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THE DEPOSITION AND CLEARANCE OF DUST FROM THE LUNGS

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An understanding of the pathophysiology of the pneumoconioses requires some knowledge of the mechanisms involved in the deposition and disposal of inhaled dust. The physicists have studied pulmonary dust deposition in some detail, and much is now known concerning the physical processes involved. Its subsequent transport from the sites of deposition to other regions is less well understood.

The basic anatomy of the lung has been known for many years, and by applying this knowledge, certain outstanding workers formulated many of the theoretical concepts of dust deposition and respiratory mechanics long before the appropriate fast response electronic equipment became available to confirm their hypotheses.[1,2] The advent of sophisticated and sensitive electronic measuring devices has led to a rebirth of interest in the acute and chronic effects of inhaled particles.

DUST DEPOSITION

In 1935 Findeisen constructed a model designed to provide information about how dust particles are deposited in the lungs.[3] The model assumed that dust deposition in lungs depended on Newtonian mechanics and Stokes' Law, the latter being the physical law which describes the fall of small particles. It has been known since the days of Lister that while inhaled air contains numerous bacteria, exhaled air, apart from the early expirate which is composed of the dead space, is free of the bacteria and particles. This was first demonstrated by Tyndall, who, by means of the tyndalloscope, showed that expired air under normal cir-

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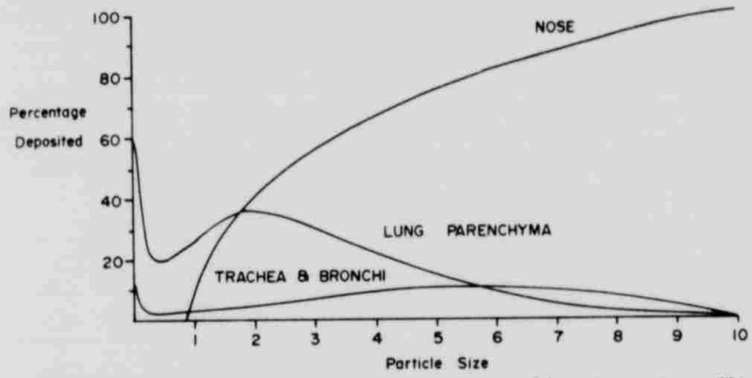


Figure 3–1 Regional deposition of particles as a function of their size in microns. This assumes a respiratory rate of 15 per minute and a tidal volume of 700 to 750 ml. (Based on Health Physics 12, 179, 1966.)

cumstances contained no particles and hence was invisible in a strong light. When a person takes a breath, air is drawn through the nares into the nasopharynx and trachea and hence into the conducting system of the lungs. From thence it reaches the alveoli by way of the terminal bronchioles, respiratory bronchioles, and atrial ducts. The entire bronchial surface of a healthy subject is lined by a film of mucus which is continuously being propelled upward by ciliary action.

As the inspired air enters the trachea, its flow rate decreases slightly. A further reduction in velocity takes place in the main and segmental bronchi. When the third, fourth, and fifth divisions of the bronchi are reached there is a marked slowing of the inspired air, so that by the time the terminal bronchiole is reached the flow rate is not more than 2 to 3 cm. a second.

Deposition of particles occurs as a consequence of several different physical processes, namely, sedimentation, inertial impaction, and diffusion.

Sedimentation

Particles sediment under the influence of gravity, each falling at a constant speed. The speed at which a particle falls is known as the terminal velocity and is directly dependent on its density and the square of its diameter. Large particles, as might be expected, fall more rapidly.

Inertial Impaction

When a particle is being carried along in an air current, and the latter changes its direction, the momentum of the particle will momen-

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tarily carry it along in its original direction. As a consequence, so particles are deposited by impaction at those regions of the bronch tree where a bifurcation is present. Deposition under these circu stances is mainly related to the momentum of the particle, i.e., speed and density.

Most inhaled particles are deposited on the walls of the dead spa long before the respiratory bronchiole is reached. Nearly all particles 20 microns and over come in contact with the walls of the bronchi, eitl as a consequence of gravity or from impingement. In contrast, most p ticles below 3 microns reach the respiratory bronchioles and are d posited either in them or, more commonly, in the alveoli. With particl of this size, sedimentation and diffusion are mainly responsible f deposition.

It is therefore obvious that in the pneumoconioses it is the small particles which are likely to be harmful, viz., those between 0.5 and microns; the larger are effectively removed by the ciliary mechanis The dust that settles on the mucous film of the dead space epithelium conveyed to the pharynx within 3 to 4 hours. It is then either coughed u or swallowed. The subsequent ingestion of the dust carried by the mu cous film may explain why the gastrointestinal tract and the lungs ar both prone to develop neoplasia following the inhalation of asbest fibers.

Those particles that get as far as the respiratory bronchiole c further are cleared by a different mechanism. There are good reasons fo believing that alveolar clearing is less efficient than is bronchial clear ing, with the result that a much greater proportion of particles are re tained in the distal air spaces. Were it completely efficient, then neithe pneumonia nor pneumoconiosis would occur, since the pathogenesis o both depend on small particles settling in the alveoli. If one allows fo the fact that a normal subject's alveoli are continually being exposed t bacteria, dust, and viruses, then the relative infrequency of diseas caused by these agents testifies to the adequacy of the defense mechan isms of the lung parenchyma under normal circumstances.

In a normal adult subject there are three hundred to four hundred million alveoli, each of which has a diameter of about 250 microns. No all are used at the same time, and there is a regional variation in ventila tion which depends on alveolar size. While most are given off from atria ducts, some arise directly from the walls of the respiratory bronchioles A normal person breathes about 5 to 6 liters per minute. If it is assumed that his tidal volume is 450 ml., then at a respiratory rate of twelve his minute volume will be 5.4 liters. Given a dead space of 150 ml., his dead space ventilation in 1 minute will be 1.8 liters and his alveolar ventilation is 3.6 liters. When it is remembered that the functioning alveoli increase their volume by less than 300 ml. with each breath, and that the residual volume of most normal subjects is around 2 liters, it will be realized that there is not much of an increase in alveolar size with

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inspiration. In reality, the mean increase in diameter of the alveoli during inspiration is probably less than 5 per cent when the subject is breathing quietly. This fact indicates that, in contrast to the conducting system and the respiratory bronchioles, the gas in the alveoli is turned over at a slower rate and tends to be "stagnant." Because of this slower turnover, the particles which reach the alveoli are likely to be retained in the alveoli long enough to be deposited. Most particles between 2 and 5 microns will settle in the alveoli in as little as 2 to 3 seconds, and it is for this reason that expired air is almost free from particles of this size. With particles below 0.5 micron, sedimentation is rare and deposition from this cause is minimal. When the particles are between 0.5 and 2 microns, a varying proportion will sediment out. The sedimentation rate depends on the time available for deposition, the particle size, and the reciprocal of the diameter of the alveolus.

Diffusion

Aside from sedimentation and impaction, some particles are deposited as a result of their Brownian motion. Since the movement of small particles in air is completely random, those that are in close proximity to the alveolar wall are likely to collide with it and hence to be deposited. The rate of deposition depends on the speed with which the particles are moving and this in turn depends on the size of the particles, smaller ones moving faster and being much more likely to be deposited.

It has been calculated that diffusion or Brownian motion is a significant factor in the deposition of particles up to 2 microns in diameter. For particles of below 0.5 micron, diffusion is the main mechanism, while it is the only mechanism for particles below 0.2 micron. Exceedingly small particles, viz., around 0.01 to 0.03 micron, are all deposited, most in the larger airways.[4] It must be remembered that although Brownian motion is not dependent on the density of the particle, the latter property influences sedimentation. Thus in the case of pneumoconiosis producing dusts, those particles of between 0.5 and 5 microns and with a high density are most dangerous.

Deposition by interception occurs only with elongated particles such as asbestos, fiber glass, and talc. If the particles are over 5 to 10 microns in length, they mostly lodge in the smaller bronchioles. Since they are not removed by macrophages, they produce a fibrous reaction at the site of deposition. Such fibers are capable of limited penetration and migration.

DUST RETENTION

The problem of particle retention has also received much study. Davies has calculated the likelihood of a particle being deposited in the

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lungs based on the alveolar volume in different phases of respiration, the rate of breathing, and the tidal volume.[5] He has shown that an atmospheric concentration of 500,000 particles per milliliter is necessary to ensure that each alveolus will receive at least one particle. A dust concentration such as this far exceeds that found in any industry. Concentrations of particles which are causally related to pneumoconiosis seldom exceed five thousand per milliliter. Thus, under these circumstances it requires something around one thousand breaths to guarantee that a particle will first reach, and second be deposited in, an alveolus.

A coal miner working in a mine for 40 hours a week and exposed to an atmosphere containing eight hundred to a thousand particles per milliliter, all below 50 microns, for approximately 60 per cent of the working time inhales between 100 and 150 gm. of dust in a year. Of the dust inhaled about 1 to 10 gm. is deposited in the alveoli but only approximately 0.5 gm. is permanently retained. This is less than a hundredth of the total inhaled.

In some miners exposed to these conditions radiographic changes would start to develop in about 10 to 15 years. Since dust levels in the United States and Britain are now generally well below the hypothetical concentrations mentioned above, the likelihood of developing category 1 simple pneumoconiosis before 25 to 30 years is small. It must, however, be remembered that factors other than dust concentration influence the development of pneumoconiosis, e.g., individual susceptibility. There is every reason to believe that given the same environmental dust conditions, certain subjects are prone to develop the disease more rapidly than others, and that such differences are probably related to the varying efficiency of the clearing mechanisms and possibly to differing minute ventilations. It must be remembered too that the chemical nature of the deposited particles and hence their pathological effects are of prime importance. Thus at death many coal miners are found to have 20 to 30 gm. of coal dust in their lungs despite the fact that during life they did not suffer from respiratory disability and moreover eventually died of an unrelated disease. In contrast, the pulmonary deposition of 5 gm. of silica would be fatal.

Finally, it is necessary to point out that all the models and phenomena mentioned up to now in this chapter assume normal structure and function of the lungs. In reality this supposition is fallacious since most of the pneumoconioses profoundly affect both pulmonary structure and function. The distribution of inspired air and particles is influenced by cigarette smoking, probably by air pollution, and certainly by diseases such as emphysema and chronic bronchitis. Despite all the extraneous influences that may modify the fate of inhaled foreign particles, the theoretical models described by Findeisen, Landahl, Davies, and others have fully justified themselves in the practical prevention of dust-induced disease.

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CLEARANCE OF THE LUNGS

Two separate transport or clearance mechanisms are present in the lung. These systems are anatomically and physiologically distinct, although they demonstrate some degree of interdependence. An excellent general description of the lung defenses is to be found in the Amberson Lecture of Green.[6]

Tracheobronchial System. Those particles deposited in the tracheobronchial tree are removed by the "mucociliary escalator." This extends from the terminal bronchiole to the glottis. Nevertheless, it must be remembered that many particles are deposited in the upper airways, especially the nasal passages, long before they reach the lungs themselves. Airways obstruction as seen in asthma and bronchitis increases the fraction of particles trapped in the larger airways.[7] When a particle is deposited on a bronchus or nonrespiratory bronchiole, it impacts on the thin layer of mucus which covers the epithelium. The latter is secreted by the mucous glands and goblet cells of the bronchial tree. Normal man secretes around 100 ml. of mucus in a day and this is continually swept up by ciliary action. The rate of transport is around 3 mm. per minute. Most particles (80 to 90 per cent) are removed from the bronchi within 2 hours. When mucus production is normal, the subject is not aware of its formation. As it reaches the pharynx, it is subconsciously swallowed. In contrast, when there is an abnormally high production, such as is the rule in cigarette smokers, the subject usually complains of an early morning cough.

The mucociliary stream is continually fed by the alveolar transport system, which deposits alveolar cells, secretions, and particles on the "escalator." It is the latter phenomenon which explains the presence of alveolar cells in the sputum.

Bronchial mucus is a complex mucopolysaccharide that is arranged in two layers. The outer is a viscous gel which will not absorb water. The internal layer is a liquid sol phase, and it is in this medium that the cilia are beating. The integrity and function of the inner layer is affected by dehydration. The beating of the cilia, and hence ciliary transport, are influenced by ionic charges, the presence of oxidants, cigarette smoke, high concentrations of oxygen, and low concentrations of adenosine triphosphate.

Alveolar Transport System. Particles, cells, and secretions that need to be removed from the alveoli and respiratory bronchioles are transported either to the tracheobronchial ciliary mechanism or to the perivascular and peribronchial lymphatics. Knowledge about this system is fragmentary, and a detailed understanding is lacking. It has been suggested that three different mechanisms exist, all of which have different time courses. The first involves surface transport from the proximal areas of the lobule along the surface to the respiratory bronchiole. It

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has been estimated that 50 per cent of the material deposited is cleared by this process in 24 hours. A second and slower process has a 50 per cent clearance time of closer to 100 hours. The second process probably involves septal transport of material that has been phagocytized within the septa. The third mechanism, with a 50 per cent clearance of around 50 to 100 days, represents foreign particles that have reached "dead end" pathways in the perivascular and peribronchial spaces.

Deposited particles may be carried either in a free state or, in some instances, intracellularly. The mode of transport appears to depend on the physical properties and number of particles deposited. After large challenges with particulate matter, the cellular transport mechanism is overwhelmed and many particles will be seen to be lying free on the alveolar surface and interstitial region of the septa.

The means whereby the particle is transported from its site of deposition to the nearest phagocyte is unknown. It is thought unlikely that macrophages "chase" the particles and it has been suggested that the particles themselves have kinetic activity which conveys them rapidly toward the nearest phagocyte.

Alveolar transport depends on the alveolar epithelium, the interstitium of the septa, and the fluid and secretory pathways. The alveolar epithelium is composed of two kinds of cells, usually known as types 1 and 2 pneumocytes. The former act as a barrier between the lumen of the alveolus and the interstitium and capillary. It is assumed that their function is the transport of gases across the alveolar-capillary membrane. The type 2 cell is the major secretory cell of the primary lobule, and is felt by most to be responsible for the synthesis, storage, and secretion of the surfactant. Debate is still taking place, however, about the origin and chemical composition of this substance which is responsible for the integrity of the alveoli. This is maintained through the low surface tension of surfactant, and in its absence, the alveoli collapse and the lungs become atelectatic. Surfactant may also have a function in the coating and transport of deposited particles.

The other cell found in the alveoli is the alveolar macrophage. This is a mononuclear cell felt by some to be derived from the tissue histiocyte and which is responsible for alveolar phagocytosis. It differentiates in a unique fashion in order to adapt to the high oxygen tension that is present in the alveoli. By the same token, its activity and metabolism are seriously affected by hypoxia. After particulate material has been taken up by the alveolar macrophage, it may be acted upon by this cell's enzyme system or may be retained unchanged prior to being transported out of the lung.

The interstitium of the septa is made up of the basement membranes of the epithelium and capillary and the capillary endothelium. It contains connective tissue stroma and is primarily affected in pulmonary

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edema. It may act as a pathway whereby the macrophage leaves the alveolus in order to reach the respiratory bronchiole.

Alveolar transport is also dependent on fluid dynamics. Again, this process is poorly understood. Fluid is probably formed by the epithelial cells and tissue lymphatics. It than drains toward the respiratory bronchiole through the lymphatics. The driving force is not known, but it has been suggested that gradients in surface tension are involved. Inadequate gas exchange in the alveoli impedes the transport of particles from the alveoli.

DETOXIFICATION

Aside from the removal of particulates, normal lung defenses are dependent on the detoxification of noxious inhaled particulate matter. This latter process has as its mainstay the alveolar macrophage; however, polymorphonuclear leukocytes and histiocytes can also assume this function should the need arise. Humoral agents such as specific immunoglobulin play a dominant role against bacterial invasion, but various surface active agents, viz., enzymes such as lysozymes and lipoproteins, probably need to be present for the bactericidal properties of the phagocytes to be fully effective. These mechanisms are pre-eminent in the elimination of inhaled bacteria. The phagocytic properties of the macrophage are inhibited by hypoxia such as occurs in obstructive airways disease. This may in part explain the predisposition of subjects with chronic bronchitis and emphysema to infection.

The alveolar macrophage is thought to be derived from the bone marrow, although in its adult form it differs significantly in structure, physiology, and metabolism from its parent cell.[6,8] This differentiation is necessitated by the macrophage's shift to aerobic pathways for metabolic activities. By means of radioactive tagging of inhaled bacteria, it has been shown that 99 per cent of a bacterial challenge is detoxified in the first 24 hours. In contrast, only 50 per cent of the bacteria that are deposited in the lung are removed.[6] Phagocytosis is affected by the acute and chronic effects of alcohol, by steroids and immunosuppressive agents, by starvation and extreme climatic conditions, and by various air pollutants. Finally, and most deleterious of all, is the effect of cigarette smoking on the function of the alveolar macrophage.

The number of macrophages in the alveoli as well as the exchange rate from the blood to the interstitium and alveoli are affected by the presence of inflammation and by the host's immunological response to the inhaled material. Normal macrophages have the capacity to destroy many airborne organisms, including nonpathogenic streptococci and *Escherichia coli*; however, they are unable to kill *Mycobacterium tuberculosis* and *Listeria monocytogenes*. In contrast, when activated by the

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mechanisms of cellular immunity, they acquire the capacity to destroy pathological organisms.[8]

Lymphocyte-mediated activation of macrophages is the chief means of defense against inhaled intracellular parasites that are deposited in the lung parenchyma. This type of acquired immunity is operative in tuberculosis and histoplasmosis and may also play a role in berylliosis. Cellular immunity has the propensity to generate a vigorous and occasionally destructive tissue response in the lung parenchyma, viz., granulomata and sometimes necrosis. The mechanisms that control and effect cell-mediated immunity and its relationship to tissue necrosis need further study.

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