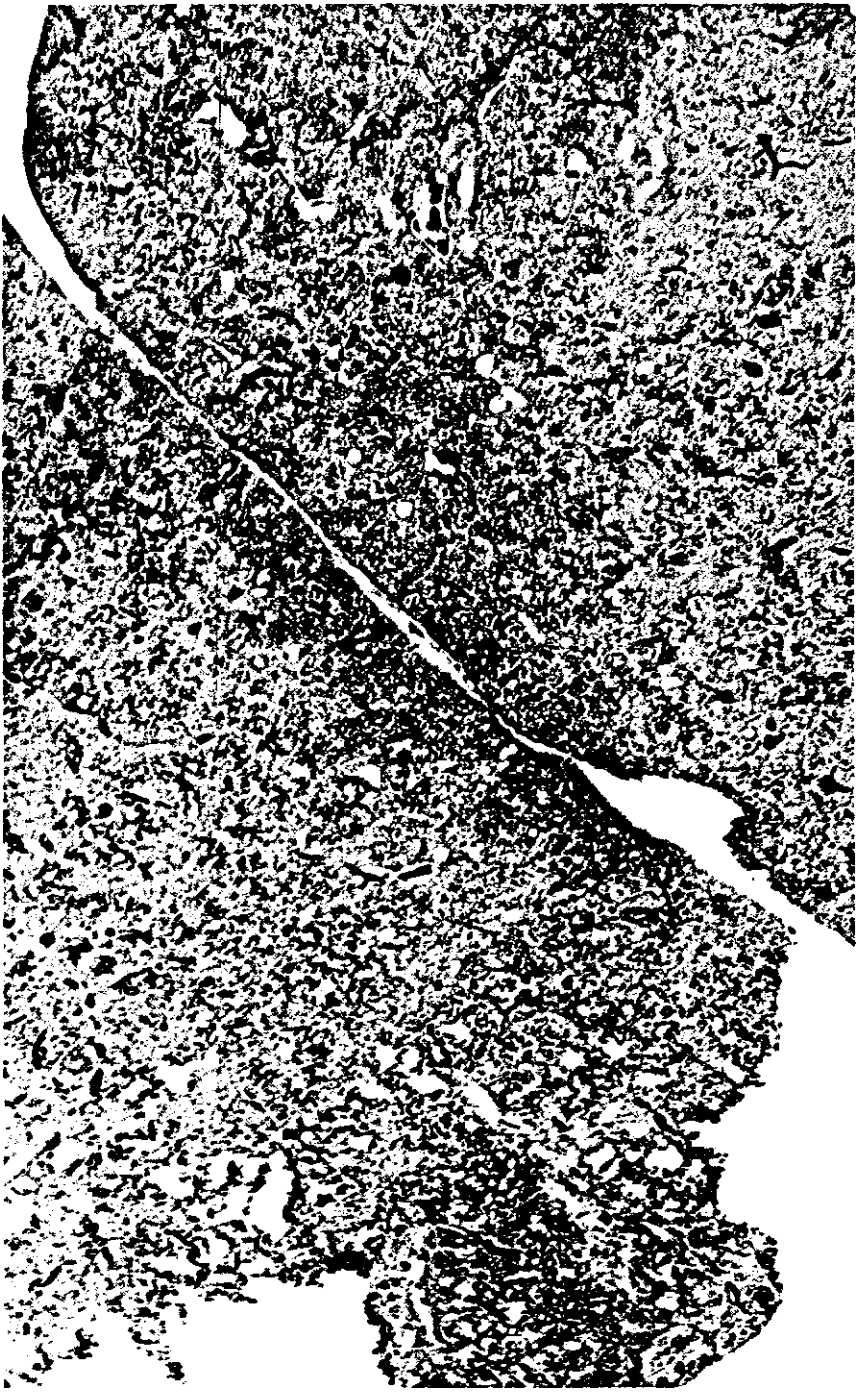

Figure 5. Coal worker's pneumoconiosis — Gough section.

DISEASES OF THE AIRWAYS AND LUNGS

W. Keith C. Morgan, M.D., and N. LeRoy Lapp, M.D.

AIRWAYS MECHANISMS AND RESPONSES

Gas exchange takes place in the acini of the lung parenchyma; that is, in those portions of the lung from the first order of respiratory bronchioles down to the alveoli. These respiratory bronchioles originate from the terminal bronchioles which are the smallest airways not concerned with gas exchange. Before inspired air can participate in gas exchange it must travel through a series of conducting tubes (the bronchial tree) until it finally reaches the first order respiratory bronchioles. The conducting system of airways does not participate in gas exchange and is, therefore, often known as the dead space. Inhaled particles may be deposited either in the lung parenchyma (the respiratory bronchioles, atrial sacs, and alveoli) or in the dead space. Some of the inhaled particulates are breathed in and out of the respiratory tract without deposition.

The site of deposition of an individual particle is governed by three factors: first, the aerodynamic properties of the particle, viz. the size, shape, speed, and density; secondly, the circumference and shape of the airway; and thirdly, the breathing pattern. Particles between 0.5 and 5 microns in diameter tend to be deposited in the alveoli and respiratory bronchioles and may, under certain conditions, cause a group of diseases known as the pneumoconioses to develop. Larger particles are in the main deposited in the conducting system of the lungs. The effect of an inhaled dust is, therefore, dependent partly on its site of deposition and partly on its toxic and antigenic properties. See Figure 5.

AIRWAYS RESISTANCE

Before considering the various occupational insults that may be inflicted upon the conducting system of the lung, certain basic anatomical and physiological considerations should be borne in mind. The resistance to air flow in the human airways can be partitioned into central and peripheral components (1). The central component comprises the resistance that is located in the upper airways, trachea, and main and segmental bronchi down to the airways that have diameters 2 mm or greater. The distal component is located in those airways whose diameter is less than 2 mm, including the gas exchanging units of the lung. Macklem and Mead have demonstrated that, of the total airways resistance, no less than 80 to 90 percent is located in the larger airways and only around 10 percent resides in the smaller airways (1). Thus, changes in the resistance to flow in the smaller airways have little influence on total airways resistance. Similarly, those indices of ventilatory capacity that are derived from the forced expiratory volume maneuver are little affected by an increase in the resistance of the small airways because these

indices for the main part reflect changes in the larger airways during dynamic compression.

Although some of the smaller air passages of the respiratory conducting system, e.g., the terminal bronchioles, are included in the peripheral airways, the remainder of the conducting system is comprised of the central airways. The respiratory symptoms and respiratory impairment that are associated with the deposition of particles in the larger airways are both more obvious and more easily demonstrated than are those associated with particulate deposition in the smaller airways (2).

RESPONSES TO DUST DEPOSITION

The deposition of inhaled dust in the central airways of the lung may induce one or more of the following four basic responses:

1. Immunologically induced airways constriction. This includes both Type I and Type III Reactions (3) and is best termed occupational asthma.
2. Pharmacologically induced airways constriction.
3. Acute irritation and reflex broncho-constriction.
4. Non-specific response to dust, viz. chronic bronchitis. This type of response is not related to the toxic properties of the dust or to its propensity to generate an immunologic reaction. Each of these responses are dealt with in turn.

IMMUNOLOGICALLY INDUCED (Asthma)

Bronchial constriction or occupational asthma may be induced by either a Type I or Type III immunological reaction (3). Type I reactions are immediate and are mediated by a specific immunoglobulin IgE. The concentration of IgE in the blood may be increased in subjects with extrinsic asthma. When a susceptible subject, viz. an atopic individual, is exposed to an antigen, there is an increase in the IgE specific to that antigen. The specific IgE binds to the mast cells present in the bronchial wall and as a result histamine and a slow reacting substance (SRS-A) are liberated. The Type III responses, which are related to the Arthus phenomenon and are associated with the presence of precipitins in the blood, occur several hours after the challenge. They are due to immunoglobulin, IgG.

Individuals with occupational asthma complain of wheeziness and shortness of breath. Initially, these symptoms occur only while the individual is at work, but later they may persist at home and on weekends. Workers who are atopic are more prone to develop occupational asthma and may do so with a relatively short exposure. Nevertheless, normal individuals may be affected although their symptoms often do not appear for several years; that is, until they have become sensitized. *Rhinitis* and *conjunctivitis* are common accompaniments of occupational asthma.

The diagnosis is made from the occupational and medical history and, if necessary, by appropriate challenge tests. When the subject is

exposed to the appropriate antigen, a decline in ventilatory capacity is usually induced. If it is a Type I reaction, the reduction in forced expiratory volume in 1 second (FEV_1) and in forced vital capacity (FVC) is usually evident within 10 to 15 minutes. If it is a Type III response, the decline is often delayed for 3 to 4 hours. Skin testing for immediate flare and wheal response is useful; however, cutaneous and bronchial responses do not necessarily correlate well with each other.

Potential exposure resulting in occupational asthma is commonly found in the following occupations: (4-17)

Grain and cereal workers, including bakers.

Woodworkers including carpenters, joiners, and sawmill operators. Western red cedar, mahogany, oak, and iroko have all been incriminated as potent sensitizing agents.

Printing. In this case gum arabic is responsible for the sensitization.

Manufacturers of detergent enzymes. These enzymes are manufactured from the products produced by fermentation of *Bacillus subtilis.* The enzyme responsible is also known as alcalase.

Soldering. This is usually due to the flux which contains aminoethylethanolamine.

Isocyanate workers. Isocyanates are used to manufacture polyurethane foams. Two compounds have been incriminated as causes of occupational asthma. These are toluene diisocyanate (TDI) and diisocyanatodiphenyl methane (MDI).

Electroplaters, photographers, and persons exposed to platinum.

Less commonly, asthma may be associated with occupational exposures to the following: nickel, chromium, the Mexican bean weevil, locusts, silkworms, coffee, castor beans, and tungsten carbide.

PHARMACOLOGICALLY INDUCED (Byssinosis)

Airways constriction may be induced by the deposition of certain dusts in the airways in the absence of an immunological reaction (18). Thus, when certain dusts settle on the bronchial walls, the liberation of naturally occurring broncho-constrictors such as histamine and possibly serotonin may take place. Since this does not involve any immunological mechanism, the liberation of such substances can be said to be a pharmacological response to an extrinsic agent.

Although there is still some doubt, the broncho-constriction seen in byssinosis may be of this type. There is good evidence to suggest that the cotton bract contains an agent which, when it comes into contact with the bronchial mucosa, leads to the liberation of excess histamine. Byssinosis is seen in cotton, hemp, and flax workers and a similar condition possibly occurs in workers who are exposed to sisal.

The usual history of byssinosis is that the worker develops chest tightness and wheezing on return to the mill on a Monday morning. In the early course of the disease the symptoms disappear by Tuesday or Wednesday. However, with continued exposure, the tightness and shortness of breath begin to persist for longer periods until it is present all

the time. In established long standing byssinosis, the worker ends up continually short of breath and with over-distended lungs. The diagnosis is established by measuring the patient's ventilatory capacity before he starts work on Monday and again after he has finished.

IRRITANTS

If the bronchi are insulted by irritant gases or fumes, they constrict in a reflex fashion (19). Such constriction is usually accompanied by coughing, and both the coughing and bronchial constriction are mediated through vagal reflexes. Irritant gases such as chlorine, ammonia, ozone, sulfur dioxide, and the oxides of nitrogen may all produce an acute *tracheitis* and *bronchitis* which are associated with reflex broncho-constriction and coughing. With large and prolonged exposures, the lung parenchyma may also be affected. The solubility of the inhaled gas will determine whether there is a predominant proximal or distal involvement of the airways.

Aside from the above gases to which workers may be exposed as a result of industrial mishaps, certain occupational groups may be routinely exposed to other noxious fumes and aerosols in their working environment. These include: beryllium, boron hydrides (volatile), cadmium, chromium compounds (hexavalent), hydrofluoric acid, zinc chloride, manganese, mercury, osmium, and vanadium pentoxide.

DUST

Prolonged exposure to dust may lead to *industrial bronchitis* (20). The heavier the dust exposure, the more likely is the development of industrial bronchitis. The characteristic features of this condition are cough and sputum in the absence of localized destructive disease of the lungs.

The symptoms of industrial bronchitis differ in no way from those seen in chronic bronchitis due to cigarette smoking. Both conditions are characterized by production of excess mucus. The mucus is secreted by the goblet cells and more particularly the mucus glands of the bronchial tree. Airways obstruction is seen less often in industrial bronchitis than it is in the naturally occurring form of chronic bronchitis due to cigarette smoking.

Coal miners and steel workers are particularly prone to this form of airways disease. The symptoms tend to regress when dust exposure is reduced.

REFERENCES

1. Macklem, P. T., and J. Mead. 1967. Resistance of central and peripheral airways measured by a retrograde catheter. J. Appl. Physiol. 22:395.
2. Small particles in small airways, Editorial. 1973. Lancet 2:948.
3. Pepys, J. 1969. Monographs in Allergy: Hypersensitivity diseases of the lungs due to fungi and organic dusts. Vol. 4. S. Karger, Basel and New York.
4. Duke, W. W. 1935. Wheat hairs and dust as a common cause of asthma among workers in wheat flour mills. J. Am. Med. Assoc. 105:957.

5. Lunn, J. A. 1966. Millworkers' asthma, allergic responses to the grain weevil. Br. J. Ind. Med. 23:149.
6. Lunn, J. A., and D. T. D. Hughes. 1967. Pulmonary hypersensitivity to the grain weevil. Br. J. Ind. Med. 24:158.
7. Sossman, A. J., D. P. Schlueter, J. N. Fink, and J. J. Barboriak. 1969. Hypersensitivity to wood dust. N. Eng. J. Med. 281:977.
8. Gandevia, B., and J. Milne. 1970. Occupational asthma and rhinitis due to western red cedar. Br. J. Ind. Med. 27:235.
9. Greenberg, M. 1972. Respiratory symptoms following brief exposure to cedar of lebanon dust. Clin. Allergy 2:219.
10. Bohner, C. B., and J. M. Sheldon. 1941. Sensitivity to gum acacia, with a report of ten cases of asthma in printers. J. Allergy 12:290.
11. Pepys, J., F. E. Hargreave, J. L. Longbottom, and J. Faux. 1969. Allergic reactions of the lungs to enzymes of Bacillus subtilis. Lancet 1:118.
12. McCann, J. K. 1964. Health hazard from flux used in joining aluminum electricity cables. Ann. Occup. Hyg. 7:261.
13. McKerrow, C. B., H. J. Davies, and A. P. Jones. 1970. Symptoms and lung function following acute and chronic exposure to tolylene di-isocyanate. Proc. Soc. Med. 63:376.
14. Roberts, A. E. 1951. Platinosis. A five-year study of soluble platinum salts on employees in a platinum laboratory and refinery. Arch. Ind. Hyg. Occup. Med. 4:549.
15. Wittich, F. W. 1940. Allergic rhinitis and asthma due to sensitization to the Mexican bean weevil. J. Allergy 12:42.
16. McConnell, L. H., J. N. Fink, D. P. Schlueter, and M. G. Schmidt, Jr. 1973. Asthma causer by nickel sensitivity. Ann. Intern. Med. 78:888.
17. Morgan, W.K.C., and Seaton, A. 1975. Occupational Lung Disease. Chapters 6 and 12. W. B. Saunders Co., Philadelphia.
18. Schilling, R. S. F. 1956. Byssinosis in cotton and other textile workers. Lancet 2:261 and 319.
19. Bidstrup, P. L. 1972. Clinical Aspects of Inhaled Particles, Chap. 8. F. A. Davis Co., Philadelphia, p. 156.
20. Kibelstis, J. A., E. J. Morgan, R. Reger, N. L. Lapp, A. Seaton, and W. K. C. Morgan. 1973. Prevalence of bronchitis and airway obstruction in American bituminous coal miners. Amer. Rev. Respir. Dis. 108:886.

EXTRINSIC ALLERGIC ALVEOLITIDES

The inhalation of organic dusts may lead to two distinct pulmonary responses. First, and more common, is that mediated by reaginic antibody and usually referred to as the Type I. It occurs most commonly in atopic subjects and is characterized by changes in the airflow resistance in the conducting system of the lungs. This type of response has been described in the preceding discussion of diseases of the airways. The second and less common type of reaction affects the lung parenchyma, viz., the respiratory bronchioles and alveoli and does not appear to be related to atopy. Pepys coined the term extrinsic allergic alveolitis (hypersensitivity pneumonitides) to describe this response (1), which is also known as hypersensitivity pneumonitis.

CAUSATION

Although a large number of organic dusts have been identified as causes of extrinsic alveolitis, the pathophysiological effects are similar no matter which dust is responsible. The demonstration of specific precipitins in the serum of subjects affected by allergic alveolitis led Pepys to hypothesize that the basic mechanism in extrinsic allergic alveolitis is an Arthus or Type III reaction (1). Since most of the antigenic dusts

that produce extrinsic allergic alveolitis are organic, and since the serum of afflicted subjects often contain specific precipitins, there is an obvious resemblance to serum sickness. In the latter condition, the antigen is introduced into the body by injection, while in contrast, in extrinsic allergic alveolitis the antigen is inhaled.

Although not everybody who is repeatedly exposed to the antigen develops extrinsic allergic alveolitis, a small percentage does. Similarly, while there is good evidence that a substantial proportion of the subjects who are exposed to the antigen develop antibodies, the presence of antibodies alone is not necessarily an indication that the patient has or is likely to suffer from hypersensitivity allergic pneumonitis. Most subjects who develop allergic pneumonitis do so as a consequence of occupational exposure, but in some instances the person's avocation is more likely to be responsible.

The main differences between Type I and Type III pulmonary responses are shown in Table 1. It is important to add that since Pepys first called attention to the syndrome of extrinsic allergic alveolitis, its recognized causes have doubled or tripled (2).

CLINICAL FEATURES

Whatever the antigen, the clinical features of the condition are relatively similar. The acute form of the disease is more easily recognized and usually presents the symptoms of a sudden onset of fever, chills, shortness of breath, and a dry cough which appear between 4 to 8 hours following exposure. The patient may be severely distressed and on physical examination shows the presence of cyanosis, marked tachypnea, often of around 35 to 40 per minute, and diffusely scattered crepitations at both lung bases.

During the acute phase, pulmonary function tests show desaturated blood, reduced arterial PCO_2, and a mild to moderate respiratory alkalosis. The lung volumes are greatly reduced, especially the vital capacity; however, there is no evidence of increased resistance to flow in the airways.

Measurements of the mechanical properties of the lungs indicate that the lungs are stiffer than normal and that their compliance is greatly reduced. The radiographic appearances are those of a diffuse acinous filling process predominantly affecting the mid and lower zones. The appearances in an air bronchogram are somewhat suggestive of pulmonary edema; however, there is no cardiac enlargement. Symptoms and signs gradually regress over a period of a week to ten days.

Besides the acute form of hypersensitivity pneumonitis, a more chronic form exists. This occurs with repeated lesser exposures, and although on the first two or three occasions there may be mild fever and chills, the continued lesser insults are not so obviously related to occupational exposure. In the chronic form which appears over a period of several months, the afflicted subject notices the onset of dyspnea, sometimes with occasional mild fever. This is usually accompanied by loss of weight, and general lethargy.

Table 1. Pulmonary response differences (2).

	Extrinsic allergic asthma (Type I)	Extrinsic allergic alveolitis (Type III)
Predisposing factors	Atopy	None known
Region affected	Conducting system of the lungs: bronchi to terminal bronchioles	Acini, respiratory bronchioles, and alveoli
Histology	Mucous plugging, bronchial edema, and eosinophilic infiltration	Granulomatous pneumonitis, occasionally undergoing organization and leading to interstitial fibrosis.
Onset of symptoms	Immediate	4 to 6 hours
Systemic reaction	None	Usual and accompanied by fever
Signs	Wheezes (rhonchi)	Crackles (crepitations)
Radiographic signs	Overdistension	Acinous filling pattern, often coexisting with some reticulonodulation in more chronic forms of the syndrome
Serological findings	Elevated IgE	Precipitins present (90% of cases)
Pulmonary impairment	Increased air flow resistance	Restrictive pattern
Eosinophilia	Common	Transient and uncommon
Skin tests	Immediate and urticarial	Edematous reaction appearing in 4 to 6 hours

Physical examination may reveal some cyanosis, clubbing may be present, and there may be diffuse scattered crepitations in both lower zones. The radiographic appearances are more suggestive of chronic interstitial fibrosis than of extrinsic allergic alveolitis. Pulmonary function tests in the subacute and chronic forms of the syndrome show restrictive disease with small lungs.

As the disease progresses, the lungs become smaller, the dyspnea worsens, and the end result resembles fibrosing alveolitis. In the established chronic case, the histological appearance cannot be distinguished from that seen in chronic interstitial fibrosis of unknown etiology. Both farmer's lung and pituitary snuff allergic alveolitis have been known to present a chronic interstitial fibrosis appearance.

PREVENTION

Elimination of personal exposure to the antigen can prevent the development or recurrence of the disease. This necessitates either environmental controls or personal protection. Environmental controls may include the elimination of conditions conducive to bacterial and fungal growth, process changes preventing the production of the antigen, or ventilation and particulate controls that eliminate contact of the antigen with the worker.

Personal protection can best be provided by the use of respirators to prevent inhalation of the antigen. The appropriate respirator should be selected on the basis of the characteristics of the dust or spores, the situation involved, and individual acceptance. When protection is inadequate for an individual with the hypersensitivity, removal of that individual from the offending environment is indicated.

PATHOLOGY

In the acute phase of the disease, the histological appearances of the lung show that the alveolo-capillary membrane is thickened, and that there is histiocytic, lymphocytic, and plasma cell infiltration. There may also be an edema-like fluid present in the alveoli. Numerous epithelioid tubercles may be seen but caseation necrosis is absent, and tubercle bacilli and fungi are not seen. The one exception to this is that occasionally in maple bark disease, *Cryptostroma corticale* spores may be seen in the lung parenchyma. Even so, maple bark disease is not a true fungal infection, but an allergy to the spores of this organism. The general appearance of extrinsic allergic alveolitis is that of a granulomatous interstitial pneumonia, with the granulomata bearing a resemblance to those seen in sarcoidosis.

Early in the disease, there is often an increase in the number of reticulin fibers but later on collagenous fibrosis predominates. A bronchiolitis affecting the respiratory bronchioles may also be present. Pathological changes found in chronic farmer's lung and other extrinsic allergic alveolitis are those of an interstitial fibrosis with collagenous thickening of the septa and lymphocytic infiltration. The fibrosis is often worse in the upper lobes and there may be frequent pigment laden macrophages present in the alveoli. Later on the intima of the pulmonary arteries is thickened and when this occurs pulmonary hypertension supervenes. In the terminal stages, cystic areas with honeycombing may be present in the lungs.

IMMUNOLOGY

The abrupt onset within three to four hours of exposure argues against this syndrome being an infective process. In addition, inhalation of aqueous extracts of mouldy hay will reproduce the clinical features of farmer's lung as will extracts of *Micropolyspora faeni.* The reaction develops several hours after the challenge and is associated with a

Table 2. Common clinical conditions (2).

Clinical condition	Source of offending agent	Precipitins against
Farmer's lung	Mouldy hay	*Micropolyspora faeni* *Thermoactinomyces vulgaris*
Baggassosis	Mouldy bagasse	*Thermoactinomyces vulgaris*
Mushroom worker's lung	Mushroom compost	*Micropolyspora faeni* *Thermoactinomyces vulgaris*
Suberosis	Cork dust	Cork dust
Maple bark disease	Maple bark	*Cryptostroma corticale*
Sequoiosis	Redwood sawdust	*Graphium* *Pullaria*
Papuan lung (New Guinea lung)	Mouldy thatch dust	Thatch of huts
Wood pulp worker's disease	Wood pulp	*Alternaria*
Malt worker's lung	Mouldy barley	*Aspergillus clavatus* *Aspergillus fumigatus*
Dog house disease	Mouldy straw	*Aspergillus versicolor*
Bird fancier's lung (Pigeon breeder's lung)	Pigeon, parrot and other bird droppings	Sera, protein, and droppings
Pituitary snuff taker's lung	Bovine and porcine pituitary snuff	Pituitary antigens
Wheat weevil disease	Wheat flour	*Sitophilus granarius*
Furrier's lung	Animal hairs	
Coffee worker's lung	Coffee bean	Coffee bean dust
Paprika splitter's lung	Paprika	
Lycoperdonosis	Puffball Lycoperdon Pyriform	

decline in ventilatory and diffusing capacities. In addition, there is a rise in the temperature of the patient which is usually accompanied by marked hyperventilation.

During the acute stage, precipitins are nearly always present in the serum of the affected subject, but with convalescence the titer often drops and may become negative if further exposure does not occur. Nevertheless, the presence of precipitins does not confirm the diagnosis of extrinsic allergic alveolitis; neither does their absence exclude it.

This syndrome is produced by a large number of different antigens, of which some of the more common ones are shown in Table 2. If a subject presents the clinical features of the syndrome, a detailed occupational history should be taken to see whether an antigen of organic nature in the patient's working environment might be responsible. It is also necessary, however, to stress that certain conditions develop as a result of the patient's avocation, e.g., pigeon fanciers' disease, pituitary snuff hypersensitivity pneumonitis. Therefore, if extrinsic allergic alveolitis is suspected, the patient's serum should be examined for precipitins against the offending antigens, and if present, the patient may be challenged with the aerosolized antigen and his ventilatory capacity or preferably his diffusing capacity assessed at intervals for four to eight hours following the challenge. If either falls, then the diagnosis of extrinsic allergic alveolitis can be made.

REFERENCES

1. Pepys, J. 1969. Monographs in Allergy: Hypersensitivity Diseases of the Lungs Due to Fungi and Organic Dusts, Vol. 4. S. Karger, Basel and New York.
2. Morgan, W.K.C., and A. Seaton. 1976. Occupational Lung Diseases. Chapter 15. W. B. Saunders Co., Philadelphia.

PNEUMOCONIOSES

The word "pneumoconiosis" literally means dust in the lungs. Not all dusts that can be deposited in the lungs cause recognizable disease, so that the most widely accepted definition of pneumoconiosis is that of the International Labour Organization which states that "Pneumoconiosis is the accumulation of dust in the lungs and the tissue reaction to its presence. For the purpose of this definition, 'dust' is meant to be an aerosol composed of solid inanimate particles (1)."

DEPOSITION OF PARTICLES

Inhaled particles closely follow the movement of the air in which they are suspended as they are carried into the lungs during the inspiratory phase of respiration. They are, however, acted upon by certain forces which tend to promote their deposition within certain anatomic regions of the lung (2). The first of these, gravitational sedimentation, refers to the fact that the falling speed or terminal velocity of an airborne particle under the influence of gravity is proportional to its density and the square of its diameter. Thus, larger and more dense particles settle out more rapidly than smaller, less dense particles. This mechanism is responsible for most of the deposition of particles during breathing.

The second factor promoting deposition of particles in the lungs is inertial impaction and refers to the fact that a particle tends to maintain its original direction of travel despite a change in direction of the airstream in which it was suspended. This mechanism is largely responsible for the deposition of particles in the nose and at bifurcations of the lower airways.

The third factor promoting deposition of particles in the lungs is termed diffusion or, preferably, Brownian motion. All airborne particles are moving at random owing to their constant bombardment by gas molecules. In general, only the particles smaller than about 0.1 micron in diameter acquire sufficient Brownian motion to become deposited as a result of this mechanism alone.

Aerodynamic behavior refers to the mobility of particles regardless of their apparent size and shape. Thus, a relatively large, loosely aggregated clump of particles may behave aerodynamically in the same fashion as a much smaller dense particle. A fiber nearly 100 microns long but with a 3-micron diameter may behave in much the same fashion as a spherical particle about 3 microns in diameter as regards its ability to penetrate into the deeper regions of the lungs.

Other factors that appear to be important in determining the deposition of airborne particles are the pattern of breathing; namely, nose versus mouth breathing, and possibly individual variation in the filtration efficiency owing to differences in size and shape of the airways.

The International Commission on Radiological Protection has calculated the probabilities for the regional deposition of aerosols as a function of particle size based upon certain breathing patterns (3). In general, these curves show that the majority of particles larger than 15 microns will be deposited in the nose. However, as the particle size decreases to about 10 microns, an increasingly larger percentage will be deposited in the tracheobronchial tree; between about 5 microns and about 0.5 microns, the particles will be deposited in the alveoli and respiratory bronchioles. It is the deposition of particles of approximately 0.5 to 5 microns in the alveoli and respiratory bronchioles that gives rise to the group of diseases known as the pneumoconioses.

CLEARANCE OF PARTICLES

The conducting airways down to the terminal bronchioles are lined by a ciliated epithelium covered by a layer of mucus secreted by glands located in their walls and by goblet cells interspersed at intervals in the epithelium. The mucous layer is continuously propelled upward toward the mouth by the motion of the tiny hair-like cilia. Particles deposited in this layer are cleared usually within 24 hours to the oropharynx where they are swallowed along with the mucus. Wide variations in bronchial clearance are known to exist in man, but the reasons for these are not entirely clear (4).

Particles that penetrate to and are deposited in the alveolar areas of the lungs are cleared much more slowly than those deposited in the conducting airways. Evidence indicates that the particles are engulfed by alveolar macrophages and are somehow carried to the mucus escalator system to be cleared. The rate of clearance of an alveolar dust load probably depends to a large extent upon the availability of alveolar macrophages (5). The rate of alveolar clearance is also in part determined by the relative biological toxicity of the dust particles to the alveolar macrophages and, in part, by the total amount of dust already

present within the lungs (2). Nonetheless, both bronchial and alveolar clearance of dust particles are relatively efficient since abundant evidence exists that only a small fraction of the total dust load deposited in the lungs is retained in even the most advanced cases of pneumoconiosis.

PATHOLOGY

The different forms of pneumoconiosis are difficult to classify. One useful classification is that of Nagelschmidt in which four types of reaction appear to be distinguishable (6):

1. Hyaline-nodular fibrosis (classical silicosis)
2. Simple pneumoconiosis of coal miners
3. Mixed dust pneumoconiosis
4. Diffuse interstitial fibrosis

SILICOSIS

The characteristic lesion of silicosis is the silicotic nodule (7). In its simplest form the silicotic nodule consists of a central core of hyalinized reticulin fibers arranged in concentric layers which, towards the periphery, blend with coarser fibers of collagen to form a relatively distinct capsule. Early in the course of silicosis these nodules occur adjacent to, or in the walls of, the respiratory bronchioles. These nodules are thought to be formed by the death of macrophages laden with fine silica and the fibrosis resulting from the release of intracellular enzymes along with the ingested particles. The silica particles are ingested by new macrophages which are in turn killed, thereby releasing their potent intracellular enzymes to promote further fibrosis and, thus, the process becomes progressive (8).

The upper lobes and hilar lymph nodes are often more severely affected than the lung bases. In early stages, the nodules may remain isolated, but as the disease progresses the nodules crowd closer together until they appear to form a continuous mass of fibrous tissue. However, on close inspection, discreet nodules can usually be distinguished and what appeared to be a diffuse fibrosis is in reality many compressed nodules.

Silicosis not only favors the growth of tubercle bacilli, but may suppress the usual features of epitheloid cell proliferation, giant cell formation, and lymphocytic reaction to the extent that caseous necrosis in the center of a silicotic nodule may be the only indication of coexistent tuberculosis infection (9). Silicosis is also associated with pulmonary hypertension and cor pulmonale, probably partially as a consequence of damage by adjacent nodules to the walls of blood vessels which produces mechanical obstruction, and partially as a result of abnormal blood gas tensions leading to vasoconstriction.

COALWORKERS' PNEUMOCONIOSIS

The characteristic lesion in coalworkers' pneumoconiosis is the coal macule which consists of an accumulation of dust-laden macrophages

around respiratory bronchioles surrounded by a halo of dilated airspaces (10). In addition to the accumulations of coal in the macule, there is a slight increase in reticulin fibers and, to a lesser extent, collagen fibers. The presence of coal macules around the walls of the respiratory bronchioles may lead to atrophy or even to disappearance of the smooth muscle, this leading to a permanent dilatation of these small airways commonly called focal emphysema.

In about 1 to 2 percent of miners with simple dust accumulation, large, solid, black masses develop which represent accumulations of coal dust within macrophages and between reticulin and collagen fibers. These lesions are commonly formed in the upper lobes and differ from silicotic conglomerate masses in that the masses are not composed of discreet compressed nodules. The cause of the large lesions ("progressive massive fibrosis") in coal workers is not known. They are probably not due to coexisting tuberculous infection, but may represent an immunological reaction to the accumulated dust load. See Figure 5.

Caplan described the appearance of multiple rounded nodules in the lungs of coal miners with rheumatoid arthritis that subsequently proved to be necrobiotic nodules resembling those seen in rheumatoid arthritis (11). Microscopically, these lesions demonstrate a pale, necrotic center surrounded by granulomatous tissue having a typically "palisaded" appearance at the periphery of the nodule. Typical Caplan nodules have subsequently been reported in other occupations than coal mining, suggesting that they are not specifically related to coal dust exposure.

MIXED DUST PNEUMOCONIOSIS

In the mixed dust pneumoconioses the pathology depends to a large extent upon the relative proportion of free silica or quartz present in the airborne dust. Those with a quartz content of less than about 0.1 percent tend to develop small nodular areas in the lungs in almost direct proportion to the total amount of dust deposited, but little in the way of reticulin or collagen fibrosis, and very little emphysema. The pathological lesions more nearly resemble those found in coal miners.

On the other hand, dusts in which the quartz content ranges from about 2 percent to about 18 or 20 percent of the total dust tend to produce lesions that more nearly resemble those seen in classical silicosis.

Some examples of dusts that contain almost no free quartz are kaolin, talc, iron oxide associated with welding, coal, and coke used in making carbon electrodes.

DIFFUSE INTERSTITIAL FIBROSIS

There are a number of pneumoconioses that tend to produce diffuse interstitial fibrosis as their characteristic pathological lesion (6). Among these are berylliosis, aluminosis, Shaver's disease, and asbestosis. It appears likely that certain slowly dissolving constituents in the dusts give

rise to a peculiar disseminated interstitial fibrosis rather than to the focal or nodular types seen in coal miners or silicosis. As a general rule, the amount of dust found in the lungs in this type of pneumoconiosis is small and the fibrotic reaction that occurs is out of proportion to the amount of dust deposited.

RADIOGRAPHIC DIAGNOSIS

Unfortunately, the ability to diagnose the presence of pneumoconiosis during life is not as precise and clear-cut as the pathological responses described above. There are two general patterns of radiographic response recognizable. Both classical silicosis and the mixed dust pneumoconioses, including that seen in coal workers, tend to produce nodular opacities or a combination of reticular-nodular opacities on the chest roentgenogram. These are basically rounded shadows and are classified by type, profusion, and extent under the ILO U/C Classification of the pneumoconioses (12).

The pneumoconioses that produce the diffuse interstitial pathology are generally manifested as reticular and linear opacities on the chest roentgenograms. These likewise are generally classified by type, profusion, and extent as irregular opacities under the ILO U/C Classification of pneumoconiosis. Both rounded and irregular opacities may be present as the background upon which complicated pneumoconiosis or progressive massive fibrosis develops.

CLASSIFICATION

The ILO U/C Classification is intended to provide a simple reproducible means of systematically recording the radiographic changes associated with the inhalation of all types of mineral dusts. It is likely to be most useful in relating the radiographic features to indices of dust exposure and changes in lung function, particularly in epidemiological studies. It should also make possible comparison of data obtained in studies from other countries.

The system basically classifies the radiographic features by small (less than 1 cm) and large (greater than 1 cm) opacities; thus, simple pneumoconiosis is diagnosed when none of the opacities exceed 1 cm in diameter, and complicated pneumoconiosis is diagnosed when one or more of the opacities exceed 1 cm in diameter. Within the small opacity category, one recognizes the type, profusion, and extent of involvement of the lungs by the opacities.

The simple pneumoconiosis is further subdivided into small rounded opacities and small irregular opacities. The small rounded opacities are classified into types p, q, r, according to the approximate diameter of the predominant opacities. The p type includes rounded opacities up to about 1.5 mm in diameter; the q (m) type includes rounded opacities exceeding about 1.5 mm up to about 3 mm in diameter; the r (n) type includes rounded opacities exceeding about 3 mm and up to about 10 mm in diameter.

CATEGORY

Profusion refers to the number of small opacities per unit area. Thus, the lung fields are divided into three zones on each side, and the number of opacities within each zone is graded. Standard radiographs are available for comparison which divide the profusion into categories 0, 1, 2, and 3. Category 0 refers to the absence of opacities or the presence of less profuse opacities than in category 1; category 1 shows small rounded opacities present, but few in number, and the normal lung markings are usually visible; category 2 shows numerous small rounded opacities, and the normal lung markings are still visible; category 3 shows very numerous small rounded opacities, and the normal lung markings are partly or totally obscured.

Actually, there is a continuum of changes from normality to the most advanced category and, to recognize this, the British National Coal Board developed a 12-point scale (13). This scale permits subdivisions of profusion into finer grades and is useful in epidemiological studies where progression of pneumoconiosis is important. The radiograph is classified into one of the four categories in the usual way by comparison with the standard midcategory films. If, during the process, the category above or below was considered as a serious alternative, this is also recorded. Thus, if a category ½ is recorded, it means that on comparison with standard radiographs the radiograph most nearly matched the category 1, but category 2 was seriously considered as an alternative.

The extent of pneumoconiosis is recorded by noting which of the lung zones are involved. Each lung is divided into three roughly equal zones by imaginary lines drawn at approximately one-third and two-thirds of the vertical distance between the apex of the lung and the dome of the diaphragm. Thus, each lung is divided into upper, middle, and lower zones for the purposes of recording the extent of pneumoconiosis.

IRREGULAR OPACITIES

Small irregular opacities are classified in much the same way as the small regular opacities, by type, profusion, and extent. Irregular opacities characteristically occur in asbestosis, but also occasionally in the other pneumoconioses. The variability, however, of these opacities in shape and width makes it virtually impossible to provide quantitative dimensions as is done in the rounded opacities; therefore, the types are divided on the basis of thickness. The s type refers to fine irregular, or linear, opacities; the t type refers to medium irregular opacities, and the u type refers to coarse (blotchy) irregular opacities. Standard radiographs of the three types of irregular opacities are available for comparison. Profusion of irregular opacities is graded in exactly the same way as is done in the rounded small opacities.

PLEURAL CHANGES

Certain pleural changes have recently become recognized as accompaniments to the parenchymal changes referred to above as part of

some pneumoconioses. Therefore, the ILO U/C Classification records pleural thickening by site (costophrenic angles, chest wall, diaphragm), width, and extent.

Pleural calcification is also classified by site and extent. When the cardiac outline and diaphragm are ill-defined, this is also recorded. A number of obligatory and optional symbols are also included in the classification for the benefit of a more complete description of the radiographic findings. The reader is referred to the complete ILO U/C Classification for details regarding these features which are beyond the scope of this chapter (12).

PHYSIOLOGICAL RESPONSES

The lungs have relatively few ways of responding to the dust burdens presented to them. Physiologically, two major patterns of response can be identified: an obstructive impairment and a restrictive impairment.

The obstructive pattern is characterized by a reduction in expiratory air flow, usually associated with either an increased airway resistance or a loss of lung recoil, or both. Increased airway resistance most commonly results from intrinsic narrowing of the airways owing to spasm of the smooth muscle in the walls (such as occurs in asthma), or to edema, inflammation, and mucus plugs (such as occurs in chronic bronchitis). These aspects have been more fully discussed in the chapter on airways mechanisms and responses.

OBSTRUCTIVE IMPAIRMENT

The obstructive pattern of physiological impairment in the pneumoconioses is more likely the result of localized or diffuse abnormalities in the lung recoil, owing to destructive changes in and around the small airways (less than 2 mm diameter) caused by the dust deposits. In simple pneumoconiosis these changes may be severe enough to cause alterations in the distribution of the inspired air and minor degrees of mismatching of ventilation and blood flow detectable only by using very sensitive techniques. These physiological impairments could prove disabling for heavy physical activities, but not for ordinary activities or at rest.

Spirometric tests of ventilatory capacity are usually within normal limits, or very nearly normal, in simple silicosis, simple coalworkers' pneumoconiosis, and the simple mixed dust pneumoconioses, unless asthma, chronic bronchitis, or emphysema, coexist. In the complicated form of the pneumoconioses (PMF), ventilatory capacity as measured by spirometry is often abnormal and consists of elements of both obstruction and restriction. Here, in addition to the loss of lung recoil owing to focal emphysema, some of the obstructive impairment may be attributable to distortion and kinking of airways by the large conglomerate masses. These large masses also generally interfere with gas exchange by reducing the surface area available for diffusion and the obliteration of the capillary bed.

Table 3. Agent, pathology, and impairment associated with pneumoconioses.

Agent	Type of Pathology	Type of Respiratory Impairment
1. Silica		
Simple	Nodular fibrosis	Restrictive, diffusion
Complicated	Conglomerate nodular fibrosis	Restrictive, obstructive, diffusion
2. Hematite	Nodular fibrosis	Restrictive, diffusion
3. Mixed dusts		
Iron and silica	Nodular fibrosis (Rarely conglomerate nodular fibrosis)	Restrictive, diffusion
4. Silicates	Nodular fibrosis	Restrictive, obstructive
Talc	(Rarely conglomerate nodular fibrosis)	
Kaolin		
Bentonite		
Diatomite		
Tripoli		
Fuller's earth		
Mica		
Sillimanite		
Cement	Nonspecific bronchitis	Obstructive
5. Coal		
Simple	Peribronchiolar macules, focal emphysema	Obstructive (small airways)
Complicated	Conglomerate nodular fibrosis	Obstructive, restrictive, diffusion
6. Graphite	Peribronchiolar macules, focal emphysema	Obstructive (small airways)
7. Aluminum	Interstitial fibrosis	Restrictive, diffusion
8. Asbestos	Interstitial fibrosis	Restrictive, diffusion
9. Beryllium	Interstitial fibrosis (granulomata)	Restrictive, diffusion
10. Tungsten carbide	Interstitial fibrosis	Restrictive, diffusion
11. Barium	Simple dust accumulation	None known
12. Cerium	Simple dust accumulation	None known
13. Iron	Simple dust accumulation	None known
14. Tin	Simple dust accumulation	None known
15. Titanium	Simple dust accumulation	None known

The simple forms of classical silicosis, coal workers' pneumoconiosis, and the mixed dust pneumoconiosis, generally demonstrate mild obstructive impairment; whereas, the complicated forms (PMF) usually present mixtures of obstruction, restriction, and abnormalities of gas exchange.

RESTRICTIVE IMPAIRMENT

The restrictive pattern of physiological response is characterized by a reduction in lung volumes and ventilatory capacity, usually unaccompanied by an increased air flow resistance or hyperinflation. The restrictive pattern is also associated with an increased lung recoil, reduction in surface area for gas exchange and/or thickening of the air blood interface of the lungs.

The pneumoconioses that lead to diffuse interstitial fibrosis usually present the restrictive pattern of physiological impairment. In these, the earliest impairments are those involving gas exchange and diffusing capacity, and may be detectable only during exercise. In the later stages, gas exchange and diffusion abnormalities are detectable also at rest and are associated with a reduction in lung volumes, such as the vital capacity, total lung capacity, and the inspiratory reserve volume. Again, in cases where pneumoconiosis coexists with asthma or chronic bronchitis, this restrictive pattern may be associated with some element of obstructive impairment.

Asbestosis, berylliosis, aluminosis, and Shaver's disease are examples of pneumoconioses that are characteristically associated with the restrictive pattern of physiological impairment.

A summary of agent and type of pathology and respiratory impairment is given in Table 3.

REFERENCES

1. International Labour Office. 1972. The definition of pneumoconiosis. Page 1558 *in* Encyclopedia of Occupational Health and Safety, Vol. II, Appendix VII. McGraw Hill Book Co., New York.
2. Muir, D. C. F. 1972. Dust Inhalation, Retention, and Elimination. In: J. M. Rogan, ed. Medicine in the Mining Industries. p. 55. F. A. Davis Co., Philadelphia.
3. International Commission on Radiological Protection. 1966. Deposition and retention models for internal dosimetry of the human respiratory tract. Health Phys. 12:173.
4. Lippmann, M., and R. E. Albert. 1969. The effects of particle size on the regional deposition of inhaled aerosols in the human respiratory tract. Am. Ind. Hyg. Assoc. J. 30:257.
5. Brain, J. D. 1971. The effects of inhaled particles on the numbers of alveolar macrophages. In: M. H. Walton, ed. Inhaled Particles III, Vol. 1. p. 209. Unwin Bros., Ltd., Old Woking.
6. Nagelschmidt, G. 1960. The relation between lung dust and lung pathology in pneumoconiosis. Bri. J. Ind. Med. 17:247.
7. Steele, R. A. 1972. The pathology of silicosis. In: J. M. Rogan, ed. Medicine in the Mining Industries. p. 20. F. A. Davis Co., Philadelphia.
8. Heppleston, A. G. 1969. The fibrogenic action of silica. Br. Med. Bull. 25:282.
9. Spencer, H. 1968. Pathology of the Lung, 2nd ed. Pergamon Press, Oxford.

10. Heppleston, A. G. 1968. Lung architecture in emphysema. In: G. Cumming and L. B. Hunt, eds. Form and Function in the Human Lung. p. 6. The Williams and Wilkins Co., Baltimore.
11. Caplan, A. 1953. Certain unusual radiological appearances in the chest of coal miners suffering from rheumatoid arthritis. Thorax 8:29.
12. Jacobson, G., and W. S. Lainhart, eds. 1972. I.L.O. U/C 1971, international classification of radiographs of the pneumoconioses. Med. Radiogr. Photogr. 48:65.
13. Liddell, F. D. K., and D. C. Lindars. 1969. An elaboration of the I.L.O. classification of simple pneumoconiosis. Br. J. Ind. Med. 26:89.

BIBLIOGRAPHY

Dinman, B. D. 1974. The Nature of Occupational Cancer. Charles P. Thomas, Springfield, Illinois.
Enterline, P. E. 1974. Respiratory cancer among chromate workers. J. Occup. Med. 16:523.
Gross, P., P. A. Theodos, R. L. H. Murphy, W. C. Cooper, and W. K. C. Morgan. 1976. The pulmonary response to fiberglass dust. In: Report of the Committee on Environmental Health, American College of Chest Physicians. Chest 69:216.
Hendrick, D. J., and D. J. Lane. 1977. Occupational formalin asthma. Brit. J. Ind. Med. 34:11.
Patel, R., N. Janakiraman, R. Johnson, and J. B. Elman. 1973. Pulmonary edema and coma from perchloroethylene. J. Am. Med. Assoc. 223:1510.

OCCUPATIONAL DISEASES

A Guide to Their Recognition

Revised Edition

June 1977

Editors —

Marcus M. Key, M.D.
Austin F. Henschel, Ph.D.
Jack Butler, M.D.
Robert N. Ligo, M.D.
Irving R. Tabershaw, M.D.
Manuscript Editor —
Lorice Ede, J.D.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402

Stock No. 017-033-00266-5

Mention of company name or product does not constitute endorsement by the National Institute for Occupational Safety and Health.

The opinions, findings, and conclusions expressed herein are those of the authors and not necessarily of the National Institute for Occupational Safety and Health. The basic compilation from which the text was produced was prepared under Contract HSM-99-73-90 by Tabershaw-Cooper Associates.

DHEW (NIOSH) Publication No. 77-181
Library of Congress Card No. 78-600985