

# Indoor Air Quality and Human Health

*Truth vs Mass Hysteria*

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## Abstract

Indoor air quality is an important issue, because anything we breathe can potentially affect our health. To determine if there is a real health risk, well-designed scientifically valid studies must be performed. Although much attention has focused on sick building syndrome, chemical sensitivities, and mycotoxicosis, there actually is very little evidence that these conditions have an adverse effect on human health. In contrast, real health issues have been shown to exist regarding indoor air triggers of allergies and asthma. Outdoor allergens are difficult to avoid because the pollen grains we encounter outdoors, which are the size that can cause allergies, are windborne and can travel for miles. However, indoor allergens can cause severe allergic symptoms and may also have a priming effect on an individual's susceptibility to simultaneous or subsequent exposure of other outdoor allergens. Therefore, it is important to minimize exposure to indoor allergens. Determination of individual susceptibility can be paired with knowledge of the patient's indoor exposure pattern to produce a customized management plan of avoidance, which can be used in conjunction with pharmacological treatment of allergies and asthma, as well as immunotherapy.

## Index Entries

Indoor air quality; molds; hygiene hypothesis; allergen avoidance; atopy; environmental exposures; sick building syndrome.

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## Introduction

### *The Increasing Importance of Indoor Air Quality*

The percentage of time that people spend indoors has been increasing progressively, particularly in developed countries and more advanced societies. Coinciding with this change in lifestyle, there has been an increase in the prevalence of allergies and asthma. Several theories have been proposed for this increase, including a more mobile lifestyle and a switch from a predominantly T-helper (Th)1-based immune system to a Th2-based immune system. Theories attempting to explain this switch include the hygiene hypothesis, which is discussed later. Additionally, the role of changes in building style cannot be ignored, but the data has often been misleading. Houses have become more airtight, often with poor ventilation systems. Most homes have ventilation properties of only 0.2 to 0.5 air changes per hour. In addition to allergies, other complaints attributed to indoor air quality have surfaced, and different components of air have been blamed for these health issues. Although many of these complaints have not been substantiated by well-designed or well-executed clinical trials, the mere occurrence of symptoms in a group of individuals in a single building has given rise to conditions of mass hysteria, as in the case of sick building syndrome (SBS).

Over the years, the subject of indoor air quality has been brought to the forefront of the allergy community by the litany of lawsuits involving indoor air contaminants. These have included asbestos, urea formaldehyde, carbon monoxide, environmental cigarette smoke, and, most recently, mold exposure. Some of these claims possess truly defined health effects, whereas some possess no supporting scientific data. Nonetheless, indoor air quality is an important issue and embodies both truths and myths. This article attempts to separate the truth from the myths, to discuss the basis for

indoor air-related health complaints and the relationship between indoor air quality and the hygiene hypothesis, and, finally, to make recommendations based on current available data, with the caveat that as new data presents itself, recommendations may need to be modified.

## **Historical Events**

### *Early Descriptions of Allergies and Avoidance Tactics*

Even before the concept of allergies was developed, there were descriptions regarding the importance of avoiding substances that caused illness. In the 16th century, the Italian physician Gerolamo Cardano was summoned to the home of John Hamilton, the Archbishop of Saint Andrews, who was suffering from respiratory complaints that were believed to result from tuberculosis. After observing the Hamilton's lifestyle and environment for 6 wk, the doctor tried various dietary and supportive modes of therapy but coincidentally recommended that the Archbishop switch his feather bed for one made of unspun silk. Hamilton complied, and his symptoms disappeared. Of course, the source of Hamilton's symptoms is a matter of speculation, but more than likely, it was the feathers. This marked the first historical recording of a successful clinical attempt to decrease symptoms by avoidance measures (1). The terms *allergen* and *allergy* were coined by Baron Clemens von Pirquet in 1903 (2). From the Greek, the terms translate into "altered response." In 1913, one of the first clinical descriptions of an allergy to an indoor allergen was presented by William Philipps Dunbar, who wrote of the case of a woman who developed itching in the eye after touching the fur of a cat with her hand and then touching her own cheek (1). The clinical importance of exposure to airborne substances was first proposed in the Western world in a 1954 article by Brown on the asthmogenic effects of odors and fumes (3).

### *Modern Building Styles and Occupant Lifestyles*

As we become more affluent, we spend more of our time indoors. It is estimated that we now spend over 90% of our time indoors. The ability to build structures that are increasingly focused on occupant comfort and luxury, along with the emphasis toward conservation of energy, has led to the construction of airtight buildings with few operable windows and minimal airflow. Installation of heating, ventilation, and air conditioning (HVAC) systems to generate a comfortable environment has also led to an additional source for airborne allergenic particles (4). Condensation is a byproduct of operating HVAC systems, thus allowing for mold growth and generating an additional source of allergens. Urban indoor pet ownership (usually dogs or cats) is a function of an affluent society, and animal dander is another significant source of indoor air contaminants.

### *The SBS*

Illnesses that have been attributed to the occupancy of building structures have been described since the 1970s (5). The SBS was first described in the mid-1980s (6–8) and was sensationalized soon after by the media (9). However, a large European study of 3757 municipal workers in government buildings found no association between the worker complaints and any building feature or chemical or biological component within the building (10). The parameters measured included relative humidity, temperature, noise levels, air current, levels of chemicals such as carbon dioxide (CO<sub>2</sub>), formaldehyde, volatile organic compounds, static electricity, dust, and the presence of microorganisms.

The clinical syndrome associated with SBS has never been accurately defined, partly because of the huge variation in complaints among patients. Symptoms that have been ascribed to SBS include ocular irritation, difficulty breathing, tinnitus, nasal congestion, runny nose, headaches, difficulty concentrating, fatigue

and malaise, arthralgias, postnasal drip, myalgias, neurological complaints, and gastrointestinal complaints. With such a great diversity of complaints, the reason that SBS has never been well-defined becomes apparent (11). Building components or contaminants that have been held responsible for SBS include formaldehyde, volatile organic chemicals (VOCs), fungi, bacteria, and viruses (12). Interestingly, nonmold indoor allergens, the component of indoor air that has the most evidence regarding its harmful health effects, was never seriously considered in cases of SBS, which indirectly cast doubt as to the validity of SBS as a real entity.

## **Indoor Air Contaminants**

### ***Types of Indoor Air Contaminants***

There are many types of indoor air contaminants, and they may be in gaseous form or particulate matter. Sulfur dioxide (SO<sub>2</sub>), nitric dioxide (NO<sub>2</sub>), formaldehyde, and ozone are gaseous substances. Environment tobacco smoke can contain a mixture of gases and particulates. Mold spores are particulate, whereas nonmold indoor allergens are proteins that may be carried by a variety of different vehicles. Larger, heavier particles tend to settle more quickly because they are less likely to be rendered airborne by disturbances in airflow. However, the airborne levels of indoor air allergens can vary greatly if the air is disturbed, such as in the case of vacuuming or making the bed. A list of potential indoor air contaminants is provided in Table 1. The greatest impact on human health is caused by allergenic proteins or glycoproteins, which cause atopic diseases, including allergic rhinoconjunctivitis, asthma, atopic dermatitis, and a variety of comorbid conditions, such as sinusitis, otitis media, sleep apnea, insomnia, and so forth.

### ***Effects of Indoor Air Contaminants***

Foreign matter can affect human health only if sufficient contact is made with the body.

Table 1  
Types of Potential Indoor Air Pollutants

<i>Allergenic agents</i>	
	Pollens
	Molds
	Nonmold indoor allergens
	Dust mite
	Dog
	Cat
	Rodents
	Cockroach
<i>Infectious agents</i>	
	Viral
	Bacterial
	<i>Pneumocystis carinii</i>
	Fungal
	<i>Aspergillus fumigatus</i>
	Allergic fungal sinusitis
	Humidifier fever
	Hypersensitivity pneumonitis
<i>Toxins</i>	
	Gases
	SO <sub>2</sub>
	NO <sub>2</sub>
	Formaldehyde
	Radon
	VOCs
	Particulates
	Environmental tobacco smoke
	Asbestos

This may involve inhalation, ingestion, or skin contact. Indoor air contaminants may consist of gases and particulate matter of various sizes and shapes. The ability of a particle to remain airborne depends on several factors, including gravity, air current, and the physical characteristics of the particle itself (13). The type of ventilation system can also affect the way in which air is circulated (14). In the case of indoor air quality, we generally are concerned with the effects that occur as a result of inhalation. The size of the particle affects the extent of penetration into the respiratory tract.

There are five ways that indoor air contaminants can affect the health of an individual. These include toxic effects, irritant effects, infectious diseases, allergic disorders, and psychological effects.

Toxic effects have been described to result from gaseous products or particulates, such as SO<sub>2</sub>, NO<sub>2</sub>, environmental tobacco smoke, asbestos, formaldehyde, and ozone. There are also many other VOCs, which are released from cleaning solutions, new carpeting, electronic equipment, paints and glue, building materials, printed material, and heating equipment. These compounds can be categorized as alcohols, aldehydes, alkanes, aromatic hydrocarbons, benzenes, terpenes, acrylates, and xylenes. Although one might think that each compound or class of compound exerts different clinical effects in humans, the clinical effects of these compounds generally are discussed as a group; this again casts doubt on the validity of adverse health effects occurring as a result of exposure to VOCs. Because many of these compounds coexist in normal building air, it is impossible and impracticable to isolate the clinical effects of a single substance. Therefore, identifying a cause-and-effect relationship is extremely difficult. In addition to "toxic" effects, these agents can also cause irritant effects, which are poorly defined complaints that are usually related to the eyes, throat, nasal passages, and airways. The etiology or pathogenesis for these effects is not clear, but toxic and irritant effects have primarily been blamed for SBS.

Initially, Legionnaire's disease (caused by *Legionella pneumophila*) (15,16) and Pontiac fever (a nonpneumonic disease caused by *L. pneumophila* or *Legionella anisa*) were described as causes of SBS (17). Other viral infections, including those caused by various strains of influenza, also have been associated with outbreaks of SBS (18,19). Last year, in the midst of the severe acute respiratory syndrome (SARS) epidemic in Asia, the spread of the SARS virus (a coronavirus) was demonstrated as the cause of a cluster of 187 cases from the Amoy Gardens Housing complex in Hong Kong (20). It was shown that the airborne route was the probable mode of transmission. A summary of infectious diseases associated with SBS is shown in Table 2.

Table 2  
Summary of Features of Infectious Diseases Associated With SBS

Disease	Legionnaire's disease	Pontiac fever	SARS	Influenza A
Causal agent	<i>Legionella pneumophila</i>	<i>Legionella anisa</i> , <i>Legionella pneumophila</i>	<i>Coronavirus</i>	<i>Influenza A</i>
Microbial characteristics	Gram-negative bacilli	Gram-negative bacilli	SARS-CoV, positive-stranded RNA virus of the Coronaviridae family (79)	Orthomyxovirus, three antigenic types A, B, and C
Clinical features	Respiratory, can be systemic, including nervous, gastrointestinal and renal system involvement, respiratory failure, and death	Chills, fever, myalgia, nonpneumonic	High fever, headaches, body aches, respiratory symptoms, pneumonia, mortality rate over 10%	Fever, chills, headache, malaise, diffuse myalgia, dry cough, sore throat, nasal congestion, gastrointestinal, or conjunctival symptoms
Source	Contaminated A/C systems <sup>a</sup> , evaporative condensers, potable water	Contaminated A/C systems, potable water	Contaminated sewage	Person-to-person spread
Incubation period	2–10 d	1–2 d	2–10 d	1–3 d
Reported as a cause of SBS	Philadelphia, PA, 1976 (16)	Pontiac, MI, 1968 (17)	Hong Kong, 2003 (20)	King, WI, 1996 (18)
Number of cases in outbreak	111	144	187	68
Treatment	Erythromycin, rifampin	Erythromycin, rifampin	Palliative, vaccine under development	Vaccine available, anti-viral pharmaceuticals available
Comments	Decontamination by hyperchlorination and/or superheating of water			

<sup>a</sup>A/C—air conditioning

Table 3  
Types of Reactions Potentially Caused by Different Triggers

Insult	Pollutants	Chemicals	Fungal	Bacterial	Viral	Nonmold allergens
Toxic	+	+				
Allergic			+			+
Infectious			+	+	+	
Psychological	+	+	+			

NO<sub>2</sub> may play a role in asthma exacerbations. In a study of 16 subjects with mild asthma and allergies to birch pollen, those exposed to a combination of NO<sub>2</sub> and the allergen in a controlled allergen chamber environment experienced a greater drop in forced expiratory ventilation for 1 min compared to those exposed to ambient air and allergen (21). Unfortunately, although the results were statistically significant, the number of subjects evaluated in this study was small. A more recent prospective study of 114 children was conducted. The relationship between exposure to high levels of NO<sub>2</sub> was investigated in the context of severity of virally induced asthma exacerbations. In this study, high levels (>14 µg/m<sup>3</sup>) of NO<sub>2</sub> appeared to cause a higher severity of symptoms in virally induced asthma (22).

The indoor air contaminants that can cause allergies include animal products, insect products, and mold spores. Most allergens are either proteins or glycoproteins. Psychological effects may result from anxiety over the real or imagined health effects of an exposure. In some cases of SBS in which a small number of people complained about a building component, there was a mushroom effect, where many more people suddenly became sick. Although the incidence of psychosomatic effects is not known for these cases, almost anything, real or not, can lead to significant psychological disorders. Table 3 presents a breakdown of potential effects of different classes of indoor contaminants.

### **Sizes and Quantity of Indoor Air Contaminants**

The size of indoor contaminants varies greatly. In the case of gases, molecules are admixed with other gaseous substances in air, and thus are able to virtually penetrate wherever "air" can penetrate. In the case of particulate matter, penetration of the particle into the respiratory tract depends on the size of the particle. Mold spores range from 5 to over 100 µm in length, whereas most other indoor allergens are carried on particles that are between 2 and 15 µm in diameter. Pollen grains are generally between 10 and 40 µm in diameter. Smaller particles have the capability of deeper penetration into the respiratory tract. Most particles greater than 5 µm will not enter the lower respiratory tract, and their effects are a result of local nasal passage or conjunctival stimulation. There are two possible mechanisms by which larger particles can cause asthma: a) the particles carrying the allergenic protein are fragmented, leading to smaller actual particle sizes, and/or b) the particles act on tissues further up in the airway, but cellular and chemical factors generate a systemic allergic reaction leading to lower respiratory tract symptoms such as coughing and wheezing (23,24).

A study that collected and sized pollen grains provided support for the first mechanism. Although the intact pollen grains are too large to enter the lower respiratory tract, the study demonstrated that many of these particles are released in fragmented form—between 0.12 and 4.67 µm (25). It is possible that most mold spores in the air may be fragmented as

Table 4  
Common Allergenic Determinants of Indoor Allergens

Allergenic determinant	Derived from	Scientific name	MW (kd)	Size of airborne particles ( $\mu\text{m}$ )	Origin	Range of reported household levels <sup>a</sup>
Der p 1	Dust mite	<i>Dermatophagoides pteryonissinus</i>	24	>4.7, but some on smaller particles 1.1 to 4.7 (80), in some studies >10 (81)	Dust mite feces	1 to 22 $\mu\text{g/g}$ dust (82)
Der p 2	Dust mite	<i>D. pteryonissinus</i>	24			
Der f 1	Dust mite	<i>Dermatophagoides farinae</i>	25			
Der f 2	Dust mite	<i>D. farinae</i>	14			0.2 to 2.1 $\mu\text{g/g}$ dust (82)
Blo t 1	Dust mite	<i>Blomia tropicalis</i>	25 (83)			
Can f 1	Dog	<i>Canis familiaris</i>	27	Not known	Skin and saliva	0.06 to 860 $\mu\text{g/g}$ dust (84)
Fel d 1	Cat	<i>Felis domesticus</i>	35	5 (85)	Skin and saliva	0.016 to 28.0 $\mu\text{g/g}$ dust (84)
Bal g 1	Cockroach	<i>Blattella germanica</i>	20	>10	Feces (86)	0.2 to 15000 U/g dust (87–89)
Bla g 2	Cockroach	<i>B. germanica</i>	36			0.1 to 2000 U/g dust (88,90)
Mus m 1	Mouse	<i>Mus musc.</i>	19	5.8 (91)	Mouse urinary protein	0.9 to 4.6 $\mu\text{g/g}$ dust (92), 0 to 618 $\mu\text{g/g}$ dust (93)
Rat n 1	Rat	<i>Rattus norvegicus</i>	19	7 (81)	Rat urinary protein	Not known
Asp f 1	Mold	<i>Aspergillus fumigatus</i>	18 (94)	2.5–3 (conidia size)	Mitogillin family of cytotoxins	Absent to low levels, 1.8–3.6 $\text{ng/m}^3$ in air
Alt a 1	Mold	<i>Alternaria alternans</i>	28 (95)	12–50	Not known (spore size)	3.0 to 1000 U/g of dust (96)

<sup>a</sup>The range of observed concentrations varies tremendously depending on climate, building components and style, living habits, and so on.

well. The size of common allergic indoor air contaminants is shown in Table 4.

The conduits that are responsible for the interaction between site of exposure and location of a clinical response include the circulatory system and the nervous system. Factors involved in this interaction are the classical cellular and hormonal mediators of the acute

allergic reaction, including cytokines, neurotrophins, eosinophils, leukotrienes, T lymphocytes, adhesion molecules, antigen presenting cells, and components of the vascular epithelium and bone marrow (24). These reactions may be early-phase reactions occurring immediately or late-phase reactions occurring from 8 to 24 h after exposure.

## Infections and Indoor Air

Any virus or bacteria that is airborne has the potential to cause illness. There may be situations where small outbreaks can occur among occupants of a building or house. SARS is an example of a virus that is spread through the air.

Fungi can also cause infections. Examples of fungal-associated conditions that may be infectious in nature include allergic fungal sinusitis, acute bronchopulmonary aspergillosis (ABPA), humidifier fever, and a group of conditions known as hypersensitivity pneumonitis. Humidifier fever is characterized by flu-like symptoms, including tightness of the chest, dyspnea, chills, fever, and malaise. No specific organism has been causally linked to humidifier fever. Hypersensitivity pneumonitis is a group of conditions usually believed to be occupationally induced in individuals who are exposed to organic dust (26,27). Examples of hypersensitivity pneumonitis include farmer's lung, pigeon breeder's disease, and mushroom worker's disease. Symptoms are similar to humidifier fever, and although fungi such as *Microsporypha faenia* and *actinomyces* spp. have been blamed for hypersensitivity pneumonitis, no definitive causal relationship has been found (28).

The most common etiological agent of allergic fungal sinusitis and ABPA is *Aspergillus fumigatus*, although other fungi can cause similar conditions (29,30).

## Allergies and Indoor Air

Allergies and asthma are the most well-characterized illnesses that result from exposure to airborne particles. Allergic reactions can affect any part of the body that is exposed to foreign substances, including the eyes, lower and upper respiratory tracts, gastrointestinal tract, and skin. Allergies occur as a result of an IgE response to a foreign antigen, usually a protein or a glycoprotein. Allergies have been found to occur after exposure to pollen grains,

molds, and indoor allergens such as dust mite feces, cat and dog dander, and cockroach. Many of the allergenic determinants of indoor allergens have been defined. Table 4 presents a list of these determinants. Although most of the other types of effects of indoor air contaminants are often poorly characterized, allergic diseases are caused by a well-defined mechanism. Allergic diseases affect 10 to 20% of the population, and asthma affects between 5 and 15% of the population of the developed world.

### Nonmold Indoor Allergens

Although not all particulates are allergens, any protein has the potential to cause allergic disorders. Common outdoor allergens include grass, weed, and tree pollens. For indoor allergens, nonmold indoor allergens are of far greater importance than the molds. These allergens are ubiquitous and are responsible for the majority of allergy symptoms experienced by individuals as a result of exposure to components of indoor air. Prevalence data on nonmold allergens indicates that a far greater percentage of atopic individuals are sensitized to nonmold indoor allergens. Dust mites, cats, and dogs are the most common sensitizers. The allergens of these species are carried on particles up to 20  $\mu\text{m}$  in diameter. Particles will settle without air movement, and it is generally after disturbing the air that these allergens become airborne and exert their allergenic effects.

The most common of these allergens include Group 1 and Group 2 allergenic determinants of various dust mite species, including *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, and *Euroglyphus maynei*. Group 2 allergens are more resistant to extreme heat and pH changes. These proteins probably function as digestive enzymes and, therefore, are found in high concentrations in dust mite feces. Other common indoor allergens come from domestic animals such as cats and dogs, other pets such as rodents, and cockroach. The prevalence of sensitivities to each of these



allergens varies greatly among regions and among studies. In one study of inner-city asthmatics, the prevalence of dust mite sensitivity was 61% in adults and 49% in children. Incidentally, the prevalence of cockroach sensitivity was also very high in these individuals, starting at 41% in asthmatic adults and 42% in asthmatic children (31). The levels of these allergens in indoor air and household dust varies dramatically. Dust mite levels greater than 2 µg Der p 1 per gram of dust have been positively associated with an increased risk factor for asthma in genetically predisposed individuals (32). Significant reductions in dust mite levels (>95%) are necessary to observe clinical improvement in patients with allergic asthma who are sensitized to dust mite (33).

Cat and dog allergen levels also vary tremendously. Cat allergen is present in high concentrations in dust from homes in which no cat resides, and it is believed that the allergen can be transferred on the clothes of people visiting the home. Cockroach allergen also is very prevalent, with the highest levels existing in inner-city apartments in the northeastern portion of the United States, probably because of the heat and humidity in the summer. A Bla g 1 or 2 level of greater than 2 U/g of dust is associated with an increased relative risk for asthma (34). High cockroach allergen levels also correlate with high mouse allergen levels; other predictors of high mouse allergen levels include low maternal education and living in the city (35). Children between the ages 6 and 17 yr were more likely to develop mouse sensitivity if they were exposed to high levels of mouse allergen.

### **Molds**

Mold contamination is a frequent problem in homes and buildings. In fact, mold spores are ubiquitous and under normal circumstances, originate outdoors. The level of mold spores outdoors varies with the macro- and microclimate of the local environment. Areas

with high relative humidity and cool temperatures favor the growth and dissemination of molds, whereas dry climates tend to have lower levels of mold spores. Daily or even hourly variations in rainfall affect the level of mold spores outdoors. Under normal circumstances, the indoor mold level should be no higher than that of outdoors. However, the presence of mold spores indoors does not necessarily lead to ill health. In some climates, mold counts are always very high. If a high level of indoor exposure is discovered, this is indicative of an indoor environment that facilitates the growth of spores, such as a water leak, standing water, or high relative humidity. Molds grow on various types of substrates (both living and nonliving), including rotting vegetables, decaying wood and other vegetation, bread and cheese, houseplants, and cellulose-rich materials such as damp paper products, wood, cardboard, and wall boards.

The allergenic determinants of most molds have not been clearly defined, and it is likely that there is a great deal of homology among different mold genera and species, leading to a high degree of clinical crossreactivity among molds. Two antigenic determinants, Asp f 1 and Alt a 1, have been characterized for *A. fumigatus* and *Alternaria alternans*, respectively. Some molds have been found to release gaseous substances, which are frequently referred to as mycotoxins. The role of mycotoxins—or lack thereof—in human health is discussed later. Allergies and allergic asthma are the only scientifically proven health effects from exposure to molds. The prevalence of mold sensitivity among allergic individuals has been estimated to be between 11 and 30% (36–38).

### **The Biological and Clinical Effect of Mycotoxins**

Mycotoxins include several different chemicals released by mold spores. Examples of fungi that produce mycotoxins include *Fusarium*, *Stachybotrys*, *Acremonium*, *Penicillium*

and *Aspergillus* (39). The term "mycotoxin" carries the implication that these chemicals are toxic to humans, which may or may not be true. Mycotoxins include the trichothecenes, aflatoxins, zeralanone, secolonic D, and verrucaric acid, as well as the satratoxins.

*Stachybotrys chartarum* first surfaced as a potential health problem in the 1930s, when it was associated with an epidemic of rhinitis, stomatitis, and death in horses. *S. chartarum* (commonly known as Black Mold) frequently is found in indoor environments where there is increased moisture, such as in with water leaks.

More recently, there was a report of an association between exposure to the mycotoxins of *Stachybotrys* and infant pulmonary hemorrhage (40). One of the earlier reports occurred in the Cleveland, Ohio area in 1994, where 10 infants were diagnosed to have infant pulmonary hemorrhage (41). Five had recurrent hemorrhage after discharge from the hospital. Initially, mycotoxins released by *S. chartarum* were believed to be responsible. A subsequent reassessment by the Centers for Disease Control found that the association was weak and that no conclusions could be made regarding infant pulmonary hemorrhage and exposure to mold (38,42). Problems were identified in the earlier reports, including inconsistent data collection, nonuniform definitions of water damage, and fungal exposure. In some cases, evaluation of the exposure to molds did not correspond to the time of disease onset. There also was little reproducibility from previous studies of exposure to *Stachybotrys*. Additionally, although the presence of *Stachybotrys* is widespread, infant pulmonary hemorrhage is rare; thus, making a cause-and-effect relationship difficult to establish.

Mycotoxins may exert their effects either by inhalation or ingestion. Satratoxin is a mycotoxin present in *Stachybotrys* spores in the outer plasmalemma and inner wall layer of the phialide-apex walls (43). The amount of mycotoxin present on a mold spore is about  $10^{-4}$  to

$10^{-6}$  g of satratoxin per mold spore. Although mycotoxins have been studied in vitro and have been demonstrated to have adverse effects at the cellular level as well as immunosuppressive properties, the amount of mycotoxin and the corresponding quantity of mold spores that is necessary to cause clinical effects is approx  $2 \times 10^6$  spores per cubic meter. A concentration of this magnitude in indoor air is not realistically achievable in most of the cases in which mold toxicity is blamed for illness.

The cellular and immunosuppressive properties of mycotoxins have been extensively studied (Table 5). When cultured in the presence of low levels of satratoxin H, isosatratoxin F, roridin A, and verrucaric acid, EL-4 thymoma cells were found to produce elevated levels of interleukin (IL)-2, as analyzed by enzyme-linked immunosorbent assay. IL-2 production was suppressed at high concentrations of these mycotoxins (44). There also was a cytotoxic effect that was mycotoxin dose-dependent. Other cellular effects of mycotoxins include inhibition of protein synthesis and DNA synthesis (45–47), bone marrow suppression in mice (48), and induction of apoptosis of human leukaemia cells (49). Mycotoxins have also been shown to have effects on production of lung surfactant by rabbit type II alveolar cells (50). However, there have not been any placebo-controlled, double-blind studies showing any direct evidence of adverse effects on lung function in humans exposed to mycotoxins. Moreover, with the exception of allergies and asthma, there are no proven, long-term, ill effects from exposure to mold (51).

### **Environmental Avoidance Is a Cornerstone of Asthma and Allergy Management**

#### *Avoidance in the Treatment and Management of Sensitized Patients*

The concept of avoiding allergens that may cause allergic exacerbations has been utilized in the treatment of allergies and asthma since the 17th century. Numerous avoidance tech-

Table 5  
Trichothecenes

Trichothecenes	Deoxynivalenol, diacetoxyscirpenol, nivalenol, satratoxins, T-2 toxin, trichoverrins, trichoverrols, verrucarins, verrucarol
Cellular effects	Inhibition of DNA synthesis, inhibition of protein synthesis, early apoptosis (49,97)
Immunosuppressive effects	Depressed T- and B-cell activity, changes in lymphocyte subset balance (97), inhibition of NK cell activity (98)
Proven human health effects	None

NK, natural killer

niques have been proposed to counter the effects of allergens that are derived from dust mites, cats, dogs, cockroach, and molds, and the data support avoidance as a general rule for individuals who are already sensitized to allergens.

The efficacy of allergen avoidance was evidenced by pollen chamber experiments (52) in which subjects who were exposed to higher levels of allergen developed allergy symptoms (53). Specific studies of dust mite have also demonstrated that exposure has an adverse effect on bronchial hyperresponsiveness (54). Avoidance measures are not always successful, as demonstrated by recent studies that used mattress and pillow encasings to reduce dust mite exposure and improve patient symptomatology (55). In this case, only one avoidance measure was studied, and this was actually ineffective in reducing exposure. Dust mite exposure can be reduced when a total management plan of avoidance is used (56,57). Additionally, different allergens require different avoidance measures. Avoidance measures should be specifically targeted to remedy actual detectable high levels of environmental allergens. Therefore, evaluation of the environment is an important component of an allergy or asthma management plan. Additional information regarding a patient's individual atopic risk or sensitization status can also help dictate implementation of avoidance measures. A sample avoidance protocol for indoor allergens is shown in Fig. 1.

### *Avoidance in the Prevention of Allergic Sensitization*

Before a patient reacts to allergen, he or she must first be sensitized. Early avoidance of food and environmental allergens has been studied as a means to decrease the risk of developing allergic rhinitis, asthma, or atopic dermatitis (58). Studies have shown that exclusive breastfeeding with delayed introduction of solid foods and formula can delay the onset of dust mite sensitization (59). As to animal allergens, cat exposure at an early age was associated with an increased risk of sensitization to cat allergen, whereas dog exposure had no effect on sensitization to dog allergen. Cat and dog ownership was associated with a reduced risk of sensitization to other allergens (60). In fact, there may be a bell-shaped relationship between sensitization risk for cat allergen and cat exposure. In this case, moderate exposure to cat allergen may pose the greatest risk for sensitization. In the case of dust mite and cockroach allergen, early exposure is associated with higher risks of sensitization to dust mite and cockroach, respectively. It is clear that although there are numerous studies attempting to identify factors related to exposure risk, there are significant obstacles to such studies. Limitations and obstacles include the elimination of confounding variables, accurate measurement of exposure levels, identification of similar and different characteristics of subjects, validity, and definition of parameters such as "ownership," and so forth. It is likely that risk of allergic sensitization may be spe-

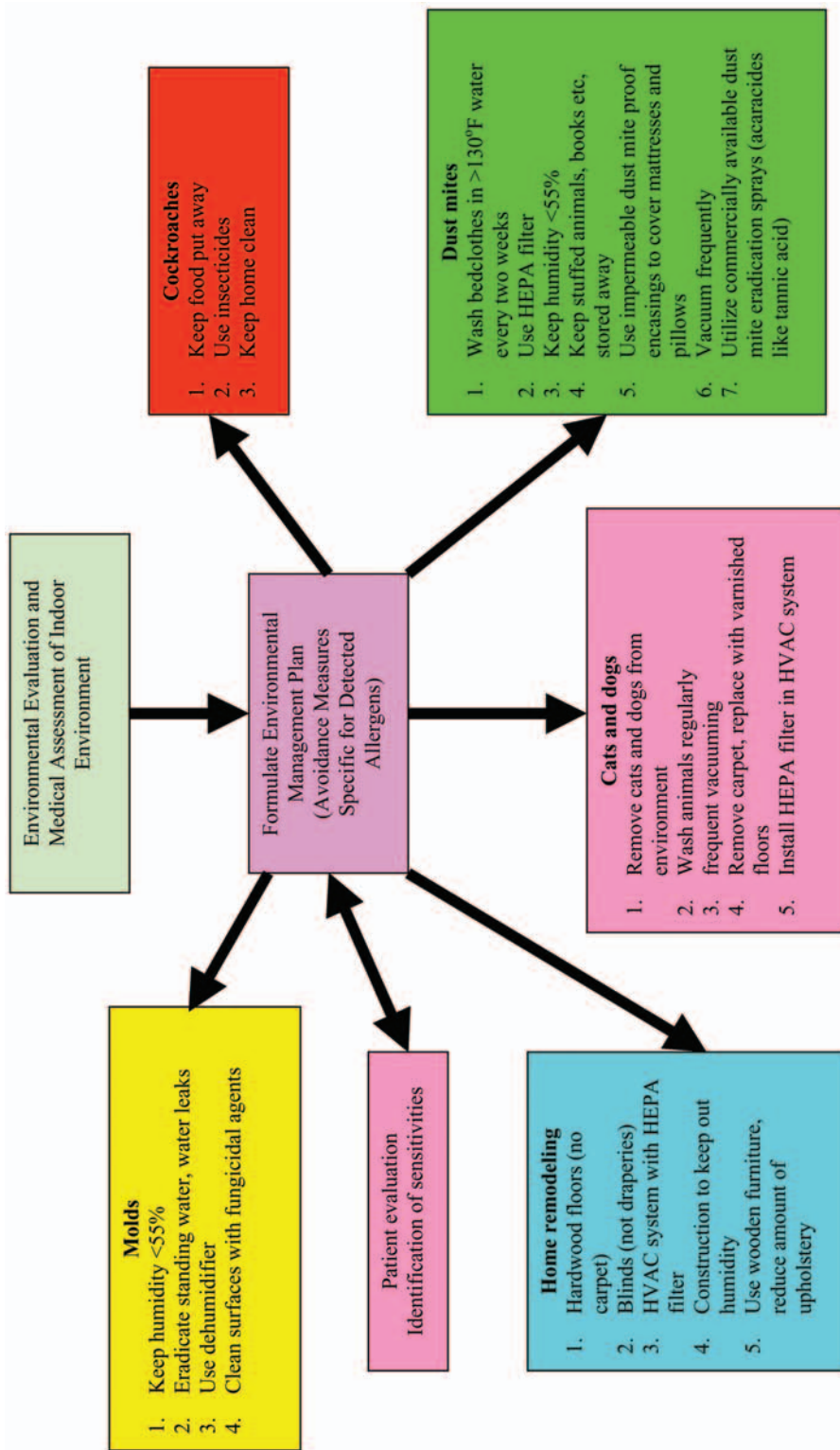


Fig. 1. An avoidance strategy for indoor allergens.

cific to the individual allergen studied and may also be dependent on as yet undefined host phenotypes. Currently, there is sufficient data to continue recommendations that high-risk individuals practice avoidance as a means to primary prevention of atopy.

### **Assessment of the Environment**

It is the current standard of care to investigate and identify the allergens that may cause symptoms in a given individual. This generally is done using skin testing or radioallergo-sorbent testing. Once the sensitivities of a patient have been determined, the primary advice to the patient is to avoid exposure to those particular allergens. However, this advice is given in general fashion, without ever truly knowing what the patient may have been exposed to. Additional treatment may be provided in the form of medications (mainly nonsedating antihistamines and intranasal corticosteroids) and immunotherapy. A missing link in the management of allergies and asthma has been the evaluation and identification of allergens in the patient's environment. Outdoor daily or weekly pollen counts now are reported in the media in selected cities and towns, but these data are based on a single sampling, and variability in counts exists depending on weather, time of day, and surrounding vegetation. Similarly, the levels of allergens in the indoor environment depend on the building construction, local weather, living conditions, occupant habits, and so on. Although there are currently no standards or uniform programs for testing indoor environments, indoor allergen measurements would be a useful adjunct in the treatment of patients with allergies or asthma, because one could correlate exposure with sensitivity and clinical symptoms. Achievement of the goal of reducing exposure then could be matched with the patient's specific sensitivities as well as his or her ongoing symptom monitoring. In the case of asthma, less exposure may lead to decreased inflammation, leading to a decrease in long-term airway remodeling.

Table 6  
Economic Parameters and Allergic Diseases

Country	GDP (per capita) <sup>a</sup>	Prevalence of asthma (99)
Algeria	1691	3.9
Australia	20,462	14.7
Belgium	23,981	6.0
Canada	23,484	14.1
Chile	4161	5.1
China	966	2.1
Ethiopia	91	3.1
France	24,037	6.8
Germany	24,209	6.9
Indonesia	839	1.1
Iran	1604	5.5
Israel	16,094	9.0
Italy	20,554	4.5
Japan	31,433	6.7
Korea	6681	3.9
Malaysia	4194	4.8
Mexico	6446	3.3
Morocco	1271	3.8
New Zealand	14,949	15.1
Poland	4896	4.1
Romania	1911	1.5
Russia	2403	2.2
Singapore	21,429	4.9
Spain	16,457	5.7
Sweden	26,966	6.5
Thailand	2019	6.5
United States	36731	10.9

<sup>a</sup>Data from 2002, <http://www.studentsoftheworld.info/infopays/rank/PIBH2.html>.

### **What Does the Hygiene Hypothesis Tell Us About Indoor Air Quality?**

The prevalence of allergies and asthma has sharply increased in the developed world. In February 2004, the Global Initiative for Asthma published its "Global Burden of Asthma." Asthma prevalence has a positive correlation with "national wealth." In poorer countries, the prevalence generally remains low, as shown in Table 6. One of the more popular recent theories suggested to explain this trend is the increasingly sanitized living conditions in "richer" countries; this has been termed "the hygiene hypothesis," and was first proposed by Strachan

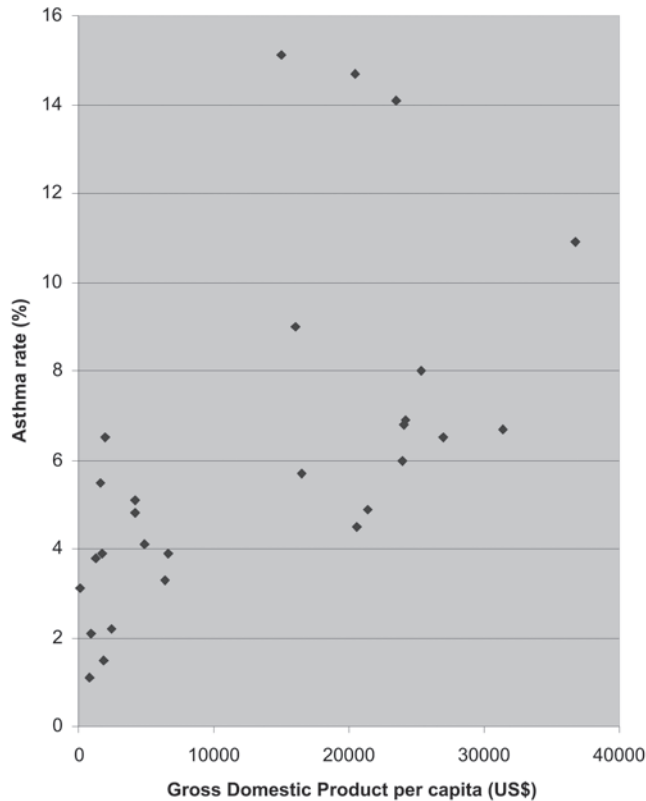


Fig. 2. Asthma rates vs gross domestic product per capita (US\$).

in 1989 (61). Figure 2 shows the relationship between asthma prevalence and gross domestic product (GDP) per capita for select countries.

Although the relationship is not universal for all countries, there is generally an inverse relationship between GDP per capita and the prevalence of asthma. The hygiene hypothesis suggests that as society becomes more affluent or advanced, it is able to curtail exposure to the many infectious pathogens that plagued our ancestors. In less advanced societies, these pathogens include parasitic, viral, and bacterial infections. Bacteria can also produce endotoxins that may steer the development of our innate immune system to a direction where protection against infections plays the major role. The potential result of this clonal selection may explain the observations in European farm communities (62). In the absence of envi-

ronmental microbial stimuli, the immune system develops in a direction that favors and triggers the expression of atopy.

It is clear that the development of allergies or atopy is a multifactorial event and that two of the primary factors affect atopy: (a) an individual's own genetic makeup and (b) how the environment modulates an individual's genetics. Currently, the relative importance of genetics vs environment remains unknown. Atopy is not inherited in Mendelian fashion; however, the strong genetic influence is supported by the significant family histories of atopy that are elicited during history and physicals of patients. In fact, when one parent is atopic, there is a 48% chance that an offspring will be atopic. This rate rises to about 70% when both parents are atopic. As we learn more about the genetics of asthma, it may be possible to determine which individuals' will be affected by the different environmental stimuli that they might encounter after birth.

### ***Environmental Modulation of Atopy***

The environmental triggers that may stimulate the development of atopy in a genetically susceptible individual comprise a complex set of seemingly unrelated entities. Allergens lead to the development of allergic sensitization by stimulating the production of IgE antibodies to that allergen. This is similar to the scenario by which vaccination to an infectious agent generates a response that includes, but is not limited to, the production of IgG for protection against subsequent exposures. However, there may also be immunological characteristics of a genetically susceptible individual that predispose certain individuals to release either Th1 or Th2 cytokines, leading to an atopic state. Initially, it was believed that certain environmental factors encountered by an individual early in life affected the balance in the development of Th1 and Th2 responses. The prenatal or neonatal immune system is innately and predominantly driven by Th2. A predominantly Th1-based immune system develops as a result

of microbial stimuli to fulfill the need of the host to protect itself against such stimuli. In the absence of this microbial pressure, the immune system fails to switch from a Th2-driven system to a balanced Th1–Th2 system. Atopy is the clinical result of a predominantly Th2-based immune system.

Other environmental triggers that may modulate the development of atopy include endotoxin, environmental pollutants, and infectious agents. Pre- and postnatal exposure to ETS has been observed to increase the risk of atopy. In a prospective birth cohort study of 342 neonates, the effect of exposure to ETS was studied; the endpoint was the development of seroatopy to food allergens and indoor and outdoor inhalant allergens by age 3. It was found that ETS exposure led to a 2.2- to 2.3-fold increased risk of developing food allergies by age 3 (63). This effect was not observed for inhalant allergens, in which case, primary risk factors were family history of atopy and cat and dog exposure levels. The authors concluded that ETS exposure had an adjuvant effect on the development of allergies to which neonates and infants were mainly exposed—namely foods.

A study of 1884 full-term, healthy neonates examined the incidence of atopic eczema and respiratory symptoms as a function of endotoxin exposure. The authors discovered that there was a significant decrease in the risk of atopic eczema in neonates who were exposed to higher concentrations of endotoxin. Coincidentally, there was an increased risk of wheezing and nonspecific respiratory infections in those neonates who were exposed to higher levels of endotoxin (64).

A study of 441 children enrolled at birth and followed till ages 6 to 7 yr showed that the incidence of atopy, seroatopy, or allergic sensitization at age 6 to 7 yr decreased with the number of times that the neonates developed fever in the first year of life. This study supported the idea that increasing infections at an early age may inhibit the development of atopy

(65). In a German study of over 1300 children studied from birth to age 7 yr, the frequency of runny noses before age 1 yr appeared to be inversely associated with the frequency of asthma, although there was a positive correlation between lower respiratory virus infections such as respiratory syncytial virus (RSV) and the incidence of asthma, bronchial hyperresponsiveness, and wheezing at a later age (66). Other studies have confirmed an association between RSV infection in infancy and subsequent wheezing.

What do endotoxin and infections have to do with exposure to indoor air allergens? It has been observed that exposure to farm stables and farm animals has an apparently protective effect on the development of atopy (62). This type of environment also has a high level of endotoxin. In fact, endotoxin is ubiquitous in nature. It is a cell wall component of Gram-negative bacteria that carries with it immunostimulatory activity.

Immunostimulatory activities of endotoxin are depicted in Fig. 3. In atopic individuals, endotoxin can be a trigger for allergic symptoms. However, it also appears to have a preventive effect on the development of allergies early in life. The presence of cats and dogs also has been associated with high endotoxin levels (67–69). High levels of endotoxin appear to correlate with high levels of Th1 cytokines, IL-12, interferon (IFN)- $\gamma$ , and high levels of Th1 cytokine-producing T cells (70). IL-12 is a cytokine that is produced by antigen presenting cells and helps stimulate the differentiation of T cells into Th1 cells (71).

But does that mean that cat and dog ownership in affluent urban environments has the same protective effect on the development of atopy as living on a farm? The answer is probably no. Clearly, the hygiene hypothesis does not completely explain the reason that some individuals become sensitized to allergens and others do not. It may be that the entire environment must be considered when studying the immunomodulatory effects of such envi-

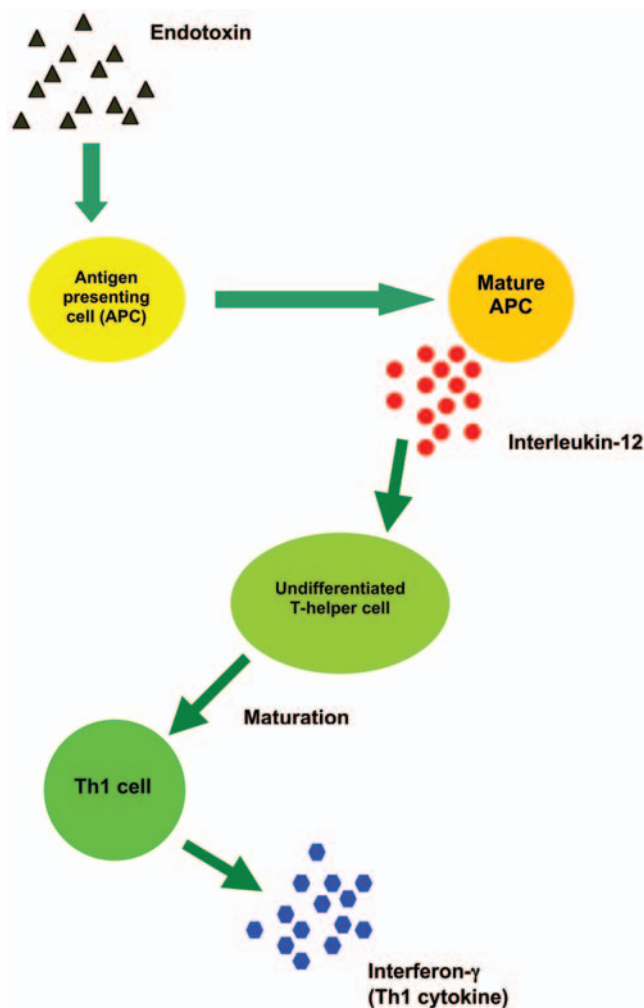


Fig. 3. Immunostimulatory effects of endotoxin.

ronments on allergic sensitization. Table 7 illustrates some of the environmental agents, including tobacco smoke, viruses, and allergens, that may affect the development of atopy.

Sorting out the complete story of allergen sensitivity is not an easy task. The complexity of any living environment leads to numerous confounding variables that must be excluded when studying the effect of any single factor on sensitization rates. Differences in host factors also play a role in the extent to which environment can affect the development of atopy. Additionally, explaining the development of atopy merely on the basis of a Th1–Th2 immune system balance is clearly an oversimplification. The role of regulatory T cells must be accounted

for, and the effect relationships among genes, receptors, infectious agents, and environmental allergens must be considered.

Recently, Rowe and colleagues (72) showed that risk factors for the early development of atopy in high-risk infants included a high level of IFN- $\gamma$  production by CD8<sup>+</sup>T cells. Others have found that an attenuation of the IFN- $\gamma$  expression in CD4<sup>+</sup> T cells is associated with high atopic risk (73,74). Actually, both conditions may contribute to atopy risk, and there may be some aspects of a predominantly Th1 cell clonal system that may positively contribute to an increased risk of atopy.

### Genetics vs the Environment

There is no clear answer to the question regarding relative importance of genetic and environmental factors in the development of atopy. Certainly, the way an individual reacts to exposure is unique to that individual. Identifying phenotype expression of as yet undefined “asthma or allergy genes” would help to predetermine the potential for sensitization to allergens. One frequently discussed issue deals with whether or not exposure to one or more allergens increases the likelihood of sensitization to other allergens. In early childhood, this seems to be true. A Swedish study showed that exposure to cat allergen early in life protected against asthma and birch sensitivity (75). In an adult study, current cat ownership in adults seemed to protect against cat and dog allergen sensitivity but not against dust mite or pollen sensitization (76).

An interesting association has been observed between hepatitis A and atopy. Hepatitis A virus (HAV) is epidemiologically associated with a decreased risk of developing atopy. A novel T-cell immunoglobulin domain–mucin domain gene family, designated the *TIM* gene family, was observed to encode transmembrane proteins expressed by CD4 T cells (77). The *TIM* family of genes was shown to regulate development of atopy. Particularly, the variants of the *TIM-1* gene were shown to pro-



Table 7  
Cleanliness and the Development of Atopy

Early exposure	Type of agent	Atopic correlation	Reference	Comments
Ascaris lumbricoides	Infectious	–	100	Patients with high total serum IgE or anti-IgG4 antibodies to <i>A. lumbricoides</i> had decreased allergen skin test reactivity in school age children
<i>Campylobacter jejuni</i>	Infectious	+	101	In contrast to markers of poor hygiene, bacterial pathogens may lead to increased risk for atopy
Cat	Allergenic	±	60,70	May influence sensitization to other allergens
<i>Clostridium difficile</i>	Infectious	+	101,102	<i>C. difficile</i> IgG levels have positive correlation with atopy
Cockroach	Allergenic	+	87	Abatement of cockroach allergen possible
Dog	Allergenic	?	67,70,103	Data is equivocal
Dust mite	Allergenic	–	103,104	May influence sensitization to other allergens
Endotoxin	Infectious	±	70	Increased wheeze early in life, but decreasing incidence later
<i>Helicobacter pylori</i>	Infectious	–	101	Orofecal pathogen
Hepatitis A	Infectious	–	101	Previous hepatitis A infection may protect against atopy in some patients
Herpes virus	Infectious	None	105,106	No increased risk or protective effects of herpes virus exposure on atopy
Respiratory syncytial virus	Infectious	+	107–111	RSV infection may stimulate Th2 cytokine responses
Shistosoma	Infectious	–	112	
Tobacco smoke	Pollutant/ toxin	+	63	Includes prenatal exposure
<i>Toxoplasmosis gondii</i>	Infectious	–	101	Orofecal pathogen
<i>Yersinia enterocolitica</i>	Infectious	+	101	In contrast to markers of poor hygiene, bacterial pathogens may lead to increased risk for atopy

- + signifies a positive correlation (i.e. exposure leads to increased risk of sensitization);  
 – signifies an inverse correlation (i.e. exposure leads to decreased risk of sensitization);  
 ? Data is not consistent

fect against atopy in humans but only in humans who had been previously infected with HAV. The *TIM-1* gene product also functions as the cellular receptor for HAV, so it is proposed that the HAV may activate T cells through its interaction with the receptor, thereby facilitating differentiation to a predominantly Th2-based immune system. In the future, our understanding of the interaction between asthma genes and exposure to viral infections and the effect on the development of atopy may play an important role in determining intervention and management strategies for the prevention and treatment of asthma, respectively.

## The Financial Implications of a Comprehensive Evaluation and Avoidance Plan

A comprehensive allergy or asthma management plan that incorporates evaluation of the patient; evaluation of the environment; development of asthma or allergy action plans; a comprehensive avoidance plan; the proper use of medications; and the use of adjunct supportive modes of therapy such as immunotherapy, peak flow monitoring, and regular spirometry testing will likely result in a significant decrease in health care costs (Fig. 4). Patient

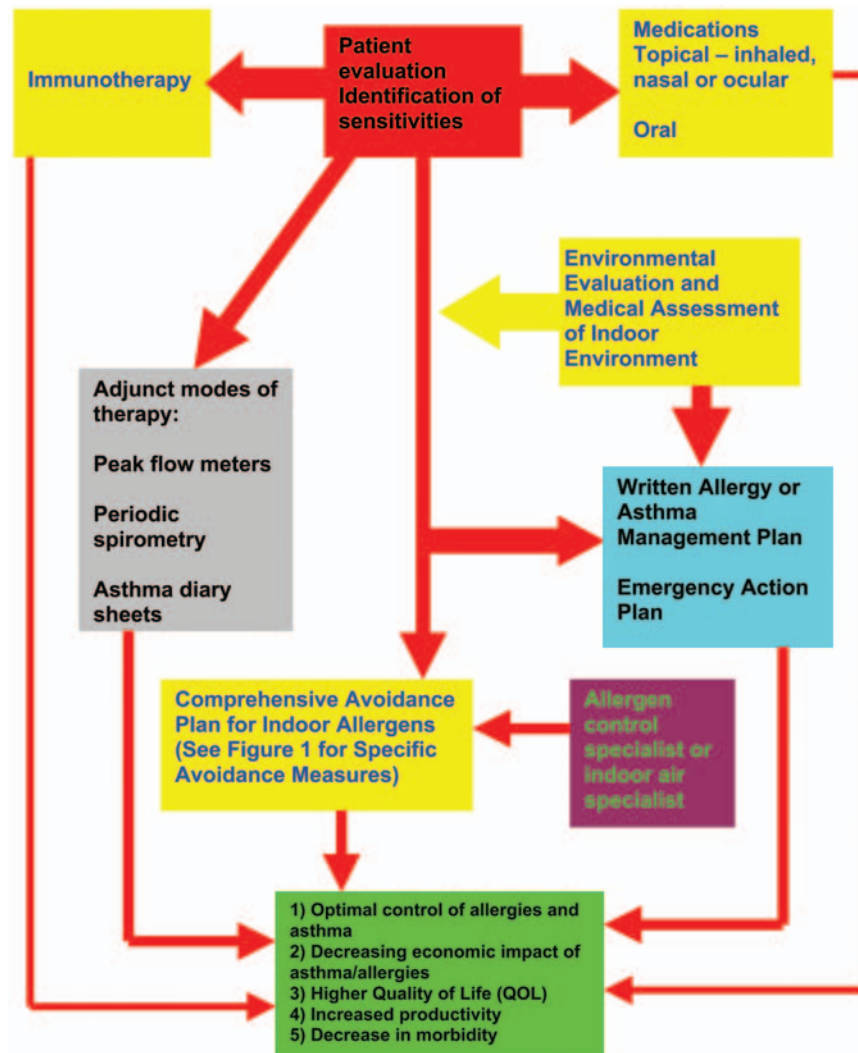


Fig. 4. A comprehensive patient allergy and asthma management plan.

compliance with avoidance measures has been shown to improve with the use of a medical indoor environment counselor, leading to a significantly better success rate at lowering allergen levels in the home (78). Decreasing exposure leads to less inflammation of the airway epithelium, which leads to improved long-term outcomes. Other parameters that may be indirectly affected by the use of a comprehensive asthma or allergy action plan include work or school productivity, number of work days or school days lost, side effects of medications, morbidity or mortality as a result of immunotherapy, or complications from comorbid conditions, such as those mentioned previously.

## Recommendations and Conclusions

Although indoor air quality has been a compelling environmental issue in the past two decades, a huge gap still exists in our knowledge regarding the extent of adverse effects on human health for many of the known components of indoor air. Therefore, exposure standards have been difficult to establish, and the regulation of indoor air and building components has been fraught with confusion and inaccuracies (4). The past issues played out in courtrooms and the media first concerning SBS and then mold toxicosis has clearly placed a blemish on the science of indoor air.

Our knowledge of the genetics and pathology of asthma and allergies has increased greatly in the past 30 yr, and there is no evidence that suggests a change in our recommendations regarding avoidance to people with allergies. Avoidance measures remain an important facet to the treatment of allergies and asthma. The recommendations for patients already sensitized, in terms of relief of symptoms and improvement of pulmonary function in asthmatic patients, is to avoid contact with allergens to which the patient is already sensitized. The levels of allergens that may cause worsening of symptoms in most patients with asthma is known for the nonmold indoor allergens, including dust mite, cat, dog, cockroach, and so forth. The level of mold allergens that may lead to worsening asthma or allergy symptoms depends on the individual's atopic predisposition. When treating a patient for allergic disorders such as allergies and asthma, it is not just the patient that must be evaluated but also his or her environment. Environmental evaluation is important in matching an individual's sensitivity with their environmental exposures. In the future, this type of "targeted" approach to the treatment of allergies and asthma will contribute to a better and more customized plan of management for the patient with allergies or asthma.

Finally, regarding the nonallergic adverse health effects of molds, the role of mycotoxins in human health has been extensively studied. The health effects of "mycotoxins" have not been proven, and although there are studies demonstrating in vitro cellular and immunosuppressive effects of various mycotoxins, studies have been unable to demonstrate any evidence for toxic, neoplastic, or neurological effects of mycotoxins.

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