

Rostrum

Are indoor molds causing a new disease?

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Three mechanisms for disease caused by mold—infection, allergy, and toxicity—are established and well recognized by clinicians. In each case the corresponding diseases are specific to a particular fungus. The mechanisms involved include a recognized inflammatory pathology that leads to objective clinical evidence of disease. Recent widespread litigation has arisen out of an unproved assertion that exposure to indoor molds causes an ill-defined illness. This illness is characterized by the absence of objective evidence of disease and by the lack of a defined pathology. There is usually no specificity for the involved fungus purported to cause the illness. Those publications that claim such an illness are reviewed. They are found to lack scientific validity, often on the basis of faulty methodology and insufficient information. There is no coherent clinical description for the presumed illness. Recommendations are offered for published reports and studies to address this problem. (*J Allergy Clin Immunol* 2004;113:221-6.)

Key words: *Fungi, toxic molds, Stachybotrys species, litigation, controversies*

There is a current wave of litigation sweeping the country. Residents living in homes, apartments, or condominiums are suing building owners, contractors, builders, and others, claiming personal injury caused by “toxic molds.” Some of these cases are occasioned because of water intrusion through flooding, faulty construction, or other means. Physicians are being enlisted by attorneys representing either plaintiffs or defendants to offer “expert” testimony. Allergists in particular are sought because of their knowledge of environmental molds as allergens and their familiarity with the problem on a day-to-day basis in their practice.

The role of the medical specialist as an expert witness is to provide the court with opinions grounded on facts relevant to the case. The challenge is to base these opinions on a foundation of the best scientific and medical evidence available rather than on conjecture.

MECHANISMS OF FUNGAL DISEASE

Experience, logic, and the vast majority of accumulated data at the present time lead to the conclusion that

Abbreviation used

ABPA: Allergic bronchopulmonary aspergillosis

there are but 3 mechanisms for the pathogenesis of human disease caused by mold. These are infection, allergy, and toxicity. Furthermore, in the case of each of these 3 mechanisms, the corresponding diseases are always specific to a particular mold. (Fung and Hughson¹ have added a fourth mechanism, irritation, but this is based on their review of the same publications cited below and not on any scientific experimentation.)

Infection

Fungal infections of human beings are often localized to the skin or lungs, although they might be systemic. Infections involving the central nervous system, bones, joints, or lymph nodes are distinctly less common, and tissue abscesses or disseminated disease in any organ or serosal surface are more apt to occur as opportunistic infections in the immunocompromised host. The presence of candidiasis, cryptococcosis, aspergillosis, mucormycosis, and other infections is likely under these conditions. Opportunistic infections also occur in diabetes, alcoholism, and neutropenia and during the course of corticosteroid therapy, as well as with the use of broad-spectrum antibacterial drugs.

Nonopportunistic fungal infections in the absence of these underlying conditions are often geographically segregated in endemic regions. These include infections by actinomycetes (*Nocardia* and *Actinomyces* species) and by the dimorphic fungi, such as histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, sporotrichosis, and penicilliosis.

For diagnostic purposes, evidence of the specific fungus in tissues usually requires culture or biopsy of the inflamed sites, although the presence of yeast on mucous membranes (eg, *Candida albicans* in the gastrointestinal tract and vagina) are common in the general population as commensal organisms without generating an inflammatory response.

Allergy

Respiratory diseases caused by inhalation of mold spores mediated by allergic mechanisms are well recognized by allergists.² They encompass only 4 known diseases: atopic asthma, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis (ABPA), and allergic fungal sinusitis.

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Atopic asthma. Fungal allergenicity has been well documented since 1873, when Blackley³ proposed that inhalation of mold spores might produce respiratory allergy. Numerous publications since 1924 document specific molds as a cause of allergic asthma.^{4,5} IgE sensitization to fungi is well established. Allergens from spores, conidia, mycelia, and other fungal particles are all capable of inducing IgE antibodies. Individual fungal species contain 40 or more distinct allergens for human beings. Sensitivity is specific, but cross-reactivity is a common feature of fungal allergy.

Atopy is expressed commonly as allergic rhinitis, asthma, and atopic dermatitis but rarely also as allergic gastroenteropathy. However, asthma is the only well-documented form of IgE-mediated disease in which airborne fungal allergens are involved. Allergic rhinitis caused by fungi is sometimes suspected and indeed might occur, but it is difficult to diagnose with certainty. Sensitivity to molds in the complete absence of any other common inhalant allergens (eg, pollens, animal danders, and the house dust mite) is quite unusual, so that the presence of these other sensitivities invariably dominate the clinical expression of allergic rhinitis.

Deuteromycetes (fungi imperfecti) make up the large majority of allergenic fungal genera that induce IgE sensitization of human subjects. These fungi account for the prolific production and aerial dissemination of most sexual spores and are found both indoors and outdoors. Basidiomycetes (mushrooms, toadstools, puffballs, rusts, and smuts), on the other hand, are rarely encountered indoors.

Thoughtful and experienced allergists who are especially sensitive to the patient's history will attest to the difficulties in the diagnosis of fungal atopic diseases. There are thousands of species of molds, and although only about 200 of them are known allergens, that is a much greater number than the number of recognized pollen allergens of importance in a localized area. Airborne spores are ubiquitous, with minimal geographic variation compared with pollen. There are poorly defined seasonal patterns for mold sporulation in contrast to the pollination of plants. Spore identification is difficult, and there is variable expression of allergens both within the same species and among different species, which is often dependent on culture conditions. As a result, allergen extraction is problematic, and few purified allergens are currently available for research purposes or clinical use.

Nevertheless, epidemics of fungal asthma have been described and correlated with several specific outdoor fungi. There have indeed been several examples of such epidemics, probably related to unusual atmospheric conditions.⁶

Hypersensitivity pneumonitis. Hypersensitivity pneumonitis, also known as *extrinsic allergic alveolitis*, is an allergic disease of the peripheral airways and interstitium caused by inhalation of the allergen on airborne organic particles.⁷ It is a chronic disease that might progress to pulmonary fibrosis. Most reported cases are occupational, and most of the reported allergens are based on single

case reports.⁸ Inhalation of mold spores has been implicated in only a minority of cases, usually as part of a mixed flora with bacteria and other microorganisms. The disease might occur in stages, each with a characteristic pathology. The acute stage is marked by a mononuclear cell pneumonitis, the subacute stage by interstitial granuloma formation, and the chronic stage by granulomatous inflammation resulting in interstitial fibrosis.

Both the sensitization phase and the elicitation of the disease pathology and its clinical manifestations require the inhalation of large, if not enormous, quantities of the organic antigen. The result is a panimmune response, which is both local and systemic. The cellular immune response is of primary importance in the pathogenesis of all forms of the pulmonary disease, whereas the humoral response might be pathogenetic in the acute phase. All immunoglobulin isotypes are induced, but there is a particularly intense IgG response generating specific precipitins that are useful in identifying the suspected allergen and in documenting necessary exposure, but they are not in themselves diagnostic, as one time thought.

ABPA. ABPA is a complication in some patients with atopic asthma or cystic fibrosis. A unique pathogenetic mechanism is involved, wherein the spores of *Aspergillus fumigatus* (and rarely other species of *Aspergillus*) are trapped in thick mucus, leading to sensitization with production of IgE and IgG antibodies and specific T cells. Sensitization is induced by the mycelial phase of the organism but only after its germination in mucus. The most common allergen in this case is Asp f 1. This allergen is undetectable in air or present at best in exceedingly low concentrations, even when the air is disturbed. Even low levels can be detected only in the air above compost, where billions of *Aspergillus* species spores per cubic meter typically exist.

The disease is a noninfectious, immunologically induced bronchial inflammation affecting primarily the proximal airways. ABPA is characterized clinically by cough, wheeze, sputum, fever, weight loss, pulmonary infiltrates, and expectoration of mucus plugs. The clinical course is one of remissions and exacerbations, resulting in progressive central bronchiectasis and fibrosis and deteriorating pulmonary function, and it is potentially fatal.

Allergic fungal rhinosinusitis. Allergic fungal rhinosinusitis was first described in 1976,⁹ but the diagnostic criteria and even the definition of the disease remain controversial.¹⁰ The prevalence and specific causes vary geographically and are usually attributed to the ubiquitous dematiaceous fungi, notably *A fumigatus* (in which case allergic fungal sinusitis might accompany ABPA) and *Bipolaris spicifera*. The clinical presentation consists of recurrent hypertrophic sinusitis in a patient who is usually atopic. Nasal polyposis is common. The fungus can be cultured from nasal/sinus mucus. There is a positive, immediate wheal-flare skin test response to the organism, and the total serum IgE level might be elevated. Eosinophils and lymphocytes are prominent in the mucosal inflammation, and hyphae can be observed microscopically in inspissated mucus. Recurrences are common in spite of surgery and systemic glucocorticoid treatment.¹¹

Toxicity

Toxicity is governed by the adage “The dose makes the poison.” In other words every chemical substance to which the body is exposed is either toxic or nontoxic, depending on the dose and the route of exposure.¹²

All microorganisms generate chemicals that are necessary for their survival and nutrition. Each of these chemical moieties is both toxic and nontoxic, depending on the substrate (eg, tissue, organ, and whole organism, including the human being) and the dose and route of exposure. It is also defined by and dependent on what is being detected or measured. In the case of mycotoxins, a number of them have been exploited for their therapeutic benefit, notably as antibiotics, immunosuppressants, and cholesterol-lowering drugs.

The natural hosts for fungi are plants, including agricultural crops (cereal grains, human foods, and animal feeds). They might colonize these crops saprophytically, or they might be pathogenic by means of tissue invasion. Therefore the effects of mycotoxins on human subjects are recognized as the result of ingestion. Human effects are largely based on ingestion of *Fusarium* species-contaminated grains in Japan and the former Soviet Union and are referred to as “alimentary toxic aleukia.” The disease is characterized by gastrointestinal symptoms, weakness, and aplastic pancytopenia,¹³ and it is believed to be caused by the so-called T-2 toxin.¹⁴

Ingestion of mycotoxin-containing foods is a potential worldwide problem, but unfavorable climatic and sociologic conditions restrict the occurrence of clinical mycotoxicoses (mushroom poisoning, ergotism, aflatoxicosis, Balkan endemic nephropathy, yellow rice disease, and others).¹⁵ Appropriate agricultural practices in recent years have largely eliminated the problem. Available evidence establishes a role for the ingestion of mold in cases of toxicity but not the inhalation of mold spores.

CONTROVERSIES IN FUNGAL DISEASE

In sharp contrast to these recognized diseases, the overwhelming majority of claims for illness that generate litigation are attributed to the presence of *any* indoor mold or combination of molds. There is no specificity for the mold that is believed to be responsible. There is no specificity for the disease manifestations; there is rather a sense of illness, often without any objective physical findings. There is no currently identified mechanism of pathogenesis for the illness.

Furthermore, there is no current clinical description of the putative “disease.” There is no current body of clinical data defining a disease or pathology in those who claim illness from indoor mold growth because of water intrusion. Table I is a listing of the publications¹⁶⁻²⁸ that purport to provide information on illness caused by inhalation of indoor mold spores.

Croft et al¹⁶ were the first to publish a report of disease from a home supposedly contaminated by mold. The 4 family members and the maid were said to have a “vari-

ety of recurring maladies” that were not identified for each individual, but their physical examination and laboratory testing results were said to be negative.

Johanning et al¹⁷ described workers in a remodeled office building in New York with presumed excessive exposure to mold. An “epidemiologic study” was performed in which the subjects were those seen in an occupational health clinic and not randomly selected. They were examined by means of a health complaint questionnaire, but there was no control group for comparison. No physical examinations were performed. Hodgson et al¹⁸ also reported illness in a Florida county courthouse. This was also an “epidemiologic study” in which the subjects were selected by volunteering. “Interstitial lung disease” was diagnosed on the basis of self-reporting of 2 of 3 symptoms (fevers, myalgias, and chest symptoms). Spirometry was done, but no physical examinations were performed. In this case, the indoor total airborne molds were only 50% of outdoor concentrations.

In another office environment subject to flooding and mold growth, 53 workers completed a health questionnaire and were tested for immune functions and antibodies to molds. There were 21 control subjects, but this report does not describe how they were matched to the subjects. A greater proportion of affected workers had a “history of infections and symptoms in all major organ systems.” Subjects were not examined. Of the 24 laboratory measurements, only 1 (CD3⁺ lymphocytes in peripheral blood) was significantly different from the control measurements, although the mean values for these were well within the normal range.¹⁹

Cooley et al²⁰ investigated 622 adult workers at 48 schools in Southern states where there were complaints of poor indoor air quality. The investigators found evidence for mold spore concentrations inside the classrooms exceeding those found outdoors in 20 of the 48 schools. By means of a questionnaire but no objective examinations, they found that the complaints at all schools were health related, mostly of a respiratory nature. They reported no comparison with symptoms or measurements of mold concentrations from noncomplaining schools.

Johanning et al²¹ reported a descriptive study of 22 children and 125 adults seen in their clinic with multiple symptoms (especially respiratory and eye symptoms and fatigue) that they attributed to excessive mold in their homes. A physical examination is included in the research protocol, but the results were not given in the published report. Laboratory data on immunologic function and allergy to molds were also not reported but were said to “remain difficult to interpret . . . because of only very small differences and variations in observed trends.”

Several reports dealt specifically with the effect of dampness or mold on the prevalence of respiratory illness. Brunekreef et al²² surveyed 6273 children in the United States, and Li and Hsu²³ surveyed 1370 children in China by means of respiratory questionnaire and self-report of “water damage” and “mold or mildew” in the homes. Both reported a positive association between respiratory

TABLE I. Clinical data from published cases

Reference	History attributed to mold exposure	Physical examination	Affected building	Specific mold(s) implicated
Croft et al, 1985 ¹⁶	5 persons: cold, flu, sore throats, diarrhea, headaches, fatigue, dermatitis, alopecia, malaise	Repeatedly negative	Home	<i>Stachybotrys</i> species
Brunekreef et al, 1989 ²²	6273 US children (respiratory questionnaire); no control subjects	Not done	Homes	Total molds, spores
Platt et al, 1989 ²⁵	1169 UK children in 597 households: excess bad nerves, aching joints, nausea and vomiting, backache, blocked nose, fainting spells, constipation, breathlessness	Not done	Homes (measured dampness or mold)	Total molds, spores
Strachan et al, 1990 ²⁴	Children with asthma wheezed more in homes with higher mold counts	Yes, spirometry	Homes (mold quantitation)	Total molds, spores
Hyndman, 1990 ²⁶	345 Bengalis in London: depression was only symptom related to mold spore count	Not reported	Homes	Total molds, spores
Johanning et al, 1993 ¹⁷	43 workers: questionnaire to elicit symptoms but no control subjects	Not done	Office	<i>Stachybotrys</i> species
Augur et al, 1994 ²⁸	13 members of 4 families: chronic fatigue and URIs on the basis of alleviation of symptoms after relocation	Not reported	Homes	<i>Penicillium</i> species, <i>Trichoderma viride</i> , <i>Phoma</i> species
Li and Hsu, 1996 ²³	1370 children: questionnaire for self-report of dampness, mold, and respiratory symptoms	Not done	Homes	Total molds, spores
Johanning et al, 1996 ¹⁹	53 workers and 21 control subjects: questionnaire history (air and surface sampling for molds not done for control subjects)	Not done	Office	<i>Stachybotrys</i> species
Hodgson et al, 1998 ¹⁸	197 workers: questionnaire history, "case-control" study (control buildings not tested for mold quantitation)	Not Done	Office	<i>Aspergillus</i> species, <i>Penicillium</i> species, <i>Stachybotrys</i> species
Cooley et al, 1998 ²⁰	622 adult workers at 48 schools with indoor air quality complaints; no control subjects	Not done	Schools	<i>Penicillium</i> species, <i>Stachybotrys</i> species
Johanning et al, 1999 ²¹	Descriptive study: 22 children and 125 adults with multiple symptoms	Done but not reported	Homes (no data on fungal exposure)	<i>Stachybotrys</i> species
Santilli and Rockwell, 2003 ²⁷	Rhinitis questionnaire: 85 students and teachers	Not done	2 schools	Total molds, spores

UK, United Kingdom; URI, upper respiratory tract infection

illness and mold. Strachan et al²⁴ found that wheezing of asthmatic children was positively correlated with mold concentrations in the home, but these indoor concentrations were far lower than those found outdoors in the summer. Platt et al²⁵ surveyed homes to measure "overall dampness" and mold concentrations and compared these with a variety of symptoms in children, but no physical examination or testing was done. Statistically, there was a positive association with dampness/mold and number of symptoms, as well as bad nerves, aching joints, nausea and vomiting, backache, blocked nose, fainting spells, constipation, and breathlessness. Hyndman²⁶ surveyed 345 Bengalis living in 60 flats in London. Health information was supplied through a questionnaire and spirometric results were obtained, but the subjects were not examined. Spore counts and humidity levels were measured. The only association between fungal spore counts in the home and reported health effects was depression.

In a recent report,²⁷ 2 schools were investigated for mold contamination. Case reports of students and teachers

with asthma and allergic rhinitis were cited, and a school nurse reported that others had "some type of allergy symptoms." The implication that an excessive prevalence and severity of allergy was related to mold contamination of these schools was not verified on the basis of proper epidemiologic investigation and is therefore only speculative.

In a very brief report, Augur et al²⁸ cited relief of symptoms on relocation as the sole reason for assuming that airborne molds were responsible for chronic fatigue and upper respiratory tract infections in 13 persons.

Thus there is no description of a disease specific for indoor molds. Most of these reports cite the results of an epidemiologic survey as "evidence" that inhalation of mold spores causes a building-related disease, because of an excess number of "health complaints" rather than a specific disease. In some cases, self-reported improvement occurred when subjects were out of the building.

For the most part, laboratory testing is used to search for any abnormalities rather than for confirmation of a disease entity. Obviously, the more tests performed, the greater the

likelihood of uncovering a statistically significant difference. Dales et al²⁹ compared peripheral blood lymphocyte counts in children living in homes with more fungal contamination with those in children from homes less contaminated with mold. They found a larger number of CD3 cells expressing CD45RO in the former group and suggested that fungal contamination results in chronic lymphocyte stimulation. The difference was significant on the basis of statistical analysis, but the overall results were within expected limits.²⁹ One study compared self-reported dampness, mold or mildew, moldy odors, and water damage with actual fungal quantitation in homes and found a correlation with mold in dust samples but not in air samples. Furthermore, in this study the inaccuracy rate was high and there was a systematic reporting bias in those with allergic disease, who were more likely to report visible mold growth.³⁰

Thus there is no clear definition of the mechanism of pathogenesis of the presumed illness.

THE CASE OF *STACHYBOTRYS*

Many of these cases of putative illness believed to be caused by indoor mold contamination are attributed to *Stachybotrys atra* (also known as *Stachybotrys chartarum* or *Stachybotrys alternans*). This is a greenish-black saprophytic mold that requires substantial humidity and grows on cellulose with a low nitrogen content. It is found in soil and especially on substrates, either natural or synthetic, that are rich in cellulose. These include cereal grains, plant debris, straw, hay, fiberboard, gypsum, paper, dust, lint, carpet, insulation materials, and wood pulp.

It is a slow-growing fungus, with spores that die readily on release into the atmosphere. As a result, spores are rarely found outdoors and are difficult to isolate indoors. It was present in only 2.9% of homes in southern California, and the mean concentration was a mere 0.3 spores per cubic meter.³¹

There are no reported cases of human infections with *Stachybotrys* species. There is only 1 report of a possible allergy to the inhalation of *Stachybotrys* species spores in a boy with asthma,³² but there was no indication that the patient had been tested for allergy to this mold.

Thus the implication is left that the presumed disease is caused by toxicity. Trichothecenes are the principal mycotoxins of *Stachybotrys* species, but they are also the same ones produced by *Fusarium*, *Acremonium*, *Trichoderma*, *Trichothecium*, *Myrothecium*, and *Cylindrocarpus* species. A particular isolate of *Stachybotrys* species might or might not produce a particular toxin, because biosynthesis depends on the age of the hyphae, nutrients, and physical conditions.

The Cleveland, Ohio, experience is frequently cited as an example of the toxicity of *Stachybotrys* species. Initially, a cluster of cases of pulmonary hemorrhage-hem siderosis in very young infants was reported, with 10 cases in a 2-year period (1993-1994) at the Children's Hospital of Case Western Reserve University occurring in a localized geographic area. This contrasted with a single case in 9 years previously. An environmental survey

uncovered 2 risk factors in the homes: water damage from flooding and the presence of adult smokers.

Stachybotrys species was found in most of the homes, and this led to a series of publications³³⁻³⁶ that concluded that the disease in these infants was probably caused by a toxin from inhaled *Stachybotrys* species spores. It should be emphasized that unlike the reported cases cited above, a specific disease—ie, acute pulmonary hemorrhage exclusively affecting very young infants, caused by a particular species of mold, and involving a presumed mode of pathogenesis—was described. The results were incorporated into published guidelines by the American Academy of Pediatrics on the toxic effects of indoor molds.³⁷ There has been widespread media coverage, resulting in the closure of some public buildings.

The Centers for Disease Control and Prevention, which had participated in these studies, responded to critics with 2 expert panels who reviewed the data and reported "serious shortcomings." For example, there was no case definition, sampling of case and control homes differed and were not standardized, results were skewed by extremely high outlying values, there were concerns about quantitation of water damage, and there was doubt about whether measurements of exposure to *Stachybotrys* species or its toxins were clinically significant as opposed to contamination. The Centers for Disease Control and Prevention investigation concluded in 1999 that "a possible association between acute pulmonary hemorrhage . . . and [mold] exposure . . . was not proven."³⁸ A recent review addresses similar concerns about the Cleveland study.³⁹

All forms of fungi are capable of producing spores. They are a major component of the respirable atmosphere throughout the world, both outdoors and indoors. Indoor spores come from either outdoor spore invasion or a specific indoor organic source, such as plants or garbage. Although most fungi flourish optimally at high humidity, a few are actually xerophilic. Most grow optimally at 20°C to 40°C, and there is a wide variety of specific host requirements. Guidelines for the concentration of indoor molds have been published by a number of governmental and nonpublic entities, but to date, none of these guidelines are based on scientific data regarding the effects on human health or any specific disease.⁴⁰

RECOMMENDATIONS

A suspicion of a "new" disease affecting occupants of domestic and public buildings has been raised, in spite of the existence of fungi on earth for an estimated 550 million years. There have been sufficient published reports in both the professional literature and the popular press to arouse this suspicion. It is now time for scientifically rigorous data to be used to answer the question about the effects of indoor mold exposure on human health.

1. At the very least, a thorough history, physical examination, review of prior medical records, appropriate laboratory testing, and imaging studies should be

used to define the physiologic and anatomic abnormalities in suspected cases. It is inappropriate to use laboratory testing as a "fishing expedition."

2. The specific mold responsible for the disease should be identified, and scientific evidence for a causal connection must be presented.
3. The mechanism by which the presumed disease is believed to occur must be identified by means of appropriate testing.
4. The mode of exposure must be identified. If exposure is believed to occur through inhalation of fungal spores, quantitative data should be provided to establish the threshold dose required to produce disease. If exposure is through some other route (eg, on surface samples), an explanation needs to be given as to precisely how the contact with the mold has occurred.
5. So-called "epidemiologic studies" are inappropriate to establish causation, although they might be appropriate to suggest a hypothesis or to estimate the extent of risk factors in the cases of proved causation.
6. Cases in litigation should be clearly identified as such.

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