On the Cover: *Penicillium chrysogenum* in culture. *P. chrysogenum* is a fungal species commonly found in water-damaged environments. (Image courtesy of Dr. De-wei Li of P&K Microbiology Services, currently with the Connecticut Agricultural Experiment Station)

Guidance for Clinicians on the Recognition and Management of Health Effects Related to Mold Exposure and Moisture Indoors

Eileen Storey MD MPH
Kenneth H. Dangman MD PhD MPH
Paula Schenck MPH
Robert L. DeBernardo MD MPH
Chin S. Yang PhD
Anne Bracker CIH MPH
Michael J. Hodgson MD MPH

University of Connecticut Health Center
Division of Occupational and Environmental Medicine
Center for Indoor Environments and Health
263 Farmington Avenue
Farmington, CT 06030-6210

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1. Introduction and Goals of this Book

A culture of *Aspergillus ochraceus*, one of more than 150 species of *Aspergillus*. Several different species of *Aspergillus* have been recognized for infectious, allergic, or toxic health effects. (Image courtesy of Dr. De-wei of P&K Microbiology Services)

Patients present to primary care services with symptoms and health concerns that require consideration of environmental factors. In some cases, patients' exposure to molds in their homes, offices, schools, and workplaces may be having a significant effect. This guidance is designed to help the healthcare provider address patients with illnesses related to mold in the indoor environment by providing background understanding of how mold may be affecting patients. With an appreciation of the time pressures in the clinical medical setting today, the book presents "tools" to help the provider evaluate the patient and help the practitioner explore environmental relationships to illness.

Goals of the Book

This guidance is provided to:

- Underscore the role of physicians in the identification of environmental disease.
- Explain the current understanding of the relationship between mold exposure and illness.
- Outline approaches to diagnosis in children and adults.
- Provide an approach to environmental assessment.
- Provide strategies for clinical management and preventive intervention.
- Suggest readily available resources for assessment and remediation.

The environment often has a role in the development and progression of disease (Institute of Medicine 1988, Menzies and Bourbeau 1997). The recognition of environmentally induced illness

provides the physician and patient with opportunities to prevent disease progression or to reverse the disease process entirely. It also provides protection to other exposed persons in family units, schools, or work groups if it leads to remediation of the causal factor.

The recognition of environmentally induced illness provides the physician and patient with opportunities to prevent disease progression or to reverse the disease process entirely.

Physicians can use specific strategies to evaluate possible environmental disease in their patients. These include the pursuit of a specific diagnosis, an evaluation of the temporal pattern of symptoms and pathophysiologic changes, and an office-based evaluation of the patient's environment. When this process leads to a strong probability that the environment is playing a role in a patient's illness, the physician can assist the patient in accessing resources for environmental assessment and remediation.

In particular, intervention in the environment represents an opportunity to decrease the morbidity of asthma and other respiratory illness, and possibly combat the increasing prevalence of asthma in our communities. We know that microbial agents in the indoor environment contribute to asthma. The Committee on the Assessment of Asthma and Indoor Air, Division of Health Promotion and Disease Prevention, Institute of Medicine, published "Clearing the Air: Asthma and Indoor Air Exposures" and stated that exposure to molds is associated with exacerbations of asthma (Institute of Medicine 2000).

There is strong evidence that significant disease can result from dampness and fungi in the home or workplace (Brunekreef et al.1989, Dales et al.1991, Garrett et al.1998, Kilpalainen et al. 2001). Dust mites in damp environments explain some of the relationship between dampness and respiratory symptoms. However, the causal relationship between the damp environment and health symptoms, including respiratory symptoms, headache, fatigue, and recurrent infections, is less well understood, and mold seems to represent part of the explanation (Bornehag et al. 2001). Although this guidance focuses on mold in the indoor environment and the relationship between exposure and occupants' health, the authors recognize that other microbes including bacteria—gram positive, gram negative, and mycobacteria—grow on substrates in indoor environments and may contribute to occupants' health symptoms. Recent work in Finland has identified bacterial species growing with mold that could also produce toxins (Myatt and Milton 2000, Peltola et al. 2001, Falkinham 2003).

The scientific and medical evidence is inconclusive on how exposure to molds in indoor environments may affect patients' overall well-being and health. However, there is a developing body of literature documenting specific effects of mold on respiratory disease. Recent publications explore effects of mold exposure on allergic sensitization and asthma severity (Zureik et al. 2002). In addition, patients present with irritant symptoms and a broad array of possible "toxic effects" that include neuro-psychiatric, cognitive deficits and digestive system problems that some re-

searchers and clinicians have noted could be associated with mold exposure. Patients may have their own anecdotes and perceived symptoms, or they may be responding to alarming notices in the lay media. This review provides the reader with a context for discussing the risk with the patient as well as suggesting resources for patients who want to address mold and moisture in their homes, schools, and building environments.

Strategies for Healthcare Providers

- Document Disease
- Document Exposure
- Plan Management
- Intervene in Environment
- Follow up

Three factors combine in indoor environments to support mold growth and the corresponding potential for human exposure to mold:

- Building materials that can become sources of nutrition for mold.
- Moisture from leaking roofs, leaking pipes, or from condensation on or water intrusion through walls or basements.
- Inadequate or poorly maintained ventilation systems that may not provide enough air for dilution or dehumidification or that may themselves harbor sources of mold or disperse mold spores into the occupants' breathing zone.

This book summarizes information regarding indoor molds and their effects on human health, provides practitioners with strategies to recognize environmentally related clinical problems, explores approaches used in environmental assessment, and provides access to resources available for patients when environmental remediation is indicated.

2. Illustrative Clinical Experience

The fungus *Serpula lacrimans*, which can cause dry rot in a house. (Image courtesy of Ray Woodcock, CIH, of RC Woodcock, Ltd.)

Clinical case studies are helpful in demonstrating the range of illness associated with indoor exposure to molds, approaches to diagnosis, and remediation strategies. School buildings are particularly vulnerable to indoor air problems (Bayer et al. 1999), and increasing numbers of teachers have sought evaluations for symptoms they associate with working in (usually) damp, moldy environments. Over the past decade there has been increasing documentation of teachers with occupational illnesses relating to working in school buildings (Filios et al. 2002). In this section, we highlight clinical experience where diagnoses of serious disease in teachers and office workers have been associated with working in an environment that is highly suspect for mold contamination.[1] The first four cases reflect the experience of the authors evaluating patients in our occupational and environmental medicine specialty clinic. Case 5 is a child from a pediatric practice where the authors conferred with the treating physician on environmental influences and remediation. The cases are concerned with:

1. Successive respiratory diseases
2. Sarcoidosis
3. Occupational asthma

[1] In a number of these cases, species of mold were identified because they were known and may be of interest to the reader. However, environmental associations were drawn based on history, chronology, and factors for mold growth such as chronic water incursion. Specific identification of fungal species did not add substantially to this process.

4. Upper respiratory symptoms and rash progressing to occupational asthma
5. Serious recurring respiratory illness

Case 1: A Middle School Teacher with Successive Respiratory Diseases

In Brief: A career elementary school teacher with adult-onset asthma was evaluated and diagnosed with building-related respiratory disease. Leaving the environment for a few months (under doctor's orders) led to nearly complete resolution of symptoms. After returning to work and moving to a second school building contaminated with mold, the teacher became quite ill with respiratory disease, the pattern being more consistent with hypersensitivity pneumonitis. The case description that follows demonstrates (1) some of the essential factors in recognizing and treating environmentally related respiratory disease including consideration of temporal relationships in clinical evaluations, (2) the importance of managing the illness by changing the environment, and (3) the difficulties inherent in "fixing" environmental exposures.

Clinical Evaluation

A 57-year-old woman who had taught fifth grade for 20 years presented in the fall, complaining of a 6-year history of cough, which was initially worse at school and cleared in the summers when the teacher was away from the school building. She had been treated for asthma over the preceding 18 months with oral and inhaled steroids and with inhaled bronchodilators. She also had been treated with allergy immunotherapy shots. Her medical history identified pneumonia at age 32, and 10 years of cigarette use prior to quitting 20 years before presentation.

Physical examination was normal and included normal pulmonary function testing. However, spirometry bracketing the work week reflected a 20-percent decline in both Forced Vital Capacity (FVC) and Forced Expiratory Volume in the first second (FEV1) over the course of the week.

That winter, the treating physician removed the patient from the work environment to her home, and 2 months later her only remaining symptom was rare wheezing. She had discontinued her medications.

The elementary school where she taught had a history of poor air quality. Because of the chronology and her response to removal from the school, the patient transferred to a different school building and began teaching sixth grade. Within a month, she complained of cough, raspy voice, metallic taste, fatigue, multiple skin rashes, and mental confusion. Physical examination revealed bilateral basilar crackles. A chest radiograph demonstrated middle lobe atelectasis, and pulmonary function tests revealed a 20-percent decline in FVC relative to her summer baseline.

Further clinical evaluation over the fall showed a decreased single breath diffusion capacity (DLCO) (56 percent predicted), a measure of the exchange of gases at the membranes between lung and blood vessels. The treating physician again removed the patient from work. She again experienced resolution of symptoms and physiologic changes. A clinical diagnosis of hypersensi-

tivity pneumonitis was made. The metallic taste, skin rashes, and mental confusion were not explained by that diagnosis. These symptoms resolved with restriction from the building.

Building Environment

The teacher had transferred to a middle school where her classroom was characterized by a moldy smell, wall-to-wall carpet on asbestos tile, water-damaged ceiling tiles, leaky skylights in the hallway, a crawl space under the classroom with mold (among others *Aspergillus sp.*), and a mulch pile outside window. Over the next 3 years, as the school brought in consultants to help mitigate the indoor air quality in the building, the school successively and incrementally improved the classroom by removing the carpet and asbestos tile, replacing old ceiling tiles, adding a room air conditioner, maintaining cleanliness in the room, and cleaning the crawl space under the classroom. Prior to each set of improvements, the patient was sequentially removed from work, felt better at home and then after the room was improved in some way, returned to the classroom where she became increasingly symptomatic again. Although the individual classroom was renovated, there were plausible pathways for exposure to other sources of mold, an open window with mold-laden wood chips beneath it and an accessible plenum under a corroded deck with chronically wet areas. Major renovation to address these concerns would occur over a multi-year time frame.

Resolution

By her second year in the middle school, the patient was not able to tolerate any exposure in the school. Her physician removed her from work, and she retired from teaching. Her symptoms became infrequent, and she required no medication.

Cases 2 and 3: Two Teachers in a Rural School That Was Plagued with Water Intrusion and Mold; Patient "A" Was Diagnosed with Sarcoidosis and Patient "B" with Occupational Asthma

In Brief: Patient "A" presented to an occupational medicine specialty clinic with recurrent respiratory symptoms occurring for 3 years, but only during the school year. This woman was clinically evaluated and subsequently diagnosed with biopsy-confirmed sarcoidosis. The treating physician, following a sentinel case model, considered the patient an index case, which triggered an outbreak investigation of her school. Over the course of the school year an epidemiological study and environmental site investigation confirmed an outbreak of lung disease linked with a chronically wet, moldy work environment. A second teacher from the same school, patient "B," was diagnosed with occupational asthma. The cases are presented to illustrate (1) idiopathic disease may be associated with environmental factors, (2) a sentinel case model can protect potentially sensitized workers from developing allergic disease, and (3) site investigations are complex and generate useful environmental data.

Patient "A" Clinical Evaluation

A 40-year-old female middle school teacher developed sore throat, hoarseness, cough, wheezing, and shortness of breath. She reported a 3-year history of symptoms developing in school each

October, improving on the weekends, and clearing up altogether during the summer. She used antihistamines and an inhaler intermittently, but had no diagnosis of asthma.

She had worked in the middle school for 17 years. Her classroom was carpeted, as were the library and conference room in which teachers held meetings. She associated her cough with the heat coming on. She kept her windows open throughout the year.

Because patient "A" presented in the late spring with mild symptoms, she was evaluated in detail over the subsequent summer. Her pulmonary function studies and chest radiograph were normal. During the subsequent school year, she interpreted intermittent respiratory symptoms as evidence of viral infection. She was asymptomatic the next summer and upon return to school developed severe coughing episodes within a week. These occurred in carpeted rooms, particularly the library. She presented for clinical evaluation 2 months into that fall semester. At that time she was noted to have bilateral hilar adenopathy with enlarged paratracheal nodes. Her diffusion capacity declined from 85 percent predicted to 63 percent predicted. A lung biopsy demonstrated well-defined epithelioid granuloma with occasional giant cells and no inflammatory infiltrate.

The physician diagnosed sarcoidosis. Removal from the school resulted in resolution of symptoms, radiographic changes, and the diffusion deficit.

A Sentinel Case Model

Because patient "A" noted that she had experienced symptoms in a temporal relationship with school sessions and an environmental building assessment confirmed mold and uncontrolled moisture in the building, the physicians and school district considered it prudent to offer spirometry screening to others at the school who had symptoms. This screening program identified another teacher (patient "B") who was at risk for asthma. After a 10-day break from school, the results of cross work week spirometry testing revealed that patient "B's" pulmonary function significantly declined between Monday morning and Friday afternoon from 3.03 liters (91 percent of predicted) to 2.52 liters (76 percent of predicted) FVC and from 2.44 liters (96 percent of predicted) to 2.14 (83 percent of predicted) FEV1. These results correspond to a 19.8-percent decline in FVC and a 12.3-percent decline in FEV1 over the work week.

Patient "B" Clinical Evaluation

This 45-year-old teacher was evaluated in the occupational medicine clinic. Patient "B" was a lifetime non-smoker, took no regular medications, and had a negative medical history other than childhood hay fever. She had been teaching fifth grade in this school for the past 24 years, and she reported a 6-year history of progressively worsening chronic cough, along with recurrent bronchitis and sinusitis. Her respiratory problems had consistently resolved over each summer vacation, and then recurred each fall upon return to the school building. Patient "B" also reported that her cough was better whenever she was outside of the school, but it generally recurred within 30 minutes of entering the building each morning. In addition, her cough appeared to be consistently worse in some of the schoolrooms than in others. When patient "B" presented, she also reported a recent history of dyspnea and wheezing, lethargy, and fatigue. Pulmonary function studies on the

day she presented showed her FVC was 87 percent of predicted, FEV1 was 86 percent, and FEF 25 percent-75 percent (Forced Expiratory Flow of air expelled from the lungs during the middle half of the spirometry test) was 55 percent prior to bronchodilator treatment; the respective values were 91 percent, 89 percent, and 65 percent of predicted after albuterol treatment. These improvements were not significant. The results were interpreted as being caused by obstructive changes, with the drop in FVC resulting from air trapping and not from restrictive disease. The same day, her single breath diffusion capacity was 115 percent of predicted, and the chest X-ray was unremarkable. Serial peak flow measurements recorded over the next few months demonstrated evidence consistent with asthma related to the school building.

Patient "B" was diagnosed with occupational asthma and recurrent sinusitis. Treatment with loratidine, albuterol and beclomethasone inhalers, and later salmeterol, provided partial relief of symptoms. She initially refused to consider being restricted from her workplace and continued to be symptomatic during the remainder of the school year. The following year the spirometry screening program was repeated at the school after a vacation. The results of her tests reflected an 11-percent decline in FVC and a 12-percent decline in FEV1 over the workweek. The next school year she transferred to another school in the district and did well. Her upper and lower respiratory symptoms disappeared, she no longer felt abnormally fatigued, and she tapered her medications, with follow-up by her local physicians.

Environmental Assessment of the School

The school had been built in four periods after 1945 and 1980. Parts were constructed slab-on-grade on a hillside. There was a long history of roof leaks and water seepage from the ground. Prior to the diagnosis of patient "A" with sarcoidosis, an environmental consultant had reported the school's air quality to be "no problem," even though his report documented elevated carbon dioxide levels (which usually means poor air exchange in the rooms) and indoor levels of mold three times higher than outdoor levels. In accordance with the sentinel case model, the environment was more fully investigated. Because of the pattern of moisture incursion in the building, the investigators used a detailed protocol of semi-aggressive microbiological sampling which was designed to explore for sources of mold in flooring. Again the assessment reflected mold levels many more times higher in the indoor air than outside air and confirmed amplification (growth) of molds indoors. Sources were found in tile flooring and carpet samples in specific rooms. Species identified included *Paecilomyces sp., Penicillium sp., Aspergillus sp.* and *Stachybotrus sp.* Sources of mold growth were resolved by (1) the reconstruction and replacement of certain floors and (2) roof repairs and improved drainage around the building to eliminate uncontrolled moisture incursion.

Case 4: An Office Worker Initially Seen for Upper Respiratory Symptoms and Work-related Rash Developed Occupational Asthma after Serial Exposures to Mold in the Work Place

In Brief: An office worker developed respiratory symptoms and rash temporally associated with mold remediation activities in her office building. Although her work location was repeatedly changed with the intention of eliminating her exposure to mold, she intermittently continued to be exposed and developed increasingly severe symptoms. Her story is included here to illustrate (1) the role of regular medical follow-up and monitoring of environmental illnesses as part of an adequate approach to management, especially where exposure to mold is a concern, (2) an example where pulmonary function declined with continued exposure, and (3) the difficulty of eliminating exposures to occupants while renovating adjacent spaces.

Clinical Evaluation

A case of respiratory disease associated with mold exposures (*Stachybotrys* among others*)* occurred in a 42-year-old office worker, who came to the occupational medicine clinic in the spring. She had complaints of work-related sneezing and coughing, accompanied by dizziness, fatigue, headaches, upper respiratory irritation, and rashes, which had been present intermittently for 2 years. She reported that her respiratory symptoms generally resolved if she left the office and went outside for fresh air, but that the headaches would persist for 1-2 hours after she left at the end of the day. Her primary care physician had prescribed non-sedating antihistamines that had partially relieved her symptoms. Her visit to the clinic was precipitated by a recent exacerbation of her symptoms, which appeared to be associated with the beginning of a renovation project on the floor of the office building where she worked.

This building had long-standing problems with water incursion and mold growth, including *Stachybotrys chartarum*, in many areas of its upper stories. The patient's workspace was on an upper floor of the building, where the water damage had been most severe. Renovations had begun near her workplace to repair this water damage.

The initial physical exam was unremarkable, and her spirometry that day was entirely normal. The only abnormality found was that her sedimentation rate (ESR) was mildly elevated. Her symptoms were attributed to allergic and irritative symptoms from the mold exposures, and her employer quickly moved her to a "safe" location in the building where there was no known water damage. Initially, she did well. Several months later she reported another flare up of her symptoms coincident with additional renovation work, which had been started near her current workspace. Physical exam that day revealed a blanching erythematous rash on her extremities. Her spirometry did not decline. The employer moved her a number of times over the next 2 months. Each time she was better for several days to weeks and then would note recurrent symptoms, at which point it was recognized that renovations were occurring nearby. At her last site, she did well until her supervisor brought her a large stack of papers from the office space on the upper floors where her illness had initially developed. Within the hour, her symptoms returned with rash, cough, sore throat, hoarseness, and wheezing. She worked the next day, with continued symptoms, and then left for a 1-week vacation, during which all of her symptoms promptly abated. She was seen again

in the clinic at the end of that vacation week; she was completely asymptomatic and had normal spirometry. She was sent back to work under the assumption that, while her irritative and allergic symptoms were certainly aggravating and interfered with her productivity, they were not something that would lead to chronic impairment. She was to follow up promptly if she had further difficulties, and she was to continue to work in the lower floor office that had no known water damage and no plans for any repair work.

After her return to work, the patient did well at first, but then again had problems with symptoms and sinusitis associated with an apparent upper respiratory infection followed by frequent headaches that developed repeatedly at the end of the workday a few weeks later. She was moved back to a workplace on an upper floor of the building where renovations had been completed. She initially did well in this new location. She was seen 2 months later and was given antihistamines for upper respiratory symptoms. When seen again 2 months later, she had been moved once more to a workplace on a lower floor of the building, which had no known history of water damage. However, she had problems there as well, with complaints of sinus congestion, headache, and rhinitis. Water damage and mold behind wallpaper was identified in that general area. Physical exam again was unremarkable except for erythema of the nasal mucosa and a maculopapular rash on her forehead, upper chest, and thighs. Her symptoms continued to smolder at a low level over the next several months, during which time she was undergoing immunotherapy for her mold allergy and being treated with a steroid cream for her rash, which improved significantly. Pulmonary function tests were ordered after 6 months. These demonstrated decrements from her previous tests, with significant reversibility with albuterol. Her diffusion capacity was also decreased, to about 70 percent of predicted, and arterial oxygen pressure was 73 mmHg with an A-a gradient of 28 mmHg. Subsequently, no pulmonary abnormalities were appreciated on a high-resolution computerized tomography scan of the chest and pulse oximetry was normal. Eighteen months after her initial visit to the clinic, she was diagnosed with occupational asthma. At that time, she was treated with salmeterol and inhaled steroids and restricted from work in the problem office building. She obtained a new position in another building. She was followed closely in the new building. There, her symptoms slowly improved, and her cross shift spirometry showed no decrement.

Case 5: An Infant Treated for Serious Recurring Respiratory Illness Had Most Symptoms Resolve in Substantially Mold- and Moisture-free Environments.

In Brief: A 1-month-old female infant developed serious respiratory illness culminating in admission to the regional pediatric hospital's intensive care unit. She was treated with antibiotics and recovered rapidly. The child presented two additional times with increasing symptoms and in each case responded well. Blood work for pathogens with each visit was negative. With concerns over possible pulmonary hemorrhage and learning on the last visit that the home had moisture incursion, the physician requested that an industrial hygienist visit the home and discharged the child to the grandmother's home. After leaks were corrected and damaged areas with copious fungal growth removed, the child returned home and the pattern of emergency respiratory events ceased. Although this case does not conclusively identify exposure to mold as the cause of the infant's illness, it is included here (1) to illustrate the importance of a pediatric environmental history, (2) to provide an example where respiratory symptoms became increasingly serious with recurring illness co-incident with mold exposure, and (3) to show that mold exposure may be one of many factors that contribute to the illness including family history and other environmental exposures.

Clinical Evaluation

A previously healthy, full-term, well-developed 1-month-old infant developed upper respiratory symptoms and a non-productive cough over the New Year's Day holiday. She lived with her parents and 56-month-old asthmatic brother in a suburban single family house. The parents did not use tobacco.

The patient had been afebrile, but after her cough had worsened over 4 days, her mother took her to her pediatrician for evaluation. At that time, her temperature was 100.8° F, but her physical exam was otherwise unremarkable, with lungs clear to auscultation, and she was discharged home with close monitoring. That evening, she became acutely ill and appeared dusky, pale, and listless. She was taken to the emergency room at the local hospital, where she was found to have a temperature of 102° F, with tachycardia (220/min), tachypnea (66/min), oxygen saturation of 76 percent, and with increased work of breathing. A chest X-ray revealed a right upper lobe infiltrate.

She was transferred in respiratory distress to the regional pediatric hospital by helicopter and admitted to the intensive care unit. An admission chest X-ray was read as clear, and she was treated with antibiotics and did well. Multiple laboratory investigations, obtained in the emergency room as well as during her hospitalization, remained negative for bacteria, respiratory syncytial virus, pertussis, and chlamydia. She was transferred to the floor after 72 hours. She was discharged home after 5 days on a 7-day course of an oral cephalosporin.

She did well at home for about 3 weeks, but then again developed an upper respiratory tract syndrome with rhinorhea, cough, and intermittent fevers. She was seen by her pediatrician on two occasions over the next 2 weeks and then on a subsequent weekend at the local hospital emergency room. She was given symptomatic treatment after each of these visits. The emergency room workup had included a negative chest X-ray, blood tests, and cultures. Over the next week,

the cough worsened, and the family again returned to the emergency room, where the chest X-ray and blood work were again negative.

The next morning, the patient was taken for an office visit with her pediatrician, was diagnosed with otitis media, and treated with amoxicillin. For the next 4 days, the patient's condition remained stable, but she then developed respiratory distress with abruptly worsening cough, tachypnea, increased work of breathing, and vomiting on the evening of the fourth day. She was again taken to the local hospital emergency room, where she was afebrile but had a respiratory rate in the mid-80s and an oxygen saturation of 60 percent on room air, which improved to 98 percent after 100 percent oxygen and suctioning. After she was stabilized, she again was transferred by helicopter to the regional pediatric hospital. There, the physical exam revealed retractions with inspiratory crackles over the right lung fields and no wheezes. The admission testing included a chest X-ray that showed right middle and upper lobe infiltrates, and a white blood count of 35.3, and 4 bands, 44 polymorphonuclear leukocytes, and 50 lymphocytes. Her arterial blood gases showed an oxygen tension of 211 on 100 percent oxygen. She was admitted to the intensive care unit and rapidly recovered, not requiring intubation. She was treated intravenously with a second generation cephalosporin and transferred to the floor after about 18 hours. Again, laboratory investigations for pathogens (including bacterial, atypical, and viral agents) were negative, and her quantitative immunoglobulins were within normal limits. At time of transfer from the intensive care unit, she had decreased breath sounds at the right base and harsh wheezes that cleared over the next 2 days. At that point she was discharged home, alert, smiling, afebrile, and breathing comfortably, but with an occasional cough.

Then, after about 24 hours at home, she returned to the local emergency room, again after developing cough, tachypnea at about 80/min, increased work of breathing, and respiratory distress. She was documented to have oxygen saturation of about 80 percent, which improved to 90 percent on supplemental oxygen. Her chest X-ray showed patchy infiltrates in the right upper and left lower lobes. She was again transferred to the pediatric hospital and admitted to the intensive care unit. She was maintained on continuous positive airway pressure (CPAP), treated with ceftriaxone and erythromycin intravenously, and transferred to the floor within 24 hours. During this hospitalization, concerns developed about water damage in the home environment. Specifically, there were concerns about possible pulmonary hemorrhage associated with exposures to indoor fungal growth in the recreation room of the patient's home, where she spent many of her waking hours. Given these concerns, when the patient was discharged after 72 hours in the hospital, she was taken to her grandmother's home rather than to her parent's house. She did well in her grandmother's house, which had no visible mold growth or water damage. She then recovered uneventfully.

One week after discharge, the patient returned to the pediatric hospital for bronchoscopy and lavage by her pulmonologist. The bronchoscopy was reported as unremarkable, and the lavage provided scant fluid. No differential cell count was reported, and only 4 lipid-laden macrophages, with no evidence of intracellular hemosiderin accumulation, were noted.

A week after the bronchoscopy, an industrial hygienist surveyed the child's home, and found copious fungal growth by inspection. This impression was confirmed by cultures of bulk and wipe samples from environmental surfaces in the home, from chronically damp areas of the basement recreation room and downstairs bathroom. The dominant species isolated in the cultures were *Stachybotrys chartarum* and *Aspergillus versicolor* (from the lower wall of the downstairs bathroom, and the baseboard and carpet in the basement recreation room), and *Aspergillus* alone in the ceiling tiles of the downstairs bathroom.

The family was advised to correct the problems with water leakage in the home, and remove and replace any mold-contaminated building materials, before allowing their daughter back into the house. This was done, and the child did not develop any further episodes of respiratory distress. A specific diagnosis for these episodes remains elusive. The child was left, however, with some residual bronchospasm, which gradually resolved over the next 2-3 years, being labeled as "infant asthma" and treated with inhaled bronchodilators and steroids for about 1 year. The only triggers for exacerbations identified during this follow-up period were viral illnesses.

3. About Fungus and Mold

An appreciation of fungi and their ecological role will help the healthcare provider guide patients who express concern over indoor mold.[1] This section briefly identifies factors about fungi that providers should find helpful in understanding the role mold exposure may or may not have in patients' symptoms and in interpreting environmental reports.[2]

Mushrooms produced on hardwood floor where there has been long-term water incursion. (Unknown or anonymous author. Image courtesy of Dr. Chin S. Yang of P&K Microbiology Services)

Many atopic patients experience allergic symptoms related to molds commonly encountered outdoors. The presence of mold spores in the indoor environment is not in itself a problem when the source is the normal interchange of outside air and the amount and types of spores inside are the same or less than outside. However, mold actively growing on an indoor substrate may affect the quality of the environment by degrading the surrounding materials (weakening the structure) and, more important, by potentially adding unhealthy chemicals and bioaerosols to the indoor air. Higher levels of mold spores inside than outside or the presence of different species inside than outside reflect this "amplification" of mold. The next section discusses health effects that may be associated with fungi in the indoor environment.

[1] Throughout this guidance, the term "mold" is spelled according to American usage. The alternative spelling "mould" is also commonly used in literature.

[2] Two helpful references used throughout this summary are chapter 19 of the American Conference of Governmental Industrial Hygienists reference *Bioaerosols: Assessment and Control* (Burge and Otten 1999) and the subchapter on biological contamination in the *Encyclopedia of Occupational Health and Safety* (Flannigan 1998).

Fungi Classification

Mycologists classify fungi by their presumed evolutionary biological relationships. The three most common groups of fungi are Zygomycetes, Ascomycetes, and Basidiomycetes. Although all can contaminate buildings, the most common fungi that colonize building materials belong to the Ascomycetes group (Burge 1997). In chapter 19 of *Bioaerosol: Assessment and Control* (Macher 1999), Burge and Otten discuss fungi as a "kingdom of eukaryotic organisms, without chlorophyll, that have cells bound by rigid walls usually formed of chitin and glucans." They further discuss that the term "mold" is an artificial grouping similar to the term "weed" used by gardeners. It has no taxonomic significance. Mold generally refers to a visible colony of fungi growing in an indoor environment. "Mildew" is a layperson's term referring to mold growing in and on substances such as fabrics and wood. This section presents a brief discussion of the morphology and ecology of fungus in the indoor environment.

Mold actively growing on an indoor substrate—resulting in indoor amplification—may affect the quality of the environment by degrading the surrounding materials, weakening the structure, and, more important, by potentially adding unhealthy fungal products and bioaerosols to the indoor air.

Ecology and Structure

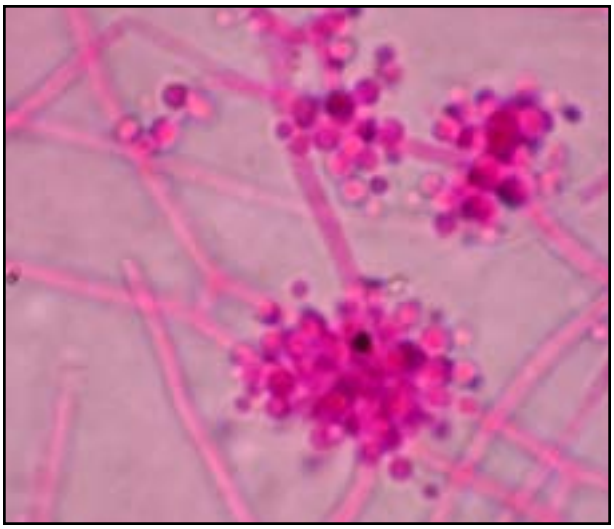
Fungi are ubiquitous in the natural environment. They share characteristics of both plants and animals and are classified in a unique kingdom. Fungi can be saprophytic, parasitic, or symbiotic. Most fungi are saprophytes, and saprophytic fungi thrive by first exuding enzymes and acids that act on surrounding dead and decaying materials and then by absorbing nutrition from the breakdown, fulfilling a critical ecological role by degrading waste material.

Fungi exist in many forms: single-celled yeasts, microscopic filaments (termed hyphae), large visible mats of mycelium (an aggregate of hyphae), and visible spore-producing fruiting bodies known as basidiomycetes, which include common mushrooms. Different fungi are associated with different health effects, and specific components of fungi (such as glucans in the cell walls) or forms of the fungi (spores) are thought to be agents associated with illness.

Other Microbial Agents Indoors

It is important to note that bacteria also grow on building materials and are likely contributors with fungi of bioaerosols to the indoor environment. In a water-damaged environment, environmental bacteria such as gram-negatives and actinomycetes may amplify along with molds. The growth of environmental bacteria may also produce a variety of byproducts, such as endotoxins and bacterial volatile organic compounds (VOCs). Some bacterial species, e.g., *Pseudomonas*

aeruginosa, may cause opportunistic infections. The response to water damage by gram-negative bacteria is very rapid. In contrast, amplification of actinomycetes is often due to long-term or chronic water damage. Peltola reports that gram positive bacteria species were isolated with a toxigenic fungal species from a home where the occupant experienced substantial symptoms and the bacterial species have been shown to produce toxic metabolites (Peltola et al. 2001).



Photomicrograph of *Beauvaria bassiana,* which is relatively common indoors. A natural insect parasite, *Beauvaria bassiana* has been studied as a biocontrol agent of insects. It can become a significant issue indoors because of moisture problems leading to insect amplification and, hence, growth of the fungus on insects, both alive and dead. (image courtesy of Dr. De-wei Li of P&K Microbiology Services)

Nutrition and Growth

The type and characteristic/life stage of fungi in the environment is influenced by moisture, nutrition, light, oxygen, and temperature. In some species, light facilitates sporulation more than mycelial growth. Fungi will grow anywhere indoors and outdoors over a broad temperature range where there is sufficient moisture and a nutrient source. Most fungi prefer a temperature of 15°C-30°C (59°F-86°F), but there are varieties that will grow below or above these temperatures. For example, thermophiles have optimal growth from 35°C -50°C (95°F -122°F).

Fungi can use dirt, dust, wood, paper, paint, insulation, or other common materials for nutrition. This means mold can be established in upholstery, carpet, wall board, ceiling tiles, and even in dirt on glass. Because they are involved in the decaying process, their source of nutrient is almost any organic material, and specific species may have preferences. *Stachybotrys* prefers cellulose and grows exceptionally well on wallpaper or the paper and gypsum of wallboard. Because of these growth preferences, cultures from interior room surfaces or air do not necessarily represent the true distribution of mold in the indoor environment. When conditions are appropriate, fungi may produce secondary metabolites that may be toxic to humans and animals or other organisms.

In most indoor environments, the availability of moisture becomes the limiting factor to amplification or growth of mold. Moisture must be continually present for a colony to grow. Extensive growth has most often been associated with the presence of water in materials or condensation from high humidity, but the environment does not have to be “wet” to support mold associated with health problems. Dampness, which is noted only by minor moisture/condensate, is adequate for some mold, including species of *Aspergillus* and *Penicillium*, molds that are thought to be a problem to the health of some building occupants. Other, more hydrophilic, molds (*Stachybotrys*, *Fusarium*, and *Acremonium*) grow in higher moisture content. Moisture is referred to by mycologists in terms of water activity, i.e. the measure of water within a substrate that an

organism can use to support its growth. Optimal water activity varies according to mold species. Wall relative humidity (because it reflects water activity in the substrate) has been shown to be a better indicator of *Stachybotrus chartarum* that relative humidity (Boutin-Forzano et al. 2004).

Reproduction and Dispersal

Fungi reproduce by sexual (via meiosis) or asexual (via mitosis) means in the form of spores. Fungi normally reproduce by mitosis and cell division, growing colonies. Most fungi survive undesirable conditions and disperse into the environment in spore forms. Individual spores are dispersed and then produce complete fungal organisms in response to appropriate growth conditions. Some spores are slimy and (more) easily stick to substrates, while others are powdery (dryer) and more easily aerosolized. Most spores are respirable (2-10 mm), but some spores can well exceed respirable size (100 mm). In the outside environment, mold spores are dispersed naturally in a diurnal and seasonal pattern. Without an indoor source, indoor air is often reflective of outdoor air (Burge et al. 2000). This diurnal pattern adds to the variability and difficulty in interpreting indoor air mold sampling results. When sources of mold are from the indoor environment, it is unclear how spores are dispersed. Although some spores may be released by colonies and carried by normal air currents similar to what happens in the outdoor environment, human activities inside may disperse mold spores. Reservoirs of mold spores in carpet, walls, ceilings, or furniture may very well be dispersed by any activity such as vacuuming, walking, sitting down on upholstered furniture (Chao et al. 2003), or other disturbances to the building materials.

Fungal Products

Mold products include compounds that are common to all molds, such as glucans, a major structural component, and ergosterol. These can be measured to estimate total mold burden in an environment. Molds secrete enzymes that degrade nutrient-containing substrates on which molds grow. Products of this metabolic activity may be absorbed by the mold organisms or remain in the environment. Byproducts of this metabolism are carbon dioxide, water and ethanol or lactic acid, and sometimesVOCs. The VOCs may include alcohols, esters, aldehydes, hydrocarbons, and aromatic compounds. Some fungi produce secondary metabolites. These VOCs and secondary metabolites may be responsible for the characteristic “musty” odors in buildings where molds grow.

Fungal metabolic byproducts may have toxic, allergenic, or immunologic effects. Although their role in fungal ecology is unclear, some of these substances have had specific effects on humans (Etzel 2003a). For example, fungal metabolites include important antibiotics (e.g., penicillin), potent toxins (e.g., aflatoxin) and psychoactive compounds (e.g., psilocybin) (Burge 1992). For specific fungal species, toxic metabolites may provide the organism with a competitive advantage over other species. There are hundreds of known mycotoxins, in a large variety of structural types, with different biological properties (Norred and Riley 2001). Some of these metabolites are produced by a number of unrelated species, and others are very specific. If an individual becomes allergic to a structural component or metabolite that is found across species, he or she will react

allergically to a number of different molds. Fungi produce non-volatile mycotoxins that can injure or cause the death of eucaryotic cells. Most mycotoxins are heterocyclic organic molecules, generally having molecular weights of 300-750 daltons. Animal studies have confirmed teratogenic, carcinogenic, immune-suppressive, and other associations with a variety of mycotoxins (Robbins et al. 2000). Although they are not usually volatile by themselves, mycotoxins may readily enter the air in spores and fungal fragments when the substrate is disturbed. For example, children may become exposed when playing on mold-contaminated carpet.

Specific Molds

Appendix A presents brief descriptions of a selected list of fungal species commonly found in the indoor environment and whose exposures may be of concern to your patients' health. They include *Aspergillus spp., Alternaria spp., Acremonium spp., Cladosporium spp., Dreschslera spp., Epicoccum spp., Penicillium spp., Stachybotrys spp.,* and *Trichoderma spp.* (Assouline-Dayan et al. 2002). Because patients may have concerns over mycotoxins in general, some species that are not commonly found in the indoor air environment, but have been shown to produce toxins, are also listed in the appendix. However, this list is not designed to cover all fungi. If interested in more information on fungi, clinicians should consult a competent mycologist or these suggested references from the mycological literature:

- *Introduction to Food- and Airborne Fungi Sixth Edition*, 2000; Samson, Hoekstra, Firsvad, and Filtenborg; The Netherlands.

- Microorganisms in Home and Indoor Work Environments: Diversity, Health Impacts, Investigation and Control, 2001; Ed: Flannigan, Samson and Miller; Taylor & Francis; London and New York.

- *The Fifth Kingdom* on CD-ROM. Version 2.5, 2001; Kendrick; Mycologue Publ, Sidney.

- *Fungal contamination as a major contributor of sick building syndrome* in *Sick Building Syndrome*; 2004; Li, Yang; Academic Press, San Diego.

4. Health Effects of Fungi and Mycotoxins

Mixed cultures of *Penicillium chrysogenum* and *Stachybotrys chartarum* recovered from water-damaged, moldy dry wall. (Image courtesy of Dr. De-wei Li of P&K Microbiology Services)

Fungi can cause disease in humans and animals by a variety of biological mechanisms, which can be classified into four groups: (1) infections, (2) allergic or hypersensitivity reactions, (3) irritant reactions, and (4) toxic reactions. In the setting of indoor exposures, good evidence exists for occurrence of disease in humans by the first three of these mechanisms, whereas the role of toxic reactions is less clear. Because an understanding of the mechanism underlying the clinical manifestation of the health effect is helpful in diagnosing and treating the patient, this chapter provides a brief discussion of the disease mechanism followed by a summary of the pertinent illnesses. The clinical outcomes discussed in this chapter are:

- Fungal infections (page 22)
- Allergic rhinitis (page 24)
- Asthma (page 24)
- Hypersensitivity pneumonitis (extrinsic allergic alveolitis) (page 25)
- Interstitial lung disease (page 25)
- Bronchopulmonary aspergillosis (page 26)
- Allergic fungal sinusitis (page 26)
- Allergic dermatitis (page 26)
- Irritant symptoms (page 26)
- Organic dust toxic syndrome (page 28)
- Pulmonary hemorrhage in infants (page 29)

Because of the interest and concern patients may have about health effects from exposure to toxins produced by molds, particularly by *Stachybotrys chartarum*, a detailed discussion on reactions to mycotoxins is included as appendix B.

Fungal Infections

Perhaps the most familiar fungal diseases occur by either systemic or superficial infection. Some of these infectious diseases are associated with typical settings. For instance, *Coccidioides immitis* can cause a flu-like syndrome ("Valley Fever") or sarcoid-like syndrome and pulmonary coin lesions; it typically occurs following inhalation of spores from arid soils in the southwestern United States or Mexico. The origin of this particular fungus is most likely from the outdoors, and it usually would not be considered associated with wet buildings. *Histoplasma capsulatum* can cause interstitial or cavitary pneumonia. It typically occurs in spelunkers and others exposed to bat guano or bird droppings in the Mississippi or Ohio River valleys where Histoplasmosis is endemic. *Cryptococcus* typically causes self-limited infections, although in immuno-compromised individuals it can cause meningoencephalitis or cavitating pneumonia. It has been associated with exposure to pigeon droppings on windowsills or air conditioning units in urban office buildings. Sporotrichosis can be manifest by cutaneous or lymphangitic lesions, or by pulmonary involvement and disseminated disease. It typically occurs in gardeners, often after they have been pricked by thorns. Dermatophytes cause the typical infections of the skin, hair, and nails (e.g., tinea cruris, corporis, and pedis). These skin infections too may have environmental associations. For example, tinea pedis may develop following use of locker rooms at public swimming pools or school gymnasiums.

The typical etiologic exposures and clinical syndromes associated with these fungal infections are well described in standard medical texts and are beyond the scope of this document. They will not be described further in the present discussion, beyond pointing out that occasionally it may be necessary to restrict immuno-compromised or otherwise sensitive individuals from environments that may place them at risk for infection. Examples include restricting a child with cystic fibrosis from a school environment known to be laden with *Aspergillus* and restricting an AIDS patient from office buildings significantly contaminated with pigeon droppings. Similar concerns pertain to patients with compromised immunity from chemotherapy.

Allergic and Hypersensitivity Reactions to Fungi

It is well established that fungi can cause allergic reactions in humans. Mold antigen preparations are typically included in the skin test panels used clinically by immunologists to screen for environmental triggers in atopic patients. Moreover, the prevalence of allergic responses to molds is such that news programs in some areas of the United States offer routine reports of local airborne mold spore as well as pollen counts during their weather reports.

Antigens (or more properly, antigenic epitopes) are segments of macromolecules, typically proteins or glycoproteins. In fungi, these macromolecules can be structural components of the

cell, enzymes, or metabolic byproducts (Simon-Nobbe et al. 2000). Individuals' immune responses to these antigenic molecules are determined by their genetic makeup and environmental factors. Important among these factors are the frequency of exposure to the antigens and the intensity of the exposures. The immune system may ignore the epitopes to which it is exposed, in which case there will be no immune or allergic response. If the individual does react, he or she may form antibodies to the antigens, most typically of the IgG, IgM, or IgE classes. If the individual reacts by forming antibodies, how specific the subsequent immunological response will be is determined by the component of the antigen that the individual recognizes as "foreign."

Hypersensitivity reactions result from immunologic responses to antigens. Multiple components of fungi, e.g., proteins, can serve as antigens. The hypersensitivity responses can be of different types, as initially delineated by Gell and Coombs. The most common hypersensitivity responses to fungi are the type I or immediate allergic responses, but type III and type IV or delayed hypersensitivity responses also can contribute. Development of sensitization to antigens generally requires repeat exposures, often to high ambient concentrations of the sensitizing material. Once sensitization to an antigen has developed, it requires a much lower concentration upon re-exposure to elicit the reactive phase that we recognize as the clinical manifestation of disease. In general, the higher the exposure and the degree to which one has been sensitized, the more severe the allergic or immune-mediated response.

Allergic Rhinitis and Asthma

The most common types of illnesses directly related to mold are the type I responses of allergic rhinitis and asthma. These type I responses begin with sensitization. After allergen exposure, the antigenic macromolecule is phagocytosed and processed by an antigen-presenting cell (APC). The APC then exteriorizes antigen epitopes onto its membrane surface proteins and secretes interleukin-1 (IL-1). The antigen fragment is recognized by T_H2 lymphocytes specific for that epitope, which then produce interleukins (IL-4 and IL-5). IL-4 stimulates specific IgE production against that epitope by B lymphocytes, and IL-5 stimulates production of eosinophils. The newly produced IgE, which is directed against the mold antigens, then binds to high-affinity receptors on mast cells and basophils. These cells then migrate to the nasal mucosa and pulmonary interstitium, with resultant sensitization of the respiratory mucosa to mold antigen. The patient's subsequent re-exposure to airborne mold spores or fragments can lead to an early inflammatory response characterized by mast cell degranulation and liberation of histamine and other inflammatory mediators (tryptase, leukotrienes, platelet activating factor and prostaglandins) in the respiratory mucosa. This is followed after 6-8 hours with a late response involving liberation of a second wave

Multiple components and metabolites of fungi can serve as antigens.... The most common hypersensitivity responses to fungi are the type I or immediate allergic responses, but type III and type IV or delayed hypersensitivity responses also can contribute.

of mediators, including interleukin-8, RANTES (regulated on activation of normal T cells expressed and secreted) and Eotaxin, leading to eosinophil chemotaxis.

Clinically, it is well recognized that molds can be major triggers in atopic individuals (Jacob et al. 2002, Bush and Portnoy 2001). Exposure to mold antigens has long been implicated in the development of symptoms of perennial **allergic rhinitis** (Seuri et al. 2000, Lasley and Shapiro 1999, Mandell 1968, Gravesen 1979). These reactions also occur in fungus-contaminated buildings. The early phase of the allergic response causes symptoms including clear rhinorrhea, nasal congestion, sneezing, post-nasal drip with sore throat, coughing, and hoarseness; and the late phase leads to increased nasal obstruction and non-specific hyperresponsiveness. There is concern that chronic symptoms of rhinitis represent a response to colonization with fungi. Because fungi can be cultured from both healthy subjects and patients with rhinosinusitis, the evidence for this is not clear. (Virant 2000a).

In the lower airway, allergic inflammation can trigger bronchospasm, chest tightness, and shortness of breath, leading to either new onset of **asthma** or asthma exacerbations in sensitized individuals (Lasley and Shapiro 1999, Virant 2000, Etzel 2003). Upper respiratory syndromes resolved in patients after reservoirs of fungal organisms in contaminated ductwork of the air delivery systems were eliminated with rigorous maintenance in the building's heating, ventilation and air-conditioning (HVAC) system (Hiipakka and Buffington 2000). More recently an association was shown between total fungal concentration recovered from chair dust in chairs in office buildings and upper respiratory symptoms in office workers (Chao et al. 2003). In homes, lower respiratory illnesses in children in the first year of life have been associated with elevated household fungal levels (Stark et al. 2003).

A report from the European Community respiratory health survey (Zureik et al. 2002) suggests that in patients with asthma, the severity of symptoms is increased significantly in those with allergic sensitization to outdoor molds (*Alternaria* and *Cladosporium* species) and dust mites, but not to pollen or cats. The findings on fungal antigen sensitization are in agreement with earlier reports implicating exposure to environmental mold in the etiology of asthma (Jaakkola et al. 1993, Seuri et al. 2000, Flannigan et al. 1991, Beaumont et al. 1985). While there is growing evidence that moisture in buildings is associated with the onset of asthma in children and adults, there is not consensus as to the role of fungi in the initiation of new asthma. In a recent report, the Institute of Medicine noted that there is "inadequate or insufficient evidence to determine whether an association (with presence of mold or other agents) exists" with development of asthma. The report also noted exposure assessment limitations and difficulties in defining specific causative agents (Institute of Medicine 2004).

Clinically, it is well recognized that molds can be major triggers in atopic individuals.

Early in the development of hypersensitivity, the inflammatory responses and symptoms subside between episodes of exposure. These responses then follow a recurrent temporal pattern after re-exposure to the antigen. Appreciation of this pattern will facilitate diagnosis of the immunologic nature of the symptoms. Over time, the symptoms and inflammatory responses become more-and-more chronic

and less-and-less specific, eventually making recognition of the immunologic instigator quite difficult. Furthermore, it is now evident that asthma and allergic rhinitis have similar pathophysiological mechanisms and that upper respiratory allergic symptoms can presage the development of asthma in a significant percentage of patients (Sarva et al. 2002, Nickel et al. 2002). This central progression of disease may occur either through increased oral breathing and consequent lower respiratory allergen exposure in patients with chronic rhinitis, or through induction of nasal-bronchial reflexes leading to obstructive changes in the airways (Virant 2000).

Patient's upper respiratory allergic syndromes resolved after improved HVAC maintenance cleaned up reservoirs of mold in the building where the patient worked.

Hypersensitivity Pneumonitis and other Interstitial Lung Disease

Exposure to mold antigens has long been implicated as one cause of **hypersensitivity pneumonitis** (HP) or **extrinsic allergic alveolitis**, by provoking cellular (Gell and Combs type III and IV) hypersensitivity reactions (Rom 1998, Patel et al. 2001).

Mold exposures are linked to several forms of hypersensitivity pneumonitis, including farmer's lung and Japanese summer-house HP, as well as less common forms of the disease (Patel et al. 2001, Ikeda et al. 2002, Lee et al. 2000, Seuri et al. 2000, Wright et al. 1999, Yocum et al. 1976).

Inhalation exposure to bioaerosols has been associated with development of i**nterstitial lung disease** (ILD) above and beyond hypersensitivity pneumonitis. These diseases have been reported to occur in excess in occupations where respiratory exposure to microbial antigens or organic dusts is common, such as farming, woodworking, and metalworking. Prominent among these forms of ILD are "usual interstitial pneumonitis" (UIP), also called "cryptogenic fibrosing alveolitis," and "idiopathic pulmonary fibrosis" (IPF) (Hubbard et al. 1996, Scott et al. 1990, Mullen et al. 1998, Baumgartner et al. 2000). It is unclear whether UIP or IPF in these settings simply represents later stages of HP, or whether they constitute separate responses to antigenic agents (which may also cause HP) that are driven by different gene distributions.

Allergic Bronchopulmonary Aspergillosis and Allergic Fungal Sinusitis

Two conditions involve a more intense immunologic response to fungi: **allergic bronchopulmonary aspergillosis** (ABPA) and **allergic fungal sinusitis** (AFS). ABPA occurs in patients with underlying asthma or cystic fibrosis who develop *Aspergillus* colonization of their airways and subsequent hypersensitivity to this organism. Initially, they have peripheral eosinophilia and

Exposure to mold antigens has long been implicated as one cause of hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis.

circulating IgG and IgE antibodies to *Aspergillus*. Later, central bronchiectasis typically develops. Patients with allergic bronchopulmonary aspergillosis typically present with worsening pulmonary function from eosinophilic pneumonia, mucous plugs, or asthma exacerbations. Exacerbations may be prevented by inhaled steroids and can be managed with oral steroid and itraconazole therapy (Mandell et al. 2000).

Rhinosinusitis in a minority of patients involves chronic fungal growth in the sinuses, with a marked immunologic response to the fungal antigens. This results in the production of mucin to the point of adjacent tissue destruction. This syndrome (AFS) includes polyposis and may be associated with asthma. These conditions do not involve tissue invasion by fungi (Bent and Kuhn 1994). Management of AFS involves surgery, immune suppression (steroids), and immunotherapy (Marple 2001). While these conditions affect a minority of patients with clinical syndromes related to environmental mold exposure, early recognition and treatment of these can prevent significant morbidity in these patients (Corradini et al. 2003, Huchton 2003).

Allergic Dermatitis

Various dermatologic responses to mold have been described, including dryness, pruritus, and skin rashes (Rylander et al. 1992). Whether there is an immunologically mediated form of dermatitis in response to mold exposure in indoor environments is not clear, but in support of this, case reports of occupational contact dermatitis and contact urticaria secondary to mushroom or mold exposure provide evidence that intensive, repetitive exposure can result in immunologically mediated dermatitis (Maes et al. 1999, Maibach 1995).

Two uncommon conditions involve a more intense immunologic response to fungi, allergic bronchopulmonary aspergillosis (ABPA) and allergic fungal sinusitis (AFS).

Irritant Reactions to Fungal Metabolites

Indoor growth of molds can lead to the production of a variety of VOCs (Bush and Portnoy 2001). Molds generate various mixtures of VOCs depending on the species of fungi present and the amount of water and kind of substrate available. These VOCs may include alcohols, esters, aldehydes, and aromatic compounds. Very low concentrations of these VOCs can cause the characteristic "musty" odors of a moldy environment. Although mold and mildew odors often are regarded as more of a nuisance than a true health hazard (Health Canada 1987, Jarvis 1995), in slightly higher concentrations than those which cause odors, these VOCs can be highly irritating to mucous membranes (Horner and Miller 2003). In sufficient concentrations, these fungally derived VOCs may lead to eye irritation, conjunctivitis, skin rashes, rhinitis, laryngitis and hoarseness, cough, and even chest tightness. Mucosal exposure to irritants may also produce headache and fatigue. The characteristic of irritant symptoms is their relatively prompt resolution upon removal from exposure to the environment in which symptoms occur.

Mold growth can also lead to mucosal membrane irritation by exposure to small, non-volatile cellular constituents. These compounds include beta-1, 3-glucans (Fogelmark et al. 1992, Rylander et al.1992), which are not mycotoxins *per se*. Airborne beta-1,3-glucans are glucose polymers in fungal cell wall fragments that have important immune modulating properties. Inhalation of these agents can decrease production of soluble antibodies and enhance eosinophylic infiltration of the airways. Exposure to beta-1,3-glucans has been shown to increase the severity of nose and throat irritation (Rylander and Lin 2000). In a study comparing symptom complaints from occupants in buildings and levels of glucan, the investigators found that the beta-1, 3-glucan levels in indoor air significantly correlated with complaints of dry cough and itching skin reported by building occupants. Glucan was not detected in the office building selected as a control where occupants were not known to have similar symptoms (Rylander et al. 1992).

Although from a mechanistic standpoint, irritation and diseases from hypersensitivity are different, they may be difficult to differentiate clinically. Symptoms of irritation consist of cough, skin irritation, and burning or itching of the eyes and nose during exposure that subside quickly when exposure ceases. Mild allergic symptoms can be identical. One distinguishing feature is that with repeated exposures, allergic symptoms usually become progressively worse because of increased sensitization, whereas irritant reactions do not.

It should be noted that there is no consensus regarding the relationship of indoor growth of mold to these irritative upper respiratory symptoms (Nevalainen 2002) because there can be multiple sources of VOCs indoors and few, if any, of the VOCs are specific end-products of fungal metabolism. Many of them may be liberated in indoor environments from areas of water damage as a result of other types of chemical or biological decay.

In sufficient concentrations, fungally derived VOCs may lead to eye irritation, conjunctivitis, skin rashes, rhinitis, laryngitis and hoarseness, cough, and even chest tightness.

Reactions to Mycotoxins

This section briefly describes mycotoxins, discusses mycotoxins in the indoor environment, and highlights two illnesses associated with mycotoxin exposure: organic dust toxic syndrome and pulmonary hemorrhage in infants. The reader is directed to appendix B for an expanded discussion of health effects of mycotoxins.

Some fungi can produce complex secondary metabolites called mycotoxins (Burge 2001, Health Canada 1987, Newberne 1974). Most mycotoxins are heterocyclic organic molecules, generally having molecular weights of 300–750 daltons. Unlike allergens, mycotoxins in sufficient concentration can elicit responses in virtually anyone with whom they come into contact. There are many hundreds of mycotoxins with different biological properties (Norred and Riley 2001, Etzel 2002). The different chemical groups of mycotoxins include aflatoxins, fumonisins, ochratoxins, rubratoxins, and trichothecene toxins (Wannemacher and Wiener 1997), all with different biological properties (Jarvis 1995). A single fungal

genus (e.g., *Penicillium*) may produce more than 100 different mycotoxins. Moreover, the amount of mycotoxin produced by a given strain of toxigenic fungus may vary according to the specific isolate and the prevailing growth conditions. Some of these growth conditions include temperature, nutritive status, light level, and the growth phase (e.g., rapid growth, stationary, or senescence) of its life cycle (Health Canada 1987). Low levels of mycotoxins are ever present in the environment—toxigenic fungi are contaminants of agricultural products and house dust (Health Canada 1987) and are very stable under different environmental conditions (Wannemacher and Wiener 1997).

The toxicity of mold products in humans is best documented in situations involving ingestion of moldy foods, direct skin contact with concentrated toxins, and inhalation of molds at very high concentrations. In recent years, there have been numerous reports in both the medical literature and the popular media that indoor exposure to fungi or fungal toxins has caused significant disease or death in the occupants of water damaged homes or workplaces. These locations had significant (generally visible) fungal growth and odors, typically reported as from the "black mold," *Stachybotrys chartarum*. (It should be noted here that many molds are "black" in appearance.) *S. chartarum* is a ubiquitous organism, growing on cellulose products exposed to water or high humidity. In moist buildings, *S. chartarum* frequently grows on wallpaper, wallboard, ceiling tiles, carpets (especially those with jute backing), insulation (e.g., urea–formaldehyde foam) in the spaces between inner and outer walls, around leaking window frames or water pipes, and in HVAC air ducts containing lint or other organic debris. Some reports of *Stachybotrys*-related disease have involved celebrities, and these and other incidents have triggered widely publicized litigation against builders and insurance companies.

The notion that indoor mold growth can lead to significant toxicity in occupants of "moldy buildings" has been very controversial in the scientific literature and likely will remain so for the foreseeable future.

Concerns relating to the health effects of mycotoxins as encountered in indoor environments focus on respiratory, neurological, and dermatologic effects. As discussed in appendix B, the evidence linking mycotoxins to these kinds of effects in indoor settings is inconclusive.

Organic dust toxic syndrome (ODTS) is a general term, covering illness caused by inhalation of either bacterial endotoxins or fungal toxins (CDC-NIOSH 1994). It is characterized by a flu-like syndrome with prominent respiratory symptoms and fever, which occurs abruptly a few hours after a single, heavy exposure to dust containing organic material, including fungi (e.g., species of *Aspergillus* and *Penicillium*). The symptoms of ODTS are quite similar to those of hypersensitivity pneumonitis, but are not mediated by immune responses. Therefore, ODTS typically occurs immediately after the first heavy exposure to the causative agent; repeated exposures are not required (Perry et al. 1998). OTDS has been documented in workers handling material contaminated with fungal or gram-negative bacterial growth in both outdoor (agricultural) and indoor (demolition) settings (Yoshida et al. 1989, Richerson 1990, Von Essen et al. 1999, Malmberg 1990).

Pulmonary hemorrhage in infants occurs in some settings with water damage and mold growth. While extensive research is ongoing to understand precise causes of this syndrome, the link with moisture characterized by mold growth is strong enough to warrant removal of such infants from the environment until remediation is completed (Etzel 2003a).

There are other reports suggesting that inhalation of mycotoxins can produce diseases other than ODTS and pulmonary hemorrhage in humans. Both patients and clinicians have raised concerns regarding potential neurotoxicity following exposure to molds. The literature which raises concerns regarding neurotoxicity is summarized by Baldo et al. in an article where they present a study of neuropsychological performance of patients following mold exposures (Baldo et al. 2002). An excellent review and carefully presented study, it demonstrates the problems clinicians face when evaluating complaints of memory loss, difficulty concentrating or personality change in patients attributing their symptoms to mold exposure. The problems include poorly defined exposures to mold, less-well-defined exposure to mycotoxins, lack of a consistent pattern of deficits on neuropsychological testing that would begin to define a syndrome of toxicity attributable to mold, and the presence of other morbidities such as depression that can result in measurable impairment on neuropsychological tests. While clinical and epidemiologic data remain elusive, case reports are worrisome and the subject remains open to further investigation. (Sudakin 1998, Sudakin 2003, Lees-Haley 2003). It is not possible to recommend a diagnostic strategy at this point because the syndromes remain poorly defined and mechanisms unknown (Sudakin 2003).

Acknowledging that scientific uncertainty centers on how occupants are exposed to mycotoxins while living or working in contaminated indoor environments, reviews and guidance still advocate for addressing indoor environments contaminated with mold or water damage because of possible toxic effects as well as other less controversial effects of mold (concern for asthmatic patients and other allergic effects) (Ammann 2000, Burge 2001, US EPA 2001, CDC 2002, NYC 2002, ACOEM 2002). The American Academy of Pediatrics recommends that pediatricians inquire about mold and water damage in the home when treating infants with pulmonary hemorrhage and when mold is present, encourage parents to try to find and eliminate sources of moisture (American Academy of Pediatrics 1998.). Experience with infants with this syndrome supports their removal from the environment in which the illness developed until water damaged and mold-contaminated materials are fully remediated. It also supports rigorous avoidance of tobacco smoke because cases have recurred in the presence of tobacco smoke after removal from the home. Avoidance of exposure to environmental tobacco smoke is always recommended but has additional urgency in the presence of a case of pulmonary hemorrhage.

In January 2002, the Board on Health Promotion and Disease Prevention of the Institutes of Health initiated a comprehensive review on the relationship between damp or moldy environments and adverse health effects. The request from the Centers for Disease Control and Prevention (CDC) specifically noted a “focus on fungi and their secondary metabolites, including mycotoxins.” In May 2004 the final report of the NIH review panel was released. The rigorous review found “sufficient evidence of an association” between “the presence of mold indoors” and upper respiratory symptoms, asthma symp-

toms in sensitized persons, hypersensitivity pneumonitis in susceptible persons, and "limited or suggestive evidence" of an association with respiratory illness in healthy children. The board concluded that there is currently "inadequate or insufficient information" to establish an association with a number of health outcomes including the development of asthma, acute idiopathic pulmonary hemorrhage in infants, skin symptoms, and neuropsychiatric symptoms. However the panel recommends that "greater research attention to the possible role of damp indoor environments and agents associated with them in less well understood disease entities is needed" and specifically "encourages the CDC to pursue surveillance and additional research on acute pulmonary hemorrhage in infants." (Institute of Medicine 2004)

5. Recognition and Management of Mold- and Moisure-related Illness

We recognize that the medical community has not agreed on what conditions and even what types of diseases could be classified as "mold-related illness." The discussion in the preceding chapter's review of current literature on health effects from exposures to mold and guidance such as the American College of Occupational and Environmental Medicine position statement "Adverse Human Health Effects Associated with Molds in the Indoor Environment" (ACOEM 2002) suggest that attention to mold and moisture in the environments of patients with certain allergic and hypersensitivity illnesses is appropriate.

Many mold colonies growing on dry wall in a residence. (Image courtesy of Dr. Chin S. Yang of P&K Microbiology Services)

While we focus on mold, we want to emphasize that the risk factor clearly associated with symptoms and illness is chronic or severe moisture incursion into buildings with subsequent growth of microbial agents. The potential role of bacterial agents, dust mites, and pests associated with moisture in buildings should not be ignored.

We provide an algorithm with which physicians can evaluate and manage patients' concerns. It addresses conditions likely related to mold exposure and some which are less clearly associated with mold or moisture in the environment. We also provide guidance for the evaluation and management of patients whose principal concern is perceived exposure to mold. Copies of the algorithm and each of the tables are included in this chapter and in Appendix D.

Recognizing that symptoms or illness may be related to exposure to molds or a moist environment requires that the healthcare provider (1) characterize the signs and symptoms, define the patho-physiology, and determine the diagnosis; (2) through a history taken in the office, evaluate the environment sufficiently to determine whether a significant mold exposure likely exists; and (3) look for links between

the exposure and the symptoms or illness. Management of illness related to mold requires intervention on the environmental factors as well as medical management.

In situations where confirmation of a growing source of mold is important, a home visit by a qualified person would be instructive (see chapter 6).

We have organized the process into three areas: patients, evaluation, and management and remediation.

Patients

The scheme begins with three different groups of patients:

1. Patients with conditions that in themselves warrant an environmental assessment because they are so frequently induced by environmental factors, including moisture and mold.

2. Patients with common, less-specific symptoms that have a clear temporal relationship with specific environments or activities.

3. Patients concerned over perceived exposure to mold.

Patients Whose Conditions Warrant an Environmental Assessment Because They Are Frequently Induced by Environmental Factors, Including Moisture and Mold

Table A lists medical conditions that, in the absence of an alternative explanation, should prompt an environmental history especially with inquiries about possible exposure to moisture and molds. New onset and exacerbated asthma, interstitial lung disease, hypersensitivity pneumonitis, sarcoidosis, and pulmonary hemorrhage in infants are conditions that can lead to chronic, progressive disease or death if an etiologic agent is responsible and not recognized. We also suggest that healthcare providers consider pursuing an environmental history with patients who have any of the three precursor conditions listed on the right hand side of the table: mucosal irritation, recurrent rhinitis/sinusitis, and recurrent hoarseness. While they are in themselves of less importance to overall health, their presence in an individual who seeks care because of exposures in an environment of concern would warrant intervention to prevent progression to more serious illness in the future. If a patient has a condition listed in Table A, then the physician may proceed to the questions in Table C to explore possible environmental exposures.

An Algorithm for the Healthcare Provider's Office

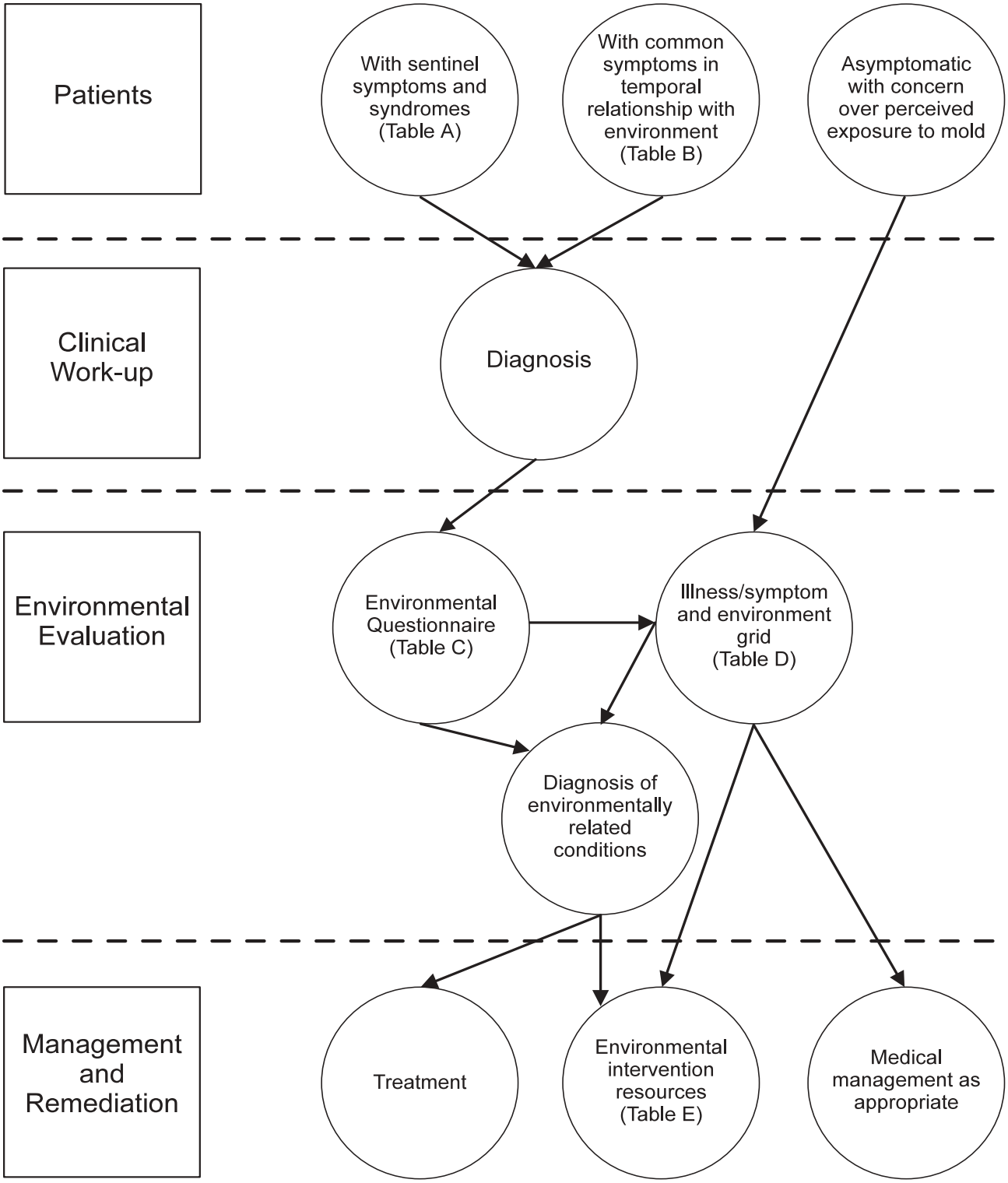


Table A: Sentinel Conditions* Symptoms and Syndromes That May Suggest Mold or Moisture in the Absence of an Alternative Explanation	
Conditions of Concern	**Precursor Conditions**
New onset asthma Exacerbated asthma Interstitial lung disease Hypersensitivity pneumonitis Sarcoidosis Pulmonary hemorrhage in infants**	Mucosal Irritation Recurrent rhinitis/sinusitis Recurrent hoarseness
* "Sentinel condition" has great utility as a concept in the broader area of occupational and environmental health. The diagnosis of an individual with a "sentinel" illness associated with exposures in a particular environment may indicate that these exposures may also deleteriously act on others. Intervention in the environment to limit identified exposures is an opportunity for primary prevention. A broader list of conditions that suggest a pertinent occupational exposure is found in Rutstein 1984. Bracker and Storey present a detailed discussion on exposure characterization and hazard identification for physicians whose patients have occupational and environmental asthma, inhalation injury, and granulomatous disease where bioaerosols as well as other agents in the environment are a concern (Bracker and Storey 2002).	
**The American Academy of Pediatrics has developed a policy statement advising pediatricians when treating infants with pulmonary hemorrhage to inquire about mold and water damage in the home and, when mold is present, to encourage parents to try to find and eliminate sources of moisture (American Academy of Pediatrics 1998). Suspected cases should be reported to State Health authorities (CDC 2004).	

Patients with Common Symptoms That Have a Clear Temporal Relationship with Specific Places

Some conditions are so common that an environmental cause should only be sought when symptoms occur in a temporal relationship with exposure in particular environments. Because any patient may be exposed to something relevant to his or her health either at the workplace or while in other environments, we recommend that healthcare providers ask all patients the questions in Table B (Wilms and Lewis 1991). (Environmental exposures other than mold, such as other allergens or chemical toxins may be related to a patient's symptoms. These should be evaluated if identified.)

If a patient notes that symptoms change in particular environments or that areas of their environment have recurrent moisture problems, he or she should answer the questions in Table C. Negative responses to the questions regarding moisture and mold reassure the healthcare provider and the patient that mold is unlikely to be playing a significant role in the patient's presenting problem. Positive responses begin an assessment which is appropriately pursued if the clinical evaluation leads to a judgment that the environment is contributing to symptoms or disease. This is discussed at length in chapter 6.

Table D provides a list of symptoms about which the clinician should inquire if exposure to moisture or mold is suspected.

Patients Concerned over Perceived Exposure to Mold

With increasing recognition that exposures to mold in the indoor environment may affect health and with media attention emphasizing the potential of poor health consequences, patients may present in the office with few symptoms but with serious concerns over their exposures to mold. Table D provides a strategy to help explore with these patients the breadth of illnesses and symptoms potentially present and their temporal relationship to the environment.

A Note on Potential Occupational Factors

A broad spectrum of environmental characteristics may affect health. Consequently patients' responses to the questions in Table B may identify concerns other than moisture and mold exposure. To understand the significance of specific occupations, jobs, or exposures, the reader is referred to a general occupational medicine text, such as *Occupational Health: Recognizing and Preventing Work-Related Disease* by Barry S. Levy and David H. Wegman or William Rom's *Environmental and Occupational Medicine*. Another excellent reference to search for the significance of a particular chemical exposure is *Chemical Hazards of the Workplace* by Gloria J. Hathaway, Nick H. Proctor, and James P. Hughes.

Evaluation

In some respects, the clinical evaluation of patients suffering from conditions related to environmental exposures is identical to other evaluations. Careful assessment through medical history, physical examination, and judicious use of laboratory tests is essential in establishing a precise diagnosis. The evaluation differs in two important respects: the history must take into account variation in symptoms in relationship to potential exposures, and diagnostic assessment may require trials in and out of exposure settings.

Table B: Questions for Patients with Common Symptoms

1. What is your current occupation?

2. What are your current job and job tasks?

3. Do you notice any change in symptoms at home, work, or in any environment in particular?

4. Do you associate your symptoms with any activity or hobby?

5. Are you exposed to chemicals, fumes, or dusts at work?

6. Are there areas of your home or work that have recurrent moisture problems?

General Clinical Evaluation

The diagnosis of asthma or hypersensitivity pneumonitis can be pursued with spirometry, full pulmonary function tests including lung volumes and diffusion capacity. Challenge testing with methacholine or histamine is used to confirm asthma when spirometry fails to demonstrate reversible bronchospasm in a patient with symptoms consistent with asthma. Chest radiographs, high-resolution computerized tomography (CT), and lung biopsies help to confirm hypersensitivity pneumonitis, but are not sensitive tests. CT of the sinuses will distinguish chronic sinusitis from chronic rhinitis.

Laboratory tests for immune function, organ function (liver, kidney), and inflammatory responses are non-specific. They may help to focus the diagnostic process but do not assist in assessing causal relationships. Total IgE can indicate atopic status. Acute idiopathic pulmonary hemorrhage is marked by the sudden onset of pulmonary hemorrhage in a previously healthy infant. It is associated with acute, severe respiratory distress. Often bilateral infiltrates are seen on chest radiographs (CDC 2004).

A Note on the Health Effects of Mold

The majority of reactions to mold and moisture in the environment are allergic in nature and manifest themselves as asthma or allergic rhinitis. Delayed hypersensitivity is not uncommon and often less well recognized and manifests as chronic rhinitis, sinusitis, or hypersensitivity pneumonitis. Moisture in buildings has been associated with an irritant symptom complex: headache, drowsiness, occasionally cough, dermatitis, and most often burning and irritation of the eyes, nose, and throat. The term “sick building syndrome” is commonly used to describe these irritant symptoms if they resolve, sometimes immediately, without long-term consequences, after the person leaves the environment.

Although toxic syndromes are not well defined from inhalation exposure of mold or mold products in indoor environments, many patients and some physicians have attributed cognitive and other neurological syndromes to mold exposures. There is no consensus as to the nature, pathophysiology, or etiology of these syndromes. (See chapter 4 and Appendix B for discussion on health effects of molds.)

Clinical Evaluation Relative to the Environment

Often the most powerful diagnostic strategy is to evaluate the patient before and after exposure to the environment of concern. When the etiology of a condition is unknown and the individual is working or living in the environment of concern, judicious trials away from and back in the environment allow the physician and the patient to evaluate the likelihood that a job or home is playing a role in an illness. Such trials should be coupled with careful measurement of pertinent physical exam, laboratory, or physiologic parameters. Bracketed spirometry, for example, involves spirometry after at least 2 full days away from the environment and again after exposure (usually at the end of the same day or after the onset of symptoms). Serial peak flow measurements obtained at least 4 times a day for 2 consecutive weeks may assist in evaluating physiologic response to an environment.

Because the late phase of asthma, hypersensitivity pneumonitis, and chronic rhinitis may take several weeks or even months to improve after removal from exposure, a longer duration may be required for adequate evaluation of pre- and post-exposure. The diffusion capacity is a more sensitive indication of an interstitial process such as hypersensitivity pneumonitis and can be used over time to

monitor responses to changes in environment. This kind of trial best follows an environmental assessment, which increases the suspicion that the medical condition is environmentally induced.

Antibodies to specific antigens can be measured in the blood (radioallergosorbant test [RAST] or ensyme-linked immunoassay [ELISA]) or with skin prick tests. IgG antibody testing to mold or other antigenic exposures may be used to confirm a preliminary diagnosis of hypersensitivity pneumonitis. IgE testing is used to confirm an allergic mechanism (such as in asthma or rhinitis). Specific IgE antibodies for a variety of allergens are available. The validity of either test depends on the purity and specificity of the antigenic reagents used. Most reagents for mold consist of crude extracts of the substance; very few test reagents have been standardized. Studies have shown that there is a wide variation in the antigenic potency from one company that manufactures these extracts to another. (This is in contrast to dust mite, pollens, and some animal antigen reagents, which are well identified and purified. As a result, the clinical reaction to dust mite, pollens, and some animal antigen reagents correlates well with the laboratory test.) Because reagents to many molds are not commercially available and knowledge of the specific life stage or component of the mold that creates the sensitization is limited, the correlation between positive tests and clinical disease is poor. With skin testing there is a high degree of false positive results because of irritants and non-specific histamine releasers in the mixture, and there is a high degree of false negatives by RAST and ELISA testing because of the allergens used. A more extensive discussion of approaches to testing for specific antibodies is provided in Appendix C because of the interest patients express in being "tested for mold."

A Note on Discussing Mold and Moisture with Your Patient

Recurring leaks or continuous moisture are indicative of environments that support indoor growth of mold. Questions about the frequency of water leaks and presence of moisture in the home allow the health provider to explore the potential that microbial growth in the patient's home is contributing to the patient's illness. Suggested subjects include air conditioners and dehumidifiers (and maintenance practices designed to control accumulation of water and dirt in the system including in drip pans); roof, window, basement and plumbing leaks; and conditions (especially in bathrooms and kitchen) that encourage condensation.

Appropriate conclusions drawn from this discussion may be counter-intuitive. For example, occasional mold spots on shower curtains that are appropriately cleaned are not likely significant. Conversely, the presence of an air conditioner or dehumidier that is not maintained carefully (even though air conditioners and dehumidifiers are used to improve the indoor environment) may suggest concern.

Evaluation Tools

Two questionnaires are provided to help the healthcare provider evaluate the patient further when an environmental component is suspected. The first one, Table C: Environmental Questionnaire, is designed for the patient to fill out independently in a few minutes. It consists of a set of questions that explore moisture and mold in the patient's home, school, or work environment. Any positive response (except to questions on environmental tobacco smoke) may indicate uncontrolled moisture with a corresponding potential for biological growth. We recommend providing these patients (who presented with sentinel conditions or have temporal patterns of concern) with the list of suggested references in

Table C: Environmental Questionnaire (For Patients with Sentinel Conditions, Symptoms that Vary by Environment, or a History of Recurrent Moisture Incursion)		
About hour home		
Do you have a **central humidifier or air conditioner**? If yes, is the system cleaned infrequently?	☐ Yes ☐ Yes	☐ No ☐ No
Do you have **room humidifiers or air conditioners**? If yes, is the system cleaned infrequently?	☐ Yes ☐ Yes	☐ No ☐ No
Is there **wall-to-wall carpet** in your bedroom?	☐ Yes	☐ No
Do you **regularly see mold on tiles, ceilings, walls, or floors** in your bathroom (other than occasionally on the shower curtain or tub enclosure)?	☐ Yes	☐ No
Do you see **mold** in your **basement on walls, ceilings, or floors**?	☐ Yes	☐ No
Do you **usually smell a musty odor** anywhere in your home?	☐ Yes	☐ No
Does your **roof leak**? If yes, how often? ☐ Daily	☐ Yes ☐ Monthly	☐ No ☐ Once a year
Does the **plumbing in your kitchen or bathroom leak**? If yes, how often? ☐ Daily	☐ Yes ☐ Monthly	☐ No ☐ Once a year
Are there **wet spots anywhere in your home, including your basement**?	☐ Yes	☐ No
Do you often see **condensation (fog) on the inside of windows and/or on cold inside surfaces**?	☐ Yes	☐ No
Environmental Tobacco Smoke*		
How many people who live in your home, or visit it regularly, smoke on a daily basis?	___Adults	___Children
*We include this question because of the broad and often synergistic health effects from exposure to environmental tobacco smoke.		

Table C: Environmental Questionnaire (Continued) (For Patients with Sentinel Conditions, Symptoms that Vary by Environment, or a History of Recurrent Moisture Incursion)		
About other environments		
Sometimes people experience symptoms in places other than the home. Children spend considerable time in school environments. For adult patients, please consider the locations and work environments where you spend most of your time outside your home to answer these questions. For children or their parents, please answer about the child's school.		
Outside the home, I (or my child) spend(s) most time at _____		
For adults, my occupation is _____		
How many days a week are you at your workplace or are you (or your child) at school?	___Days per week	
How many hours each day are you at your workplace or are you (or your child) at school?	___Hours per day	
Do you see **mold** anywhere (including ceilings and walls) in this place or general work area?	☐ Yes	☐ No
Do you usually **smell a musty odor** anywhere in this place or general work area?	☐ Yes	☐ No
Are there areas with recurring **wet spots** in this place or your general work area?	☐ Yes	☐ No
Has there been **a history of leaks or flooding** in the building at this place or at work?	☐ Yes	☐ No
Do you often see **condensation (fog) on the inside surface of windows and/or on cold inside surfaces such as metal shelves**?	☐ Yes	☐ No
Is there **carpet** in this place or classroom, or at your **general work area?** Has it been **frequently wetted** by spills and/or leaks?	☐ Yes ☐ Yes	☐ No ☐ No
Positive responses to the questions on Table C indicate that further discussion with the patient on the environment would be helpful to explore if it is contributing to symptoms or disease. Negative responses to the questions regarding moisture and mold reassure the provider and the patient that mold is unlikely to be playing a significant role in the patient's presenting problem.		

Table E: Environmental Remediation Guidance. We provided qualifying questions about air conditioning, roof leaks, and plumbing leaks to enable the clinician to explore the likelihood of problem moisture.

The second environmental evaluation tool, Table D: Current Symptoms - History and Relationship to Home, Work, or School, is a grid the healthcare provider can use to guide an exploration with the patient of his or her particular symptoms and how he or she experiences them in specific home or work environments. This questionnaire can be completed either independently by the patient or used to guide a conversation between practitioner and patient. Once an association with a moist and/or moldy environment has been established for patients with either sentinel conditions (Table A) or common symptoms in temporal relationship with certain environments, especially wet or moldy ones (Table B), a discussion about the responses to Table D is helpful to more fully explore the patient's potentially mold-related symptom(s). In addition, as stated earlier, we suggest this tool would be instructive with the third group of patients (those who are concerned generally over a potential mold exposure).

A Note on Humidifiers, Air Conditioners, and the Resource List

With concern over growth proliferating in drain pans, the presence of humidifiers and air conditioners may be a reason to provide the patient with the Resource List. Unless diligently maintained, these appliances hold substantial potential for supporting sources of unhealthy bioaerosals. This is especially true for central air conditioners. When a patient is experiencing illness or symptoms with even a suspicion of environmental association, it is useful to provide the references on mold remediation.

A Public Health Model: The Sentinel Case

Once a building relationship is established, the healthcare provider is encouraged to exclude a more general public health problem related to the building. Without requesting names, the provider should ask whether other individuals in the building have similar symptoms.

In many states, physicians must report occupational diseases of any type to the state department of health or labor. In all states, if multiple individuals are involved, the conditions should be reported to the state health department, and an industrial hygienist or someone with experience in evaluating buildings for building-related illnesses should evaluate the building to identify the cause of the illness. Sources of water intrusion and mold amplification need to be identified and recommendations for repairs need to be made.

Management and Remediation

Medical Management and Follow-up

Patient care for the treatment of building-related illnesses include (1) removal from the environment, (2) rectifying the condition in the building causing the illness, and (3) medical therapy of the underlying condition. Too frequently, the first two are ignored and only treating the underlying condition is emphasized. Removal from the environment needs to be seriously considered when the condition is severe or seems to be progressive over time. It is especially important in conditions that may become irreversible, such as asthma and hypersensitivity pneumonitis. The prognosis for resolution of occupational asthma is related in part to the duration of exposure to the instigating agent prior

Table D: Current Symptoms - History and Relationship to Home, Work, or School (For Patients in Which a Potential Exposure to Mold Exists)										
Symptoms that may be related to mold	**Please circle your response**									
Are you troubled by:			**How is it at home?**			**How is it at work or school?**			**Comments**	
Wheezing or whistling in your chest?	Y	N	Better	Worse	Same	Better	Worse	Same		
Waking up first thing in the morning with a feeling of tightness in your chest?	Y	N	Better	Worse	Same	Better	Worse	Same		
Waking up during the night with shortness of breath?	Y	N	Better	Worse	Same	Better	Worse	Same		
Shortness of breath when you are not doing anything strenuous?	Y	N	Better	Worse	Same	Better	Worse	Same		
Waking up during the night by an attack of coughing?	Y	N	Better	Worse	Same	Better	Worse	Same		
Chest tightness when you were in a dusty part of the house or with animals (for instance dogs, cats, or horses) or near pillows (including quilts)?	Y	N	Better	Worse	Same	Better	Worse	Same		
Chills or fever?	Y	N	Better	Worse	Same	Better	Worse	Same		
Aching all over?	Y	N	Better	Worse	Same	Better	Worse	Same		
Runny, blocked, or stuffy nose?	Y	N	Better	Worse	Same	Better	Worse	Same		
Headaches?	Y	N	Better	Worse	Same	Better	Worse	Same		
Extreme or unusual lethargy and/or tiredness?	Y	N	Better	Worse	Same	Better	Worse	Same		
Frequent sinus congestion?	Y	N	Better	Worse	Same	Better	Worse	Same		
Frequent nose bleeds?	Y	N	Better	Worse	Same	Better	Worse	Same		
Hoarseness?	Y	N	Better	Worse	Same	Better	Worse	Same		
Feelings of unsteadiness when walking?	Y	N	Better	Worse	Same	Better	Worse	Same		
Memory loss?	Y	N	Better	Worse	Same	Better	Worse	Same		
Difficulty recalling names of people you know?	Y	N	Better	Worse	Same	Better	Worse	Same		
Nausea?	Y	N	Better	Worse	Same	Better	Worse	Same		
Vomiting?	Y	N	Better	Worse	Same	Better	Worse	Same		
Diarrhea?	Y	N	Better	Worse	Same	Better	Worse	Same		
Skin conditions?	Y	N	Better	Worse	Same	Better	Worse	Same		

to removal (Chan-Yeung and Malo 1995). This makes timely recognition of the condition and removal of the patient from exposure important.

Administrative issues arise when the environment of concern is a place of work (worker's compensation), a school, a rented home, or a situation insured against loss related to mold or moisture. Healthcare providers need to provide clear documentation regarding diagnosis, temporal relationships of symptoms, and findings relative to exposures and conclusions.

Environmental intervention could be a "fix-it" solution to eliminate moisture incursion and moldy materials by, for example, repairing a leaky roof and replacing damaged materials, or it could involve a program of improved maintenance. (Remediation is discussed in chapters 6 and 7.) It has been shown that patients with upper respiratory allergic syndromes, who work in buildings with significant airborne loads of fungal antigens, can have their symptoms resolve after the reservoirs of fungal organisms are eliminated by instituting a more rigorous maintenance program for the building's heating, ventilation, and air-conditioning (HVAC) system (Hiipakka and Buffington 2000).

A Note on the Use of Antifungal Agents

Some clinicians have raised the possibility of treating symptomatic patients who have been exposed to indoor mold growth with oral antifungal agents (typically azoles). There is no support in the medical or scientific literature for this approach in the absence of documented tissue invasion, and we do not recommend the use of antifungal agents.

After remediation, clinical follow-up is critical in evaluating the success of the intervention. Frequently, the offending mold can be decreased to a tolerable level, but once an individual is sensitized, this may not always be possible. Unfortunately, current methods of mold detection are not sensitive or quantitative enough to be able to determine if the exposure has been sufficiently decreased. The only assessment for someone very sensitized to mold is to allow the individual to return to the environment and monitor his or her condition carefully to determine if there is an exacerbation of symptoms. Once an individual has developed asthma, the asthma may not subside completely, even when exposure to the original agent has ceased (Chan-Yeung and Lam 1986, Chan-Yeung and Malo 1995). So, one must monitor the severity of asthmatic symptoms and the quantity and type of medications that are required for asthma control. The severity of the asthma must be carefully assessed according to the Asthma Task Force Guidelines (NHLB 1997) and the patient must be treated accordingly until the symptoms are stable at the lowest level of severity. At that point, the patient may be returned, on a trial basis and with careful oversight to detect exacerbation, to the remediated building.

The medical management of allergic and irritant syndromes is no different for those related to mold exposure than for other types. Antihistamines, inhaled nasal corticosteroids, and inhaled pulmonary corticosteroids can be prescribed as needed. The clinician needs to be aware of the possibility that symptoms are suppressed in the setting of ongoing exposure to pertinent agents, particularly antigens. This may result in greater morbidity over the long term because removal from the environment of concern may not occur. Concomitant use of medical therapy during evaluation and remediation of an environment is, however, not only acceptable but important in the recovery of the individual.

Environmental Intervention

The health care provider can provide a list of resources (Table E) to the patient who has been identified as potentially having problem mold in his or her home or workplace, either because specific conditions in the home are indicative of mold and moisture (Table C) or a pattern of symptoms is associated with a particular environment (Table D).

Table E: Environment Intervention Guidance (Selected World Wide Web Resources)

United States Environmental Protection Agency
Indoor Air-Mold
http://www.epa.gov/mold/
http://www.epa.gov/iaq/molds/moldresources.html

Mold Remediation in Schools and Commercial Buildings
http://www.epa.gov/iaq/molds/mold_remediation.html

A Brief Guide to Mold, Moisture and Your Home
http://www.epa.gov/iaq/molds/moldguide.html

California Department of Health Services
http://www.dhs.ca.gov/ps/deodc/ehib/ehib2/PDF/MOLD_2001_07_17FINAL.pdf
Mold in My Home: What Do I Do

Canada Mortgage and Housing Corporation
http://www.cmhc-schl.gc.ca/en/burema/gesein/Momo/index.cfm
Fighting Mold; Moisture and Air: Problems and Remedies

University of Minnesota
http://www.dehs.umn.edu/iaq/flood.html
Managing Water Infiltration into Buildings

New York City Department of Health and Mental Hygiene Bureau of Environmental and Occupational Disease Epidemiology
"Guidelines on Assessment and Remediation of Fungi in Indoor Environments"
http://www.ci.nyc.ny.us/html/doh/html/epi/moldrpt1.html

6. Environmental Assessment

When exposure to mold plays a role in the patient's health, consideration of the environment becomes a key element in understanding and treating the patient's illness.

Fruiting bodies of a *Peziza sp.* in a room with chronic water damage. *Peziza sp.* is an ascomycete (producing sexual ascospores in a structure called the ascus) and is also known as one of the cup fungi. It is occasionally found on chronically wet or water-damaged wood products (such as plywood subfloor). *Peziza* can be identified only when the sexual fruiting body is present. In culture, its vegetative state is named *Chromelosporium sp.* (Image courtesy of Michael Underhill, CIH, CSP of Trident Environmental Services, Inc.)

This chapter gives practitioners an abridged version of the principles that underlie a professional environmental assessment so they can (1) better evaluate patient information about their environments and (2) use environmental assessment as a tool to prevent mold-related illnesses and to treat individual patients presenting with symptoms and illnesses exacerbated by mold in their environment.

Resources to initiate a professional assessment are most often absent or at best limited. Consequently, when exposure to mold indoors is potentially associated with symptoms, the healthcare provider may choose to give the patient a home checklist (Table C) and a list of references (Table E) as guidance on how to minimize mold growth in his or her environment, without initiating elaborate environmental assessments to confirm the presence of mold.

The reader is referred to the following references for detailed guidance on how buildings are evaluated for bioaerosols and mold:

- *Bioaerosols: Assessment and Control*, 1999; Ed: Janet Macher, American Conference of Governmental Industrial Hygienists.

- *Mold Remediation in Schools and Commercial Buildings,* March 2001; U.S. Environmental Protection Agency; EPA 402-K-01-001.

- *Fungal Contamination in Public Buildings: A Guide to Recognition and Management,* June 1995; Federal-Provincial Committee on Environmental and Occupational Health; Health Canada.

- Microorganisms in Home and Indoor Work Environments: Diversity, Health Impacts, Investigation and Control, 2001; Ed: Flannigan, Samson and Miller; Taylor & Francis; London and New York.

When is it important to intervene in the home or work environment? The algorithm presented in chapter 5 provides guidance for the physician. An assessment of mold in the environment may become especially important for patients with specific symptoms and syndromes (see Table A in chapter 5) or for patients with other common symptoms and syndromes (see Table B and Grid D in chapter 5) that are worse in a particular environment. The reader should note that the authors do not advocate air sampling to initially address concerns over mold in the indoor environment. This is in part because air test results are often not representative of the biological exposures a patient may face and, therefore, can be misleading and not helpful. Because the health provider may be given reports and information that includes air-sampling results, this chapter provides guidance on planning an indoor air assessment for mold and on interpreting air-sampling results.

Consultant Selection and Staff Training

Patients may bring healthcare providers reports with contributions from different types of professionals, including specialists in ventilation, industrial hygiene, environmental science, architecture and building physics, occupational and environmental medicine, mycology, and public health. To evaluate and then use the information in these assessments, it is critical to know the context of the assessment and the background and credentials of the individuals who performed them. The US EPA provides guidance on hiring assistance for indoor air quality assessment and remediation in various programs: the I-Beam Visual Reference Index (www.epa.gov/iaq/largebldgs/qref_frame.htm), Indoor Air Quality Tools for Schools (EPA Tools for Schools Kit,www.epa.gov/iaq/schools/tfs/guidea.html) and Indoor Air Quality in Large Buildings (Building Air Quality, www.epa.gov/iaq/largebldgs/graphics/sec_8.pdf).

For the healthcare provider who may look to suggest an outside environmental assessment, the following paragraphs briefly discuss three categories of professionals who will most likely bring a learned approach to the challenge of assessing the environment for exposures to bioaerosols: industrial hygienists, indoor environmental quality consultants, and environmental health professionals. Although not as common, other professionals may provide assessments or specialized expertise to address indoor environments. **Experience conducting environmental assessments with a focus on bioaerosols** is a key qualification for any of these professionals.

Frequently, it is also helpful to consult with mycologists and building scientists. Mycologists knowledgeable about indoor-mold-contamination issues bring a critical perspective to designing sampling programs and interpreting results. Building scientists (usually architects or engineers who have specialized expertise) bring helpful skills and an understanding of the movement of moisture and air in the building, which are often instrumental in finding and remediating moisture intrusion.

Industrial Hygienists

In the broadest sense, an industrial hygienist focuses on exposures that affect the health and well-being of workers. These individuals are well versed in measuring and assessing occupational hazards. The American Board of Industrial Hygiene (ABIH) certification program requires a bachelor's degree in an associated field (usually engineering or one of the natural sciences), passage of an examination covering a broad range of relevant subjects, and a minimum of 5 years' experience in some association with a practicing Certified Industrial Hygienist (CIH). The ABIH had offered certification in indoor air quality; however that certification is no longer available. Certified Industrial Hygienists have the training to develop the broad perspective required to address mold in the environment. However, because (1) exposure to bioaerosols is not readily identified by standard air-monitoring methods, (2) home and office environments are different than industrial sites, and (3) the biology of mold is complex, an assessment is best completed by an industrial hygienist **experienced with mold assessment**.

A qualitative assessment that identifies factors that support the growth of indoor fungi and makes recommendations for correcting these factors provides helpful guidance for the healthcare provider and the patient. Measurements of fungal colonies and spore counts are not as helpful.

Indoor Environmental Quality (IEQ) Consultant.

Individuals who practice as indoor environmental/air quality consultants come from many different backgrounds (engineering, basic sciences, planning, and design) and different professions (ventilation, building engineering, industrial hygiene, environmental science, construction, and architecture). Some IEQ consultants bring an appreciation of agents in the environment and exposure because they have worked on environmental problems with a concern for health impacts. However, other environmental professionals, though competent in their individual expertise, lack either the broad health perspective or specific knowledge regarding bioaerosols needed for an adequate assessment when mold may be an issue. For example an IEQ consultant may have specialized experience with ventilation systems, but lack an understanding of sources and distribution of bioaerosols in the environment. As with Certified Industrial Hygienists, IEQ consultants who are **experienced in determining exposures from mold in the environment** provide the better assessments.

Environmental Health Professional

Because an understanding of the building occupants' illnesses and symptoms has become critical to appropriately focus the investigation in many situations, environmental health professionals have assumed an active role in environmental assessment. Occupational and environmental medicine physicians and nurses, as well as public health professionals (Masters in Public Health and graduate-level epidemiologists), bring relevant background to environmental assessment. The patterns and locations where occupants experience symptoms help direct where to look for mold sources. Moreover, the local health director or state official is not infrequently the person who directs or orders an environmental assessment in a public building, such as a school, when poor indoor environmental quality is suspected because of a high level of health complaints.

Patient or Family Member as Investigator of Environment

The patient or a family member may assess the environment for mold. One caution: if you suspect mold is present and may be playing a role in illness and you direct your patient to investigate his or her environment beyond the home checklist, it would be prudent to suggest that the patient use care when exploring his or her environment. If the individual develops symptoms while investigating, he or she should be cautioned to ask someone else to explore for and clean up mold contamination if needed. Guidance on personal protection and how to remediate mold contamination is addressed in the next chapter of this book.

Qualitative Approach to Environmental Site Assessment

A qualitative assessment that identifies factors that support the growth of indoor fungi and makes recommendations for correcting these factors provides helpful guidance to the healthcare provider. We use the term "assessor" to identify the individual conducting the evaluation. The assessor can be the patient, a family member, or a professional.

The environmental assessor seeks to identify sources of mold growth (reservoirs) and to define the pathways in the environment that may bring mold and any associated toxins into contact with the building occupants (Burge and Otten 1999). The objective is to find areas where mold is amplified (growing) and then disseminated into the breathing space. Normally, people should not see or smell mold or mildew in their indoor spaces. A moldy odor or visible evidence of mold colonies or mildew on materials indicates the presence of mold. However, mold may be present even if not smelled or seen.

Interview and Walk-through Assessment

The assessor gathers qualitative data by interviewing the occupants and taking a walk-through site tour. If the assessor is the patient, noting where in the home environment and under what conditions (such as heat on or off) he or she experiences symptoms will indicate where to look. The walk-through will explore the immediate outside environment and the physical structure of the home or building; note water or moisture incursion from past and present leaks, spills, and condensation; review ventilation and

note apparent mold, mildew, and areas with moldy, musty odors. Likely places where moisture may accumulate, such as crawlspaces, should be noted.

Focused Qualitative Assessment

The assessor will minimally address the following (adapted from Macher 1999, Health Canada 1995):

- A review (visual assessment) of the immediate outside environment and building exterior for:
  - Sources of outside molds (for example, leaf piles).
  - Damage to the building (roof, wall, windows and foundation), especially damage that would allow water intrusion.
  - Accumulations of organic material in or near air intakes (e.g., bird or bat droppings because they support the growth of pathogenic fungi and plant material that generally supports fungal growth).
  - Grading (poor drainage and below-grade air intakes or basement windows).
  - Evidence of standing water where it may be affecting the indoor environment.

- Heating, ventilation, and air-conditioning (HVAC) system assessment of:
  - Filters (dampness and microbial growth, dirt).
  - Heat exchangers (e.g., cooling coil section including drain pan), ductwork, and air diffusers (for dampness, microbial growth, dirt, and rust).

- Occupied space survey of:
  - Water damage (leaks, high humidity, musty or moldy odors).
  - Chronic condensation (typically cool surfaces such as outside walls and windows).
  - Air conditioners (standing water, microbial growth, dirt).
  - Carpet (for evidence of water damage).
  - Other fabric materials such as upholstery, furniture, and drapes (for dampness, microbial growth, and dirt).
  - Portable humidifiers (for standing water, microbial growth, and dirt).
  - Plants (for mold growth on dirt and on plants and for water damage on flooring beneath pots).

Ventilation System Review

Because the way air moves in the building and the condition of the HVAC system, if present, are critical aspects of bioaerosol exposure, a systematic review of the mechanical ventilation system should be part of the initial walk-through assessment. Indoor environments are ventilated with different systems. For example, the simplest system may be operable windows that allow outside air into homes and buildings. More complex ventilation will use central intakes to bring in air, filter and condition it, and then disburse the conditioned air into the space. This section describes key elements of reviewing ventilation systems and is followed by a brief discussion of home ventilation.

Ventilation systems in buildings often operate differently from the design specifications when they were first engineered. Because the amount and quality of the air flowing through the system can be of critical importance to the indoor air quality, a qualitative assessment of the ventilation system is a key aspect of assessing the patient's environment.

Ventilation with outside air can dilute the concentration of indoor contaminants. Mechanical ventilation systems should be properly maintained to optimize the volume of dilution air and to minimize the accumulation of contaminants, specifically microbial growth, within the ventilation systems themselves. Ventilation systems can supply buildings with tempered and dehumidified outside air. It is important to note, however, that ventilation effectively dehumidifies buildings only when the outdoor air dew point is less than 55°F. Above dew points of 70°F or so, ventilation is likely to become the dominant source of indoor water vapor.

Although mechanical ventilation systems have varying design characteristics, the following approach can be followed to qualitatively evaluate the system's cleanliness from a microbial growth perspective. When evaluating a ventilation system, it is helpful to have the assistance of the building's maintenance or mechanical engineering personnel. These individuals can provide access to the unit, are familiar with the unit's maintenance history, and can describe the system's design parameters.

Mechanical ventilation systems should supply buildings with outside air. As part of a ventilation system evaluation, the assessor should identify the location of the outside air intake. These intakes should be at least 20 feet from potential microbial reservoirs such as cooling towers, standing water, and gutters filled with leaves, pigeon droppings, or other organic material. Because all outside air contains bioaerosols, ventilation systems should have efficient filters that can remove some of this material from the incoming air stream. These filters should be replaced regularly (ideally quarterly) as part of a preventive maintenance program.

Once the outside and/or recirculated air passes through a bank of filters, it may be tempered by passing over either heating or cooling coils. Because cooling coils remove moisture from the air stream, a drain pan should be located below the coils to collect condensate. This pan should be sloped to prevent the build-up of standing water and microbial growth in the pan. If the ventilation system is designed to humidify the air — not recommended unless special circumstances call for humidification — care should be taken to prevent the humidification system itself from becoming a microbial reservoir and amplifier.

The condition of the filters and the drain pan can be evaluated visually by opening the air-handling unit when the system is not in operation.

After the air has been tempered, it may pass through a series of ducts until it is distributed to the occupied spaces. A visual assessment of the ductwork may be possible through access panels.

Ducts without internal lining are desirable. Ducts with internal lining or duct board can become microbial reservoirs and amplifiers if they become humid and dirty. A combination of internal fiberglass insulation and condensate water blowing off the cooling coil causes the most extensive mold growth in ducts.

Environmental assessment in homes focuses on good maintenance practices to ensure dirt and moisture do not accumulate and to provide adequate ventilation.

Ventilation in Homes

Outdoor air enters and leaves a house by infiltration, natural ventilation, and mechanical ventilation. Most home heating and cooling systems, including forced air heating systems, do not mechanically bring fresh air into the house. A home's ventilation rate can be increased by opening windows and doors, operating window or attic fans when the weather permits, and running a window air-conditioner with the vent control open. Environmental assessment in homes focuses on good maintenance practices to ensure dirt and moisture do not accumulate and to provide adequate ventilation.

When concerned about a patient's symptoms that may be related to exposure to bioaerosols in the home, the clinician should inquire about the home's air handling systems and maintenance. Before the heating season, forced air heating systems should be inspected and, if necessary, cleaned. Before the cooling season, several components of the central air conditioning system should be cleaned. Bushes and vegetation should be trimmed around the outside condenser unit and the coil and fan should be cleaned. The system's filters should be replaced or cleaned several times per season and the condensate drain should be regularly checked to ensure that it is carrying off excess moisture.

When mold is a concern, a good initial assessment notes:

- **Water damage** (from leaks, high humidity) and any **musty or moldy odors**.
- **Chronic condensation** (typically cool surfaces-outside walls, windows) and any **standing water** possibly from air conditioners, humidifiers.
- **Carpet condition** (especially any sign of water damage and age).
- **Condition of fabric and porous materials** such as upholstery, furniture, drapes, ceiling tiles, partitions, books (again, dampness and microbial growth, dirt).
- **Plants** (mold growth on dirt; consistent water spillage).

A window-installed air conditioner has the same components as a central system. Routine upkeep of these units should include keeping the filters and coils clean. In addition, the condenser coil and the intake vents should be free from obstruction and the condensate drain outlet should be kept unplugged and positioned away from the house.

Summary of Qualitative Assessment

The assessor will evaluate the information gathered from the walkthrough, interviews, and ventilation review. If the information is adequate, the assessor may identify how the patient has become exposed to

mold in the environment and may suggest changes to the environment to limit the exposure. When there is evidence of moisture incursion, a good assessor suggests that the causes for the unplanned moisture be fully investigated and fixed, mold present on nonporous materials be cleaned, and all repeatedly wetted, water damaged porous materials be discarded. Often the qualitative evaluation is sufficient to begin planning appropriate improvements to the environment that will limit the patients' exposures from microbial growth.

When there is evidence of moisture damage, the causes of moisture intrusion should be fully investigated and fixed, mold present on nonporous, easily accessible materials cleaned, and other damaged materials discarded.

Sampling and Analysis

During some walk-through assessments, the assessor may have determined that water or dampness has provided an environment conducive to mold growth, but the assessor may be unsure about the extent of the mold contamination. If building-related illness is strongly suspected, mold is thought to be a potential problem for the patient, and there is insufficient information to broadly suggest where mold is growing, the assessor may need to implement a well-planned program of sampling and microscopic analysis in order to develop information on which to base guidance on appropriate intervention in the environment.

A well-thought-out sampling plan is the first step. The plan should reflect an understanding of the purposes of the investigation, the characteristics of mold, and the potential for exposure, along with an understanding of pathways and the limitations of both sampling and laboratory techniques. With the intent to determine exposures, when, where, and how the environment is sampled are critical to producing useful information. The quality of the results also depend on the education and training of the analyst and quality of the mycology laboratory. At the end of appendix A we have included charts summarizing air-sampling methods, source-sampling methods, and analytical methods that the healthcare provider may find helpful when navigating technical reports with indoor mold sampling results.

Generally, the assessor may use two types of sampling: *source sampling* of materials where mold may be growing (such as wood, carpets, wallboard, and adhesives on wallpaper) using swabs,wipes, or adhesive tapes and *air sampling*, where a standard volume of air is passed through a filter or impacted on growth media plates or greased microscopic slides to collect mold and spores. The American Conference of Governmental Industrial Hypienists (ACGIH) guidance *Bioaerosols Assessment and Control* (Macher 1999) *and Microorganisms in Home and Indoor Environments* (Flannigan et al. 2001) discuss sampling protocols. A competent mycologist should be consulted, especially when you are uncertain as to the specific mold species or molds likely to be present in the indoor environment.

Source Sampling and Microscopic Assessment

Once moisture becomes available, mold will grow on a variety of substrates normally found in our indoor environments. Although mold growth may not be evident by visual inspection, the assessor with microbiological training will often confirm mold growth on materials with a tape sample. This microscopic examination of the residue picked up by clear tape may indicate the type of mold present. For comparison, the assessor will sample areas not indicating moisture or mold.

Bulk and Settled Dust Sampling and Microbial Culturing

The assessor may collect bulk samples of suspected mold-contaminated materials or collect dust from the materials to be analyzed for mold, as well as other allergens. The results will identify levels and dominant species, which will help the assessor characterize the burden of mold from the particular source sampled.

Air Sampling

A qualitative assessment, as outlined in this chapter, is often more valuable than air sampling to determine whether there is likely exposure to problem mold. This is because colonies of mold isolated from sampled air do not identify an unhealthy environment. More important, the failure of mold colonies to develop from sampled air does not indicate a healthy environment.

There is substantial natural variability in the amount of mold in air. Understandably, the EPA and other government agencies have not set numeric standards for indoor concentrations of mold or mold spores.

Mold is measured in air samples as colony forming units per cubic meter of air (CFU/m^3) by culturing. (Techniques to assess for mycotoxins and mold components, such as ergosterol and beta-1,3-glucans, are available and useful in a research setting .) Most often the assessor will use volumetric samplers to capture a specific volume of air and allow it to pass by a plate with the appropriate nutrient media so that, when incubated properly at a laboratory, any viable and culturable spores present will grow into mold colonies that can be identified and counted. Malt extract agar is typical for a general fungal population, but when *Stachybotrus chartarum* is suspected, cornmeal agar or Czapek cellulose agar is more appropriate. Because this technique samples the air for a short time (most often 1-8 minutes) in one discrete location, plus the fact that there is considerable spatial and temporal variation of airborne fungi, the number, time, and location of samples are critical to data quality. Appropriate reference samples are also required, because the results are often meaningful only in relation to the outdoor environment.

Another partially quantitative approach is to collect spores on membrane filters or slides. Spores are counted and provide some information about the type of fungal spores present. These “spore trap” techniques can estimate the burden of mold in environments that are (heavily) contaminated. Because they require less time than standard air sampling, where incubation often requires multiple days or weeks, spore trap techniques can be helpful in screening.

Several Polymerase Chain Reaction (PCR) technologies to detect and quantify fungi and bacteria have been developed, including a technology patented by the US EPA research laboratories in Cincinnati, Ohio (US EPA 2004). The measurement tool is based on the *in vitro* exponential amplification of species-specific DNA sequences so that they can be detected using fluorescent spectrometry. The technology is called Real-Time Polymerase Chain Reaction (Real-Time PCR) or Quantitative PCR (QPCR). The QPCR technology is very sensitive and requires exceptionally good laboratory practice to minimize cross-contamination and false-positives. Several laboratories have licensed and commercialized the technology. The use and application of the technology as a tool in mold testing and assessment is in the early stage. In order to fully understand the principles and details of the technology when reviewing and interpreting results, practitioners may want to discuss the technology with an experienced professional.[1]

Limitations and Difficulties with Mold Concentration Standards

Establishing standards based on fungal concentration threshold levels may appear reasonable at first glance, but this assumption is fundamentally incorrect. Based on fungi ecology, our current knowledge of health effects associated with fungal exposure, and basic environmental assessment and industrial hygiene principles, not enough is well understood about the short- and long-term dose-response relationships, fungal concentration variability over time, and toxic effects of fungal elements to support a standard.

Quantification of bioaerosols and their active components in the indoor environment may be a necessary element of research programs. Nevertheless, the cost and complexity of meaningfully interpreting air-sampling data limit their utility in patient care.

Interpretation of Air-sampling Data

An environmental assessor will review air data carefully to determine if there is mold growth or amplification and if species that might merit added concern are present. Methods for sampling have limitations, and the ecology of fungi and mold complicates sampling. (Fungi are ubiquitous in the environment, characterized by multiple forms, may integrate into substrate materials, and follow seasonal and diurnal patterns.)

The review and interpretation of air sampling results is fraught with complexity.

The healthcare provider should review the results of air sampling with an understanding of this difficulty. The ACGIH (Macher 1999) and Health Canada (Health Canada 1995) provide detailed guidance on interpreting air-sampling data. In summary, these references suggest:

[1] Although this discussion addresses environmental samples, PCR technology has been used to detect *Aspergillus fumigatus* in rabbit lung tissue and bronchial lavage fluid. If this PCR assay technique proves applicable to humans, it may have utility in diagnostic evaluation for pulmonary aspergillosis (O'Sullivan et al. 2003).

- Mold indoors should reflect the outside species and the movement of outside air into the indoor environment. Mold identified in air sampled indoors should be at lower concentrations and of similar types to molds identified in air sampled from the outside. If the concentration inside is higher or the species different from the outside air, mold is suspected to be growing (amplifying) inside.[2]

- A specific species (other than, perhaps, species that may reflect a particular outside type dominant in certain climates at certain times) should not dominate the mold in the indoor air. If other species occur as a significant percentage indoors, and they do not correspond to outdoor relationships, an indoor source of the species is more probable.[3]

There is an allure to establishing a fungal concentration standard for indoor air to guide decisions. However, threshold levels of fungal concentrations in the indoor air have not been established and with our current knowledge would not be helpful in understanding exposure risk to patients.

- It is important to explore for indoor moisture and areas where the mold may be growing if certain toxigenic or highly allergenic molds—species of *Stachybotrys*, *Aspergillus*, *Penicillium*, and *Fusarium*, for example—are confirmed in the indoor air and are more dominant than in the outside samples. **Remediation should not be based on air sampling alone, however, even if these certain species are present in the sampling results.**

- Air sampling is limited, and negative results do not document the absence of mold exposure. For example, mold may be growing in carpets or on walls and wallpapers, yet not be airborne at the time of the sampling. Where there are other indications, such as moisture noted where it should not be, further investigation for hidden sources is indicated.

Additional Quantitative Approaches

We began this chapter emphasizing that, with concern over bioaerosol exposure, a good assessor will begin with a qualitative assessment to identify sources of moisture in the indoor space, and we conclude by noting two quantitative approaches directed at moisture that may be helpful additions. Haverinen and colleagues published a model demonstrating that moisture characterized by location and

[2] Readers who would like to review individual case studies for examples of one scientific approach to interpreting data should see chapter 4.4 in Flannigan, Samson, and Miller (Morey 2001).

[3] For an example, the reader may refer to a study in which fungal profiles inside buildings (where occupants had health complaints) tended to remain unchanged with *Penicillium sp*. dominant, while outdoor concentrations changed continuously over 6 hours (McGrath et al. 1999).

size of damage, duration of presence, and type of damage and material correlated with health symptoms (Haverinen et al. 2001). This suggests that measurements of the area of moisture damage may provide useful information in environmental assessment.

With water as the critical limiting factor for mold growth, measurements of temperature and relative humidity (RH) in the room and (when growth on building material is suspected) in the walls may be helpful to indicate water activity. (Water activity is the measure of water available within a substrate that an organism can use to support its growth.) High relative humidity in the walls was shown to correlate well with *Stachybotrys chartarum* growth (Boutin-Forzano et al. 2004). When a source of growth is indicated but not apparent, RH measurements may help direct the assessor to sampling locations and minimize the need for destructive sampling and the taking of unnecessary bulk samples.

7. Environmental Remediation Guidance

Step Approach to Remediation

This chapter of the guidance provides a three-step approach to remediation of mold in the environment.

Visible mold growth, including *Stachybotrys chartarum*, in an outside air-intake plenum in a commercial building. (Image courtesy of Dr. Chin S. Yang of P&K Microbiology Services)

Step 1: Mitigate Moisture Incursion into the Home or Work Environment

Abate leaks and moisture migration into the building envelope (roof, walls, floors and basement) and leaks from the building's plumbing system. Ensure that heating, ventilation, and air-conditioning (HVAC) system drip pans are clean and unobstructed.

Step 2: Maintain Low Indoor Humidity

The relative humidity (RH) of the indoor air and the ventilation system should be below 60 percent. Ideally, RH should be kept between 30 and 50 percent because at an RH of 50 percent or more hydroscopic dust will absorb water that may allow the growth of fungi and house dust mites on indoor surfaces. Dust mites are associated with other biota, including fungi, both of which can be highly allergenic (Burge 1994).

Step 3: Clean or Remove Mold-damaged Building Materials, Furnishings, and Other Items

Remove and discard porous building materials, furnishings, and other items that have been repeatedly wetted or subjected to long periods of dampness. Water-damaged ceiling tiles and mattresses are examples of porous materials that should be discarded. In some cases, restoration and water damage professionals can clean valuable porous items such as treasured books or upholstered furnishings. Care should be taken to not contaminate clean environments during the removal of contaminated materials.

Homes with water damage caused by flooding will require extensive cleanup. The Federal Emergency Management Association and American Red Cross booklet "Repairing Your Flooded

Home" is very helpful. This publication is available at www.redcross.org/services/disaster/0,1082,0_570_,00.html and www.fema.gov/hazards/floods/. In addition to guidance on cleanup, the publication emphasizes important safety precautions that must be observed when returning to a flood home (e.g., structural and electrical hazards).

Mold found on non-porous building materials (bathroom tubs, between tiles) can be cleaned with water and mild detergent on a damp wipe. In its *Mold Remediation in Schools and Commercial Buildings*, the EPA warns that the use of biocides and household chemicals such as chlorine bleach are not recommended as a routine practice during mold cleanup (US EPA 2001).

Protection While Removing or Cleaning Mold-contaminated Materials

When the healthcare provider has concerns that exposure to mold in the home or work environment has affected a patient's health, it is important that the patient be cautioned and provided guidance on personal protection and containment practices while removing or cleaning mold-contaminated materials. **Because mold remediation will involve exposure to mold spores, it is prudent to suggest that individuals other than the patient do the cleanup.** In addition, remediators and building occupants should be protected from exposure to mold with personal protection. At a minimum, a fitted respirator with N95 filter protection, eye protection, and gloves should be worn when small mold remediation projects are undertaken. Larger projects require more respiratory protection and the uses of practices that separate the area contaminated with mold from other spaces in the home or work environment (full containment).

Indoor Air Quality During Renovation

When construction or renovation activities are planned to address mold and moisture damage in occupied buildings such as schools and offices, it is important to pay attention to minimizing exposures for the occupants. The New York City Guidelines provide specific information on remediation for mold damage (NYC 2002). The Sheet Metal and Air Conditioning Contractors National Association has guidelines that detail appropriate practices for maintaining indoor air quality in buildings under construction (SMACNA 1995). Practices include segregating the construction area, directing air movement from the occupied area, minimizing dust, and establishing a level of monitoring.

Table E, which lists useful mold remediation guidance documents, is repeated on the following page from appendix D.

Table E: Environment Intervention Guidance (Selected World Wide Web Resources)
United States Environmental Protection Agency Indoor Air-Mold http://www.epa.gov/mold/ http://www.epa.gov/iaq/molds/moldresources.html Mold Remediation in Schools and Commercial Buildings http://www.epa.gov/iaq/molds/mold_remediation.html A Brief Guide to Mold, Moisture and Your Home http://www.epa.gov/iaq/molds/moldguide.html
California Department of Health Services http://www.dhs.ca.gov/ps/deodc/ehib/ehib2/PDF/MOLD_2001_07_17FINAL.pdf Mold in My Home: What Do I Do
Canada Mortgage and Housing Corporation http://www.cmhc-schl.gc.ca/en/burema/gesein/Momo/index.cfm Fighting Mold; Moisture and Air: Problems and Remedies
University of Minnesota http://www.dehs.umn.edu/iaq/flood.html Managing Water Infiltration into Buildings
New York City Department of Health and Mental Hygiene Bureau of Environmental and Occupational Disease Epidemiology "Guidelines on Assessment and Remediation of Fungi in Indoor Environments" http://www.ci.nyc.ny.us/html/doh/html/epi/moldrpt1.html

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Appendix A: A Short Description of Selected Molds and Summary Charts on Sampling and Analysis for Fungi in the Indoor Environment

A Short Description of Selected Molds

Molds and fungi found in water-damaged environments are likely to include both those of outdoor origin and those growing on water-damaged materials. For information on specific species or molds that are identified from an indoor environment, a consultation with a competent mycologist is helpful.

Acremonium (including some species formerly classified under *Cephalosporium*): Several species of *Acremonium* are commonly isolated from water-damaged indoor materials including drywall, wood, and paper products. *Acremonium strictum* is the most common species detected; this is a moisture-loving fungus. This species was previously called *Cephalosporium strictum*. Other species that may be found indoors are *A. kiliense, A. butyri, A. furcatum,* and *A. murorum* (synonym *Gliomastix murorum*).

***Alternaria*:** Spores of *Alternaria* are often isolated from air. Most of the isolates from air are probably *A. alternata* (synonym *A. tenuis*). There are more than 20 species in the genus *Alternaria*, and most of them are host-specific plant parasites. *Alternaria alternata* and *A. tenuissima* are the two most common species in the genus *Alternaria*. *A. alternata* is extremely common and cosmopolitan; it has been isolated from many kinds of plants and other substrates including seeds, soils, foodstuffs, wood and wood pulp, fungicide-treated utility poles, and textiles. *A. tenuissima* has a similar ecological niche as *A. alternata*. Both species are considered saprophytes, but may invade weakened plants. *A. alternata* is an occasional contaminant of water-damaged indoor materials. This fungus is known to produce mycotoxins.

***Aspergillus*:** The genus *Aspergillus* is large, consisting of approximately 150 species. To the untrained eye, many *Aspergillus* species are similar or identical, and misidentification is common. Spores belonging to the genus *Aspergillus* are a common component of the outdoor aerospora, but their isolation frequency is not as common as those of *Cladosporium, Penicillium,* and mushroom spores. Species of *Aspergillus* are notorious for producing mycotoxins. In addition, several *Aspergillus* species are a serious concern in health care facilities and to immune-deficient individuals because of their infection potential.

A few species of *Aspergillus* have been known to cause diseases in animals and humans. Three types of diseases have been recognized: (1) infection in living tissues by the fungus causing mycosis, (2) allergic reactions, and (3) toxicosis due to ingestion of foods containing toxins produced by the fungus

(or through other entry routes). *A. fumigatus* is well known as an opportunistic pathogen and an inducer of allergic reactions. Several common indoor species are discussed here. They are *A. flavus, A. niger, A. ochraceus, A. ustus, A. versicolor, A. sydowii,* and a few species of xerophilic[1] *Aspergillus* and *Eurotium*. *Eurotium* is a teleomorph (sexual state) of some *Aspergillus* species.

- ***A. flavus*** is often associated with grains and foodstuff. It is a well-known producer of potent mycotoxins: aflatoxins. It can also cause human infections. It is generally considered an outdoor mold; however, it has been observed growing on water-damaged indoor materials on a few occasions. Another similar mold, *A. parasiticus,* also produces aflatoxins and can cause infections.

- ***A. fumigatus*** is a thermotolerant-thermophilic species, common in the environment, and known to have a worldwide distribution. It can grow in a temperature range of 12°C to 57°C, with an optimal range of 37°C to 43°C. Because of its thermotolerance, it has been isolated from decaying plant materials, compost, wood chips, hay and crops, as well as a variety of organic substrates, including stored grains and stored sweet potatoes. It has been isolated from filters of air-conditioning systems and air ducts. Its growth requires a high water activity of greater than 0.90. Although it does not normally grow indoors, it has occasionally been found to amplify indoors where ideal growth conditions (e.g., steam leaks) exist.

- ***A. niger*** is a cosmopolitan fungus. It grows well at 37°C, with an optimal temperature of 20°C to 40°C. It has been isolated from a number of substrates, including house dust, soil, plant litter, dried nuts and seeds, textile materials, and water-damaged products. It has been found growing on water-damaged books and documents. This fungus is used in the industrial production of citric acid and enzymes.

- ***A. sydowii and A. versicolor*** are two very common contaminants of water-damaged materials in buildings. Like other *Aspergillus spp*., both have a wide niche and can grow on many substrates. They have been reported from soils, plant parts, paper pulps, photographic optics, and other substrates. These two species of *Aspergillus* are morphologically and ecologically very similar. *A. versicolor* is known to produce mycotoxins sterigmatocystin, a precursor of aflatoxins. *A. sydowii* produces no known mycotoxins.

- ***A. ustus*** is a very common fungus associated with water-damaged materials indoors. It is known to produce a number of toxic metabolites.

- **Xerophilic species** of *Aspergillus* and *Eurotium* include *A. restrictus, A. penicillioides, Eurotium amstelodami, E. rubrum, E. repens,* and *E. herbariorum*. These fungi usually grow on indoor materials subjected to high humidity or in indoor environments with prolonged high

[1] "Xerophilic" ("dry loving") fungi are fungi that require low water content (or low water activity) in a substrate for spore germination and for growth.

relative humidity, such as libraries without air conditioning. Carpets on concrete slabs are also susceptible to xerophilic species of *Aspergillus* and *Eurotium*. Another source of these fungi is preserved food products, such as fruit jams and food of high sugar content. These species are not known to produce mycotoxins. For the isolation and detection of these fungi, xerophilic media, such as DG18 or MEA plus 40 percent sucrose, are recommended.

***Aureobasidium pullulans*:** It is a phylloplane[2] fungus and likes to grow on wet surfaces, such as shower walls and house sidings.

***Chaetomium*:** This is a genus of ascomycetes. Species of the genus are well known as wood decay fungi and destroyers of paper products. Several species are found on water-damaged wood and paper products. They are *C. globosum, C. funicola, C. cochlioides, C. murorum, and C. elatum. C. globosum* is the most common and a moisture-loving fungus.

***Cladosporium*:** This is another large fungal genus with more than 500 names. The most common species are *C. herbarum, C. cladosporioides*, and *C. sphaerospermum*. They are associated with leaves and vegetation in nature throughout the world; their spores are the most abundant in outdoor air, however, they are also common colonizers of fibrous glass insulation materials in heating, ventilation, and air-conditioning (HVAC) systems. Cold surfaces subjected to condensation (window panes, cold storage rooms, etc.) are frequently colonized by them.

***Drechslera*:** Species of this genus are mostly associated with grasses. Many of them are agriculturally and economically important because they infect corn, rice, sorghum, and other grass crops. They produce large spores (9 to 32 mm wide and 16 to over 300 mm long) of non-respirable size.

***Fusarium*:** Species of the genus are common in nature. They are either soil-borne or found in association with plants. Several species of the genus are well-known plant pathogens. In addition, species of the genus are known producers of trichothecene mycotoxins. *F. moniliforme* is an opportunistic pathogen.

***Epicoccum nigrum*:** This is a common outdoor species often found in decaying wood. It has been observed occasionally on the paper of water-damaged drywall.

***Memnoniella echinata*:** This is a species closely related to the genus *Stachybotrys*. In fact, the species may be found growing with *Stachybotrys chartarum* on water-damaged paper products. The fungus has been demonstrated to produce trichothecene mycotoxins.

[2] Phylloplane" fungi, whose spores are commonly found in air samples, grow most often on plant leaf surfaces or vegetation.

***Penicillium*:** This genus consists of approximately 250 to 300 species. Some species are extremely common in the environment, but a few species have very unique ecological niches. *P. italicum, P. expensum,* and *P. digitatum* are pathogens of citrus fruits (oranges and grapefruits). Some are soilborne and used in cheese production (*P. roquefortii* and *P. camemberti*). This genus includes species that can grow in xerophilic to hydrophilic conditions. Some species are known to produce a variety of mycotoxins. Common species found in water-damaged environments are *P. aurantiogriseum, P. brevicompactum, P. chrysogenum, P. purpurogenum, P. variabile,* and *P. viridicatum*. The taxonomy of the genus is not totally clear. Some species are well defined, while some are, at best, considered a complex. Species identification of *Penicillium* requires a highly experienced mycologist.

***Pithomyces*:** *P. chartarum* is perhaps the most common species of the genus and is best known as the causal agent of facial eczema in sheep in New Zealand. It has also been isolated on paper and is common on dead leaves and stems of more than 50 different plants. Spores of *P. chartarum* are frequently isolated in air samples, particularly outdoors, and in carpet dust samples. The spores are particularly abundant in the fall, which suggests the source of the fungus is outdoors.

***Paecilomyces variotii*:** This species is commonly associated with water-damaged wood products (such as wood subfloor) and with dust. It is a good indicator of water damage.

***Stachybotrys chartarum*:** This species is one of approximately 20 species in the genus *Stachybotrys*. (It is also known as *S. atra*.) *S. chartarum* is known for its ability to degrade and use cellulose-containing materials, as a hydrophilic fungus and a mycotoxin producer. It is an excellent indicator of chronically water-damaged paper products. The fungus produces dark, slimy, ellipsoidal to broadly ellipsoidal spores measuring 6-12 x 4-10 mm. The spores may be dispersed by insects, small animals, water, or through air when disturbed. The aerodynamic size of the spore allows it to infiltrate the respiratory airway. As a saprophyte, the fungus is easily isolated and cultured on the common fungal media. However, for the correct identification of the fungus, cornmeal agar and 2-percent malt extract agar are recommended. *S. chartarum* produces trichothecene mycotoxins as well as a hemolysin. Three chemotypes of *S. chartarum* were recently recognized, depending on the types of mycotoxins produced. The fungus has been associated with indoor-air-quality complaints.

***Trichoderma*:** *Trichoderma spp.* are fast-growing, common soil fungi. The taxonomy of this genus is still not clear. The isolation and detection of *Trichoderma* in indoor environments may be from house plants, outdoors, or water damage. They have been found in various substrates including soils, roots, straw, wood, wood pulp, timber, paper, textiles, jet fuel, and rotting wood. They also have been found on woodpiles and logs used in fireplaces. They often produce green spore masses on wet wood outdoors and in basements and crawl spaces. They have been observed on water-damaged, wet furniture made of wood and particleboard. This fungus may produce a strong musty, moldy (or coconut-like) odor when growing in a closed space, such as a basement. *T. koningii, T. harzianum, and T. viride* are the common species encountered indoors. *Trichoderma* species can produce trichothecene mycotoxins.

***Wallemia*:** The genus contains only one species, *W. sebi*. It is a xerophilic fungus and grows better on xerophilic media (such as MEA plus 40-percent sucrose or DG18). The fungus is found chiefly on substrates with high sugar or salt content (low water activity), but has been isolated from soils, samples of paper, and food stuffs including jam, bread, cakes, salted fish, milk, and fats. It has been implicated in indoor air quality allergy complaints in Japan. The fungus has been reported to occur in air, hay, textiles, and man. *W. sebi* produces walleminol, a mycotoxin.

Summary Charts on Sampling and Analysis for Fungi in the Indoor Environment

Because there are no numeric guidelines for results of airborne mold testing, the recommended approach is indoor and outdoor comparisons (ACGIH 1999, AIHA 1996). Airborne mold spores vary according to spatial and temporal differences. There are situations where outdoor air sampling is difficult or impossible. Sampling in snow-covered conditions in northern states or on rainy days may affect outdoor airborne mold spores. However, snow cover and rain are part of the natural weather pattern. Professionals need to take this into consideration when planning for sampling and when interpreting the results. It may be instructional to compare results from the indoor area being investigated with other indoor "non-problem" areas.

All samples taken for molds require analysis in a laboratory to minimize contamination. Indirect measurements of airborne mold spores by direct read-out instruments have been attempted. Particle counters may detect airborne particles, including mold spores, but there is no ratio that can be used to calculate concentrations of airborne mold spores. A direct read-out meter measuring mold-specific enzymatic activity has been introduced in the last few years, but the reading is qualitative and there is little field data to support its application.

Air Sampling Methods			
	Filtration	**Impaction**	**Spore trapping**
Media	Membrane filters of various diameter and varying pore size	Petri plates with various nutrient media	Grease-coated slide or MCE filter
Collection Mechanism	Air pump with a cassette	Air pump and impactor	Air pump with a cassette or an impactor
Analysis	Microscopic spore counting or culturing	Culturing	Microscopic spore counting
Results	Qualitative and quantitative	Qualitative and quantitative	Qualitative and quantitative

Source Sampling Methods					
	Micro-vac dust	**Wipe**	**Bulk**	**Contact**	**Sticky tape**
Collection tools	Membrane filters of various diameters and varying pore sizes	Sterile wipe kit	Sterile sharps and clean plastic bags	Rodac plates of various nutrient media	Clear, transparent sticky tape
Collection mechanism	Air pump with a cassette	Swabbing of surface	Cutting and removing a piece of material	Contact of agar on a surface	Contact of sticky surface on a surface
Analysis	Culturing	Culturing	Microscopic examination or culturing	Culturing	Microscopic examination
Results	Qualitative and quantitative	Qualitative and semi-quantitative	Qualitative by microscopic exam; Qualitative and quantitative by culturing	Qualitative and semi-quantitative with a narrow range of colony counts	Qualitative

Analytical Methods				
	Spore Counting	**Culturable**	**Direct exam**	**QPCR***
Test method	Optical microscopy	Culturing on nutrient media	Optical microscopy	Molecular genetic method
Results	Qualitative and quantitative	Qualitative and quantitative	Qualitative	Qualitative and quantitative
Quantitative	Subject to analyst and lab variation; wide statistical deviation	Actual spore counts underestimated due to viability, dormancy, and limitation of media used	Not applicable	Accurate, based on calibrators; low detection and quantitative limits
Authority and protocol	No standardized protocol	Conventional mycological method	Conventional mycological method	Several patented technologies with specific protocols
Sample time (air sample)	Short duration - a few minutes	Short duration - a few minutes	Not applicable	Longer duration - hours to days

* Quantitative Polymerized Chain Reaction

Note: The quality of the results depends on the limitations of sampling protocols and analytical methods, the education and training of the analyst, and the laboratory's quality assurance program.

Appendix A References

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American Industrial Hygiene Association (AIHA). 1996. Field Guide for the Determination of Biological Contaminants in Environmental Samples. Fairfax, VA.

Appendix B: Health Effects; Reactions to Mycotoxins

Some fungi can produce complex secondary metabolites called mycotoxins (Burge 2001, Health Canada 1987, Newberne 1974). Most mycotoxins are heterocyclic organic molecules, generally having molecular weights of 300–750 daltons. Unlike allergens, mycotoxins in sufficient concentration can elicit responses in virtually anyone with whom they come into contact. There are many hundreds of mycotoxins with different biological properties (Etzel 2002, Norred and Riley 2001). The different chemical groups of mycotoxins include aflatoxins, fumonisins, ochratoxins, rubratoxins, and trichothecene toxins (Wannemacher and Wiener 1997), all with different biological properties (Jarvis 1995a). A single fungal genus (e.g., *Penicillium*) may produce more than 100 different mycotoxins. Moreover, the amount of mycotoxin produced by a given strain of toxigenic fungus may vary according to the specific isolate and the prevailing growth conditions. Some of these growth conditions are temperature, nutritive status, light level, and growth phase (e.g., rapid growth, stationary, or senescence) of the strain's life cycle (Health Canada 1987). Low levels of mycotoxins are ever present in the environment—toxigenic fungi are contaminants of agricultural products and house dust (Health Canada 1987) and are very stable under different environmental conditions (Wannemacher and Wiener 1997).

In recent years, there have been numerous reports in both the medical literature and the popular media (both print and electronic) that indoor exposure to fungi or fungal toxins has caused significant disease or death in the occupants of water-damaged homes or workplaces. These locations had significant (generally visible) fungal growth and odors, typically reported as from the "black mold," *Stachybotrys chartarum*. (It should be noted here that many molds are "black" in appearance.) *S. chartarum* is a ubiquitous organism, growing on cellulose products exposed to water or high humidity. In moist buildings, *S. chartarum* frequently grows on wallpaper, wallboard, ceiling tiles, carpets (especially those with jute backing), insulation (e.g., urea-formaldehyde foam) in the spaces between inner and outer walls, around leaking window frames or water pipes, and in air ducts of the heating, ventilation, and air-conditioning (HVAC) system containing lint or other organic debris. Sorenson found that aerosolized cultures of *S. chartarum* produced respirable particles (with aerodynamic diameters of 5–15 mm) composed primarily of conidia (85 percent) and hyphal fragments (6 percent) (Sorenson et al. 1987). These particles can contain several trichothecene mycotoxins. Cruse reported that although *Stachybotrys* molds have historically been speciated by morphologic criteria, their studies indicate that two separate phylogenetic species of "*S. chartarum*" can be recognized based on cell surface markers. There was no correlation between genetic and geographical distribution; that is, both genotypes had wide geographical distribution in the United States, and both species or subspecies could be found within single locations (apartments) in Oakland, CA (Cruse et al. 2002). What remains to be answered is whether these two subspecies produce similar toxins under similar growth conditions.

Media interest in mycotoxins has grown over the last decade. Some reports of *Stachybotrys*-related disease have involved celebrities, and these and other incidents have triggered widely publicized litigation against builders and insurance companies. A wave of lawsuits has brought mold and its potential health and economic consequences to the public's and the media's attention. Congressman John Conyers of Michigan introduced legislation (the U.S. Toxic Mold Safety and Protection Act, HR 5040, also known as the "Melina Bill") in the summer of 2002. It is named for the 9-year-old daughter of the manager of his Detroit office (The Detroit News 2002). Melina reportedly developed severe asthma exacerbations within 24 hours of moving into a new home in Southfield, MI, which was later found to have mold contamination; her family moved out of the house within 24 days. Although not passed, this and other proposals have contributed to the public's heightened concern over mold in the indoor environment.

Background on Assessing Toxicity Risk

Despite the extensive attention and concern, there is no consensus in the scientific medical literature regarding toxic effects of mold as encountered by humans in non-industrial, non-farm indoor environments (Fung et al. 1998, Shum 2002, Roponen et al. 2002, King and Auger 2002, Miller et al. 2003, Kuhn and Ghannoum 2003). To review the reasons for this, we will briefly review some intrinsic limitations and difficulties involved in risk identification in toxicology. Most physicians obtain their introduction to toxicology as a branch of pharmacology. We perhaps first think of toxic manifestations of drugs, which can occur as extensions of the therapeutic effects. This type of toxicity occurs most frequently with medications that have low therapeutic indices. (Examples include digitalis toxicity, which causes high degrees of heart block due to excess vagal tone, and triggered ventricular extrasystoles caused by intracellular calcium overload.) We also may think about independent toxicities from medications, such as gastrointestinal upset induced by erythromycin, and torsade-de-pointes arrhythmias related to non-sedating antihistamines or neuroleptic agents. Finally, we may think of the toxic effects of environmental agents, including heavy metals (mercury, cadmium, and lead) and airborne toxic agents (such as carbon monoxide and diesel exhaust particles). Brief consideration of the issues will lead to the conclusion that the toxicologist faces significant problems, as compared to the pharmacologist, in terms of quantifying the relationships between the "agent" and the "response." That is, when a clinical pharmacologist studies a given medication, he or she typically knows the precise concentration or dose of the agent that is present and the exact time the treatment started. The pharmacologist then studies the "usual" or most common effect of that agent. The data can be used to derive a rather precise and predictable log-dose response curve for most agents.

In contrast, the toxicologist or epidemiologist studying clinical effects of naturally occurring toxins has none of this information and thus labors under several disadvantages. First, he or she often does not know with certainty the concentration of the toxic agent that was present in the environment when the pathology was induced. *Ex-post facto* estimations of these exposure concentrations are often a limitation of the science, even if good analytic techniques for the toxin are available. Moreover, the subjects of a toxicologist's inquiries are often unusual responses, which occur in "sensitive populations" (or sensitive members of a given population) at or near the threshold concentrations for

the biological effects of the toxin or chemical. These and other factors necessarily introduce significant uncertainty in the development of dose-response curves for many toxic substances. In view of these limitations, toxicologists who develop permissible levels, "reference doses" (RfDs) for general population exposures to chemicals with known toxic effects, routinely build in large safety factors. They set the RfDs several orders of magnitude or more below the "no observed adverse effect level, or NOAEL" (Faustman and Omenn 1996). The intrinsic difficulties encountered with exposure assessment and outcomes evaluation in the clinical setting may help explain the long controversy and delays involved in validating hypotheses about whether cigarette smoking causes lung cancer, as well as ongoing controversies (such as the putative relationships between electromagnetic fields and cancer and between silver amalgam dental fillings and disease).

Proving cause-and-effect relationships for clinical diseases potentially resulting from mycotoxins has additional limitations. There are no standardized methods for qualitative or quantitative analysis of airborne mycotoxins in the indoor (or outdoor) environment, and there are few known biomarkers for measuring exposure to these toxins (Cloeren 2002). Most studies attempting to gain insight into these issues measure surrogate variables, such as (1) numbers of spores or hyphal fragments, identified by microscopic examination of micropore filters that have been used in metered pumps which process known volumes of ambient air and (2) the number of viable spores, expressed as colony-forming units (CFU) per cubic meter of air, as determined by culture of similar filtered air samples. Neither of these measurements provides a direct assessment of mycotoxin levels because mycotoxin concentrations may not necessarily correlate with either the total volume of fungal material or the total number of viable spores.

Given these limitations, what then can we conclude with respect to mycotoxins and human disease?

Toxicity from Ingestion of Mycotoxins

The clearest evidence that mycotoxins can cause human disease derives from the effects noted after ingestion of fungus-contaminated food. The best known of these diseases is perhaps "ergotism" or St. Anthony's Fire, which occurred in large-scale epidemics in Europe in the Middle Ages. It was caused by the ingestion of rye or other grain infested with fungi (*Claviceps purpura*) containing "ergot," which is a complex and variable mixture of alkaloids. Some of these alkaloids are vasoconstrictors, and their ingestion can lead to blistering, gangrene, and loss of limbs in some patients. Consumption of ergot can also result in neuropsychiatric effects, including bizarre behavior, hallucinations, dementia, and convulsions. It has been speculated that such behavioral changes induced by ergot poisoning led to the Salem witch trials in 1692. Outbreaks of ergotism have occurred as recently as 1951, when over 200 persons in Provence, France, developed severe symptoms; 32 went insane, and 4 died from eating bread made from contaminated rye (University of Georgia 2001). Consistent with these clinical effects, there is evidence for neurotoxicity from mycotoxins in sheep and cattle that consumed contaminated feed (Mantle et al. 1978, Shlosberg et al. 1991).

Mycotoxin ingestion also has been implicated in carcinogenesis (Sorenson 1999). Aflatoxin B1 (AFB1) is a potent carcinogen produced in contaminated foodstuffs by several species of *Aspergillus*. Clinically, it has been identified as causing hepatic carcinomas in patients who ingest it in contaminated grain or peanuts, particularly if they have a coexisting hepatitis B infection. Laboratory studies of AFB1 indicate that it can selectively suppress immune function, which could result in increased susceptibility to growth of neoplasms. These effects include inhibition of phagocytosis, microbiocidal activity, and cytokine production by human monocytes (Cusumano et al. 1996, Rossano et al. 1999) and cell-mediated immunity in rats (Raisuddin et al. 1993). In agreement with these observations, veterinary reports of animals that ingest aflatoxin found in moldy hay have documented suppressed cell-mediated immune responses with reduced phagocytosis and depressed production of complements and interferon. Acquired immunity from vaccination programs has also been shown to be substantially suppressed (Pier 1992).

Two episodes of severe aflatoxin poisoning were reported in horses, with encephalomalacia of cerebral hemispheres, fatty degeneration, necrosis, bile duct hyperplasia, fibrosis of the liver, fatty infiltration of the kidney, hemorrhagic enteritis, and myocardial degeneration. Hypoglycemia, hyperlipidemia, and depletion of lymphocytes were also noted. The diagnosis was based on gross and histopathologic observations, consistent with observations of other species poisoned with aflatoxin, and on isolation of the toxin from feed and animal tissues (Angsubhakorn et al. 1981).

Other maladies that have been associated with ingestion of mycotoxins by humans are Kashin-Beck disease (KBD) and alimentary toxic aleukia. KBD is a syndrome of short stature estimated to affect 1 million to 3 million people in China, Tibet, and Siberia. It is associated with ingestion of foodstuffs made from barley that was not dried after harvest and was stored through the fall and winter in moist conditions, typically in Yak-skin and Yak-hair bags (Allander 1994, Haubruge et al. 2001). The lesions of KBD occur when multiple focal necroses occur in the growth plates of long bones in children who consume these contaminated cereals; the necrosis is caused by effects of mycotoxins on chondrocytes in these plates and subsequent abnormal collagen production and failure of long bone growth (Wang et al. 1991).

Alimentary toxic aleukia (ATA) is associated with *Fusarium* molds on wheat, millet, and barley that have been over-wintered in the fields (Locasto et al. 2001). This food-related disease has occurred sporadically in Russia, probably since the nineteenth century. The most notable outbreak probably occurred in the Orenberg district, near the Siberian border, during World War II. Various reports indicate that chronic consumption of grain contaminated with a trichothecene (T-2) mycotoxin resulted in a mortality rate of 10-60 percent of the local population during the years 1942-1947 (Locasto et al. 2001, Wannemacher and Wiener 1997). The full course of ATA, seen with ongoing exposure to the mycotoxin, occurs in four phases. The first phase develops within 72 hours of initial consumption of the contaminated foodstuffs. It results in gastrointestinal inflammation leading to abdominal pain, nausea, and vomiting, often accompanied by headache, weakness, fatigue, and tachycardia. The second, or "latent," phase is characterized by development of leukopenia and progressive lymphocytosis, and the third phase is heralded by the appearance of cherry-red petechial rashes, which gradually expand and become confluent on the trunk and extremities. If the disease

progresses further, ulceration and necrosis can occur in the larynx, which in the most extreme cases leads to aphonia and death from asphyxiation. This can be accompanied by bleeding diatheses in the upper respiratory and gastrointestinal mucosa. If patients survive these insults, they may expire from secondary infections, including pneumonia. If they do recover, the convalescence can be protracted, with up to 8 weeks required for recovery of bone marrow leukopoiesis and peripheral cell counts (Wannemacher and Wiener 1997).

There is also evidence of potent effects produced in farm animals that have consumed feed contaminated by trichothecene mycotoxins; the effects in poultry include excess mortality, reduced growth rates, beak deformities, and compromised immune systems. In mammals (cattle and swine), slow growth, lowered milk production, sterility, hemorrhagic bowel syndrome, and death can occur (Jacobsen et al. 1993).

Thus a variety of clinical reports, as well as supporting laboratory studies, lend credence to the idea that ingestion of sufficient quantities of mycotoxins can cause significant disease or even death in humans and lower animals.

Toxicity from Effects of Parenteral Exposure to Mycotoxins

It is thought that the events in Orenberg in the 1940s led to the recognition of the potential use for T-2 and other trichothecene mycotoxins in biological warfare. It is further thought that subsequent weaponizing of T-2 toxins occurred, and that these agents were used in "yellow rain" attacks in Cambodia, Afghanistan, and Iraq, (Wannemacher and Wiener 1997, Bennion and David-Bajar 1994, Kianifar et al. date unknown). These weaponized toxins are lipophilic and easily cross human skin, gut, and pulmonary epithelium. Following direct contact, they cause severe eye and skin irritation (erythema, edema, and necrosis) in humans, and at larger doses can yield incapacitation and death within minutes to hours. After respiratory exposure to these toxins, human victims can develop nasal pain and epistaxis, sore throat, vocal changes, cough, dyspnea, and hemoptysis (Wannemacher and Wiener 1997, Kortepeter et al. 2001).

In toxicology studies in laboratory animals, mice, rats, and guinea pigs die within 12 hours of inhaling high doses of these aerosolized trichothecene mycotoxins, with no evidence of pulmonary edema or lung lesions. Quantitatively in rodents, trichothecene mycotoxins have LD_{50} (lethal dose for 50 percent of the subjects) values as low as 0.5 milligram/kilogram (mg/kg) when tested intramuscularly, 0.7-1.0 mg/kg intravenously (iv), and 0.05 mg/kg by the inhalation route. In cats, LD_{50} is < 0.5 mg/kg (subcutaneous), and in swine it is reported to be 1.2 mg/kg (iv) (Wannemacher and Wiener 1997).

Effects of Inhaled Mycotoxins

There is additional evidence of the deleterious effects of inhaled mold spores or mycotoxins (beyond the exposure to massive quantities of mycotoxins in biological warfare noted above).

One example is organic dust toxic syndrome (ODTS). ODTS is a general term, covering illness caused by inhalation of either bacterial endotoxins or fungal toxins (CDC-NIOSH 1994). It is characterized by a flu-like syndrome with prominent respiratory symptoms and fever, which occurs abruptly a few hours after a single, heavy exposure to dust containing organic material including fungi (e.g., species of *Aspergillus* and *Penicillium*). The symptoms of ODTS are quite similar to those of hypersensitivity pneumonitis, but are not mediated by immune responses. Therefore, ODTS typically occurs immediately after the first heavy exposure to the causative agent; repeated exposures are not required (Perry et al. 1998). OTDS has been documented in workers handling material contaminated with fungal or gram-negative bacterial growth in both outdoor (agricultural) and indoor (demolition) settings (Yoshida et al. 1989, Richerson 1990, Von Essen et al. 1999, Malmberg 1990).

There are other reports suggesting that inhalation of mycotoxins can produce diseases other than ODTS in humans. Both patients and clinicians have raised concerns regarding potential neurotoxicity following exposure to molds. A case report suggested that neurotoxicity can also occur after airborne exposure to mycotoxins; Gordon reported a 16-year-old farmhand with encephalopathy consisting of progressive somnolence, slowness of thinking, and incapacitating tremors after being exposed to these agents while removing moldy fodder from a silo (Gordon et al. 1993). The literature that raises concerns regarding neurotoxicity is summarized by Baldo et al. in an article where they present a study of neuropsychological performance of patients following mold exposures (Baldo et al. 2002). An excellent review and carefully presented study, it demonstrates the problems clinicians face when evaluating complaints of memory loss, difficulty concentrating, or personality change in patients attributing their symptoms to mold exposure. The problems include poorly defined exposures to mold, less-well-defined exposure to mycotoxins, lack of a consistent pattern of deficits on neuropsychological testing that would begin to define a syndrome of toxicity attributable to mold, and the presence of other morbidities, such as depression, that can result in measurable impairment on neuropsychological tests. While clinical and epidemiologic data remain elusive, case reports are worrisome, and the subject remains open to further investigation. (Sudakin 1998, Sudakin 2003, Lees-Haley 2003).

Exposure to airborne aflatoxins in an industrial or farm setting has been associated with cancers of the liver, intestine, and kidney in animals and humans (Hendry and Cole 1993). Occupational exposure to AFB1 by inhalation has been associated with primary lung cancer (Kelly et al. 1997). Finally, increased rates of premenopausal endometrial cancer, as well as spontaneous late-term abortion, have been reported in female farmers exposed to fungal spores during work with contaminated grain products. These health effects were reported to be consistent with hormonal effects of the inhaled mycotoxins during pregnancy (Kristensen et al. 2000).

Stachybotrys chartarum, a Discussion of the Current Issues

Stachybotrys chartarum has drawn attention because of a number of dramatic case reports and because it has been identified as a contaminant in settings where unexplained symptoms have occurred. *S. chartarum* grows on material with a high moisture content. The species has been increasingly identified indoors where building design, materials used, recurrent leaks or chronic moisture incursion support

environmental conditions selective for this fungus. The characteristic sticky spores are not readily aerosolized when wet, so its presence in air samples is unusual except when reservoirs have dried and been disturbed. When found, *S. chartarum* usually indicates amplification/growth (Ammann 2000). In high-exposure settings, illness due to *S. chartarum* and associated mycotoxins appears well identified. It is in low-exposure settings such as non-industrial indoor environments where the relationship of symptom to exposure and the nature of the pathologic response has yet to be characterized. A detailed review in **Medical Mycology** provides more information (Miller et al. 2003).

S. chartarum is a soil fungus that has been documented to be a plant pathogen (Li and Hartman 2000). Andrassy reported that inhalation of mycotoxins from straw contaminated by *S. chartarum* growth induced respiratory disease in agricultural workers. The signs and symptoms included dyspnea, shortness of breath, sore throat, epistaxis, "burning" ocular pain, periorbital edema, weakness, and exhaustion, providing a constellation of symptoms somewhat different than those of ODTS (Andrassy et al. 1979). In humans, as in animals, exposure to these mycotoxins in contaminated hay or straw can lead to "stachbotrytoxicosis," with protein synthesis inhibition, T-cell proliferation, thrombocytopenia, leukopenia, immune system suppression, and bleeding from the nasal and tracheal mucosa (Hintikka 1977, Jarvis et al. 1995b, Hendry and Cole 1993, Sorenson et al. 1987).

Concerns regarding indoor contamination began when Croft and co-workers (Croft et al. 1986) reported an outbreak of disease in a house in Chicago that occurred over a 5-year period and was attributed to exposure to *S. chartarum*. Five occupants of the house (three adults and two children) suffered general malaise, fatigue, recurring colds and "flu," sore throats, diarrhea, headache, dermatitis, and intermittent focal alopecia. Air samples taken in the house revealed "numerous spores" of *S. chartarum*. Inspection of the forced air heating system revealed that the interior walls of the air ducts were coated with a 2-cm thick layer of "dark brown debris" from lint and carpet fibers. The debris in the ducts was moist and harbored many viable *Stachybotrys* spores. This home had a long history of plumbing and roof leaks, which "produced chronic moisture accumulation on which the black sooty fungus grew in abundance." It was reported that mycotoxins were isolated from the black fungal colonies and spores found throughout the house. After the roof and plumbing system were repaired and the contaminated duct, insulation, and ceiling panels were replaced, the family re-occupied the house without experiencing recurrences of the symptoms noted earlier (Croft et al.1986).

Reports of chronic respiratory complaints, eye and skin irritation, and fatigue occurring in patients living or working in buildings infested with *S. chartarum* have been published (Hodgson et al. 1998, Johanning et al. 1996, Johanning et al. 1999, Auger et al. 1994). Johanning and Landsbergis proposed the term "fungal syndrome" for a particular constellation of multisystem complaints (including inflammation of the upper and lower respiratory tract, skin, and mucous membranes, along with central nervous system symptoms such as headaches, nervousness, difficulty concentrating, dizziness, and excessive fatigue) occurring in patients exposed to toxigenic fungi including *Stachybotrys chartarum*, *Aspergillus sp*. and *Penicillium sp.* (Johanning and Landsbergis 2001).

Thus, numerous reports in both the medical literature and popular media have implicated *S. chartarum* toxicity in human disease. Even though some studies have shown an association between mycotoxin exposure and health, the body of literature is not sufficiently extensive to satisfy the requirements for showing a causal association. Epidemiological studies of small populations in individual buildings may not have sufficient power to find strong associations.

One of the more serious illnesses that has been associated in the literature with indoor exposure to *S. chartarum* is an acute pulmonary hemorrhage/hemosiderosis syndrome. A cluster of cases was reported in Cleveland occurring in infants 6-26 weeks of age (CDC-MMWR 1995). All of the first 10 cases were African-American (9 were male) and ranged in age from 6 weeks to 6 months (mean age, 10.2 weeks). Fifty percent experienced recurrent pulmonary hemorrhaging after returning to their homes, where water damage and fungal growth had not been remediated (Montana et al. 1997). The geographic clustering and incidence suggested an environmental etiology. Most of the infant's homes had significant water damage from roof leaks, plumbing leaks, or sewer flooding, and it was postulated that infants with pulmonary hemorrhage were more likely than controls to live in homes where *Stachybotrys* was present (CDC-MMWR 1997, Etzel et al. 1998). A summary of the outbreak (Dearborn et al. 1999) revealed that 37 infants presented to hospitals in greater Cleveland from 1993-98 with pulmonary hemorrhage and hemosiderosis, and 12 of them died. Thirty were African-American and lived in older housing stock in the eastern districts of the city. Epidemiologic investigations of pulmonary hemorrhage in infants in Cleveland found an association with exposure to *S. chartarum* and other indoor fungi. Exposure to environmental tobacco smoke was an additional risk factor in the presence of *S. chartarum* (Etzel et al. 1998, Dearborn et al. 1999). Conclusions regarding association have not been drawn with certainty because of the difficulties in characterizing water damage, quantifying exposure to toxigenic mold, and the presence of multiple potential factors (CDC 1999, CDC-MMWR 2000, Etzel 2003). This is further complicated because of variations within the species of *S. chartarum*, the multiple natural toxic products that this fungi produces, and other fungal species with toxigenic properties that may also be present (Jarvis 2003). For example, *Memnoniella echinata*, a fungus that produces multiple mycotoxins including grisofulvins (a toxin not produced by *S. chartarum*) was isolated from homes in the Cleveland outbreak (Jarvis et al. 1998).

Three case reports in other settings provide further evidence that acute pulmonary hemorrhage/hemosiderosis may develop in the setting of exposure to mold. A case report was published about a 1-month-old boy from a suburb of Kansas City, MO, who developed pulmonary hemorrhages after being exposed to contamination by a highly toxigenic *S. chartarum* in his bedroom (Flappan et al. 1999). Also, Elidemir reported a case from Houston in which *Stachybotrys* was isolated from the bronchoalveolar lavage fluid of a 7-year-old child with pulmonary hemorrhage and from his water-damaged home. The patient was removed from the home environment immediately and the home was cleaned. The child recovered substantially and was able to return to the home safely after the fungal contamination had been alleviated (Elidemir et al. 1999). A recent report from North Carolina (Novotny and Dixit 2000) highlights this issue: a 40-day-old male infant developed a life-threatening pulmonary hemorrhage after being exposed to environmental indoor fungi in St. Louis, MO, for a discrete 2-week

period followed by acute exposure to environmental tobacco smoke. Two fungi were cultured from surface samples in the residence: *Penicillium* (possibly *P. purpurogenum*) and a *Trichoderma* species. *S. chartarum* was not isolated from air or surface samples.

Dearborn reported a case series of acute pulmonary hemorrhage and hemosiderosis of the 30 patients seen by his team at Rainbow Children's Hospital in Cleveland between 1993 and 2000. The paper notes that 5 of 7 cases in which the healthcare providers had not recommended removing the infants from the residence had overt recurrent re-bleeding. This contrasts with only 1 of 21 infants experiencing overt pulmonary bleeding after changing the home environment (Dearborn et al. 2002). Interestingly, our analysis of their data suggests that if the infant returned to his original home environment, he would have an average number of 1.4 ± 0.53 re-bleeding episodes (mean $\pm$ SEM, n=7), whereas if the patient was discharged to a new home, the infant would average only 0.1 ± 0.09 re-bleeding episodes ($n=21$, $p < 0.0005$).

Efforts to identify pathologic mechanisms by which toxigenic fungi might lead to this syndrome have yielded important information. Hodgson and Dearborn reviewed the data and pointed out that significant supporting evidence for a plausible mechanism now exists from *in vivo* studies of laboratory animal models of respiratory toxicology and *in vitro* data documenting changes at the subcellular or biochemical level by mold spores or *Stachybotrys* mycotoxins (Hodgson and Dearborn 2002). Specifically, several reports have been published indicating that hemorrhagic inflammation occurs in the lungs of mice or rats after experimental intra-tracheal instillation of *Stachybotrys* spores (Nikulin et al. 1996, Rao et al. 2000a, Rao et al. 2000b, Rand et al. 2002, Yike et al. 2002a). It is also of note that animal experiments indicate that a variety of other mycotoxins (from fungi genera other than *Stachybotrys*), including aflatoxins and roridins, can cause increased vascular fragility and pulmonary hemorrhage (Ammann 2000).

At the subcellular level, studies have explored possible biologic mechanisms. For example, studies have documented that *Stachybotrys* spores can alter surfactant metabolism in mice (Mason et al. 2001) and trichothecene mycotoxins can alter alveolar surfactant phospholipid concentrations (Mahmoudi and Gershwin, 2000). Yike et al. reported that *Stachybotrys* spores can elaborate proteolytic enzymes, and they observed histologic changes on necropsy of mice treated with inhaled mold spores. Specifically, there were decreased collagen matrix fibers in lungs of infant rats and young mice in the vicinity of these spores. The authors indicate that these changes may lead to degradation of the extracellular matrix and compromise the integrity of pulmonary capillaries (Yike et al. 2002b). Kordula purified an enzyme, stachyrase A, from an *S. chartarum* strain from the home of an infant with pulmonary hemorrhage. This enzyme was found to cleave several compounds in lung tissue including proteases inhibitors, peptides, and collagen (Kordula et al. 2002, Dearborn, personal communication). Methanol extraction of the *Stachybotrys* spores removes the trichothecene mycotoxins and denatures the spore proteins. When these methanol-treated spores are tested in the rodent models, the toxic effects on the lungs are significantly reduced (Rao et al. 2000b, Yike et al. 2002b). Trichothecene mycotoxins from *Stachybotrys* have been documented to induce inflammatory changes and apoptosis in cultured cell systems (Lee et al. 1999, Yang et al. 2000). Other current research seeks to understand the local dose and toxicity of inhaled mycotoxins. (Yike et al. 2003, Gregory et al. 2003, Gregory et al. 2004). Yet another potential

disease mechanism is postulated by work which demonstrates a hemolysin known to cause hemorrhaging can be produced by several strains of *S. chartarum* isolated from the homes of infants with pulmonary hemorrhage (Vesper and Vesper 2002).

The published literature clearly outlines the uncertainty of current knowledge and calls for further research to clarify exposures, pathologic responses, and mechanisms of injury. The Institute of Medicine's Committee on Damp Indoor Spaces and Health, although concluding that there is "inadequate or insufficient information" to establish an association of *S. chartarum* and acute idiopathic pulmonary hemorrhage in infants, called for the CDC to pursue surveillance and additional research (Institute of Medicine 2004). A difficulty revolves around the management of cases of acute pulmonary hemorrhage and hemosiderosis, and the appropriate assessment of homes with water damage. Experience with infants with this syndrome supports removal of these infants from the environment in which the illness developed until water damaged and mold contaminated materials are fully remediated. It also supports rigorous avoidance of tobacco smoke because cases have recurred in the presence of tobacco smoke after removal from the home. Prompt remediation of all water-damaged materials helps to prevent mold-related syndromes and is the recommendation made by public health agencies (CDC 2002, NYC 2002). Suspected cases should be reported to state health authorities (CDC 2004).

Summary and Conclusions on Effects of Mycotoxins

There is abundant evidence for a role of ingested mycotoxins in human disease, and there is significant clinical evidence of a role for fungal spores and toxins by the respiratory route in military and agricultural settings following massive exposures. Laboratory studies in animals and at the cellular level provide supporting evidence for direct toxicity of fungal spores and mycotoxins in mammalian lungs. However, for humans residing or working in water-damaged buildings, the role of airborne fungal spores and toxins in the etiology of non-allergic disease remains controversial. Epidemiologic and clinical evidence raise the additional question of potential synergy between mycotoxin effects and environmental tobacco smoke. Recent reviews have concluded that scientific proof of the notion that the presence of fungal mycotoxins in indoor environments can lead to disease in humans is lacking (Robbins et al. 2000, Burge 2001, Terr 2001, Assouline-Dayan et al. 2002, Shum 2002, Kuhn and Ghannoum 2003, Miller et al. 2003). But there certainly is sufficient evidence available in the literature in support of this hypothesis to say that it also cannot be excluded.

If we follow the usual framework for risk assessment in environmental toxicology, the identification of a hazardous agent depends on converging lines of evidence from three or four areas of investigation: epidemiology, *in vivo* (whole animal) toxicology, *in vitro* testing (in isolated cell systems or cell-free systems), and structure-activity analyses (Faustman and Omenn 1996). In general, our knowledge of the chemistry of mycotoxins has only begun to advance to the point where structure-activity relations can contribute, and the epidemiology supporting this hypothesis has often been judged as weak. But the available toxicology data would appear to grant significant support for the biologic plausibility of the hypothesis. (These data come from studies of isolated cell and whole animal models, as well as extensive observations in human pathology after rather massive inhalation or contact exposures to mycotoxin-

laden materials, including frequent reports of upper respiratory hemorrhages.) In addition, the available case-control studies from the Cleveland outbreak cannot be dismissed, especially in view of the case reports associating acute pulmonary hemorrhage/hemosiderosis syndrome with indoor toxigenic mold exposures that have now been published by independent sources. In addition, there is the continued experience in Cleveland, where over 30 cases have occurred, 90 percent of them from environments containing *Stachybotrys* (Dearborn et al. 2002). Clinical and basic scientific research continues to explore the hypothesis that fungal exposure in indoor air of water-damaged buildings can cause pulmonary hemorrhage in infants and children, as well as other diseases in adults. Ongoing work in toxicology and epidemiology will shed further light on these issues in the future (Etzel 2003a).

Acknowledging that scientific uncertainty centers on how occupants are exposed to mycotoxins while living or working in contaminated indoor environments, reviews and guidance still advocate for addressing indoor environments contaminated with mold or water damage because of possible toxic effects as well as other, less controversial, effects of mold (concern for asthmatic patients and other allergic effects) (Ammann 2000, Burge 2001, US EPA 2001, CDC 2002, ACOEM 2002). The American Academy of Pediatrics recommends that pediatricians inquire about mold and water damage in the home when treating infants with pulmonary hemorrhage and, when mold is present, encourage parents to try to find and eliminate sources of moisture (American Academy of Pediatrics 1998). Avoidance of exposure to environmental tobacco smoke is always recommended, but has additional urgency in the presence of a case of pulmonary hemorrhage.

While methods under development to better characterize biological effects of and exposure to mycotoxins will aid our understanding, it should be useful to remember the words of Bennion and David-Bajar, which appear in their discussion of the use of trichothecene toxins in biological warfare:

> The diagnosis of mycotoxin-related disease will be a challenge for medical personnel. The specific signs and symptoms that result from exposure depend on a large number of variables including the specific mycotoxin or mycotoxins involved, the method of delivery, the dose received, the specific vehicle used, the portal of entry into the body, climatic conditions, the use of protective gear, and the nutritional status and general health of the casualty. Because of the large number of variables determining the clinical presentation, the spectrum of disease resulting from exposure to mycotoxins will likely be very broad. (Bennion and David-Bajar 1994, 20)

These, or even more complicated, considerations revolve around the situation that obtains during exposures to a "wet building" with chronic mold growth and low-level exposures to fungal allergens, volatile organic compounds, and mycotoxins, with resultant occupational diseases or residential "building-related disease." In these cases, the patient may suffer chronic exposures to mycotoxins, combined with other co-factors, one or more of which may be at dose levels at or fluctuating around the threshold for adverse effects.

Appendix B References

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Appendix C: Evaluating Patients For The Presence of Specific Antibodies to Molds

There are essentially two methods of testing for specific antibodies: skin testing and serum testing. Although they both test for specific IgE, there is some difference. Skin tests depend on the amount of IgE that is tissue-fixed on the mast cell, whereas the radioallergosorbant (RAST) and enzyme-linked immunoassay (ELISA) blood tests depend on the circulating IgE. Since IgE has a high affinity for tissue, the concentration in the skin is greater and lasts longer, a matter of years, as opposed to circulation, which has a half-life measured in months. There is a very high correlation between the two types of tests, but not a direct one-to-one correlation.

A skin test is performed either by placing a drop of the antigenic reagent on the skin and pricking through it or scratching with a needle, or injecting a small amount of substance intradermally. A positive reaction is wheal and flare, which is cause by histamine release in the skin when the antigen reacts with the mast cell that has been sensitized by the specific IgE. The disadvantage of the test is that if the concentration is too great or not standardized, a false positive result can be obtained. There is also a risk of causing an anaphylactic reaction in ultra sensitive patients.

RAST and ELISA tests are similar except for the detection method. The RAST uses radiation detection, and the ELISA uses an enzymatic colorimetric change. Both tests are done in a laboratory on a sample of serum. They use particles that have been coated with the antigen to be tested, then incubated with the serum. Antibody in the serum attaches to the antigen, and then an anti-IgE antibody with a radioactive or enzymatic tag is reacted to detect the level of specific IgE present.

Ideally, the laboratory or allergist should do only tests that have reasonable specificity and sensitivity and should run positive and negative controls. Unfortunately, many allergists and laboratories do not adhere to these standards. Research efforts to identify specific IgG, IgE, and IgA antibodies to molds and mycotoxins have yielded intriguing results. Such efforts may produce useful clinical tests in the future. (Larsen et al. 1997, Lander et al. 2001, Vojdani et al. 2003, Van Emon et al. 2003, Patovirta et al. 2003). Needed are systems to detect antibodies to molds endemic in particular regions and to molds that commonly amplify in indoor environments in particular regions. Not only must the antigens used reflect those found in nature (and buildings), issues of cross-reactivity between molds must be better understood to interpret positive results (Gupta et al. 2002).

Hypersensitivity Pneumonitis (HP) Antibody Screen

Testing for hypersensitivity pneumonitis consists of testing the serum of a patient for antibody to the substance in question. The usual antibody is of an IgG class, and the test is done by immunodiffusion.

The antigen in question is mixed with a gel medium. Serum is placed in small holes cut in the gel to accommodate a small measured volume. Positive and negative controls are placed in adjacent wells. As the serum diffuses in the gel, a precipitant line is formed at the zone of equivalence. This line should merge and fuse with the line formed by the positive control.

RAST or ELISA methods as described above can also be used. The only variation is that an anti-IgG antibody is used instead of an anti-IgE antibody. This method is more sensitive than immunodiffusion and will pick up non-precipitating antibodies as well.

A screen consists of performing the above tests for a number of specific antigens. The antigens are selected to represent those that are known to cause hypersensitivity pneumonitis. Most of these are molds, but other antigens such as pigeon serum are included as well. The limitations are the same as for allergy testing. The test is only as good as the reagents used, so there are many false-negative results.

A positive result can be due to non-specific reactions, but it has also been shown that individuals can develop antibodies to these substances without experiencing any disease. This is particularly true if the more sensitive RAST or ELISA test is used. This test should be considered testing for exposure to the substance in question that gives an antibody response, but is not diagnostic of disease.

Appendix C References

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Appendix D: Recognition and Management of Mold-related Illness

An Algorithm for the Healthcare Provider's Office

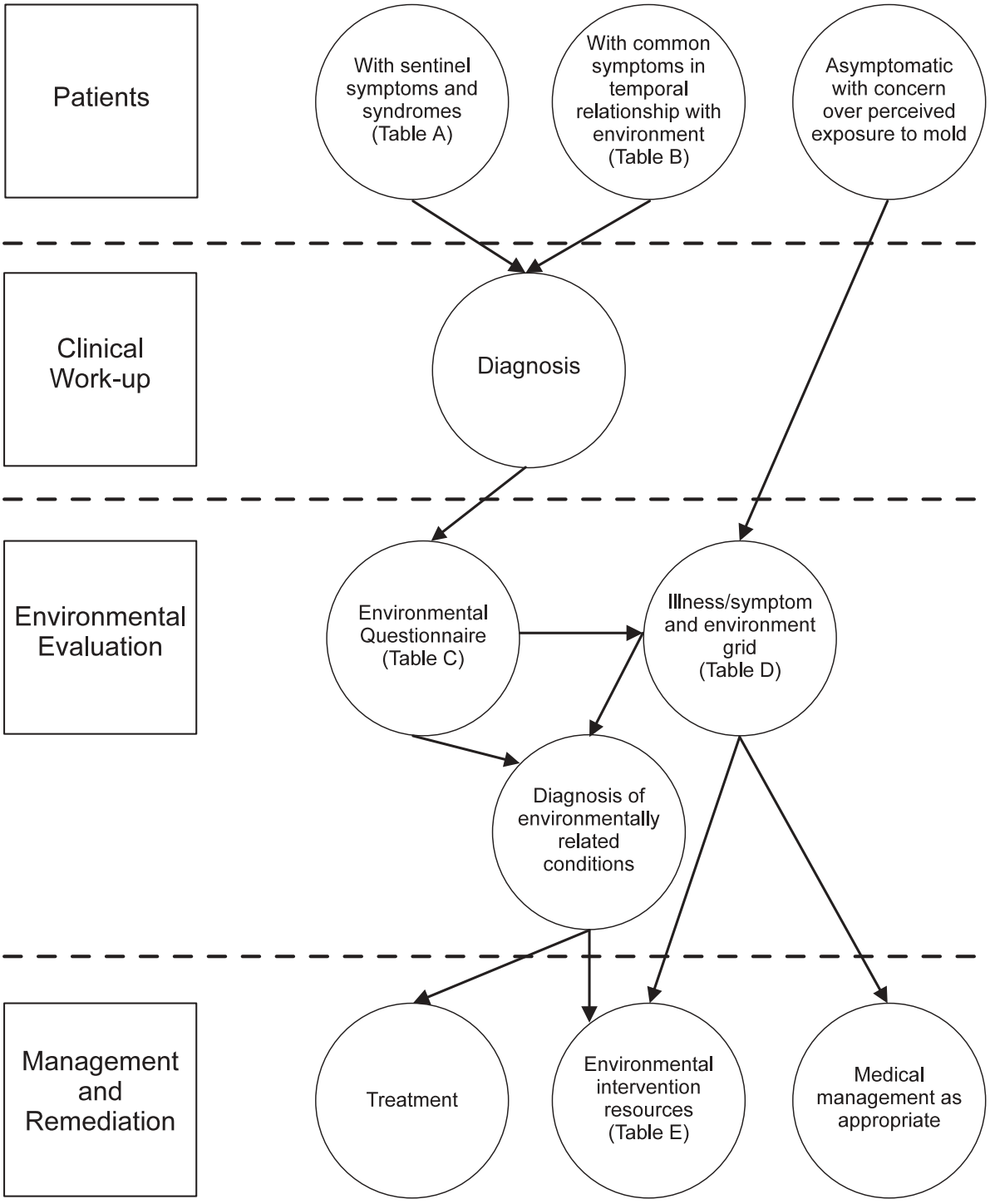

Table A: Sentinel Conditions*

Symptoms and Syndromes That May Suggest Mold or Moisture in the Absence of an Alternative Explanation

Conditions of Concern	Precursor Conditions
New onset asthma	Mucosal Irritation
Exacerbated asthma	Recurrent rhinitis/sinusitis
Interstitial lung disease	Recurrent hoarseness
Hypersensitivity pneumonitis	
Sarcoidosis	
Pulmonary hemorrhage in infants**	

* "Sentinel condition" has great utility as a concept in the broader area of occupational and environmental health. The diagnosis of an individual with a "sentinel" illness associated with exposures in a particular environment may indicate that these exposures may also deleteriously act on others. Intervention in the environment to limit identified exposures is an opportunity for primary prevention. A broader list of conditions that suggest a pertinent occupational exposure is found in Rutstein 1984. Bracker and Storey present a detailed discussion on exposure characterization and hazard identification for physicians whose patients have occupational and environmental asthma, inhalation injury, and granulomatous disease where bioaerosols as well as other agents in the environment are a concern (Bracker and Storey 2002).

**The American Academy of Pediatrics has developed a policy statement advising pediatricians when treating infants with pulmonary hemorrhage to inquire about mold and water damage in the home and, when mold is present, to encourage parents to try to find and eliminate sources of moisture (American Academy of Pediatrics 1998). Suspected cases should be reported to State Health authorities (CDC 2004).

Table B: Questions for Patients with Common Symptoms

1. What is your current occupation?

2. What are your current job and job tasks?

3. Do you notice any change in symptoms at home, work, or in any environment in particular?

4. Do you associate your symptoms with any activity or hobby?

5. Are you exposed to chemicals, fumes, or dusts at work?

6. Are there areas of your home or work that have recurrent moisture problems?

Table C: Environmental Questionnaire (For Patients with Sentinel Conditions, Symptoms that Vary by Environment, or a History of Recurrent Moisture Incursion)		
About hour home		
Do you have a **central humidifier or air conditioner**?	☐ Yes	☐ No
If yes, is the system cleaned infrequently?	☐ Yes	☐ No
Do you have **room humidifiers or air conditioners**?	☐ Yes	☐ No
If yes, is the system cleaned infrequently?	☐ Yes	☐ No
Is there **wall-to-wall carpet** in your bedroom?	☐ Yes	☐ No
Do you **regularly see mold on tiles, ceilings, walls, or floors** in your bathroom (other than occasionally on the shower curtain or tub enclosure)?	☐ Yes	☐ No
Do you see **mold** in your **basement on walls, ceilings, or floors**?	☐ Yes	☐ No
Do you **usually smell a musty odor** anywhere in your home?	☐ Yes	☐ No
Does your **roof leak**?	☐ Yes	☐ No
If yes, how often? ☐ Daily	☐ Monthly	☐ Once a year
Does the **plumbing in your kitchen or bathroom leak**?	☐ Yes	☐ No
If yes, how often? ☐ Daily	☐ Monthly	☐ Once a year
Are there **wet spots anywhere in your home, including your basement**?	☐ Yes	☐ No
Do you often see **condensation (fog) on the inside of windows and/or on cold inside surfaces**?	☐ Yes	☐ No
Environmental Tobacco Smoke*		
How many people who live in your home, or visit it regularly, smoke on a daily basis?	___Adults	___Children
*We include this question because of the broad and often synergistic health effects from exposure to environmental tobacco smoke.		

Table C: Environmental Questionnaire (Continued)
(For Patients with Sentinel Conditions, Symptoms that Vary by Environment, or a History of Recurrent Moisture Incursion)

About other environments

Sometimes people experience symptoms in places other than the home. Children spend considerable time in school environments. For adult patients, please consider the locations and work environments where you spend most of your time outside your home to answer these questions. For children or their parents, please answer about the child's school.

Outside the home, I (or my child) spend(s) most time at

_____

For adults, my occupation is

_____

How many days a week are you at your workplace or are you (or your child) at school?	___Days per week	
How many hours each day are you at your workplace or are you (or your child) at school?	___Hours per day	
Do you see **mold** anywhere (including ceilings and walls) in this place or general work area?	☐ Yes	☐ No
Do you usually **smell a musty odor** anywhere in this place or general work area?	☐ Yes	☐ No
Are there areas with recurring **wet spots** in this place or your general work area?	☐ Yes	☐ No
Has there been **a history of leaks or flooding** in the building at this place or at work?	☐ Yes	☐ No
Do you often see **condensation (fog) on the inside surface of windows and/or on cold inside surfaces such as metal shelves**?	☐ Yes	☐ No
Is there **carpet** in this place or classroom, or at your **general work area?**	☐ Yes	☐ No
Has it been **frequently wetted** by spills and/or leaks?	☐ Yes	☐ No

Positive responses to the questions on Table C indicate that further discussion with the patient on the environment would be helpful to explore if it is contributing to symptoms or disease. Negative responses to the questions regarding moisture and mold reassure the provider and the patient that mold is unlikely to be playing a significant role in the patient's presenting problem.

Table D: Current Symptoms - History and Relationship to Home, Work, or School (For Patients in Which a Potential Exposure to Mold Exists)

Symptoms that may be related to mold Are you troubled by:	Please circle your response								Comments
			How is it at home?			How is it at work or school?			
Wheezing or whistling in your chest?	Y	N	Better	Worse	Same	Better	Worse	Same	
Waking up first thing in the morning with a feeling of tightness in your chest?	Y	N	Better	Worse	Same	Better	Worse	Same	
Waking up during the night with shortness of breath?	Y	N	Better	Worse	Same	Better	Worse	Same	
Shortness of breath when you are not doing anything strenuous?	Y	N	Better	Worse	Same	Better	Worse	Same	
Waking up during the night by an attack of coughing?	Y	N	Better	Worse	Same	Better	Worse	Same	
Chest tightness when you were in a dusty part of the house or with animals (for instance dogs, cats, or horses) or near pillows (including quilts)?	Y	N	Better	Worse	Same	Better	Worse	Same	
Chills or fever?	Y	N	Better	Worse	Same	Better	Worse	Same	
Aching all over?	Y	N	Better	Worse	Same	Better	Worse	Same	
Runny, blocked, or stuffy nose?	Y	N	Better	Worse	Same	Better	Worse	Same	
Headaches?	Y	N	Better	Worse	Same	Better	Worse	Same	
Extreme or unusual lethargy and/or tiredness?	Y	N	Better	Worse	Same	Better	Worse	Same	
Frequent sinus congestion?	Y	N	Better	Worse	Same	Better	Worse	Same	
Frequent nose bleeds?	Y	N	Better	Worse	Same	Better	Worse	Same	
Hoarseness?	Y	N	Better	Worse	Same	Better	Worse	Same	
Feelings of unsteadiness when walking?	Y	N	Better	Worse	Same	Better	Worse	Same	
Memory loss?	Y	N	Better	Worse	Same	Better	Worse	Same	
Difficulty recalling names of people you know?	Y	N	Better	Worse	Same	Better	Worse	Same	
Nausea?	Y	N	Better	Worse	Same	Better	Worse	Same	
Vomiting?	Y	N	Better	Worse	Same	Better	Worse	Same	
Diarrhea?	Y	N	Better	Worse	Same	Better	Worse	Same	
Skin conditions?	Y	N	Better	Worse	Same	Better	Worse	Same	

Table E: Environment Intervention Guidance (Selected World Wide Web Resources)
United States Environmental Protection Agency Indoor Air-Mold http://www.epa.gov/mold/ http://www.epa.gov/iaq/molds/moldresources.html Mold Remediation in Schools and Commercial Buildings http://www.epa.gov/iaq/molds/mold_remediation.html A Brief Guide to Mold, Moisture and Your Home http://www.epa.gov/iaq/molds/moldguide.html
California Department of Health Services http://www.dhs.ca.gov/ps/deodc/ehib/ehib2/PDF/MOLD_2001_07_17FINAL.pdf Mold in My Home: What Do I Do
Canada Mortgage and Housing Corporation http://www.cmhc-schl.gc.ca/en/burema/gesein/Momo/index.cfm Fighting Mold; Moisture and Air: Problems and Remedies
University of Minnesota http://www.dehs.umn.edu/iaq/flood.html Managing Water Infiltration into Buildings
New York City Department of Health and Mental Hygiene Bureau of Environmental and Occupational Disease Epidemiology "Guidelines on Assessment and Remediation of Fungi in Indoor Environments" http://www.ci.nyc.ny.us/html/doh/html/epi/moldrpt1.html