CHAPTER 18

Indoor Air Quality

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The focus of occupational health has been transformed in many ways by the increasing proportion of the workforce employed in offices and other kinds of public facilities, merging in many respects with the concerns of environmental health. Once considered safe by crude comparison with industrial settings such as construction, mining, and agriculture, experience has proved that these indoor environments are not free of significant health hazards. Moreover, the workers engaged in these sectors are neither experienced with environmental risks, nor as well prepared in general to think about hazards of work as their industrial counterparts were even long before the modern regulatory era. Because almost all previous attention has focused on the kinds of conditions and hazards that arise in more traditionally dangerous settings, the regulatory framework has not evolved forms of controls that ensure, at least in law, that work will be safe. This chapter is divided into two sections. The first deals with the spectrum of problems that occur indoors in nonindustrial buildings, focusing on common features of implicated facilities. The second deals with the spectrum of clinical complaints related to low-dose chemical exposures (relative to doses that occur in industry), which have received increasing attention. Although these problems of chemical sensitivity most often occur in association with indoor nonindustrial environments, they may also be seen in a range of other work settings as well as in the nonwork environment. Their distinguishing feature is the occurrence of symptoms or other clinical problems at levels that are far below those at which knowledge of toxicology would predict effects and typically far below accepted standards in industry for human exposures (see Chapter 13). These somewhat vexing problems have challenged many of the cherished paradigms of occupational health about what is safe and what is not and form a special challenge for the occupational medicine specialist, as well as the primary care provider whose patients may complain about chemicals at levels deemed "safe."

BUILDING-RELATED CONDITIONS

Nonspecific Building-Related Illness

Since the 1970s, office workers worldwide have frequently complained of mucous membrane irritation, fatigue, and headache when working in specific buildings, with improvement within minutes to an hour of leaving the building. This constellation of symptoms, with tight temporal association to building occupancy, is called *sick building syndrome*, or, more recently, *nonspecific building-related illness*. It is the most frequent of the building-associated health complaints in industrialized countries, which also include diseases caused by infection, allergic hypersensitivity, or specific toxins. Researchers have estimated that as many as 30 percent of office workers report symptoms attributed to poor air quality, and workers in buildings not known to have indoor air-quality problems have many complaints attributed to the indoor work environment.

Despite the effects on productivity and employee morale when many workers in a building have building-related symptoms, the causes of these symptoms are incompletely understood. Early investigations of this phenomenon sometimes

concluded that symptoms were caused by mass psychogenic illness because no specific contaminants were measured in concentrations that could account for symptoms. However, the endemic nature of complaints in specific buildings and the consistency of complaints from workers in tight buildings across the world did not satisfy diagnostic criteria for mass psychogenic illness. Fortunately, such attribution to psychological cause is no longer common or acceptable, although work stress is associated with reporting of symptoms among occupants of specific buildings (see Chapters 16 and 26). Occupants of buildings with high levels of complaints are often angry and fearful, in no small part due to resistance of managers to investigation of the cause(s) of their problems, inconclusive results of investigations that are conducted, or ineffectual remediation for a syndrome for which causes remain elusive.

The recognition of building-related complaints by public health authorities in the United States followed an energy crisis in the 1970s, during which ventilation standards were lowered to supplying 5 cubic feet of outdoor air per person per minute. This observation led to the hypothesis that building-related symptoms were attributable to lower rates of ventilation in relation to indoor contaminant sources. Some evidence exists, both in cross-sectional and experimental studies, that ventilation rates are related to the prevalence of nonspecific building-related complaints, especially for ventilation supplying outdoor air at less than 30 cubic feet per person per minute. Indoor air-quality consultants commonly measure carbon dioxide levels in buildings with high complaint rates. However, human occupants, who are the source of increased concentrations of carbon dioxide in recirculated indoor air, are not the likely source of contaminants that would explain sick building syndrome. Carbon dioxide level is not predictive of nonspecific building-related complaints.

The American Society of Heating, Refrigerating and Air-conditioning Engineers (ASHRAE) publishes consensus standards for ventilation of various types of buildings that are frequently adopted into building codes. These standards are not health-based, nor are they performance standards for operating ventilation systems. Rather, they stipulate ventilation rates for design purposes. The latest ASHRAE Standard (62.1-2004) recommends 17 cubic feet per minute of outdoor air per occupant in office buildings, in the absence of cigarette smoking. Measuring effective ventilation is technically difficult, expensive, and rarely done apart from research settings. Indoor air consultants examine ventilation systems for possible entrainment of contaminants in the outdoor air source; design and operation of air flow; filter condition and maintenance schedules; cleanliness of the cooling coils and drip pans, which commonly support microbial growth because of moisture and dirt; condition of the duct lining, which commonly supports microbial growth if wet; and postdesign changes in occupancy, activities, and layout that may impact air quality.

Interesting work on causes of nonspecific building-related illness comes from cross-sectional epidemiologic studies of occupants of buildings selected without regard to known indoor air-quality complaints. These studies suggest that certain building features and occupant characteristics are related to symptom prevalence. The variation in prevalence of building-related complaints among buildings suggests remediable causes. Occupants of buildings with air-conditioning have been shown to have higher rates of building-related symptoms than occupants of naturally ventilated buildings or buildings with mechanical ventilation that does not alter air temperature or humidity. This observation suggests that the ventilation system itself may be the source of poor air quality in some buildings. A double-blind multiple crossover trial of ultraviolet germicidal irradiation in office ventilation systems reduced microbial contamination of cooling coils and drip pans as well as work-related respiratory and mucosal symptoms.[1] Building dampness, associated with bioaerosols, is also frequently accompanied by nonspecific building-related illness. Measurable indices of bioaerosols are being intensively investigated as correlates of building-related illness, with some evidence implicating endotoxin, β-1,3-glucan, and culturable microbes, particularly in dust samples. Other environmental correlates include carpeting, high occupancy, and video display terminal use. Personal factors associated with building-related symptoms in many cross-sectional studies include female gender, allergies, and job stress or dissatisfaction.

Health care providers faced with the challenge of responding to indoor air-quality complaints must proceed without the benefit of a complete scientific understanding of what may be a multifactorial syndrome. No single measurement establishes whether air quality is adequate or inadequate, and a

determination of the acceptability of indoor air quality rests with the occupants, and not a laboratory. In the difficult situation of indoor air-quality complaints, a multidisciplinary approach allows attention to design and maintenance of air-conditioning systems, exclusion of obvious contaminant sources or water damage in the occupied space, and reassurance of occupants that nonspecific building-related illness, in the absence of respiratory symptoms, is a self-limited condition. Indoor air-quality investigations customarily assess the ventilation in relation to occupant load by measuring carbon dioxide, identify remediable deficiencies in ventilation system maintenance and cleanliness, assess water damage and moisture incursion, and examine smoking policies. Health care providers, on a multidisciplinary team alongside industrial hygienists and ventilation engineers, have an important role to play in ruling out the possibility of less common, but more medically serious, building-related diseases, such as asthma and hypersensitivity pneumonitis, that frequently occur with a background of nonspecific building-related complaints among other workers.

Building-Related Allergic Disease

A 48-year-old social services eligibility technician began working in an office building in October. She had a history of sinus symptoms and a 15 pack-year history of cigarette smoking, having been an ex-smoker for 10 years. In January, she began to have insidious onset of dry cough, which, in March, was diagnosed as asthma. Skin prick tests were negative to common aeroallergens. She was referred to an occupational medicine clinic in August, when she noted symptom deterioration during the workday (when she needed to use inhaled bronchodilators) and recovery in the evenings and on weekends (when she did not need to use them). Her asthma became much worse when she manipulated dusty records while her desk was being moved. Self-monitoring of peak flow showed reproducible, striking air-flow limitation shortly after entering the building, with partial recovery during lunch breaks outside the building and full recovery on weekends (Fig. 18-1). Methacholine challenge testing in September and November, before a 16-day vacation, found the provocative concentrations (PC_{20}) for a 20% decrement in forced expiratory volume in 1 second (FEV_1) to be 0.29 mg/mL and after the vacation to be 0.47 mg/mL (normal $PC_{20} > 15$ mg/mL). These results confirmed a diagnosis of asthma and suggested slight improvement in airway hyperreactivity with a short work absence. Although she had notified her employer, her relocation to another building was delayed until late February, after her third course of prednisone treatment. After this relocation, her work-related air-flow limitation (documented by peak-flow measurements), her symptoms, and her need for asthma medications all resolved. Her PC_{20} normalized to above 25 mg/mL 3 months after her relocation.

Nine months later, she was moved back to the original building into a set of offices that shared no ventilation system with the offices that she had previously occupied. Over the next 6 weeks, she

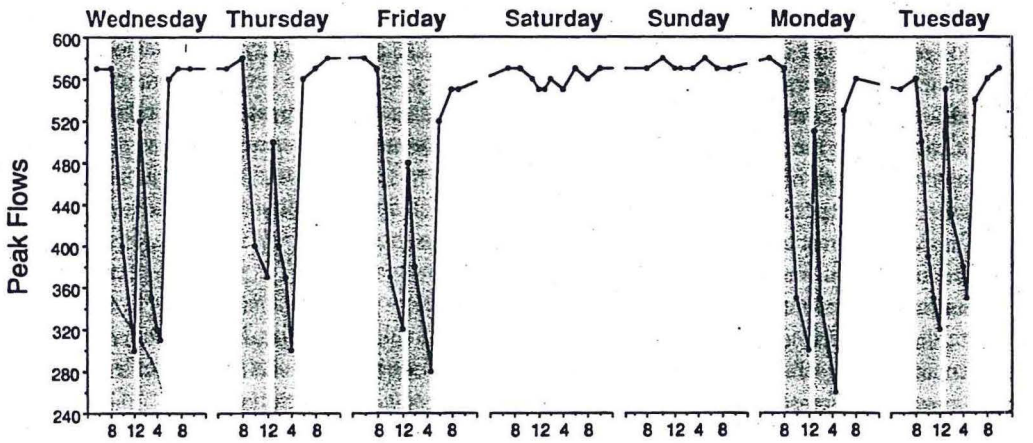

FIGURE 18-1 ● Peak-expiratory flow measurements, by hour and day, in a case of office building–related asthma. Stippled columns indicate time at work.

experienced increasing symptoms and air-flow limitation, once again requiring daily medication, and her PC_{20} fell to 0.22 mg/mL. She was medically restricted from the implicated building, with resolution of her work-related decrements in peak flow, decrease of her medication requirements, and increase in her PC_{20} to 5.19 mg/mL over the following 6 weeks. She has had no further difficulty with clinical asthma since then.

This building was built into an earthen bank, and workers reported musty odors and visible mold growth on the interior wall that abutted the bank. *Aspergillus* species of fungi were detected in the interior air but not in simultaneous measurements of outdoor air, suggesting amplification and dissemination of this fungus indoors. The presumed source of the woman's asthma was fungal bioaerosols associated with moisture coming in from the earthen bank.

Building-related asthma is infrequently recognized by physicians, although it can lead to chronic irreversible illness, unlike nonspecific building-related illness. Early recognition and removal from the building, as in this woman's case, can result in cure of asthma. Permanent asthma can result when recognition of occupational etiology is delayed and asthma becomes severe before the patient leaves the implicated exposure. Such sentinel cases of asthma imply risk for other workers. In this case, public health investigation after two sentinel cases showed that co-workers had nearly five times the prevalence of physician-diagnosed asthma with onset or exacerbation since building occupancy, compared with workers in another social service agency.[2]

Building-related asthma occurs in water-damaged buildings and in relation to microbially contaminated humidifiers or biocides used in them. Biological aerosols containing mold spores and possibly bacteria are the sensitizing agents. Characterization of bioaerosols is difficult because few laboratories have expertise in identifying saprophytic fungi, in contrast to fungi that cause human infection. In addition, no air measurement of viable fungi or spore count has been shown to predict hazard in the nonindustrial environment. An indoor source of microbial amplification and dissemination can be inferred from looking at the rank order of mold species concentrations indoors compared to outdoors, but no quantitative standards exist or are likely to be developed based on exposure–response studies. Experts counsel that visible mold (Fig. 18-2) and moldy smells should be remediated without demonstrating specific mold air levels by culture or air sampling. Despite the difficulty in characterizing the exposure, the affected individual's symptom history and peak-flow measurements can be valuable in documenting the occupational nature of building-related asthma. Cases of building-related asthma may occur along with cases of hypersensitivity pneumonitis in water-damaged buildings.

A 46-year-old pediatrician had been followed by an allergist for 10 years for upper respiratory and chest complaints after moving into an office suite. At first, he complained of sinus drainage and a sore feeling in his nose and throat. Over the years, he had acquired achiness in his chest associated with fever, productive cough, chest tightness, wheezing, fatigue to exhaustion, and shortness of breath on exertion. His forced vital capacity (FVC) fell within 3 years of building occupancy, consistent with a restrictive pattern. He had been treated with nasal cromolyn, inhaled steroids, bronchodilators, theophylline, antibiotics, and intermittent oral corticosteroids, without receiving a diagnosis. A year before his referral to an occupational medicine specialist, he had noted exacerbation of his chest symptoms when he returned to his office suite after a week away from work. He then began to suspect an office-related cause to his symptoms, with increased cough, chest tightness, and achiness when he entered his suite, and resolution over hours after leaving and improvement on weekends. He noted a musty smell and fungal discoloration of wall board in the suite bathroom, which resulted from leaking pipes.

On referral, he was found to have basilar rales, bronchial hyperreactivity on histamine-challenge testing, and reduced exercise tolerance with excessive respiratory rate at rest and excessive minute ventilation for oxygen consumption. Chest x-ray was normal, but a high-resolution CT scan showed fine centrilobular nodules. Bronchoalveolar lavage showed a lymphocytic alveolitis compatible with hypersensitivity pneumonitis. A transbronchial lung biopsy showed a mild, patchy lymphocytic interstitial pneumonitis. His symptoms resolved with prednisone and removal from the office suite.

However, 2 months later, chest aching, exertional shortness of breath, profound fatigue, and chilly feelings recurred within 45 minutes of using a musty restaurant bathroom that had been water-damaged from recurrent roof leaks. He had a prolonged

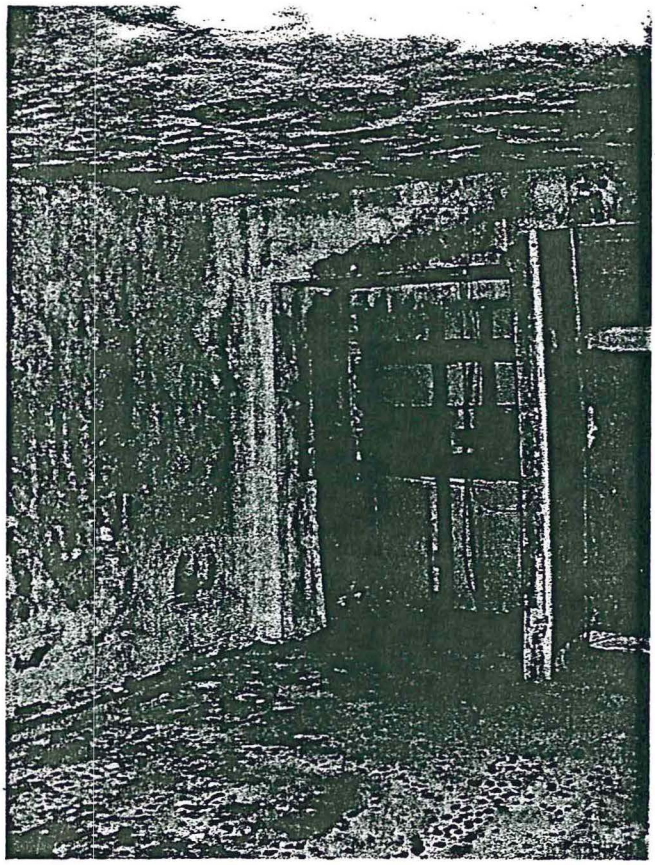

FIGURE 18-2 • Extensive mold growth in a room of a former hotel in New Orleans. (Photograph courtesy of Michael R. Gray.)

recovery time, requiring systemic steroids for 7 months. A year after this acute exacerbation, he again had a recurrence of chest symptoms, within hours of handling medical records from his previous office suite that had become wet while stored in his basement (because of a hot water heater leak). He again required months of prednisone use and did not fully recover his health until 1 year later.

This case of building-related hypersensitivity pneumonitis illustrates the typical medical delay in suspecting and diagnosing a building-related etiology for symptoms. Few physicians are aware that office settings can be associated with diseases related to organic antigens. In contrast to building-related asthma, however, there are many published case reports and epidemic investigations of hypersensitivity pneumonitis and humidifier fever.[3] Typically, people with hypersensitivity lung diseases may not be able to reoccupy a building in which they were sensitized to biological aerosols from humidifiers, ventilation systems, or water-damaged materials on which fungal growth has occurred. Even after remediation of the conditions that led to sensitization and disease, low levels of exposure can trigger recurrent symptoms. Because hypersensitivity pneumonitis can lead to irreversible lung fibrosis after recurrent acute episodes or prolonged exposure, early recognition and restriction of affected people from the implicated building are the best measures for preventing progression. Remediation is warranted to prevent cases in co-workers who are not yet sensitized. Occupational medicine physicians can encourage specialists to proceed with diagnostic tests before the affected individuals develop classic late-stage abnormalities, such as those evident on chest x-rays. The above case suggests that this pediatrician was sensitized to an antigen that was not unique to his water-damaged office setting. Cases of hypersensitivity pneumonitis are often accompanied by systemic symptoms of myalgia, fever, and profound fatigue. These symptoms are not usually present in asthma, although both diseases commonly share chest symptoms, such as cough, chest tightness, and wheezing. In contrast to asthma and hypersensitivity pneumonitis, sick building syndrome alone is not accompanied

by chest symptoms. When indoor air-quality complaints exist, health care providers should evaluate occupants for building-related asthma and hypersensitivity pneumonitis. The occurrence of building-related chest disease dictates evaluation for sources of fungal and bacterial growth and means of dissemination from areas of water damage or from the ventilation system. The presence of chest disease also requires more aggressive medical restriction from the building to prevent irreversibility of the condition.

Many patients report that they have building-related nose and sinus symptoms. Allergic rhinosinusitis can occur, in a way analogous to the response of airways and lung tissue to building-related antigen exposure. Little research has been done on this common clinical complaint to determine its epidemiology, to distinguish it from nonimmunologic mucous membrane complaints in sick building syndrome, or to link it to exposures in implicated buildings. Unfortunately, there are no practical ways of measuring antigens related to indoor microbial bioaerosols, although research is underway on antigen identification, measurement, and size differentiation. However, rhinitis may precede or exacerbate asthma. If the temporal association suggests that the nasal or sinus symptoms are building-related, the same attention to identifying and removing sources of water damage and attending to the maintenance of the heating, ventilation, and air-conditioning system is needed as for building-related chest diseases. In residential environments, allergic disease commonly occurs in relation to indoor allergens, which are more diverse than those in office settings. Antigens from dust mites, cockroaches, and animal danders are implicated in asthma beginning in childhood. Environmental intervention to lower these antigen exposures, such as by using antigen-impermeable mattress covers, vacuum cleaners equipped with high-efficiency particulate air (HEPA) filters, HEPA air purifiers, and professional pest control, can reduce childhood asthma morbidity when they are tailored to the sensitizers affecting an asthmatic child.[4]

Building-Related Infection

In 1976, a total of 182 cases of a mysterious pneumonia occurred among members of the American Legion attending a convention in Philadelphia. After months of laboratory investigation, a newly discovered bacterial organism, *Legionella pneumophila*, was found to be the responsible agent. We now know that, in the absence of vigorous attempts to eradicate it, this common environmental organism frequently grows in the warm water of building cooling towers. When contaminated cooling tower mists are entrained in air intakes of large buildings, cases of infection with this organism (legionellosis) can occur. Outbreaks have also been recognized as a result of contaminated industrial water sprays, hospital shower heads, and hot tubs.

When legionellosis occurs, molecular biology techniques are now used to identify specific strains by DNA fingerprinting. Possible sources can be tested for the same strain in environmental reservoirs. This matching of aerosol source with clinical cases can help prioritize environmental controls through disinfection of hot water systems and avoidance of entrainment of contaminated aerosols.

In addition to pneumonia, *Legionella* organisms have been associated with another building-related disease called *Pontiac fever*, which is a self-limited disease characterized by fever, chills, headache, and myalgia. This disease was first described in 1968, in a building-related epidemic of 144 cases in a county health department in Michigan. The attack rate was nearly 100 percent, with an average incubation period of 36 hours.

In addition to infections that cannot be spread to other people, such as *Legionella* pneumonia, building ventilation characteristics are important to the spread of infections that can be passed on to other people, such as viral respiratory infection. Military studies have shown that types of housing with different ventilation characteristics, such as air-conditioned buildings (as compared with tents or naturally ventilated barracks), are associated with increased incidence of respiratory symptoms and signs of communicable disease in troops. Other airborne infectious diseases, such as tuberculosis, pneumococcal disease, varicella, and measles, may be affected by ventilation rates. A major concern in hospitals, prisons, and shelters is control of tuberculosis, for which ventilation and air disinfection techniques are critical (see also Chapter 15).

Building-Related Complaints Due to Specific Toxic Agents

Health professionals responding to building-related complaints must also consider specific toxic exposures as a possible explanation. This is particularly important when complaints differ from

those of nonspecific building-related illness or occur in epidemic—rather than endemic—fashion. For example, complaints of headache and nausea dictate consideration of carbon monoxide poisoning, which can occur when internal combustion sources are not exhausted to the outdoors or when air intakes entrain fumes from loading docks, parking garages, or boiler stack emissions. Building-related itching without rash can occur with fibrous glass exposure, which can result when air-duct lining is entrained in the airstream entering the occupied space. Epidemic coughing, dry throat, and eye irritation can result from detergent residues after the misapplication of carpet cleaning products. In instances of building-related complaints associated with specific exposures, a careful evaluation of types of symptoms, their distribution among building occupants by location or job, and their temporal onset may point investigators to the cause and to remediation resources.

Environmental tobacco smoke may contribute to the irritant symptoms of sick building syndrome. In many buildings, environmental tobacco smoke is circulated throughout the building as air is recirculated, with modest dilution from outdoor air ventilation. In buildings with indoor air-quality complaints, restriction of smoking to areas with separate exhaust ventilation can result in improved air quality for the remainder of the building. In addition to mucous membrane irritation, environmental tobacco smoke contributes to exacerbation of asthma, accelerated decline in lung function, and increased occurrence of infections in infants and children.

INDOOR CARCINOGEN EXPOSURE

Environmental tobacco smoke has been the most common indoor carcinogen, but public tolerance of this exposure is decreasing across the United States, as reflected in state and municipality ordinances prohibiting smoking in workplaces, restaurants, and bars. Sometimes building-related carcinogen exposures do not lead to occupant symptoms but nonetheless pose a health risk. For example, radon gas emitted from building materials, water, and soil surrounding foundations poses increased risk of cancer. Radon exposures can be measured with simple devices. The Environmental Protection Agency (EPA) has guidelines for elevated exposures and effective remediation, such as sealing of foundations and subsurface ventilation. Similarly, asbestos in insulation and some building materials in older buildings poses risks of cancer of the lung and other sites (as well as nonmalignant lung disease) if it is disturbed during occupant activities or renovation. Because of latency and dose–response considerations, occupational health specialists and other health professionals are often called to help communicate risks of asbestos exposure to building occupants or the public during removal of asbestos from older buildings. Most states license asbestos abatement professionals who are trained to protect remediation workers with respirators and other personal protective equipment, while maintaining negative pressure in asbestos removal areas to prevent asbestos fibers from entering occupied spaces. For all of these carcinogens, primary prevention is through identification and management.

MULTIPLE CHEMICAL SENSITIVITIES

Since the 1980s, a new clinical syndrome has been recognized in occupational and environmental health practice characterized by occurrence of multisystem symptoms after exposure to low levels of synthetic chemicals. Diagnoses and treatment are uncertain and controversial. Unlike any other building-related illness, this disorder recurs in affected people in a diverse array of environmental situations and cannot be readily reversed by attention to any single exposure situation. The following is a representative example of what is now most widely referred to as multiple chemical sensitivities (MCS):

A 46-year-old library worker enjoyed good health until the onset of eye, nose, and throat irritation and recurrent headache associated with a renovation of the library where she worked. She and many co-workers complained primarily of dust and paint fume exposures, which were initially poorly controlled. After several weeks of effort, the employer succeeded in establishing temporary ventilation for the work area and conducting most of the construction activities at night. Almost all of the patient's co-workers improved dramatically after these changes were instituted. She, however, felt no better and began experiencing similar symptoms in her car, at various stores, and whenever she was around anything she termed "scented," especially experiencing these symptoms in the office. She

believed she was experiencing effects from the small residual levels of construction-related exposures, but temporary transfer to another part of the library brought no relief. New symptoms, including difficulty breathing, muscle and joint aches, and confusion occurred both at work and at home, triggered by an increasing list of offensive odors, irritants, and products. Efforts to clean her house of such materials, as well as a trial leave of absence from work (without the benefit of workers' compensation), resulted in only minimal improvement.

On clinical evaluation, the patient appeared well and had no abnormal physical findings. Laboratory tests, including workup for respiratory and central nervous system abnormalities, were unrevealing. Consultations in pulmonary medicine, rheumatology, and neurology were obtained but were unhelpful. Attempts at empirical therapy with various inhalers, nonsteroidal anti-inflammatory agents, and migraine therapies also failed to relieve her symptoms. Because of the disparity between complaints and findings, the patient was referred to a psychiatrist who confirmed some depressive features but could not explain the patient's symptoms. A trial of selective serotonin reuptake inhibitor (SSRI) antidepressants was initiated but was not tolerated by the patient, who discontinued the drugs after 3 days.

Finally, frustrated by unsympathetic physicians and her employer, the patient took advice she obtained from the Internet and sought evaluation from a non-traditional environmental medicine physician, who advised total avoidance of all chemical exposures, including quitting her job, and a variety of nontraditional remedies, based on results of blood and hair tests in an alternative laboratory, which reported organic chemicals and heavy metals as well as immunologic responses to a range of widely found chemicals, such as formaldehyde. She remains highly symptomatic.

Although this case occurred in the setting of building-related illness, MCS may develop in occupational and nonoccupational settings, and in people who have experienced one or more episodes of chemically induced illnesses, due to solvents, pesticides, or other chemicals. Once the problem begins, however, affected individuals experience symptoms they associate with many types of environmental contaminants in air, food, or water at doses well below those that clinically affect others. Although there may not be measurable impairment of specific organs, the complaints are associated with dysfunction and disability. Although MCS as severe as in the above case is not common, it is prevalent enough to have generated substantial controversy. However, research has not yet elucidated its cause and pathogenesis, nor ways to treat or prevent it.

Multiple Chemical Sensitivities: Definition and Diagnosis

There is no general consensus on a definition for MCS, but certain features are sufficiently characteristic to raise suspicion and differentiate it from other occupational and nonoccupational health problems. Its major features are as follows:

- Symptoms usually occur after an occupational or environmental inhalation or toxic exposure. This precipitating event may be a single episode, such as an exposure to a pesticide spray, or recurrent, as in the case presented previously. Often the initial event or reaction is mild and may merge without clear demarcation into the syndrome that follows.
- Symptoms resembling those associated with the preceding exposure begin to occur after exposures to surprisingly lower levels of various materials, including chemicals, perfumes, and other common work and household products, especially materials that have a pungent odor or are irritating.
- Symptoms appear referable to many organ systems. Central nervous system problems, such as fatigue, confusion, and headache, occur in almost every case.
- Complaints of chronic symptoms, such as fatigue, cognitive difficulties, and gastrointestinal and musculoskeletal disturbances, frequently complicate the temporal relationship between specific exposures and effects. These more persistent symptoms may even predominate over acute reactions to chemicals in some cases.
- Objective impairment of the organs that would explain the pattern or intensity of complaints is typically absent.
- No other diagnosis easily explains the range of responses or symptoms. Although the patient may, in fact, have other physical or emotional ailments, such as allergy or anxiety, symptoms related to MCS will often not resolve despite appropriate treatment of these concurrent illnesses. However, because illnesses such as asthma and panic attacks are both treatable and potentially life-threatening, it is important to make a positive diagnosis and to treat them when found.

Not every patient meets these criteria precisely. But because the diagnosis of MCS is, in the end, based on subjective information, each point should be carefully considered. Each serves to rule out other clinical disorders that MCS may resemble, such as generalized anxiety disorder, classic sensitization to environmental antigens (such as occupational asthma), late sequelae of organ system damage (such as reactive airways dysfunction syndrome after a toxic inhalation), or systemic disease (such as systemic lupus erythematosus). On the other hand, the diagnosis of MCS does not require the exclusion of all other possibilities, and exhaustive testing is not required in most cases.

In practice, diagnostic problems are seen in two clinical situations. Early in the course of the disorder, it is often difficult to distinguish MCS from occupational or environmental health problems that may have preceded it. For example, patients who have experienced symptomatic reactions to pesticide spraying indoors may find that their reactions persist even when they avoid direct contact with these chemicals. In this situation, a clinician might assume that significant exposures could still be occurring and may focus entirely on altering the environment further, which usually does not relieve the recurrent symptoms. This is especially troublesome in an office setting, where MCS may develop as a complication of nonspecific building-related illness. Although most co-workers improve after steps are taken to improve air quality, the patient who has acquired MCS continues to experience symptoms despite the lower exposures achieved. Later in the course of MCS, diagnostic dilemmas arise because of the chronic aspects that may obscure the patient's intolerance to common odors and chemicals. After many months, patients with MCS are often depressed, anxious, and frustrated about their health. Physical inactivity, often with weight gain, sleep disturbances, and significant social dysfunction are common. These phenomena demand considerable attention therapeutically.

Pathogenesis

The sequence of pathologic events that leads from apparently self-limited episodes of an environmental exposure to the development of MCS in certain people is not known. There are several current hypotheses.

A group of nontraditional environmental medicine physicians, initially called clinical ecologists, have hypothesized that MCS is a form of immune dysfunction caused by insidious accumulation of exogenous chemicals over a lifetime. They propose susceptibility factors that include nutritional deficiencies (such as vitamins and antioxidants), the presence of subclinical infections (such as candidiasis), or other host factors. In this approach, the precipitating exposure or exposures are important because of their contribution to lifelong chemical overload.

Another biologically oriented hypothesis is that MCS represents an atypical biological sequela of chemical injury, such as a new form of neurotoxicity due to solvents or pesticides, or injury to the respiratory tract after an acute inhalational episode. In this approach, MCS is seen as a final common pathway of different primary disease mechanisms.

A more recent concept has focused on the relationship between the mucosa of the upper respiratory tract and the limbic system, especially the close anatomic proximity of the two in the nose. Under this view, relatively small stimulants to the nasal epithelium could result in amplified limbic responses (as occurs in addicted people to the substances to which they are addicted), explaining the dramatic and sometimes stereotypic responses to low-dose exposures. This hypothesis also may explain the prominent role of stimuli with strong odors, such as perfumes, in triggering responses in many patients.

Many investigators and clinicians with experience have invoked primarily psychological mechanisms to explain MCS, linking it to other anxiety or affective disorders. Some believe that MCS is a variant of post-traumatic stress disorder or a conditioned response to a toxic experience. One hypothesis suggests MCS is a late-life response to early childhood traumas, such as sexual abuse. In these hypotheses, the precipitating illness plays a more symbolic than biological role in the pathogenesis of MCS. Host susceptibility is obviously very important in these approaches, particularly the predisposition to somaticize psychological distress.

Although there is much published literature, few clinical or experimental studies have been presented or published to support strongly any of these views as the single best explanation for MCS. Research has been hampered by variously defined study populations, inappropriately matched control groups, and lack of "blinding" of subjects and investigators. As a result, most available data are descriptive. Perhaps most difficult of all, debate over the etiology of MCS has been heavily dominated by

dogma. Major financial decisions, such as patient benefit entitlements and physician reimbursement, may depend on how MCS is viewed. These theories may be well-known to patients as well, and they may also have very strong views.

Epidemiology

Detailed information about the epidemiology of MCS is not available. Estimates of prevalence in the U.S. population range as high as 6 percent; the rate found in military "controls" for veterans of Gulf War I was about 2.5 percent, while veterans of the conflict suffered MCS-like symptoms twice as frequently. Although many people find chemicals and other odors objectionable and report life modifications to avoid exposure to them, MCS in clinically overt form remains uncommon. Although much available data come from case series by various practitioners who treat patients with MCS, some general observations appear recurrently in the reports:

- MCS occurs most commonly in midlife, although patients of virtually all ages have been described.
- Workers in higher socioeconomic status jobs seem more often affected, whereas economically disadvantaged workers seem underrepresented; this may be an artifact of differential access to occupational and environmental health services or a diagnostic bias.
- Women are more frequently affected than men.
- Some host factor or susceptibility is important because mass outbreaks have been uncommon, and only a small fraction of victims of chemical overexposures acquire MCS or anything like it. Although few host factors have been adequately studied, common atopic allergic disorders do not appear to be an important risk factor for MCS.
- Several classes of chemicals have been commonly implicated in the initial presentation of MCS, specifically organic solvents, pesticides, and respiratory irritants, perhaps a function of the widespread exposure to these materials. The other commonplace setting in which many cases occur is in the "sick building" situation, with some patients evolving from nonspecific building-related illness into MCS, as in the patient described in the previous case. Although the two illnesses have much in common, their epidemiologic features serve to distinguish them: Nonspecific building-related illness usually affects a high proportion of people sharing a common environment, whereas MCS occurs sporadically and is not location-specific.

Finally, there is great interest in whether MCS is a new disorder or a new presentation of an old one. Views on this are divided, much as is opinion on the pathogenesis of MCS. Those favoring a biological role for chemicals argue that MCS is a "20th-century disease" with rising incidence related to widespread chemical usage. Those who support psychological mechanisms see MCS as an old somatoform disorder with a new societal metaphor—the social perception of chemicals as agents of harm.

Natural History

MCS has not yet been studied enough to delineate its clinical course completely, although reports of large series of patients have provided some clues. The general pattern is early progression as the process evolves, followed by less predictable periods of small improvements and exacerbations. These modest changes are often perceived by the patient in relation to environmental factors or treatments, but no scientific basis for such relationships has been established.

Two important observations have been made. First, there is little evidence that MCS is a progressive disorder. Patients do not get worse from year to year in any demonstrable physical way or have resultant complications, such as organ system failure, unless there is intercurrent illness. Despite patients' perceptions, MCS is not lethal—a basis for a hopeful prognosis and reassurance. Unfortunately, complete remissions are unlikely, given current treatment (or lack thereof). Although significant improvement may occur, this is usually related to better patient function and sense of well-being. The underlying tendency to react to chemical exposures persists, although symptoms may become tolerable enough to allow a normal or near-normal lifestyle.

Clinical Management

There remains no established treatment for MCS. Many traditional and nontraditional strategies have been tried, although few have been subjected to the usual scientific standards to document success or failure, such as a blinded clinical trial. Approaches to treatment of the disorder have followed

theories of pathogenesis. Those who believe that MCS is caused by biological consequences of large burdens of exogenous chemicals have focused attention on avoidance of further exposures through the use of "natural" products and the radical alteration of lifestyle. Diagnostic tests of unproved significance, including body fluid assays for trace organic chemicals and antibodies to common chemicals, have been developed as a basis to attempt to develop desensitization approaches. Dietary supplements, such as vitamins and antioxidants, have been recommended to improve host resistance to chemical effects, again without evidence of efficacy. A more radical treatment involves elimination of toxic chemicals from the body by chelation or accelerated turnover of fat, where lipid-soluble pesticides, solvents, and other organic chemicals may be concentrated. Unfortunately, serious side effects have occurred with some alternative therapies, including repeated chelation (renal damage), ozone therapy (anemia), and high levels of pyridoxine (peripheral nerve damage). In the absence of proven benefit, a major tenet should be to do no harm.

Those who take to a psychological view of MCS have tried approaches consistent with these theories. Supportive individual therapies and behavioral modification techniques have been described, although the efficacy of these therapies remains unproved, and some approaches, such as group therapy or breathing exercises, may be counterproductive. These patients tend to be intolerant to pharmacologic agents used to treat affective and anxiety disorders, making treatment plans much more difficult.

Despite limitations of current knowledge, certain treatment principles can be synthesized:

- To the extent possible, the search to "get to the bottom" of MCS in an individual patient should be minimized—it is counterproductive to starting support and treatment. Many patients have already had considerable medical evaluation by the time MCS is first recognized, and further evaluation, unless necessary to exclude treatable diseases, is often a distraction.
- Whatever the particular beliefs of the clinician, the existing knowledge and uncertainty about MCS should be explained to the patient, including that its cause is unknown.
- The patient must be reassured that consideration of psychological complications that commonly arise does not mean that the illness is not real, serious, and worthy of treatment.
- The patient may also be reassured that MCS is neither progressive nor fatal, but that complete cures are not likely with current modalities.
- Uncertainty about pathogenesis aside, it is most often necessary to modify patients' work environments to remove them from triggers of symptoms. Although radical avoidance is counterproductive to the goal of enhancing function, regular and severe symptomatic reactions must be limited to allow the patient to begin the supportive care he or she needs in a trusting doctor–patient relationship. Often this requires a job change. Workers' compensation may be appropriate in the perspective of MCS as a complication of a work exposure, which often appears to be the case.

The goal of all therapy must be improvement of function because the underlying problem cannot be changed given current knowledge. Psychological problems, such as adjustment difficulties, anxiety, and depression, must be treated, as should coexistent clinical disorders, such as atopic allergies. Because patients with MCS do not tolerate chemicals in general, nonpharmacologic approaches may be necessary. Most patients need direction, counseling, and reassurance to adjust to life with an illness such as MCS. Whenever possible, patients should be encouraged to increase activities to their premorbid level. Passivity and dependence, common responses to the disorder, should not be reinforced by prescriptions of avoidance, however well intended.

Prevention and Control

Primary prevention strategies cannot be developed without knowledge of the pathogenesis of the disorder or the host risk factors that predispose some people to become affected. However, reduction of opportunities in the workplace for the overexposures that seem to lead to MCS in some people, including especially respiratory irritants, solvents, and pesticides and the products of war, may reduce the occurrence of MCS. Better ventilation in offices and other nonindustrial workplaces would also help.

Secondary prevention would appear to offer some greater control opportunities, although no specific interventions have been studied. Because psychological factors may play a role in victims of occupational overexposures, careful and early

management of people seeking care after acute toxic exposures or symptoms related to buildings is advisable even when the prognosis from the exposure itself is good. Patients seen in clinics or emergency departments immediately after acute exposures should be assessed for their reactions to the events and should probably receive very close follow-up when undue concerns of long-term effects or persistent symptoms are noted. Obviously, efforts should be made for such patients to ensure that preventable recurrences do not occur because this may be an important risk factor for MCS by whatever mechanism is causal.

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These two papers represent a refereed review of MCS.

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