage 0 is characterized by the absence of abnormal chest radiographic findings. However, active alveolitis is invariably present. Stage 1 is characterized by the presence of bilateral symmetric hilar and paratracheal lymphadenopathy without pulmonary parenchymal involvement. State 2A is characterized by pulmonary and hilar lymph node enlargement and interstitial disease. Stage 2B is characterized by interstitial pulmonary disease without lymph node enlargement. Stage 3 is characterized by radiographic evidence of pulmonary fibrosis (diffuse honeycombing, hilar retraction, etc.) and the absence of pulmonary adenopathy. Of sarcoid patients, 5–10% present with stage 0, 40–50% with Stage 1 and 40% with Stage 2A. The remaining 5–10% present with Stage 2B or 3. Endobronchial sarcoid is common. At times, endobronchial granulomas are large enough to cause airway obstruction.

Pulmonary function studies typically show restrictive defects. The presence of airflow obstruction should suggest the presence of endobronchial obstruction or another coexisting disease. Diffusing capacity is often diminished. At times, pulmonary function studies may be normal despite the presence of radiographic infiltrates. The presence of resting hypoxemia usually indicates advanced disease.[141]

Pulmonary complications include progressive fibrosis, respiratory failure and cor pulmonale. Other uncommon complications include pneumothorax, hemoptysis and pleural effusion.

Extrapulmonary involvement is common. Some of the common extrapulmonary sites of involvement are shown in Table 23.15.

The diagnosis of sarcoidosis usually rests on typical clinical findings and biopsy evidence of non-caseating granulomas. Common biopsy sources include the skin, conjunctiva, minor salivary glands, lymph nodes and lung (bronchial or transbronchial). Other studies, such as cytologic examination of bronchial alveolar lavage samples, serum angiotensin-converting enzyme levels and gallium-67 scanning, may be of prognostic value but are not diagnostic.

Table 23.15. Sarcoidosis: frequency of occurrence and types of extrapulmonary manifestations.[141]

Site	Frequency	Manifestation
Nervous system	5%	Cranial nerve palsy
		Vestibular disturbance
		Peripheral neuropathy
		Meningitis
		Seizures
		Cerebellar lesions
		Spinal cord
Heart	5–10%	Heart block
		Ventricular ectopy
		Dilated cardiomyopathy
		Restrictive cardiomyopathy
		Cor pulmonale
		Sudden death
		Pericardial effusion
		Pericarditis
Liver	40–70%	Hepatic granulomas, usually asymptomatic
		Cholestasis
		Portal fibrosis
Eyes	22%	Uveitis
		Conjunctival and lachrymal granulomas
		Optic neuritis
Reticuloen dothelial	28%	Lymphadenopathy
		Splenomegaly
Kidney	15–40%	Renal granulomas (usually asymptomatic)
	10%	Nephrolithiasis
	5%	Nephrocalcinosis
Endocrine	10–20%	Hypercalcemia
	60%	Hypercalcuria
	1%	Hypopituitarism
		Diabetes insipidus
		Syndrome of inappropriate ADH secretion
Skin	18%	Erythema nodosum
		Subcutaneous nodules
		Lupus pernio
Musculoskeletal	4%	Bone cysts
		Arthralgias, myalgias
		Polyarthritis

Siltzbach *et al.*[141] reported a retrospective series of 1609 patients with sarcoidosis from London, New York, Paris, Los Angeles and Tokyo; 70% of patients were under age 40 at the time of presentation, 55% were women, 54% were white, 22% were black and 18% were Japanese. Overall, approximately 10% of patients presented with Stage 0 disease; 40% with Stage 1; 35% with

Stage 2; and 15% with Stage 3. Chest radiograph abnormalities resolved in 63% of patients with Stage 1; 50% of patients with Stage 2; and 18% of patients with Stage 3.

Sharma has reported that cardiac involvement occurs in up to 20% of patients; however, it is clinically recognized in only 5%.[143] Complete heart block is the most common abnormality. Ventricular ectopic beats and sustained or unsustained ventricular tachycardia are also common. Other conduction defects and supraventricular arrhythmias may also occur. Sudden death due to ventricular tachyarrhythmias or conduction defects is stated to account for 30–50% of deaths due to sarcoidosis. Progressive cardiac failure has been estimated to cause 25% of cardiac deaths and is the second most common cause of death in patients with cardiac sarcoidosis.[143]

Neurologic involvement may manifest as headache, vertigo, facial weakness, hemiparesis, ataxia, seizures, visual disturbance or dementia. Cranial and peripheral neuropathies, meningitis, and mass lesions in the cerebral hemispheres, basal ganglia, brain stem, cerebellum or spinal cord may occur.

In a series of 68 patients with neurosarcoid, 26 had optic nerve involvement and 23 had other cranial nerve involvement, 19 had spinal cord involvement and 14 had brain stem or cerebellar involvement. Of the 23 with cranial nerve involvement, 13 had only facial nerve involvement, which was said to have a good prognosis. However, other types of neurologic involvement had worse prognoses. Despite treatment, 60% with optic nerve involvement and 70% of cases with spinal cord involvement demonstrated progressive deterioration. Neurosarcoid presenting with seizures is also said to have a poor prognosis.[144]

Hepatic granulomas are common in sarcoidosis but are usually asymptomatic. Active liver disease is rare. The two hepatic complications, portal hypertension and cholestasis, are almost exclusively seen in black males over the age of 40 who have extensive pulmonary involvement.[145,146]

Corticosteroids remain the primary mode of therapy for sarcoidosis. The indications for corticosteroid treatment have been recently reviewed.[140,147] Patients with Stage 1 and 2A disease, who are asymptomatic and have good pulmonary function, should be followed without treatment until their disease progresses. Symptomatic Stage 1 and 2A patients, Stage 2A patients who have significant impairment in lung function and Stage 2B and Stage 3 patients should receive treatment. Patients with Stage 3 disease may be candidates for pulmonary transplantation. Cardiac, neurologic, upper airway, ocular involvement and significant hypercalcemia or hypercalcuria should also be treated. Other agents such as chloroquine and methotrexate are sometimes used as an adjunct to corticosteroids, but further studies are needed to define their effectiveness and proper role.

Risk selection

Siltzback *et al.*[142] reported a 6% overall mortality in their series: 5% as a direct result of sarcoidosis and 1% from unrelated causes. Patients who present with Lofgren's syndrome (erythema nodosum, arthralgias and bilateral hilar adenopathy) almost invariably have a good prognosis. Patients with Stage 1 pulmonary disease have a better prognosis than those with Stage 2 who, in turn, have a better prognosis than those with Stage 3. Failure of radiographic resolution over 1 year has been stated to be a poor prognostic sign. Radiographic resolution lasting for 2 or more years has been said to indicate a cure.[148] A worse prognosis may be anticipated for patients over the age of 40 at disease onset, those who have cardiac sarcoid, neurosarcoid, sarcoidosis involvement of more 3 organ systems, and those who have Stage 3 pulmonary disease. Although the overall prognosis for sarcoidosis is good, as many a 50% of patients have residual organ impairment.

Idiopathic interstitial pneumonias

The idiopathic interstitial pneumonias are characterized by expansion of the interstitial compartment (i.e. that portion of the lung parenchyma sandwiched between the epithelial and endothelial basement membranes) with an infiltrate of inflammatory cells. The inflammatory infiltrate is sometimes accompanied by fibrosis, either in the form of abnormal collagen deposition or proliferation of fibroblasts capable of collagen synthesis. In general these disorders are characterized by an increase in the elastic recoil of the lungs, a restrict-

ive pattern on pulmonary function testing, a reduction in carbon monoxide diffusing capacity (DLCO) due to diminished alveolar-capillary surface area, and hypoxemia (especially with physical exertion). Although clinical history and imaging studies can be suggestive of a specific type of interstitial pneumonia (*see* Table 23.16), it is increasing acknowledged that either VATS (video-assisted thoracoscopic surgery) or open lung biopsy, combined with HRCT (high-resolution CT lung scanning) is required to make a definitive diagnosis.

Usual interstitial pneumonia (UIP) is the 'usual' pathological finding in patients with suspected idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis. Most cases are sporadic and occur in patients who present in the 5th or 6th decade of life complaining of slowly progressive dyspnea and nonproductive cough. Men are affected more commonly than women by a ratio of nearly 2:1. UIP/IPF usually follows a relentlessly progressive course, with most patients dying of respiratory failure with a mean survival of 5.6 $\pm$ 3.7 years.[149] Periodic exacerbations associated with increased symptoms and an accelerated decline in pulmonary function are the rule.[150–152] Treatment options are limited.

Desquamative interstitial pneumonitis (DIP) is a distinct clinicopathologic entitiy that differs substantially from UIP. It is relatively uncommon and typically affects cigarette smokers in their fourth or fifth decades of life. Corticosteroids and smoking cessation lead to near-normal mortality, but resumption of smoking usually leads to relapse, with worsening prognosis the longer the patient continues to smoke.

Table 23.16. Classification of idiopathic interstitial pneumonias.

Histologic pattern diagnosis	Clinical-Radiologic-Pathologic
UIP (usual interstitial)	IPF/Cryptogenic fibrosing alveolitis
NSIP (nonspecific interstitial)	NSIP
DIP (desquamative interstitial)	DIP
RB (respiratory bronchiolitis)	RB-ILD
Organizing pneumonia	COP (cryptogenic organizing pneumonitis)
Diffuse alveolar damage	AIP (acute interstitial pneumonitis)
LIP (lymphocytic interstitial)	LIP

Respiratory bronchiolitis-associated ILD (RB-ILD) and DIP share several overlapping clinicopathologic features, most notably improvement and apparent cure with cigarette-smoking cessation. Many experts feel that RB-ILD is simply an early form of DIP.[153] Whereas DIP reveals homogeneous distribution of numerous mononuclear cells within most of the distal air spaces (smokers' histiocytes, not desquamated pneumocytes as previously thought), RB-ILD is characterized by a patchy, inhomogeneous distribution of pigmented macrophages within the lumen of respiratory bronchioles. The macrophages in both DIP and RB-ILD contain dusty brown pigment that stains positively for iron.

Acute interstitial pneumonia (AIP), unlike the slower-onset and progression of most interstitial pneumonias, is typically explosive in onset and rapidly progressive to death. This clinically entity was formerly called 'Hamman-Rich syndrome' and the majority of patients die of respiratory failure in weeks to months.[154] Histologically, AIP is identical to the organizing or proliferative stage of diffuse alveolar damage (DAD), with extensive interstitial fibroblast proliferation within an edematous-appearing stroma. Alveolar septa are dramatically thickened and are lined by hyperplastic type II pneumocytes that are often cytologically atypical.[155]

Nonspecific interstitial pneumonia/fibrosis (NSIP) lacks the histopathologic features typical of UIP, DIP, RB-ILD or AIP, and therefore falls into this grouping. There is a relatively uniform appearance at low magnification due to a cellular interstitial infiltrate of mononuclear inflammatory cells, associated with varying degrees of interstitial fibrosis. NSIP has a significantly better prognosis than UIP; nearly 75% of patients with NSIP improve or recover, versus none who have UIP.[156,157] NSIP with a predominantly cellular pattern, as opposed to a fibrotic pattern, has an especially good long-term prognosis.[158]

Pulmonary eosinophilic granuloma

Pulmonary eosinophilic granuloma is one of the entities comprising the Langerhans cell granulomatosis (histiocytosis X). It is a disorder of unknown etiology, in which there is a proliferation of Langerhans cells around bronchioles early in the disease process; it later progresses to involve the interstitium surrounding alveolar units. The radiographic appearance of pulmonary eosinophilic granuloma is that of diffuse reticular, nodular and reticular nodular infiltrates primarily involving the mid-lung zones.

Pulmonary eosinophilic granuloma is a disease of young and middle-aged adults and is more common in heavy smokers. Approximately 25% of patients may be asymptomatic at the time of diagnosis, the diagnosis being made in the course of evaluating an abnormal chest radiograph. Other patients present with the symptoms of cough and dyspnea. Pneumothorax is a common complication, occurring in 14% of patients. Pulmonary function testing reveals a combination of obstructive and restrictive ventilatory defects. The adult form of eosinophilic granuloma usually remains confined to the lungs. Bone involvement may occur in 5% of patients and hypothalamic involvement in 10%. This is in contrast to the multifocal forms of Langerhans cell granulomatosis, which manifest in childhood and include the entities of Hand-Schuller-Christian disease (bone defects, diabetes insipidus and exopthalmos) and Letterer-Siwe disease (disseminated differentiated histiocytosis).

The prognosis of pulmonary eosinophilic granuloma is variable. Some cases resolve spontaneously and others progress to respiratory failure. Poor prognostic factors include either young or old age, multi-organ involvement, extensive pulmonary disease, low carbon monoxide diffusing capacity and recurrent pneumothoraces. Because of the association of pulmonary eosinophilic granuloma with tobacco use, all patients should quit smoking. Although treatment with corticosteroids and cytotoxic agents may be tried, results are usually unsatisfactory.[92]

Adult respiratory distress syndrome (ARDS)

ARDS refers to Type 1 respiratory failure resulting from the accumulation of protein and water in the alveolar spaces following acute lung injury. A small amount of water normally moves from the vascular space into the lung interstitium and alveolar spaces. The amount of water moving from one space to the other is determined by the pulmonary venous pressure and the concentration of protein in the vascular space. The central event in ARDS is damage to the capillary endothelium producing increased permeability to protein and water, which in turn results in the abnormal accumulation of water and protein in the lung. An intense inflammatory response also occurs. ARDS is a disorder affecting the total body rather than a dysfunction limited to the lungs. In fact, some physicians now describe this process as 'increased permeability edema with acute lung injury'.

A large number of insults may cause ARDS, and it is not within the scope of this chapter to review these initiating events. Suffice it to say that the vast majority of ARDS patients are critically ill and spend days to weeks requiring ventilator support. Approximately 40% of patients who develop ARDS die, but in the majority of the 60% who survive, there is an eventual return towards normal health.[159] Of those patients who have residual lung damage, the severity of pulmonary impairment can best be assessed by complete pulmonary function studies. The most common residual of ARDS is an abnormal diffusion capacity (D_L CO). Other ARDS survivors are left with reactive airways disease.[160] The diffusion capacity (expressed as a percentage of predicted) is inversely correlated with the degree of lung damage (i.e. the lower the diffusion capacity the greater the residual damage).

Of greatest relevance to underwriting an applicant who has survived ARDS is to define, as accurately as possible, the degree of residual impairment and how that impairment might affect future morbidity and mortality. Lung function improves most rapidly during the first 3–6 months following recovery from acute injury, and proceeds more gradually during the next 6 months. Pulmonary function reaches a plateau by 1 year after ARDS onset. Therefore abnormal clinical findings during the first 6 months may prove reversible, but abnormalities that persist for 1 year are unlikely to resolve.[161] However, pulmonary

fibrosis demonstrated on chest radiographs or on computerized chest tomography usually does not reverse.[162]

Pulmonary alveolar proteinosis (PAP)

PAP is classified as primary (idiopathic) or secondary (associated with or provoked by another disorder). Secondary PAP may be associated with pulmonary infections (*Nocardia, Myocobacteria, Pneumocystis carinii*), leukemia, lymphoma and inhalation of dusts and fumes (silica, aluminum, titanium, insecticides).[163]

Primary pulmonary alveolar proteinosis is a disorder of unknown etiology in which proteinaceous material is deposited in alveoli, producing hypoxemia. Little inflammation occurs and pulmonary fibrosis is minimal.

The natural history of idiopathic PAP is variable: one-third of patients are said to die due to progressive hypoxia or superinfection, one-third remain stable and one-third spontaneously improve.[98] Although various treatments have been tried, including the corticosteroids, potassium iodide, trypsin, acetylcysteine and heparin, only whole lung lavage has proven of benefit. Whole lung lavage is performed under general anesthesia. The patient is intubated with a double lumen Carlens endotracheal tube, and while one lung is ventilated, the other is lavaged 10 or 15 times with saline over a period of 1–2 hours. The other lung is lavaged the next day. This treatment has been shown to be very effective; however, some patients require repeat whole lung lavage at intervals of 6–12 months before the disease becomes quiescent. Although no large series have been reported, the prognosis of patients treated with whole lung lavage is said to be good. In a series of 21 patients with primary PAP followed for periods ranging from 1–19 years, a total of 3 patients died, 2 from motor vehicle accidents and 1 from pulmonary fibrosis.[164]

IMMUNOLOGIC LUNG DISEASE

Hypersensitivity pneumonitis

Organic material existing as fine particulate matter or aerosols may be inhaled and, if antigenic to the person inhaling this material, may cause acute and chronic reactions in the lungs. These organic agents include vegetable dusts (especially fungal spores), proteins of animal and avian origin, various micro-organisms (bacteria, *Rickettsia* and *Chlamydia*) and certain organic chemicals. The acute reaction consists of constitutional symptoms, the generation of specific precipitating antibodies (precipitins), and lymphocytic infiltration and sarcoid-type granulomas in the walls of alveoli and small airways. The chronic reaction is characterized by an irreversible and often progressive diffuse intrapulmonary fibrosis.

One important characteristic of these various allergens is that the particles are respirable (i.e. they are small enough to be inhaled and deposited in the gas-exchange portion of the lung parenchyma). The disease is usually associated with an occupation or hobby, because a high level of exposure to the allergen is required to induce sensitization. The classic form of this illness is farmer's lung, caused by the inhalation of both thermophilic bacteria and several fungal species.

Risk selection

A history of a limited number of episodes of acute hypersensitivity pneumonitis would be expected to be associated with little excess mortality if current pulmonary function testing is normal and if subsequent exposure to offending antigens is avoided. However, continuing exposure may result in chronic low-grade pulmonary inflammation and progressive pulmonary disease in the absence of acute episodes. In these cases, the mortality risk of hypersensitivity pneumonitis is related to the degree of pulmonary impairment present and to the degree to which antigen exposure is likely to continue.

A study from Mexico City of 74 female and 4 male patients (mean age 41 years) with chronic pigeon breeder's lung, revealed a survival rate of 71% 5 years from the time of diagnosis. The median survival from the beginning of symptoms was 134 months. At the time of diagnosis, mean predicted FVC was 45% and the mean predicted TLC was 70%. Using a Cox proportionate hazards model and after controlling for the effects of age, sex, clubbing, FVC and TLC, the investigators found that the extent of fibrosis and the

presence of honeycombing on chest radiographs remained significantly and inversely related to survival with relative mortality risks of 220% and 290% respectively.[165]

Goodpasture's syndrome

Goodpasture's syndrome is an autoimmune disease characterized by diffuse alveolar hemorrhage and glomerulonephritis. In this disorder, circulating IgG antibodies become bound in a linear fashion to glomerular and alveolar capillary basement membranes. Accordingly, this disease is sometimes referred to as anti-basement membrane antibody disease. Circulating anti-basement membrane antibody can be detected in over 90% of cases.

Histopathologic examination of lung tissue reveals diffuse alveolar hemorrhage, hemosiderin laden macrophages, mild to moderate interstitial fibrosis and proliferation of type II pneumocytes. Renal lesions consist of a focal segmental necrotizing glomerulitis with crescent formation. Most often pulmonary and renal disease occur simultaneously; however, in 25–33% of cases, renal disease occurs alone.

Young adult males are most commonly affected, and alveolar hemorrhage occurs with increased frequency in smokers. Hemoptysis, cough and dyspnea usually precede the manifestations of renal disease. Fatigue is also common, and some degree of iron deficiency anemia is usual. Chest radiographs reveal patchy or diffuse alveolar infiltrates corresponding to alveolar hemorrhage. With resolution of the hemorrhage, reticular-nodular infiltrates may develop. A restrictive pattern is seen on pulmonary function testing. Due to the presence of blood in the airspaces, carbon monoxide diffusion capacity is increased during episodes of acute alveolar hemorrhage.

Treatment of Goodpasture's syndrome consists of corticosteroids, cytotoxic agents and plasmapheresis. Renal transplantation is recommended for anuric patients. Despite advances in treatment, the prognosis remains poor. Overall, the 2-year survival rate is 50%. Most patients die from alveolar hemorrhage. Severe renal failure is associated with a 6-month survival rate of 50%.[166]

Wegener's granulomatosis

Wegener's granulomatosis is a systemic necrotizing vasculitis that affects the upper airways, lungs, glomeruli, eyes, heart, joints, and peripheral and central nervous systems. Sinusitis is the most common initial manifestation. Some 95% of patients have upper airway disease, over 90% have lung disease and 85% have glomerulonephritis. The term limited Wegener's granulomatosis refers to those cases of Wegener's granulomatosis in which glomerulonephritis is absent. Limited Wegener's granulomatosis is felt to have a better prognosis than classical Wegener's. Pericarditis, myocarditis or cardiomyopathy occur in approximately 10% of patients. Other manifestations include episcleritis, uveitis, retro-orbital masses, arthralgias, arthritis, mononeuritis multiplex, cranial nerve palsies and subcutaneous nodules.

Pulmonary manifestations of Wegener's include pulmonary infiltrates and multiple bilateral or solitary nodules which may or may not cavitate. Atalectasis, pleural effusions and hemoptysis may also occur.

Although the diagnosis of Wegener's granulomatosis is usually made on the basis of biopsy evidence of a necrotizing granulomatous vasculitis, the presence of serum antineutrophil cytoplasmic antibodies (ANCA) has been shown to be a highly specific marker for Wegener's granulomatosis. Two patterns of neutrophil staining by these antibodies have been reported: diffuse cytoplasmic (C-ANCA) and perinuclear (P-ANCA). P-ANCA staining is seen in other vasculitities including Churg-Strauss vasculitis, idiopathic glomerulonephritis, polyarteritis nodosum and systemic lupus erythematosus (SLE). In contrast, C-ANCA is highly specific for Wegener's granulomatosis.

In the past, Wegener's granulomatosis was fatal within a few months, death usually resulting from renal failure. However, treatment with cytotoxic agents, such as cyclophosphamide alone or in combination with corticosteroids, has significantly improved survival. Yet relative mortality ratios remain high. In a study of 77 patients with Wegener's granulomatosis enrolled in the American College of Rheumatology vasculitis classification study and followed for a mean of 7.1 years, the

standardized mortality ratios were 680% for females, 400% for males and 470% for males and females combined.[167]

Pulmonary eosinophilia

This is a heterogeneous group of disorders characterized by abnormal accumulation of eosinophils either in lung issue or in the blood stream, or both.

Transient pulmonary infiltrates with eosinophilia (Loffler's syndrome)

Persons with this disorder are usually asymptomatic. The disorder is often discovered in the course of evaluating an abnormal chest radiograph obtained as part of a routine examination. Common symptoms include transient cough, mild fever and malaise. Pulmonary infiltrates are seen on chest radiographs. These infiltrates are typically bilateral, peripheral in location and transient, usually resolving spontaneosly in 2–4 weeks.

Loffler's syndrome has been shown to result from exposure to a variety of agents, including parasitic infections and exposure to drugs and chemicals.

Ascaris infections (*Ascaris suum* or *Ascaris lumbricoides*) are classically associated with Loffler's syndrome. Pulmonary infiltrates are seen 10–16 days following ingestion of Ascaris larvae, when the larvae have migrated through the intestinal wall into the mesenteric lymphatics and venules, eventually to be filtered out in the pulmonary microcirculation. The larvae migrate into the aiveoli and up the bronchial tree, to be swallowed and to re-enter the intestinal tract for maturation. Parasites and ova will not appear in the stool until 6–12 weeks later, so the diagnosis is often missed. Corticosteroids offer dramatic relief, and if the ingested larvae are Ascaris, a single dose of piperazine (4 g) is curative. Other parasites (*Entamoeba histolytica*, *Strongyloides slercoralis* etc.) may also cause this disorder

A similar illness may occur as a consequence of inhaling organic and inorganic chemicals or ingesting medicines that elicit an inflammatory or hypersensitivity reaction. A large number of medicines have been implicated in Loffler's syndrome. Usually such reactions are self-limited and resolve with discontinuance of the medication, but not always. The best-described instance of this reaction causing permanent lung damage is with the drug nitrofurantoin, a medicine commonly used as a suppressant against chronic urinary tract infections.

Tropical pulmonary eosinophilia

Tropical pulmonary eosinophilia is a disorder related to Loffler's syndrome, but is more serious. It is caused by mosquito-borne parasites that produce an eosinophilic alveolitis. The classic causes of tropical pulmonary eosinophilia are due to the filarial nematodes *Wuchereria bancrofti* and *Brugia malayi*. The blood eosinophilia is much more severe than in simple Loffler's, and patients are usually much more symptomatic. Prompt treatment (Diethylcarbamazine at 6 mg/kg per day for 3 weeks) is usually curative, but chronic disease or delayed treatment may lead to significant pulmonary fibrosis.

Acute eosinophilic pneumonia

This is a newly described entity, usually occurring in young people and presenting with acute dyspnea and ground-glass or reticulonodular infiltrates on chest x-ray. Half of affected patients have pleural effusions. The diagnosis is made by bronchoalveolar lavage or transbronchial lung biopsy. There is rapid clinical improvement and roentgenographic clearing within days of instituting corticosteriod therapy. No long-term sequelae have been reported.[168–170]

Chronic eosinophilic pneumonia (Carrington's eosinophilic pneumonitis)

This disorder occurs most commonly in women in the fourth or fifth decades of life but may occur in either sex at any age. It is characterized by the coexistence of blood eosinophilia, elevated sedimentation rates, and pulmonary infiltrates due to the accumulation of eosinophils in alveolar and interstitial spaces. Asthmatic symptoms may also occur. The chest X-ray presentation is distinctive and consists of peripheral infiltrates in the upper lobes, the so-called 'photographic negative of pulmonary edema'. The cause is unknown, and the disease is usually curable with corticosteroids, although prolonged therapy may be required.

Allergic bronchopulmonary mycoses

Inhalation of fungal spores in patients with asthma may result in endobronchial colonization of the respiratory tree. The clinical picture is that of asthma with recurring lung infiltrates or areas of atelectesis due to mucous-plugging. The most common of these syndromes is allergic bronchopulmonary aspergillosis (ABPA) caused by inhalation and colonization with *Aspergillus fumigatus*. Therapy consists of oral and inhaled corticosieroids. This syndrome may cause some increased morbidity and should therefore be of concern to health insurance underwriters, but it would be a rare cause of mortality by itself.

Hypereosinophilic syndrome

This is a rare disorder in which there is massive infiltration of eosinophils in the lung, heart, CNS, skin and other organs. Males are predominantly affected, and symptoms are often severe. The heart is involved in more than half of all cases, and severe dysrhythmias and valvular incompetencies are a usual cause of death. Pulmonary embolism is also a common cause of death. Although an initial response may be seen with corticosteroid treatment, relapse and death ultimately occur.

Allergic granulomatosis with vasculitis (Churg-Strauss syndrome)

This is a vasculitic syndrome which often results in granuloma formation and necrosis in lung tissue. Persons with this disorder have asthma, marked eosinophilia and systemic symptoms. The diagnosis is established by lung biopsy demonstrating an eosinophilic vasculitis affecting small and medium-sized arteries and veins. High-dose prednisone therapy (and, in resistant cases, azathioprine) may achieve 5-year survival rates of 60%, with 50% surviving 9 years.[171]

Pulmonary eosinophilic granuloma

This disorder is part of the clinical spectrum of histiocytosis X, a group of disorders characterized by proliferation of Langerhans' histiocytes. Peripheral eosinophilia is not part of the clinical picture of eosinophilic granuloma, but the infiltrates on chest x-ray are due to eosinophilic accumulations (For a further discussion of pulmonary eosinophilic granuloma, see 'Interstitial and Infiltrative Lung Disease' above.)

PULMONARY HYPERTENSION

The pulmonary arterial tree is a low-pressure system. Normal mean pulmonary arterial pressure is only 14 torr, about 17% that of the systemic arterial pressure. Pulmonary arterial pressure normally rises very little with exercise, due to the capacity of the pulmonary vasculature to recruit vessels normally not perfused at rest. When pulmonary systolic pressure rises above 30 torr, or mean pulmonary pressure rises above 18 torr, pulmonary arterial hypertension is said to be present. Pulmonary venous hypertension is present when mean pulmonary venous pressure rises above 12 torr.[172] As pulmonary pressure rises, the right ventricular workload increases and right ventricular hypertrophy may occur. Elevation of right ventricular end diastolic pressure is indicative of right ventricular failure. The term cor pulmonale has been defined variously as meaning right ventricular hypertrophy (the preferred definition of the World Health Organization) or right ventricular failure.[173]

The etiologies of pulmonary hypertension have classically been described in terms of precapillary and postcapillary causes (*see* Table 23.17).

In most instances the presence of pulmonary hypertension is associated with increased mortality.

Primary pulmonary hypertension (PPH) is a disease of unknown etiology. Diagnositic criteria require a mean pulmonary artery pressure above 25 torr at rest or above 30 torr during exercise. PPH is for the most part a diagnosis of exclusion: all other known causes of pulmonary hypertension must be ruled out. However, it should also be noted that characteristic histopathologic changes have been described in muscular pulmonary arteries. These changes include medial hypertrophy, intimal proliferation and fibrosis, vascular dilatation and occlusion, plexiform lesions and necrotizing arteritis.

Although PPH has traditionally been regarded as a disease of young women, it affects both men and women of all ages. The prevalence of PPH has been estimated to be 1.3/1000 in an autopsy

Table 23.17. Causes of pulmonary hypertension.

Precapillary causes	Postcapillary causes
Vascular	Cardiac
Left-to-right shunt	Left ventricular failure
Primary pulmonary hypertension	Mitral stenosis
Pulmonary embolic disease	Left atrial myxoma
Pulmonary vasculitis	Cor triatriatum
Low ambient oxygen tension (e.g. high altitude)	
Pleuro-pulmonary disease	Pulmonary-venous
Emphysema	Congenital stenosis
Interstitial disease	Pulmonary veno-occlusive disease
Fibrothorax	Anomalous pulmonary venous return
Kyphoscoliosis	
Alveolar hypoventilation	

series.[174] Some cases of PPH may have been related to ingestion of toxins or medications. Aminorex, an appetite suppressant, was suspected of causing cases of PPH in Europe in the late 1960s. More recently another appetite suppressant, fenfluramine, has been shown to increase the risk of PPH.[175]

The prognosis of PPH is poor. In 1991, survival data from the Patient Registry for the Characterization of Primary Pulmonary Hypertension were published.[176] The estimated median survival was 39 months for men and 32 months for women.

SLEEP APNEA

The sleep apnea syndromes are a group of disorders characterized by the presence of periodic pauses in breathing during sleep. These pauses may either be complete, during which airflow totally ceases (apneas), or partial, during which airflow is significantly diminished but does not entirely cease (hypopneas). Sleep apnea may be the result of a failure of the brainstem to continue to stimulate breathing during sleep (central sleep apnea or Ondine's curse) or it may be due to airflow obstruction at the level of the pharynx or hypopharynx (obstructive sleep apnea). The combination of central apneas followed by obstructive apneas is termed mixed sleep apnea. By far the most common form of sleep apnea is the obstructive sleep apnea syndrome (OSAS), which consists of pure obstructive apneas and/or mixed apneas.

The consequences of sleep apnea include: repetitive drops in blood oxygen levels during sleep (oxygen desaturations); complete or partial aroUSls from sleep (sleep fragmentation); excessive daytime sleepiness (EDS or hypersomnolence); arrhythmias (sinus pauses, transient heart block, and atrial and ventricular arrhythmias during apneas); hypertension; impaired neuropsychological functioning (including altered libido, impotence, irritability, personality disturbances, inability to concentrate, fatigue and an increased risk of industrial and driving accidents); and sudden death.

An uncommon but particularly severe form of sleep apnea is the Pickwickian syndrome, which is also called the obesity hypoventilation syndrome (OHS). This syndrome consists of obesity, sleep apnea, daytime hypersomnolence, hypercarbia and hypoxemia during wakefulness, and evidence of pulmonary hypertension or right heart failure.

Diagnosis

Obstructive sleep apnea is usually suspected when a history of loud snoring is present in addition to one or more of the following features:

- witnessed apneic episodes
- hypersomnolence

- change in personality or ability to concentrate
- insomnia
- significant obesity (however, many persons may have sleep apnea without being significantly overweight).

Even though sleep apnea may be suspected from clinical symptoms, the diagnosis requires confirmation by nocturnal polysomnography. Typically, a full polysomnographic study consists of: monitoring and recording EEG activity; extraocular eye movements; submental EMG activity; nasal and oral airflow; respiratory effort (by impedence plethysmography, respiratory strain gauge or esophageal ballon); ear oximetry; ECG and lower extremity EMG activity. An accurate diagnosis of sleep apnea requires at least 6 hours of monitoring and includes recording of sleep stage, airflow, respiratory effort, blood oxygen level (oxygen saturation) and ECG.

Sleep apnea severity is usually expressed in terms of an apnea index (AI) or a respiratory disturbance index (RDI). The AI is defined as the average number of apneas occurring per hour of sleep. The RDI, also known as an apnea-hypopnea index, is defined as the average number of apneas and hypopneas occurring per hour of sleep.

In 1999, research criteria were proposed to standardize the diagnosis of OSAS.[177] These 'Chicago Criteria' consist of five or more obstructive breathing events per hour of sleep demonstrated by overnight monitoring and/or excessive daytime sleepiness, along with two or more of the following: choking or gasping during sleep, recurrent awakenings from sleep, sleep that is not refreshing or restorative, daytime fatigue, and impaired concentration.

Although these criteria have merit for research purposes, they seem too liberal to be guidelines for treatment or risk appraisal. It is known, for example, that the frequency of apneas and hypopneas increases with age. If the Chicago Criteria were applied to the Wisconsin Sleep Cohort, 6.5% of women and 17% of men would meet the criteria for OSAS. For those age 50–60, 16% of women and 31% of men would be classified as having OSAS. Accordingly, many clinicians consider an AI < 5 or a RDI < 15 as normal.

Recently, a new syndrome, the upper airway resistance syndrome (UARS) has been identified.[178] UARS is characterized by respiratory effort related arousals (RERA). In RERA, partial upper airway obstruction is present, but to a lesser degree, and apneas and hypopneas do not occur. Instead, the partial upper airway obstruction leads to an increased work of breathing which results in increased respiratory efforts and aroUSls from sleep. These aroUSls fragment sleep and have similar consequences as those following apneas and hypopneas.

Consequences

Apneas and hypopneas result in episodic oxygen desaturations. The severity of desaturations correlates with the length and frequency of apneas and the presence of underlying pulmonary disease. Desaturations are commonly defined as drops in oxygen saturation 4% or more below the baseline oxygen saturation level. In cases of severe sleep apnea, these desaturations may occur frequently and be prolonged and severe. Desaturations to 40% or lower, occuring at a frequency of 40 or more per hour, and lasting 60 seconds or more, are not uncommonly seen in sleep laboratories. The consequences of recurrent hypoxemia include: bradycardia; other cardiac dysrythmias; pulmonary hypertension; congestive heart failure; sleep arousal and fragmentation; and hypoxic cerebral depression.[179] However, little is known about the severity or frequency of the desaturations that are necessary to produce these adverse consequences. There is little evidence to suggest that oxygen desaturations occurring during sleep in the absence of waking hypoxemia contribute to pulmonary hypertension or cor pulmonale,[180–182] and whilst nocturnal oxygen desaturations may eventually be shown to be the cause of the excess mortality associated with sleep apnea syndrome, there is presently no definitive evidence to confirm this hypothesis.

There is some evidence, however, that nocturnal oxygen desaturations are at least in part responsible for the diminished daytime vigilance seen with sleep apnea syndrome. Oxygen saturations of 60% or lower during the night have been shown to correlate with a mean time to sleep onset

of less than 5 minutes, which is indicative of pathological sleepiness. Lowest nocturnal oxygen saturations of 60–95% have been shown to be associated with mean sleep latencies in the intermediate range of 5–10 minutes.

Arrythmias are common in OSAS. Over 75% of patients with OSAS have sinus bradycardia and 10% of patients may have sinus pauses up to 13 seconds. Mobitz Type 2 AV block may occur in 4–8% of patients. Ventricular ectopy occurs in 57–74% of OSAS patients. However, this frequency is not different from what would be expected in a cross section of middle-aged men. When oxygen saturations drop to less than 60%, however, ventricular ectopy increases threefold. Above a saturation of 60% there is no increase in ventricular ectopy.[183,184]

Recently studies have implied that nocturnal hypertension may be the mechanism by which sleep apnea causes excess mortality. Normally blood pressure dips at night. However, microarousals during sleep may result in cardioacceleration and nocturnal hypertension. In some patients, nocturnal microarousals may also contribute to waking hypertension.[185]

In a study from Japan, Noda *et al.* studied 51 patients with sleep apnea, 34 of whom had waking hypertension. Polysomnograms, echocardiograms and 24-hour blood pressure monitoring were performed. Patients with an apnea index (AI) of more than 20 had a higher incidence of left ventricular hypertrophy (LVH) than those with an AI of less than 20. They also found that levels of total plasma norepinephrine after waking were significantly increased, compared with levels before sleep, and that this increase was correlated with the duration of oxygen saturation below 90%, but not with the AI. The authors postulated that sleep apnea may cause nocturnal hypertension through the stimulation of the adrenergic nervous system and thereby produce LVH.[186]

Neuropsychiatric complications of sleep apnea are common. Excessive daytime sleepiness (EDS) is probably the most common presenting symptom in patients with obstructive sleep apnea. Cognitive impairment is another well recognized complication of obstrictive sleep apnea. Sleep fragmentation and nocturnal hypoxemia have been implicated as causes for both. As a consequence of EDS and cognitive impairments, patients with obstructive sleep apnea have lower job performance scores and higher accident rates.[187] Findley *et al.* found that patients with obstructive sleep apnea had motor vehicle accident rates 7 times greater than controls and 2.6 times greater than all licensed drivers in Virginia.[188] Stoohs reported that long-haul commercial truck drivers with sleep-disordered breathing had a twofold higher accident rate per mile than drivers without sleep-disordered breathing.[189]

Mortality risk

Only a few studies have been reported that attempt directly to assess the mortality risk associated with obstructive sleep apnea. One of the earliest studies was reported by Gonzales-Rothi *et al.*[190] They compared the course of 91 patients having polysomnographically documented sleep apnea, between July 1978 and June 1986, with a control group of 35 patients who had symptoms but no polysomnographic evidence of sleep apnea. Nine of the sleep apnea patients and four of the control patients died by the end of the study, a statistically insignificant difference. This study has been criticized on the basis of its small size, the difference in age between the two study groups and an excessively high death rate among controls.

Partinen *et al.* reported on 190 patients with obstructive sleep apnea, who were either advised to lose weight (127 patients) or treated with tracheostomy (71).[191] Despite the fact that patients treated with tracheostomy had more severe sleep apnea (AI = 69 versus 43) all of the 14 deaths that occured during the 5-year study occured in the group that was only advised to lose weight.

In 1988 He *et al.* reported the results of a study of 706 patients with obstructive sleep apnea who were followed for up to 9 years.[192] Their data indicate that mortality is increased for men who had an AI > 20. The relative mortality risk for males in this study over the age of 50 having an AI > 20 is estimated at 168% compared with mortality expectations derived from 1979–81 USA life tables. Similarly, for males under age 50 who have an AI > 20, the relative mortality risk is estimated to be 425%. The authors of this study also reported that treatment with nasal continuous

positive airway pressure (NCPAP) restored mortality to normal whereas surgery designed to remove redundant tissue from the posterior pharynx (uvulopalatopharyngoplasty or UPPP) did not.

More recently, data have been reported suggesting that some of the risk attributed to sleep apnea may be due to the presence of comorbid factors such as hypertension, heart disease and lung disease. Lavie *et al.* reported a series of 1456 men and 164 women with sleep apnea between the years 1976–88.[193] They found that sleep apnea syndrome, defined as an AI >10, was associated with significant excess mortality in men between the ages of 30 and 50. The relative mortality ratios for ages 20–30 and 50–70 were also greater than unity, but not significantly so. The authors then used a Cox proportionate hazard model to determine independent risk factors for subsequent mortality. They found that although the AI was identified as an independent predictor of death from all causes, it was not a predictor of death from cardiopulmonary causes or of death due to MI. Even in the analysis of deaths from all causes, the AI made the least contribution to the model.

In agreement with the study reported by Lavie, other studies have also indicated that sleep apnea may be less of a risk factor for mortality in the elderly than in younger persons. In 1988 Bliwise *et al.* reported that, in their study of 198 persons having a mean age of 66.6 years, an RDI of 10 or greater was associated with a 2.67 relative risk of mortality, but the 95% confidence intervals included unity.[194] In 1990 Pollack *et al.* studied sleep problems in 1855 community-living elderly. For females, the presence of symptoms of sleep apnea was not a predictor of mortality. Although the relative mortality risk for males who reported a history of sleep apnea was 131%, this increase was not statistically significant.[195]

More recently Mant *et al.* followed a cohort of 163 non-demented community-dwelling individuals (mean age = 80.6) for 4 years. The presence of sleep apnea (defined as a RDI \geq 15) was not found to be predictive of mortality.[196]

Treatment

Central apnea may be treated with diaphragm pacemakers, nocturnal ventilation or medication. Obstructive apnea may be treated by: varying the position of the patient during sleep (position therapy); weight loss; medication (protriptyline, medroxyprogesterone, theophylline, almitrine, oxygen); surgery (UPPP, nasal, maxillary or mandibular surgery, or tracheostomy); by various appliances (tongue retaining devices); or by nasal continuous positive airway pressure (NCPAP) or continuous positive airway pressure (CPAP). All these therapies require repeat polysomnography in order to determine whether they have effectively eliminated apneas. Only tracheostomy and NCPAP have been demonstrated in clinical studies to significantly reduce mortality. NCPAP therapy is often perceived as disagreeable by the patient and a significant percentage of patients prescribed NCPAP will eventually discontinue its use. NCPAP compliance is about 75% at 6 months and 66% at 1 year; ultimately 50% will discontinue the use of NCPAP at 2 years or beyond.[197,198]

Risk selection

In summary, the few studies on the mortality risk of sleep apnea provide evidence that sleep apnea is associated with excess mortality, especially in those under 50 years of age at the time of diagnosis. Studies indicate that although NCPAP is an effective treatment for sleep apnea and restores mortality to normal, there is relatively poor long-term compliance with this form of treatment. Other studies indicate that although upper airway surgery such as UPPP can improve obstructive apneas, significant improvement occurs in only about half of those so treated and that follow-up nocturnal polysomnographic studies are indicated to determine if significant improvement has occurred and whether additional treatment is warranted. There is also evidence to suggest that a portion of the risk attributed to sleep apnea may be due to the presence of co-morbid factors, such as hypertension, heart disease and lung disease, that may have already been considered in the underwriting process.

PLEURAL DISEASE

Although many disease processes affect the pleural linings of the lungs, the pleura respond in

only a few ways: pain (pleurodynia), effusion, the development of a pneumothorax and fibrosis. The importance of these manifestations is determined by the underlying etiology and the degree to which pulmonary function is impaired.

Pleuritis and pleurisy are non-specific terms referring to pain produced by pleural inflammation. Pleuritis can have many causes. Pleural inflammation without effusion has been termed 'dry pleurisy'. Pleural pain usually diminishes as an effusion develops ('wet pleurisy'). One of the most common causes of dry pleurisy is infection with Coxsackie virus. Pleural inflammation caused by Coxsackie virus is so severe, spasmodic and paroxysmal in nature that this disorder has been called 'the devils grippe'. The infection is self-limited and only symptomatic treatment is required. It has no significant mortality implications.

Pleural effusions may result from many causes. The mortality implications of a pleural effusion are determined primarily by the underlying disorder. Pleural effusions have been characterized as transudates or exudates, depending on their composition. An exudative pleural effusion associated with a bacterial pneumonia, bronchiectasis or lung abscess is termed a parapneumonic effusion. Parapneumonic effusions are described as 'complicated' if a tube thoracostomy is required for them to resolve. An empyema is defined as pus within the pleural space, and almost always requires drainage. Pneumothoraces may result from many causes. Spontaneous pneumothoraces are those that occur in the absence of obvious trauma or underlying lung disease. Secondary pneumothoraces are those that occur as a result of trauma (traumatic pneumothorax, iatrogenic pneumothorax), or underlying lung disease (secondary spontaneous pneumothorax).

The mortality implication of a pneumothorax depends on the underlying cause and the extent to which pulmonary function is compromised. Primary spontaneous pneumothorax is fairly common, occurring at an incidence of 7.4 per 100,000 per year in men and 1.4 per 100,000 per year in women. Most are believed to be caused by the rupture of apical subpleural blebs. Smokers are at seven times the risk of non-smokers for primary spontaneous pneumothorax. Many primary spontaneous pneumothoraces resolve spontaneously, or are easily treated by aspiration or tube thoracostomy. Persons who have already had one primary spontaneous pneumothorax are at increased risk of having recurrences. Pleural sclerosis or open parietal pleurectomy has been recommended for persons having more than two primary spontaneous pneumothoraces and for those having an episode of bilateral pneumothorax. With few exceptions, one or more episodes of primary spontaneous pneumothorax that have been adequately treated would be expected to result in little if any excess mortality.

Secondary spontaneous pneumothoraces, by definition, occur in the presence of underlying lung disease, and accordingly the mortality risk is increased. COPD is the most common underlying disease, and the risk of pneumothorax increases as the severity of COPD increases. The many other causes include pulmonary tuberculosis, pulmonary fibrosis, sarcoidosis, pneumoconiosis, lung abscess, bronchogenic carcinoma and asthma.

Risk selection

The Medical Impairment Study 1983 recorded 328 deaths out of 10 to 180 policies issued from 1952 to 76 to persons having histories of pleurisy, pleural effusion or empyema within the preceding 3 years. The overall relative mortality ratio was 118% compared with standard insured lives mortality. Males over age 50 at the time of policy issue had a relative mortality ratio of 148%.[199] The study also recorded 291 deaths out of 16 804 policies issued to persons having histories of spontaneous pneumothorax from 1952–76. Only subjects who were thought to be free of other diseases were included in the study. The overall relative mortality ratio was 140% compared with standard insured lives mortality. There did not appear to be a significant difference in mortality by issue age or by duration.[200]

INFECTIOUS RESPIRATORY DISEASE

Infectious respiratory diseases comprise a large number and variety of disorders. Infectious bronchitis, bronchiolitis, pneumonia, lung abscess,

parapneumonic effusions and empyemas fall into this category. In general the short-term prognosis of infectious lung disease depends on the immune status of the individual, the infecting organism, the nature and severity of the infection and the adequacy of treatment. The long-term prognosis depends primarily on the immune status of the individual, the degree of residual pulmonary impairment and the presence of coexisting disease.

Acute pulmonary infections

Many acute respiratory infections are associated with substantial mortality risk during the stage of active infection. Overall, community-acquired pneumonia is associated with a case-fatality rate of 6–24%, and hospital-acquired pneumonia has a case-fatality rate of 2–53%.[201] The mortality due to anaerobic lung abscess has been reported to be as high as 15%,[202] and the mortality due to empyema varies: 8–15% in healthy young persons and 40–70% in elderly patients and those with serious underlying disease.[203]

Pulmonary tuberculosis

The worldwide incidence of tuberculosis diminished steadily from the 1960s and reached a nadir in the mid-1980s. Since then, the incidence has again been increasing. It is estimated that currently one-third of the world's population and one-fifth of the USA population are infected with *Myobacterium tuberculosis*, as indicated by a positive tuberculin skin test. The World Health Organization estimated that by the year 2000 the worldwide annual incidence of tuberculosis would rise to over 10 million new cases, an increase of over 35% compared with the 1990 incidence. Of the 3.5 million deaths from tuberculosis that were expected in 2000, 85% were expected to occur in Africa, South-East Asia and the western Pacific.

The rising tuberculosis incidence and death toll are related, in large part, to the spread of the HIV epidemic. Other factors include poverty, crowding, homelessness, malnutrition, immigration and the lack of effective tuberculosis control programs. As the prevalence of tuberculosis increases, so does the prevalence of drug-resistant mycobacterium. In some countries primary resistance may reach 25% and acquired resistance 75%.[204]

Nevertheless, the overall mortality of adequately treated tuberculosis remains low. Prior to the availability of effective antimycobacterial chemotherapy, 50% of patients died within 2 years, 25% remained chronically infected and acted as reservoirs of infection within the community, and 25% experienced a spontaneous cure. Now, with good therapy, 98% of patients are cured, 1.2% still die and 0.8% continue to have chronic active disease.[204] Recommended treatment regimens for non-resistant cases of *Mycobacterium tuberculosis* consist of: (1) 9 months of isoniazid and rifampin; or (2) 2 months of isoniazid, rifampin and pyrazinamide followed by 4 months of isoniazid and rifampin.[205]

Risk selection

Persons infected with *Mycobacterium tuberculosis*, as evidenced by a positive tuberculin skin test, but who do not have active disease, are at an increased risk of developing active tuberculosis some time in the future, unless prophylactic treatment is given. The annual risk of developing active tuberculosis is relatively small and has been estimated to be 0.5–1 cases per 1000 per year. The risk is substantially higher, however, if infection has been acquired within the preceding 2 years (recent converters) or if there are coexisting conditions, such as: intravenous drug abuse; silicosis; chronic use of immunosuppressent agents or oral or parenteral corticosteroids; diabetes; end-stage renal disease; Hodgkin's disease or other hematologic malignancies; gastrectomy; HIV infection; malnutrition; or substantial rapid weight loss.[206] It should also be noted that false-positive reactions to tuberculin occur, notably among persons who have received immunization with BCG.

Two insured lives mortality studies of tuberculosis have been reported. The *Medical Impairment Study 1983* reported on 49,511 life insurance policies issued on persons having a history or evidence of tuberculosis. The average annual death rate in this cohort compared with that of standard insured lives was 0.3 per 1000 per yr for men and 0.7 per 1000 per yr for women. Relative mortality ratios were 107% and 127% for men and women respectively.

In a study of male policyholders issued life insurance by the Prudential Assurance Company of London who were coded as having pulmonary tuberculosis at the time of policy issue, no excess mortality was seen in those coded as having mild disease. Those coded as having moderate or severe disease and those who were treated with pneumothorax or surgery had mortality ratios ranging between 121% and 144% compared with those of standard insured lives.

SPECIAL CLINICAL PROBLEMS

Hemoptysis

The significance and the mortality implications of hemoptysis depend on the underlying cause. The amount of blood produced may range from a few flecks to cupfuls. With few exceptions, every case of new or appreciable hemoptysis should be carefully evaluated. Some of the underlying causes of hemoptysis are listed in Table 23.18.

Solitary pulmonary nodule (SPN)

The incidental finding of a solitary pulmonary nodule (SPN) on a chest radiograph is not uncommon. A SPN is defined as a well circumscribed radiographic density less than 3 cm in diameter and completely surrounded by aerated lung. There are more than 40 different etiologies for SPNs. Although most are benign, 40% are malignant. Densities 3 cm or greater in diameter have been termed solitary pulmonary masses, and are more likely to be malignant.

The only way to be certain that a SPN is benign is by excisional biopsy. However, excisional biopsies are done less frequently now compared to the past. Instead, a clinical appraisal of the likelihood of malignancy, based upon criteria similar to those in Table 23.19, is made. Then an additional radiographic procedure or 'watchful waiting' is often recommended.

Two of the more common radiographic studies done to evaluate SPNs are contrast enhanced computed tomography and positron emission tomography (PET). Malignant pulmonary nodules, due to their increased vascularity, have been shown to enhance with contrast and to increase in radiographic density. And, because malignant lesions are metabolically active, malignant SPN often enhance when PET scans are done following the administration of flourodeoxyglucose

Table 23.18. Selected causes of hemoptysis.

Naso-pharyngeal or upper airway bleeding
Chronic bronchitis
Bronchiectasis
Bronchial adenoma
Bronchogenic carcinoma
Tuberculosis
Bacterial pneumonia
Lung abscess
Fungal infections
Pulmonary infarction
Pulmonary arterio-venous fistula
Congestive heart failure
Mitral stenosis
Goodpasture's syndrome
Wegener's granulomatosis
Bleeding diatheses

Table 23.19. Characteristics of SPN.

Suggestive of benign process	Suggestive of malignancy
Age under 35	Age over 35
No use of tobacco	Tobacco use
Diameter $\leq$ 2 cm	Diameter $>$ 2 cm
Central calcification, lamellar or punctate calcification	No calcification or eccentric calcification
Smooth well defined margins	Lobulated or irregular margin
No enlargement for 2 or more years	Documented enlargement
Very rapid growth*	Intermediate growth rate
No prior history of malignancy	
Prior history of malignancy	
CT density $>$ 185 Hounsfield units	

*Very rapid growth is suggestive of infection or inflammatory process.

(F-18-FDG). Nevertheless, false positive and false negative results do occur. Many SPN are too small for there to be certainty about the presence or absence of enhancement. In addition, some vascular and inflammatory lesions also enhance. Although it was thought that F-18-FDG PET scanning might have decreased sensitivity in diabetics, due to the competitive uptake of blood glucose with F-18-FDG, a recent review reported no such problem. However, slow growing malignant lesions may have a benign appearance on F-18-FDG PET scans.[207,208] Thus, next to excisional biopsy, the most reliable indication of a SPN's benignity is the lack of growth over time or the very rapid growth of the nodule over a short period. This is commonly expressed in terms of the time it takes for the nodule to double in volume. Since nodules are roughly spherical, a doubling in volume equates to a 25% increase in diameter. The doubling time of malignant tumors may range from 1 month to 1 year. Very fast growth, such as that indicated by a doubling time less than 7 days, is most likely due to an inflammatory process. Conversely, if a SPN remains unchanged in size for a period of 2 years, it is also most likely to be benign. However, the apparent lack of change in a nodule's diameter over a relatively short period of time, such as a few months, provides little reassurance that it is not malignant.

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