Pulmonary Host Defense Mechanisms*

Ruth N. Harada, M.D.;† and John E. Repine, M.D.

The major function of the respiratory system is to procure oxygen from the external environment and to eliminate carbon dioxide from the body at rates required by tissue metabolism. Unfortunately, ambient inspired air contains not only oxygen which is vital to survival, but also noxious gases and a multitude of particulates, including viable microorganisms, which the lungs must exclude to maintain good health. Toxic substances in air are derived from many sources. For example, naturally occurring processes can give rise to large amounts of aerosolized particles. The latter includes resuspension of soil and emissions from volcanic activity, forest fires, photochemical reactions, and even sea spray. Airborne particles also include biologically derived viruses, bacteria, fungi, algae, spores, and pollens. In addition, industrial and occupational sources add sulfur dioxide, carbon monoxide, nitrogen dioxide, ammonia, hydrocarbons, ozone, and inorganic and organic particles to our inspired air.

This article will briefly overview the various pulmonary defense mechanisms which usually prevent the development of lung disease by resisting invasion by pathogenic organisms and by absorbing, detoxifying, and/or removing toxic gases and inanimate particulates. Although the respiratory tract defenses encompass many interrelated responses, for simplicity of presentation, we have arbitrarily divided them into two major parts (Table 1). One is referred to as physical defense mechanisms which primarily comprise structural and physiochemical adaptations in the proximal upper and lower airways and their lining layers. The second is cellular defense mechanisms which operate mostly in the distal alveolar parts of the lung. The latter largely depends on alveolar macrophages (AM) and their ability to mediate phagocytic and immunologic responses. Finally, although the aforementioned proximal and distal lung defense mechanisms provide an impressive barrier against the environment, they are limited in their ability to protect the host, and in some circumstances, may contribute to lung injury.

Physical Defense Mechanisms

The first line of lung defense is the proximal upper and lower airway mechanism which by physical means reduces access of gases and particulates to the lung. The effectiveness of this system depends on the specific physical nature of each inhaled particle or gas molecule (Table 2). For example, the nose is a remarkably efficient upper airway defense mechanism that removes most airborne particles and water-soluble gases from inspired air. Indeed, the high linear velocity of the inspired air and the bend in the airstream in the anterior part of the nares usually causes impaction of a large proportion of the particles that enter the nasal airway. Nearly all particles with an aerodynamic size >10 μ are deposited within the nose and nasopharynx. In contrast, particles smaller than 2 μ often pass beyond this site into the lung. This is important because droplets carrying infectious microorganisms are often smaller than 2 μ in diameter (Fig 1). The aforementioned anatomic mechanism is augmented by sneezing and coughing reflexes. Sneezing is a forceful, explosive exhalation triggered by receptors in the nose and nasopharynx. Coughing is also a sudden and forceful expulsion of air from the lungs triggered by stimulation of the epipharynx, larynx, and tracheobronchial tree. These reflexes clear unwanted substances from the nose, pharynx, and large airways.

Table 1—Pulmonary Defense Mechanisms

<table>
<thead>
<tr>
<th>A. Physical (airway)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Upper airway filtering systems</td>
<td></td>
</tr>
<tr>
<td>2. Reflexes</td>
<td></td>
</tr>
<tr>
<td>a. sneezing</td>
<td></td>
</tr>
<tr>
<td>b. coughing</td>
<td></td>
</tr>
<tr>
<td>3. Mucociliary escalator</td>
<td></td>
</tr>
</tbody>
</table>

B. Cellular (alveolar)

1. Phagocytic
   a. alveolar macrophages (AM)
   b. neutrophils (PMN)

2. Immunologic
Table 2—Relative Size of Airborne Gases and Particles

<table>
<thead>
<tr>
<th>Type</th>
<th>Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Gases</td>
<td>0.0001-0.0006</td>
</tr>
<tr>
<td>SO₂, CO, NO, NO₂, NH₃, CO₂, O₂, Hydrocarbons</td>
<td></td>
</tr>
<tr>
<td>B. Particles</td>
<td></td>
</tr>
<tr>
<td>1. Organic</td>
<td></td>
</tr>
<tr>
<td>a. Pollen</td>
<td>10-100</td>
</tr>
<tr>
<td>b. Spores</td>
<td>6-60</td>
</tr>
<tr>
<td>c. Fungi</td>
<td>3-100</td>
</tr>
<tr>
<td>d. Cotton flax</td>
<td>2-100</td>
</tr>
<tr>
<td>e. Grain and wood dust</td>
<td>0.1-1000</td>
</tr>
<tr>
<td>f. Algae</td>
<td>0.5</td>
</tr>
<tr>
<td>g. Bacteria</td>
<td>0.3-15</td>
</tr>
<tr>
<td>h. Viruses</td>
<td>0.15-0.45</td>
</tr>
<tr>
<td>2. Inorganic</td>
<td></td>
</tr>
<tr>
<td>a. Cement dust</td>
<td>3-100</td>
</tr>
<tr>
<td>b. Foundry dust</td>
<td>1-1000</td>
</tr>
<tr>
<td>c. Metal oxides</td>
<td>0.1-1</td>
</tr>
<tr>
<td>d. Salt nuclei (sea water)</td>
<td>0.03-0.5</td>
</tr>
<tr>
<td>e. Tobacco smoke</td>
<td>0.01-1</td>
</tr>
</tbody>
</table>

Another airway defense mechanism for clearance of inhaled materials is the mucociliary escalator. This system consists of overlying mucus layer and an underlying ciliary-epithelial network. The mucus is secreted by submucosal glands and goblet cells that exist in the upper and lower airways. It contains micromolecules (electrolytes and amino acids) as well as macromolecules (lipids, carbohydrates, nucleic acids, mucins, immunoglobulins, enzymes and albumin) that trap particles, absorb gases and facilitate their removal by the cilia. Slight alterations in the composition and/or volume alters rheologic (flow) properties of mucus. The rheologic properties of the overlying mucus are important in that they affect the underlying cilia of epithelial cells which line the airway down to the distal bronchioles. Ciliary movement directs overlying mucus-containing particulates and absorbed gases toward the pharynx where they are swallowed or expectorated. Cilia beat at a frequency of between 1,000 to 1,500 cycles per minute propelling the overlying mucus at progressively increasing rates up the airways. The linear velocities of mucus transport range from rates of 0.5 to 1 mm per minute in small airways to as much as 5 to 20 mm per minute in the trachea and main bronchi. As a result, particles that are deposited in the trachea or the initial bronchial divisions are cleared with a half-time of about 30 minutes while those deposited more deeply are removed with half-times approaching several hours. Accordingly, virtually all material deposited on ciliated epithelium is removed within 24 hours.

Optimal mucus volume and rheologic properties as well as good ciliary function must be maintained for efficient mucociliary transport and adequate defense against disease. Optimal conditions for mucociliary clearance are lost in some disease states, such as in purulent bronchitis, where decreased elasticity and increased viscosity of the mucus lining layer contributes to decreased mucus transport. Disturbed mucociliary transport is also observed in infected patients with cystic fibrosis. In addition, a number of external agents appear to be ciliotoxic. Cigarette smoke irritates the ciliated epithelium and is usually associated with ciliostasis and decreased particle transport. Atmospheric pollutants, such as sulfur dioxide, nitrogen dioxide, and ozone also irritate the respiratory mucosa and depress mucociliary function. In addition, general anesthetics, alcohol, and viral infections may decrease mucociliary clearance. In contrast, pharmacologic agents may improve transport by changing the volume and physical properties of fluid and mucus or by improving ciliary activity. Adrenergic agents, cholinergic agents, biologically active amines, and methylxanthines may be therapeutic in diseases associated with impairment of mucociliary transport.

**Cellular Defense Mechanisms**

In spite of the adequacy of the physical defense mechanisms of the upper and lower airways, a substantial quantity of fine particulates and soluble material constantly escape these mechanisms and are deposited in alveoli. Fortunately, additional cellular defense...
mechanisms exist to deal with agents that have passed through upper airway defenses. Alveolar macrophages (AM) play a central role in these cellular defense mechanisms by participating in phagocytic and immunologic reactions.

**Phagocytic Reactions**

Elimination of foreign particles and microbes from the distal air-spaces of the lung initially depends upon the immediate phagocytic capability of strategically located AM.\(^\text{10-17}\) Phagocytosis by AM is a complex energy dependent process that has been divided into seven phases as follows: (1) particle recognition; (2) reception of the message to initiate phagocytosis; (3) transmission of the message from receptor to effector; (4) adhesion of the plasma membrane to the particle; (5) assembly of pseudopodia; (6) movement of pseudopodia to engulf the particle; and (7) fusion of the pseudopodia. Opsonization of particles and microbes enhances their phagocytosis by AM. Once phagocytosis has occurred, the particle is then encased in a phagocytic vesicle which subsequently fuses with lysosomes to form phagolysosomes—the prime compartments for digestion of particles and killing of engulfed bacteria. During phagocytosis, AM generate highly reactive toxic products of \(O_2^\cdot (O_2\) radicals) such as hydrogen peroxide (\(H_2O_2\)) or hydroxyl radical (\(OH\)), which work in conjunction with hydrolytic and proteolytic enzymes from degranulating lysosomes to kill bacteria within the phagocytic vacuole.

Phagocytic host responses to inhaled bacteria are often more complex than just having microorganisms engulfed by resident AM. In some cases, they involve recruitment of polymorphonuclear leukocytes (PMN) or neutrophils from the blood. Phagocytic responses in the lung have been elegantly elucidated by many investigators.\(^\text{18-19}\) In aggregate, they indicate that clearance mechanisms depend on the specific microorganism and even more specifically, opsonization requirements and/or innoculum size. Briefly, while AM are largely responsible for clearance of some Gram-positive bacteria, such as *Staphylococcus aureus*, other organisms, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, usually require neutrophils for optimal clearance (Fig 2). Considerable evidence also suggests that AM can initiate accumulation of neutrophils in the lung by releasing chemotaxins or chemoattractants (chemical messages that attract neutrophils).\(^\text{12,13,20}\) Neutrophil chemotaxins can be derived from a variety of other sources such as bacterial factors, complement fragments, lymphokines, peptides, lipids including prostaglandins and leukotrienes, immunoglobulin fragments, fibrinogen, collagen fragments, and immune complexes.\(^\text{21}\) Once recruited to the lung, neutrophils then ingest and kill opsonized microbes and other foreign substances by mechanisms which are similar to those described for AM. Neutrophils are well suited for killing certain bacteria and possess potent antimicrobial defenses which are spearheaded by myeloperoxidase augmented oxygen radical mediated toxicity.\(^\text{15,17,22}\)

**Immunologic Reactions**

When immediate phagocytic responses are inadequate, immunologically-specific mechanisms of host defense responses are ultimately provided by lymphocytes. Frequently interactions of lymphocytes with AM appear necessary for initiation, modulation, and expression of pulmonary immune reactivity. AM participate in these pulmonary immune responses in several ways. First, AM may initiate induction of humoral and cellular immune responses by ingesting particulates or soluble antigens and thereby "processing" and "presenting" these antigens for specific antigen-reactive B- and T-lymphocytes. This "processing" and "presenting" of antigen by AM stimulates both B- and T-lymphocytes to proliferate and differentiate into effectors of humoral (antibody production) and cell-mediated (cytotoxic lymphocytes) immunity. These responses form the basis of antimicrobial immunity and are important in acute and chronic infections. They may also act as a surveillance mechanism against malignancy. AM may also serve an important immunoregulatory role in suppressing proliferation, differentiation, or functional activity of antigen-stimulated lymphocytes. The aforementioned alveolar defense mechanisms provide a surveillance system against infection and injury and thereby protect against the development of disease. When directed appropriately, these major responses are essential in combatting infectious agents; however, as we have indicated, these mechanisms can become harmful when they are misdirected and result in inflammation and structural admissions.
damage to the lung.

**Misdirected Lung Defense Mechanisms**

Improved understanding of lung defense mechanisms, especially those in the distal airspaces, has led to a better appreciation that "lung-defense like mechanisms" may also contribute to lung injury. Indeed, it has become increasingly apparent that AM and neutrophils can function not only as phagocytic cells in the distal lung, but also as initiators of inflammatory and immune responses that lead to lung injury.

**Role of AM in the Pathogenesis of Acute Lung Injury**

By mechanisms resembling those operable in host defense, AM may also contribute to lung injury. AM do this by functioning as secretory cells which release inflammatory mediators and/or toxins such as lysozyme, hydrolases, complement components, reactive oxygen metabolites (O$_2$ radicals), bioactive lipids (arachidonate metabolites), and neutrophil activators. Although the diversity of chemical structures and the apparent biologic effects of AM-derived substances found *in vitro* is striking, their existence and significance *in vivo* remain unknown.

A good example of the potential detrimental effects of AM secretions can be appreciated in studies using pulmonary oxygen toxicity as an experimental model of acute lung injury. Studies include the following observations: exposure of animals to hyperoxia elicits an inflammatory response in lungs which is characterized by preterminal accumulations of neutrophils and stimulants of neutrophil recruitment and activation. In addition, when exposed to hyperoxia in culture, AM also release neutrophil chemotaxins and neutrophil O$_2$ metabolite stimulants which are chemically similar to chemotaxins and stimulants obtained from lung lavages of animals exposed to hyperoxia *in vivo*. Thus, AM appear to be a likely source of neutrophil chemotaxins and O$_2$ metabolite stimulants found in lungs of animals exposed to hyperoxia. These studies serve as a good example of the way in which AM can use "defense-like mechanisms" to contribute to lung injury (Fig 3).

**Role of Neutrophils in the Pathogenesis of Acute Lung Injury**

Although important in protecting against bacterial infection, neutrophil accumulation and activation in the lung can contribute to acute lung injury. Studies of pulmonary oxygen toxicity suggest that neutrophil depletion decreases acute edematous lung injury in animals exposed to hyperoxia, and moreover, that O$_2$ radical scavengers can decrease lung injury from hyperoxia. These findings suggest that neutrophils and neutrophil-derived O$_2$ radicals participate in acute lung injury seen in pulmonary oxygen toxicity. Thus, when generated by neutrophils, oxygen radicals are not only a major mechanism for antimicrobial activity but also a mechanism for lung injury. Further evidence supporting the possibility that oxygen metabolites from neutrophils cause acute lung injury are studies in isolated lungs which show (1) that stimulated normal but not oxygen radical deficient chronic granulomatous disease neutrophils cause acute edematous injury, and (2) that chemical production of oxygen metabolites also causes acute edematous lung injury which is decreased by pre-addition of oxygen metabolite scavengers, such as catalase and dimethylthiourea. So again, mechanisms which are vital to host defense, in this instance, recruitment of neutrophils to the lung and their release...
of oxygen metabolites can, under untoward situations, contribute to lung injury. These corresponding mechanisms of neutrophil mediated lung defense and lung injury are shown schematically in Figure 4. This concept of duality whereby lung defenses can confer protection as well as cause lung injury has only recently been appreciated and needs further definition. This review has considered only one example of how lung defense mechanisms might participate in lung injury but similar functions should be considered for each host defense mechanism.

CONCLUSIONS

The lung normally exposes an enormous surface area to the external environment which contains many noxious gases and particulates, including microorganisms, that must be excluded to maintain good health. Turbulent flow in the nose leads to deposition and absorption of a majority of particulates and gases in the upper airways. These are then cleared by sneezing, coughing, and/or the mucociliary escalator. Despite the importance of efficiency of these upper and lower airway physical defense mechanisms, a substantial quantity of particles and soluble material constantly reaches the distal lung. At this level, AM contribute in a major way. The AM act not only as phagocytes but also as secretary cells which release factors which attract and activate neutrophils and initiate immune and inflammatory responses involving lymphocyte interactions. Unfortunately, while lung defense systems are instrumental in protecting against disease, they can also contribute to lung injury.

REFERENCES

1. Brain JD, Proctor DF, Reid LM. Respiratory defense mechanisms, Part I and II. New York: Marcel Dekker, Inc. 1977

Chest / 87 / 2 / February, 1985 251
30 Bowman CM, Harada RN, Fox RB, Shibao GA, Repine JE. Hyperoxia stimulates alveolar macrophages to produce and release a factor which increases neutrophil adherence. Inflammation 1983; 7:331-38
37 Weissmann G. Activation of neutrophils and the lesions of rheumatoid arthritis. J Lab Clin Med 1982; 100:322-33
41 Bowman CM, Butler EN, Repine JE. Hyperoxia damages cultured endothelial cells causing increased neutrophil adherence. Am Rev Respir Dis 1983; 128:469-72
42 Repine JE, Tate RM. Oxygen radicals and lung edema. Physiologist 1983; 26:177-81
44 Tate RM, VanBenthuysen KM, Shasby DM, McMurtry IF, Repine JE. Oxygen-radical mediated permeability edema and vasoconstriction in isolated perfused rabbit lungs. Am Rev Respir Dis 1982; 126:802-06