Current Concepts

BUILDING-RELATED ILLNESSES

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OVER the past 30 years, a new man-made ecosystem has developed — the controlled indoor environment within the sealed exterior shells of modern office buildings. This new environment has considerable potential to affect public health because more than half the adult work force in North America and Western Europe works in offices or "office-like" nonindustrial environments.[1] The indoor environment of modern office buildings may be affected by the occupants, their work activities, equipment, plants, furnishings, building materials, ventilation systems, and outdoor air pollution. In the vast majority of buildings, this complex environment is controlled by one or two technicians who monitor the highly automated heating, ventilation, and air-conditioning systems. These technicians have no way to measure indoor air-pollution levels and little direct contact with the building's occupants.

In the past two decades a group of health problems related to this ecosystem — termed building-related illnesses — has emerged. In this review we attempt to provide advice to health professionals who are evaluating workers with health problems that may be related to this work environment. The evidence cited has been restricted to descriptions of outbreaks in which a causative agent could be identified, population-based studies of office workers, and experimental manipulations of exposure to substances present in the office environment.

DEFINITIONS

In this review, the term "building-related illness" will be used for illnesses that arise in nonindustrial, nonresidential buildings, of which the majority are office buildings. The term "specific building-related illnesses" refers to a group of illnesses with a fairly homogeneous clinical picture, objective abnormalities on clinical or laboratory evaluation, and one or more identifiable sources or agents known to cause infectious, immunologic, or allergic diseases. "Nonspecific building-related illnesses" will be used to refer to a heterogeneous group of work-related symptoms — including irritation of the skin and mucous membranes of the eyes, nose, and throat, headache, fatigue, and difficulty concentrating. These are considered illnesses on the basis of the occurrence of symptoms, even though affected workers do not have objective clinical or laboratory abnormalities and causative agents cannot be found. The symptoms may be considered building-related even if the only supportive evidence is workers' reports. We avoid the term "sick building syndrome,"[2] since it suggests that buildings require investigation and treatment, whereas physicians are confronted with individual workers with potentially work-related health problems. The term is also inaccurate in suggesting that there are two populations of buildings — sick and healthy; this conclusion is not supported by epidemiologic surveys of workers in many buildings.[3-12] Moreover, the designation of "healthy buildings" may be harmful because it suggests that in such buildings, the symptoms of affected workers can be presumed to be unrelated to the work environment.

SPECIFIC BUILDING-RELATED ILLNESSES

Table 1 summarizes the chief specific building-related illnesses. Transmission of certain respiratory pathogens[16-18] may be increased by crowding or a reduced outdoor-air exchange rate. A single causative agent may result in building-related outbreaks with very different manifestations. For example, *Legionella pneumophila* can result in legionnaires' disease, a pneumonia with a case fatality rate of 10 to 15 percent,[13,15] or Pontiac fever, a milder, flulike illness.[14,15] Similarly, hypersensitivity pneumonitis and humidifier fever were originally described as separate disorders but may coexist and result from similar immunologic responses to fungi, bacteria, or protozoa contaminating humidifiers or ventilation systems.[19-22] Manifestations of both disorders include fever, chills, malaise, and the presence of specific antibodies to the microbial agent. Hypersensitivity pneumonitis has additional features of cough, chest tightness, dyspnea, lung-function abnormalities, and occasionally, radiographic abnormalities. When all exposed workers have been carefully examined, there is a wide spectrum of manifestations.[20-22] For example, in one group of 14 workers exposed to levels of penicillium of 5000 to 10,000 colony-forming units per cubic meter, hypersensitivity pneumonitis developed in 1 nonsmoking worker, asthma developed in another with a history of atopy and cigarette smoking, and 6 others had nonspecific respiratory symptoms.[21]

Outbreaks of asthma related to exposure in office buildings have been reported rarely, although the causative agent in such outbreaks has not been identified.[23,24] Exposure to common indoor allergens such as dust mites, plant products, and passively

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TABLE 1. SPECIFIC ILLNESSES KNOWN OR SUSPECTED TO BE RELATED TO BUILDINGS.*

DISEASE	TYPE OF STUDY	TYPE OF BUILDING	INDOOR SOURCE	AGENT OR EXPOSURE
Infectious				
Legionnaires' disease and Pontiac fever	Case reports (sporadic or epidemic)[13-15]	Large buildings (offices, hospitals, hotels)	Cooling tower, air conditioning, or humidifier, potable water	*Legionella pneumophila*
Flulike illness and common cold	Cross-sectional study[16]	Office buildings	Human source	Respiratory virus
	Longitudinal study[17]	Military barracks		
Tuberculosis	Index case followed by cross-sectional study[18]	Office buildings	Human source	*Mycobacterium tuberculosis*
Immunologic				
Hypersensitivity pneumonitis and humidifier fever	Case reports[19]	Office buildings	Humidifier	Multiple bacteria, fungus, actinomycetes
	Index cases followed by cross-sectional study[20-22]	Office buildings, factory	Air conditioning, humidifier, ventilation unit	Aspergillus, penicillium, multiple organisms
Allergic				
Dermatitis, rhinitis, and asthma	Case reports	Office buildings	Surface dust, carpet, clothing	Dust mites, plant products, animal allergens, fungus
	Index cases followed by cross-sectional study[23,24]	Office buildings and factory	Humidifier	Unknown
Rhinitis				
Contact urticaria, laryngeal edema	Case reports[25-28]	Office buildings	Carbonless copy paper	Alkylphenol novolac resin
Irritation				
Dermatitis, upper and lower respiratory tract irritation	Case reports[29-31]	Office buildings	Ceiling boards	Glass fibers
	Case report[32]	Office buildings	Tobacco smoke, vehicle exhaust, any combustion process	Combustion products (e.g., carbon monoxide, nitrogen dioxide)

*Data are from case reports, studies of index cases followed by epidemiologic evaluations, or field studies (when available).

transported allergens may occur in any occupied building. Challenge tests with photocopier fumes have produced hypersensitivity angiitis,[25] and tests with carbonless copy papers have produced urticaria and laryngeal edema[26,27] or pharyngitis.[28]

Dermatitis, conjunctivitis, and upper and lower respiratory tract symptoms may also represent irritant responses due to exposure to nonallergenic agents. Exposure to man-made vitreous fibers has produced itching skin, burning eyes, sore throat, and cough.[29,30] Glass fibers may be released from ceiling boards through direct physical damage or indirectly through the movement of boards by building vibrations or room-pressure changes when doors are opened or closed.[29,30]

Carboxyhemoglobin levels of 2.0 to 3.5 percent have been measured in nonsmokers exposed to indoor carbon monoxide concentrations of 4 to 10 ppm. Therefore, exposure to levels of 20 to 50 ppm from heavy cigarette smoking[33] or intake of exhaust fumes[32] could result in carboxyhemoglobin concentrations of 5 to 10 percent, which can diminish cognitive function and alertness[34] and produce symptoms of headache and dizziness — so-called occult carbon monoxide poisoning.[35] Indoor exposure to nitrogen dioxide can occur as a result of the intake of exhaust fumes or from high outdoor levels[36,37] and can result in mucosal irritation with respiratory symptoms and an increase in respiratory tract infections. Formaldehyde is well recognized as a mucosal irritant, but there are no well-documented outbreaks of illness related to exposure to this agent in office buildings.[38]

NONSPECIFIC BUILDING-RELATED ILLNESSES

In cross-sectional surveys in buildings selected without regard to the occupants' health status, up to 60 percent of workers reported at least one work-related symptom, and 10 to 25 percent reported that such symptoms occurred twice weekly or more often.[6,7,9,11,12,39] The associations of such symptoms with a younger age, female sex, and a history of atopy (Table 2) may reflect heightened physiologic responses at lower thresholds[46-49] or greater occupational exposure.[50] The association of symptoms with psychosocial factors does not mean that "the problem is all in the workers' heads." The results of psychological testing of symptomatic and asymptomatic office workers are similar,[51] psychosocial factors are associated with cardiovascular disease,[52] and such factors can result from, rather than cause, health problems.[53]

As reviewed extensively elsewhere,[54] exposure to environmental tobacco smoke in nonwork environments (primarily the home) has been consistently

TABLE 2. RELATION OF PERSONAL, WORK, WORK-SITE, AND BUILDING-VENTILATION CHARACTERISTICS AND NONSPECIFIC BUILDING-RELATED ILLNESSES AMONG OFFICE WORKERS.

CHARACTERISTIC	STUDIES FINDING AN ASSOCIATION			STUDIES FINDING NO ASSOCIATION		
	NO. OF STUDIES	NO. OF SUBJECTS	REFERENCE	NO. OF STUDIES	NO. OF SUBJECTS	REFERENCE
Personal						
Female sex	7	23,764	3-5, 7, 12, 41, 42	1	3,948	10
Younger age	4	17,166	4, 10, 12, 42	2	8,450	3, 5
Atopy, allergy, asthma	9	23,662	3, 5-7, 10, 12, 40-42	0	—	
Cigarette smoking						
Active	2	8,433	7, 12	4	13,944	3, 5, 10, 42
Passive	3	15,017	4, 12, 41	2	5,338	7, 10
Psychosocial factors	7	21,762	3, 5, 7, 10, 12, 40, 41	0	—	
Work						
Clerical work	3	9,301	3, 4, 7	2	6,489	5, 42
Work with video-display terminals	6	22,277	3, 5, 7, 10, 12, 42	1	880	43
Work with carbonless paper	4	16,373	3, 5, 12, 43	0	—	
Work with or near photocopiers	4	10,720	3, 5, 7, 43	1	3,948	10
Work site						
Open-concept office	2	6,489	5, 42	1	3,948	10
Crowding	3	11,430	3, 12, 43	0	—	
Presence of carpets	3	8,335	3, 10, 43	1	4,943	5
Surface dust	2	7,455	3, 10	2	11,986	5, 12
Noise	2	5,338	7, 10	0	—	
Building						
Ventilation						
Simple mechanical	3	8,168	8, 9, 44	2	12,977	6, 11
Air conditioning	5	26,838	8, 9, 11, 12, 44	0	—	
Humidification	2	9,721	8, 12	1	11,627	11
Ventilation rate <10 liters/sec/person	3	4,959	6, 39, 41	0	—	

associated with a number of adverse health effects, including lung cancer. It has been suggested[55] that this evidence should be extrapolated to the office environment, in support of a ban on smoking in such buildings, despite the rather limited evidence, as seen in Table 2.

Surface dust and carpets are reservoirs of fungi,[56] volatile organic compounds,[57,58] and house-dust mites,[59] which may be released when disturbed, resulting in adverse effects on health. No studies have demonstrated a reduction in symptoms after the removal of carpets, although improvement has been shown to be associated with better cleaning.[60,61] Fungi and bacteria have been implicated in building-related illnesses because of the association of nonspecific symptoms with indicators of potential microbial contamination, such as high humidity,[4,57,62] surface dust,[3,10] carpets,[3,10,43] and air conditioning.[8,9,11,44] Microorganisms, their toxins, or both have been detected in high concentrations at sites of localized water damage,[63] and in heating, ventilation, and air-conditioning systems — on cooling coils,[64] filters,[65] ducts,[66,67] humidifiers,[24] drip pans,[64] and air-cooling units.[19,21,64] Nevertheless, levels of airborne microbes have been low and associated only inconsistently with symptoms in field studies, as shown in Table 3.[44,57,72-75]

Volatile organic compounds are produced from a wide variety of sources, including new building materials or furnishings (they account for the "new-car smell"), cleaning agents, paints, solvents, and equipment such as photocopiers.[58] In three single-blind chamber studies, controlled exposure to a mixture of volatile organic compounds commonly found in office environments resulted in mucosal irritation (Table 4).[49,77,78] However, the concentrations of volatile organic compounds used (5000 and 25,000 μg per cubic meter) were far higher than levels detected in most field studies (Table 3),[50,57,74,76,79] and there are no studies of controlled exposure to volatile organic compounds at the concentrations usually found in the office environment.

The controversy regarding the ventilation rate (defined as the amount of outdoor air supplied to the indoor environment) has been largely resolved by a recent synthesis.[88] The prevalence of symptoms has been found to be higher in buildings with an outdoor-air supply of less than 10 liters per second per person,[6,7,39,41] and experimental increases in ventilation reduced symptoms (with one exception[84]) if

TABLE 3. ASSOCIATION OF BUILDING-RELATED ILLNESSES WITH MEASURED ENVIRONMENTAL FACTORS.

VARIABLE (UNIT)	TYPE OF STUDY	LEVEL AT WHICH NO SYMPTOMS ASSOCIATED			LEVEL AT WHICH SYMPTOMS ASSOCIATED			
		MEAN LEVEL	RANGE	REFERENCE	MEAN LEVEL	RANGE	REFERENCE	SYMPTOM
Temperature (°C)	Field observational	23.0	22.0–24.4	57	23.0	21–26	42	Headache, fatigue
					23.3	21–26	68	Total no. of symptoms reported
Relative humidity (%)	Chamber	50	50–80	69	18		69	Eye, nose
		10	10–70	70				
		9	9–50	71				
	Field observational (long-term)				>40	10–20	68	Mucosal
							4, 62	Systemic
Fungi (colony-forming units/m^3)	Field observational	32	0–111	57	97	2–978	44	Nose, throat, skin
		27	2–200	72				
		45	28–75	73				
		14	8–17	74				
		10	1–100	75				
Bacteria (colony-forming units/m^3)	Field observational	574	120–2100	57	22*	10–33*	73	Total no. of symptoms reported
		342	80–961	44				
		42	25–240	75				
Volatile organic compounds ($\mu g/m^3$)	Chamber				5,000		77	Mucosal
					25,000		49, 77, 78	Mucosal, headache, fatigue
	Field observational	220	30–3930		1247		50	Mucosal, systemic
		70	3–740	76	941	160–2353	74	Mucosal
		834	100–2630	57	380	50–1380	79	Mucosal, systemic
Dust ($\mu g/m^3$)	Field observational	30	6–110	44	16	8–24	79	Eye
					22	13–29	74	Systemic
					133	10–962	80	Eye
Formaldehyde ($\mu g/m^3$)	Field observational	36	12–60	74	1,044	140–1920	81	Eye, headache, mucosal, fatigue
		11	0–30	79	31	11–59	76	
		40	0–80	57				Headache, mucosal, fatigue, skin
Carbon monoxide (ppm)	Field observational	4.5		50				
		3.9	2–5.5	74				

*The value refers only to gram-negative bacteria, since only gram-negative bacteria were associated with symptoms.

the base-line ventilation rates were below 10 liters per second per person but had no effect if base-line ventilation rates were higher.[42,82,89] Hence, changes in ventilation strongly influence indoor levels of pollutants when ventilation is at low levels, but they have much less effect at higher ventilation rates.

In summary, a number of personal factors appear to be associated with nonspecific building-related illnesses, possibly because they indicate increased susceptibility. Symptoms are also associated with markers of individual exposure, such as the use of carbonless paper, photocopiers, and video-display terminals or the presence of carpets and dust, yet the specific agents responsible for the associated effects on health have not been identified. The importance of building-wide factors, such as the type or presence of mechanical ventilation[6,8,9,11] or humidification,[11,12] remains unclear. Studies to examine these factors were confounded by differences between buildings in the characteristics of the occupants or their work, and the results may have been biased by the occupants' awareness of the study and their attitudes. Although the prevalence of symptoms has been consistently associated with temperature and humidity,[42,68,82] this has not been the case for measured chemical and microbial levels, despite the indirect evidence implicating these factors. This lack of association may reflect the multiple agents present, their spatial and temporal variability, and the fact that current methods of measurement are expensive and insufficiently precise for the low levels usually present in office environments.

SYNTHESIS OF EVIDENCE REGARDING OFFICE-BUILDING–RELATED ILLNESSES

Nonspecific building-related illnesses may be explained by three phenomena: a wide range in the threshold of response in any population (susceptibility), a spectrum of response to any given agent, and variability in exposure within large office buildings.

Symptoms may develop in people exposed to agents at concentrations above their threshold of response. As Figure 1 shows, among healthy adults there is a wide range in the threshold for the detec-

TABLE 4. EFFECT OF EXPERIMENTAL INTERVENTIONS ON SYMPTOMS OF NONSPECIFIC BUILDING-RELATED ILLNESSES.

VARIABLES THAT COULD BE MEASURED	REDUCTION IN SYMPTOMS				NO CHANGE IN SYMPTOMS			
	REFERENCE	NO. OF SUBJECTS	BASE-LINE LEVEL	POST-INTERVENTION LEVEL	REFERENCE	NO. OF SUBJECTS	BASE-LINE LEVEL	POST-INTERVENTION LEVEL
Temperature (°C)	82	339		1.5°C lower				
Relative humidity (%)	82	339	25	40	71	8	9	50
	69	12	18	50				
	83	211	24	33				
Outdoor-air ventilation (liters/sec/person)	41	940	<7.5	25	82	339	12	24
					42	1546	14	30
					84	75	6	20
Ionization (negative ions/cm^3)	82	339	60	26,000	85	77	9500	6500

INTERVENTIONS THAT COULD NOT BE MEASURED	INTERVENTION EFFECTIVE		INTERVENTION INEFFECTIVE	
	REFERENCE	OUTCOME	REFERENCE	OUTCOME
Workstation cleaning	61	Diminished symptoms	—	—
	60	Diminished symptoms		
Cleaning of heating–ventilation–air-conditioning system	—	—	61	Symptoms unchanged
Personal control over ventilation	86	Diminished symptoms	—	—
	87	Increased productivity		
Portable air filters	—	—	82	Symptoms unchanged
			61	Symptoms unchanged

tion and irritant effects of formaldehyde[90,91]; the same has been demonstrated for volatile organic compounds[92] and environmental tobacco smoke.[80] Similar variability in the threshold has been demonstrated for physiologic responses to temperature[47,48]; ozone, sulfates, and particulates[93]; and endotoxin.[94] Although these thresholds vary markedly among individual subjects, there is much less variation in values for the same subject.[93] Thresholds of response are lower among workers with asthma,[93] those with previous building-related symptoms,[49] and those who are female[46,48] or relatively young.[46,48] In addition, thresholds for physiologic responses to allergens, volatile organic compounds, and environmental tobacco smoke are lowered by concomitant exposure to ozone,[95] higher temperature,[96] and lower humidity,[69] respectively.

Although initially specific building-related illnesses are identified when several workers present with similar clinical manifestations and objective abnormalities, an important but overlooked finding in outbreaks has been the wide spectrum of clinical response to the same agents.[20-22] Typically there are a few seriously affected workers with specific clinical abnormalities. Among other exposed workers, a few (often more than the number of initial sentinel cases) have mild objective abnormalities such as leukocytosis or changes in lung function, whereas others have nonspecific symptoms, and some are asymptomatic yet have specific antibodies.[20-22] Without the sentinel cases, the cause of the symptoms in the other affected workers might be missed, or the outbreak might be ascribed to sick building syndrome.

Modern high-rise office buildings are designed to provide a stable and uniform indoor environment, but there is considerable temporal and spatial variation in the actual environment. Temporal variation results from changes in outdoor-air supply and outdoor air-pollution levels as well as changes in occupants and their activities.[36,37] Spatial variation results from differences in local sources of pollutants — the occupants, their work activities, equipment, and furnishings, and materials that absorb and later re-emit contaminants[58] — and from variation in the local effectiveness of ventilation due to renovations and the normal wear and tear of the ventilation system.[97] This variability may create quite different microenvironments throughout a large building.[75,98]

If there is independent variation in the concentration of different agents within a large office building, and in workers' susceptibility to these agents, then individual workers could be symptomatic because of localized exposure to one or more agents at levels exceeding their threshold of response. This hy-

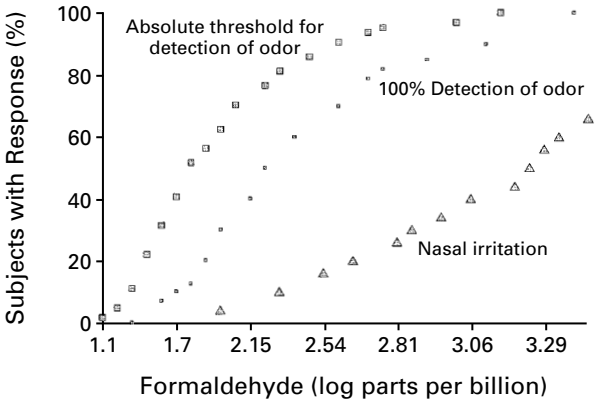

Figure 1. Threshold for the Response to Controlled Exposure to Formaldehyde.

The figure shows the absolute threshold for the detection of the odor of formaldehyde (from Ahlstrom et al.[90]), the concentration at which the odor of formaldehyde was detected in 100 percent of challenges (from Ahlstrom et al.[90]), and the concentration of formaldehyde causing nasal irritation (from Horvath et al.[91]).

pothesis is difficult to test, because of the large number of agents and symptoms and the difficulty of accurately characterizing exposure. However, it could explain why past epidemiologic surveys failed to identify relations between environmental factors measured at a limited number of work sites and the symptoms of all workers within these buildings.[12,57,99,100] This concept also provides the rationale for moving affected workers to another work site — a simple solution that has never been evaluated formally. Personal control over ventilation would enable workers to mitigate adverse local conditions, even if they did not know by what they were affected. This approach has been associated with reduced symptoms[12,86] and improved productivity.[87]

AN APPROACH TO THE PATIENT

Given the complexity of the indoor environment in office buildings and the numerous contributing factors, it is difficult to specify a simple, standardized approach to an office worker with a potentially work-related health problem. However, certain principles can be enunciated.

A careful history taking is an essential first step. Workers may fail to recognize the office environment as the source of their symptoms, so it is important to obtain a thorough description of the onset and course of symptoms and their temporal relation to the work environment. On the other hand, if workers attribute their symptoms to the work environment, it is still important to exclude other, nonoccupational causes.

The physical examination is usually normal in nonspecific building-related illnesses, but findings may be abnormal in specific illnesses. Additional investigations may be appropriate to identify specific entities; examples are chest radiography and lung-function tests for hypersensitivity pneumonitis or asthma and skin tests and serum IgE assays for allergic manifestations.

If a building-related illness is suspected, a walk through the work site is a valuable starting point in the evaluation of the office environment. A team including the physician, industrial hygienist, and engineers is best able to identify and resolve problems in this complex indoor environment. Clinicians should familiarize themselves with public or occupational health officials at the municipal, state, or federal level who have expertise in the evaluation of similar problems. An important advantage of contacting such authorities is that they may receive reports of other affected workers in the same building. Such reports should prompt more thorough environmental assessment and may enable workers to receive compensation or similar benefits. Environmental air sampling may be indicated if specific indoor contaminants are suspected, but it is expensive and requires considerable expertise in measurement and interpretation.

Interventions demonstrated to mitigate nonspecific building-related illnesses (Table 4) should be considered, although they may not be applicable in all settings. Another possible (although untested) solution for the worker with nonspecific and unexplained symptoms would be to change his or her microenvironment by changing the work sites, even within the same building.

CONCLUSIONS

Symptoms of nonspecific building-related illnesses are common; their heterogeneity suggests that they do not represent a single disorder. Although there is little convincing, direct evidence to implicate specific causative agents, there is sufficient indirect evidence to support a number of recommendations. For example, it seems prudent to maintain an outdoor-air supply of more than 10 liters per second per person; to select the building materials, furnishings, and equipment that are least likely to release pollutants such as formaldehyde or volatile organic compounds; to ensure proper maintenance and cleaning; and to avoid materials that may act as substrates for the proliferation of microbes or dust mites.

Workers in the indoor environment of office buildings make up more than half the entire work force of industrialized countries. A substantial proportion have symptoms at work. Given the enormous population apparently affected and our current limited understanding of the health effects of this environment, further research is urgently required. Susceptibility should be assessed in experimental studies of exposure to individual and multiple pollutants at concentrations typically found in the

office environment. Proposed interventions should be evaluated in properly designed trials that incorporate standardized case definitions, questionnaires, and environmental measurement methods. Such studies could help to ensure that the man-made ecosystem within modern office buildings is a healthful work environment.

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