

Building-related illnesses

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As we develop a better understanding of the adverse effects of the indoor environment on health, the pathophysiologic mechanisms contributing illnesses caused by indoor environmental factors will become more clearly defined. The term building-related illness applies to those adverse health effects for which we have a well-defined link between environmental agents in a specific building and the resultant health disorders. This class of illnesses frequently involves the skin and respiratory tract because of the ease with which indoor environmental contaminants come in contact with these tissues. Agents that cause building-related illnesses generally induce illness by one of four mechanisms: (1) immunologic, (2) infectious, (3) toxic, or (4) irritant. Some agents may work through more than one mechanism. This article discusses the different mechanisms that cause building-related illness, the different types of this class of illnesses, and the evidence validating the connection between the environmental agents and the diseases they cause. (J ALLERGY CLIN IMMUNOL 1994;94:351-62.)

Key words: Building-related illness, HVAC, irritants, ventilation, indoor air, contamination

The terminology used to describe illnesses caused by building environmental factors can cause confusion. Building-associated illness refers to any illness caused by indoor environmental factors. We divide building-associated illness into two categories: sick building syndrome (SBS) and building-related illness (BRI). Excluded from these categories are illnesses that have a long latency period (e.g., lung cancer caused by radon exposure). SBS describes a complex of vague, predominantly subjective complaints consisting of neurobehavioral symptoms such as memory loss, headache, depression, dizziness, and respiratory complaints such as chest tightness, coughing, and shortness of breath. Burning eyes, nose, throat, and sinuses are symptoms of mucous membrane irritation that are frequently associated with

Abbreviations used

BRI:	Building-related illness
HF:	Humidifier fever
HP:	Hypersensitivity pneumonitis
HVAC:	Heating, ventilation, and air-conditioning
SBS:	Sick building syndrome

“sick” building complaints. Itching and rashes may occur. However, the exact pathophysiologic mechanisms explaining how environmental factors cause “sick” building symptoms remain elusive. Studies, both in the United States and in Europe, conducted over the past 20 years indicated that many of these buildings shared a common problem of inadequate ventilation. Yet, data to support the hypothesis that inadequate ventilation in the absence of identifiable pathogenic levels of contaminants causes human illness remain sparse. Even more importantly, it has been difficult to demonstrate, in properly designed studies, objective evidence of cause and effect between the ubiquitous chemical compounds

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found in all indoor environments and many of the neurobehavioral symptoms reportedly associated with SBS. However, a few well-designed studies suggest that certain functions, such as short-term memory, mental efficiency, and visuospatial functioning, may be adversely affected by volatile organic compounds.^{1, 2} The term *building-related illnesses* refers to reasonably well characterized human illnesses caused by indoor environmental factors that can be related to the clinical and laboratory findings in those building occupants with health complaints, based on *validated* principles of pathophysiology.

The development of outbreaks of SBS originated with the institution of building codes and regulations during and after the Middle East oil embargo of 1973. Construction of nonresidential buildings is regulated by federal and state codes to a much greater degree than for homes. Since the oil embargo of 1973, these regulations have mandated tighter, more energy-efficient buildings. As a result, in the past 20 years we have seen the replacement of naturally ventilated buildings by buildings with tight shells that are wholly or substantially dependent on mechanical ventilation. Heating, ventilation, and air-conditioning (HVAC) system design, structural design, and material finishes are specified to a large extent by architects, mechanical engineers, and interior designers to meet building codes and, at the same time, provide aesthetic appeal along with structural integrity. Unfortunately, building requirements necessary to promote the health of occupants of buildings have historically been neglected or given minimal attention. This switch to tighter buildings combined with a lack of knowledge of and attention to the potential adverse health effects of ineffective ventilation and indoor air contaminants has spawned a marked increase in the number of reports of human illnesses linked to the indoor environment.³⁻⁷ Although the documentation of certain types of BRIs predates the development of SBS, other BRIs, such as legionellosis, have been recognized only since the advent of this era of tight, mechanically ventilated buildings. The focus of this article is BRIs.

Some contaminants causing ill health have been identified within buildings for decades (e.g., paint containing lead and allergenic components of mold spores). Indoor environmental contaminants cause BRI through four major mechanisms: (1) immunologic, (2) infectious, (3) toxic, and (4) irritant. Because the agents causing BRI routinely coexist, it is not unusual to have two or more

mechanisms of disease operating simultaneously within a problem building. The challenge is to identify the cause or causes of the health complaints of those who allege that they have become ill as a result of a building they occupy and then locate the source or sources. The first step in solving the mystery is to develop a solid understanding of the mechanisms of BRIs and the offending agents associated with each mechanism. The purpose of this article is to provide such an understanding.

IMMUNOLOGIC MECHANISMS

Hypersensitivity pneumonitis and humidifier fever

Hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis presents in one of three forms: acute, insidious, and intermediate. The acute form is first seen as recurring episodes of pneumonia with pulmonary infiltrates associated with fever, myalgia, cough, chest tightness, and dyspnea. The insidious form develops over a period of years and initially is often asymptomatic. A clinical picture of progressive cough, dyspnea, and fatigue, gradually progressing to end-stage pulmonary fibrosis and restrictive lung disease, characterizes this form of HP. The least common form, that of an intermediate presentation, has characteristics of both acute and insidious HP. Antigens associated with fungi, bacteria, protozoa, insects, and possibly chemicals and endotoxin have been related causally to HP in buildings.⁸ The antigens that cause HP are typically associated with particles of 1 to 5 μm in diameter, the size that can enter the distal airways. Although large amounts of antigen are needed to sensitize susceptible individuals, only minute amounts are needed subsequently to produce exacerbations of HP. Consequently, those affected by this illness must be removed completely from environments that place them at risk of exposure to the relevant antigen. Nonspecific SBS symptoms are almost always present in others in the contaminated environment who are not affected with HP but are exposed to the antigen.⁹ Precipitins can be found in a relatively large number of those who do not have HP but are exposed to the antigen.¹⁰

The diagnosis of HP is made when history, results of physical examination, and laboratory findings are consistent with the disease. The latter consist of spirometry, arterial blood gases, lung volumes, diffusing capacity measurements, and if necessary, exercise challenge testing to demonstrate the characteristic restrictive defect. These

are often accompanied by serum precipitins (IgG) to the causative antigens, identified by the Ouchterlony technique or ELISA. However, 50% or more of exposed individuals who are free of symptoms may demonstrate precipitins. As a result, the presence of precipitins is only supportive and not diagnostic. Lung biopsy specimens may show granulomas and interstitial fibrosis, which can also be detected by a chest roentgenogram in the latter stages of this disease. High-resolution computed tomographic scans of the chest are more sensitive and significantly more expensive than routine chest roentgenography and may be useful if routine chest roentgenography fails to identify interstitial fibrosis. A positive inhalation challenge test response to the causative antigen would confirm the diagnosis, but this test should only be performed by those skilled in this technique because it can be dangerous.

Steroids can have a beneficial effect early in the disease before the development of pulmonary fibrosis. Because of the significant risk to those who have HP and are re-exposed to the antigen, the presence of *any* measurable antigen in the environment precludes a return of the affected person to the contaminated area. Contaminated reservoirs for the pathogenic organisms or antigens are usually associated with water or water damage (e.g., HVAC condenser pans, humidifier reservoirs, and water-damaged furnishings or building structures). In epidemic situations, if the source cannot be located, part or all of the building may need to be abandoned.

Humidifier fever (HF) is first seen as a respiratory flulike illness with fever, chills, myalgia, and malaise without the prominent pulmonary symptoms, such as cough, which are seen in cases of HP. Like HP, HF has been associated with indoor air contamination by biological agents. Although the exact pathophysiologic mechanisms remain unclear, some cases may be caused by inhaled endotoxin. This illness, which is not as severe as HP, develops within 4 to 8 hours of exposure (frequently on Mondays in the workplace), often resolves as the work week progresses, and recurs the following Monday. Abnormal chest roentgenograms are usually not a feature of HF, and attack rates in HF outbreaks (approximately 100% in some cases) are generally much higher than those for HP. Because of its similarity in expression to virus-induced respiratory "flu" and the relatively mild nature of HF, many affected individuals are misdiagnosed or do not even consult a physician. One of the most notable cases

occurred in the General Services Administration building in Washington, D.C., in 1986.¹¹ More than 80,000 mold spores per cubic foot were found in that building's indoor air, which is comparable to the degree of contamination in a chicken coup. Serum immunologic responses have been found to microbial antigens in those working in contaminated areas associated with HF, but the response to inhalation challenge with these antigens has been inconsistent.¹²⁻¹³ Inhalation challenge with endotoxin produced HF-like effects in approximately 50% of unexposed volunteers.¹⁴

The distinction between HP and HF, however, may not be simple. Chest roentgenograms showing pulmonary fibrosis can be found in isolated cases of HF but are usually normal in outbreaks.¹⁵ Also, outbreaks of *acute* HP have been associated with high attack rates and fewer abnormal chest roentgenograms.¹⁶ Finally, the phenomenon of a Monday peak of symptomatology in HF has been noted in the United Kingdom but not in the United States.¹⁷ Consequently, HP and HF may both belong to the group of organic dust toxic syndromes with somewhat varying mechanisms that cause variations in disease presentation.

Asthma

Asthma most recently has been defined as a lung disease with (1) airway obstruction that is reversible (but not completely so in some patients) either spontaneously or with treatment; (2) airway inflammation; and (3) airway hyperresponsiveness to a variety of stimuli.¹⁸ The inflammation found in the airways of patients with asthma is chronic. Thus by definition, for many patients with asthma, symptoms are chronic or recurrent. The prevalence of asthma in the United States has been estimated at 4.3% of the population,¹⁹ and approximately 15% of asthma is thought to be related to the workplace (i.e., occupational asthma²⁰). The prevalence of and mortality rates for all forms of asthma have increased by 29% between 1980 and 1987. In 1988, asthma-related health care expenditures exceeded \$4 billion in the United States alone.¹⁵ The reasons for the increasing morbidity and mortality rates, despite the availability of safer and more effective medications, are complex but likely include inadequate diagnosis, insufficient treatment (including patient education and prevention), and inadequate financial resources.

Irritants and allergens (immune mechanisms) constitute the major precipitating factors for

TABLE 1. Potential sources of selected indoor air contaminants

Contaminant	Sources	
VOCs	Perfumes	Paints, stains, varnishes, strippers
	Hairsprays	Wood preservatives
	Furniture polish	Dry cleaned cloths, moth repellants
	Cleaning solvents	Air fresheners
	Hobby and craft supplies	Stored fuels and automotive products
	Pesticides	Contaminated water
	Carpet dyes and fibers	Plastics
	Glues, adhesives, sealants	
Formaldehyde	Particleboard, interior grade plywood	Urea formaldehyde foam insulation
	Cabinetry, furniture	Carpet, fabrics
Pesticides	Insecticides (including termiticides)	Fungicides, disinfectants
	Rodenticides	Herbicides (from outdoor use)
Nitrogen dioxide	Improperly operating gas or oil furnace/hot water heater, fireplace, wood stove	Unvented gas heater/kerosene heater Tobacco products, gas cookstove Vehicle exhaust
Sulfur dioxide	Combustion of sulfur-containing fuels (primarily, kerosene heaters)	
RSP	Fireplace, woodstove	Tobacco products
	Unvented gas heater	Unvented kerosene heater
ETS	Tobacco products	
Biological contaminants	Carpets	Bacteria, fungi, protozoa
	Plants, animals, birds, human beings	Standing water
	Pillows, bedding, house dust	Humidifiers, evaporative coolers
	Wet or damp materials	

Modified from Introduction to indoor air quality—a self-paced learning module. Environmental Protection Agency, 1991. VOCs, Volatile organic compounds; RSP, respirable particulates; ETS, environmental tobacco smoke.

asthma in indoor environments (Table 1). Occasionally in occupational settings pharmacologic mechanisms may play a role (e.g., agents that block receptors, induce nonimmunologic degranulation of mast cells, or activate complement).²¹ Regardless of cause, asthma is first seen clinically with any of the following signs or symptoms: cough, dyspnea, chest tightness, fatigue, and wheezing. Because wheezing typically occurs only with more severe airway obstruction, recurring cough or chest tightness may be the only presenting sign or symptom. Characteristically, both allergic (IgE) and nonallergic stimuli will provoke asthma in the majority of patients with asthma. And both allergic and nonallergic stimuli abound in the indoor environment (Table 1). Consequently, indoor air quality in both residential and nonresidential environments can play a major role in the health and well-being of many patients with asthma.

Particularly in residences, antigens or allergens associated with biological contaminants such as molds, animal dander, and fecal particles of dust mites and cockroaches can sensitize genetically susceptible inhabitants. Even pollen can enter the

residential environment through open windows and doors and present a potential hazard. Re-exposure to allergens to which someone with asthma is already sensitized produces increased bronchospasm and lower airway inflammation. The resulting inflammation often results in a heightened sensitivity not only to that allergen but also to other unrelated allergens and irritants. Indoor irritants include cigarette smoke, airborne particulates from wood burning (e.g., in a stove or fireplace), sulfur dioxide, ozone, and volatile organic compounds that are emitted as gases from household and industrial cleaning products, furniture, carpets, and other finishing materials. Finally, upper and lower respiratory tract infections caused by indoor exposure to viruses and bacteria may precipitate acute asthma exacerbations and may contribute to the development of asthma.^{22, 23} Consequently, proactively minimizing allergenic, irritant, and infectious contaminants indoors should reduce the risk of asthma exacerbations and decrease nonspecific airway hyperresponsiveness in patients with asthma.²⁴ A proactive approach aimed at minimizing allergen exposure

indoors could also reduce the risk of developing asthma for genetically susceptible individuals.

Additional health risk factors exist in nonresidential indoor environments, especially those in which persons spend a significant amount of time, such as schools or workplaces. Commercial office buildings, schools, hospitals, and larger residential buildings (e.g., retirement homes, high-rise apartment buildings) generally depend on mechanical ventilation, HVAC systems, to provide fresh air and clean the large amount of indoor air that is recirculated. Poorly designed or maintained HVAC systems are common.²⁵ Typically, these buildings are designed with tight structural envelopes to conserve energy. Additional sources of potential environmental contamination abound in nonresidential buildings: office machinery (volatile organic compounds), manufacturing products and processes (volatile organic compounds, particulates, acids and bases, metals), nearby traffic or manufacturing plants (particulates, carbon oxides, nitrogen oxides, sulfur dioxide), and the HVAC system itself (microbial growth, fiberglass liners). These factors can all result in a concentrating effect of contaminants indoors, potentially exposing those with susceptible airways (e.g., patients with asthma, allergic rhinitis, or recurring sinusitis) to stimuli that may exacerbate their disease. Numerous books and articles have been written about the causes of occupational asthma, which is usually a BRI caused by various chemical and biological contaminants (Tables II and III).

The diagnosis of asthma is frequently made on the basis of the clinical presentation of wheezing or the signs and symptoms of less severe bronchospasm noted earlier. Complications of asthma such as recurring bronchitis, pneumonia, and even croup (in younger children) may also suggest its diagnosis. Pulmonary function testing, most frequently spirometry, can confirm the diagnosis. However, spirometry results are often normal in patients with mild and sometimes moderate asthma, because airway obstruction may be intermittent, occurring only when stimuli relevant for that individual are present. In these cases inhalation challenge testing for nonspecific bronchial hyperresponsiveness with methacholine, cold air, or histamine may be helpful. Challenge testing with specific allergens or irritants is usually only performed in a research setting or medical specialist's office for certain occupational situations. Skin testing or blood testing for specific IgE can be very helpful, because as many as 75% to 85%

of patients with asthma may have a significant allergic component to their illness.²⁶

The preferred treatment of asthma is to minimize exposure to stimuli that can trigger bronchospasm and increased inflammation. For this reason, the identification of all allergens and irritants relevant for the patient with asthma becomes a key to successful therapy. Because asthma triggers are ubiquitous (both outdoors and indoors) and because airway inflammation in the patient with asthma often persists for years, pharmacotherapy with antiinflammatory and bronchodilator agents may be required to permit an optimal quality of life. However, the availability of antiasthma drugs should never diminish the effort to minimize exposure to *relevant* etiologic agents. This is particularly applicable to some forms of occupational asthma, which can progress to fixed obstructive airway disease with continued exposure. Only recently has immunotherapy been clearly shown to provide significant benefit to some patients with an allergic component to their asthma.¹⁸ Expert diagnosis and the management of pharmacotherapy, relevant environmental stimuli, and, if indicated, immunotherapy can provide marked improvement in the quality of life and productivity of patients with asthma. Conversely, suboptimal management of asthma is likely to result in a diminished quality of life for the individual with asthma and contribute to the undesirable trend in asthma morbidity, mortality rates, and cost that we have been experiencing for the past decade.

Allergic rhinitis and conjunctivitis

Upper airway allergy, which affects 20% of the U.S. population,²⁷ often presents with any combination of nasal pruritus, obstruction, serous rhinorrhea, and sneezing. Other symptoms of upper airway inflammation include sinus headaches, recurring scratchy throat, hoarseness, cough, mouth breathing, and ear pain or plugging. If there is conjunctival involvement, complaints may include itching, watering, redness, or puffiness of the eyes. Physical examination findings often support these complaints but may be normal. The causes of upper airway inflammation are virtually identical to those in the lower airways. Like patients with asthma, many individuals with upper airway allergy find that both allergic and nonallergic stimuli can aggravate their symptoms. However, upper airway occupational disease has been reported much less frequently than occupational asthma. This probably relates to a lack of atten-

TABLE II. Causes of occupational asthma and disease mechanisms: Animal, plant, and fungal proteins

Agent	Occupational exposure	Mechanism		
		Ir	Im	Ph
Animal proteins				+
Dander excreta, secretions, serum	Animal breeders, laboratory workers, veterinarians, farmers, hunters, egg processors			
Cows, pigs, poultry, deer, mice, hamsters, rabbits, rats, bats, guinea pigs, eggs				
Insect dusts and parts				+
Meal worms, mites, silk filatures, bees, locusts, cockroaches, flies (caddis, screw-worm, sewer, fruit, river, house), moths, crickets, bee moth	Breeders, sewerage workers, beekeepers, laboratory workers, flight crews, entomologists, sericulturists			
Sea animals				+
Crab, shrimp, sea-squirt body fluid, marine sponge, hoya, shrimp meal, mother-of-pearl	Breeders, processors			
Vegetable materials				
Dusts, flours	Bakers, millers, textile mill workers, grain handlers			+
Wheat, rye, buckwheat,		?	?	?
Cotton dust		?	?	
Grain dust, soybeans, buckwheat, rice				
Fruits, seeds, leaves, pollen				
Green coffee, castor beans, roasted coffee, devil's tongue, baby breath, weeping fig, pollens, spices, tobacco, hops, tea	Processors, seamen, florists, agricultural workers, food processors, tobacco processors, brewery chemists, tea workers	+		+
Wood dusts, extracts				
Western red and eastern white cedar, California redwood, African maple, Kejaat, soapbark, mahogany, oak, African zebrawood, cedar of Lebanon, Iroko, Central American walnut	Carpenters, sawyers, cabinetmakers, construction workers	?	?	?
Enzymes				+
<i>Bacillus subtilis</i> , papain, bromelain, pepsin, hog trypsin, pancreatic extracts	Detergent and pharmaceutical manufacturers, food processors			
Gums				
Gum acacia and tragacanth	Printers, gum manufacturers			+
Fungal proteins				
Mushrooms	Soup processor, grower			+
<i>Alternaria</i> , <i>Aspergillus</i> spp.	Poultry vendor			?
Fungal amylase	Baker			?
<i>Verticillium albo-atrum</i>	Greenhouse worker			?

From Salvaggio J. Pathogenetic mechanisms in occupational hypersensitivity states. *Immunol Clin North Am* 1992;12:718. Ir, irritant; Im, immunologic; Ph, pharmacologic; +, yes; ?, maybe.

tion to and subsequent diagnosis of this problem because of its perceived lower morbidity rate compared with asthma, rather than a lower incidence; in addition, the affected worker may be more reluctant to report annoying symptoms, which are tolerable, rather than risk his or her job.²⁵

Diagnosis of allergic rhinitis and conjunctivitis

parallels the process for asthma. A compatible clinical history together with physical signs consistent with this disorder and appropriate laboratory findings (skin or blood testing, nasal smear of secretions, or cytologic evaluation for eosinophils and basophils, and occasionally nasal challenge) confirm the diagnosis. The mainstay of treatment for most patients with allergic rhinitis or conjunc-

TABLE III. Causes of occupational asthma and potential mechanisms: Pharmaceuticals, chemicals, metals, and miscellaneous agents

Agent	Occupational exposure	Mechanism		
		Ir	Im	Ph
Pharmaceuticals				
Antibiotics and related compounds including penicillins (G-APA, ampicillin, benzylpenicillin), phenylglycine, acid chloride, tetracycline, spiramycin, sulfonamides	Pharmaceutical workers		?	?
			+	
Other pharmaceuticals				
Psyllium	Pharmaceutical workers; nurses		+	
Glycyl compound (salbutamol intermediate)			?	
Methyldopa, amprolium, HCl			?	
Cimetidine			+	
Organic dyes and inks	Printers, nurses, ECG technicians			
Sterilizing agents				
Chloramine, sulphone chloramide, hexachlorophene	Abattoir, kitchen, and hospital workers		+	
Inorganic chemicals				
Metal fumes and salts including platinum, nickel, chromium, cobalt, aluminum fluoride, vanadium, zinc, stainless steel welding fumes	Chemical industry workers, metal refiners, platers, grinders, welders			+
				+
			?	?
			?	?
Ammonium persulfate	Hairdressers	?	?	?
Organic chemicals				
Acrylates (methacrylate and cyanoacrylates)	Chemical, electronic, plastic, rubber workers; photographers; beauticians; fur handlers		+	
Amines (diamines, ethanolamines, tetramines)				
Isocyanates (TDI, MDI, HDI, IPDI)	Manufacturers, painters, foamers	?	?	?
Anhydrides (phthalic, trimellitic, tetrachlorophthalic, himic)	Epoxy resin workers	+	+	
Adipic acid				
Azobisformamide				
Formaldehyde (including urea formaldehyde)	Plywood particle makers, biomedical workers, manufacturers	?		
Insecticide (organophosphates)				+
Plexiglass dust		?		
Polyvinyl chloride		?		
Styrene		?		

From Salvaggio J. Pathogenetic mechanisms in occupational hypersensitivity states. *Immunol Clin North Am* 1992;12:718-9.
Ir, Irritant; Im, immunologic; Ph, pharmacologic; +, yes; ?, maybe; TDI, toluene 2, 4-diisocyanate; HDI, hexamethylene diisocyanate.

tivitis currently consists of antihistamines, decongestants, topical steroids, and topical cromolyn. (Nedocromil is not currently approved for treating allergic rhinitis or conjunctivitis.) Relevant effective environmental control and immunotherapy, when appropriate, can contribute significantly to ameliorating the symptoms of disease and improving the quality of life.

Urticaria, eczema, and dermatitis

Certain types of rashes, typically those that are red and/or itchy, may be associated with exposure to indoor environmental contaminants. A cause can often be identified for acute urticaria. The causative factors of chronic urticaria (i.e., hives persisting for more than 6 weeks) remain indeterminate 80% or more of the time.⁴⁹ Contact urti-

TABLE IV. Examples of epidemic disease resulting from indoor aerosols

Disease	Source	Type of structure	Numbers affected	Percent attack rate	Reference numbers
Influenza	Infected person	Commercial aircraft	38	72	82
Inhalation anthrax	Wool, rags	Textile factory	50 (deaths)	ND	23, 24
Inhalation anthrax	Goat hair	Textile factory	5 (4 deaths)	ND	25
Ornithosis	Infected turkeys	Rendering plant	27	75	32, 33
Psittacosis	Infected turkeys	Abattoir	28	49*	83
Brucellosis	Slaughtered animals	Abattoir	387	1-11†	35
Brucellosis	Brucella laboratory	School building	45	ND	46
Byssinosis associated with gram-negative organisms	Cotton spinning	Cotton mill	86	33	38
Hemorrhagic fever	Animal excreta	Laboratory	113	ND	84
Tuberculosis	Infected person	U.S. naval vessel	140 TU tuberculin reactions 7 active cases	45.5 2.3*	47 ND
Measles	Infected person or ventilation system	Grade school	60 children	6.9	3, 48
Legionellosis (Pontiac fever)	Air-conditioning system	Public building	135	29-95†	53
Legionellosis	Ventilation system	Hospital	39	1.7-3.4†	54

From Moser MR, et al. Am J Epidemiol 1979;110:1-6.

ND, No data.

*Calculated.

†Depending on location or length of exposure.

caria may develop as a result of skin exposure to animal dander (e.g., petting a cat), to pollen (e.g., rolling in the grass), or to dust mite and mold antigens (e.g., young child crawling or playing on the floor). Inhaled allergens, such as pollens and molds, can also cause urticaria. Eczema and contact dermatitis often present with a combination of itching, scaling, erythema, papules, or vesicles. Chronic inflammation from poorly controlled dermatitis may result in hypopigmentation, hyperpigmentation, or lichenification.

Allergens in the environment can also cause atopic eczema or contact dermatitis, either through contact with the skin or through inhalation.^{30, 31} Indoor allergens causing eczema include animal dander, mold, dust mite, and even pollen, if present in sufficient concentrations indoors. Contact dermatitis can develop from exposure to numerous chemicals found indoors associated with house cleaning and finishing products, computers, printers, copying machines, and paper products. Another indoor source of contact allergens is clothing contaminated with the resin from *Rhus* plants (poison ivy, oak, and sumac). Irritant particulates, most notably mineral wool and fibrous glass (often released by damaged or im-

properly installed insulation) can cause a very pruritic papular rash on exposed areas of skin.¹⁵ If such material is deposited on the eye, it can cause severe conjunctivitis and corneal ulcerations. Occupational dermatitis, a significantly underdiagnosed disorder, develops after exposure to allergens or irritants in the workplace.³² Treatment consists of reducing or eliminating the exposure of the affected individual to all stimuli causing the dermatitis and frequently the use of topical or systemic steroids. Immunotherapy has not been found to be effective for these disorders, except possibly for reactions to *Rhus* species. However, side effects from this desensitization procedure occur so commonly that they make episodic treatment of exacerbations of the dermatitis preferable to long-term desensitization therapy with the extract.³³

Infections

Some of the same structural, mechanical, and ambient factors responsible for the development of irritant and immunologic BRIs have been linked to infectious epidemics (Table IV), particularly those associated with mechanical ventilation systems. *Legionella pneumophila*, a ubiquitous

gram-negative rod, can produce two patterns of illness: pneumonia and one resembling HF. A contaminant source associated with a building has almost always been identified in outbreaks of *L. pneumophila* pneumonia (legionnaires' disease), first identified at the Bellevue Stratford Hotel in Philadelphia in 1976 during a convention of legionnaires. The ensuing pneumonia, accompanied by gastrointestinal, kidney, or central nervous system disease, can be fatal (16% of the 182 cases in the Bellevue Stratford outbreak). The incubation period is 5 to 6 days, and only a relatively small number of those exposed to high concentrations of these organisms become ill. Certain characteristics distinguish those at increased risk for death: age greater than 50 years, chronic obstructive pulmonary disease, smoking, diabetes mellitus, alcohol abuse, immunosuppression, the need for intubation, and employment in a water tower.^{17, 34} *L. pneumophila* pneumonia is a relatively frequently underdiagnosed disease. An estimated 50,000 to 100,000 cases occur annually, representing 1% to 27% of community-acquired pneumonias and approximately 10,000 deaths. The *Legionella* bacteria is transmitted almost exclusively by the airborne route from contaminated water sources, such as cooling towers, humidifiers, whirlpools, industrial cooling systems, soil, and even showerheads. One investigator has proposed that oropharyngeal colonization with *Legionella*, followed by aspiration or ingestion, is another possible route of infection.³⁵ The diagnosis is made when an epidemic consistent with the disease is accompanied by any findings indicating recent infection with *L. pneumophila*: (1) a four-fold increase in serotype-specific (matching organisms from the contaminated source, usually serotype 1) IgG antibody titer or a rise in titer greater than 1:256, (2) documentation of bacteria in tissue with direct immunofluorescence, or (3) culture of organisms from body fluids or tissue matching the serotype of those contaminating the indoor environment or suspected water reservoir. Treatment primarily consists of administration of a macrolide or other appropriate antibiotic plus supportive therapy.

Another *Legionella* syndrome is Pontiac fever, named for the city in Michigan where it was first discovered. In 1968, 144 persons working in the County Health Building in Pontiac, Michigan, had infection accompanied by fever, chills, myalgia, and headaches lasting 3 to 5 days. Although the attack rate approximated 100%, there were no deaths, and all persons recovered without se-

quelae. The incubation period was 12 to 36 hours. The majority of those affected showed evidence of seroconversion.³⁶

Legionella bacteria are ubiquitous. Risk factors for colonization have been identified in residences and hospitals: low water temperature, electric heaters, vertical versus horizontal water tanks, convoluted plumbing systems, blind sump ends, and accumulation of sediment and scale in tanks. Disease has been caused by dissemination of the organism from contaminated cooling towers and hot water systems in commercial buildings. Once a contaminated source has been associated with human illness, even though the source is removed or effectively treated, regular biocidal treatment may be indicated to prevent recurrences.

Outbreaks of viral infections (varicella,³⁷ influenza,³⁸ measles^{39, 40}) have been traced to contaminated HVAC systems. Of potentially more widespread significance, two studies have documented that occupants of buildings ventilated predominantly or exclusively by mechanical systems have a higher rate of absenteeism and a 2½-fold increase in frequency of acute upper respiratory tract infections compared with those in naturally ventilated buildings.^{41, 42} Overcrowding of an area together with reduced clearance of microbes because of poor effective ventilation (ventilation at the occupant's breathing zone) could enhance the likelihood of outbreaks of infection by increasing exposure of the occupants to higher concentrations of infectious agents. This could contribute to the increased occurrence of infectious diseases such as sinusitis, otitis media, pharyngitis, bronchitis, and pneumonia in overcrowded areas indoors and during seasonal respiratory tract infection epidemics. Those with preexisting airway inflammation, caused by allergens or irritants, would be at increased risk of infection.

Biocontaminants shed by animals as bioaerosols from the respiratory tract, hide, fecal droppings, and urine can contaminate indoor air and surfaces in structures housing animals or those nearby. Likewise, structures in which animal products are processed (e.g., abattoirs, rendering plants, dairies, and textile mills) can spread infectious agents and antigens. Indoor transmission of viruses, bacteria, and *Rickettsia* organisms causing adverse effects on human occupants has been well documented for anthrax in textile mills, psittacosis in rendering plants, brucellosis in abattoirs, histoplasmosis in chicken coops, and rickettsial disease (Q fever) in buildings housing infected sheep, goats, and cattle.⁴³

Mycobacterial infections have dramatically increased in the past 3 years in the United States, particularly those caused by strains resistant to previously effective antibiotics. Two well-documented outbreaks of tuberculosis, one in a shelter for the homeless in Seattle, Washington,⁴⁴ and one on a Navy ship,⁴⁵ implicate ventilation systems in the spread of disease. Saprophytic bacteria and fungi, as well as potentially pathogenic ones, are pervasive in the air we breathe and can become even more concentrated in poorly ventilated indoor environments. These contaminated environments place large subgroups of our population at even greater risk: the very young, the elderly, the infirm, those predisposed to hypersensitivity, and those with immunodeficiency diseases including acquired immunodeficiency syndrome.

Although the mechanisms causing human illness after exposure to toxins found indoors are generally well understood, some of the irritant mechanisms are not. A toxin is a poison that by itself, in combination with another agent, or through metabolism produces a deleterious effect in a biological system.⁴⁶ Pesticides, combustion by-products, carcinogens, and mycotoxins are examples of toxins. Irritants often induce their ill effects because of pH extremes, as desiccants (remove water from tissues), or through sense organ overstimulation. Respiratory tract and contact irritants can be commonly found in construction and finishing materials, cleaning products, office equipment by-products, cigarette smoke, combustion products, and any material producing a strong odor. Some practitioners have attempted to link even less well-defined or poorly validated mechanisms to controversial (because of a lack of scientific validation) "diseases" such as multiple chemical sensitivity syndrome and immune dysregulation.⁴⁷ Others have propagated concepts based on scientifically valid constructs that adverse health effects, such as miscarriage, are caused by certain environmental factors, such as electromagnetic radiation from video display terminals. However, careful epidemiologic studies to date do not support a cause-and-effect relationship for many of these proposed disorders.⁴⁸ Although there is evidence that inhaled mycotoxins can cause adverse health effects,^{49, 50} the concept that this problem is widespread is not supported by current scientific evidence. These more controversial subjects are discussed in depth in other articles of this symposium.

BRI are established, scientifically validated health problems caused by agents that can be identified, measured, and quantified in the indoor

environment. Agents causing BRI do so by one of four mechanisms: irritation, intoxication, induction of immunologically mediated inflammation, and infection. This article has focused primarily on infectious and immunologically mediated mechanisms. Removal or reduction of the concentration of these agents from the environment of those adversely affected should be the primary focus of treatment, along with pharmacologic management of the resultant adverse health effects. However, more emphasis needs to be placed on producing and maintaining a hygienic indoor environment by *all* experts contributing to the construction and management of buildings. This can only be achieved through a proactive approach that seriously considers and addresses the multitude of factors that can result in building contamination.

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