CHAPTER 33

THE INFLUENCE OF INDUSTRIAL CONTAMINANTS ON THE RESPIRATORY SYSTEM

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INTRODUCTION

Those persons responsible for evaluation and control of the industrial environment for the purpose of preventing respiratory injury should have (1) knowledge of the anatomy of the respiratory system, (2) an understanding of the factors governing entry, deposition, removal and retention of gases and particles presented to the system and (3) some knowledge of the way in which tissues of the respiratory system react to gases and particles.

The type and severity of tissue response is related to the dose and the nature of the specific agent present. Air, which looks dirty or has an offensive odor may, in fact, pose no threat whatsoever to the tissues of the respiratory system. In contrast, some gases essentially odorless or at least not offensive, and some particles even when present in numbers too small to make the air appear dirty, can cause severe and serious tissue injury. Information about these matters provides an essential motivation to the industrial hygienist and his co-workers and gives them a more balanced approach to their activities. Lack of such knowledge converts a responsibility which should be most interesting and rewarding into a series of rather dull activities.

The progenitors of man evolved in an environment which probably contained a higher concentration of particles and noxious gases than exists now. One could anticipate therefore, that man might retain some ability to overcome such hazards or his genetic precursors would not have survived during that distant period. The fact is, man does possess anatomical and physiological mechanisms which protect the tissues from injury by many airborne agents. The multiple branchings and tortuous course of the narrow passageways through which air is conducted on its way to the deeper portions of the lungs favor the deposition of particles upon the more resilient surface of the proximal conducting tubes, rather than the fragile, more distal gas exchanging surface. The entire surface of the air-containing parts of the lung is covered by a thin layer of fluid which, not only serves as a protective layer, but also as a carrier or vehicle upon which particles are transported from the lung to the pharynx via the mucociliary escalator. This mechanism, plus that of the phagocytic system, is extraordinarily efficient in removing particles or storing them within cells, the macrophages, which are capable of tolerating many kinds of particles without injury. The surface cells of the lung replicate at a high rate and when they are injured, they are rapidly replaced by normal cells. Recovery from tissue injury via these regenerative forces is often surprisingly complete. These various mechanisms of upper airway deposition, surface protection, particle transport and cell regeneration make it possible for man to tolerate surprisingly high concentrations of airborne particles and noxious gases. Nevertheless, the system can be overwhelmed with subsequent persistent injury depending upon the concentration and the kind of gases and airborne particles to which it is exposed. This chapter is aimed at setting forth the principles governing the reactions of the respiratory system to the environment. It is not a compendium of occupational respiratory diseases, nor is it in any sense a textbook of pulmonary anatomy and physiology.

PERTINENT FEATURES OF THE ANATOMY AND PHYSIOLOGY OF THE RESPIRATORY SYSTEM

The human lung is much like a fish's gill, developed in the course of our evolution in a position inside rather than outside the body. It is a gas-exchanging mechanism comprised of a large membrane, on one side of which blood flows and on the other side of which there is a gas phase. A high gradient for oxygen and CO_2 exchange is maintained by the flow of venous blood over one side, and by the pumping of air into and out of the lungs, thus maintaining an optimum concentration of oxygen and CO_2 in the gas phase overlying the other side of the membrane. The gas-exchanging surface is comprised of blood capillaries overlaid by a very thin single cell layer having an effective surface of approximately seventy square meters. Blood is brought to this membrane via pulmonary arteries and conducted away from it via the pulmonary veins. A second system of tubes, the bronchial system, conducts air to and from the gas phase contained in the alveoli, the thin walls of which contain the capillaries. The heart pumps blood through the system, and the muscles of respiration move the chest bellows, and thus pump the respired air to and from the gas phase in the alveoli. One of the marvels of animal construction is that this highly complex and effective system is housed in a relatively small space and is protected from mechanical injury by being contained within the chest cavity. In this discussion we will be concerned chiefly with the air-conducting system and the terminal air spaces or alveoli, the walls of which constitute the membrane separating the gas from the blood phase.

The air-conducting system begins with the

nose, mouth and pharynx. The mouth and oral-pharynx are a globular, open chamber. The nasal and naso-pharyngeal chambers, in contrast, contain ridges or projections, the turbinates. The passages through the nose are semi-separate, narrow and tortuous and this causes the airstreams traversing this system to be turbulent and to change direction frequently, and to be so narrow that the center of the moving airstream is close to the wall of the passages. This arrangement favors deposition of the particles and makes for a more effective gas absorbing surface in this region than exists in the mouth and oral pharynx.

A single tube or airway, the trachea, emerges from the pharynx. This tube divides into the right and left bronchus, each of which further divides into branches entering each lobe of the two lungs. The bronchial system undergoes twenty-three branchings, each of slightly smaller diameter than its parent. The walls of the bronchial tubes become progressively thinner and at the seventeenth branching, small out pouchings or chambers — the alveoli — begin to appear. Subsequent branchings have walls composed essentially of alveoli. Progressing from the trachea toward the ultimate end structures, all divisions devoid of alveoli are called bronchi or bronchioles. When a few alveoli appear in the wall of the conducting system, the tube is designated as a respiratory bronchiole and, when many are present, the tube is an alveolar duct. The ultimate structure at the very end is a wider chamber, the atrium, and from this room only alveoli project.

Air conduction or mass movement of air traverses all bronchi and bronchioles, but at the alveolar duct, or some more distal point, mass movement of air ceases. Further movement of gas molecules into the alveoli, or from the center of the alveoli to the surface of the alveolar membrane, is by diffusion. The anatomical point at which the transition from mass movement of air to pure diffusion occurs is uncertain and probably varies with depth of breath. The location of this interface where mass movement of air ceases and diffusion becomes the only mechanism for more distal movement of particles is of some importance. Particles larger than 0.5 microns do not diffuse, but move through the airways by being entrained in mass movement of air. Hence, particles larger than 0.5 microns penetrate the lung only where mass movement of air occurs and the majority that are deposited fall on the walls of the conducting tubes. Based upon position, some undoubtedly fall by gravity effect into the alveolar openings and thus onto the alveolar surface. A relatively small proportion of the total particles larger than 0.5 microns in diameter entering the lung actually reach the alveolar surface.

The surface of the nasal passage is approximately 160 cm^2 and in most places the air flows through channels approximately one millimeter in diameter. These dimensions, plus the fact that the air stream changes its direction several times and is turbulent at various points during its passage through the nasal structures, makes the nasal passageway effective as a filter for airborne particles and also as a gas absorber, particularly for those gases such as sulphur dioxide which have a rather high solubility in the fluids covering the inner surface of the nose. In adults, the trachea is approximately twenty millimeters, the third or fourth branching of the bronchi five millimeters, and the sixteenth branching 0.5 millimeters in diameter. Further branchings arrive at a tube approximately 0.4 millimeters in diameter. The conducting tubes become slightly wider during each inspiration and narrower during expiration. The frequent change of direction of the branching air tubes and their small diameter greatly favors the deposition of particles from the air passing through them. Thus, those airways proximal to any point in the conducting system act as a filter protecting those passages located more distal to that point.

The nasal passages and the air conducting tubes are lined by a mucous membrane having most important characteristics. The surface of the membrane is covered by mucous, a liquid which arises in part from cells making up the surface of the membrane, and in part from secreting glandular structures located beneath the surface of the membrane, but connected to that surface by a tubular structure. The mucous forms a sheet overlying the tissue surface and would rather rapidly fill the lumen of the conducting system if it were not for the fact that a mechanism exists for propelling the mucous from the deeper parts of the lung towards the pharynx, where it either can be swallowed or expectorated. The majority of the cells making up the surface of the mucous membrane lining the nasal passages and conducting tubes bear a multitude of cilia on their luminal surface, located just underneath the mucous blanket. The cilia beat rhythmically in a fashion which propels the overlying mucous sheet in the direction of the mouth and thus constantly removes the secretions. The mucous blanket serves two obvious purposes. First of all, it acts as a protective layer on top of the delicate cells which line the respiratory conducting system. Equally important, the blanket provides a vehicle for removal of particles which are continuously deposited upon it from the overlying air mass. Thus the mucociliary escalator system becomes a very potent mechanism whereby the lung undergoes continuous self-cleansing. The mucociliary apparatus extends from the pharynx down through the fifteenth or sixteenth generation of branching. The surface of subsequent branchings, including that of the alveoli, is lined by a thin liquid film, which according to recent studies, is constantly being replaced but at a far slower rate than that of mucous secretion. This thin lining probably is removed by a push from the film-forming cells combined with a pull by its attachments to the mucociliary sheet. In essence, there is a continuous cleansing phenomenon provided by removal of a film of varying thickness and composition, extending all the way from the alveolar surfaces up to the pharynx.

A second cleansing mechanism is provided by phagocytic cells, the macrophages, which are found primarily in the alveolated parts of the lung. The origin of the macrophages is not certain, but the

evidence suggests there are always some present, and these can be enormously and rapidly augmented by local cell division and, via the blood stream, by cells of a similar nature formed in other parts of the body. Macrophages are large enough to engulf particles measuring as much as fifteen microns in their largest aspect. These cells also form clusters around even larger particles and produce giant multinucleated cells. The macrophage individually or in clusters, may live for a long period of time with their engulfed particles, provided the nature of the particle is not such as to cause the death of the macrophage. Some macrophages, since they are mobile, find their way out onto the mucociliary escalator and are excreted together with their engulfed particles by that cleansing mechanism.

A third mechanism of lung cleansing is provided by the lymphatic system. There is a liquid filled space between the capillary blood vessels and the surface of the alveoli, into which particles can penetrate or perhaps be carried by phagocytic cells. This liquid filled space is in direct continuity with the lymphatic tubular system which provides for the flow of a liquid, the lymph, in a direction paralleling the bronchi and directed towards progressively larger tubes. Ultimately the lymph is discharged into the venous system, but enroute it passes through aggregates of lymphoid tissue cells, including the large aggregates or lymph nodes at the lung root. Some of the particles that penetrate into this tissue space just below the alveolar surface ultimately appear in and are held by these collections of lymphoid cells. Other particles appear to traverse the lymph nodes and ultimately are discharged into the venous system. The exact mechanism of this transport of particles and their storage is unknown. A substantial proportion of the particles suspended in the inhaled air remain airborne and leave the lung during exhalation. Those particles which are deposited on the surface of the conducting and more distant portions of the airway are removed by the mucociliary escalator, engulfed by macrophages, pass into the lymphatics, become retained in the lymph nodes or enter the blood stream and some portion of the total remain free in the tissues of the lung.

It is worth noting that particles deposited on the distal portions of the mucociliary escalator can traverse the distance from the fourteenth or fifteenth generation of bronchi up to the pharynx within as little as thirty minutes. Cleansing of this portion of the air-conducting tubes therefore is quite rapid. Those particles deposited in a more distal area move much more slowly; it may take days or weeks in order to be cleared or sequestered. Some particles, either naked or engulfed by macrophages, simply remain indefinitely on the surface or in the interstitial tissues between the alveoli.

Bands of smooth muscle encircle the conducting system throughout its entire length. The utility of this muscle tissue is unclear but because of its presence, the lumen of various portions of the conducting system can be markedly narrowed when this muscle contracts. The mucous producing cells can respond quite rapidly to stimuli of various kinds with an augmentation of flow of mucous. Under the influence of some kinds of stimulation, the mucous membrane becomes engorged with blood retained in the capillaries and by an excess production of interstitial tissue fluid. These various mechanisms lead to some degree of narrowing of the airway and consequent elevation of resistance to airflow through the conducting system. These phenomena likewise can be reversed quite rapidly, either by removing the stimulus or by applying appropriate drugs. The muscular system is under the control of nerve impulses and the same appears to be true, to some degree at least, of the mucous secreting glands and possibly even of the ciliary action.

The surface cells, blood vessels, lymphatics and conducting tubes, especially those that are thin walled, are supported by an interlacing network comprised of strands of collagen, reticulin and elastic tissue, termed the connective tissue. This tissue also has its substrate of cellular components, chiefly fibroblasts. The replication rate of this tissue is slower than that of the surface cells or blood vessels, but can proceed in an orderly fashion. If injured, however, the replacing tissue may lose its properly organized structure, and instead form masses of fibrosis or scar tissue. The precise mechanism whereby this occurs is uncertain. As will be discussed later, some kinds of particles evoke a rather marked fibrosis and persistent cellular reaction, while other particles are quite inert and produce little or no such reaction. This brief account of the anatomy and physiology of the conducting system and alveolar structures should be of help in understanding the manner in which the respiratory system reacts to inhaled gases and particles.

Behavior of Gases Which Enter the Respiratory System

Gases are made up of particles of molecular size which move both by mass transfer, as in the flow of gas along a tube, and also by diffusion under the influence of the gravitational forces between molecules. If one breathes back and forth into a bag containing a foreign gas of low solubility, the mass movement of air and diffusion forces will lead to an even distribution of gases through the lung-bag system within three or four minutes of quiet breathing, and within a matter of a few seconds if one takes rapid deep breaths. If the foreign gas has a high index of solubility in the fluids lining the conducting system and the gas is of relatively low concentration, the major portion of the inhaled gas may be absorbed in the upper airways, especially in the nose, and the concentration of the gas reaching the depth of the lung will be lower than at the point of entry. This is particularly true during breathing through the nose. For this reason, gases such as SO_2 will predominantly affect the nose and upper airways, whereas gases of low solubility, such as nitrogen dioxide, will affect the airways rather evenly throughout their entire length. Some gases, as for example nitrogen and carbon monoxide,

appear to be totally inert insofar as their influence on the cellular structure of the respiratory system is concerned. Other gases such as phosgene, nitrogen dioxide, sulphur dioxide, and ozone may have a profound effect on the tissues dependent upon the concentration presented to the cells making up the tissues at the point of contact.

Behavior of Particles Which Enter the Respiratory System

If, by suitably gentle technique, one digests the lungs of fifty- to sixty-year-old individuals, including those who may have worked in the dusty trades, one will obtain a residue which can be assumed to have come from exogenous sources via the airborne route over the years. These tiny particles have a most interesting size range. Many will be found to be so small as to be visible only by electron microscope magnification, while others, generally those larger than 0.5 microns in diameter, can be visualized by appropriate illumination and 450x magnification. Of this entire population of particles retained over a period of many years, approximately half will be smaller than 0.5 microns in diameter. Of those that are larger, almost all will be between 0.5 and 5.0 microns in diameter. Fewer than 0.2 of a percent of the total will be larger than 5 microns in diameter, and less than 0.002 percent will be larger than 10 microns in diameter. If one defines a fiber as a particle having an aspect ratio such that the length is three or more times its diameter, one will observe fibers for the most part to be less than fifty microns in length, although some may be as much as two hundred microns long. Even so, the diameters of these fibers will be distributed as indicated above. If, in contrast, one samples 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. It is incumbent upon us, therefore, to reach an understanding of why it is that the long term retention of particles is limited to the sizes just described, in spite of the fact that millions of particles of greater diameter become airborne and, therefore, have the potential for entry into the respiratory system. The explanation for this arises from our knowledge of the behavior of particles suspended in air (aerosols) and the anatomical and physiologic peculiarities of the lung as described in the preceding paragraphs.

For the immediately ensuing paragraphs we will consider particles to be of a non-fiber character. Particles can vary markedly as to shape and, dependent on composition, as to density; both of these factors play a role in the behavior of particles in air suspension. For our purposes we will consider all particles as being spheres of unit density with the understanding that there could be some variation between particles as to speed of settling, depending on their shape and density. For this part of the discussion we will also think of particles as being far larger than those of molecular size. In this respect the major point would be that those particles larger than 0.5 microns will exhibit essentially zero diffusion activity, and even those down to 0.1 will have minimal such reaction. Those of electron microscope size down to .01 microns and lower will respond to molecular bombardment, and thus exhibit a considerable diffusion activity.

Several physical forces are conducive to the removal of particles from an airborne suspension and their deposition upon surfaces of the respiratory system. Particles suspended in a moving air stream 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 will tend to continue in its previous direction and be precipitated upon the surface. This effect is directly proportional to the size of the particle, the speed of the air stream, and thus of the particle, and inversely proportional to the radius of the tube. Gravitational forces also remove particles from the air stream 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 to 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 velocity is in fact predominantly related to particle density and diameter. The degree to which deposition on the basis of gravity will occur is thus related to these two factors, plus the distance through which the particle must fall and the time permitted for the event to occur.

Particle deposition by diffusion is limited essentially to those particles having a diameter smaller than 0.5 microns and, in fact, smaller than 0.1 micron. The smaller the particle the more rapidly diffusion movement 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 electron microscope sized particles are found in the lung residue indicates that diffusion can play a major role in the deposition of this size particle. Electrostatic and thermal forces have been thought possibly to play a role in deposition of particles in the lungs, but this is still uncertain.

On the basis of known behavior of particles in air suspension and the anatomical arrangement of the conducting tubes, it was predicted that particles larger than ten microns in diameter would be removed completely in the passage of the air stream through the nose and upper airways and that particles between five and ten microns in diameter would be deposited primarily in the upper airways on the mucociliary escalator. Only those particles in the range of one to two microns would be likely to penetrate into the deeper portions of the lung where some deposition in the alveoli might occur by gravity. Particle deposition would, on the basis of these calculations, be least for those particles having a diameter of 0.5 microns. 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 of location of deposition. For nasal breathing it has been shown that particles larger than ten microns in diameter are almost completely removed and few, if any, reach the conducting tubes of the lungs per se. Some smaller particles also are deposited in the nose, but the majority of these pass through and then are deposited, dependent primarily upon their diameters, along the upper or lower airways. It can be seen from these studies that particles greater than three microns in diameter will have very little opportunity to penetrate deeply and be deposited in the most distal portions of the conducting tubes, where the cleansing action and mucociliary apparatus would be less effective. Since almost 100% of the particles larger than three microns in diameter would fall on the mucociliary escalator and be removed, there is a reasonable explanation for the fact that so few particles of larger size are found in the lung residue after a lifetime of exposure to aerosols of ambient air which undoubtedly contained particles of larger size.

A fiber, defined as a particle the length of which is three or more times its diameter, represents a special case in terms of deposition. As is true of other particles, the settling velocity of a fiber is dependent primarily upon its diameter. One can think of a fiber as being a string of non-fibrous particles insofar as the settling velocity is concerned. In a moving air stream, fibers tend rather strongly to align their length parallel to the direction of air flow. Those fibers that are straight and rigid will therefore present an end-on aspect essentially that of their diameter. Fibers that are curved, curled, or bent in a U shape will have an end-on aspect equal to the width of the curl or curvature. Insofar as interception is concerned there thus will be a much greater chance for deposition of the non-straight fibers, a factor of considerable importance in the narrow airways and in 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. Length becomes important also to the degree that the fibers are distributed in a random way in the moving air stream. Thus a fiber one hundred microns long oriented at right angles to the direction of flow will have a much greater change of impacting on the surface than will those oriented parallel to the direction of flow. While one does observe an occasional fiber two hundred microns long in the lung dust residues, by far the majority are shorter than fifty microns in length.

Factors Governing the Reaction of the Lung to Gases and Particles

The recognition of whether or not a lung reaction in response to a stimulus has occurred is to a high degree dependent upon the tools and criteria used for such recognition. This is a matter of great importance and often ignored when determining the significance of a specific reaction with respect to whether or not the cellular changes have led to impairment in terms of function, life expectancy, and employability. Cell death and replacement by replication characterizes the organism from conception to death. Physical factors and external agents, such as bacteria and viruses, constantly influence the orderly progression of cell death and replacement during the state that we call good health. From time to time these external agents may exert an influence of sufficient magnitude to interfere with function or life expectancy, and these episodes are thought of as representing disease.

When one examines the body of a healthy person, utilizing the light microscope one can always find some areas of inflammation and scarring and mild disorder of cell replication which is termed metaplasia. As one examines tissues with the electron microscope, one can recognize alterations of cell structure under circumstances which the light microscope will not recognize. During life one is usually limited to the use of less refined tools in order to recognize the presence of abnormalities, and in general our concept of disease is based upon these tools. Such tools are coarse to the degree that the quantitative aspects of abnormality must reach a certain extent before they will disclose the presence of injury. There is thus a quantitative aspect as well as a qualitative aspect in our concept of disease. There is a further factor involved in deciding whether or not an injury is meaningful and thus deserves the appellation of disease. This has to do with whether or not the impairment is of sufficient magnitude to interfere with life and normal pursuits which make up one's life style. For example, some scars representing the end stage of injury are found in the lungs of every adult. Nevertheless, when these scars are minor in extent they do not in any way interfere with function or shorten the life expectancy of the person. In the light of these statements, it is imperative that one realize there is no sharp line of demarcation between being healthy or ill, normal or diseased, injured or uninjured. We can speak in rather broad terms of the way in which gases and particles may or may not injure the lung, but one must bear in mind that the quantitative aspects are probably more important under most circumstances than are the qualitative ones.

The above comments are germane to a balanced understanding of the factors that govern the import of tissue reaction to external agents. Three characteristics determine whether or not tissue injury will occur and be of an extent great enough to impair function, or shorten life. These factors are (1) the nature of the agent, (2) the quantity or dose of the agent brought to bear in action upon the tissues, and (3) the reactivity of the tissues, oftentimes referred to as the host-factor.

Particles and gases vary as to their inherent physical and chemical nature, and this influences whether or not injury occurs. There are some gases as for example nitrogen, and particles such as carbon and most silicates, which under almost all circumstances are essentially inert in terms of evoking tissue reaction. Such particles, when retained in the lung, are engulfed in macrophages

and ultimately come to reside in the tissue, or in lymph nodes where the reaction is either nonexistent, or at most a mild foreign body inflammatory process. Under unusual circumstances of exceedingly high concentration, as for example nitrogen under several atmospheres of pressure, or carbon particles in extra-ordinarily excessive amounts, a cell reaction of greater significance may occur. In contrast, there are some gases such as phosgene and particles such as free crystalline silica, which, because of their inherent quality, are biologically quite active and when present in high enough concentrations can evoke a biological reaction of important magnitude. Bacteria are a special case because these particles, when deposited in the lung, may either be destroyed by macrophages or may grow in large enough numbers to produce disease. In ordinary life pursuits most particles and many gases are inert or relatively inert in the concentrations commonly met with.

On the basis of much evidence, it is generally held that there is a dose or quantity of potentially biologically active particles that will be tolerated without overt evidence of tissue reaction. In terms of an important reaction, this is certainly the case. In terms of recognition of a cellular reaction such as macrophage accumulation in the lung, or subtle changes recognized only by electron microscope or biochemical disturbance of cell structure or function, there is some question as to whether or not this is true. It must also be recognized that the cell reaction to the agent may be an appropriate one and considered a normal reaction rather than an abnormal one. For example, premature death of a cell and its replacement by a normal cell can be thought of as a normal body mechanism for tolerating exogenous agents. In the same sense, the phagocytic action of macrophages with storage of inert particles therein is a normal body function and can scarcely be considered an injury. For our purposes, all injury of a meaningful sort is dose related. This appears to be the case, at least in the minds of most students of the problem, even with respect to carcinogenesis.

The host factor plays an important role, but unless the dose can be accurately measured it is very difficult to quantitate the host reactivity. There are striking examples of true allergic hypersensitivity causing a person to react violently to doses of allergen readily tolerated by the nonallergic. There is also a considerable variation from individual to individual in terms of their immune responses and cellular responses, which is not on an allergic basis. This ordinarily is referred to as hyperreactivity and it accounts for the fact that more serious tissue injury may develop in one individual than in another even though the dose administered to both individuals is the same. This is an important phenomenon because it requires us either to set safe levels for specific agents in terms of the effect on those who are most reactive, or it requires us to find some means of excluding from contact with such agents, those people who are hyper-reactors.

Taking into consideration these three major factors it is no wonder that there is considerable personal variation in terms of whether or not disease occurs in response to deposition of particles or exposure to gases, and that there should be some confusion in the minds of the uninformed with respect to the fact that some gases and particles can exist in high concentrations without ensuing disease.

VARIOUS WAYS IN WHICH THE RESPIRATORY SYSTEM CAN REACT TO AIRBORNE PARTICLES AND NOXIOUS GASES

All parts of the respiratory system can be injured with consequent impairment of function as a result of the inhalation of certain kinds of gases and particles. Among the manifestations of such injury or stimulation are (1) changes of resistance to airflow through the conducting tubes, (2) hypersecretion of mucous, (3) paralysis of the mucociliary escalator, (4) mobilization of macrophages in the tissues and air spaces of the lung, (5) cell injury with consequent acute inflammatory processes or pulmonary edema, (6) chronic inflammation of a granulomatous nature, (7) the development of pulmonary fibrosis or scar tissue, and (8) cell transformation or carcinogenesis. As indicated at the outset of this chapter, it would not be appropriate to discuss all these in detail, but some comments with respect to each of these will be useful.

Changes of Resistance to Airflow

An increase of resistance to airflow, either of an acute and reversible nature or of a chronic and persistent nature, may develop as a result of inhalation of certain noxious gases and particles. It has been shown that deposition of finely divided particles or the inhalation of certain gases such as SO_2 or hydrochloric acid mist will appreciably increase the resistance to airflow and that this is readily reversible following removal of the stimulus or by the use of appropriate drugs.

The site of the stimulation is both in the nose and along the course of the tracheo-bronchial tree. It is presumably caused by contraction of the circular smooth muscle plus some engorgement of the mucosa with consequent anatomical narrowing of the lumen of the conducting system. It is probable that all kinds of finely divided particles may do this to some degree. The dose required for this reaction is usually quite large except in those persons truly allergic. If a specific allergen is deposited in the nose or upper airways, the sensitized person will respond with rapid and oftentimes very severe bronchial narrowing. In this instance the dose may be extremely small. It is also of interest that in this circumstance the particle size can be quite large. Most pollens are greater than ten microns in diameter. These are readily deposited in high concentration in the nose and upper airways where they trigger the acute response. The ability to cleanse these areas by the mucociliary escalator removes the pollens and terminates the episode. Perhaps the most exquisite example of this in an industrial setting is the severe asthmatic response of those who have been sensitized to toluene-2, 4-diisocyanate (TDI).

Hypersecretion of Mucous

Many gases and most particles are irritating to the mucosa of the nose and conducting system of the lungs. When the dose is sufficiently large and the stimulus strong enough, there is an outpouring of mucous from the appropriate cells, leading to cough and an increase of sputum. Acute short term exposures produce a reaction that is fully reversible and in all probability this should be considered a normal phenomenon and not a disease manifestation.

There is some evidence, especially among heavy cigarette smokers, that a persistent stimulation by irritant gases and particles will produce persistent hyper-secretion and enlargement of the mucous secreting glandular system. This is to some degree reversible on removal of the stimulus, but in some individuals there appears to be a persistent hypertrophy and hypersecretion even after the stimulus is removed. The excess secretion leads to chronic productive cough and this condidition is termed chronic bronchitis. The accumulation of secretions in the lumen of the air tubes and the thickening of the mucosa consequent to hypertrophy of the glandular system causes a reduction in the lumen of the air tubes and therefore an increase of resistance to airflow. Such individuals not only have chronic cough and excess sputum production, but also evidences of chronic obstructive airway impairment. There is controversy as to whether this occurs as a result of industrial exposure to gases and particles, but it is generally agreed that industrial environments characterized by high levels of irritant gas or particles aggravate chronic bronchitis.

Paralysis of Mucociliary Escalator

There is evidence in experimental animals that gases such as SO_2 and NO_2 paralyze, at least temporarily, the cilia and thus interfere with the effective removal of mucous secretions. There is some evidence that in response to certain doses there may be a stimulation of the cilia. Recovery from this kind of paralysis appears to be rapid and there is no evidence to indicate that persistent or permanent paralysis of cilia occurs under ordinary life circumstances. The combination of daily excess mucous production and impairment of ciliary action, however, leads to an excessive accumulation of mucous in the conducting tubes. This in turn leads to an increase in resistance to airflow and to inadequate cleansing of the lung with the result that colonization of bacteria can occur with greater ease. As a result, acute bronchitis or pneumonia may ensue. Prolongation of the "residence time" of some biological agents also may occur and be an important influence in causing tissue injury.

Mobilization of Macrophages

Though essentially all of the particles larger than ten microns, and a large proportion of those two to five microns, lodge on the mucociliary escalator and thus are removed, a substantial proportion of those under five microns, and particularly those that are under two microns in diameter, will penetrate far enough out into the lung to be deposited beyond the mucociliary escalator and in the alveolous bearing portion of the lung. Under normal circumstances there are relatively few macrophages in this portion of the lung at any one time. These are present in part for the purpose of sequestering, removing or digesting foreign material taken into the lungs from the general environment. When greater numbers than usual of particles are deposited, there is an augmentation of the macrophage population and in some circumstances the numbers can become very large. This macrophage response is a normal function and cannot, in itself, be considered to constitute a disease.

Macrophages engulf the particles either as single cells or functioning as clusters of cells and retain the particles for the lifetime of the macrophage. The exact life of the macrophage is unknown, but it is measured in weeks and probably in months. Presumably when the macrophage dies and the particles are released, they are rephagocytized by another macrophage.

When inert particles are injected intratracheally into the lungs, there is an initial massive outpouring of macrophages in the regions where the particles are distributed. Over an ensuing period of weeks and months the number of macrophages becomes less and the number of free particles in the lung tissue becomes smaller. One can at this later time observe numerous macrophages filled with particles lying on the surface of the alveoli or in the interstitial tissues and large numbers of particles may be seen in the regional lymph nodes. Fibers shorter than ten to fifteen microns also are phagocytized. Segments of longer fibers may be incorporated in one or more macrophages or entirely surrounded by a cluster of macrophages. At any one time, particles, including fibers, may be seen entirely outside of macrophages even years after they have been introduced into the lung. It is not known whether they have never been phagocytized or are at that moment between periods of residence within a macrophage.

Macrophage reaction is clearly a very important one for removal and sequestration of particles. It is tempting to speculate that the macrophage surrounds the particles and either coats the particle or, by surrounding it with its own protein, breaks the direct contact between the surface of the particle and other cells in the tissues and therefore renders the particle innocuous. There are some circumstances, as for example, free crystalline silica, where those particles small enough to be phagocytized by the macrophage actually kill the macrophage within a matter of a few days. The released particles are rephagocytized and again kill the macrophage. The importance of this phenomena will be discussed under the paragraph on pulmonary fibrosis.

Cell Injury with Acute Inflammation or Pulmonary Edema

Acute cell injury is limited essentially to reaction to noxious gases rather than to particles. Exception to this would be a consideration of bacteria as particles. Gases such as phosgene and nitrogen dioxide and to a lesser degree sulphur dioxide or sulphurous acid mist will, dependent

upon the concentration, produce anything from a mild irritation manifested by hypersecretion of mucous to a severe reaction characterized by death of the cells lining the airways and most distal portions of the lung. In the latter circumstances the lining cells of the conducting tubes are destroyed with the exception of the most basal layer of cells. From this basal layer there is the potential for a reconstitution of the normal cell system lining the conducting tubes. In the alveolar bearing areas, cell injury may lead to destruction of the alveolar surface cells and also of the capillary cell wall with a resultant pouring out of blood plasma or whole blood leading to hemorrhagic pulmonary edema. Depending upon the severity of the reaction, there can be a very rapid outpouring of liquid with death virtually due to drowning in the accumulation of fluid in the deep portions of the lung. With lower concentrations of these gases, the death of the cells making up the alveolar wall is slower and there is a delayed pulmonary edema occurring four to six hours after the exposure. This can be just as fatal as the more acute and sudden reaction. When there is a still lower intensity of exposure, the walls of the alveoli may maintain their physical integrity and gradually be reconstituted in a normal fashion. It is of interest that when particles are inhaled, their distribution within the lung is localized or patchy in nature. The same is true for the inhalation of gases, if the period of inhalation is rather brief, as for example, only a few minutes rather than hours. For this reason not all parts of the lung are involved equally in the severe reaction, and a patchy distribution of pulmonary edema is the rule. If the individual survives the acute reaction, the subsequent course is one of recovery with little or no residual injury. This kind of chemical pneumonia in its earliest stage is a hemorrhagic edema, but in the later stage there is an outpouring of leukocytes and sometimes actual bacterial infection supervenes followed by lobar or bronchial pneumonia. In some unusual circumstances, as for example, exposure to the salts of beryllium, there may be a more gradual or sub-acute development of the chemical pneumonia. Experiments have shown an astonishing ability of animals to recover from this kind of acute cell injury with reconstitution of lung tissue that has in all facets the appearance of normal lung tissue.

Chronic Inflammation of a Granulomatous Nature

This is sometimes termed "chronic interstitial lung disease" and it occurs in individuals exposed to some salts of beryllium, farmers exposed to moldy hay and in certain other occupations such as the handling of bagasse and removal of bark from trees. The exact nature of this disease from an etiologic point of view is uncertain, but it would appear to be predominantly a hypersensitivity reaction with the development of a chronic inflammatory disease in the distal parts of the lung. The nature of the injury is such as to lead to more or less persistent changes which can fluctuate in severity and be reversed to some degree by steroids. Occasionally the injury is such as to lead to the development of pulmonary fibrosis. In some circumstances the exciting agent is thought to be a thermomycete. In all of these cases there appears to be a rather high degree of individual susceptibility. Depending on the extent of the disease, clinical manifestations can either be absent or severe.

Pulmonary Fibrosis

A classical example of pulmonary fibrosis secondary to the inhalation of particles is the reaction to the inhalation of substantial amounts of free crystalline silica. The hypothesis for pathogenesis of this disease, silicosis, having the strongest scientific support is as follows. The particles of free silica, when deposited beyond the mucociliary escalator and picked up by the macrophages, appear to kill the macrophage and in the process release a material capable of stimulating the connective tissue of the lung to produce fibrous scars. This clearly is a dose-related disease.

There are two kinds of scar production, probably based on two separate mechanisms. The particles of silica appear to be collected in focal areas in the lungs inside the macrophages and, at the death of the macrophage, they release the fibrogenic agent which leads to the development of a nodular kind of dense connective tissue characterized by a proliferation of fibrous tissue elements and the laying down of a central area of collagen. These focal points of fibrosis, scattered through the lung, characterize what is termed simple discreet nodular silicosis. In many individuals this is the only reaction that occurs.

In some such individuals, however, a second reaction characterized by the development of a massive irregular scar sometimes reaching five or more cm. in diameter develops. The nodular character is lost and the predominant feature is the large mass of scar tissue. Around the periphery the reaction is more cellular in nature. In contrast to the simple discreet nodular reaction, which appears to be self-limited after removal from exposure to dust, the massive scars tend to continue to enlarge and hence the term "progressive" massive fibrosis. It is postulated that the discreet nodular lesion is the reaction to a fibrogenic material released locally and hence its discreet focal character. In contrast the progressive massive fibrotic lesion is thought to be caused by coalescence of the simple nodular lesions plus the laying down of large amounts of gamma globulin. In other words, the progressive massive fibrosis is in part an immunological reaction and hence its progressive nature. There is not full agreement with this hypothesis. It is of considerable interest that the coal miner, whose nodular lesion is very different from that of the silicotic nodule in that far less scar tissue develops in the "coal worker nodule," nevertheless may go on to develop the large scars of progressive massive fibrosis. The same can apparently occur following unusually heavy exposure to iron oxide or to pure carbon black. It would appear that progressive massive fibrosis is an immunological reaction and thus is a manifestation of hyper-reactivity or an unusual host factor.

In contrast to the nodular lesion produced by the focal collection of free crystalline silica and the reaction to silica in the lung, the reaction to asbestos fiber is of a quite different nature. In this case, the very short fibers, less than five microns long, are phagocytized by the macrophage and appear to reside in the macrophage without harming it. Longer fibers which cannot be totally enclosed within the macrophage and remain naked in the lung tissue or on the surface of the alveolus lead to a cellular reaction which is of a granulomatous nature. If the reaction becomes mature enough, actual fibrous tissue is laid down in a non-nodular manner creating a pattern distinctly different from that of silicosis. Progressive massive fibrosis does not appear to develop as a result of exposure to asbestos, but the question of whether or not the granulomatous and fibrotic reaction to the asbestos fiber is progressive even after removal from exposure is unsettled. The reaction to asbestos fiber is not as focal and is much more generalized than is the reaction to free crystalline silica. In all of these examples where extensive scar tissue forms, lung substance is lost and a restrictive type of pulmonary function impairment occurs. Because of the focal nature, with normal intervening lung tissue, the silicotic reaction is accompanied by less impairment of blood gas exchange than occurs in the more generalized kind of tissue reaction characterizing the response to inhalation of asbestos fibers.

Carcinogenesis

There are numerous cell types in the lungs, most of which undergo division or replication within the lung in order to replace the senile and dying cells or, under intermittent stress, to augment certain cell types such as the macrophage. The epithelial or lining cells of the airways and alveoli are estimated to replace themselves completely every few weeks. It is probable that this rate of replication is accelerated under the stimulus of surface cell injury or irritation. Normally, cell division proceeds in an orderly fashion with the continuous development of identical, normally formed and constituted cells. In response to the influence of irritation and other factors, the cells may gradually change their character and organization and undergo metaplasia. If the alteration is of a particular kind, the cells lose their customary organization and orderly replication and undergo malignant transformation. The frequency with which this happens is unknown, but in some individuals the cancerous cells survive, become established and propagate to produce clinical malignant tumors. It is known that some kinds of inhaled particles foster the development of metaplasia and cancer. For example, the frequency of lung cancer is excessively high in workers exposed to particles of chromium, nickel, asbestos, uranium and other agents. Cigarette smoke, a complex of irritating gases, including nitrogen dioxide, when combined with small particles and hydrocarbons, has carcinogenic action. While single agents have been shown to be carcinogenic in experimental animals, a much higher yield of tumors is obtained if agents are combined. For example, if the surface cells of the bronchi are caused to replicate in an accelerated manner by SO_2 or trauma, benzo (a) pyrene becomes a potent carcinogen, even though it is a weak one when used alone. It would appear that cells are more vulnerable to malignant transformation when they are replicating at a high rate. The concept of co-carcinogen action and multi-factorial influences in carcinogenesis seems to be well established. That there is a host factor as well is very likely.

RESIDENCE TIME AND COMBINED EXPOSURE

Two other concepts with respect to the action of particles deposited on the surface of the lung need to be pointed out in order to establish a better understanding of the possible biological effects of dust and gases. While the deposition of particles on the surface of the proximal conducting airways protects the more distal air tubes and favors particle removal by the mucociliary apparatus, there is an appreciable "residence time" of such particles. During that period of minutes to hours, the biological effects leading to chronic bronchitis, metaplasia and lung cancer could be initiated. If co-existing gases paralyze the cilia and reduce their effectiveness, the residence time would be prolonged.

A second potentiating effect might occur by reason of the fact that particles, which might ordinarily be inert, can become carriers by having biologically active agents adsorbed upon their surface. This might concentrate the active agent and prolong the effect when the coated particle is deposited in the lung.

These two factors might play a role not only in carcinogenesis but also in the other biological effects discussed in this chapter. The importance of taking into account multiple co-existing exposures is becoming more and more apparent and reveals a heretofore inadequately appreciated responsibility of the industrial hygienist.

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