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CHAPTER SEVEN

The Pulmonary Effects of Inhaled Inorganic Dust

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1 INTRODUCTION

Dust-laden air is the normal environment of man. There is continuous exposure to inhaled particles that vary from time to time in number and chemical and physical properties. It seems likely that the remarkable ability of the respiratory apparatus to cope with inhaled particles accounts in part for the survival and evolution of man, since we developed through our various stages in an environment that over long periods of time was in all probability even dustier than now as the result of volcanic activity and the scouring effect of wind flowing across the land. Fortunately the respiratory apparatus intercepts a large portion of inhaled particles as they move through the nose or mouth and along the course of air-conducting channels before they reach the more delicate distal parts of the lung. Moreover the lung has a large capacity to remove deposited dust by way of the mucociliary escalator and macrophage system. It also is important that the lung cells comprising the surfaces in contact with air normally have a rapid turnover or replacement rate, hence partially damaged surface cells are quickly replaced by new and normal cells. In addition, mechanisms are available for the repair of injured tissue in the lung. As is true of all other organ systems, however, the capacity for self-protection and repair of injury can be exceeded, and excessive dust deposition can cause adverse effects within the breathing apparatus.

Depending on the intrinsic chemical and physical nature of the inhaled particles and also the chemicals adsorbed onto their surfaces, the biological response may be noninjurious, slight or serious, or even fatal. Of equal importance governing the biological out-

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come are the quantity of particles deposited and the amount retained. The weight of evidence thus far overwhelmingly supports the conviction that all biological responses to nonliving agents are dose related.

Dust particles in contact with tissue cells evoke a response specific to each particular kind of cell. This response may be fleeting or temporary with no persistent or serious cell injury. On the other hand, persistent injury or death of the cell may occur, leading to secondary tissue alterations of varying degrees of gravity. Because of variations in the number of cells responding, the capacity or normality of cell replacement and repair and immunologic cell surveillance, and the hyperreactivity or sensitivity of the reacting cells, the overall tissue response can be expected to differ considerably in magnitude among individuals exposed in quite similar ways.

There are many kinds of respirable particles in the total environment of man. Some are essentially peculiar to the occupational environment, but others occur commonly in both the general and occupational environment. Thus biological effects of the occupational environment must always be related to the sum of the particles in the total environment, including those of nonoccupational origin. There is also the possibility that coexisting particles of different kinds and from various sources may act not only additively but also in a synergistic or even an inhibiting manner.

Those interested in industrial toxicology and hygiene or in occupational medicine quite properly are concerned with the biological reactions of humans exposed to dust comprised of various agents acting alone or in combination and in varying concentrations. One must be aware not only of the biological effects but also of the mechanisms underlying and controlling their occurrence. Such toxicological knowledge provides the *raison d'être* for industrial hygeine programs aimed at prevention of injury.

This chapter discusses principles relating the lung response to inorganic dust particles occurring in occupational environments. Specific agents are used to exemplify various kinds of reaction, but the biological effects of all the kinds of particle coexisting with other gases and fumes throughout all sorts of industrial environments cannot be covered. The reader is urged to consult more comprehensive texts for greater medical detail or to rectify omissions of the effect of specific agents. Among such texts, the recent one by W. Raymond Parkes, *Occupational Lung Disorders* (16) is recommended.

2 PERTINENT ANATOMY OF THE LUNGS

The primary purpose of the respiratory apparatus is to act as a gas exchange mechanism. A very thin layer of venous blood, pumped into the lungs by the right ventricle via the pulmonary artery system, is circulated through the pulmonary capillaries, which are arranged in a network over the surface of approximately 300 million air-containing alveoli. The total effective gas exchange surface of the alveoli has been estimated at ± 70 m^2. The tissue barrier separating the blood from the gas phase is the alveolocapillary wall, which averages 0.55 μm in thickness. During passage of venous blood over the surface of this barrier, the diffusion gradient favors the rapid

movement of molecular oxygen from the air into the blood and of carbon dioxide out of the blood into the air phase. Thus the blood becomes arterialized in its transit over the alveolocapillary surface.

As can readily be appreciated, the partial pressure of these gases in the blood and gas phase would quickly become equal unless the air phase is continuously maintained at partial pressures of O_2 and CO_2 favoring the gradient for diffusion. External respiration brings ambient air low in CO_2 and high in O_2 content to the gas phase overlying the alveolocapillary membrane by mass movement and continuous replacement of air within the lungs. Mass movement of air does not go all the way to the surface of the alveolar wall, and there is an interface, probably within the alveolar sac, across which the final pathway for molecular delivery to the alveolar membrane occurs by diffusion.

After moving through the nose or mouth, inspired air enters the larynx and then the trachea, which divides into two main bronchi, each leading into a lung. Each main bronchus divides into 16 further generations of branches that serve solely the purpose of air conduction (Figure 7.1). There are seven subsequent generations of branching having alveoli in their walls. Counting limbs and twigs, there are approximately 116,300 solely air-conducting bronchi including the terminal bronchioles. Additional air-conducting branches that are also alveolus bearing, the so-called transitional and respiratory zone, bring the total number of branched limbs and twigs through which air moves to about 82 million. The main bronchi measure 1.2 cm in diameter. By the eleventh generation the lumen is reduced to 1 mm, and by the sixteenth and subsequent generations to 0.5 mm (1). These dimensions and numbers have major implications with respect to deposition and clearance of particles entering the lung while entrained in the respired air. The opportunity for impingement of air-entrained particles at the myriad of bifurcations before reaching any alveoli or gas exchange area is enormous. This means that particles of aerodynamic size favoring deposition by impingement, sedimentation, or interception will fall on and be removed by the mucociliary escalator, a structure that extends through the first 16 generations of branching. Hence the probability that a particle suspended in the air bolus of a single breath will actually reach and be deposited in a specific alveolus-bearing portion of the lung is small. Moreover, because of the extremely large number of branched units and their small individual volume, the probability that the moiety of air entering a single unit during a single breath will contain an entrained particle is very low by the time the bolus of air has passed beyond the seventh or eighth generation of branching and is small indeed by the time it has reached or passed the eighteenth generation. This type of distribution reduces the likelihood of overloading any single small conduit during prolonged exposure and helps maintain a high efficiency of dust removal.

Equal in importance to an understanding of the morphometric aspects of the respiratory apparatus is knowledge of the histologic or cellular structure of the lung. These components determine the manner in which dust particles entering the lung are disposed of and also what kind of biological reaction does or does not ensue. For details of the normal lung histology, the reader is referred to standard texts of histology and to the special texts on the lung (2, 3).

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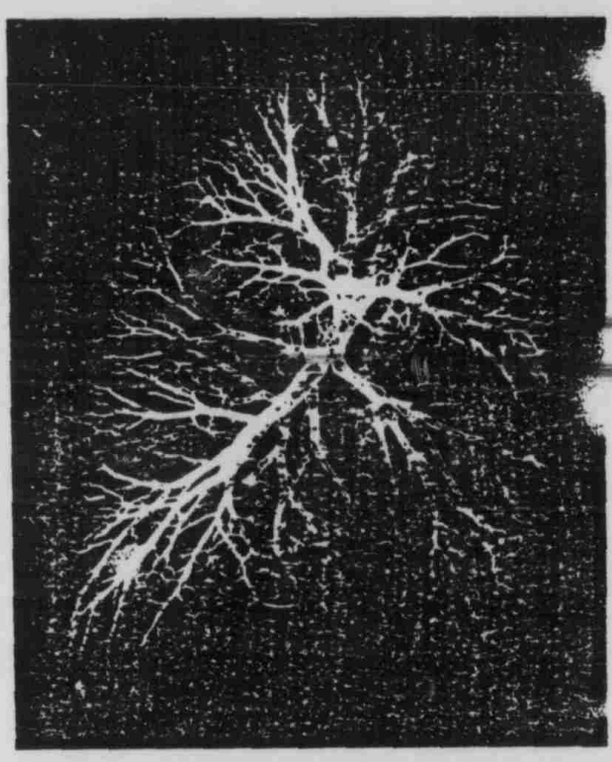


Figure 7.1 Radiograph of airway of distended human lung; right main bronchus with lobar and a few subsequent branchings (probably not beyond eighth generation) as outlined by contrast media.

The first few generations of the air-conducting system, the trachea and bronchi, have rather thick connective tissue walls containing cartilaginous plates that support the wall except in the posterior aspect where the encircling plates are incomplete. There is also a thin layer of smooth muscle located just beneath the mucous membrane lining these conduits. The muscle bundles are arranged in a spiral fashion encircling the conducting tube. As the air tubes further divide, the cartilaginous elements disappear and the walls become thinner, but the spiraling smooth muscle becomes proportionately larger. As the last few generations of conducting airways are reached, the wall becomes still thinner,

and by the time the terminal bronchiole, the sixteenth generation, is reached it is very thin. In the seventeenth generation of branches an occasional small outpouching appears in the wall. This cup-shaped outpouching is the alveolus, the site of molecular gas exchange between air and blood. The airways having only a few alveoli protruding from the walls are termed resiratory bronchioles, but when the alveoli make up most of the wall they are called alveolar ducts. When the final division is reached and the walls are entirely formed by alveoli, the passage is termed an alveolar sac or atrium. Elastic fibers, coursing roughly parallel to the air tubes, exist from the trachea all the way to the alveolus, where they form a network within the alveolar wall.

Lining the surface of the air tubes is a membrane comprised of an epithelial layer supported on a base of interlacing reticulin, collagen, and elastic fibers embedded in a proteinaceous matrix, the ground substance, containing cells such as fibroblasts and macrophages. The epithelial surface of the trachea and bronchi as far out as the terminal bronchioles is composed of columnar and cuboidal ciliated cells; interspersed between these are mucus-secreting goblet cells, discharging onto the surface of the airways. In addition, there are clusters of large mucus-secreting glands scattered throughout the subepithelial region of the bronchi out to the ninth or tenth generation. These glands discharge their contents by way of ducts opening onto the surface of the airway lining. Their discharge plus that form the goblet cells form a carpet of mucus that is distributed rather evenly over the surface of the ciliated cells, which extend out to the terminal bronchiole or sixteenth generation of airways. This carpet of mucus is continuously moved by the action of the underlying cilia from the places of manufacture up through the trachea, where the mucus is then swallowed or expectorated. This system, known as the mucociliary escalator, is the mechanism whereby particles deposited on the airway surface are removed.

Beyond the terminal bronchiole the surface lining of the airways is no longer ciliated and becomes thinner as the cuboidal cells grow shorter and assume the shape of progressively flatter cells. The alveolus is the terminal unit, whether it arises from the wall of the respiratory bronchiole, from the alveolar duct, or from the lumen of the alveolar sac. The alveoli are clustered in a tightly packed manner, abutting upon themselves and the walls of conducting airways of their own and adjacent units. Each alveolus is lined by large, flat, very thin cells, the type I pneumocytes. These lie on a thin layer of reticulin plus elastic fibers that cover a network of capillaries. The capillaries in turn are separated from the reticulin and elastic fibers of the interstitium by large flat cells making up the endothelium that lines the capillaries. A scant amount of ground substance plus occasional connective tissue cells and macrophages lie in the interstices of the reticulin network. The alveoli are so closely packed that a single pulmonary capillary usually serves two or more alveoli abutting upon the pulmonary capillary network. The net pressure of the blood within the capillaries is below that in the interstitial space; thus liquid normally does not pass into the alveolar spaces.

Other cells of importance are found in the alveolar unit. The type II pneumocyte is found scattered at various places in the alveolocapillary wall as part of the surface lining cells. It apparently secretes surfactant, a material that affects the surface tension of the

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ultra-thin liquid layer located at the actual air–tissue interface of the alveolus. Alevolar macrophages (4), large free cells of the reticuloendothelial system measuring 10 to 50 μm in diameter, are located both in the interstitial tissue and within the alveolar spaces lying free on the alveolar surface. These are large mobile cells whose most spectacular function is phagocytosis. They also are involved in immunologic reactions. The number of these cells can be greatly augmented by the presence of dust particles within the alveoli. Particles not exceeding 10 μm in greatest dimension are readily ingested by the macrophage. The fate of such particles is discussed later.

The major branches of the pulmonary artery and veins follow closely the branching of the airways. In addition to these there are very thin walled vessels, the lymphatics, which begin within the interstitial spaces at the level of the respiratory bronchiole and alveolar ducts and ascend in a merging fashion with lymphatic channels from other regions of the lung along the course of the arteries and veins. Similar vessels underlie the pleura, the membrane that covers the lungs and lines the chest cage. These channels are for the purpose of removing excess interstitial fluid. Along their course are collections of lymphoid tissue, the smallest being arranged in cuffs around the respiratory bronchiole and adjacent arterioles. The lymph fluid flows toward the lung root, and larger aggregates of lymphoid tissue are found along the course of these lymphatics as the channels coalesce and become larger. The nodular clusters of lymphoid tissue in the root of each lung are quite large. The various regional aggregates of lymphoid cells serve as collecting points where particles penetrating to the interstitial fluid can be sieved or filtered out of the liquid phase and accumulated in the lymphoid tissue, thus minimizing introduction of such particles into the circulating blood by way of the main lymph vessels that spill their contents into the innominate veins.

Each lung is covered by a thin membrane except at its root, where the main bronchi, blood vessels, and lymph channels pass into or out of the lung. This membrane, the pleura, reflects off the lung root and passes onto the surface of the inner aspect of the thoracic cage, thus forming a closed sac bordered by the lung, the chest wall, and the mediastinum. It contains a small amount of constantly exchanged fluid. Covering the surface of the pleura are large flat cells of mesothelial origin lying on a thin layer of loose areolar connective tissue containing blood and lymph vessels, nerves, and a well-developed layer of elastic tissue along with its complement of macrophages and fibroblasts. Of particular importance for this discussion is the fact that alveoli abut directly onto the inner aspect of the elastic layer and supporting structures of the pleura. Hence there is the possibility that particles reaching these alveoli might pass directly on into the pleura. In this way particles in addition to those that move by way of the lymphatics might ultimately come into contact with cells of the pleura.

3 BEHAVIOR AND FATE OF PARTICLES THAT ENTER THE RESPIRATORY SYSTEM

Dust deposition is to a large degree dependent on the concentration and the physical nature of the specific dust particles in the air. A substantial body of information exists

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with respect to the respirability of particles of differing dimensions and shapes, their deposition in various compartments of the air-conducting and distal spaces of the lung, and the speed and effectiveness with which rapid and slow clearances occur (5–7).

If, by suitably gentle technique, one digests the lungs of older individuals who have worked in the dusty trades, a residue will be obtained that can be assumed to have come from exogenous sources by way of the airborne route over the years (8). These tiny particles have a most interesting size range. Approximately half will be smaller than 0.5 μm in diameter. Of those that are larger, almost all will be between 0.5 and 5.0 μm in diameter. Fewer than 0.2 percent of the total will be larger than 5.0 μm in diameter, and less than 0.002 percent will be larger than 10 μm in diameter. If a fiber is defined as a particle having parallel sides and an aspect ratio of 3 or more, fibers for the most part will be observed to be less than 50.0 μm long, although some may be as long as 200 μm. The diameters of these fibers will be less than 3 μm. In contrast, in samples of the ambient air to which the general public or those who work in the dusty trades are exposed, one finds particles of these dimensions, but in addition, many of much larger diameter and length. Why is the long-term retention of particles limited to the sizes just described, even though millions of particles of greater diameter or length become airborne, therefore have the potential for entry into the respiratory system? The explanation arises from our knowledge of the behavior of particles suspended in air (aerosols) and the anatomical structure of the lung as described in the preceding paragraphs.

Particles can vary markedly in shape and density, and both these factors play a role in the behavior of particles in air suspension. For our purposes we consider all particles as being spheres of unit density, with the understanding that there could be some variation between particles with respect to speed of settling, depending on their shape and density.

Several physical forces are conducive to the removal of particles from an air suspension and their deposition on surfaces of the respiratory system (5). Particles suspended in a moving airstream possess inertial forces tending to maintain the direction of motion of the particle. When the air column changes its direction, as at a branching point of the conducting system, or in the tortuous passages of the nose, the entrained particle tends to continue in its previous direction and to be cast on the surface. This effect is directly proportional to the size of the particle and the speed of the airstream, thus of the particle, and inversely proportional to the radius of the tube. Gravitational forces also remove particles from the airstream and precipitate them on the surface of the respiratory system. The terminal settling velocity of a particle is directly related to its density, the gravitational constant, and the square of the particle diameter. It is inversely related to air viscosity. Since the gravitational constant and air viscosity are the same at all times, the terminal settling velocity is predominantly related to the other two factors, plus the distance through which the particle must fall and the time permitted for the event to occur. Deposition of particles by diffusion is limited to those of a diameter smaller than 0.5 μm and predominantly to those smaller than 0.1 μm. The smaller the particle, the more rapid the diffusion movement that can occur. The electron microscope size particles are relatively uninfluenced by any deposition force other than that of diffusion, and the fact that such large numbers of particles of this size are found in the lung residue indicates that diffusion can play a major role in their deposition. It has been sug-

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gested that electrostatic and thermal forces may play a role in deposition of particles in the lungs, but this is still uncertain.

On the basis of known physical behavior of particles in air suspension and the anatomical arrangement of the conducting tubes, it can be predicted that particles larger than 10 μm in diameter would be removed completely in the passage of the airstream through the nose and upper airways and that the particles between 5 and 10 μm would be deposited primarily in the upper airways on the mucociliary escalator. Only the particles in the range of 1 to 2 μm would be likely to penetrate into the deeper portions of the lung, where deposition in the alveoli could occur by gravity and diffusion. On the basis of these calculations, particle deposition by sedimentation would be least for particles having a diameter of 0.5 μm; but deposition of particles smaller than this might be increased by diffusion, particularly in the most distal portions of the air system. Numerous actual experimental determinations have confirmed this general distribution for location of deposition. Particles larger than 10 μm in diameter are almost completely removed in the nose, and few, if any, reach the smaller conducting tubes of the lungs. Some smaller particles also are deposited in the nose, but the majority pass through and then are deposited, dependent primarily on their diameters, along the upper or lower airways. Particles greater than 3 μm in diameter have very little opportunity to penetrate beyond the mucociliary apparatus and to be deposited in the most distal alveolated portions of the conducting tubes. Since almost all the particles larger than 3.0 μm in diameter fall on the mucociliary escalator and are removed, there is a reasonable explanation for the very small number of particles of larger size that are found in the lung residue after a lifetime of exposure to aerosols of ambient air that undoubtedly contains particles of larger size.

A fiber represents a special case in terms of deposition. As is true of other particles, the settling velocity of a fiber is dependent primarily on its diameter. In a moving airstream, fibers tend to align their length parallel to the direction of air flow. The fibers that are straight and rigid therefore present an end-on aspect essentially that of their actual diameter. Fibers that are curved, curled, or bent in a U-shape have an end-on aspect equal to the width of the curl or curvature. Insofar as interception is concerned, there is thus a much greater chance for deposition of the nonstraight fibers, a factor of considerable importance in the narrow airways and along the boundaries of air flow close to the surface. It has been demonstrated that curly fibers penetrate to the deeper portions of the lung much less readily than do straight fibers of equivalent diameter (9). Length becomes important also to the degree that the fibers are distributed in a random way in the moving airstream. Thus a fiber 100 μm long oriented at right angles to the direction of flow will have a much greater chance of impacting on the surface than will fibers oriented parallel to the direction of flow. Although occasionally a fiber 200 μm long is observed in the lung dust residues, by far the majority are shorter than 50 μm.

The particles deposited beyond the terminal bronchiole and mucociliary escalator experience one of five fates. It has been suggested that the mucus sheet of the terminal bronchiole is contiguous with a more distal, slow-moving liquid layer manufactured by

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the Clara cell and the type II pneumocyte. Particles falling on this sheet could slowly be pulled up onto the mucociliary system, thus be removed. As a second fate, there is abundant evidence that particles deposited in the alveolus-bearing part of the lung can quickly be ingested by macrophages. The small size of the particles deposited in this area favors ingestion by the macrophage except for the long fibers thin enough to penetrate to this area but too long to be completely engulfed. The limiting length has not been proved, but fibers up to 10 μm long are readily ingested, and even longer fibers can become surrounded by the spreading membrane of the macrophage. By the mechanism of ingestion, particles of various shapes are taken into a cell whose function is to house and process foreign material. In addition, many of the mobile macrophages with their ingested particles move up onto the mucociliary escalator and appear in the sputum or are swallowed. Other macrophages filled with particles simply live out their life and die, discharging the particles, which are reingested by new macrophages. This process is repeated indefinitely. The life of the macrophage under ordinary circumstances is measured in terms of weeks and perhaps even a month or more. Its life can, of course, be shortened if the ingested particles are especially toxic, as is the case with free crystalline silica, which kills the macrophage in a period of hours or days. Materials such as coal, iron, asbestos, and glass do not appear to substantially alter the longevity of the macrophage.

A third fate of particles involves their movement, either naked or inside the macrophage, across the alveolar surface and into the interstitial substance. Once having moved there, some particles appear to remain in this space either free or within macrophages, and others enter the lymphatics and are sieved out in the regional lymphoid tissue, where they may remain indefinitely. A few particles pass on through by way of the lymph into the systemic blood, which then carries them to other organs of the body. The precise mechanism by which particles move through the alveolar surface may involve more than one method, and there is little agreement on this question. A fourth fate of particles is simply to remain free on the surface of the alveolus.

The fifth fate of particles is to be dissolved partially or completely or to disintegrate into smaller particles over a period of time. The small diameter of the respirable particles, hence the large ratio of surface area to weight, promotes the rate at which these reactions can occur. Some inorganic particles such as those comprised of $CaSO_4$ (gypsum) or $CaCO_3$ (limestone, marble, dolomite) are sufficiently soluble in body fluids to be more or less rapidly removed. Fibers of asbestos or glass, thin enough to be respirable, commonly are thought of as being impervious to the influence of body fluids and enzymes such as those contained within macrophages. Evidence is accumulating, however, to show that fibers of this nature fracture transversely into shorter fragments. Moreover, there now is reason to believe that both glass and asbestos fibers of diameters below 0.5 μm actually may dissolve within the lung tissue.

The self-cleaning mechanism of the lung appears to be efficient. Although there is some variation of this capacity between individuals, it has been reported that less than 1 percent of the total calculated amount of dust inhaled remains more or less permanently in the lung (5, 10). The paucity of studies bearing on this effect in humans warrants

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some caution in accepting the figure of 1 percent as applying under all conditions. Nevertheless, the mechanism for removing deposited particles is remarkably effective. It should be borne in mind that the process of lung cleansing adds a portion to the total gastrointestinal tract exposure to exogenous particulates, since a substantial part of the dust brought up on the mucociliary apparatus is swallowed.

4 THE RESPIRATORY FUNCTION OF THE LUNGS

A continuous supply of oxygen to and removal of carbon dioxide from the environment of tissue cells is an essential requirement for life. The demand varies from the resting state to the 10 times or more higher metabolic rates encountered during heavy exercise. The respiratory and cardiovascular systems are intimately associated in this accomplishment. The mass movement of air into and out of the lungs required to satisfy this wide range of demands by the tissue cells is accomplished by the rhythmic application of muscle force to the thoracic boundaries, causing the thorax to enlarge and diminish its volume in the familiar act of breathing. The lungs are attached to the thoracic boundaries by a thin layer of liquid that permits them to follow the excursions of the thoracic walls, thus change their volume in a spatially even manner. The lungs not only are stretchable but in addition are elastic and can recoil by virtue of the abundant elastic tissue in the walls of the airways, alveoli, and blood vessels, and also because of the tension in the ultra-thin layer of liquid overlying the surface of the alveoli. This overlying liquid layer is elastic by reason of its simulation of a "bubble," with consequent surface tension properties. In fact, this force would collapse the lung if not counteracted by phospholipid particles, the "surfactant" manufactured by the type II pneumocyte and discharged into the thin liquid layer (11).

The rate of air exchange within the lungs reflects the depth and frequency of respiration, which in turn is controlled by the respiratory center. Under normal circumstances the ratio between alveolar ventilation and capillary blood flow is essentially the same throughout the lungs, and the arterialized blood is maintained at a remarkably constant oxygen and hydrogen ion concentration over a wide range of physical activity. There is, however, an inequality of distribution of air and blood flow to the individual units of the lung, the lower or more dependent units receiving a larger portion of the total air and blood flow than do the units higher on the vertical axis.

Since both the respiratory and cardiovascular systems are intimately involved in the movement of oxygen and carbon dioxide between the ambient air and the body cells, it is important to know which of these systems is the limiting factor. Without going into the details, the evidence supports the view that the cardiovascular system limits maximum ability for physical performance in normal persons. Because of this, in an overall sense the respiratory apparatus has a larger reserve capacity for function than does the cardiovascular system. Therefore a substantial impairment of pulmonary function can occur before there is a recognizable loss of capacity for physical effort, especially since the lungs are made up of literally millions of identical units and most types of pulmonary injury involve only some of the units while sparing the others.

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5 REACTION OF THE LUNG TO INHALED PARTICLES OF DUST

Utilizing knowledge of the cellular components and organization of the lungs plus the manner in which cells respond to stimulation or injury, one might anticipate the various reactions this organ would display to the deposition of dust. As stated earlier, whether such reactions will develop depends on the nature and number of specific particles deposited and retained, as well as the influence of coexisting inhaled agents and the reactivity of the host or individual.

That dust particles can stimulate the smooth muscle distributed in a circular fashion within the thin-walled portions of the airways, thus narrowing the lumen and raising the resistance to airflow, has been demonstrated to occur as a reversible reaction following the inhalation of high concentrations of dust (12). This response in most persons requires high concentrations of dust and is not recognized to occur commonly in the workplace. In persons who for one or another reason are hyperreactive, however, lower concentrations of dust may evoke a recognizable response.

The deposition of dust on the mucociliary apparatus normally stimulates a flow of mucus. If the production of mucus is excessive, or if it is not removed adequately, it can accumulate in the airways, thus reducing the lumen of the conducting tubes and elevating the resistance to airflow. Furthermore, prolonged stimulation of the mucus-secreting glands and cells can lead to hypertrophy or enlargement of these structures. The enlarged subepithelial glands can encroach upon the lumen and cause persistent narrowing of the airways and elevation of resistance to airflow.

Particles of dust lodging on and beneath the surface of the alveoli stimulate the recruitment and accumulation of macrophages in this area. There can be enough of these cells to partially or completely fill some alveoli, but because of the cells' ability to move out onto the mucociliary escalator or into the lymphatics, this is unusual. Some particles are always found lying free on the surface of the alveolus, but whether these have never been phagocytized or whether they are waiting for reingestion cannot be determined. Presumably particles could stimulate any of the lung cells they come directly or indirectly into contact with, or they may act through the intermediary of cells such as the macrophage. Some particles lodged on or just beneath the alveolar surface appear to induce a proliferative reaction and become overgrown by the surface cells—at least they are found embedded in a mass of cells involving the surface and the immediate substructure of the alveoli. This reaction can evolve to include cells such as lymphocytes, macrophages, and polymorphonuclear leucocytes, as well as other components of the interstitial or connective tissue and the regional lymphoid collections of the lung. At times such reactions are transitory, but they may become chronic or persistent.

Since fibroblasts are present in the interstitium of the lung, these cells may be stimulated to form excessive amounts of reticulin or collagen. Excessive collagen formation is likely to accompany prolonged or chronic inflammation in most organs of the body. This is a part of the familiar formation of scar tissue, whether it be in the skin or in deeper portions of the body or in the lung. Pulmonary fibrosis is a common sequela of chronic pulmonary inflammation. The pathogenesis of pulmonary fibrosis caused by deposition of some kinds of dust is not entirely clear. It has been postulated in recent years that

since the macrophage contains small vesicles holding potent enzymes, these substances may be released by certain ingested particles, but not all kinds, thus altering the cell milieu and causing premature death of the macrophage. The products released by the macrophage are then believed to stimulate the fibroblasts to lay down excessive amounts of collagen, thus promoting the development of tissue fibrosis (13). It has also been suggested that fibers not completely engulfed within the macrophage but protruding through the wall permit leakage of the macrophage content, and this material might also stimulate the fibroblasts to increased activity (14). These concepts are interesting because some dust particles are known to be relatively inert and not capable of causing an excess of fibrous tissue production. Such particles, though readily ingested by the macrophage, do not cause the premature death of the macrophage. In contrast, free crystalline silica, a known fibrogenic dust, has been demonstrated to exert this effect.

Malignant transformation can be the fate of any cell that can divide, and those of the lung are no exception. The cells lining the surface of all the airways and alveoli have a particularly fast turnover rate, hence are probably more vulnerable to carcinogenic alteration by a dust or other agents. In addition, particles lodged on the surface of the air-conducting tubes might promote an even higher turnover rate of the surface cells, *thus making them unusually vulnerable to carcinogenic substances. Toxic agents adher*ing to particles could leach off onto the cells with a similar effect. A combination of these effects could lead to metaplasia or could play a role directly or indirectly in malignant transformation of the cells lining the conducting airways.

On the basis of the foregoing considerations, one could anticipate that dust deposited in the lungs might induce:

1. Little or no reaction of any kind.
2. Hyperproduction of mucus secretion.
3. Hypertrophy of mucus-secreting glands.
4. Macrophage recruitment and ingestion of particles.
5. Chronic proliferative or inflammatory reaction.
6. Reticulinosis.
7. Fibrosis.
8. Cell metaplasia or malignant transformation.

6 INFLUENCE OF ALTERED LUNG STRUCTURE ON PULMONARY FUNCTION

Narrowing of the airways, whether caused by muscle contraction, accumulation of mucus, or hypertrophy of the mucous glands, will increase the resistance to airflow through the involved tubes. It should be noted that resistance to airflow through a tube is a function not only of the length of the tube but of the fourth power of the radius (*Poiseuille's law*). For this reason, relatively small changes in the radius over a substantial length of the tube have a marked influence on the resistance to airflow. If the increased resistance to airflow occurs more or less uniformly throughout all the lung, the

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work of breathing is commensurately increased, and the volume of air moved per unit of effort is reduced. This not only decreases the maximum available capacity for mass movement of air but causes the expenditure of unusual respiratory effort at all volumes of air movement. Breathlessness or "shortness of breath" is closely related to the awareness of respiratory effort; hence the increased use of respiratory force to move each unit of air leads to the development of breathlessness at lower than normal levels of exercise and to a reduction of the maximum capacity for physical effort. If, as is usually the case, there is focal or regional variation of airway resistance, there will be a shunting of airflow away from the alveoli supplied by the airways experiencing the higher resistance. This leads to regional alveolar underventilation and produces a mismatch between ventilation and capillary blood perfusion in the lung region involved, causing the blood leaving the underventilated area to have a subnormal oxygen and an elevated carbon dioxide content. As a consequence, the arterial blood going to the tissues will be below normal in oxygen content. To some degree, coexisting overventilated alveoli can compensate by increased carbon dioxide removal; but if the regional hypoventilation is extensive, there can also be an accumulation of carbon dioxide in the arterial blood returning to the tissues.

The body attempts, with partial success, to correct this mismatch between ventilation and perfusion in the following manner. The low alveolar oxygen tension developing in the hypoventilated regions produces an effect on the alveolar blood capillaries causing partial closure of the capillaries, thus an increase in capillary blood flow resistance and a shunting of blood from the hypoventilated alveoli to those that are more normally ventilated. If the number of underventilated alveoli involved is relatively small, this is an effective mechanism; but if many alveoli are involved, the narrowing of the alveolar capillaries produces an elevated resistance to blood flow in the entire pulmonary circuit, with consequent pulmonary artery hypertension and the bad effects that flow from it. From these comments it can be seen that airway narrowing can lead to rather serious malfunction of the cardiorespiratory system and can be the cause of severe physical impairment, ultimately leading to death.

Chronic intrapulmonary inflammatory and fibrotic changes cause distortions of pulmonary architecture leading to functional derangements. In regions where the cellular infiltrate or fibrosis destroys functioning lung tissue *en bloc*, the effect is similar to that of simply removing this amount of lung. If the volume of tissue involved is relatively small, there is little or no measurable alteration of pulmonary function. If the volume of destroyed tissue is large, the remaining normal lung will be much smaller and will behave in an overall less compliant fashion than would a larger volume of lung. In addition, there will be a measurable loss of pulmonary vascular bed or diffusing surface. Moreover, because of the loss of arterioles and capillaries, more force will be needed to drive the normally required total amounts of blood flow through the pulmonary circulation. This in turn leads to pulmonary artery hypertension and the abnormalities consequent to that condition. If the fibrotic or inflammatory reaction is arranged as ribbons running diffusely throughout the lung, the entrapped normal lung units will be less compliant and the work required to change lung volume and produce a unit of mass

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movement of air will be increased. The work of breathing will be augmented, and the maximum ability to move air into and out of the lungs will be curtailed. Some portions of the entrapped normal lung between the ribbons of diseased tissue will be underventilated, and a mismatch between ventilation and perfusion will ensue.

It is of interest to observe that although an elevated resistance to airflow and a decrease in pulmonary compliance affect lung mechanics differently, the end results in terms of overall physiological impairment of the respiratory apparatus are quite similar. Both cause an increase in work of breathing, a loss of maximum ability to move air into and out of the lungs, a mismatch of the ventilation perfusion relationship, with consequent arterial hypoxia, and an elevation in the pulmonary artery pressure. One difference is that in airway obstruction there is carbon dioxide retention and an elevation of arterial pCO_2, whereas in the abnormalities associated with loss of compliance caused by chronic inflammation or fibrosis, carbon dioxide transfer is interfered with relatively slightly or not at all and an elevated pCO_2 usually does not develop.

7 CRITIQUE OF THE METHODS USED TO STUDY THE PULMONARY EFFECTS OF INHALED INORGANIC DUST

Knowledge about the way in which humans will respond to inhaled dust should be derived from the demonstrable effects of inhaled particles as observed in humans. Extrapolation from other modes of study such as animal experimentation or cell culture is speculation, even though this may be warranted or even necessary under some circumstances. Unfortunately the technical conditions imposed on observations of humans, especially when retrospective observations are made or new substances are being considered, at times limit the availability of the human study modality. Therefore experimental animals or isolated organ or cell systems are often utilized to explore the possibilities of inducing tissue reaction in the lung, the factors that control the reaction, and the biological mechanisms involved. The animal and cell modalities are used most appropriately for examining aspects of the overall question that cannot be approached by human study alone. This does not, however, assure the validity of extrapolating from animal studies to human experience.

The advantages provided by animal or cell experiments are several. The exposure can be controlled with respect to varying its concentration, its duration, and whether single agents or combinations are presented. The opportunity to follow the course of events by serial sampling of the tissue is available only with animal or cell experiments. Also it is possible to repeat experiments under controlled conditions in animals. The shorter life span of small animals is an advantage in that the process of carcinogenesis is telescoped into a shorter period of time, thus shortening the duration of the experiment. Although the methods used for examining tissues anatomically or biochemically are essentially the same whether animals or humans are being examined, there are some advantages to the use of animal tissue. Since dust particles are distributed in a nonhomogeneous way, the effects have a patchy distribution also. There is an advantage then to being able to

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examine whole lung slices and to do biochemical analysis, such as for hydroxyproline on whole lungs of animals.

These manifest advantages explain why the animal or cell models are so widely used. There are, however, some very important and virtually insurmountable disadvantages associated with the use of these models if one intends to extrapolate to human experience. With respect to isolated cell systems, there are two important disadvantages. First, the systems are not under the normal influence of humoral and cellular controls provided by neighboring cells or emanating from other organs and circulating cells that exist in the intact animal or man. Second, long-term experiments cannot be done, since cell survival is rather brief in any event.

Animal experiments avoid these two difficulties but are limited in several other ways. There is always the influence of species difference with respect to carcinogenesis. Humans are but a single species of animal and do not invariably mimic the tissue reactions of other species. Also, experimental animals usually are kept under environmental conditions quite different from those of humans. For example, animals other than man do not smoke tobacco, a common biologically active coexisting agent in human respiratory exposure patterns. Although a 2-year-old rat may be equivalent to a 60-year-old human with respect to cell line aging, it will have had 58 fewer years of exposure to the coexisting agents usually being studied. Moreover, physical and emotional stress induced by caging conditions can influence the biological response of animals. How similar are the environmental conditions of man throughout his lifetime to those of the experimental animal in this respect?

The exposure concentrations used in animal experiments are usually at a level very much higher than those occurring in human experience. Understandably, this is done deliberately to guarantee an effect in animals if it is at all possible to produce one. Unfortunately, when a biological effect is produced, there is all too often little effort to determine or take into account the response at lower concentrations—the dose–response curve.

There is also a difficulty posed by the number of animals available for use in experimental protocols. Contrary to popular belief, an unlimited number of animals—or, in many experiments, the number actually needed for the kinds of extrapolation commonly made—is not realistically available for most animal experiments. This is especially true of the experiments seeking a no-effect level, as well as when the biological response of any type is meager. As a matter of fact, the number of individuals at risk and as controls is usually superior in human epidemiologic studies to the number available for most animal experiments. Few research laboratories can afford to buy or breed, feed, and house the number of animals needed to establish epidemiologic validity in their studies. Because of this fundamental defect, the conclusions reached by some animal studies are of questionable validity.

Observation of the effects of inhaled dust in humans has been the conventional way for establishing whether a biological reaction occurs. Clinical and autopsy or histological examination of the lungs of men working in the presence of the agent under study is the mainstay of this approach. A difficulty arises, however, because the cellular components

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of the lung will react in the same manner to a number of different kinds of stimulating agent. For example, the development of a biological abnormality in a person employed in a particular way might suggest the possibility of a relationship between an agent in the occupational environment and the biological disturbance observed. On the other hand, since the same biological abnormality of the lung can develop from various causes, the single isolated case may in fact be caused by something other than the agent present in the specific dust exposure. Therefore, although the clinical and histological approach is of great importance in determining whether an abnormality is present, other modalities to prove its relationship to a specific agent must be used. For this purpose the techniques of epidemiology are useful, and the reader is referred to Chapter 5 for discussion of this discipline.

To return to the advantages and disadvantages inherent in observation of human populations, it cannot be stressed too strongly that the greatest advantage of this approach is that no extrapolations are needed. Moreover, the exposure is that of a real-life circumstance with respect to the multiple other factors that may be playing a role. There is an advantage also in the greater possibility for observation of larger numbers of persons both at risk and in the control population. These advantages sometimes are offset by other problems that pose large difficulties. The first of these is the difficulty of making retrospective estimates of the total exposure of the individual to the specific agent in question, expressed in quantitative terms over long periods of time. At times the only available expression is that of duration of employment. Undocumented changes in the environment of the workplace over the many years of employment and the lack of records or measurements of the various agents present during the same period cannot be corrected for. Under such circumstances one can only compare the overall clinical or mortality experience of the observed group to that of some other group, usually the population at large. From such observations it is impossible to derive information usable for establishing the dose–effect relationship. Under such circumstances one also cannot be sure of just which of several coexisting agents is the cause of the biological reaction. Nor can one be sure that cofactors are not operating as the ultimate biological stimulus. To attribute the biological reactions observed to specific agents under such circumstances, though at times a temptation, is a practice of questionable validity.

A second disadvantage associated with human epidemiologic studies is that whereas in animals the lungs may be examined by microscope or chemical methods at any point in time relative to the exposure, these modalities are available in human epidemiologic studies only at death. Since only a portion of the deaths from any population are autopsied, there is a strong possibility of bias posed by autopsy selection, and epidemiologic data derived from autopsy studies must be accepted with some caution. In addition, autopsies rarely are done with the epidemiologic study in mind, and important observations may be lacking, whereas the opposite is true in animal experiments. To the extent that epidemiological studies are dependent on death certificates, they are subject to faults such as erroneous diagnosis, "styles" or "fashions" of diagnosis, incomplete diagnosis, and very commonly, partial unavailability of death certificates. These faults become

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particularly grievous when small numbers of a highly localized population are compared to the population of a state or of the entire country.

Because of the difficulties attending the use of mortality data, an alternate epidemiological approach is to relate the data derived by medical or physiological examinations during life to exposure up to that point in time. This approach does not take into account the results that might occur over a full life-span, and it is particularly limited with respect to the search for relationships between dust exposure and carcinogenesis. Nevertheless, with respect to ill health or impairment of function, a properly designed epidemiologic study during life can in a very useful way serve to compare the frequency of types of impairment or disease in the study group versus an internal control population ranked by the severity of exposure or to an external control population of persons not exposed to the agent in question. This approach has a high degree of validity.

It is certain that biological reactions too minor in extent or intensity to be discovered occur in lung tissue before evolving to an extent recognizable by our methods of searching for these changes during life. How should one view the importance of these subclinical alterations of tissue? The goal is to *prevent disease,* with its associated impairment of function leading to a reduced capacity for normal activity and in some instances to shortened life expectancy. Therefore it is important to distinguish between a small and limited area of tissue injury and what we mean by disease. The differentiation hinges on whether impairment of vital function will occur or has occurred. Cell death and orderly replacement by replication of cells characterizes the human lung from birth to death. Physical factors and external agents such as viruses and bacteria active in small areas of the lung commonly influence the orderly process of cell death and replacement during the state we call "good health." When one examines the body of an adult who has given no prior evidence of lung disease, some pulmonary fibrosis representing the end stage of injury is invariably found. Since these effects are minor in extent and occur in an organ possessing more reserves than can be used by normal persons, such minor scars do not in any way interfere with pulmonary function or life expectancy. There is, therefore, a quantitative as well as a qualitative aspect to body impairment and disease. In the light of these comments, it is imperative to realize that there is no sharp line of demarcation between being well or ill, normal or diseased, or injured or uninjured. We can speak in rather broad terms of the way in which gases and particles may or may not affect the lung, but insofar as impairment or disease is concerned, the quantitative aspects are probably more important under most circumstances than are the qualitative.

With the exception of sputum cytology, microscopic examination of the lungs of humans is not available for the purpose of early recognition of change in the individual. Epidemiologic studies during life are limited, therefore, to clinical, radiologic, pulmonary function, and sputum cytology modalities. Advantageous as these are, their inherent weaknesses must be recognized if the validity of conclusions derived from their use is to be evaluated.

The clinical history is subjective and difficult to confirm. Physical examination, chest radiography, and pulmonary function measurement, although more objective, exhibit a

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rather large variation of values among normal persons. Therefore, the recognition of "change" in an individual is difficult unless the observation can be made before as well as after the onset of exposure. This difficulty can be lessened by comparing the average of observations of one group to that of another group serving as a control. The various techniques for these examination modalities require skilled personnel and equipment not always available. In spite of these difficulties, virtually without exception these modalities, when properly used, will permit recognition of deviation from normal before there is interference with vital body functions, thus they are of great use for studying the tissue reaction to inhaled dust during life.

The chest radiogram exhibits shadows cast because of the greater absorption or deflection of X-ray photons by tissues of greater density. Highly cellular or fibrotic tissue is more dense than normal tissue, and when the difference is great enough or when the shadow is located where it should not exist, the normal shadows are altered. A difficulty arises because there is considerable variation between normal persons in the shadows cast by normal lung structure such as blood vessel and supporting lung tissue. Grossly abnormal lungs are readily recognized by alteration of the normal pattern of shadows, but minor tissue alterations make either no or very slight change in the pattern of densities. Therefore there is always a gray area of differing opinions between readers of the films from persons experiencing slight tissue alteration: are the shadows present in the radiogram those of normal or abnormal structure? For epidemiologic studies, these differences can be lessened by the use of multiple readers using the UICC system of notation and standard reference films (15).

Measurements of pulmonary function are aimed primarily at recognition and quantification of changes in pulmonary airway resistance, pulmonary compliance, the alveolar ventilation–perfusion relationship, and the total effective area of the alveolocapillary membrane. Using rather sophisticated methods, these aspects of pulmonary mechanics can be measured rather accurately. Recognition that an alteration of any of these functions has occurred is hampered by the wide range of values existing between normal persons. One of the less difficult, thus more widely used measurements, is the fast vital capacity (FVC), or volume of air expelled by prolonged, explosively applied maximum expiratory force beginning at the position of full inspiration. This not only indicates the stroke volume of the respiratory pump but also, because maximum expiratory effort is applied rapidly, it reflects the speed with which the air can be pushed through the distribution system, and this in turn reflects airway resistance. For this purpose, the volume expelled in the first second (FEV_1), expressed either as a percentage of the predicted volume or as a percentage of the total volume expelled, serves as the reflection of airway resistance. Other portions of the expiratory curve can be used for the same purpose.

With a few exceptions, such as the presence of large space occupying masses within the thorax or extreme obesity, pulmonary compliance is in part reflected by the total lung volume at maximum inspiration. Accurate measurement of total volume requires the use of a tracer gas or a plethysmograph, and it is therefore seldom used. An indirect expression of compliance can be obtained in the following manner. Both an elevated

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airway resistance and a lessened compliance will cause a reduction in FVC, thus when looked at alone will not differentiate between the two conditions. When airway resistance is the cause of the subnormal FVC, however, the FEV_1/FVC ratio is substantially lower than normal. In contrast, when the subnormal FVC is caused by a lessened compliance, this ratio is either normal or slightly reduced, or it may actually be increased.

The foregoing methods of measurement are useful in epidemiologic studies when a contrast between normal and moderately severe alteration of pulmonary function is expected. They will not suffice for recognition of minor changes in airway resistance or pulmonary compliance. This calls for more sophisticated measurement, utilizing body plethysmography.

In most circumstances the ventilation perfusion relationship is reflected by the arterial blood–gas measurements. Alteration in the size and character of the alveolocapillary membrane is best measured by the diffusion coefficient for carbon monoxide. Since these measurements require carefully controlled technical procedures that are not always available, they are rarely used in epidemiologic studies. Nevertheless, when one searches for biological reactions to dust in the lungs, these modalities should be used at some point in the overall study.

8 BIOLOGICAL EFFECTS OF SPECIFIC INHALED INORGANIC DUSTS

The variety of inorganic dusts to which humans are exposed either in pure or mixed form is large. A prototype of the effects of several will demonstrate the biological effects produced.

8.1 Nonfibrogenic or "Inert" Dust

Although some dusts are classified as biologically inert, the designation can be misleading. A more correct implication would be that such dusts do not cause pulmonary fibrosis, physical impairment, or disease. In that context, the classification is useful.

All durable inorganic dusts will evoke mobilization of macrophages. This response is a daily occurrence in all walks of life. Depending on the number of particles entering the alveoli over a period of time and the resistance of such particles to destruction by the macrophage, there will be an accumulation of these particles either free or inside macrophages within and around the alveoli. Particles classified as being inert (16) appear to be slightly if at all toxic to the macrophage in which they come to reside. The host macrophage dies after a normal or near-normal cell life-span, and the ingested particles are released but then undergo reingestion by another macrophage. Repetition of this cycle appears to have no limit.

After a long period of exposure to durable nonfibrogenic particles of respirable size, the particles will be found distributed within alveoli; within the interstitial tissue supporting the alveoli, airways, and blood vessels; and within the small and large collec-

tions of lymphoid tissues scattered throughout the lung. The particles at any point in time may be found free or within macrophages at any one of these locations. The particles attached to the alveolar surface at times appear to be overgrown by the type I alveolar pneumocyte, forming a plaque within the alveolar wall. In locations where the particles accumulate in small collections, within either the supporting connective or the lymphoid tissue, there is a slight proliferation of monocytic cells accompanied by a slight increase of interlacing reticulin fibers. Collagen fibers, thus genuine fibrosis, do not develop either in these small dust foci or within the lymphoid tissue more centrally located along the course of the lymphatics. The size of the focal collection of dust particles is directly related to the intensity and duration of the exposure.

Insofar as an effect on pulmonary function or longevity of life is concerned, it is of paramount importance that these particles evoke neither fibrosis or alteration of the basic lung structure. The tiny particles are present, but no destruction or replacement of normal tissue occurs. Since the fundamental mechanical quality of the lung is that of distensibility and elasticity based on the arrangement of tissue fibers having elastic qualities combined with an intact surface lining of the alveoli, one can understand why the mere physical presence of small foci of particles scattered sparsely in the interstices or on the surface of the alveolus would not affect the physical quality of the lung. It is only when the normal structure of the lung is destroyed or immobilized by replacement with nondistensible fibrous tissue that measurable impairment of pulmonary function ensues.

When the nonfibrogenic dust has a low atomic number, the foci of accumulated particles do not interrupt or deflect sufficient X-ray photons to cast a shadow, and the radiogram exhibits no unusual pattern of densities. In contrast, foci of nonfibrogenic particles having a higher atomic number do interrupt and deflect X-ray photons sufficiently to cast shadows, even though they do not evoke an inflammatory or fibrotic reaction within the tissues. They cause the radiogram to have a striking appearance when sufficient quantities of the particles have been accumulated. Among the inert dusts having a high atomic number are iron, tin, barium, and antimony.

Workers may be exposed to oxides of iron either as a dust or as a fume, as during welding, and the biological result is referred to as siderosis even though no fibrosis is induced (17). When the lungs are examined, they are rust-brown as a result of the focal depositions of iron, and microscopic examination reveals particles of iron oxide distributed in the manner common to all respirable particles. Characteristically, the particles are collected in discrete foci or macules associated with lymphoid tissue and around the smaller blood vessels. There is the usual minor accumulation of reticulin fibers and monocytes in the focal deposits of particles, but no true fibrotic reaction occurs. The dust foci of this material of higher atomic number cast a distinct, small, rounded nodular shadow on the film, tending to be no greater than 1 to 2 mm in diameter. When materials of an even higher atomic number such as tin or barium are inhaled, the shadows cast by the focal deposits may have a very sharp margin, and the large collections of particles in the lymph nodes at the lung root may cause these structures to be unusually radioopaque because of their metal content, but they are not enlarged as is so

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often the case in silicosis. There is no evidence of any impairment of cardiopulmonary function or any reduction of life expectancy in individuals with siderosis.

An excess of malignant transformation manifested as bronchogenic cancer has been reported among iron ore miners, but unusually high levels of radon have been reported in the same mines, and this is considered to be the more likely cause (18). The evidence to incriminate iron oxide or any of the inert dusts as a carcinogen is not convincing. As is the case with other of the inert dusts, exposure to iron oxide, especially in mining, is often combined with exposure to free crystalline silica, and siderosilicosis is the resulting entity. It should be borne in mind that silica is the etiologic or active agent in any impairment that ensues.

The possibility must be recognized that deposition of inert particles on the surface of the upper airways where the mucus-secreting apparatus is located might stimulate that mechanism to an inordinant degree. Such stimulation might lead to excessive production of mucus and to hypertrophy of the mucous glands or to impairment of the ciliary system. Thus although inert dusts do not produce tissue fibrosis, they could lead to excessive production of mucus and mucous gland hypertrophy and to increased airway resistance. The question of whether chronic bronchitis is an outcome of heavy exposure to dusts of various kinds over a long period of time is discussed later in this chapter.

8.2 Fibrogenic Dusts

8.2.1 Free Crystalline Silica

In contrast to the inert dusts, particles of free crystalline silica (FCS) have a strikingly different biological end effect (19). Silicon, the element, does not exist free in nature. It occurs most commonly as silica in the combined form of crystalline or amorphous silica (SiO_2) or as SiO_2 combined with one or another cation as a simple or complex crystalline or amorphous silicate.

FCS exists as quartz, tridymite, cristobalite, coesite, and stishovite. Of these, stishovite is essentially nonfibrogenic, whereas cristobalite and tridymite are more fibrogenic than quartz. In nature, quartz occurs as the most common of the three forms and is the one most frequently encountered during occupational exposures. It is converted to tridymite when heated to between 860 and 1470°C, and above 1470°C to it becomes cristobalite.

When the intensity and duration of exposure are too high to be defended against effectively, respirable sized particles of FCS accumulate in the alveolated regions of the lung. As is the case with inert dust particles, at any point in time the FCS particles will be distributed throughout the lung tissue in the manner described earlier for all respirable particles. Thus focal deposits of FCS, either free or within macrophages, will form in a discrete fashion throughout the lungs and lymphoid tissue. It has been suggested that FCS particles move more easily, therefore in larger numbers, through the alveolar wall to the interstitium and the lymph nodes than is the case with inert particles. This may be because particles of FCS are toxic to the macrophage. The life of the host

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macrophage is thus greatly shortened, their number diminished, and the defense against movement of particles into the interstitium and lymphoid tissue is thereby reduced.

The subsequent course of events within the foci of FCS particles is strikingly different from that characterizing similar foci of inert particles. At first, but with greater speed of development, fibroblasts increase in number and reticulin fibers are laid down in an interlacing fashion throughout the focal deposit. Instead of stopping at the point of reticulin development, which is the case with inert particles, the foci of FCS go on to develop masses of interlacing collagen fibers, and mature fibrosis characterized by the deposition of hyalin ensues.

With the passage of time the focus or nodule undergoing fibrosis enlarges, the active process going on at the periphery leaving behind a progressively larger central mass of mature fibrous tissue. The mature nodule has a characteristic whorled fibrous tissue appearance almost devoid of cells at its center. This mass is surrounded by a zone of reticulin and collagen fibers containing a few fibroblasts, and surrounding this layer is a peripheral zone of cells in which can be seen the process of laying down reticulin and collagen by fibroblasts, mixed in with macrophages and other mononucleated cells, in the process of forming fibrous tissue. At first the nodules are spaced rather far apart, the intervening lung or lymphoid tissue being free of abnormality. As the number of nodules increases, there is a tendency for them to coalesce and form a larger multicentric nodule, which may reach several millimeters in diameter. At all times large amounts of normal lung tissue persist between the individual or clustered nodules. In many individuals the reaction does not progress beyond this point, and the lung can be described as being the site of simple discrete nodular fibrosis. In other cases, however, there develops massive conglomeration of nodules, merging in a cement of dense fibrosis. These masses can become quite large, occupying in some cases as much as half of each lung. On the immediate periphery of the larger conglomerate masses and even some of the large single discrete nodules, the airspaces of the lung are larger than normal. This type of perifocal emphysema should not be confused with diffuse generalized emphysema of the lung, which is not a characteristic part of the anatomical alterations accompanying the interaction between FCS and lung tissue.

In most cases the fibrotic tissue development in the advanced nodular stage and especially in the conglomerate stage will extend to involve the pleura. As a result, the pleural space commonly is bridged by adhesions or is obliterated over large parts of the lung surface. The pleura itself may be unusually thickened, sometimes markedly so, over a large portion of the lung.

There is no precise location in the lung structure at which a silicotic nodule can be said to begin. A cluster of alveoli and adjacent subalveolar tissue, including small aggregations of lymphoid tissue, become involved virtually simultaneously. The air passages and pulmonary capillary bed caught up in this reaction are destroyed in the process of formation of the nodule. The lung tissue intervening between the nodules remains free of any discernable change. This is true even when large conglomerate masses also are present. Although there is undoubtedly some migration of the particles of FCS from their locus of deposition into aggregates or foci, the distribution of the

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nodules and the freedom from abnormality in the intervening tissues strongly suggests that the FCS particles taken into the lung are not dispersed in a completely even manner. One must assume that some regions of the lung receive far fewer particles than do others, and the lung cleansing mechanism keeps the total particles in such areas below a critical level.

In a similar manner, although the small regional lymph collections are usually destroyed in the fibrotic mass of the nodule, in the lymph nodes at the lung root the development of silicotic nodulation with sparing of intervening lymhpoid tissue is the rule. The involved lymph nodes become quite large and firm or hard as a result of the process. In some cases the nodules, whether located in lung or lymph node, may become calcified, producing a striking radiograph.

A number of explanations for the mechanism whereby FCS stimulates fibrogenesis have been put forth over the years. The most compelling, and the one having the greatest experimental support, is that developed by Heppleston (13). Leaving aside the question of just how the silica surface disrupts cell membranes, it can be stated that the ingested particles of silica rather quickly kill the host macrophage. In cell culture this happens wihin hours, but in the normal milieu of the body it probably takes considerably longer, perhaps several days. Heppleston deduces from his studies that "on present evidence it may be concluded that silica in some way reacts with cell constituents, probably lysosomal, to produce or activate a relatively soluble substance capable of stimulating collagen formation, possibly acting in low concentrations." Since the fibrogenic action of FCS is dependent on a continuous supply of macrophages in the foci where the particles have accumulated, a mechanism to promote this recruitment is needed. On the basis of his own work and that of others, Heppleston further suggests that the lipid material abundantly released from the dying macrophage killed by FCS acts as a stimulant for the accelerated production and delivery of macrophages to the foci containing FCS.

There is evidence that interaction between the membranes of the macrophage and the surface of the silica particles is the key to the death of the host macrophage. Alteration of the surface of the FCS particles by polyvinylpyridine-*N*-oxide and other agents, including dusts such as clay or iron, which commonly coexists with silica in occupational exposures considerably lessens or may even prevent the fibrogenic response.

On the basis of both human epidemiologic study and animal experiments, as is true of other toxicological reactions, the fibrogenic activity of FCS appears to be a dose-related phenomenon. One can envision the following train of events. A critical amount of FCS must accumulate and be ingested by a sufficient number of macrophages to supply the necessary amount of stimulation to fibroblasts before the process is pushed beyond the stage of reticulin formation into that of collagen formation. The development of hyalin, to reach the mature stage of the nodules, is more complex and appears in part to involve immunological processes. The rate at which the entire process goes on, once it has reached the critical concentration of FCS and macrophages, is related to the speed with which silica particles accumulate and the rate at which the macrophages die, plus a still ill-defined immune response. The rate of FCS accumulation in the various foci is

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dependent on the balance between deposition and removal from the lung. The entire process is in constant change, even after all external exposure ceases. Some particles are removed from contact with the macrophages within the focal deposit by being sequestered within the central mass of acellular fibrotic tissue and in addition, there is a continuous migration of particles away from the pulmonary foci to the lymph nodes and even to the mucociliary escalator.

According to the concept just expressed there is a level of silica accumulation below which the fibrogenic train of events is not set in motion. This is the tolerable dose. Moreover, once the critical level is reached, acceleration of the whole process will occur if the dose of the effective factor, probably the free bonds on the surface of the crystals, is rapidly augmented. This is consistent with the facts because if FCS accumulation occurs rapidly, the biological response, though fundamentally the same, has a distribution different from the one just described. In these circumstances, it appears that not all the particles have time to be transported to foci, and they accumulate along the way with a more diffuse macrophage mobilization and consequent fibrogenesis distributed in a more widespread, nonnodular manner. This produces a linear, mixed with a nodular, fibrotic reaction that has been called acute silicosis but is probably better termed accelerated silicosis, since it requires several years to develop. The accelerated process appears to be further aggravated if the particles are not only abundant but also especially small, less than 1 μm in diameter, thus providing an unusually large surface area per unit of weight.

A third variety of reaction to FCS has been reported under circumstances of extremely severe exposure, for example, in the process of sand blasting. This reaction shows combined interstitial fibrosis plus lipoproteinosis-like lesions in which the alveoli are filled with a pink-staining, relatively acellular material. This reaction may develop within less than a year, proceeding rapidly to a fatal outcome, and it merits the term "acute silicosis" (20).

As might be anticipated from knowledge of the effects of FCS on lung tissue, the evidences observable during life that these reactions have occurred will vary. At slight stages of development there are no observable evidences of tissue alteration except by direct examination of the tissue itself. The earliest sign during life is observed in the chest roentgenograms as an increase in the size and visibility of the shadows cast by the bronchovascular structures located in the outer reaches of the lungs. Presumably these changes are caused by accumulation of FCS and the slight cellular reaction produced. When the nodules within the lung develop sufficient size and density as a result of the mature cellular and fibrotic reaction, they cast abnormal shadows ranging from barely perceptible, multiple, small, rounded densities to larger and conglomerate densities plus enlargement of the lung root shadows. The number of densities varies from scant to myriads, and the nodules are predominantly located in the upper half of each lung. The very large conglomerate shadows are almost invariably in this region. Shadows cast by thickened pleura can also be seen.

Even at the stage of easily recognized discrete nodular silicosis, there usually are no accompanying symptoms and no detectable evidence of pulmonary or overall physical impairment unless the volume of lung involved is unusually large or other nonrelated

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causes of impairment coexist. In part, this reflects the fact that the functions of the lung are not the limiting factor for physical performance. Of greatest importance, however, is the fact that in pure simple nodular silicosis, the intervening tissue is normal. Physically the diseased areas have destroyed the lung in a focal or nodular fashion, and they comprise a relatively minor part of the total lung. The normal remaining portion of the lung tissue can readily accommodate the cyclic changes in thoracic volume during respiration; in addition, it can accept an increase in blood perfusion without an elevation of arterial pressure. In this fashion, cardiopulmonary function in the range that is needed during physical exercise is maintained. It must be said that if measurements of pulmonary function could be made in each individual before occupational exposure begins and after the nodulations appear, the person could serve as his own control, and alterations of pulmonary function might be recognized at an earlier stage than is possible when the first examination occurs after the nodules are already present.

Individuals showing overt radiographic evidence of nodular silicosis who also have a lessened capacity for physical effort because of unusual breathlessness on exertion are found in most instances to have a restrictive type of functional impairment. In others, however, there is an obstructive type or a combination of the two. The restrictive type of impairment can readily be accounted for by loss of lung tissue consequent to the extensive fibrosis, and it is most readily demonstrated in those who exhibit a combined massive conglomerate and linear type of disease. When severe, this kind of impairment can lead to pulmonary artery hypertension and cardiac failure. In some persons, though by no means all, impairment of oxygen transfer with associated arterial hypoxia develops.

Restrictive impairment is consistent with the specific pathology of silicosis. An obstructive type of impairment, though sometimes observed in individuals with simple discrete nodular silicosis, is difficult to reconcile with the specific pathology attributable to FCS per se. Either chronic bronchitis or obstructive emphysema or a combination of the two are the common causes of airway obstruction in the general population. In view of the great frequency with which an obstructive impairment occurs in men over age 50 among the general population, when an obstructive impairment is observed in persons who have silicosis, it would seem to be more consistent with the facts to attribute it to causes other than FCS per se. Cigarette smoking and the nonspecific effects of FCS or other coexisting dusts and fumes in the workplace play an etiologic role in the production of chronic bronchitis and ultimately may be shown to influence the development of obstructive emphysema. Cognizance of this probability directs our attention to the need for controlling the total dust, fume, and irritant gas exposure, not just that of FCS in the workplace.

It is rather remarkable in view of the multifocal fibrosis characteristic of silicosis that there is no convincing evidence of malignant transformation or carcinogenic effect. At the same time it must be said that a properly conducted epidemiologic study designed to explore the question of carcinogenesis in those exposed to FCS has not been made.

From what has been presented thus far, it could be concluded that silicosis in and of itself is not a severe crippling or life-shortening disease unless the fibrosis is very extensive. This, in fact, is the case. Why then has silicosis been an important cause of mor-

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bidity and death? The answer lies not in the discrete nodules characteristic of silicosis but in the very adverse influence of the tissue reaction to FCS on the tissue defenses against the tubercle bacillus and similar mycobacteria (21, 22).

In years past there was little chance that a person with coexisting silicosis and tuberculosis would recover. The infection slowly or rapidly but relentlessly progressed to a fatal outcome. Moreover, in the presence of quiescent or inactive tuberculosis, the development of silicosis often converted the dormant tuberculosis to an active, spreading disease. Since until recently almost all members of the adult population harbored one or more inactive tuberculosis foci, the development of silicosis fell on fertile ground and the likelihood of reactivating the tuberculosis followed by its relentless progression was high. This is no longer the case in the United States. With the advent of specific drugs to combat the tubercle bacillus and public health measures for tuberculosis control, the proportion of the adult population harboring latent tuberculosis is now very small. Moreover, specific antituberculosis drugs are quite effective, even in the presence of silicosis.

Since the reaction of lung tissue to FCS has a demonstrable dose-response relationship, reducing the severity of occupational exposure offers the possibility of abolishing the disease. Measures for environmental control in the workplace have been effective when instituted properly. New cases in metal mines where the levels of FCS have been kept for the most part below 5 million particles per cubic foot have been few (23). One large mine under my surveillance employs several hundred underground miners, and no new cases of silicosis have developed up to the present (1976) in men initially employed after 1940. Over this period a program of dust measurement shows the exposures to FCS have been kept below 5 million particles per cubic foot with few and temporary exceptions. In the same mine prior to 1938 and before installation of extensive dust control procedures, approximately 25 percent of the underground miners had radiographic evidence of silicosis. If the even more stringent current ACGIH-recommended threshold limit value for FCS is scrupulously adhered to silicosis as a disease should be abolished. Unfortunately and regrettably, exposure to excessive levels of FCS in some places of work still exists, and silicosis continues to be induced. This is not because the recommended TLV is too high but because it is not complied with.

8.2.2 Carbonaceous Dust

Exposure to respirable particles of carbon may occur in several occupations, the most common being those associated with the mining, processing, and handling of coal. Exposure also occurs in the mining and use of graphite and in the production of carbon black and carbon electrodes. In all these cases the biological effects are similar but not identical, and only the consequences of exposure as a coal worker are discussed. "Coal workers' pneumoconioses" (CWP) is the proper term to apply to the abnormalities caused by the dust inhaled in this class of occupation. "Black lung," which is a socioeconomic term, has no meaning in the scientific or medical context.

Respirable free crystalline silica in varying concentrations from slight to high commonly coexists with coal particles in the miner's environment. Some is in the coal seam,

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some is released by roof bolting where sandstone or hard shale is present, and in mines of the United States sand used on the haulageways is ground to respirable size. In the process of mining, the exposure commonly is to a mixed dust, though in subsequent handling of the commercial product the contamination by FCS is much less.

Pure coal or graphite inhaled by experimental animals produces dust foci characterized by reticulin fibers but little or no collagen, and in all respects it can be classed as an inert dust reaction (24). In general, coal particles come to reside in the same localities in the lung as already described under inert and FCS particles. In humans, the number of coal particles retained in the lung usually exceeds by far the number observed as a result of other inert or FCS exposures.

The "coal macule" is different in appearance from the FCS nodule previously described (25). It takes on a more stellate form and is localized more intimately around the respiratory bronchiole, the alveoli of which are filled with dust-laden macrophages. The normal architecture of the alveolus persists, even though it may be shrunken. In other words, there is no actual destruction of lung tissue. Alveoli become effaced by a combination of shrinkage and filling with macrophages. A sleeve of dust-laden tissue interlaced by reticulin fibers and a few collagen fibers forms a cuff, obliterating all structures except the lumen of the respiratory bronchiole. This bronchiole may become abnormally dilated, producing a form of focal or centrilobular emphysema. It is noteworthy that not every macule is associated with the development of focal emphysema. This raises the unanswered question of why focal emphysema develops at all. The mechanism is not clear.

The coal macule is a discrete focus, the intervening tissue remaining normal. The stellate densities may be 1 to 2 mm or more in diameter. Ingestion of coal particles by the macrophage does not prematurely kill the cell; thus the coal macule is fundamentally the same as that described earlier for inert materials. The larger area involved by the coal macule and obliteration of alveolar spaces appear to be the result of overwhelming the cleansing mechanism of the lung by very heavy exposure and retention of large amounts of coal. It has been shown that the number and size of the macules in the lung is closely related to the total exposure to coal dust (26). Although the coal macule may have a slight amount of mature collagen fiber interlaced throughout, characteristically this is a rather minor development, and reticulin fibers constitute the vast majority of the fibrillar tissue. Quite often, however, there is more than the usual scant amount of collagen laid down in an irregular fashion in the structure that ordinarily would be termed a coal macule. The components of the reaction are closer to that ascribed to FCS, but the organization is quite different in that the whorled arrangement is absent. Some have referred to these structures as nodules in contrast to macules. Obviously, when collagen is present in this amount the reaction can no longer be thought of as characteristic of an inert substance. Whether this nodular form is in fact a type of mixed silicotic reaction or is a response solely to coal particles has not been determined. Since FCS exists so commonly in the coal mine workplace, the former is a likely probability.

In some individuals, superimposed on the background of simple discrete coal macules, a marked coalescence of macules and proliferation of mature fibrous tissue causes large

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masses to develop. These are referred to as progressive massive fibrosis (PMF). Since the coal macule in contrast to the silicotic nodule has rather indeterminate borders, the macules lose their identity when they are caught up in this large mass and do not exhibit the agglomerated separate structures that characterize the appearance of conglomerate silicosis. The mechanism of PMF development is not clear. It does not appear to be closely related to the coexisting FCS, although some role for this substance in the development of PMF cannot be excluded. It seems likely that PMF is related in part to the extraordinarily high content of coal dust in the involved areas. On the whole, in pure silicosis the tissue effects are induced by a lung burden of 2 to 5 g of FCS. The lung burden of coal in simple CWP or PMF is 10 or more times greater than this. It is tempting to believe that uncomplicated or simple CWP is basically a moderate to severe example of an inert dust reaction and that PMF would develop in all types of inert dust exposure if it was heavy enough. This probably is too simplistic an approach. It has been suggested that immunological factors may play a role in PMF.

A quite different kind of massive lesion, Caplan's syndrome, may develop rapidly in some persons having simple CWP (27). A large proportion of these individuals have rheumatoid arthritis, a disease having a large immunological component. The intrapulmonary mass characteristic of this syndrome does not have the histological appearances of PMF but does have some of the characteristics associated with immunological reactions. This entity clearly raises the question of whether an immunological response plays some role in the development of PMF, even though PMF is definitely not the same lesion as that characterizing Caplan's syndrome.

In contrast to the adverse effect on tissue resistance to the tubercle bacillus caused by the silicotic reaction, the coal macule does not appear to influence the body defense against this organism. When tuberculosis and simple CWP coexist, the infection may play a role in causing PMF, but rapid acceleration of tuberculosis does not occur.

For the most part, the radiographic evidences of CWP including PMF are similar to those of silicosis and need not be repeated. The shadows cast by CWP are a mixture of round and irregular shapes measuring 1 to 5 mm in diameter. The attack rate and severity of this stage of the disease is related closely to the amount of dust in the lung. Many individuals never progress beyond this stage to that of PMF, which is characterized by large, irregular shadows, usually developing in the upper lung areas.

Measurement of pulmonary function in persons having CWP shows essentially the same range of alteration with respect to type and degree as discussed for simple and conglomerate silicosis. There is less evidence of a restrictive impairment in CWP except when severe PMF exists. In simple CWP, impairment of function is so minor that it does not interfere with physical effort or shorten the life-span (28, 29). In some individuals having severe PMF, however, there is marked restrictive impairment of pulmonary function, reduction in capacity for physical effort, and shortened life-span.

Several studies searching for evidence that CWP is related to an excess risk of bronchogenic cancer have failed to reveal such an association.

It should be emphasized that some occupations in coal mines (e.g., a motorman, a roof bolter, or a development man) are characterized by a predominance of FCS

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exposure. For this reason a coal miner can develop pure nodular silicosis. If he changes jobs during his total employment, his lungs may develop coexisting coal macules, coal nodules, and pure nodular silicosis. These combinations of abnormality led, particularly in the United States, to the term anthracosilicosis, before it was demonstrated that coal in the virtual absence of FCS could produce the coal macule and PMF. Since simple CWP is strongly related to total exposure or the dose of coal, and since PMF virtually always develops on a background of simple CWP, control of the dust exposure on the mine premises will prevent CWP.

8.3 Chronic Bronchitis and Emphysema

Examination of large numbers of persons who have been exposed to inert, fibrogenic, or mixed dusts invariably discloses a paradox. One is faced with the observation that among a group of persons demonstrating mild radiologic or histologic evidences of tissue alteration—for example, simple CWP or nodular silicosis—most have no physical complaint and demonstrate no impairment of function. Nevertheless, a few will complain of moderate to severe symptoms of cough and sputum production or breathlessness on exertion and will have moderate to severe measurable alteration of pulmonary function. Almost without exception such individuals have either chronic bronchitis or destructive emphysema or both, at a stage associated with increased airway resistance. We then ask whether these two diseases are caused or influenced in their natural course by the exposure to the specific dust.

Emphysema, defined as pathological enlargement of the air spaces distal to the terminal bronchioles, has been found to involve more than 5 percent of the lung in approximately 50 percent or more of all males over age 50 at autopsy. The individuals come from all walks of life, and there is no preponderance of men from the dusty trades. Possibly 10 to 20 percent of these individuals from the population at large have severe enough involvement to exhibit moderate to severe increase of airway resistance and to have experienced abnormal breathlessness on exertion (dyspnea).

Chronic bronchitis, defined as periodic or persistent bouts of coughing caused by the production of excessive bronchial mucus, is a common condition in males after the age of 30 and is one of the rather frequent causes of death. The prevalence among adult men may be as high as 15 to 20 percent. By far the most potent factor, though not the only one causing and aggravating this disease, is cigarette smoking. In view of the high prevalence of these two conditions in the adult male population at large, it is not surprising to meet the paradox just described. Efforts to disclose the role of occupational exposure to dust as a causative factor in the development of chronic bronchitis or emphysema have been made. There is surprisingly modest support for the concept that industrial dust or the irritating fumes commonly also present play a role in the development of aggravation of chronic bronchitis or emphysema. It is difficult to accept the belief that no role is played by these agents, particularly with respect to chronic bronchitis. What seems likely is that the powerful effect of cigarette smoking, the influence of social class with respect to place of residence, medical care, and so on, and general air pollution,

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overshadow any demonstrable strong influence of industrial dust, fumes, or gases (30). In studies in which these other factors are corrected for, there is some suggestion that occupational dust per se may contribute at least to chronic bronchitis, even though it is not the most potent factor.

9 ASBESTOS

"Asbestos" is a term customarily reserved for commercially mined and milled, naturally occurring crystalline fibers of the serpentine and amphibole family of minerals. Chrysotile, the fibrous form of serpentine, is by far the most abundantly produced. The amphiboles crocidolite, amosite, and anthophyllite are produced and used as such on a lower scale, tremolite is found primarily as a contaminant of talc, and actinolite is rarely encountered in industry.

In their natural state, the fibers are found massed together, forming a layer of cross or slip fiber within parent rock of the same chemical composition. In the process of separation from their parent rock or of "opening" during milling and manufacturing uses, the airborne fibers of asbestos vary enormously in length and diameter, but some ultimately become thin and short enough to be of respirable size. Since the aerodynamic behavior of fibers is determined by their diameter rather than length, fibers more than 3 μm thick do not penetrate into the alveolated regions of the lung. As discussed earlier, length and shape as well as diameter play a role in governing deposition. Although fibers as long as 200 μm may occasionally be found in the lung, the length of the majority is less than 50 μm.

As observed in humans or experimental animals, all the ultimate fates described earlier for particles entering the upper airways occur also for fibrous particles but with some important differences. Fiber deposited on the mucociliary apparatus is removed and expectorated or swallowed. Those less than 10 μm long can be ingested readily by the macrophage. Longer fibers, though thin enough to be respirable, are not readily ingested by single macrophages; yet occasional fibers 20 to 50 μm or longer may be seen with several macrophages attached and spread out over the fiber surface. At times two or more macrophages clump together, forming a giant cell totally surrounding one or more fibers. In contrast to respirable-sized nonfibrous particles, any one of which can be ingested by a macrophage, fibers longer than 20 μm are not readily ingested, and macrophage defense against this length of fiber is impaired or not available. In spite of this, asbestos fibers free on the surface of the alveoli are relatively scant. Almost always, fibers remaining in the lung either are within macrophages or appear to be embedded within the thickened wall of the alveolus or within the interstitial tissue, which then becomes the site of fibroblast proliferation and collagen fiber deposition. Fibers longer than 10 μm within the regional lymph nodes are unusual, and even shorter ones are not found in large numbers.

Some of the fibers within both the lungs and lymph tissue become coated with a proteinaceous iron-containing substance and are referred to as "ferruginous" or "asbestos" bodies. It is believed that the coating is laid down in some way by contact

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with the macrophage. This coating persists virtually indefinitely, but it is of interest that these bodies can undergo fragmentation. Curiously, even in persons who experience moderate to heavy exposure, many and perhaps most fibers are free of this coating even after long periods of residence within the lung. There is some evidence to indicate that the coated fibers are nonfibrogenic and that the coating process is a mechanism whereby fibers entering the lung are neutralized. It should also be pointed out that ferruginous bodies may be formed by any kind of durable fiber that enters the lung, including such things as glass and vegetable fibers of silicious composition.

It has been shown experimentally that asbestos fibers shorter than 5 to 10 μm whether coated or naked, behave essentially like inert particles (31, 32). This length of fiber is readily ingested by the macrophage, and in contrast to the effect of FCS, the host macrophage is not materially damaged by the ingested fiber. Its life cycle is not shortened. Experimental animals exposed solely to asbestos fibers shorter than 5 to 10 μm do not develop pulmonary fibrosis. If longer fibers in sufficient numbers are introduced into the lungs of animals, they produce a diffuse, nonnodular type of fibrosis of the mature variety. The fibrotic reaction spreads out along the supporting structures of the lung, obliterating the alveoli and associated vascular units. The diffuse spreading nature of this involvement stands in striking contrast to the discrete nodular fibrosis that is characteristic of silicosis. Although some areas of normal-appearing lung tissue persist between the areas of fibrosis, the volume of residual normal lung tissue is less, and the amount of lung tissue entrapped between strands of fibrosis is greater than is the case in silicosis (33).

The mechanism of fibrogenesis induced by asbestos is not clear. In animals, the early stages suggest an organizing alveolitis closely associated with the presence of long fibers. Eventually the fibrosis completely destroys the alveolar architecture and its intimately related vascular structures. Commonly the extensive mature fibrotic tissue contains long asbestos fibers, singly or in clusters, distributed throughout, but they are sparse and far apart. The fibrotic reaction seems to be excessive for the few fibers visible. Nevertheless, fibrogenesis must have something to do with the fibers and specifically with their shape because nonfibrous particles having identical chemical and crystalline structures will not produce fibrosis when introduced into experimental animals. The relative paucity of long fibers in mature fibrotic tissue may be the result of fragmentation and destruction of long fibers after they have induced the fibrotic reaction. The concept that asbestos fibers are biologically indestructible cannot be supported.

It has been suggested that long fibers induce alveolitis and subsequent fibrosis, while short fibers or particles of the same chemical nature do not, because the fibers are too long to be taken entirely into the macrophage. As a result, the macrophage leaks at the point of fiber entry, and the discharge of some of the macrophage contents leads to fibrogenesis (32). It is of interest that there is little if any fibrogenesis associated with the relatively few asbestos fibers that reach the lymph nodes. It would appear that the lymphoid tissue treats even the long fibers as inert material.

That immunologic processes may play a role in fibrogenesis consequent to inhalation of asbestos or FCS has been suspected not only because of the potential role of this mechanism for governing the actual tissue response but also because there appears to be

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some variation of individual reactivity to these dusts. Measurement of antinuclear antibodies, rheumatoid factor, and the W27 antigen of the HL-A system indicates higher values in those having asbestos-induced pulmonary fibrosis than among controls or those exposed but without fibrosis (34, 35). The importance of these studies, especially with regard to recognizing prior to exposure those who would be hyperreactors, remains to be determined.

In contrast to particles of FCS, asbestos fibers tend to remain on the surface of the alveoli; the cellular reaction to them develops inside the alveolus, and this alveolitis ultimately goes on to organization, with obliteration of the alveoli and the diffuse fibrotic reaction flowing from that. Perhaps it is this difference in particle transport that explains the diffuse rather than the nodular tissue reaction to asbestos. Also, in contrast to the long-term effects of free crystalline silica, the fibrosis caused by asbestos develops more extensively in the lower half of the lungs, and it is unusual for large conglomerate masses surrounded by normal tissue to develop.

In addition to the diffuse intrapulmonary tissue reaction to asbestos, in some exposed persons there is also a fibrotic reaction of two kinds involving the pleura. First, there may be slight to widespread fibrosis of the visceral pleura associated with the underlying pulmonary fibrosis, especially in severely involved cases. Obliteration of the pleural space may occur in these areas. Second, there may be small to large plaque formation involving virtually only the parietal pleura. The plaques are thickened tissue having quite sharp, raised margins, and they are composed of fibrous hyalinized tissue that at times becomes calcified. The parietal pleura over these plaques usually is not adherent to the visceral pleura, and the space is not obliterated. When visible in the radiogram, the pleural plaques are striking, especially when they are calcified. Plaque formation can develop without pulmonary fibrosis, and the mechanism, especially the reason for its predilection for the parietal pleura, is unknown.

The pathology as seen in experimental animals and in humans is essentially the same and explains reasonably well the impairment of function and health consequent to the reaction. The diffuse fibrous bands radiating throughout the lung, especially in the lower regions, reduces the distensibility of the normal lung tissue entrapped between the strands of fibrous tissue. This plus actual loss of lung substance by replacement with fibrous tissue causes a restrictive type of pulmonary impairment. As a result, the total lung volume, vital capacity, and residual volume are reduced without an increase of resistance to airflow in the proximal conducting system. If the restrictive impairment is severe, it causes an increase of the work of breathing and a lessened maximum capacity for ventilation. Regional hypoventilation of entrapped lung plus loss of total vascular surface may lead to impaired oxygen transfer and arterial hypoxia. The volume of air breathed in response to exercise may become abnormally high, and this plus the increased work of breathing leads to abnormal breathlessness and dyspnea. If the vascular bed is sufficiently reduced, the pulmonary artery pressure rises, especially during exercise, and right ventricle hypertrophy and heart failure may ensue.

With mild asbestosis, the radiogram is not as distinctly abnormal as is the case with silicosis because the tissue changes are diffuse and the well-demarcated densities so

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characteristic of silicosis are not present. The usual appearance of asbestosis in the radiogram is that of poorly defined, small, irregular densities that obscure the normally sharp margins of the bronchovascular structures, particularly in the lower parts of both lungs. Thickened pleura may cast a diffuse haze over both lungs and often obscures the intrapulmonary densities. When the disease is severe the radiographic abnormalities are readily recognized; but in the slight stages, the question of whether the radiogram is in fact abnormal is commonly disputed and may be answered differently by the same reader on different occasions.

Physical examination in the early and subsequent stages often reveals persistent dry crackling sounds (rales), audible over the lung bases posteriorly. Clubbed fingers with or without cyanosis may or may not be present.

In any given case all the abnormalities thus far described may exist, but commonly only one or two are present. Moreover, all the physical, radiographic, and altered pulmonary function measurements are characteristic of chronic interstitial lung disease, no matter what its etiology may be. Although idiopathic chronic interstitial lung disease is rather uncommon, it occurs frequently enough to pose a diagnostic problem, especially in persons exposed very slightly to asbestos fiber—that is, for the intermittent user of this material or the general public. The diagnosis of asbestosis therefore requires exclusion of other causes of observable abnormalities plus establishment of the occurrence of adequate exposure to respirable asbestos.

In contrast to the experience with exposure to inert particles, to free crystalline silica, and to coal dust, exposure to respirable asbestos fiber is associated with an excess risk of cancer (36, 37). The excess risk of bronchogenic cancer is virtually confined to those having a long history of cigarette smoking plus heavy exposure to asbestos. The greatest risk appears to be in those exposed in the insulation working trade, where the "total" exposure to multiple factors by reason of coexisting agents in their variable working conditions may play an important role. On balance, asbestos per se is a low order carcinogen for the bronchial cells, and its role is almost certainly that of a promoter, not an initiator.

There is evidence to suggest that an excess of bronchogenic cancer occurs only among those having diffuse pulmonary fibrosis or asbestosis (38, 39). Thus since fibers shorter than 5 to 10 μm do not cause diffuse pulmonary fibrosis, it seems likely they also do not play a role in the causation of an excess bronchogenic cancer risk in persons exposed to asbestos fiber in the workplace.

Some studies, but not all, suggest an increased risk of gastrointestinal cancer among workers exposed to respirable asbestos. The excess risk appears to be of a low order and confined to those heavily exposed (36). Curiously, there is inconsistency of excess risk for different parts of the gastrointestinal tract among the various studies.

An excess risk of developing either pleura or peritoneal mesothelioma has been observed among workers exposed to chrysotile, crocidolite, and amosite, but not to anthophylite or tremolite (39). The dose at which the excess risk occurs appears to be lower than for the other kinds of asbestos-related cancers. Some believe that exposure to crocidolite carries a greater risk than that for chrysotile or amosite, but this attitude is

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not uniformly accepted (40). As is true for fibrogenesis, the risk of carcinogenesis related to respirable asbestos shows a dose–response relationship including that for mesothelioma. Reconstruction of dose data for crocidolite exposure and associated mesothelioma risk has never been presented in a fashion to exclude dose as the factor responsible for what in some circumstances appears as a higher risk of mesothelioma among those exposed to crocidolite.

Mesothelial tumors can be produced in experimental animals by placing asbestos fibers directly into the pleural or peritoneal space (41–43). Using this technique, it has been shown that long, very thin fibers induce the greatest tumor response. If fibers of thicker or shorter dimensions are used, tumor induction decreases. When the fibers used to not exceed 5 μm in length, tumor production, if it does occur, is not statistically significant.

Since all the manifestations of impaired health and function related to respirable asbestos are dose related, it should be possible to continue the use of this material under adequate controls.

10 FIBROUS GLASS

Glass, an amorphous silicate containing various other ingredients, can be produced in fiber form from the molten material by drawing, as in textile glass, or by blowing or centrifugation, as in glass wool manufacture. In view of the biological effects of asbestos fibers, concern for possible effects of fibrous glass has often been voiced.

Fibrous glass began to be produced in large amounts only after 1935–1940. Since the fibers of drawn glass characteristically were thicker than 5 μm and the same was true of most of the early produced blown glass fibers, it was believed that these would be nonrespirable. In addition, mineral wool, a blown glass, has been in use since early in this century; and although those exposed to it have not been studied by modern epidemiological methods, their clinical experience did not lead observers to believe that there was an unusual health risk. Early animal experiments using glass fibers ground to respirable lengths were not entirely satisfactory because their large diameter interfered with carrying out adequate inhalation experiments. When these were supplemented by intratracheal injection, however, the results were those of an inert dust reaction, no mature fibrosis being produced. On these grounds, fibrous glass was considered to be an inert or nuisance dust. Radiographic, pulmonary function, and clinical plus autopsy studies performed since 1965 confirmed the absence of recognizable pulmonary alteration other than those of an inert nature in persons having experienced 25 to 30 years of exposure to fibrous glass in the workplace (44–46).

More recently, technological developments and requirements have led to the production for special purposes of thinner blown glass fibers having diameters as thin as 1 μm or less. In addition, electron microscope studies of the workplace where conventional glass fiber is being produced show that a small number of fibers of this dimension are present in the air where nominally thicker glass fibers are being manufactured. It is

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apparent that fibers thin enough to be respired have been in the workplace for some time and are now being manufactured for specific purposes.

In contrast to the earlier animal experiments showing only an inert dust reaction, contemporary animal experiments using repeated intratracheal instillations of dilute suspensions of glass fibers thinner than 2 μm and longer than 25 μm have revealed the development of fibrosis in the interstitial tissues around the respiratory bronchioles (32). This reaction, though qualitatively similar, is much less severe in comparison to that resulting from asbestos fiber, thus strongly suggesting that something in addition to fiber shape and dimension plays a role in the induction of fibrosis. The same experiments also indicate that glass fibers of identical composition and diameter but shorter than 10 μm produced only an inert dust reaction (32).

Experiments over the past several years have shown that introduction of long glass fibers thinner than 3 μm directly into the pleura and peritoneum of experimental animals has produced mesothelial tumors (47). Though such experiments are important in the study of mechanisms of carcinogenesis, it should be pointed out that such implantation of large numbers of fibers of this size directly into the pleura or peritoneum completely bypasses the defense mechanisms available to minimize the movement of fibers to the pleura by the usual inhalation route in the intact respiratory system. Furthermore, the number of fibers introduced in these experiments is doubtless several orders of magnitude higher than might conceivably result by way of the inhalation route. As was the case with asbestos, these experiments show that as the length of the fiber is reduced, the yield of tumors is lessened, and when all the fibers are shorter than 8 μm, no statistically significant excess of tumors is induced (47). One would anticipate that by the normal inhalation route, the long fibers would be less likely than short ones to reach the subpleural regions, and this would tend to further lessen the number of long thin fibers ultimately reaching the pleura by the inhalation route. Although these animal experiments suggest the possibility that glass fibers thinner than 2 μm and longer than 10 μm might cause pulmonary fibrosis or induce mesothelioma in man if sufficient numbers reached the alveolar areas of the lung and the pleura, they are so artificial in their manner of placement of the fibers within the animal that they have questionable relevance to human exposures. The more relevant inhalation experiments in animals remain to be done, and firm conclusions about the potential hazard posed by long, thin fibers of glass should be postponed until these investigations have been carried out.

Human experience with exposure to these unusually thin, long fibers is quite limited, but some data are available to place animal experiments such as those just referred to in perspective. As indicated earlier, fibers of these long, thin dimensions have been present in small numbers in the air of glass wool manufacturing plants for the past 30 to 35 years. In fact, for several years they were deliberately manufactured for the production of flotation materials during World War II and for a short time thereafter. Recent epidemiologic studies of workers in manufacture of fibrous glass where long, very thin fibers were present 30 or more years ago have shown neither an excess of cancer, including mesothelioma, nor of pulmonary fibrosis in workers exposed over this period of time (48).

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11 PNEUMOCONIOSIS?

The reader must wonder why the term "pneumoconiosis" has been used only with regard to coal workers' pneumoconiosis (CWP). The author used it in that connection because in this particular circumstance it has a rather specific, well-entrenched meaning. As generally used, "pneumoconiosis" is defined as the circumstance of deposition of dust in lung tissue and the tissue reaction thereto. In this sense it has no specific implications, since all adults, no matter what their work experience, fall within this category. Moreover, some of the pneumoconioses have serious biological implications while others do not, and all too often there is a false inference that all pneumoconioses are harmful. The term is so ambiguous that its use should be discouraged, and more specific designations should be used for each of the circumstances.

REFERENCES

1. E. R. Weibel, *Morphometry of the Human Lung*, Academic Press–Springer-Verlag, New York, 1963.
2. H. von Hayek, *The Human Lung* (translated by V. E. Krahl), Hafner, New York, 1960.
3. H. Spencer, *Pathology of the Lung; Excluding Pulmonary Tuberculosis*, 3rd ed., Pergamon Press, Oxford, 1976.
4. B. Vernon-Roberts, *The Macrophage*, Cambridge University Press, Cambridge, 1972.
5. T. F. Hatch and P. Gross, *Pulmonary Deposition and Retention of Inhaled Aerosols*, Academic Press, New York, 1964.
6. W. H. Walton, Ed., *Inhaled Particles*, Vol. 3, Unwin Bros., Ltd., Gresham Press, Old Woking, Surrey, England, 1971.
7. M. Newhouse, J. Sanchis, and J. Bienenstock, *Lung Defense Mechanisms* (2 parts), *New Engl. J. Med.*, 295, 990, 1045 (1976).
8. J. Cartwright and G. Nageischmidt, "The Size and Shape of Dust from Human Lungs and Its Relation to Relative Sampling," in: *Inhaled Particles and Vapours*, C. N. Davies, Ed., Pergamon Press, New York, 1961.
9. V. Timbrell, "Inhalation and Biological Effects of Asbestos," in: *Assessment of Airborne Particles: Fundamentals, Applications and Implication to Inhalation Toxicity*, T. Mercer, P. Morrow, and W. Stöber, Eds., Thomas, Springfield, Ill., 1972, pp. 429–445.
10. C. N. Davies, "Deposition of Dust in the Lungs: A Physical Process," in: *Industrial Pulmonary Diseases*, King and Fletcher, Eds., Little Brown, Boston, 1960.
11. E. M. Scarpelli, *The Surfactant System of the Lung*, Lea & Febiger, Philadelphia, 1968.
12. J. Kaufman and G. W. Wright, "The Effect of Nasal and Nasopharyngeal Irritation on Airway Resistance in Man," *Am. Rev. Resp. Dis.*, 100, 626 (1969).
13. A. G. Heppleston, "The Fibrogenic Action of Silica," *Br. Med. Bull.*, 25, No. 3, 282 (1969).
14. J. Bruch, "Response of Cell Cultures to Asbestos Fibers," *Environ. Health Perspect.* 9, 253 (1974).
15. ILO U/C 1971, *International Classification of Radiographs of the Pneumoconioses*, in: *Medical Radiography and Photography*, G. J. Jacobson and W. S. Lainhart, Eds., Vol. 28, No. 3, Eastman Kodak Co., Rochester, N.Y., 1972.
16. W. R. Parkes, *Occupational Lung Disorders*, Butterworths, London, 1974.
17. M. Kleinfeld et al., "Welders Siderosis," *Arch. Environ. Health*, 19, 70 (1969).

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18. J. T. Boyd et al., "Cancer of the Lung in Iron Ore (Haematite) Miners," *Br. J. Ind. Med.*, **27**, 97 (1970).
19. M. Ziskind, R. N. Jones, and H. Weill, "Silicosis," *Am. Rev. Resp. Dis.*, **113**, 643 (1976).
20. H. A. Buechner and A. Ansari, "Acute Silico-Proteinosis," *Dis. Chest*, **55**, 274 (1969).
21. L. U. Gardner, "Studies in Experimental Pneumoconiosis: Reactivation of Healing Primary Tubercles in Lung by Inhalation of Quartz, Granite and Carborundum," *Am. Rev. Tuberc.*, **20**, 833 (1929).
22. L. U. Gardner, "Etiology of Pneumoconiosis," *J. Am. Med. Assoc.*, **111**, 1925 (1938).
23. "Silicosis in the Metal Mining Industry, A Revolution," U.S. Public Health Service Publication No. 1076, Government Printing Office, Washington, D.C., 1963.
24. S. H. Zaidi, *Experimental Pneumoconiosis*, Johns Hopkins Press, Baltimore, 1969, pp. 187–198.
25. A. G. Heppleston, "The Pathological Anatomy of Simple Pneumoconiosis in Coal Miners," *J. Pathol. Bacteriol.*, **66**, 235 (1953).
26. S. Rae, "Pneumoconiosis and Coal Dust Exposure," *Br. Med. Bull.*, **27**, No. 1, 53 (1971).
27. A. Caplan, R. Payne, and J. Withey, "A Broader Concept of Caplan's Syndrome Related to Rheumatoid Factors," *Thorax*, **17**, 205 (1962).
28. W. K. C. Morgan et al., "Respiratory Impairment in Simple Coal Workers' Pneumoconiosis," *J. Occup. Med.*, **16**, 839 (1972).
29. C. E. Ortmeyer et al., "The Mortality of Appalachian Coal Miners," *Arch. Environ. Health*, **29**, 67 (1974).
30. I. T. T. Higgins, "The Epidemiology of Chronic Respiratory Disease," *Prevent. Med.*, **2**, 14 (1973).
31. P. Gross, "Is Short-Fibered Asbestos Dust a Biological Hazard?" *Arch. Environ. Health*, **29**, 115 (1974).
32. G. W. Wright and M. Kuschner, *Proceedings of the Fourth International Symposium on Inhaled Particles and Vapours*, British Industrial Hygiene Society, 1975, in press.
33. A. J. Vorwald, T. M. Durkan, and P. C. Pratt, "Experimental Studies of Asbestosis," *Arch. Ind. Hyg. Occup. Med.*, **3**, 1 (1951).
34. M. Turner-Warwick and W. R. Parkes, "Circulating Rheumatoid and Antinuclear Factors in Asbestos Workers," *Br. Med. J.*, **3**, 492 (1970).
35. J. A. Merchant et al., "The HL-A System in Asbestos Workers," *Br. Med. J.*, **1**, 189 (1975).
36. J. C. McDonald et al., "The Health of Chrysotile Asbestos Mine and Mill Workers of Quebec," *Arch. Environ. Health*, **28**, 61 (1974).
37. I. J. Selikoff, E. C. Hammond, and J. Churg, "Asbestos Exposure, Smoking and Neoplasia," *J. Am. Med. Assoc.*, **204**, 106 (1968).
38. H. Bohlig, G. Jacob, and H. Müller, *Die Asbestose der Lungen*, Georg Thieme, Stuttgart, 1960, p. 60.
39. J. C. Wagner, J. C. Gibson, G. Berry, and V. Timbrell, "Epidemiology of Asbestos Cancers," *Br. Med. Bull.*, **27**, 71 (1971).
40. I. Webster, "Asbestos and Malignancy," *S. Afr. Med. J.*, **47**, 165 (1973).
41. M. F. Stanton, "Fiber Carcinogenesis: Is Asbestos the Only Hazard?" *J. Nat. Cancer Inst.*, **52**, 633 (1974).
42. M. F. Stanton and C. Wrench, "Mechanisms of Mesothelioma Induction with Asbestos and Fibrous Glass," *J. Nat. Cancer Inst.*, **48**, 797 (1972).
43. J. C. Wagner and G. Berry, "Mesothelioma in Rats Following Inoculation with Asbestos," *Br. J. Cancer*, **23**, 567 (1969).
44. G. W. Wright, "Airborne Fibrous Glass Particles: Chest Roentgenograms of Persons with Prolonged Exposure," *Arch. Environ. Health*, **21**, 175 (1968).
45. R. T. de Treville and H. M. Utidjian, "Fibrous Glass Manufacturing and Health. Part I. Report of an

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asbestosclaims.law/library/25385/37

Epidemiological Study. Part II. Results of a Comprehensive Physiological Study." Transactions Bulletin, Industrial Health Foundation, Pittsburgh, 1970, pp. 98–111.

46. J. W. Hill et al., "Glass Fibers: Absence of Pulmonary Hazard in Production Workers," *Br. J. Ind. Med.*, **30**, 174 (1973).
47. M. F. Stanton et al., "The Carcinogenicity of Fibrous Glass: Pleural Response in the Rat in Relation to Fiber Dimension," *J. Nat. Cancer Inst.*, **58**, 1977.
48. D. L. Bayliss et al., "Mortality Patterns Among Fibrous Glass Workers," *Ann. N.Y. Acad. Sci.*, **271**, 324 (1976).

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