CHAPTER FOUR

Pulmonary Effects of Inhaled Mineral Dusts

William L. Eschenbacher, MD, Gregory J. Kullman, Ph.D., CIH and Cristina C. Gomberg, RN, MS

1 INTRODUCTION

Despite advances in knowledge of the relationships between exposure to mineral dusts (asbestos, coal dust, silica) and the respiratory diseases that can occur (pneumoconioses, obstructive lung diseases, cancer, etc.), these diseases are still present and workers are still dying with these conditions. Important insight has been gained into the understanding of the mechanisms of the injury that occurs when the cells and the tissue of the lungs are exposed to these mineral dusts. However, the primary mode of protecting workers from the development of these mineral dust-induced lung diseases is by reducing or eliminating exposure to increased concentrations of the dusts in the first place. No amount of treatment can substitute for prevention in the development of these diseases.

This chapter provides the reader with background knowledge regarding the respiratory system (anatomy, defense mechanisms, physiology, assessment, and the response of the lungs to injury) and specifics of the lung diseases caused by exposure to some of the mineral dusts.

Treatment of these disorders will not be covered in great detail in this chapter. However, it remains paramount that engineering controls and personal respiratory protection be required so that these dust-induced lung diseases can be prevented.

Patty's Industrial Hygiene, Fifth Edition, Volume 1. Edited by Robert L. Harris.
ISBN 0-471-29756-9

2 PULMONARY ANATOMY

The primary function of the lung is to effect gas exchange with the environment: transfer oxygen from outside the body to the blood within the body and remove carbon dioxide from the blood to outside the body. The anatomy of the respiratory system is set up to allow for this exchange to occur in a most efficient fashion.

The respiratory system includes the lungs, the airways leading into the lungs, the pleural covering of the lungs, the blood vessels leading to, away from, and in the lungs, the muscles of the diaphragm and chest wall that allow air movement to occur and the chest wall itself which provides support and protection of the internal structures including the lungs, the heart, and the major blood vessels. The respiratory system can be divided into these separate components for convenience and also because disease when it occurs can preferentially affect one component more than another (see Fig. 4.1).

2.1 Tracheobronchial Tree

The tracheobronchial tree or airways actually begin at the nose and mouth and continue to the level of the terminal bronchiole, the smallest conducting breathing passage. Air containing oxygen enters the body through the nose and mouth and from there is inhaled

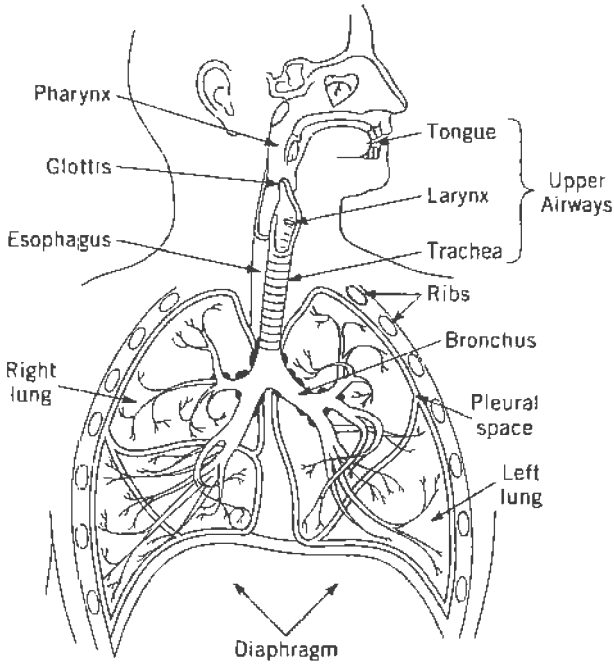

Figure 4.1. The respiratory system. Reprinted with permission from American Lung Association (1). Note figure is from 1979.

through the throat or pharynx and then through the vocal cords or larynx before entering the windpipe or trachea. From here the trachea or main airway branches into the right and left major bronchi. Air moves into these branches and then into smaller and smaller divisions of the tracheobronchial tree until the smallest conducting units or terminal bronchioles are reached. The trachea is 20–25 mm in diameter and the smaller bronchioles are less than 1 mm in diameter. However, because of the many divisions and many number of smaller bronchioles, the total cross-sectional area of the tracheobronchial tree actually increases from approximately 4 cm^2 at the trachea to 10,000 cm^2 at the level of the terminal bronchioles.

2.2 Pulmonary Parenchyma and Interstitium

The pulmonary parenchyma and interstitium refer to those parts of the lungs that are involved in functions other than air conductance. This is a network of cells and supporting matrix (including collagen) where gas exchange takes place. The next airways after the terminal bronchioles are the respiratory bronchioles which contain air sacs (alveoli) within their walls. The alveolar spaces are tiny air sacs formed by a thin cellular membrane (epithelium) abutting blood-filled capillary membranes (endothelium). There are approximately 300 million alveoli in the lungs of a human with a total surface area of a tennis court (approximately 280 sq ft). Once air reaches the bronchioles and alveoli, gas exchange occurs: oxygen diffuses across a thin cellular membrane into the blood stream and carbon dioxide is transferred from blood into the alveolar space. During exhalation, the alveolar air which now contains reduced oxygen and increased carbon dioxide moves up the tracheobronchial tree where it leaves the body at the nose and mouth.

The space between the walls of the alveoli and the walls of the capillaries is the interstitium, which is a space normally devoid of material or cells so that efficient gas exchange can occur. The interstitium can be the site for inflammatory changes. Cellular infiltrates and increased protein/collagen deposits that could occur in certain occupational diseases can make the lungs stiffer and hamper gas exchange. These diseases are varied but are collectively referred to as interstitial lung diseases.

2.3 Pulmonary Vascular Bed

Blood is carried to the lung by the pulmonary arteries from the right ventricle of the heart. The pulmonary arteries then branch and branch again, with the blood vessels paralleling the bronchi and bronchioles. Eventually the vessels become the capillaries which come into close contact with the alveolar spaces. It is thought the capillary bed is probably more a large continuous membranous surface through which blood cells and plasma flow than a conduit provided by individual vessels. After oxygen is transferred from the alveoli into the blood (actually attaching to the hemoglobin molecules within the red blood cells), the oxygenated blood leaves the capillary bed and enters the pulmonary venous system which is composed of larger and larger vessels until they become the pulmonary veins which carry the oxygenated blood to the left atrium of the heart. From here, the oxygenated blood flows to the left ventricle and then is pumped out to the rest of the body.

2.4 Pleural Surfaces

There are two adjacent layers of thin cellular coverings for the lung. In immediate contact with the lung is the mesothelium referred to as the visceral pleura. The visceral pleura is surrounded by the parietal pleura which is a thin second mesothelial covering that lines the inside of the chest wall. These two layers remain in close proximity and have smooth surfaces facing each other allowing for ease of movement of the lungs within the chest wall. The pleural surfaces can become diseased due to inflammatory changes (influx of cells and proteinaceous material) resulting in a thickened and irritated surface that can limit the expansion of the lungs. In addition, the cells present in the pleural space can mutate to dysplastic, metaplastic, or neoplastic in cases of malignancies related to the pleura (malignant mesothelioma). Also, fluid can accumulate in the pleural space between the two layers limiting lung and chest wall expansion. These pleural effusions can be benign (without malignant cells) or malignant.

2.5 Respiratory Muscles

In order for respiration (gas exchange) or ventilation (air conductance) to take place, expansion of the chest wall must occur. The respiratory muscles (primarily the diaphragm) are involved in this process. By contracting with each breath, the diaphragm descends causing the chest cavity to increase in size. This creates a negative pressure in the pleural space with a resulting expansion of the lungs. This force results in air being pulled into the lungs during inhalation as necessary for gas exchange. While inhalation is an active process requiring respiratory muscle contraction, exhalation is normally a passive process with the chest wall and the lungs relaxing back to their resting or pre-inhalation size. Diseases that affect the respiratory muscles are usually related to nerve or muscle diseases, but mineral dusts such as asbestos can result in changes to the diaphragm surface which can impact ventilation.

3 LUNG DEFENSES

3.1 Cough

The body vigilantly protects itself from foreign materials entering the tracheobronchial tree. There are many nerve fibers in the upper airways around the larynx or vocal cords and also in the trachea and major divisions of the bronchi. These nerve fibers react to the presence of any foreign object or irritant substance such as gas or particles of dust. One of the responses to stimulation of these nerve fibers in normal lungs is the cough. As part of this cough reflex, the lungs involuntarily take in a large breath, the air is then forced out with respiratory muscular effort (not passively as occurs with normal exhalation). The resulting high intrathoracic pressures generated with this forceful effort cause the major airways to narrow. The flow of air out through narrowed airways occurs at high velocities with great shear force to help expel any foreign object or substance. When cough is caused by permanent changes in the lining of the airways or in the interstitium or the lung parenchyma, then it is no longer part of a normal response but rather a symptom of a disease.

3.2 Mucociliary Escalator

The airways including the trachea, bronchi, and smaller bronchioles are covered with hairlike projections called cilia. Cells within the airways secrete mucous which layers over the cilia. The cilia beat in a rhythmic pattern moving the mucous up the airways toward the larynx or vocal cords where the mucous can then be swallowed or expectorated. A foreign substance or material that reaches the tracheobronchial tree can be trapped in this mucociliary escalator and removed from the lungs. Occasionally, however, this system can be overwhelmed by the presence of excessive amounts of foreign material such as inhaled dust. In that situation, the dust or other toxic substance can interact with airway cells and/or the alveolar spaces. Before it is adequately removed, additional damage may occur with resulting irritation and inflammation.

3.3 Macrophages

Gases, fumes and microscopic particles can eventually reach the alveolar spaces despite the cough reflex and the mucociliary escalator. The size, shape, and mass of particles determine where they are deposited within the respiratory system. Particle size can be measured in microns. A micron is 10^{-6} meters with approximately 25,400 microns in one inch. The smallest particles that can be seen by the naked eye are greater than 50 microns. To be inhaled into the lungs and into the tracheobronchial tree and the alveolar spaces, a particle is usually smaller than 5–10 microns. Particles bigger than 5 microns usually do not remain airborne long enough to be inhaled or they can be trapped on the mucosal surface of the nose. Particles of 1–5 microns are more likely to deposit in the tracheobronchial tree. Smaller particles (0.01–1 microns) are more likely to reach the smaller bronchioles and the alveolar spaces.

Once particles do reach the alveolar spaces without being coughed out or caught and removed by the mucociliary escalator, they encounter macrophages, cells that reside in the alveolar spaces. Alveolar macrophages are specialized cells that can engulf and digest particles. In time, the macrophages will then die and move up the mucociliary escalator for removal by swallowing. In this last line of lung defense, the macrophage can protect the lung (and in turn the rest of the body) from the potentially toxic effect of the particles.

However, just like the mucocilliary escalator, the macrophages can be overwhelmed by excessive quantities of particles. Particles that are not engulfed by macrophages can lead to irritation, inflammation, and disease.

4 PULMONARY PHYSIOLOGY

4.1 Ventilation

Airflow into and out of the lungs is a balance of two opposing forces intrinsic to the respiratory system: elastic recoil and flow resistance.

Elastic recoil refers to the properties of the lung that cause the lung to revert back to a resting state after the lung has been expanded. These elastic properties are produced by the networks of collagen and elastin fibers that course throughout the lungs and provide

the support structure of the lungs. As lung volume increases, these fibers are stretched, and the potential elastic recoil progressively increases. The result is for the lungs to shrink back to their pre-expansion size.

In addition to the elastic forces that must be overcome with each inhalation, resistance forces related to the flow of air through the tracheobronchial tree must also be overcome. These resistance forces depend upon the flow rate of air, the characteristics of the air including density and viscosity, and the characteristics of the tracheobronchial tree.

To achieve the required oxygen uptake and carbon dioxide removal at rest, one must breathe at a rate to move 5–7 liters of air each minute into and out of the lungs. This ventilation requirement is increased in the face of lung disease because of inefficiency of diffusion of gases or in gas exchange or in inequalities of ventilation/perfusion relationships (see below). Ventilation requirements will also be increased by increasing metabolic demands such as exercise or in certain illnesses which may include fever.

4.2 Diffusion

Once air reaches the alveolar spaces, diffusion of the oxygen molecules occurs across the alveolar-capillary membranes (through the interstitium of the lung) and carbon dioxide molecules diffuse in the opposite direction to be removed from the body. This diffusion process is most efficient if the alveolar–capillary membrane is not thickened by disease and the total surface area of the alveolar–capillary bed is not reduced by disease. Interstitial disease such as the pneumoconioses caused by the inhalation of dusts can result in both the thickening of the interstitium as well as loss of the alveolar–capillary surface area by tissue destruction. Diffusion limitation can occur in these interstitial diseases. It can also occur in other lung diseases such as pulmonary emphysema where the alveolar spaces are destroyed from years of smoking. In these circumstances, the blood leaving the lungs may not be adequately oxygenated resulting in compensatory increased demands for ventilation.

4.3 Ventilation/Perfusion Relationships

In addition to the volume of air moved in and out of the lung, the distribution of air in relation to the flow of blood in the capillary bed is important. The distribution of air to the different sections of the lungs can be affected by diseases in the airways (bronchitis, emphysema, or asthma) or by interstitial disease with alterations in regional distribution of elastic recoil forces.

Once oxygen, a component of the inhaled air, reaches the alveolar surfaces and diffuses through the alveolar-capillary membrane, it will be taken up by the hemoglobin in the red blood cells that flow through the capillary bed. There must be an even matching of the air flow (5–7 liters per minute) to the alveolar spaces with the blood flow (5–6 liters per minute) through the vascular bed. In normal circumstances, 95% of the output of the heart flows through the lung from the right ventricle to the left atrium of the heart.

Again, this matching of ventilation and blood flow or perfusion can be altered by disease. When there is mismatching, there can be increased requirements for ventilation, and the energy requirements for breathing (so-called work of breathing) can be significantly

increased and adequate gas exchange may not occur. In severe conditions, this can lead to respiratory failure and death.

4.4 Stress of Exercise

Any abnormality of pulmonary physiology, whether a problem with ventilation, diffusion, or ventilation/perfusion matching, can appear worsened with exercise. Normally at rest, humans consume 0.2 to 0.3 liters of oxygen per minute to satisfy the needs of the body. However, under conditions of exercise (work or play), the requirements for oxygen can be increased dramatically to as much as 5 to 6 liters of oxygen per minute. Under these circumstances, the total ventilation to support these oxygen requirements can increase to 100 to 140 liters of air per minute and the blood flow through the lungs from the heart can be increased from 5 to 6 liters a minute to 20 to 25 liters per minute. Because of the inefficiency of diseased lungs, these increased requirements of ventilation cannot be met. Therefore, any disease of the lungs even in the earliest stages can result in mild, then severe, limitation to exercise and possibly progress to limitations even at rest.

5 ASSESSMENT OF THE LUNGS

5.1 Lung Function Testing

The principal function of the lung is to exchange gas between air outside the body and blood within the body. In general, the body is quite efficient at adjusting and regulating the ventilation and the ventilation to perfusion relationships so that homeostatsis is maintained even in the presence of extensive lung disease. Additionally, the "pulmonary reserve"—the portion of lung capacity not normally used even during strenuous exercise—is quite adequate so even in the presence of mild lung disease, there may be no perception of limitation. Also, symptoms of respiratory disease (cough and shortness of breath) may not correlate with actual lung dysfunction. For these reasons, determination of lung health is best done by objective measurement of the physical properties of the lung: the size of the lung or the volume of air within the lung, expansibility or the elasticity of the lung, ventilatory ability (forces of breathing), and/or the efficiency of gas exchange. Pulmonary or lung function tests are physiologic measurements that can be used as a surrogate for direct knowledge about a physical property of the lung. A cautionary note: no single test can measure all aspects of lung function. Therefore, care should taken in generalizing from any one measurement, either normal or abnormal. The limits of interpretation are based on (1) level of knowledge of the physiologic principles on which the test is founded, (2) the biological variability inherent in the lung physiology being measured, and (3) the accuracy of the measurement itself. Improving the reliability and utility of test results can be best achieved by reducing the variability of testing. Quality control including test standardization is central to reducing variability.

5.2 Testing Standardization

Guidelines for the standardization of lung function tests have been developed by professional societies such as the American Thoracic Society (ATS) and European Pulmonary

Society (EPS). The documents that contain these guidelines are highly recommended reading for individuals involved in all aspects of lung function testing (2–5).

The goal of standardization is to decrease variability of laboratory testing. As variability with testing is reduced, sensitivity for detection of lung dysfunction and disease is increased. Or stated differently, the variability of the physiologic measures should seek to be as low as possible in order that the variation caused by the dysfunction or disease can be identified (6). It has been demonstrated that significant decrement in variability can be achieved with quality control principles applied to all aspects of spirometry (7) the most commonly used pulmonary function test.

Figure 4.2 from the 1994 ATS Spirometry Update lists spirometry standardization steps. Each of the components will be outlined to give a brief introduction to considerations to be made when critically assessing spirometry results. The most widely administered pulmonary function test—spirometry—is used as an illustrative example of how the standardization steps may be generally applied. Spirometry, covered in greater detail later in the chapter, is a "breathing" test measuring how much and how fast air can be inhaled or

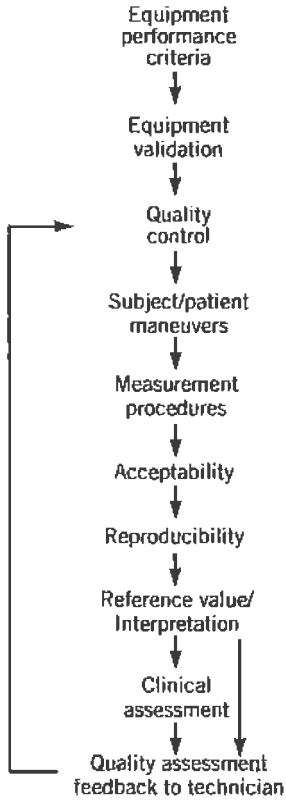

Figure 4.2. Spirometry Standardization Steps. Reprinted, with permission, from American Thoracic Society (2).

exhaled. Industrial hygienists may be asked to help design and implement screening, monitoring, or surveillance programs which include spirometry. Understanding how variability may be introduced to the measurement system is essential to obtaining acceptable results. These standardization steps with appropriate modification can be applied to any of the pulmonary function testing procedures, or any testing situation as the issue of separating the variation of interest (the signal) from the variation attributable for all other sources (the noise) is common to all testing situations.

Equipment Performance Criteria. The accuracy of spirometric equipment depends on the resolution (i.e., the minimal detectable flow) and the linearity of the entire system. Recommendations contained in ATS documents are minimal requirements. Detailed specifications for equipment to be used for spirometry are available (2).

Equipment Validation. Spirometry equipment, like all equipment, requires periodic validation to test equipment performance in meeting the pre-established equipment performance criteria.

Quality Control. Quality control is important to ensure consistency in meeting standards. Procedure manuals which include quality control plan, calibration and test performance procedures, calculations, criteria, reference values source, and emergency procedures are essential in any testing situation. Documentation of daily activities, abnormal events, continuing education and performance feedback are highly desirable. A quality control program that provides continuous feedback to the technician is increasingly seen as critical to the collection of high-quality spirometry data (2, 7).

Subject/Patient Maneuvers. Detailed description and criteria for the actual performance of maneuvers, for not only spirometry, but other pulmonary function testing as well, (i.e., methacholine challenge, diffusion capacity), is essential in obtaining consistency and standardization.

Measurement Procedures. Spirometric variables should be measured from a series of at least three acceptable forced expiratory curves (2). What should be noted is the requirement that *more than one maneuver* is needed. Additionally, the concept of acceptability and its companion concept, reproducibility, are essential and need to be defined. ATS documentation gives detailed requirements for each type of maneuver's measurement procedure.

Acceptability. Acceptability is the performance of a pulmonary function testing maneuver in accordance with criteria recommendations, usually these criteria are as set forth by the ATS (2). Acceptability criteria consists of such items as satisfactory start-of-test, minimum testing times, minimum performance variables, and end-of-test criteria. Obviously, dependent on the components and parameters to be measured, each pulmonary function test will have its specific criteria for acceptability.

Reproducibility. Reproducibility is the ability to successfully produce usually at least three acceptable maneuvers that are within a range of predefined variability, e.g., for the values of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), the largest and the second largest, should not vary more than 0.2 L (2). Again, dependent on the parameters measured, each pulmonary function test will have its specific criteria for reproducibility.

Reference Value/Interpretation. Pulmonary function tests, like all clinical measurements, are subject to (*1*) technical variation related to instrument, procedure, observer, subject, and their interactions; (2) biologic variation (the focus of interest of most of the

nonclinical biological sciences); (*3*) variation caused by dysfunction or disease. Interpretation of pulmonary function tests depends on establishing the variation of interest (the signal) and it relation to all other sources of variation (the noise). In assessing if particular pulmonary results are abnormal, the clinician uses reference equations to provide a context for evaluating an individual in comparison to the distribution of measurements in a reference population. There are multiple reference equations available. The choice of a particular set of reference values depends upon several factors including the population being studied. Recently published reference values for spirometry may become the standard in many different situations (8). [*Note*: There is significant statistical rationale and preference for determining abnormality using lower limits of normal (LLN) as determined from the regression model used in selected reference equations; rather than the relatively arbitrary 20% less than the predicted value (5).]

Clinical Assessment. Pulmonary function tests may be used to (*1*) describe dysfunction and assess its severity, and explain it in terms of diagnosis, prognosis, management, and assessment of trends over time, including response to treatment; (*2*) identify abnormality in individuals without known pulmonary disease; (*3*) and as part of a health assessment for a third party (e.g., insurance or government interest).

Quality Assessment and Feedback to Technician. The pulmonary function testing technician is critical to the successful performance of the pulmonary function testing maneuvers. Since many maneuvers require breathing in unusual, forceful, and sometimes stressful ways, a well-trained, knowledgeable, enthusiastic technician will affect significantly the quality of data obtained. Suboptimal technician performance is the most important factor causing inaccurate spirometry results. The maintenance of high quality data collection is critically correlated with regular written technician feedback regarding the quality of their efforts in obtaining results (7).

Lung Volume Subdivisions. The total volume capacity of the lungs is sometimes useful for understanding pulmonary pathology. See Figure 4.3 for subdivisions of lung. A reasonable estimate of total lung capacity can be obtained by combining several volume parameters. The most common parameters are

1. **Tidal Volume** (TV): during quiet, relaxed breathing, the volume of air that is exhaled with each breath.
2. **Residual Volume** (RV): the amount of air remaining in the lungs after the greatest exhalation possible.
3. **Vital Capacity** (VC): the maximum amount of air that can be exhaled after the fullest inhalation possible. The amount of air that can be exhaled with a *maximal effort* after a maximal inhalation is called the Forced Vital Capacity (FVC). The FVC is the volume that is measured in spirometry.
4. **Total Lung Capacity** (TLC): the sum of the vital capacity and the residual volume and a representation of total measurable lung volumes.

5.3 Spirometry

Spirometry is a medical test that measures the volume of air an individual inhales or exhales as a function of time. Flow, or the rate at which the volume is changing as a function of

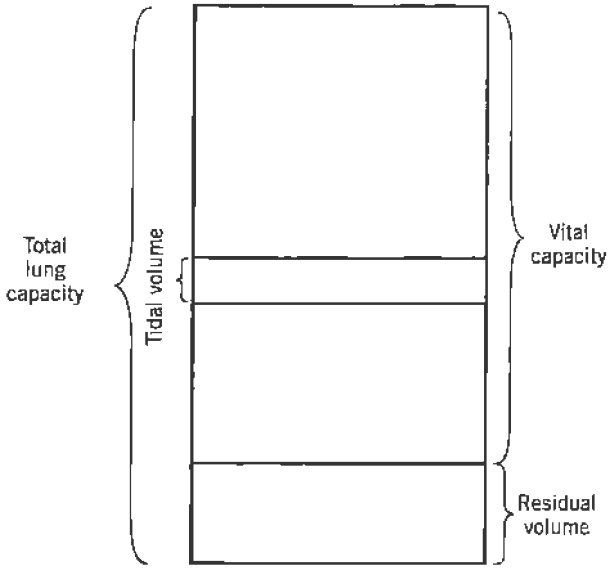

Figure 4.3. Volume subdivisions of the Lung.

time can also be measured. Spirometry is a useful screen of general health and correlates well with morbidity and life expectancy (9). Spirometry is used to gather information about respiratory function and may be used to diagnose, monitor, evaluate disability or impairment, and in public health surveillance and evaluation (10).

Spirometry refers to the measurements of exhaled air volume and flow rates from individuals who are coached by trained technicians using either volume-based or flow-based measuring equipment. The important measurements include forced vital capacity (FVC) or the greatest volume of air exhaled from a maximal inspiration to a complete exhalation; the forced expiratory volume in one second (FEV_1) or the volume of air exhaled in the first second of a FVC maneuver; and the ratio between these two values: FEV_1/FVC. These measurements can be made using either a volume-based system (such as a dry rolling-seal spirometer) or a flow-based system interfaced to a dedicated computer. All procedures should conform to standard guidelines (2). At least three maximal expiratory maneuvers or FVC maneuvers should be performed at each session. The selection and interpretation of results including the use of published reference equations should also conform to standard guidelines (5).

5.4 Bronchodilator Administration

Lung function tests such as spirometry are on occasions performed before and after the administration of an inhaled bronchodilator to measure the response to that intervention. A bronchodilator is a pharmacological agent causing the airways of the lung to dilate or become greater in diameter. Specifically, it has been proposed by the American Thoracic

Society that increases of at least 12% and 200 mL in FEV_1 or in FVC be considered to be significant (5). Bronchodilator responsiveness can be found in certain lung diseases such as asthma or chronic obstructive pulmonary disease (COPD).

5.5 Methacholine Bronchial Challenge Test

Asthma is a pulmonary condition characterized by: (*1*) airway obstruction (or narrowing) that is reversible either spontaneously or with treatment, (*2*) airway hyperresponsiveness to a variety of stimuli, and (*3*) airway inflammation (11). To assist in the diagnosis of asthma, determining the presence of reversible airway obstruction (usually to the use of a bronchodilator) or determining the presence of increased airway or bronchial responsiveness is important.

When an individual is evaluated for the possibility of asthma, baseline spirometry is first indicated. If there is presence of airways obstruction (a reduction in the ratio of FEV_1/FVC), then a bronchodilator is administered to determine the presence and extent of reversibility. If significant reversibility is present (>12% increase and a 200 ml increase in the FEV_1 or FVC) (15), then determination of bronchial responsiveness may not be necessary (4). Otherwise, the next step might be the performance of a bronchial challenge test to measure bronchial responsiveness. By far, the most commonly used nonspecific inhalation challenge agent used for such testing is methacholine.

The presence of increased bronchial responsiveness is not diagnostic of asthma but can be found in individuals with asthma. Increased bronchial responsiveness can be seen in other conditions such as smoking-induced chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), cystic fibrosis, bronchitis, and in about 5% of normal individuals (4). In addition, a few individuals with asthma may have normal bronchial responsiveness. Thus, the test for bronchial responsiveness can be useful but again is not diagnostic of any specific condition.

5.6 Lung Volume Measurement

As mentioned above (Lung volume subdivisions), the amount of air within the lungs can be represented by different volume parameters: total lung capacity, vital capacity and residual volume. Spirometry testing measures the amount of air an individual can inhale or exhale. However, even at the end of a complete exhalation, air still remains in the lung (the residual volume). Thus, spirometry is not capable of measuring all the air that comprises the total lung capacity. Knowing the total lung capacity can be useful in the evaluation of workers who may have certain lung diseases or conditions. Measurement of total lung capacity or TLC requires the direct measurement of lung volumes.

There are four methods for determining lung volumes: body plethysmography, nitrogen washout techniques, helium dilution techniques, and radiographic planimetry. Of these techniques, the one most commonly used in clinical laboratories is the body plethysmograph or the "body-box." With this method, the individual sits in an enclosed box (the size of a telephone booth) and places his or her mouth on a mouthpiece. While the individual is breathing in and out through the mouthpiece, the body-box measuring equipment senses changes in pressure surrounding the person. The resulting pressure changes are converted

to volume changes which in turn provide a measure of the total volume of air within the lungs at that time. By other calculations and breathing maneuvers, the determination of TLC can be made.

As described later in this section (Classification of Lung Function Abnormalities), the determination of a restrictive ventilatory defect requires the actual measurement of TLC as by a body plethysmograph. When the TLC as measured by one of the four methods is considered to be abnormally reduced, then a restrictive ventilatory defect is present. For an obstructive ventilatory defect, the TLC can be normal, increased or reduced.

5.7 Diffusing Capacity

Diffusing capacity of the lung (DL_{CO}) is the measurement of the transfer of carbon monoxide (CO) from inspired air to pulmonary capillary blood. This lung function test is complementary to spirometry testing in that it is a crude estimate of gas exchange and the status of the pulmonary vascular bed. Procedures for performing the test conform to standard guidelines (3). A maximum of four trials can be performed to obtain at least two values that are within 10%. The mean value of at least two acceptable tests within 10% is reported. Predicted values for DL_{CO} and the ratio of DL_{CO} to the single-breath alveolar volume (V_A) or DL/V_A are based on published predicted values (2) and are the measures of interest.

5.8 Classification of Lung Function Abnormalities

Disturbances of respiratory anatomy or physiology give characteristic patterns of abnormal lung function. A lessening of ventilatory capability can either be due to a reduction in the total capacity of the lung (restrictive pattern) or obstruction in the airways of the lung (obstructive pattern).

An obstructive ventilatory defect is defined as lessening of the respiratory system's capability to cause air to flow from the lung. Usually the total amount of air the lungs are capable of holding remains relatively stable/unchanged. It is the relationship, the ratio, of the ability to force air out of the lungs (forced expiratory volume in one second, FEV_1) relative to the maximal volume that can be exhaled (forced vital capacity or vital capacity, FVC and VC, respectively) that defines an obstructive pattern. A reduced FEV_1/VC indicates airflow limitation and suggests a reduction in the cross-sectional area of the airways or airway narrowing (5). Examples of lung diseases that can have obstructive patterns include asthma, chronic obstructive pulmonary disease (COPD) (including chronic bronchitis and emphysema), cystic fibrosis, bronchitis, bronchiolitis obliterans, and bronchiectasis.

A restrictive ventilatory defect is characterized physiologically by a reduction in total lung capacity (TLC) (5). The ratio of FEV_1/VC which when reduced defines an obstructive pattern, remains normal or can even increase. Spirometry testing which measures the vital capacity might suggest a restrictive ventilatory defect but the measurement of total lung capacity (TLC) is required to determine if a true restrictive defect is present. Examples of lung diseases that can have restrictive patterns include the pneumoconioses (asbestosis, silicosis, coal workers' pneumoconiosis), interstitial fibrosis, and sarcoidosis.

5.9 Radiographic Examination

The cornerstone of the radiologic diagnosis is the plain thoracic radiograph, or the "chest x-ray" (13). Radiographic methods record anatomic structure and the changes that can occur within these structures, such as can be present with disease. The routine views of the chest are a front view and a side view. With these two visualizations, a three-dimensional inspection of the thoracic contents and chest wall can be accomplished. When the chest x-ray is used as a screening tool, the single front view may be the only one collected (14).

Other radiographic procedures may be performed to complement the simple chest x-ray, these include: digital radiography, computed tomography (CT scans), and magnetic resonance imaging (MRI).

Digital radiography techniques offer the ability to electronically transmit and compactly store images. It is possible that in the next 25 years, use of conventional radiographic film will either disappear or become dramatically reduced.

Tomography allows the selective visualization of a specified layer of tissue, excluding all others. This selective visualization is accomplished by maintaining the "focus" between object and radiographic device for one "slice" at a time. The compilation of all the slices results in a detailed three-dimensional image. Computed tomography (CT) uses the computer to process and display the resulting three-dimensional image. High resolution CT (HRCT) scans have thinner slices which can help identify certain pathological abnormalities. CT scans are particularly helpful in the evaluation of changes within the structure of lung tissue including interstitial changes or fibrosis.

MRI, or magnetic resonance imaging, is accomplished by placing certain atomic nuclei in a magnetic field. When the nuclei are excited with a particular frequency of radio waves, they emit some of the absorbed radio wave energy as radio signals. The magnetic resonance technique allows interpretation at a chemical-physiologic level while all previous imaging techniques have permitted only anatomic inspection. Since chemical–physiologic changes may occur before actual structural changes, magnetic resonance offers the potential for earlier disease detection.

5.10 ILO Classification for Presence of Pneumonconiosis

For over 50 years, the International Labour Organization (Geneva, Switzerland) has provided guidelines for the classification of chest radiographs for the presence of pneumoconioses. The most recent updated version of this classification system was released in 1999 (15). In this classification system, each chest radiograph (single front view) is scored in different categories: technical quality, presence of small opacities (representative of pneumoconioses), large opacities, pleural changes, and other abnormalities.

The most important classification scoring for the presence of pneumoconiosis is the profusion score for small opacities. The number and concentration of the small opacities is scored using a 12-point scale and the use of standard films of four categories of small opacity concentration or profusion. The four categories for the presence of profusion of small opacities are 0, 1, 2, and 3 (0 considered to essentially without significant number of small opacities to 3 which represents the greatest number or concentration or profusion of small opacities). The film to be reviewed is compared to a standard, 22-image film set.

If the reader feels that the number and concentration of the small opacities in the film being reviewed matches exactly the profusion of small opacities in the standard film, the score for the film is then recorded.

In addition to the profusion of small opacities, scoring is done for the size and shape of the small opacities; for the size and number of large opacities; for the extent, width and presence of calcium within pleural abnormalities; and for the presence of other disease conditions such as lung cancer or heart disease.

Use of the ILO classification system allows for consistency in scoring the changes on radiographs for workers that may have pneumoconioses such as asbestosis, silicosis, or coal workers' pneumoconiosis. This classification system has been used in epidemiological surveys as well as for medical-legal determination of impairment or disability.

6 INFLAMMATORY AND FIBROTIC RESPONSES OF THE LUNG

6.1 Particle Deposition

The lung diseases that occur as a result of exposure to the inhalation of mineral dusts are determined in part by the site deposition of the particles of dust. In general, airborne particles that are in the respirable range of size (<10 micron) deposit in the tracheobronchial tree through impaction, sedimentation, interception and diffusion. The physical characteristics (length, diameter, and shape of the particles) determine the distance that the particles may travel through the tracheobronchial tree. For example, the asbestos fibers of chrysotile (serpentine) and crocidolite (amphibole) are long and narrow and can impact at the bifurcation of smaller airways such as bronchioles. Once deposited in the tracheobronchial tree or within the alveolar spaces, damage then depends on the cellular response to the presence of the dust particles.

6.2 Cellular Response of Inflammation

As discussed previously in Section 3, Lung Defenses, particles that reach the terminal airways and the alveolar spaces can be engulfed by the resident alveolar macrophages. Once these cells engulf or phagocytize the particles, these cells can produce a variety of inflammatory mediators and cell-to-cell messengers depending upon the physical-chemical characteristics of the particles themselves (16, 17). For example, alveolar macrophages can release reactive oxygen species (oxygen radicals) that can be damaging to nearby cells. These macrophages can also release mediators or factors that can lead to the recruitment and proliferation of other cell types as well as the production of protein substances that are the basis of fibrosis.

For example, macrophage-released mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), or interleukin-6 (IL-6) can lead to significant local responses in lung parenchyma and interstitium. TNF-α can lead to the recruitment of other inflammatory cells such as lymphocytes, eosinophils, and neutrophils. TNF-α can also cause the increased expression of adhesion molecules, which can result in the attraction and collection of other cell types in the region of lung injury. IL-1 and IL-6 are other inflammatory

mediators that can alter collagen synthesis in the lung, affect the balance of protein substrates in the lung acellular matrix, and can also result in the recruitment of other cell types. All of these inflammatory mediators have been found in the lavage fluids from the lungs of workers exposed to dusts such as silica, coal dust and asbestos, as well as from the lungs of animals exposed to these mineral dusts.

Other mediators released from macrophages may be more involved with the subsequent fibrosis or scarring that occurs with long-term exposure to mineral dusts. Mediators such as transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and insulinlike growth factor-1 (IGF-1) have been implicated in the recruitment and proliferation of cells involved in fibrosis such as fibroblasts. In some cases, it may be the relative proportions of these key mediators that characterizes the degree and extent of fibrotic response of the lung to the mineral dust. For example, fluids from patients' lungs with simple coal workers' pneumoconiosis (CWP) had higher concentrations of TGF-β while fluids from patients' lungs with progressive massive fibrosis (PMF) had greater concentrations of PDGF and IGF-1 (18).

In summary, particles such as asbestos fibers or coal dust or silica particles deposit in terminal airways such as respiratory bronchioles or alveolar ducts and are eaten or phagocytized by alveolar macrophages. These macrophages then release mediators that lead to inflammatory and fibrotic changes within the lung. The substances released by macrophages that may be involved include reactive oxygen species and cytokines such as interleukins (IL-1 and IL-6) as well as TNF-α, TGF-β, PDGF, and IGF-1. These mediators recruit other inflammatory cells such as lymphocytes, eosinophils, neutrophils and fibroblasts. These mediators can also damage resident cells such as the alveolar epithelial cells and endothelial cells. The activation of these recruited cells especially the fibroblasts can then lead to the production of changes within the connective tissue matrix with increased presence of collagen and resulting fibrosis.

These changes in cellular physiology, when extensive, can lead to changes in anatomy and both can be evidenced as changes in lung function.

7 MINERAL DUST-INDUCED LUNG DISEASE

7.1 Asbestos

Asbestos is a term used to describe a group of naturally occurring, fibrous magnesium silicate minerals. Asbestos is found in serpentine and amphibole mineral formations throughout the world; due to its indestructible nature and thermal insulating properties, asbestos has found many commercial applications. Asbestos has been recognized and used since ancient times in pottery, wicks for oil laps and torches, woven shrouds, and napkins or tablecloths that could be cleaned by fire (19–22). Commercial mining of asbestos began in the late 19th Century. The first asbestos textile mill in the United States began production in approximately 1896. Commercial asbestos production also began in Russia at approximately the same time. Large scale use of asbestos came with industrialization, and in particular, mass production of the steam engine which required heat resistant insulating materials for packing and seals (20–24). The production of asbestos increased rapidly during the mid 1900's as it found use in over 3000 applications.

Approximately twenty years after the start of commercial asbestos production, the first reports of pulmonary fibrosis occurred among asbestos textile workers in France (17). The considerable attention drawn to asbestos in modern times surrounds its ubiquitous use and diverse nature of attributable human health effects. Asbestos related diseases and conditions include asbestosis, small airways disease, pleural plaques, lung cancer, cancer of the larynx, cancers of the gastrointestinal tract, mesothelioma, and others (see Table 4.1) (22).

These diverse, significant health outcomes, in the context of the modern medical and legal environments, have made asbestos related respiratory disease one of the most significant occupational health issues of the 20th Century.

7.1.1 Mineralogy of Asbestos

From a mineralogical perspective, the term asbestos refers to a specific pattern of crystal formation (called asbestiform crystalline habit) producing long thin fibers with high aspect

Table 4.1. Asbestos-related Diseases and Conditions[a,b]

Pathology	Organ(s) Affected	Diseases/Condition
Nonmalignant	Lungs	**Asbestosis** (diffuse interstitial fibrosis)
		Small airway disease[c] (fibrosis limited to the peri-bronchiolar region)
		Chronic airways disease[d]
	Pleura	**Pleural plaques**
		Viscero-parietal reactions, including benign pleural effusion, diffuse pleural fibrosis and rounded atelectasis
	Skin	Asbestos corns[e]
Malignant	Lungs	**Lung cancer** (all cell types)
		Cancer of larynx
	Pleura	**Mesothelioma of pleura**
	Other mesothelium-lined cavities	**Mesothelioma of the peritoneum**, pericardium and scrotum (in decreasing frequency of occurrence)
	Gastrointestinal tract[f]	Cancer of stomach, oesaphagus, colon, rectum
	Others[f]	Ovary, gall bladder, bile ducts, pancreas, kidney

[a]Reprinted with permission from Ref. 22. Copyright© International Labour Organization, 1998. Other sources are Refs 25–30.

[b]The diseases or conditions indicated in bold type are those most frequently encountered and the ones for which a causal relationship is well established and/or generally recognized.

[c]Fibrosis in the walls of the small airways of the lung (including the membranous and respiratory bronchioles) is thought to represent the early lung parenchymal response to retained asbestos (25) which will progress to asbestosis if exposure continues and/or is heavy, but if exposure is limited or light, the lung response may be limited to these areas (26).

[d]Included are bronchitis, chronic obstructive pulmonary disease (COPD) and emphysema. All have been shown to be associated with work in dusty environments. The evidence for causality is reviewed in ref. 27.

[e]Related to direct handling of asbestos and of historical rather than current interest.

[f]Data not consistent from all studies (27) some of the highest risks were reported in a cohort of over 17,000 American and Canadian asbestos insulation workers (29) followed from January 1, 1967 to December 31, 1986 in whom exposure had been particularly heavy.

ratios (fiber length divided by width), high tensile strength, and flexibility. Although many minerals can crystallize in an asbestiform habit, only six have been of industrial use and commonly referred to as asbestos (31). These include the serpentine mineral chrysotile and the amphibole minerals crocidolite, amosite, anthophyllite, tremolite, and actinolite (Table 4.2).

Chrysotile accounts for approximately 95% of the asbestos used in the United States (24). These asbestos minerals can also have nonasbestiform crystalline habits as noted in Table 4.2. Amphibole minerals and, to a lesser degree, serpentine minerals occur widely distributed throughout the earth's crust in many igneous or metamorphic rocks. However, only in rare instances do these mineralogical occurrences contain sufficient quantities of asbestos to be economically suited to mining.

7.1.2 Production and Use of Asbestos

The world production of asbestos has increased from the late 19th Century until about 1976 with the production of approximately 5,708,000 tons in that year. Production dropped during the 1980s and 1990s as the adverse health effects of asbestos exposure became a matter of increasing public concern (21, 22). Approximately 2.7 million tons of asbestos were produced during 1994 and world mine producers, in order of output, included Russia, Canada, Kazakhstan, China, and Brazil (23). The United States asbestos consumption was less than 27,000 metric tons in 1994. Chrysotile accounts for approximately 95% of world production and a key market for this fibrous mineral is the production of asbestos cement (21, 23). Chrysotile is produced primarily in Russia, Canada, Swaziland, and Zimbabwe with minor production plants in the United States (California), Australia, Cyprus, Italy, Brazil, and China. Crocidolite is produced in South Africa and in Australia (now discontinued) and Bolivia. Amosite was produced uniquely in South Africa. Anthophyllite was produced only in Finland.

The physical properties of asbestos that have resulted in its widespread use include (*1*) good insulator (*2*) incombustibility, (*3*) flexibility, (*4*) high tensile strength, and (*5*) resistance to corrosion. By virtue of these properties, asbestos has found many industrial ap-

Table 4.2. Classification of Asbestos Minerals

Asbestos	Nonasbestiform Analogs	Chemical Formula
	Serpentine	
Chrysotile	Antigorite, Lizardite	$Mg_3(Si_2O_5)(OH)_4$
	Amphibole	
Crocidolite	Riebeckite	$Na_2Fe_5(Si_8O_{22})(OH)_2$
Amosite	Cummingtonite-Grunerite	$(Fe, Mg)_7(Si_8O_{22})(OH)_2$
Anthophyllite	Anthophyllite	$(Mg, Fe)_7(Si_8O_{22})(OH)_2$
Tremolite	Tremolite	$Ca_2Mg_5(Si_8O_{22})(OH)_2$
Actinolite	Actinolite	$Ca_2(Mg, Fe)_5(Si_8O_{22})(OH)_2$

plications including (*1*) use in cement products including pipes and shingles, (*2*) vinyl floor tile, (*3*) paper for insulation and filtering, (*4*) friction materials for brakes and clutches, (*5*) textile products including yarn, felt, rope, wicks, and others, (*6*) paints and coatings, and (*7*) spray-on materials for fireproofing, and thermal or acoustical insulation. The shipbuilding, automobile, railroad, and construction industries have been among the larger asbestos users nationally (21, 22, 32). A 1995 list of industrial applications for asbestos shows some redistribution in uses including asbestos cement (84%), friction materials (10%), textiles (3%), seals and gaskets (2%), and other uses (1%) (22).

7.1.3 Occupational Exposures and Exposure Limits

Most asbestos exposures are of occupational origin, particularly in industrialized nations, and the list of occupations with the potential for asbestos exposures is quite large. Primary asbestos exposures occur through direct asbestos production in mining and milling operations. Most asbestos mines are open-pit operations (chrysotile) with some underground mining (amphiboles). Workers are exposed as asbestos containing ores are removed, fragmented and screened. The milling process involves occupational exposures as the asbestos containing materials are further concentrated by crushing and screening, washing/drying, cyclone separation, sorting into commercial grades, and packaging for distribution. The handling of waste ores and transportation of asbestos products at mine and milling operations is also a source of occupational exposure (21, 22, 33). Asbestos exposures can also occur to workers involved in mining stone or other mineral products through asbestos contamination of parent ores (33, 34).

Secondary asbestos exposures occur in a wide range of industrial settings through the production/application of asbestos containing products or by contact with these materials. Workers have used raw asbestos in packing and lagging (e.g., steam engines and boilers), in spraying materials onto ventilation ducts and structural surfaces in buildings, and in shipbuilding. In the manufacture of asbestos cement and asbestos tiles, exposures can occur through the opening of bags of asbestos, mixing these materials into slurries, and in the machining of the end products. In the manufacture of asbestos yarns and textile products, exposures can occur by preparing, blending, carding, spinning, weaving, and calendaring the fiber. In addition, exposure to asbestos can occur in the construction industry with the application of asbestos-containing insulation materials and the cutting, drilling, and sanding of asbestos-containing construction materials. Maintenance and construction workers, including electricians, welders, pipefitters, carpenters, and others are exposed by working directly with asbestos containing materials or by working in proximity to other construction operations involving asbestos. Asbestos exposure can also occur in office settings through uncontrolled maintenance/repair of building surfaces or structures containing asbestos materials (35). Significant levels of domestic asbestos exposure have also been reported to occur through materials adhered to work clothes when they are taken home for laundry.

Historically, occupational exposures to asbestos are reported to have been as high as 100 fibers per cubic centimeter (fibers/cm^3); although, in most occupational settings, exposures were commonly between 2 to 20 fibers/cm^3 prior to occupational exposure control. Occupational disease resulting from asbestos exposures became evident during the early 1950s. During the 1960s and 1970s, large epidemiological studies confirmed clinical ob-

servations associating asbestos exposure with asbestosis and lung cancer (21–23, 32). Occupational asbestos exposures have been substantially reduced since regulatory enforcement began during the early 1970s. In the United States, the Occupational Safety and Health Administration (OSHA), enforces a Permissible Exposure Limit (PEL) for asbestos in general industry of 0.1 fibers/cm^3 as a time-weighted average (TWA). (For regulatory purposes, asbestos is defined to be chrysotile, amosite, crocidolite, tremolite, anthophyllite, and actinolite. Fibers, measured at the microscopic level, are defined as a particulate form of asbestos 5 microns or longer with a length-to diameter ratio of at least 3 to 1). The Mine Safety and Health Administration (MSHA) exposure limit for asbestos as a TWA is 2 fibers/cm^3. The National Institute for Occupational Safety and Health (NIOSH), Recommended Exposure Limit (REL) and the American Conference of Governmental Industrial Hygienists (ACGIH), Threshold Limit Value (TLV) are also 0.1 fibers/cm^3 as a TWA for all forms of asbestos. In modern industrial settings, the occupational exposure limits/criteria and the use of engineering control methods for asbestos containing dusts have been effective in reducing asbestos exposures (36–39).

7.1.4 Asbestos-Related Respiratory Disease

The primary toxic effects of asbestos on the respiratory system involve the ability of asbestos fibers to induce a fibrotic pulmonary response and cancers of the lung and pleural spaces (48). The level of asbestos exposure, fiber type, fiber dimensions, durability, and fiber surface properties influence the toxicity, fibrogenicity, and carcinogenicity. Inhaled asbestos fibers become aligned with the airstream and can penetrate to the lower, gas exchange region of the lung depending on fiber diameter. Asbestos fibers with diameters less than 5 microns have a greater ability to penetrate to the nonciliated regions of the lung where they can exert the greatest toxic effect. Particles deposited in the major airways are cleared by the action of mucus secretions/ciliated cells and are transported out of the respiratory system. Smaller diameter fibers, deposited beyond the major airways are engulfed by alveolar macrophages and can remain in the lungs for longer periods of time. There is limited clearance of asbestos fibers deposited in this region of the lung, and when clearance occurs, it is through the lung lymphatics to the interstitium, the pleural cavities, and the lymph nodes. Often the fibers penetrating to the non-ciliated regions of the lung are partially engulfed, or coated, by several alveolar macrophages forming an asbestos body, a characteristic marker of asbestos exposure (see Fig. 4.4).

Asbestos fibers retained in the lung usually invoke an inflammatory reaction with an accumulation of white blood cells followed by a macrophagic alveolitis. The subsequent release of fibronectin, chemotactic factors, growth factors, and superoxide ion release results in the proliferation of alveolar, epithelial, endothelial, and interstitial cells (21, 22, 32) (see Section: Cellular Response of Inflammation) The asbestos-related respiratory diseases and conditions described below include pleural disease, asbestosis, lung cancer, and mesothelioma.

7.1.4.1 Asbestos-Related Pleural Disease. Pleural disease is the most common manifestation of asbestos exposure and can present as benign pleurisy with effusions (collection of fluid), pleural plaques, diffuse pleural thickening, and rounded atelectasis. Benign pleu-

Figure 4.4. An asbestos body: an asbestos fiber coated by alveolar macrophages.

risy is defined by radiographic or thoracentesis (aspiration of fluid through the chest wall) confirmation of effusion, the absence of other causes of effusion, asbestos exposure, and the absence of tumor with clinical follow-up of at least three years (41). Benign pleurisy does not have a clear pathology although contact of asbestos fibers and the pleura is likely the initiating event. The latency period is generally less than 20 years and it is often the first manifestation of asbestos-related effects. Although it may precede other manifestations, it is not believed to be a precursor of other asbestos diseases. Benign pleurisy follows one of several courses including complete, painless regression; painful regression with minimal or no pleural scar; effusion of single or multiple instances, and, in limited instances, diffuse pleural thickening or rounded atelectasis (21–23).

Pleural plaques are raised, white, irregular lesions of hyalin fibrosis covered with mesothelium and found on the parietal (on the chest wall) pleura or on the diaphragm (22). Pleural plaques are most frequently a result of asbestos exposure and considered to be a good marker for such exposure. The occurrence and progression of pleural plaques appears in direct relation to amphibole asbestos exposures as contrasted to chrysotile asbestos (21). Pleural plaques are believed to be a local reaction to asbestos fibers reaching the pleural spaces during clearance from the lungs. Pleural plaques are largely asymptomatic in association with asbestosis; however, there is some evidence to suggest that pleural plaques may be associated with decrements in lung function as determined by spirometry (42, 43). The latency period between exposure and radiographic appearance of pleural plaques is approximately 20 years. It is possible to recognize plaques earlier than this, in much less well-defined stages, with the CT scan.

In contrast to pleural plaques, diffuse pleural thickening, also called pachypleuritis, is a fibrotic disease of the visceral (on the lung surface) pleura. Although not specific to asbestos exposure, diffuse pleural thickening is believed to result from fibers deposited in

the parenchymal (interstitial) subpleural areas. Diffuse pleural thickening is attributed to the combined effects of large pleural plaques, the extension of subpleural fibrosis to the visceral pleura, and scarring from exudative (fluid forming) benign pleurisy. Due to the extent of diffuse pleural thickening resulting in restriction of the lungs to expand, dyspnea (shortness of breath) on exertion is a common symptom of this condition as is dry cough. If extensive and bilateral, lung function effects can be severe to the point of causing respiratory insufficiency and failure in some instances. Diffuse pleural thickening can be identified by chest radiograph or by CT scan, unilaterally or bilaterally. By nature of its location, diffuse pleural thickening diagnosis is facilitated by the CT scan. Since diffuse pleural thickening has etiologies other than asbestos exposure, it is not a good exposure marker as pleural plaques, and the elimination of the other disease causes should be part of the initial clinical assessment.

Rounded atelectasis, a form of asbestos-induced pleural disease, is caused by scarring of the parietal and visceral pleura, thickening of the interlobar fissure and adjacent lung tissue, and, with retraction of the scar, trapping and collapse of adjacent lung tissue. This form of pleural disease is less common than other forms. Rounded atelectasis is usually asymptomatic and detected by chest radiography as a pleural-based opacity often resembling a tumor. With the CT scan, the true nature of rounded atelectasis can often be resolved without the need for surgery. Chest pain in the area of formation is occasionally the only presenting symptom. Rounded atelectasis is usually a late condition occurring long after other pleural changes have been noted (21–23).

7.1.4.2 Asbestosis. Asbestosis is a fibrotic disease of the lungs caused by the inhalation, retention, and pulmonary reaction to asbestos fibers (44). The fibrotic changes, which give rise to asbestosis, are the result of an inflammatory process caused by asbestos fibers retained in the lung. This fibrosis is diffuse, interstitial, and tends to involve primarily the lower lobes and subpleural regions of the lung. Early lesions are characterized by discrete areas of fibrosis in the regions around the respiratory brohchioles. In advanced cases, the normal lung architecture is obliterated producing a honeycomb pattern. Fibrosis of the adjacent pleura is often seen (21). The histologic features of asbestosis do not distinguish it from interstitial fibrosis due to other fibrogenic agents; however, the presence of asbestos bodies or asbestos fibers in the lung are markers for asbestos exposure. The extent of the lung fibrosis generally relates to the measured asbestos fiber burden in the lungs.

The two most significant clinical findings of asbestosis are dyspnea on exertion and end-inspiratory crackles or rales on auscultation of the chest. Dyspnea is the earliest and most consistently reported symptom. Other symptoms can include a dry cough and chest tightness.

The chest radiograph has been one of the most important diagnostic tools for determining the presence of asbestosis. The radiographic appearance of asbestosis is characterized by irregular opacities in the lower two-thirds of the fields for both lungs. When densely profuse, these opacities can obscure the cardiac outline and the dome of the diaphragm. The reduction of lung volumes is radiographically evident (see Fig. 4.5).

The diagnosis of asbestosis is based upon several separate criteria (45). This diagnosis of asbestosis by radiography has been facilitated by the International Classification of Radiographs of the Pneumoconioses established by the International Labor Office (ILO)

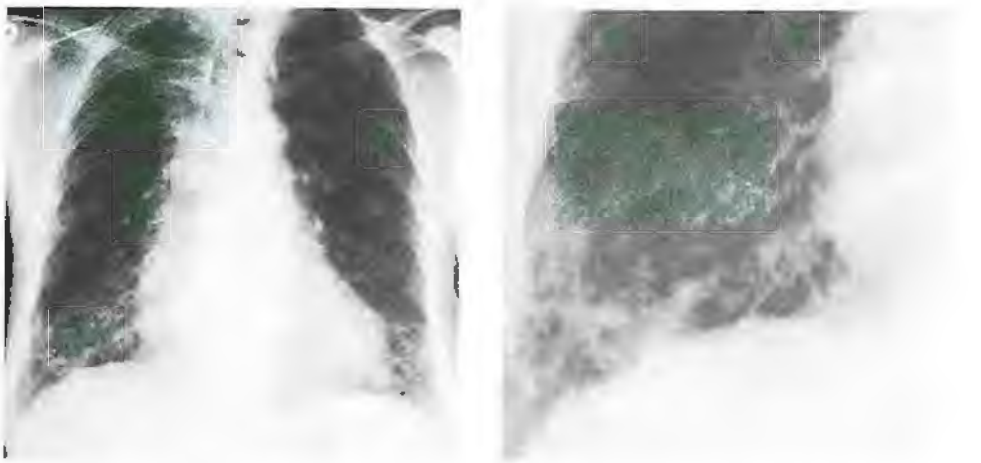

Figure 4.5. A chest radiograph of asbestosis with a close-up view of the right lower lung.

(15). The use of CT scanning and high resolution computer tomography (HRCT) have greatly increased the sensitivity for detecting asbestos-related lesions. Although, at present, no standardized reading method has been developed for HRCT. Cigarette smokers and ex-smokers have a higher prevalence of asbestos-related radiologic lesions than nonsmokers in studies of British shipyard workers. Since smokers without dust exposure have few irregular opacities on the chest radiograph, this likely reflects the impaired lung dust clearance mechanisms due to smoking (22, 23, 46). The combination of smoking and exposure has a synergistic effect.

Interstitial lung fibrosis due to asbestos is generally associated with a restrictive pulmonary function pattern. Characteristic features include reduced lung volumes, particularly vital capacity (VC); the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) is usually preserved. Reduced lung compliance and reduced diffusing capacity are of note. In addition to spirometry, bronchoalveolar lavage (washing out) is being used more frequently as a clinical tool in the investigation of asbestos related diseases of the lung (22, 23, 32).

Medical interventions in cases of asbestosis occur on initial diagnosis, in follow-up evaluations, in the treatment of respiratory infections complicating the disease, and in the treatment of hypoxemia and heart failure associated with advanced disease stages. Other forms of support include smoking cessation programs, if needed, treatment of cough symptoms or in treatment to prevent viral or pneumococcal infections. Asbestosis has no established regimen of treatment and, due to the risks of lung cancer and mesothelioma, periodic chest radiographs are recommended. Continued work in environments with asbestos exposures should be prevented; however, disease progression is noted in some cases following exposure cessation (21–23).

7.1.4.3 Lung Cancer. During the 1930s, publication of a number of clinical case reports from the United Kingdom, Germany, and the United States first suggested a possible

association between lung cancer and asbestos exposure. Today there is substantial evidence to demonstrate an association between lung cancer and asbestos exposure including exposure to all types of asbestos fibers (22, 23, 47–49). All histologic forms of lung cancer are seen in asbestos-exposed workers and the pathology of asbestos-related cancers is not distinct in type, nature, or location within the lung. There is an approximate fivefold increase in lung cancer risk for workers exposed to asbestos and lung cancer rates peak at approximately 30 years latency. Current knowledge on the pathogenesis of asbestos related cancers in incomplete. The increased risk of lung cancer in asbestos exposed smokers increases exponentially. There is some controversy that the increased risk for lung cancer exists only for those individuals where asbestosis (the presence of fibrosis related to asbestos exposure) is present (50). Others contend that sufficient, prolonged exposure to asbestos even without the development of asbestosis is associated with increased risk for lung cancer (57).

The clinical presentation of asbestos-related lung tumors is similar to that of lung tumors caused by other carcinogens, excluding the possible associated symptoms of lung fibrosis due to asbestosis. The major symptoms in lung cancer patients can include cough, dyspnea, chest pain, hemoptysis, recurrent bouts of pneumonia, localized wheezing and others. Lung cancer in asbestos exposed workers presents as a mass lesion on the chest radiograph and is indistinguishable from lung cancers associated with other carcinogens. The CT scan increases the potential for early detection of lung cancers when applied to high risk groups. The diagnosis of lung cancer is based on histopathologic grounds with cytology or tissue samples; the histologic changes are not specific to asbestos-related cancers.

The overall lung cancer survival rates remains poor with only an 8 to 10% five-year survival rate. There have been recent advances in chemotherapy, surgery, and in the understanding of the molecular pathogenesis of lung cancer. As a result of the latter, gene therapy approaches show much promise (21–23, 32).

7.1.4.4 Malignant Mesothelioma. Mesothelioma is a rare malignant tumor arising largely in the pleura and to lesser extent from the peritoneum (lining of the abdomen). In early stages of disease, mesothelioma presents as small grayish nodules on the visceral and parietal pleura that coalesce and form larger tumor masses. The tumor develops by direct extension, forming large masses that can invade adjacent structures including the chest wall, lung parenchyma, and the diaphragm (21, 23).

Malignant mesothelioma is relatively rare with an incidence of approximately two cases per million in the general population of North America. The majority of malignant mesothelioma cases have a history of exposure to asbestos through occupational or environmental sources. No other associated exposure has been found. This asbestos exposure history may be quite brief. Asbestos-exposed populations have mesothelioma incidence rates five to twentyfold higher than the general population. Wagner and colleagues (52) were the first to report a case series of mesothelioma among individuals from the crocidolite mining region and asbestos factories in South Africa. Since this report, the association between asbestos exposure and mesothelioma has been confirmed repeatedly (21–23, 52).

All types of asbestos fibers have produced mesothelioma. Amphibole asbestos fibers are considered to be the cause of most cases of mesothelioma. Mesothelioma cases have also been attributed to chrysotile exposures but much less frequently. The reasons for the

increased prevalence of mesothelioma from amphibole asbestos exposures is believed associated with the geometric properties of amphibole fibers, favoring deeper penetration into the lung, and the increased resistance of amphibole fibers to degradation, favoring persistence in lung tissue. It is also accepted that mesothelioma has no association with cigarette smoking. A characteristic of mesothelioma is a long latency period of approximately 20 to 50 years (21).

Malignant mesotheliomas are diagnosed primarily in males at ages from 50 to 70 years. The most common clinical symptom is chest pain. Cough and dyspnea are also common symptoms due largely to pleural effusions. Weight loss, fever, and general malaise often present in later stages of disease. In addition to being locally invasive, approximately 50 to 80% of malignant mesotheliomas are metastatic. The radiologic findings in mesothelioma typically reveal a thick pleural peel along the lateral chest wall with extension to the apex. There is usually pleural effusion and this is a common presenting sign. Most of these changes can be detected by plain radiography; however, the use of CT and HRCT scans add sensitivity to better evaluate the extent of the tumor progression. Biopsy is usually needed to establish a firm diagnosis of malignant mesothelioma. The various forms of treatment for malignant mesothelioma can include surgery, radiotherapy, chemotherapy, and more recently immunotherapy and cytokine therapy. The clinical course of disease is usually rapid and survival is limited; the treatments generally provide only a few months of life extension. In most instanees, medical intervention remains largely supportive in nature. Death by cardiorespiratory failure usually occurs within 2 years from diagnosis (21–23).

7.2 Other Silicate Minerals

Two of the most abundant elements on earth are silicon and oxygen; the combination of these two produces silicon dioxide (SiO_2). Silica or silicon dioxide (SiO_2) exists in both crystalline and amorphous forms. Amorphous (noncrystalline) silica occurs in natural glasses (e.g., volcanic tuff) as well as synthetic glasses such as mineral wool. Amorphous silica is characterized by a random, nonrepeating organization of silicon dioxide molecules. Crystalline forms of silicon dioxide are characterized by an organized, repeating pattern of molecules in a three-dimensional array commonly known as quartz (see 7.4 Silica-Crystalline). Crystalline forms of silica are produced by increased pressure and heat during formation in the earth's crust. Alpha-quartz is the most common, naturally occurring form of crystalline silica. Much of the silicon dioxide present in the earth's crust is combined with other elements to form silicate minerals. These silicate minerals contain the silicon dioxide tetrahedron in combination with various cations or anions including aluminum (Al), calcium (Ca), fluorine (Fl), hydroxide (OH), iron (Fe), magnesium, (Mg), sodium (Na) and others. Collectively, the silicates comprise abut 25% of known minerals and constitute over 90% of the earth's crust (53–55).

A wide variety of silicate minerals in addition to asbestos (chrysotile, crocidolite, amosite, anthophyllite, tremolite, and actinolite) and crystalline silica (quartz, cristobalite, and tridymite) can cause pneumoconiosis, cancers of the respiratory system, and other respiratory health problems. Other minerals, described in this section, can give rise to pulmonary responses, including radiographic changes, but are seldom associated with impairment and

respiratory disability. Additionally, many mining, construction, and manufacturing materials to which workers are exposed contain a mixture of silicates, often including crystalline silica, in the form of quartz or cristobalite; this combination of mineral constituents often presents a mixture of respiratory health effects caused by specific silicate minerals. The following discussions present some of the common, commercial silicate minerals according to their mineral habitat (fibrous and nonfibrous) and respiratory health effects. Silicate minerals commonly associated with fibrous contaminants are also discussed (53–56).

7.2.1 Fibrous Silicates

7.2.1.1 Attapulgite and Sepiolite. Attapulgite [$(Mg, Al)_2Si_4O_{10}(OH) \cdot 4H_2O$] and sepiolite are the commercial varieties of palygorskites, fibrous, crystalline magnesium–aluminum clays that can contain varying amounts of aluminum, magnesium, and iron. These silicates have a unique chain structure producing characteristic colloidal and absorptive properties, and as a result have a variety of industrial applications. Attapulgite is mined predominantly in the southeastern United States (Georgia and Florida). Spain is the predominant producer of sepiolite. Both are used in drilling muds, as paint thickeners, and as insulation substitutes for asbestos. Attapulgite and sepiolite are known as fuller's earth constituents as derived from use in finishing and thickening (or fulling) wool. Attapulgite is also used as an anti-diarrheal agent and as an absorbent in pet litter. Sepiolite is used as a material in cigarette filters (53, 54).

Studies on the carcinogenicity of attapulgite have resulted in variable results and this has been largely attributed to differences in the geological origins and mineralogical properties of attapulgite. Attapulgite from some geological deposits is reported to cause lung cancer and fibrosis on intrapleural injection and inhalation studies. Long attapulgite fibers have been reported to cause mesothelioma on intrapleural injection into rats; while short fibers (less than 4 microns in length) have not produced mesothelioma. There is one case report of attapulgite causing pulmonary fibrosis in a mining engineer exposed for over 2 years. A mortality study of approximately 2,300 workers, exposed to attapulgite mining and milling for one month or longer, showed a slight but significant increase in lung cancer; nonmalignant respiratory disease was not increased in this study (57).

7.2.1.2 Wollastonite. Wollastonite is a naturally occurring monocalcium silicate with a predominant acicular (or needlelike) crystalline habit with common fibers aspect ratios between 3 and 20. Wollastonite occurs in deposits throughout the world; although, the largest deposits are in the United States, Mexico, and Finland. Wollastonite is used in ceramics, in paint and bonding cements, as a substitute for asbestos in brake linings, wallboards, insulating materials, plastics, and fiberglass yarn (53–56).

Long term animal studies of wollastonite indicate low carcinogenic and fibrogenic potentials. These studies show that wollastonite fibers induced an alveolar macrophage response that resolves on exposure cessation. Wollastonite has been found to activate serum complement and increase pulmonary macrophage chemotaxis. Human morbidity studies of 103 wollastonite miners in New York suggest no significant relationship between exposure and pulmonary function or radiographic changes. A study of 46 Finnish wollastonite miners showed some mild profusion of irregular opacities (14 workers) and bilateral

pleural thickening (13 workers); airborne fiber concentrations were high with a range from 1 to 63 fibers/cc and there was also a potential for exposures to crystalline silica. Wollastonite appears to have a relative low toxicity but limited evidence suggests some potential for pleural and interstitial changes on high levels of exposure (22, 54–59).

7.2.1.3 Zeolites. Zeolites are a group of hydrated aluminum silicates with exchangeable cations. Approximately 40 different zeolite species have been identified. The zeolites contain large pores, filled with water, which can be released on heating to temperatures of 200°C. The term zeolite is derived from the Greek word meaning boiling stone. Natural zeolites can occur in both fibrous and nonfibrous crystalline habits. The fibrous zeolite minerals, erionite and mordenite, are crystalline structures that can be cleaved into long thin, respirable fibers with high aspect ratios. In the United States, the main deposits of zeolites occur in the Western Intermountain regions, especially in the Great Basin (including Nevada and portions of Utah and neighboring states). Currently there is almost no commercial mining of zeolites and the zeolite currently used in industrial applications is produced synthetically in nonfibrous form (54–56).

Zeolites have several important commercial properties including reversible selective adsorption and ion-exchange capabilities. These properties account for much of the industrial application of the synthetic form of zeolites. The mineral is used in the wastewater treatment, petrochemical, and water filtration industries. Zeolites are also used in animal litter, as dietary supplement in animal feeds, and in certain cements (54).

The nonfibrous, synthetic forms of zeolite are not considered to be fibrogenic or carcinogenic. In contrast, the natural, fibrous forms of zeolites are fibrogenic and carcinogenic as determined by both animal and human data. The fibrous zeolite erionite has been identified as the causal agent in the increased incidence of malignant mesothelioma in the Turkish villages of Tuzkoy and Karain, with an incidence of pleural and peritoneal mesotheliomas approximately 1000 times higher than the general population. Villagers were highly exposed as they carved homes into volcanic tuffs containing fibrous erionite. The fibrous zeolite mineral erionite should be handled according to all health and safety guidelines for asbestos (54–56).

7.2.2 Minerals with the Potential for Fiber Contamination

7.2.2.1 Vermiculite. Vermiculite is the geological name for a group of nonfibrous, hydrated, ferromagnesium aluminum silicates. Vermiculite has the unique characteristic of expanding many times its original size on heating. Heat converts the water, present in the spaces between the laminar mineral plates, to steam forcing the thin, flexible plates apart into an expanded, wormlike configuration. The first significant domestic deposit of vermiculite was found in 1916 near Libby, Montana and commercial production began in 1921. In the United States, commercial quantities of vermiculite are also found South Carolina and Virginia. Outside the United States, vermiculite is also mined in Phalaborwa, South Africa, and Transvall. Vermiculite, in its expanded form, is used as insulation, as a carrier for fertilizers, herbicides, and pesticides, as a soil conditioner, as an aggregate and filler for concrete and gypsum, and in water purification. Pure vermiculite is a silicate mineral considered to be a particulate or particle not classified (PNOC) without significant

pneumoconotic or carcinogenic potential. However, certain vermiculite deposits can be contaminated with amphibole asbestos fibers, thereby creating occupational exposure hazards on mining and processing. Ore from the vermiculite deposits near Libby, Montana contains actinolite and tremolite asbestos. Ore from deposits in Virginia has also been shown to contain actinolite asbestos; while, some of the vermiculite deposits in South Africa contain anthophyllite asbestos. The presence of asbestos minerals in the vermiculite presents substantially increased exposure hazards for workers. Routine monitoring of the vermiculite ores for fiber contamination is required to prevent asbestos exposures.

7.2.2.2 Talc. Talc is a layered, hydrated magnesium silicate with a chemical composition of $Mg_3Si_4O_{10}(OH)_2$. It can occur in platy, granular, and fibrous forms and occasionally as mixtures of the three forms. Commercial quantities of talc are found in several different states with the majority of commercial production from mines in New York, California, Texas, and Vermont. Outside of the United States, the major producers of talc include Australia, Austria, China, and France. Commercial talc often contains other mineral contaminants including crystalline silica as well as amphibole and serpentine forms of asbestos (54). Talc has a wide range of uses and is part of formulations for paint, paper, cosmetics, ceramics, textile materials, roofing products, rubber, fire extinguishing powders, water filtration agents, insecticides, and others. Over 500 different products are sold under the name talc and the worldwide production of talc is about 5 to 6 million tons on an annual basis (53–56).

Talc is considered to have pneumoconotic potential independent of asbestos and crystalline silica contamination. Workers exposed to the nonasbestiform varieties of talc have developed lung fibrosis. Epidemiologic studies of talc miners and millers in upstate New York revealed a progressive pneumoconiosis in older workers, disabling them with decreased vital capacity, parenchymal opacities, and pleural fibrosis. The upstate New York talc mines are contaminated with tremolite and anthophyllite (60–63). Studies of Vermont talc workers, mining ore deposits without significant asbestos and crystalline silica contamination, found evidence of pneumoconiosis on chest radiographs that correlated with exposure but not smoking (64). Some of the earlier studies of talc miners and millers suggested an association between exposure and bronchogenic carcinoma (60–63). Although, more recent studies on miners and millers working in talc deposits free of asbestos and crystalline silica have not substantiated these findings. In a study of 389 workers exposed to nonasbestiform talc, Wergeland did not observe an increase in deaths from lung cancer (65). As with vermiculite, routine monitoring of talc ore deposits is recommended to detect and prevent exposures to asbestos present as ore contaminants.

7.2.2.3 Metal Ore Deposits. Serpentine and amphibole asbestos can be present as inclusions in the ore deposits of many different metal or mineral ores including copper, gold, lead, silver, tungsten, zinc, and traprock. Careful mineralogical assessment of the ores prior to mining and milling is recommended to help prevent overexposures to asbestos minerals (54).

7.2.3 Nonfibrous Silicates

7.2.3.1 Bentonite. Bentonite is a commercial term for a group of clays formed by crystallization of vitreous volcanic ashes deposited in aqueous environments. Bentonite defines

clays that contain large percentages of sodium montmorillonite or beidelite. Bentonite takes its name from the clays found at Fort Benton, Wyoming. Within the United States, bentonite is produced in approximately 12 states. Bentonite clays are taken from open pit mines, ground, dried in kilns, and bagged for shipment. Bentonite is used in drilling muds, as catalysts in petroleum refining, as a foundry sand bond, as a filler in paints, in carbonless copy paper, in filtering agents for wine, water, or other liquids, in pharmaceuticals and cosmetics, as a component in animal feeds, and others. Pneumoconiosis has been documented among bentonite miners and millers although this is believed to be due to crystalline silica present in the clays as cristobalite (54, 56).

7.2.3.2 Mica. Mica refers to a family of nonfibrous silicate minerals occurring as complex hydrated aluminum silicates having a platy structure similar to that of talc. Micas are associated with the alkaline metals of iron or magnesium. Important mica groups include the muscovites, phlogopite, lepidolites, and biotites. The only mica groups used commercially include muscovite and phlogopite. Mica was used historically in shades for oil lamps and in windows for stoves. Continued uses include liners for steam boilers, in optical instruments, as artificial snow and flocking agents for Christmas decorations, in roofing materials, in drilling muds, in asphalt, as an electrical insulator, in ceiling tiles, and in wallboard joint cements. Epidemiologic studies of mica workers demonstrate an association with pneumoconiosis. In a study of mica workers in North Carolina, 10 of 57 workers grinding mica free of crystalline silica had radiographs consistent with pneumoconiosis. Symptoms of cough and dyspnea were identified among workers consistent with radiographic evidence of pneumoconiosis. Other human epidemiologic studies support the association between mica exposures and pneumoconiosis (46, 47, 50).

7.2.3.3 Diatomaceous Earth. Diatomaceous earth is comprised of the solidified remains of skeletons of diatoms (a unicellular algae) deposited millions of years ago. The diatom has a skeleton made of silicon dioxide. In nature, diatomite is largely an amorphous, nonfibrous silicate. For industrial applications, diatomite is calcined at approximately 800 to 1000°C producing crystalline silica in the form of quartz and cristobalite. Natural diatomite usually contains approximately 1% or less of crystalline silica; following calcining, the crystalline silica content can increase to approximately 90%. Diatomaceous earth finds industrial application based on its insulating and adsorbent properties. It is used in the lining of molds in foundries, in abrasive lubricants, and as filtering agents, in pottery glazes, and other uses. High exposures to cristobalite have been described among workers in diatomaceous earth processing mills. Exposed workers may develop lung changes involving simple or complicated pneumoconiosis. The pneumoconioses observed among diatomaceous earth workers resembles that from crystalline silica. Workers are also at increased risk for lung cancer related to cumulative exposures to crystalline silica (22, 54–56).

7.2.3.4 Kaolin. Kaolin is a nonfibrous hydrated aluminum silicate referred to as China clay. Kaolin belongs to a family of silicate minerals termed the phyllosilicates based on the platy or flaky mineral habit. Kaolin [$Al_2Si_2O_5(OH)_4$], as a clay, does not have an exact chemical composition, but is comprised primarily of kaolinite with minute and variable quantities of metal oxides that can include iron and titanium. Crystalline silica is also an

ancillary mineral contaminant in some kaolin deposits. The mining of sedimentary kaolin deposits is by open-pit methods using high pressure water jets to remove the clay materials. This wet mining technique does not generate high dust concentrations. By contrast, workers are exposed to higher dust levels during subsequent drying, processing, and bagging of the kaolin mine slurry. Some kaolin is calcined by heating to temperatures of 1000°C and this can increase the crystalline silica content. Kaolin has many industrial applications. It is used in paper products, ceramics, inks, paints, adhesives, insecticides, medicines, cosmetics, crayons, detergents, absorbents, cements, fertilizers, plastics, and rubber products.

Workers exposed to kaolin clays can develop pneumoconiosis. Kaolin workers show radiographic evidence of pneumoconiosis, with reductions in pulmonary function including FVC, FEV_1, and peak flow. The presence of crystalline silica in the kaolin deposits is believed largely attributable for these pneumoconioses and potential for kaolin to induce lung damage in the absence of crystalline silica contamination is not resolved.

7.2.3.5 Volcanic Ash. Volcanic ash is aerosolized as a result of volcanic eruptions. The nature of the particulates can be highly variable as determined by the geologic characteristics of the region. The eruption of the Mount St. Helens Volcano in Washington State on May 18, 1980, produced vertical clouds of ash and gases more then 20 kilometers into the air. A large percentage of this particulate was of respirable size fraction. The ash was comprised of plagioclase and aluminum silicates. The ash was found to contain crystalline silica, both quartz and cristobalite, at concentrations of 3 to 7%. Toxicological studies of the ash further suggested that it was moderately fibrogenic and should be considered a pneumoconiosis risk for those individuals more heavily exposed on a regular basis. Longitudinal studies of loggers exposed to variable concentrations of ash found significant declines in FEV_1 associated with exposures during the first year after the eruption. Symptoms of cough, phlegm, and wheeze were reported among the loggers. No radiographic changes were observed in the 4 year follow-up period (54, 56).

7.2.3.6 Feldspars. Feldspars are one of the largest groups of minerals comprising igneous rocks. The two major groups are known as orthoclase, a potassium based feldspar, and plagioclase, a sodium–calcium feldspar. Granite is an igneous rock containing large quantities of feldspars. Feldspars are used in the ceramics industry. In the absence of quartz contamination, the feldspars are believed to present a relatively low pneumoconotic potential (53, 54).

7.3 Coal Dust

7.3.1 Exposure

Workers involved in extracting and drilling operations to obtain coal are exposed to coal dust. The risk of coal dust-induced lung disease development is related to the length of time of exposure (job tenure), the concentration of dust in the environment, and the rank of the coal. Coal dust exposure in the work place in high concentrations leads to the development of disabling and deadly pneumoconiosis. Studies from the 1960s reported

the presence of Coal Workers' Pneumoconioses or CWP as involving as many as 46% of coal miners. In 1969, the Coal Mine Health and Safety Act was passed which mandated a reduction in dust levels in underground mines to 2 mg/m^3. As a result of this legislation, there have been reductions in dust concentrations with corresponding reductions in coal dust-induced lung disease. However, it is still estimated that exposure to 2 mg/m^3 of coal dust over 40 years of work can lead to an approximately 9–10% risk of developing simple Coal Workers' Pneumoconiosis (CWP) and an approximately 1–2% risk of developing Progressive Massive Fibrosis (PMF) (66). In addition to length of time of exposure and dust concentrations, the rank of the coal is an independent risk factor for the development of coal dust-induced lung disease. Coal rank is related to the formation of coal and is often measured by the percentage of carbon in the coal. Anthracite coal has the highest percentage of carbon and is associated with the greatest risk for development of disease.

7.3.2 Pathophysiology

The most common coal dust-induced lung disease is Coal Workers' Pneumoconiosis or CWP (see below). The characteristic pathological lesion associated with CWP is the macule which has been defined by the College of American Pathologists as "a focal collection of coal dust-laden macrophages at the division of the respiratory bronchioles that may exist within the alveoli and extend into the peribronchiolar interstitium with associated reticulin deposits and focal emphysema" (67). Macules can range in size from 1 to 5 millimeters in diameter (see Fig. 4.6).

Progressively larger lesions, nodules, can be found in the lung of coal dust exposed workers. With time and continued exposure to coal dust, nodules can coalesce to form masslike lesions which are the hallmark of Progressive Massive Fibrosis or PMF (see

Figure 4.6. Lung histology showing a coal macule.

below). These lesions are by definition greater than 10 millimeters or 1 centimeter in diameter. These various, mostly rounded lesions usually exist within the upper zones of the lung. Nodules and the masses of PMF are seen in chest radiographs and can be characterized by classification systems such as the ILO Guidelines for the Classification of Radiographs of Pneumoconiosis (15). Macules, nodules, and masses can lead to pathological changes within the interstitium of the lung causing degenerative changes including calcification, blood vessel obliteration, and collagen deposition. The affected lung substance becomes stiff and restricted in movement. Gas exchange (the primary function of the lungs) can become altered with the development of respiratory limitation, disability and in severe cases, death.

In addition to macular changes, coal dust exposure is also associated with emphysema. Emphysema is the loss of elastic recoil of the alveoli with subsequent trapping of air and the concomitant decrease in air exchange. Furthermore, there may be airway changes characterized by increases in the number and size of mucous glands within the walls of the airways (68). These findings of emphysema and airway involvement seen in pathologic samples correlate with the physiological findings of obstructive airways disease, independent of the effects of smoking.

7.3.3 Coal Workers' Pneunoconiosis

Studies from 1960s reported the presence of Coal Workers' Pneumoconiosis or CWP in as many as 46% of coal miners (69). As stated previously, greater prevalence of CWP is related to longer times of exposure, higher rank of coal (anthracite > bituminous), and greater concentrations of dust. The diagnosis of CWP is made in the presence of an appropriate exposure history and by characterization of the radiographic presence of nodules (usually rounded and located in the upper lung zones) using a classification system like the ILO Classification. CWP is the reaction of the lung to chronic inhalation of coal dust which over time has overwhelmed the normal defense mechanisms of the lung (cough, mucociliary escalator, and alveolar macrophages) with the formation of macules, nodules and in severe cases masslike lesions (70).

The term "Black Lung" is often used in describing the lung diseases associated with coal dust exposure. Black Lung is occasionally classified as a lay definition referring to any lung disease or disorder associated with work in coal mining. The legal term as used in the Coal Mine Health and Safety Act is similar to this lay definition. CWP refers to the interstitial lung disease that occurs as a result of the accumulation of coal dust within the lung.

Using the ILO Classification System, workers with CWP can be classified as having Category 1, 2 or 3 disease. These Categories are based upon the presence of small opacities with greater number of opacities associated with a higher category of classification. The presence of large opacities represents Progressive Massive Fibrosis or PMF (see below).

Miners with CWP but without PMF may have few signs or symptoms and no physiological abnormalities such as reductions in lung function testing. However, the presence of even Category 1 CWP should be a cause for concern because with continued exposure, these individuals are at risk for progressing to higher categories of CWP and also to PMF.

7.3.4 Progressive Massive Fibrosis

With time and continued exposure to coal dust (especially higher concentrations [>2 mg/m^3] and higher rank coal), miners can progress from simple CWP to Progressive Massive Fibrosis (PMF). The hallmark of PMF is the presence of mass-like lesions or large opacities (>1 centimeter) seen on plain chest radiographs. These lesions (like the rounded smaller nodules) tend to be in the upper lung zones and can be unilateral or bilateral and may be rounded or irregular in shape. It may be difficult in some instances to distinguish these lesions from lung carcinoma which may have a similar radiographic appearance.

In contrast to simple CWP with minimal signs, symptoms or physiological abnormalities, workers with PMF can have cough, sputum production, shortness of breath, and chest pain. Impairment can range from minor problems to severe disability and in some cases to death.

The physiological changes associated with PMF include restrictive pulmonary physiology with reduction in lung volumes, reduction in gas transfer capability or diffusing capacity, exercise limitations, and in some cases cardiac disability of right ventricular enlargement and right ventricular dysfunction (cor pulmonale).

There is no treatment for the pneumoconiotic conditions of CWP or PMF other than avoidance of further dust exposure. In severe cases, lung transplantation has been offered for some individuals.

7.3.5 Obstructive Lung Disease

In addition to the interstitial pneumoconiotic diseases of CWP and PMF, coal dust exposure has been linked with the development of obstructive lung disease. Early studies showing presence of airways obstruction were criticized for not completely eliminating the confounding factors of smoking (a well-known cause of obstructive lung disease) and asthma (an obstructive lung disease that can occur in the general population). Recent reviews however, have found a significant correlation between coal dust exposure and obstructive lung defects. In one recent review (71), the statement is made that "the balance of evidence points overwhelmingly to impairment of lung function from exposure to coal mine dust, and this is consistent with the increased mortality from Chronic Obstructive Pulmonary Disease (COPD) that has been observed in miners".

7.4 Silica-Crystalline

7.4.1 Exposure

Silica or silicon dioxide (SiO_2) can exist in a fixed or crystalline pattern as opposed to a random molecular arrangement defined as amorphous. It is exposure to respirable concentrations of the crystalline form that is associated with the development of disease. Specifically, the crystalline forms of silica are primarily quartz, tridymite, and cristobalite. The most common forms of crystalline silica are found in common sand and sandstone. In addition, crystalline silica may exist as minute grains cemented with amorphous silica and these composites include tripoli, flint, chalcedony, agate, onyx, and silica flour. Exposure

to respirable crystalline silica occurs in individuals engaged in the occupations of mining, quarrying, drilling, and tunneling. Other occupations with exposure to silica include sandblasters, stonecutters, pottery workers, foundry workers, and refractory brick workers. Concern also exists for individuals exposed to silica flour (72) and for drillers in surface coal mining who are involved in removing the overburden to gain access to the coal (73).

As with exposure to other dusts, the risks involved with development of disease are the length of time of exposure and the concentration of the silica to which the worker is exposed. The current U.S. Occupational Safety and Health Administration (OSHA) exposure limit for respirable silica (Permissible Exposure Limit or PEL) is based on the measurement of respirable dust and on the percent silica content of the respirable dust (74). After chemical analysis of the respirable dust to determine the percent silica ($\%SiO_2$), the PEL is calculated as:

$$PEL = (10\ mg/m^3)/(\%SiO_2 + 2)$$

The measured 8-hr time weighted average (TWA) concentration of respirable dust is compared to this PEL to determine if the concentration exceeds the exposure limit.

A study of gold miners from South Dakota predicted that exposure to 0.09 mg/m^3 over a 45-year period of time would result in a 47% lifetime risk of silicosis (the fibronodular interstitial disease of the lung associated with deposition of silica within the lung) (75). The Recommended Exposure Limit or REL by the National Institute for Occupational Safety and Health (NIOSH) for quartz, tridymite, and cristobalite is 0.05 mg/m^3.

Recent studies have examined alternatives to the use of silica sand for abrasive blasting. Although these studies have shown effectiveness of these alternative materials in their use as abrasives, silica-containing products are still used.

In contrast to exposure to coal dust and to asbestos fibers where the interstitial lung disease occurs only after a minimum of 15 to 20 years of exposure, some forms of silicosis (acute and accelerated silicosis [see below]) can occur in only a few years or less under circumstances of intense exposure.

7.4.2 Pathophysiology

The hallmark of silica-induced disease is the presence of the silicotic nodule (see Fig. 4.7). This nodular lesion contains a central acellular zone with extracellular silica particles surrounded by whorls of collagen and fibroblasts and an active peripheral zone composed of macrophages, fibroblasts, plasma cells, and additional extracellular silica. The formation of these nodules is thought to occur because of surface properties of the silica particles that activate lung macrophages with the subsequent release of chemotactic and inflammatory mediators in turn resulting in further cellular inflammatory responses. It is thought that freshly fractured silica is more toxic because of reactive radical groups found on the freshly fractured surface.

As with coal dust-induced disease, there is a predilection for these nodules within the upper zones of the lung. With continued exposure, there are increasing numbers of these nodules with coalescence resulting in larger masses. In addition to involvement within the lung parenchyma and interstitium, silica can also cause pathological changes within bron-

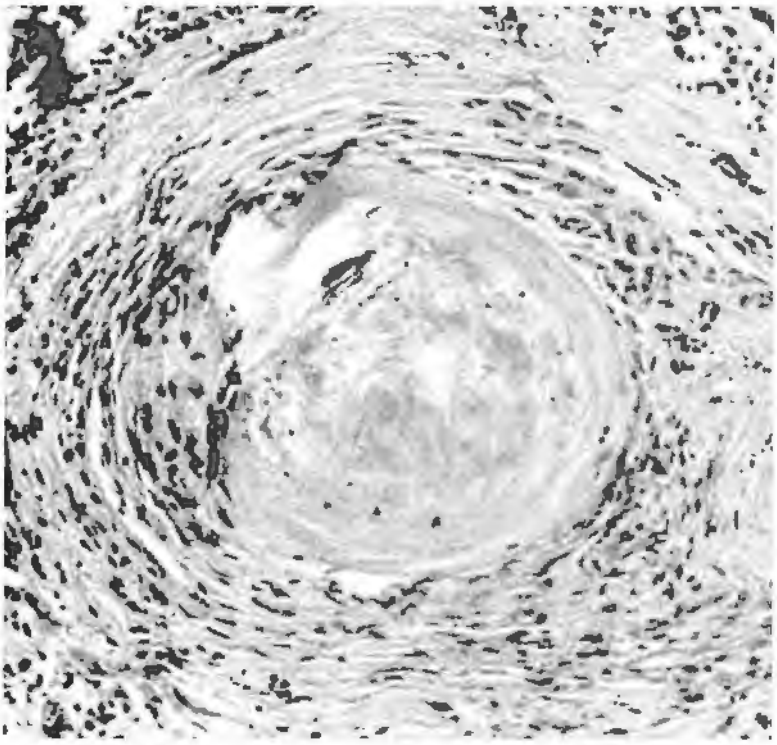

Figure 4.7. Lung histology showing a silicotic nodule.

chial associated lymphoid tissue (BALT) and within lymph nodes. Silicotic nodules can also be present in other organs within the body outside of the lung including the liver, brain, and kidney. In addition to affecting lung structure and lung physiology, silica-induced disease can alter the body's immune system increasing the likelihood of certain infectious diseases such as tuberculosis and autoimmune diseases such as progressive systemic sclerosis (76).

7.4.3 Chronic Silicosis

Chronic or Classic Silicosis occurs after 15–20 years or more of exposure to respirable crystalline silica. The presence of this form of silicosis is recognized by the appearance of the multiple small nodules on a chest radiograph. The classification of these changes seen on the chest radiograph can be made using the International Labour Organization Guidelines (15). Recent studies have examined the role of other radiographic evaluation for workers with silicosis including the use of Computed Tomography (CT) of the chest. CT examination of the chest can be more sensitive than plain chest radiography for the identification of the presence of nodules and associated emphysematous changes (77, 78). However, further studies will be required before CT examination becomes the preferred study of choice for dust-induced lung disease.

If the lesions of silica-induced lung disease remain as only individual small nodules (<5 millimeters in size), there is usually minimal if any physiological changes associated with the disease and, therefore, individuals usually have few if any symptoms. In this case, the disease is classified as Simple Silicosis.

If there is coalescence of the nodules over time with the formation of large masses (large opacities on the chest radiograph of >10 millimeters in diameter), the disease is then referred to a Progressive Massive Fibrosis or PMF (similar terminology to the changes with coal dust-induced disease) or Complicated Silicosis. In this case, individuals with PMF can have reductions in lung function with restrictive-type pathophysiology and decreases in diffusing capacity measurements. The worker may have significant respiratory and systemic symptoms of shortness of breath, productive cough, chest discomfort, with weight loss. In contrast to coal dust-induced disease (especially simple CWP), silica-induced lung disease can progress once exposure ends (79, 80).

7.4.4 Accelerated Silicosis

The pathologic and radiographic changes of silicosis can occur after only 5–10 years of exposure to higher concentrations of respirable crystalline silica. Progression occurs in these cases even if the worker is removed from further exposure. The association of rheumatological diseases such as Progressive Systemic Sclerosis (see below) can be found more commonly with accelerated silicosis as compared to chronic or classic silicosis. Accelerated silicosis can be fatal.

7.4.5 Acute Silicosis

If the concentrations of respirable crystalline silica are extremely high, disease can occur in only a few months or 1–2 years. Severe, disabling shortness of breath, weakness and weight loss can be seen with Acute Silicosis. An historical example of acute silicosis was the tragic situation of the Hawk's Nest Tunnel construction in the early 1930s near Gauley Bridge, West Virginia. Hundreds of workers died from acute and accelerated silicosis when they were exposed to extremely high concentrations of respirable silica by cutting through three miles of high-quartz sandstone without adequate respiratory protection (81).

In acute silicosis, there is filling of the alveolar spaces of the lungs with a proteinaceous material similar to that found in the disease Pulmonary Alveolar Proteinosis or PAP. This form of silicosis is associated with a relentless progressive course that is frequently fatal with death due to respiratory failure.

7.4.6 Silico-Tuberculosis

The association between the presence of silicosis and the development of pulmonary mycobacterial infections including pulmonary tuberculosis, has been known for many years. Recent studies have shown that those workers with chronic or classic silicosis have a 3-fold increased risk of developing both pulmonary and extra-pulmonary tuberculosis when compared to a similar control population of silica-exposed workers without silicosis (82). In addition, this report also suggested that those individuals with long exposures to silica dust were at a greater risk of developing tuberculosis even if they did not have silicosis

compared to workers not exposed to silica. For those workers with silicosis, the risk of incidence of tuberculosis is in direct relationship to the radiographic presence of silicotic nodules.

7.4.7 Obstructive Lung Disease

In addition to the development of the fibro-nodular insterstitial disease that is silicosis, workers exposed to respirable crystalline silica dust can also develop chronic obstructive pulmonary disease (COPD). Increased frequency of chronic bronchitis (chronic cough and sputum production, a form of COPD) has been reported in miners of coal, gold, granite, and agate (76). It is felt that the pathophysiological changes contributing to silica-induced chronic lung disease are the occurrence of silicotic nodules in close proximity to small and medium airways with narrowing and distortion of the lumen of these airways. In addition to airway lumen compromise, there may also be emphysematous-type changes especially in association with conglomerate lesions, which can be detected with radiographic CT imaging of the chest. Thus, in many workers exposed to silica who develop silica-induced lung disease, there may be the presence of both obstructive and restrictive-type ventilatory defects as measured with pulmonary function testing.

7.4.8 Lung Cancer from Silica Dust

In October of 1996, a committee of the International Agency for Research on Cancer (IARC) reclassified silica as a Group I substance described as "carcinogenic to humans,", concluding that there is "sufficient evidence of carcinogenicity in humans" (83). Although many studies have had confounding factors such as smoking and exposure to other minerals that are carcinogenic, the balance of evidence indicates that workers with silicosis have an increased risk for lung cancer. It is less clear whether long-term exposure to silica dust without development of silicosis is also a risk factor for lung cancer.

7.4.9 Progressive Systemic Sclerosis

Silica has not only been shown to be associated with diseases of the respiratory system (silicosis, obstructive lung disease, and lung cancer), it is also been shown to be associated with Progressive Systemic Sclerosis or Scleroderma. A recent review concluded that the "systemic sclerosis" associated with silica exposure is indistinguishable from idiopathic Scleroderma (84). Although it is known that silica-exposure can lead to changes within the lymphatic and immune systems with the development of auto-antibodies, the exact mechanism for the development of this systemic disease in silica-exposed workers is unclear.

7.4.10 Comparison of Silica vs. Coal Dust-Induced Lung Disease

Similarities exist between coal dust-induced lung disease and silica-induced lung disease. Specifically, both mineral dusts can lead to the development of small rounded opacities (< 5 millimeters) located in the upper lung zones identified by plain chest radiography. In addition, both may progress to show coalescence of the smaller opacities into larger opacities classified as Progressive Massive Fibrosis or PMF. In both exposure situations,

workers can also develop obstructive lung disease. In the past, it was thought that the pneumoconiosis seen in coal dust exposed workers was actually due to the silica content of the dust. However, it has been recognized in recent years that coal itself can lead to the pathological, radiographic, and physiologic changes seen in CWP and in coal dust-induced PMF.

However, despite the similarities between coal dust and silica-induced lung disease, there are significant differences. (*1*) Silica can cause changes in lymphoid tissue with involvement of mediastinal lymph nodes as well as bronchial associated lymphoid tissue (BALT); (*2*) silica can lead to systemic involvement with silicotic nodules present in different extra-pulmonary tissue; (*3*) silica has been associated with the development of systemic diseases such as Progressive systemic Sclerosis or Scleroderma; (*4*) silicosis and silica exposure can be associated with the development of mycobacterial disease such as tuberculosis; (*5*) silicosis can be associated with the development of lung carcinoma; (*6*) there are more rapidly progressive forms of silicosis (accelerated and acute silicosis) that can develop in months or a few year; (*7*) many cases of silicosis can progress after removal from further exposure. Unless the worker has PMF from coal dust exposure, it is unusual that coal dust-induced simple pneumoconiosis (CWP) will progress after removal from further exposure.

BIBLIOGRAPHY

1. *Occupational Lung Diseases: An Introduction*, American Lung Association, New York, 1979, P. 10(5).
2. American Thoracic Society, "Standardization of Spirometry—1994 Update," *Am. J. Respir. Crit. Care. Med.* **152**, 1107–1136 (1995).
3. American Thoracic Society, "Single-Breath Carbon Monoxide Diffusing Capacity (Transfer Factor)," *Am. J. Respir. Crit. Care Med.* **152**, 2185–2198 (1995).
4. American Thoracic Society, "Guidelines for Methacholine Challenge Testing," *Am. J. Respir. Crit. Care Med.* (1999), in press.
5. American Thoracic Society, "Lung Function Testing: Selection of Reference Values and Interpretative Strategies," *Am. Rev. Respir. Dis.* **144**, 1202–1218 (1991).
6. M. R. Becklake, "Concepts of Normality Applied to the Measurement of Lung Function," *Am. J. Med.* **80**, 1158–1164 (1986).
7. P. L. Enright et al., "Spirometry in the Lung Health Study. 1. Methods and Quality Control," *Am. Rev. Respir. Dis.* **143**, 1215–1223 (1991).
8. J. Hankinson et al., "Spirometric Reference Values from a Sample of the General U.S. Population," *Am. J. Respir. Crit. Care Med.* **159**, 179–187 (1999).
9. S. T. Weiss et al., "Relation of FEV_1 and Peripheral Blood Leukocyte Count to Mortality. The Normative Aging Study," *Am. J. Epidemiol.* **142**, 493–498 (1995).
10. R. O. Crapo, "Pulmonary Function Testing," *New Eng. J. Med.* **331**, 25–30 (1994).
11. National Institutes of Health, *Guidelines for the Diagnosis and Management of Asthma*. NIH Publication No. 97-4051, 1997.
12. A. Miller, "Single Breath Diffusing Capacity in a Representative Sample of the Population of Michigan, a Large Industrial State," *Am. Rev. Respir. Dis.* **127**, 270–277 (1983).

13. R. S. Fraser et al., *Synopsis of Disease of the Chest*, 2nd ed., W.B. Saunders Company, Philadelphia, 1994.
14. G. Wagner et al., "Chest Radiography in Dust-Exposed Miners: Promise and Problems, Potential and Imperfections," *Occup. Med.* **8**, 127–141 (1993).
15. International Labour Organization, *ILO 1998 International Classification of Radiographs of the Pneumoconioses*, ILO, Geneva, Switzerland, 1999.
16. W. N. Rom et al., "Cellular and Molecular Basis of the Asbestos-related Diseases," *Am. Rev. Respir. Dis.* **143**, 408–422 (1991).
17. D. Vanhee, "Cytokines and Cytokine Network in Silicosis and Coal Workers' Pneumoconiosis," *Eur. Respir. J.* **8**, 834–842 (1995).
18. D. Vanhee, "Mechanisms of Fibrosis in Coal Workers' Pneumoconiosis. Increased Production of Platelet-derived Growth Factor, Insulin-like Growth Factor Type I, and Transforming Growth Factor beta and Relationship to Disease Severity," *Am. J. Respir. Crit. Care Med.* **150**, 1049–1055 (1994).
19. NIOSH, *Workplace Exposure to Asbestos*, (1980), pp. 1–39.
20. NIOSH, *Asbestos Bibliography (Revised)*, 1997 pp. 1–212.
21. B. Begin, J. M. Samet, and R. A. Shaikh, "Asbestos," in Harber, Schenker, and Balmes, eds., *Occupational and Environmental Respiratory Disease* 1996 pp. 293–329.
22. J. M. Stellman ed., *Encyclopaedia of Occupational Health and Safety*, 4th Ed., Geneva, International Labour Office, Vol. 1. Respiratory System (D. Alois and G. R. Wagner eds., Chapt. 10), 1998 pp. 10.1–10.97.
23. W. N. Rom, "Asbestos-Related Diseases," in *Environmental and Occupational Medicine*, chapt. 24 pp. 349–375.
24. National Bureau of Standards (NBS). "Workshop on Asbestos: Definitions and Measurement Methods," U.S. Dept of Commerce/NBS Special Publication 506, 1977.
25. J. L. Wright et al., "Diseases of the Small Airways," *Am. Rev. Respir. Dis.* **146**, 240–262 (1992).
26. M. R. Becklake, "The Epidemiology of Asbestosis," in Liddell and Miller, eds., *Mineral Fibers and Health*, CRC Press, Boca Raton, FL, 1991.
27. M. R. Becklake, "Occupational Exposure and Chronic Airways Disease," in *Environmental and Occupational Medicine*, Little, Brown & Co., Boston, 1992, Chapt. 13.
28. R. Doll and J. Peto, in Antman and Aisner, eds., *Asbestos-Related Malignancy*, Grune & Stratton Orlando, FL, 1987.
29. I. J. Selikoff, "Historical Developments and Perspectives in Inorganic Fiber Toxicity in Man," *Environ Health Persp* **88**, 269–276 (1990).
30. M. R. Becklake, "Pneumoconioses." in Murray and Nadel, eds., *A Textbook of Respiratory Medicine* WB Saunders, Philadelphia, 1994, Chapt. 66.
31. Bureau of Mines, "Selected Silicate Minerals and their Asbestiform Varieties: Mineralogical Definitions and Identification-Characterization." U.S. Dept of Interior/Bureau of Mines Information Circular 8751, 1977 pp. 1–56.
32. NIOSH, *Occupational Respiratory Diseases*, 1986, pp. 287–342.
33. W. A. Burgess, *Recognition of Health Hazards in Industry*, 2nd ed., 1995, pp. 409–482,
34. G. J. Kullman. "Occupational Exposures to Fibers and Quartz at 19 Crushed Stone Mining and Milling Operations," *Am. J. Indust. Med.* 641–660, (1995).
35. EPA, *Guidance for Controlling Asbestos-Containing Materials in Buildings*, 1985, pp. 1-1 to 10-1

36. *Code of Federal Regulations*, **29** *CFR* 1910.1001, U.S. Government Printing Office, *Federal Register*, Washington DC 1995.

37. *Code of Federal Regulations*, **30** *CFR* 56.5001, U.S. Government Printing Office, *Federal Register*, Washington DC 1995.

38. NIOSH, *Recommendations for Occupational Safety and Health: Compendium of Policy Documents and Statements*, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 92-100, Cincinnati, OH, 1992.

39. American Conference of Governmental Industrial Hygienists, 1998 TLVs® and BEIs®: *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH, 1998.

40. W. N. Rom, "Asbestos-related Lung Disease," *Fishman's Pulmonary Diseases and Disorders*, 3rd ed. 1998, pp. 877–891.

41. G. R. Epler, T. C. McLoud, and E. A. Gaensler, "Prevalence and Incidence of Benign Asbestos Pleural Effusion in a Working Population," *JAMA* **247**, 617–622 (1982)

42. L. Rosenstock, S. Barnhart, N. J. Heyer, D. J. Pierson, and L. D. Dudson, "The Relation Among Pulmonary Function, Chest Roentgenographic Abnormalities, and Smoking Status in an Asbestos-Exposed Cohort," *Am. Rev. Resp. Dis.* **138**(2), 272–277 (1988).

43. D. A. Schwartz, L. J. Fuortes, J. R. Galvin, L. F. Burmeister, L. E. Schmidt, B. N. Leistikow, F. P. Lamarte, and J. A. Merchant, Asbestos-induced Pleural Fibrosis and Impaired Lung Function, *Am. Rev. Respir. Dis.* **141**(2) 321–326 (1990).

44. S. A. Levy, "Asbestosis," *Occup. Med.* 179–193 (1994).

45. Consenus Report, "Asbestos, Asbestosis, and Cancer: the Helsinki Criteria for Diagnosis and Attribution," *Scand. J. Work Environ. Health* **23**, 311–316 (1997).

46. P. C. Elms, "Inorganic Dusts," *Hunter's Diseases of Occupations*, 8th ed. pp. 410–457, 1994, pp. 410–457.

47. V. R. Doll, "Mortality from Lung Cancer in Asbestos Workers," *Br. J. Ind. Med.* **12**, 81–86 (1955).

48. W. McDonald, J. C. Liddell, F. D. Gibbs, G. W. Eyssen and G. E. McDonald, "Dust Exposure and Mortality in Chrysotile Mining 1919–1975," *Br. J. Ind. Med.* **37**, 11–24 (1980).

49. I. J. Selikoff and H. Seidman, "Asbestos-associated Deaths Among Workers in the United States and Canada, 1967–1987." *Ann. N.Y. Acad. Sci.* **643**, 1–14 (1991).

50. W. Weiss, "Asbestosis: A Marker for the Increased Risk of Lung Cancer Among Workers Exposed to Asbestos," *Chest* **115**, 536–549 (1999).

51. D. E. Banks et al., "Asbestos Exposure, Asbestosis, and Lung Cancer," *Chest* **115**, 320–322 (1999).

52. J. C. Wagner, C. A. Sleggs, and P. Marchand, "Diffuse Pleural Mesothelioma and Asbestos Exposure in the Northwestern Cape Province," *Br. J. Ind. Med.* 1965; **22**, 261–266 (1965).

53. J. E. Craighead, J. Kleinerman et al., "Diseases Associated with Exposure to Silica and Nonfibrous Silicate Minerals," *Arch. Pathol. Lab. Med.* **12**, 673–720 (July 1988).

54. J. E. Lockey, "Man-Made Fibers and Nonasbestos Fibrous Silicates," in Harber, Schenker, and Balmes, eds., *Occupational and Environmental Respiratory Disease* 1996, pp. 330–343.

55. J. F. Gamble, "Silicate Pneumoconiosis," in J. A. Merchant, ed., *Occupational Respiratory Diseases*, DHHS (NIOSH) Publication No 86-102. U.S. Government Printing Office, Washington, DC, 1986.

56. W. N. Rom, "Silicates and Benign Pneumoconioses," *Environ. Occup. Med.* **16**, 345–349 (1974).

57. R. J. Waxweiler, R. D. Zumwalde, G. O. Ness et al., "A Retrospective Cohort Mortality Study of Males Mining and Milling Attapulgite Clay," *Am. J. Ind. Med.* **13**, 305–315 (1988).

58. E. E. McConnel, L. Hall and B. Adkins, "Studies on the Chronic Tonicity (Inhalation) of Wollastonite in Fischer 344 Rats," *Inhalat. Toxicol.* **3**, 323–337 (1991).

59. M. S. Huuskonen, A. Tossavainen, H. Koskinen, et al., "Wollastonite Exposure and Lung Fibrosis," *Environ. Res.* **30**, 291–304 (1983).

60. D. P. Brown and J. K. Wagoner, "Occupational Exposure to Talc Containing Asbestos: III. Retrospective Cohort Study of Mortality," U.S. Dept of HEW. (NIOSH) Pub No 80-15, 1980.

61. M. Kleinfeld, J. Messite and M. H. Zaki, "Mortality Experiences among Talc Workers. A Follow-up Study," *J. Occup. Med.* **16**, 345–349 (1974).

62. W. T. Stille, and I. R. Tabershaw, "The Mortality Experience of Upstate New York Talc Workers," *J. Occup. Med.* **24**, 480–484 (1982).

63. J. F. Gamble, W. Fetner, and M. J. Dimeo, "An Epidemiologic Study of a Group of Talc Workers." *Am. Rev. Resp. Dis.* **119**, 741–753 (1979).

64. D. H. Wegman, J. M. Petes, M. G. Boundy, and T. J. Smith, "Evaluation of Respiratory Effects in Miners and Millers Exposed to Talc Free of Asbestos and Silica," *Br. J. Ind. Med.* **39**, 233–238 (1982).

65. E. Wergeland, A. Andersen and A. Baerheim, "Morbidity and Mortality in Talc-Exposed Workers," *Am. J. Ind. Med.* **17**, 505–513 (1990).

66. M. D. Attfield et al., "An Investigation into the Relationship between Coal Workers' Pneumoconiosis and Dust Exposure in U.S. Coal Miners," *Am. Ind. Hyg. Assoc. J.* **53**, 486–492 (1992).

67. J. Kleinerman et al., "Pathology Standards for Coal Workers' Pneumoconiosis. Report of the Pneumoconiosis Committee of the College of American Pathologists to the National Institute for Occupational Safety and Health," *Arch. Pathol. Lab. Med.* **103**, 375–432 (1979).

68. A. N. Douglas et al., "Bronchial Gland Dimensions in Coalminers: Influence of Smoking and Dust Exposure," *Thorax* **37**, 760–764 (1982).

69. R. E. Hyatt et al., "Respiratory Disease in Southern West Virginia Coal Miners," *Am. Rev. Respir. Dis.* **89**, 387–401 (1964).

70. J. Parker et al., "Coal Workers' Lung Disease and Silicosis," *Fishman's Pulmonary Diseases and Disorders*, 3rd ed. 1998 pp. 901–914.

71. D. Coggon et al., "Coal Mining and Chronic Obstructive Pulmonary Disease: A Review of the Evidence," *Thorax* **53**, 398–407 (1998).

72. D. E. Banks et al., "Silicosis in Silica Flour Workers," *Am. Rev. Respir. Dis.* **124**, 445–450 (1981).

73. D. E. Banks et al., "Silicosis in Surface Coalmine Drillers," *Thorax* **38**, 275–278 (1983).

74. Office of the Federal Register, **29** *CFR* (United States Code of Federal Regulations) 1910.1000. National Archives and Records Administration, U.S. Government Printing Office, Washington, DC 1998.

75. K. Steenland et al., "Silicosis among Gold Miners: Exposure–Response Analyses and Risk Assessment," *Am. J. Public Health* **85**, 1372–1377 (1995).

76. American Thoracic Society, "Adverse Effects of Crystalline Silica," *Am. J. Respir. Crit. Care Med.* **155**, 761–765 (1997).

77. C. J. Bergin et al., "CT in Silicosis: Correlation with Plain Films and Pulmonary Function Tests," *Am. J. Roentgenol.* **146**, 477–483 (1986).
78. G. Gamsu, "Computed Tomography and High-Resolution Computed Tomography of Pneumoconioses," *J. Occup. Med.* **33**, 794–796 (1991).
79. K. Kreiss et al., "Risk of Silicosis in a Colorado Mining Community," *Am. J. Ind. Med.* **30**, 529–539 (1996).
80. E. Hnizdo et al., "Risk of Silicosis in a Cohort of White South African Gold Miners," *Am. J. Ind. Med.* **24**, 447–457 (1993).
81. J. K. Corn, "Historical Aspects of Industrial Hygiene, II. Silicosis," *Am. Ind. Hyg. Assoc. J.* **41**, 125–133 (1980).
82. R. L. Cowie, "The Epidemiology of Tuberculosis in Gold Miners with Silicosis," *Am. J. Respir. Crit. Care Med.* **150**, 1460–1462 (1994).
83. International Agency for Research on Cancer, "Silica, Some Silicates, Coal Dust and *para*-Aramid Fibrils," IARC Monograph Evaluating Carcinoma Risk, Vol. 68, 1997.
84. M. H. Rustin et al., "Silica-associated Systemic Sclerosis is Clinically, Scrologically and Immunologically Indistinguishable form Idiopathic Systemic Sclerosis," *Br. J. Dermatol.* **123**, 725–734 (1990).