Allergic Reactions to Indoor Air Pollutants

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Inhalation of airborne chemicals can result in allergic sensitization with episodic pulmonary responses occurring on subsequent exposures. Responses may occur in the upper respiratory tract (rhinitis), the lower respiratory tract (wheeze, bronchospasm) or systemically, for example, a febrile response. The mechanisms underlying these responses are not always clear but include production of reaginic antibody, activation of T-lymphocyte subsets, and release of spasmogenic and inflammatory mediators from pulmonary cell populations. A variety of agents have been associated with elicitation of these reactions including chemical vapors, dusts and particulates, and microbial organisms. As a result of the widespread occurrence of allergy in indoor environments, conditions conducive to development of allergy have received close attention. Agent-related factors include the nature of the chemical, its concentration, and the frequency and length of exposure to the agent. Host-related factors include the sex, age, and race of the host, as well as the general physical well being. The interactive nature of the host's immune system with the environment is the ultimate determinant of allergic disease.

Introduction

Indoor air has been associated with a variety of adverse respiratory effects. The symptoms vary from acute bronchoconstrictive reactions, to systemic manifestations with late-onset occurrence, to persistent cough, weakness, and malaise. Such symptoms have been attributed to several classes of agents, including irritants such as formaldehyde, acid anhydrides, and isocyanates; infectious organisms such as Legionella; and allergens (1). Although these agents are diverse, the symptoms they cause bear similarity. Care must be given therefore to thoroughly examining subjects and to developing discriminating diagnostic procedures to allow not only appropriate treatments but to determine sources of contaminants.

It is well recognized that individuals located in the same indoor environments will demonstrate differences in their response to the environment. Numerous studies have been undertaken to identify host factors that contribute to these differences. Prominent among such factors are age, physical well being, and smoking habits. This article explores the nature of these effects while focusing on recently developed methodology, including use of animal models, to elucidate the mechanisms and manifestations of allergies due to indoor air pollutants.

The field of immunology is notorious for its specific, sizable, and frequently complex terminology. To assist in presentation and discussion of ideas, a brief dictionary of terms useful in discussion of allergic lung disorders is provided in Table 1.

| Term                | Definition                                                                 |
|---------------------|-----------------------------------------------------------------------------|
| Antigen             | Substance that can elicit an immune response and can react with the corresponding antibodies or T-cell receptors |
| Allergen            | Antigen that induces allergy                                                |
| Airway hyper-       | Exaggerated bronchoconstrictive response on exposure                        |
| responsiveness      | to a quantity of a nonspecific stimulus that does not provoke reaction in normal subjects |
| Asthma              | Reversible airway obstruction characterized by eosinophilic inflammation of the airways |
| Delayed-onset       | Mononuclear cell inflammatory reaction occurring more than 1 hr after exposure to the offending allergen. Reactions are initiated by T-lymphocytes recognizing allergen associated with histocompatibility antigens on antigen-presenting cells and are mediated by release of lymphokines from activated T-cells |
| Hypersensitivity    | State of heightened reactivity to a previously encountered antigen (synonymous to allergy) |
| Pneumonitis         | Immunologically mediated lung disease caused by inhalation of organic antigen and characterized histologically by a diffuse monocellular infiltration of pulmonary interstitium, alveoli, and terminal bronchioles. Symptoms include cough, fever, chills, and shortness of breath several hours after exposure to the offending agent. |
| Immediate-onset     | Adverse immune reaction occurring within minutes to 1 hr following encounter with the offending allergen. Responses are mediated by IgE or a subclass of IgG antibody bound to mast cells or basophils. |
| Irritation          | Reflex response of the respiratory system due to stimulation of nerve endings |
| Sensitization       | Administration of antigen (i.e., priming) to enable a heightened response (i.e., secondary immune response) upon subsequent re-exposure to the same antigen |

*Adapted in part from Rosen et al. (2).
**Indoor Air Pollutants: Agents and Sources**

Analysis of indoor air typically reveals a variety of vapor and particulate materials. Some of the most common pollutants are listed in Table 2, together with their sources. This list represents only a percentage of indoor pollutants.

Although components of indoor air are numerous, the allergenic constituents are found predominantly in the biologic category. A more detailed, but far from exhaustive, list of such materials is provided in Table 3. Some of the most potent agents of allergic lung disease are found in indoor environments. Such “aeroallergens” have been recognized for many years and cause the majority of childhood asthmatic attacks.

**Responses of the Respiratory System**

The effects of pollutants on the lung can be categorized as irritation, inflammation, bronchoconstriction, and sensitization. It should be recognized that a pollutant may be responsible for more than one type of response. For example, chemical pollutants, such as some isocyanates, can cause irritative bronchoconstriction, cellular inflammation, and sensitization (3). Conversely, a clinical syndrome can be initiated by a diverse number of agents, as exemplified by the agents listed in Table 4. The systemic syndrome of fever, chills, and cough can be an irritant response (due, for example, to purified endotoxin), an allergenic response, or result from an infectious process. The response evoked is dependent on several factors, the most important being the concentration of the chemical in the environment. Other factors that influence the response are host related, such as, the age and immunologic status of the host.

**Table 2. Sources of indoor air pollutants.**

| Pollutant                  | Source                                      |
|---------------------------|---------------------------------------------|
| Respirable particles      | Tobacco, stoves, heaters                    |
| Gases (NO<sub>2</sub>, CO<sub>2</sub>) | Ranges, heaters, garages                    |
| Formaldehyde              | Foam insulation, particle board, fabrics    |
| Radon                     | Soil, water                                 |
| Volatile organic compounds| Paints, sprays, combustion                  |
| Biological material       | Dust mites, dander, bacteria, fungi, pollen |

**Table 3. Indoor allergens.**

| Category        | Allergens                                |
|-----------------|------------------------------------------|
| Fungi           | Thermophilic actinomycetes               |
|                 | Aspergillus                              |
|                 | Penicillium                              |
|                 | Alternaria                               |
| Algae           | Bacillus subtilis                        |
|                 | Bacillus cereus                          |
|                 | Strepotyphyes albus                      |
| Amoebae         |                                            |
| Bacteria        | Dermato phagoides                        |
|                 | Pett urinary and serum proteins          |
|                 | Dander                                    |
|                 | Arthropod fragments                      |
| Animal sources  | Isocyanates                              |
|                 | Acid anhydrides                           |

**Table 4. Characteristics of respiratory reactions.**

| Agent            | Symptoms        | Examples                        |
|------------------|-----------------|---------------------------------|
| Irritants        | Fever, cough, chills | Endotoxin                      |
| Allergens        | Fever, cough, chills | Thermophilic microorganisms   |
| Infectious agents| Fever, cough, chills | Legionella                     |

**Animal Models**

Recognition of the diverse nature of agents in indoor air that are causally associated with allergic sensitization prompted development of an animal model to gain understanding of the mechanisms involved. A guinea pig model was developed over a period of 10 years (4,5). The essential features of the model are listed in Table 5. Using inhalation as the route of exposure during both the sensitization phase and for elicitation of responses, syndromes have been produced that closely resemble those associated with environmental sensitization. Key features of the model that distinguish it from others are the use of unsedated, unrestrained animals and 24-hr continuous monitoring of responses.

**System**

A schematic of the system used for chemical exposure and monitoring response is presented in Figure 1. Currently, the system has the capability to monitor four animals simultaneously (one animal is depicted in the Figure 1). Animals are exposed to the agent for sensitization while housed either in the individual glass plethysmographs or, for group exposures, in larger chambers, frequently in glass aquarium tanks. The length of the initial exposure period has been varied with adjustments made to reflect exposure lengths typical of indoor air situations. Table 6 lists two classes of allergens and the exposure periods for each that have resulted in maximal sensitization. From experiments in which both the airborne concentrations and the lengths of exposure have been varied, it has become clear that the concentration of agent is the critical factor determining sensitization (7). Extended periods of exposure to low levels of these agent have not resulted in development of a sensitized state (7,8).

**Monitoring Responses**

Re-exposure of a sensitized individual to a specific allergen may result in development of an allergenic response. The type of response evoked is dependent on numerous factors including the nature of the allergen and the immunologic responsiveness of the host. The traditional classification of these responses was proposed by Gell and Coombs (2), as outlined in Table 7. Because the symptoms may occur either within minutes of re-exposure (type I), or hours later (types II–IV), it is important to continuously monitor response over 24 hr.
Parameters Monitored

The requirement that animals be monitored for extended periods of time places considerable restriction on the parameters that can be monitored and that reflect a sensitization response. The two parameters that have proven to be of value are breathing frequency and core temperature. The breathing frequency is known to increase during a sensitization response, as seen in Figure 2 (4,6,7). Additionally shown in Figure 2 is the occurrence of airway spasms. Airway spasms are a frequent characteristic of a sensitization response and can be readily detected by whole body plethysmography.

The nonspecific nature of a change in breathing frequency necessitates careful interpretation. It is widely recognized that certain chemicals, for example, ozone, NO₂, and diphenylmethane diisocyanate (MDI), cause an increased breathing frequency as a consequence of pulmonary irritation and stimulation of nerve receptors (9). However, the latter type of response is noted on initial exposure to the agent. To detect a sensitization response, the irritation response must be avoided by using subirritation concentrations of the agent.

Febrile Responses

Fever has been associated with several types of pulmonary reactions including infection, irritations and pneumonitis. Continuous measurement of core temperature can be achieved by intraperitoneal implantation of radio-frequency transmitters. We have shown that this system can detect the pyretic response associated with exposure to endotoxin (Fig. 3) (10) and the eosinophilic pulmonary inflammation associated with late-onset hypersensitivity reactions (Fig. 4) (11). The temperature telemetry system therefore provides a passive means for 24-hr monitoring of animals and is a valuable supplement to measuring breathing frequency for detecting late-onset responses.
Airway Hyperreactivity

One of the cardinal features of asthma is hyperreactive airways (AHR). This condition is usually detected by assessing the responsiveness of an individual to known concentrations of airway constrictors such as histamine or methacholine. Accordingly, an animal model for asthma should include provision for detecting AHR.

We have incorporated measurement of airway reactivity into the guinea pig model using the basic plethysmographic system (12). Responsiveness to histamine indicates AHR and is assessed while animals are held in the individual plethysmographs. Increasing concentrations of histamine are introduced into the atmosphere, and pressure changes within the plethysmograph due to the animal’s altered breathing pattern are recorded. Airway constriction is detected by an abrupt change in plethysmograph pressure (ΔP). In the example illustrated in Figure 5, airway constriction was induced when the histamine concentration was increased to 1.9 mg/m³. The concentration of histamine required to evoke airway constriction was significantly reduced following an allergic sensitization response (Fig. 6), indicating the presence of airway hyperreactivity. Using this model, the airway reactivity of animals can be assessed repeatedly at times of particular interest during the 24 hr following allergen inhalation challenge.

Interaction of Environmental and Host-Related Factors

There are many unanswered questions related to sensitization in indoor environments. The interaction of atmospheric factors with host-derived factors holds the key to identifying those in-
FIGURE 4. Onset of responses indicating allergic reaction of a guinea pig to ovalbumin aerosol. The immediate-onset response was apparent from airway spasms and increased breathing frequency (solid line). The late-onset response was indicated by fever (dashed line), increase in respiratory rate (solid line), and pulmonary eosinophilia.

FIGURE 5. Response of a guinea pig to increasing concentrations of histamine. Upon exposure to 1.9 mg/m³ histamine, a sudden 3-fold increase in plethysmograph pressure (ΔP) was observed. Exposure at each concentration was for 15 min. From Thorne and Karol (12), with permission.

From both clinical and experimental studies, evidence has shown that the dose of allergen (or its airborne concentration) is a prime factor influencing sensitization. Studies on toluene diisocyanate (TDI) asthma (14) and sensitization to western red cedar dust (15) have found a significant correlation between exposure concentration and either the incidence of pulmonary sensitization or occupational asthma. The relationship has been more clearly defined with an animal model. In studies directed toward determining the sensitization potential of TDI, a threshold concentration was identified for sensitization (6). TDI concentrations above the threshold produced sensitization, whereas those below it did not. A similar threshold effect was noted in animal studies using the allergenic proteolytic enzyme subtilisin (8). Exposures below 41 µg/m³ were found to be without sensitization capability.

Many other factors in addition to allergen concentration influence development of hypersensitivity (as indicated in Table 8). Laboratory studies and clinical reports have both indicated that only a small proportion of those individuals who are exposed to an allergen will develop hypersensitivity. Currently, it is not possible to predict which individuals have increased susceptibility to develop the disorder. However, from epidemiologic studies it is possible to identify factors associated with sensitization. Of particular interest is the influence of cigarette smoke (16). Whereas a positive correlation has been noted between smoking and development of type I allergy, a negative association between smoking and hypersensitivity pneumonitis has been reported. Explanations for the latter finding remain unclear.

dividuals within a population who will develop a particular allergy. A brief list of factors that affect allergy is provided in Table 8. The animal model has the potential to effectively address this exciting area of environmental science.
mechanisms and immunoregulation, together with extensive use of animal model systems, will greatly reduce the incidence of allergy in indoor environments.

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Conclusions

Indoor air represents a complex mixture of chemical and biological agents present in ever-changing proportions. Given the diverse composition of this dynamic environment, it appears likely that sensitization would be an outcome in a population of individuals. For this reason it is imperative that we recognize the most potent allergens, as well as environmental and host factors most conducive to establishing sensitization. Scientific understanding in this area is far from complete, but with recent advances in immunology, understanding is growing at an exponential rate. It is expected that further elucidation of immunologic conditions conducive to sensitization.

Table 8: Conditions conducive to sensitization.

| Factor               | Type of hypersensitivity |
|----------------------|--------------------------|
|                      | Bronchoconstrictive      | Pneumonitis |
| Exposure concentration| Yes                      | Yes         |
| Atopy                | Yes                      | No          |
| Age                  | Yes                      | No          |
| Upper respiratory tract infection | Yes | No |
| Smoking              | Yes                      | No          |
| HLA (genetics)       | Yes                      | ?           |
| Irritants            | ?                        | ?           |

One of the most exciting areas in which animal models can provide important information is the relationship between genetics and sensitization to indoor aeroallergens. The genetic influence on sensitization was clearly demonstrated in studies using synthetic antigens and inbred strains of guinea pigs and mice (17). Histocompatibility genes have been linked with immune responsiveness to protein and synthetic polypeptides. Environmental influences are apparent by the induced expression of Ia antigen on antigen-presenting cells in situations of inflammation and infection. Undoubtedly, many complex interactions among multiple factors modulate a sensitization outcome.
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