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Inhaled particles and respiratory disease

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Sections

- [Aerosols](#)
- [Deposition](#)
- [Particle Clearance](#)
- [Clinical Applications of Particle Deposition](#)
- [Building-related Lung Illness Diseases](#)
- [Summary](#)
- [References](#)
- [Publishing and Reprint Information](#)
- [Articles with References to this Article](#)

- [Previous article](#) in Issue
- [Next article](#) in Issue
- [Drug links](#) from Mosby's DrugConsult
- [Genetic information](#) from OMIM
- Citation of this Article
 - View on [PubMed](#)
 - Download in [citation manager format](#)
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- [Related articles](#) in PubMed

HP/AA Hypersensitivity pneumonitis or allergic alveolitis

Within the respiratory system there exists a multilayered mechanism designed to defend against myriads of inhaled foreign particles and related substances. Particles, as defined for purposes of this article, are any small bits of material or droplets either inorganic or organic, viable or nonviable, that can become airborne. They can range from small molecules less than 0.001 μm to pollens and spores ranging between 2 and 50 μm and very large visible dust particles in the range of 1000 μm . Particles can also assume many shapes including long, fibrous varieties with a length greater than

three times diameter, spheres, oddly shaped or irregularly shaped material, oblong, crescent-shaped varieties, or other peculiar shapes, such as certain pollen grains and mold spores. Most particles occur naturally, but many are the result of alterations in human activity; some can be innocuous, others intrinsically toxic, and others highly allergenic. Of increasing importance is the recognition that material of either toxic or allergenic origin can be absorbed onto the surface of particles.

Aerosols

[TOP](#)

An aerosol, which is essentially a collection of airborne particles, might be defined as any system of solid particles or liquid droplets of sufficiently small diameter to maintain stability as a suspension in air.¹ Particles comprising an aerosol must contain droplets sufficiently large so as not to diffuse like a gas molecule but sufficiently small to remain airborne for some length of time. Particles with these properties usually range between 0.1 to 10 μm . Aerosols composed of solid particles can either be designated as dusts if the particles are produced by dispersion or as smoke if they are produced by condensation. Mists are aerosols that contain liquid particles.

Deposition

[TOP](#)

The upper airways, in particular the nasopharynx, provide air conditioning of inspired air, in addition to a wide surface area for deposition of allergens and other potentially harmful particulates. In the nasal airways the temperature of inspired air can be raised from that of room temperature to approximately 32° C and from ambient humidity to higher than 90% relative humidity before the air reaches the lungs. This is accomplished by increasing sinusoidal blood flow and by fluid shifts across the vascular mucosa.²

Aerosols, which are usually of variable particle size, can deposit on respiratory tract mucous membranes and alveolar surfaces by either inertial impaction, gravitational sedimentation, or

Brownian diffusion (■ Fig. 1).^{3 4} Most airborne particles are deposited in the anterior nasal area by inertial impaction. Air enters the nostrils in an upward direction since the opening of the nostrils is downward. It then flows horizontally to join with the pharynx and nasopharyngeal area and thus undergoes two approximate 90-degree turns before descending downward into the trachea.⁵ Other sharp bifurcations influence the fate and deposition of airborne aerosols including inhaled allergens, mold spores, and dusts. The first of these bifurcations exists at the nasal valve, a very narrow airway near the opening of the nares in which air linear velocity is very high. The great majority of particles are deposited in this area of relatively narrow constriction. Many other particles and pollutants are deposited in the nasal passage on the convoluted turbinate folds that present a relatively large cross-sectional area. Other larger particles, particularly those traveling at higher velocities, are unable to flow with the airstream as it changes directions in passing curvatures within the airway. These particles are often deposited in areas such as the carina or in other bronchial bifurcations lower down in the airways, all by inertial impaction.

Particles smaller than 5 μm often penetrate into the smaller airways and are deposited by gravitational sedimentation, different-size particles have different terminal-setting velocities.

Extremely small particles less than 0.5 µm may deposit by Brownian diffusion as they are displaced by randomly moving gas molecules and ultimately collide with airway walls.

Dust particles may deposit in any of the major respiratory zones, the upper airways, the tracheobronchial tree, and the respiratory or alveolar region by means of the mechanisms discussed and according to their size and velocity. Typical sizes for some common aerosol particles are listed in ■Table I. Major factors determining particle deposition are listed in ■Table II. With nasal breathing more than 90% of particles between 2 and 20 µm in diameter are retained in the upper nasal airways, and approximately 50% of particles in the range of 1 to 5 µm are retained in the trachea and bronchi. Very few particles in the range of 10 to 20 µm gain access to the tracheal and bronchial areas. Another 50% of particles ranging between 1 and 5 µm are retained in the alveolar area, with virtually no particles greater than 10 µm deposited in this area.

TABLE I. Typical sizes for some common aerosol particles

- Tobacco smoke: <1 µm
 - Pollens: Approximately 10-30 µm
 - Mold spores: Approximately 2-50 µm
 - Actinomycete spores: Approximately 1-2 µm
 - Foundry dusts: Approximately 50 mm
-

TABLE II. Major factors determining particle deposition

- Respiratory tract anatomy
 - Patterns of airflow
 - Mode of inhalation
 - Particle characteristics (size, density, charge)
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In the case of mouth breathing, which does not involve the nasal area, more than 95% of the larger particles between 10 and 20 µm are deposited in the trachea and bronchi. Approximately 60% to 80% of particles between 1 and 10 µm are deposited in the bronchioles and 40% or 60% of particles between 1 and 5 µm are deposited in the alveoli. As in the case of nasal breathing, virtually no particles above 10 µm descend to this level. Particle deposition always increases with particle size. Particles of irregular shape often behave in unpredictable ways. For example, asbestos fibers up to 200 µm in length but only 0.5 µm in diameter may be found in peripheral airways and lung parenchyma as may be some smaller rod-shaped or curvilinear spores. In these cases the particles have essentially been propelled down the airways like an equivalent diameter spear aligned with the air flow.

FIG. 1. Mechanisms of aerosol deposition in lung. (Modified from Murray JF, Nadel JA, eds. Textbook of respiratory medicine. Vol 2. Philadelphia: WB Saunders, 1988:313-31.)

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Particle Clearance

TOP

A healthy tracheobronchial tree necessitates efficient clearance of pollens, pollutants, infectious agents, and other cellular debris. Efficient clearance is accomplished by the process of mucociliary action, cough, and alveolar clearance mechanisms.^{6, 7} Most pollen grains, which are 10 to 20 μm , are largely deposited in the nose, whereas many smaller particles in the range of 1 to 5 μm , such as mold spores, frequently reach the distal airways. Any particles deposited on the nasal mucosa are rapidly transported to the pharynx by mucociliary transport within 15 to 30 minutes of impaction and are subsequently swallowed. Almost 100% of the water-soluble gases such as sulfur dioxide are prevented from gaining access to the lower airways because of their passage over the nasal mucosal tissue.

Mucociliary clearance

This type of clearance involves the protective mechanisms afforded by mucus, its cellular contents, and its local content of antiproteinases, lysozyme, and other antimicrobial substances. Mucus is produced from both goblet cells and submucosal glands. The latter are regulated by a variety of modulatory peptides and chemical mediators. Certain biologically active peptides such as substance P and vasoactive intestinal peptide have also been found in nerve endings adjacent to submucosal glands.⁸ Ciliated cells line the airways interspersed among goblet cells from the anterior nasopharynx to the terminal bronchi. Beating cilia penetrate the mucous layer in groups of cilia. They beat in a synchronized coordinated fashion in an overall cephalad direction. Cilia movements have been compared with those of an escalator with progressively increasing speeds from the terminal bronchiole to the trachea. Most inhaled local debris of relatively large size plus other comparatively insoluble particles will be transported in a cephalad direction up this escalator mechanism by the mucous layer to the larynx and ultimately swallowed or cleared by way of the coughing mechanism. Healthy airways usually clear such particulates within a matter of only 6 hours, and the entire escalator can be cleared within a 24-hour period in a healthy person. Effectiveness of cough clearance has been estimated in terms of a so-called "scrubbing action index." In an average cough sequence, 59% of "scrubbing action" has been found to occur with an initial cough, 22% with a second cough, and 15% with a third cough.⁹

Cough clearance

Clearance by coughing is particularly effective in the central airways. Cough clearance is especially important in conditions such as chronic bronchitis, where it may account for upward of 50% of clearance and compensate for any defect in mucociliary transport. In healthy subjects with no sputum production, cough contributes little or nothing to tracheobronchial clearance.

Alveolar clearance

Less than 20% of the extremely small particles between 0.1 and 0.5 μm are retained by the alveoli; most are exhaled. Any retained alveolar particles are cleared by two main processes, absorption or transport. Absorption can be accomplished either by direct penetration into epithelial cells and interstitial tissues or by phagocytosis. Particles are transported from the alveolar areas to the ciliated regions with ultimate removal by ciliary clearance.

Clinical Applications of Particle Deposition

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Major pulmonary diseases caused by inhalation of allergens, microbial agents, or dust aerosols are listed in ■ Table III. Allergic airway diseases include common extrinsic asthma characterized by an IgE-mediated response to organic particles of a particular size such as a wide variety of pollens, mold spores, animal danders, house dust components (e.g., mite remnants), and inhaled occupational agents. Although the large bulk of aeroallergens, such as pollen particles, are greater than 5 μm in diameter and are deposited in the nasopharyngeal area, fragments of these particles or solubilized antigen leached onto smaller aerosol droplets have been found to gain access to the lower respiratory tract and to cause asthmatic responses. Many small fungal spores and dust mite remnants are also of sufficiently small size to regularly gain access to the lower airways. The same can be said for a variety of occupational agents, including industrial chemicals haptenized onto host proteins, pharmaceutical agents, biologic enzymes, and a variety of vegetable dusts. The most complex sources of particulate allergen are pollens, mites, and fungi; the least complex are animal danders and other animal emanations such as urinary proteins. Most major allergens are located in or on a particle surface. They are usually either proteins or hapten-protein complexes that do not have any peculiar properties distinguishing them from other antigens. However, particulates and proteins that serve as allergens have certain characteristics, such as molecular complexity, easy solubility, stability, and often special abilities to breach mucosal defense mechanisms and gain access to sites controlled by the immune system.¹⁰ In addition, the more concentrated the exposure to allergenic particles, the more likely they are to induce an IgE-mediated allergic response. It has also long been known that host genetic characteristics are extremely important to determine whether an allergic IgE-mediated response will occur. For example, the ability to mount an IgE antibody response to certain low-molecular weight pollen allergens is associated with products of both class 1 and class 2 genes; the latter is especially important in presenting antigen fragments to T-helper cells for subsequent antibody production. Finally, several environmental or extrinsic factors are also important in heightening or modulating the IgE-mediated sensitization phenomenon. For example, exposure to a potential allergen together with an industrial pollutant, cigarette smoke, or viral infection may markedly enhance its allergenic potential, possibly by increasing epithelial permeability and allergen access to the immune system.^{11 12}

TABLE III. Major pulmonary diseases caused by inhalation of allergens

- Allergic airways disease (asthma)
 - Allergic parenchymal disease (alveolitis)
 - Infection (airways or parenchymal)
 - Industrial lung disease (pneumoconiosis)
 - Building-related lung diseases
-

Allergic parenchymal disease or alveolitis

Small organic particles, such as actinomycete spores, that reach the alveolar area of the lung in large quantities can cause hypersensitivity pneumonitis or allergic alveolitis (HP/AA). The small size of these particles and their site of deposition likely play a large role in determining the occurrence of alveolitis rather than bronchospasm. For example, farmers working in an environment in which aliquots of moldy hay have been disturbed have been estimated to inhale and retain their peripheral lungs approximately 750,000 actinomycete spores per minute, all of which are 1 μm or less in diameter.¹³ Not only is the antigenic load heavy, but many of the organic dusts that cause HP/AA are usually known to have a variety of peculiar biologic effects. For example, they can stimulate alveolar macrophages and directly activate the alternative pathway of complement providing the necessary mediator stimuli for increasing vascular permeability and promoting chemotactic migration of neutrophils and other cells into the lung. They can also serve as potent immunologic adjuvants, and they often contain endotoxin or similar toxic substances, many of which have enzymatic activity.^{14, 15} Thus in addition to their ability to serve as antigens and incite an immune response, the inflammatory consequences of these direct injurious and adjuvant effects are also very important factors in producing an alveolitis.

Infection

All principles of aerosol deposition discussed previously apply to transmission of infection with microbial and viral aerosols. Infection with aerosol transmission of these agents has been well known for many years. In keeping with the theme of this conference, Legionnaire's disease, which appeared as an outbreak of pneumonia in 1976, was attributed to aerosol infection from contaminated water, resulting in one of the initial examples of building-related lung disease.¹⁶

Industrial lung disease (pneumoconiosis)

The classic peripheral lung diseases of occupational origin consist of silicosis, anthracosis, berylliosis, and asbestos. Silicosis is caused by a recurrent and prolonged inhalation of free crystalline silicone dioxide. It is the most common of the pneumoconiosis caused by inorganic particulate agents and occurs in occupations such as mining, quarrying, sandblasting, and other industries in which crystalline silica dust is generated. The major forms of free crystalline silica

particles, in decreasing order of fibrogenic potential, are tridymite, cristobalite, coesite, quartz, and stishovite. A pathologic characteristic of the full-blown disease is the laminated hyalinized nodule, which may, in advanced cases, coalesce to form conglomerate hyalinized masses. It is not known whether immunologic mechanisms are directly involved in the host response to inorganic dusts such as silica, but it has long been known that the disease is associated with multiple immunologic aberrations. Prominent among these are non-organ-specific autoantibody formation, an increase in detectable rheumatoid factor and immune complexes, macrophage toxicity, and depression of many lymphocyte, monocyte, and polymorphonuclear functions.¹⁷

Anthracosis or coal worker's pneumoconiosis is a lung disease distinct from silicosis, which results from inhalation of coal dust. It can exist either in the form of a simple lesion such as the cold macule or in a diffuse progressive fibrotic form.

Berylliosis exists in two independent forms of lung disease that result from beryllium inhalation. The first is an acute chemical pneumonitis caused by heavy exposure to metallic beryllium or any of a variety of beryllium salts. This form of the disease is characterized by progressive cough and dyspnea. The second form, chronic berylliosis, is histologically characterized by noncaseating granulomas. There is strong evidence for the existence of cell-mediated hypersensitivity to beryllium as manifest by beryllium-induced production of a wide variety of cytokines and contact or delayed skin test responses in vivo in sensitized animals and workers.¹⁸

Asbestosis is a diffuse pulmonary fibrosis that clinically and pathologically resembles idiopathic fibrosis and is caused by prolonged moderate or heavy exposure to asbestos fibers usually in association with cigarette smoking. It has been recognized as a unique occupational lung disease for more than 70 years and is caused by inhalation of any of the commercially important asbestosis fiber types, namely, chrysotile, amosite, crocidolite, or anthophyllite. These asbestos fibers are composed of iron and magnesium silicate with variable amounts of calcium and free iron. They exist in two basic mineral groups, the serpentine and amphibole varieties, which are divided into six major forms. It has long been known that production and use of asbestos generates large amounts of dust and can lead to the fibrotic disease asbestosis or to fibrosis of the associated visceral pleura without involvement of the parietal pleura. The disease is also well known to be complicated by infection such as tuberculosis and bronchiectasis, plus cancer, especially pleural mesothelioma. Symptoms do not usually develop until 7 to 10 years after exposure, and the lung histopathologic findings usually consist of interstitial and alveolar fibrosis with small, 20 to 50 μm , iron-containing ferruginous bodies previously referred to as asbestos bodies. These are thought to represent asbestos fibers coated with ferritin-containing proteins, which may possibly protect against further tissue reaction. Hyalinized and calcified pleural plaques are also frequently seen. Like silicosis, the incidence of organ specific autoantibodies is increased in patients with asbestosis, and the disease is associated with many other poorly understood immunologic aberrations, including the ability of these fibers to activate the alternative pathway of complement, to be highly cytotoxic for a wide variety of immunocomponent cells, and to induce anergy.¹⁹ Depression of induced delayed hypersensitivity reactions, decrease in percentages and numbers of peripheral T cells, specifically T-suppressor cytotoxic cells, and polyclonal B-cell stimulation with hypergammaglobulinemia, have also been noted after exposure to these particulate fibers. Yet total T cells and cytotoxic suppressor cells have been elevated in the bronchoalveolar lavage cell compartment, suggesting an

immunoregulatory imbalance.²⁰ It is not known whether these immunoregulatory imbalances have anything to do with disease pathogenesis per se as opposed to representing only associated

epiphenomenon.

Building-related Lung Illness Diseases

TOP

One method of classifying building-related illnesses is to consider them to be composed of two large categories: one in which a specific cause can be identified and another in which no definite cause can be found. In the former category are many of the diseases caused by inhalation of particulate agents as previously described in this article when they occur in the form of outbreaks of acute illness among office, factory, or other workers groups. Examples of these diseases are those caused by infectious particulate agents such as Legionnaire's disease, those caused by particulate agents that induce HP/AA such as humidifier fever, and those caused by pollen, mold spores, or other sensitizing particulate allergens that induce common bronchial asthma or rhinitis. In these types of "building-related diseases," all affected workers present a uniform clinical picture (i.e., pneumonitis, asthma, infection, etc.), even though the etiologic agents may not be obvious until a detailed on site investigation has been performed. Other building-related syndromes occur in sensitized subjects who are exposed to particulates. Among these are asthma or rhinitis allegedly resulting from off gassing of building materials and chemical pollutants taken up by a ventilation system.

The second type of building-related illness often occurs in an office in which workers report vague, nonspecific protean symptoms often related to multiple organ systems. In such a setting, no identifiable causative agents can usually be found even after exhaustive study. Some refer to this category of illness as so-called "tight building syndrome," because it has been reported in highly energy-efficient, well-sealed office buildings. This hypothesis may, however, not be valid since recent evidence has shown that symptoms at work (not necessarily attributed to the buildings) and dissatisfaction with a building's environment have no relationship to the rates of ventilation with outdoor air in buildings whose ventilation rates were considerably above current standards. ²¹

In some cases office workers report nasal mucous membrane and conjunctival irritative or annoyance symptoms consistent with or difficult to distinguish from common allergic disorders of the upper respiratory tract. Although no definite proof exists, many of these illnesses have allegedly been associated with nonparticulate substances such as various volatile compounds, formaldehyde off gassing, and a wide variety of organic chemicals from various office furnishing and carpets. Others are associated with particulates such as tobacco smoke particles; yet others have been thought to represent mass hysterical or other psychogenic-type reactions. ²²

Summary

TOP

This brief discussion of inhaled particles, their manner of deposition and clearance, and their association with many human diseases has been designed to remind us of the importance of particulate agents as sensitizers, via their allergen content, as causative agents of lung inflammation via their immunotoxic properties, as inducers of inflammatory alveolitis based on their content of antigens and adjuvant-like material, and as infectious agents. All these properties can play a part in a wide variety of allergic parenchymal, infectious, and industrial lung diseases and in building-related illnesses.

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Spore germination increases allergen release from *Alternaria*
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[ABSTRACT](#)

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Immunologic orchestration of hypersensitivity pneumonitis

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