



# Fungi and Atopy

Charles Barnes<sup>1</sup>

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## Abstract

Atopy and fungi have a long associative history. Fungal spores were among the first substances to which humans were noted to be sensitized. Humans contact fungal spores in the outdoor, indoor, and occupational environments. As organisms, fungi have their own kingdom and are found in all environmental niches on earth. Currently, fungal exposure in the indoor environment especially related to wet housing conditions is of particular concern. Sensitization rates to fungi typically exceed 5% of the general public with higher rates among the atopic population. *Alternaria* is the best studied of the allergic fungi; however, cross sensitization to multiple fungi is well documented. Recent advances in understanding mechanisms of the innate immune system are beginning to explain why the fungal atopy relationship is unique and why fungal sensitivity seems to extend to many non-atopic individuals. Evidence has been accumulated that indicates fungal allergen exposure can be via intact spores as well as spore and mycelial fragments. Germinating spores produce a different and often increased allergen picture. Much evidence has been developed through animal studies that extends the mechanisms surrounding long-term low-level fungal exposure. However, it should be emphasized that the presence of fungi in the air does not necessarily equate with illness. Indeed, in the absence of an atopic individual and/or a significant immune response against fungi, there is little evidence suggesting pathology. Allergists frequently deal with patients who have concerns about indoor fungal exposure and respiratory disease in those patients with an allergic response.

**Keywords** Fungi · Atopy · Respiratory disease · Aerobiology · Indoor allergens · Fungal allergy · Indoor air quality

## Introduction

### History of Fungi and Allergy (Atopy)

Fungus has long been recognized as a player in asthma and allergic disease [1], and in the past century, this association has only become clearer. In 1949, Canadian physician Charles Walton noted, based upon several years of research, that there was a sizable group of seasonal allergies which could not possibly be explained by anything other than fungus spore exposure [2]. In 1935, Feinberg had called attention to the prevalence of sensitivity to *Alternaria* and to its marked seasonal nature. Subsequently in 1944, after the appearance of a great many reports of spore allergy, the Allergy in Practice Yearbook recognized fungal sensitivity as a most important type of inhalant sensitivity [3]. About 30 years later, it was

widely recognized that individuals with CF, who have a high frequency of *Aspergillus* infections, have an atopy rate around 50%. This is very much higher than the rate in the general public [4, 5]. Currently, exposure to fungi and associated wet housing conditions are recognized as significant factors in respiratory disease and asthma [6], as major factors in occupational-associated hypersensitivity diseases [7] and as significant contributors to hypersensitivity pneumonitis [8].

### Fungi Have Their Own Kingdom

Although taxonomy can be very contentious, in 1969, fungi were proposed to have their own kingdom. This was celebrated by the book “The Fifth Kingdom” in 1985 [9, 10]. This designation has held up under the scrutiny of DNA sequencing analysis. There has been and will probably continue to be some reorganization at the phyla, genus, and species level, but the most recent article by Levetin et al. [11] does a very good job describing the most recent fungal taxonomic assignments.

✉ Charles Barnes  
cbarnes@cmh.edu

<sup>1</sup> Allergy, Asthma, Immunology, Children’s Mercy Hospital, Kansas City, MO, USA

## Wet Housing and Asthma

The re-emergence of fungi as essential players in allergy and asthma can be dated to the release of the Institute of Medicine 2004 report “Damp Indoor Spaces and Health” (<http://www.nap.edu/catalog/11011.html>). A group of 9 scientists evaluated the epidemiological evidence and concluded that: “There is sufficient evidence of an association between exposure to a damp indoor environment and the presence of ‘mold’ and upper respiratory tract symptoms, cough, wheeze, and asthma symptoms in sensitized asthmatic people.” This initial report is followed up by a report on Microbiomes and the Built Environment [12] <http://nap.edu/23647> that states: “There is evidence of a link between exposure to indoor microorganisms and the development of respiratory and allergic symptoms, particularly those arising from exposure to microorganisms that flourish in damp indoor settings.” However, the field is very complicated, and easy to understand conclusions are not apparent. They further find that “Preliminary evidence suggests that certain microbial exposures, including early-life exposures to diverse microorganisms associated with animals, may have beneficial health effects, such as protection from allergy and respiratory symptoms.” Indeed, this is part of the hygiene hypothesis which suggests that exposure to microbes, particularly early in life, has long-term beneficial effects on health and particularly the immune system.

## Fungal Proteins Permeate the Environment

Fungi are found nearly everywhere. As terrestrial plants and microbial life evolved, fungi became the major decomposers of organic material [13]. Wherever dead or dying vegetation is found, there will be at least one and frequently many fungal species involved in extracting all the available nutrients. Fungal proteins are part of the very dirt itself, and fungal proteins and allergens are found nearly everywhere. Airborne spores and hyphal fragments travel readily through the air. Many fungi are specifically evolved for airborne dissemination [14]. Often, spores traverse many thousands of miles in the upper atmosphere [15]. Part of this fungal ubiquity is fungal external digestion that involves secretion of fungal digestive enzymes directly into the environment.

Fungi are essential for decomposing environmental organic matter and have fundamental roles in environmental nutrient exchange. They are heterotrophs or organisms reliant on carbohydrate metabolites from other organisms. Fungi have the ability to use a diverse range of simple organic substrates including nitrate, ammonia, acetate, and ethanol for growth. These substrates are derived from other, usually dead, organisms by secreting hydrolytic enzymes into the environment. Preexisting complex polysaccharides, proteins, and lipids are digested producing smaller sugars, amino acids, and fatty

acids that are absorbed as nutrients. Therefore, for practical purposes, the entire external environment functions as a stomach for fungi. As a result, the environment is absolutely loaded with the remnants of fungal digestive proteins. Fungal proteins and allergens are in the water, in the dirt, in house dust, in the air, on living plant material, and lightly coated over all but the cleanest surfaces.

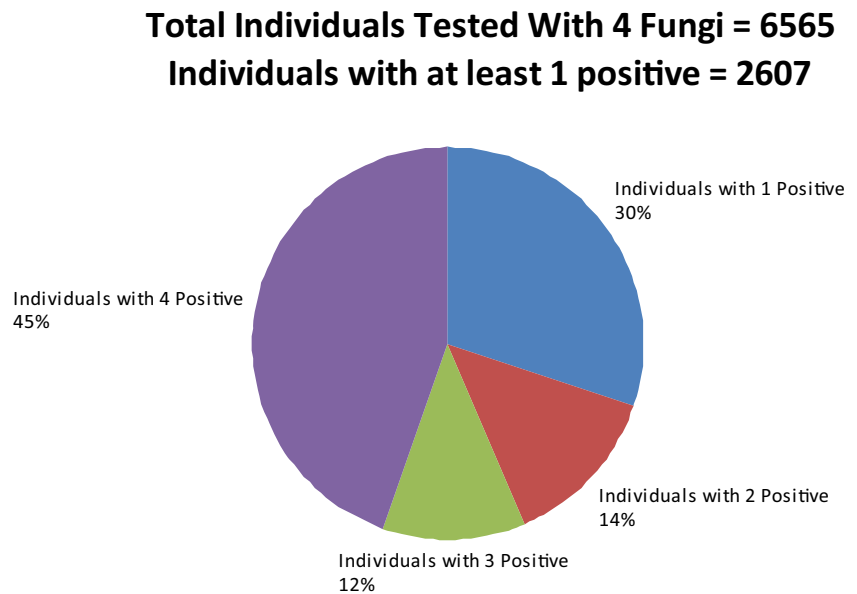
## Sensitization Rates to Fungi

The initial NHANES study tested the general public, adults, and children ( $N=9440$ ) for specific IgE against *Alternaria alternata*, and a smaller number (7268) to *Aspergillus fumigatus*. Sensitivity to both fungi varied with age. Overall sensitivity to *Alternaria* was estimated to be around 7%, and sensitization to *Aspergillus* was around 6%. Sensitivity to both fungi peaked at 20 years of age at about 15% for *Alternaria* and a little less for *Aspergillus* [16]. Previous testing to *Alternaria* via traditional skin prick methods indicated an overall sensitization rate of 12.9% [17]. Theoretically, this sensitization rate to fungi is an underestimate. With the recently developed next-gen sequencing methods and the use of ample available libraries of fungal sequences, it is being realized that the richness of the fungal presence in indoor and even outdoor spaces has not been fully appreciated previously [18, 19]. The possibilities for fungal sensitization would therefore be immense [20]. However, cross-reactive sensitization is well known among fungi, and sensitization levels to the few well-known fungi may be a reasonable proxy for fungal sensitization in general. In a study of 6565 individuals who had specific IgE testing, of individuals who had at least one positive fungal test, nearly half (1208) tested positive for all four fungi [21] (Fig. 1). It is appreciated that fungi share a great many allergens that have homologous structures and can be grouped into protein families. These include allergens that are proteolytic enzymes, stress response proteins, proteins involved in protein synthesis, and proteins involved in carbohydrate metabolism. Members of these protein families with similar functions are very cross-reactive with respect to allergen sensitization and have homologous structural elements [22]. It is recognized that many fungal allergenic proteins are not unique to an individual fungus. Cross-reactivity will be noticed by anyone who routinely performs allergen skin testing [23, 24]. It has been demonstrated by clinical history of exposure, epicutaneous skin sensitivity testing, and inhibition assays [25–27]. Recent high-throughput cloning work with fungal allergens indicates that fungi produce complex repertoires of species-specific and cross-reactive allergens [28].

## *Alternaria* and a Long History of Atopy and Asthma

*Alternaria* is clearly the chief fungal entity as far as allergy is concerned. This may be because its unique club shape with

**Fig. 1** All 6565 individuals were tested for specific IgE to *Alternaria*, *Cladosporium*, *Aspergillus*, and *Penicillium* using ImmunoCAP methods and reagents. Of those who tested positive to at least one fungus (2607), 45% tested positive to all 4 fungi



both horizontal and longitudinal septations is easily recognized by anyone looking for allergenic particles using a microscope. Or it may be because typically *Alternaria* is the fungus to which most humans are sensitized [17]. Or it may be because *Alternaria* is the fungus previously associated with asthma deaths [29]. The significance of *Alternaria* in allergy has long been recognized. Reports of allergens purified from *Alternaria* date back to 1956. In a recent study of atopy phenotypes in asthma development among school-aged children, early sensitization to outdoor allergens, especially *Alternaria*, was recognized as one of four characterized phenotypes [30]. In a study of low-grade, moderate, and severe asthma in a pediatric population, *Alternaria* sensitization was the most common among the fungi. *Alternaria* sensitization was seen to increase with age and associated with co-sensitization against other fungi [31]. In a study of allergen sensitization in children with asthma and rhinitis that collected data on 3066 patients, sensitization to the five main aeroallergens (olive, mites, *Salsola*, *Alternaria*, and cat) described 98% of atopic patients between 6 and 14 years of age. They noted especially that sensitivity to *Alternaria* occurred at an early age [32].

### Known Fungal Allergen Proteins and Families of Fungal Proteins

It is likely that the major fungal allergenic proteins to which individuals are sensitized have been identified and characterized. The allergen database Allergome (<http://www.allergome.org/>) lists 258 allergenic fungal taxa containing 594 allergenic proteins. The International Union of Immunological Societies database (<http://www.allergen.org/>) lists 29 taxa and 100 allergenic proteins.

The AllFam database (<http://www.meduniwien.ac.at/allergens/allfam/>) indicates that there are 66 recognized fungal allergen protein families with 28 families identified in more than one fungal species. The subtilisin-like serine protease family has the greatest number of individual fungi contributing at least one protein (6 *Aspergillus* species, 2 *Cladosporium* species, one *Curvulata* species, one *Penicillium* species). Major families of protein allergens are listed in Table 1 [22].

### Fungi Involved in Irritant Reactions

The presence of chitin in the cell wall of fungi distinguishes them from many other organisms. It also provides a convenient marker for the innate immune system and puts fungi in the same company with dust mites and cockroaches. Fungal interactions with the innate immune system are frequent and important. Innate immune system interactions are resultant when repetitive pathogen-associated molecular patterns are recognized by the sentinel elements of innate immunity. Chiefly, these are molecular patterns that associate with the fungal cell wall [22] including mannan (mannosylated proteins),  $\beta$ -glucan, and chitin. Although generally thought of as an outer layer of mannosylated proteins over rigid beta glucan and n-acetyl glucosamine (chitin), the fungal cell wall can be a dynamic structure. It varies in composition among the numerous fungal species as well as with phases of fungal growth and development. Therefore, fungi in one developmental stage may be highly allergenic whereas the same fungus in another stage of development may be tolerated even by highly sensitized individuals. Different fungi or even the same fungus in differing developmental stages or grown in differing media can present a differing immunological picture [33]. These varying carbohydrate pictures can be recognized by

**Table 1** Major protein allergen families and their general functions

|                                  |                                                                                                                                                                                                   |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Peroxisomal membrane proteins    | Proteins associated with peroxisome organelles. Most are involved in catabolism of fatty acids, D-amino acids and polyamines.                                                                     |
| Subtilisin-like serine proteases | Proteolytic enzymes that have a Asp/Ser/His catalytic triad as well as an alpha/beta fold containing a 7-stranded parallel beta sheet.                                                            |
| Acid ribosomal proteins          | Proteins involved in the assembly of the ribosomal unit. They are some of the most highly conserved proteins across all life forms.                                                               |
| Cyclophilins                     | A family of proteins abundant in the cytosol that bind to cyclosporin. They catalyze the isomerization of peptide bonds from trans to cis at proline residues.                                    |
| Heat shock proteins              | A family of proteins produced by cells in response to exposure to stressful conditions (heat shock). They have a chaperone function to stabilize newly formed proteins to ensure correct folding. |
| Enolase                          | The ninth step in glycolysis. An enzyme belonging to the family of hydro-lyases that cleave carbon-oxygen bonds.                                                                                  |
| Aldehyde dehydrogenase           | Enzymes that catalyze the oxidation of aldehydes.                                                                                                                                                 |
| Glutathione S Transferase        | Also known as ligandin. It is a family of metabolic isozymes that catalyze the conjugation of the reduced form of glutathione for the purpose of detoxification.                                  |
| Catalase                         | A common enzyme essential for all living organisms exposed to oxygen. It is very important for protecting the cell from oxidative damage.                                                         |

C-type lectin receptors (CLRs) that are evolved to bind and recognize many glucan and mannan structures from fungi. CLRs have names like MBL (mannose-binding lectin), Mincle (macrophage-inducible C-type lectin), DC-SIGN (dendritic cell-specific ICAM3-grabbing nonintegrin), and DNCR-1 (DC NK lectin group receptor-1). Their full importance is only now becoming understood; however, it is clear that they basically serve to recognize fungi and modulate innate immune response.

### Chronic Low-Level Fungal Exposure

Although fungal exposure is typically assessed by estimating the airborne fungal spore concentration, this value may only be a surrogate for total fungal particulate exposure. Researchers in Australia demonstrated that differing amounts of fungal allergen could be identified in differing parts of germinating fungal spores [34, 35]. It has subsequently been shown that the contribution to total fungal allergen exposure attributable to particles other than identifiable spores was substantial. Although the contribution of hyphae and fungal fragments to exposure and allergic sensitization is generally poorly understood, it is probably a substantial contributor to the reduced exposure upon fungal remediation. Researchers have reported that particles derived from fungal structures become aerosolized in concentrations 300–500 times greater than spores [36]. A study of bioaerosols sampled 39 homes of fungal allergic subjects using inhalable fraction samplers and analyzed those samples by immunostaining using the resident subject's immunoglobulin E. Fungal particles that bound the subject's IgE were 1.7-fold

(bedroom) and 1.4-fold (living room) more concentrated than that of Der p 1, Fel d 1, and Bla g 1 allergen particles combined. The study concluded that inhalable fungal aerosols in homes should be considered in future exposure assessments [37]. The development of species-specific monoclonal antibodies and an immunostaining method for particles collected directly from the air has enabled the speciation of previously indiscernible fungal fragments. Studies using these methods indicate that about one-quarter of all hyphal fragments express detectable allergen and larger fungal fragments are significant contributors of aeroallergens. Air samples collected from homes contained a broad spectrum of fungal spores, conidia, hyphae, and other fungal particulates [38]. The advances in identification of allergen containing fungal particles have reignited concerns about chronic fungal exposure. This is of particular concern in homes, schools, and office buildings. Individuals who live, study, and work in these environments may be exposed to many types of fungal components including fragments, mycotoxins, and microbial volatile organic compounds as well as spores. These concerns have been supported by recent mechanistic work on chronic fungal exposure studies in mice. Experimenters delivered *Aspergillus fumigatus* spores to the lungs of mice using a nose-only chamber two times a week for 13 weeks. Mice were evaluated for changes in lung architecture, recruitment of specific immune cells, and serum antibody responses. Researchers observed germinating *A. fumigatus* spores in lungs as well as fungal debris in perivascular spaces in the lung. These chronic repeated exposures resulted in lung pathology including pleocellular lung infiltration, epithelial

mucus hypersecretion, goblet cell metaplasia, subepithelial fibrosis, and enhanced airway hyperreactivity. Cellular infiltration in airways was dominated by CD4+ T cells expressing the pro-allergic cytokine IL-13. Also, total IgE production was augmented in these chronically exposed animals [39].

Further studies should address whether chronic fungal exposure leads to changes in the innate immune system and whether such changes are beneficial, as per the hygiene hypothesis, or whether they lead to changes in adaptive immunity such as in patients with allergies. With the increased attention and funding devoted to the field of chronic fungal exposure, the connection between subtle innate immune system elements like CLRs and fungal allergic disease is being revealed [39]. However, at present, there is no scientific evidence that exposure to mold alone has any influence on human health, unless patients have underlying allergic responses, are compromised hosts, or have hypersensitivity disorders to mold.

## Fungal Toxins

The subject of human mycotoxin exposure is old, and there is no evidence that mycotoxins within the environment are harmful to humans unless they are ingested. Mycotoxins are low molecular weight chemicals produced by fungi to compete for nutrient resources with other microorganisms in their immediate environment. Human health problems related to ingestion of mycotoxins are well documented, and mycotoxin contamination of crops is an economically important problem [40]. The concentrations of several toxins in the food supply are monitored by grain handlers, food producers, and governments [40]. However, the fungi that produce these toxins are generally not of concern in homes [41]. Numerous excellent reviews of mycotoxins and mycotoxicosis are available [42].

Mycotoxin exposure in the indoor environment has been the subject of much litigation and speculation. Neither the Institute of Medicine report on damp spaces and health nor the World Health Organization panel on mold and dampness found sufficient evidence to link indoor mycotoxin exposure to reported health effects [6, 43]. Yet, the subject remains significant in popular culture. Much of the indoor mycotoxin exposure controversy centers around exposure to *Stachybotrys chartarum*—a fungus that grows on wet cellulose-based materials and is considered a marker for damp environments [44]. The presence of *S. chartarum* means that the building has or had significant moisture problems. Allergenic proteins from *S. chartarum* have been identified and sequenced [45, 46]. However, sensitivity to *Stachybotrys* is unlikely, and the damp conditions that contribute to the growth of *Stachybotrys* also promote the growth and related population health effects from other species commonly found indoors [6]. Exposure to mycotoxins in a residential environment is not a likely cause for disease. A provider faced

with toxic mold complaints, therefore, should not focus on fungal toxicity but should instead use clinical judgment to consider more likely causes as allergy and poor indoor air quality. Currently, allergists are seeing patients who bring with them laboratory testing results that show levels of mycotoxin in blood or urine. Tests that claim to measure trichothecenes in human sera or urine are not FDA cleared and have not proven to be analytically reliable [47]. In addition, any mycotoxin metabolites found in human urine likely were ingested in contaminated food.

## Outdoor Fungal Exposure

Outdoor fungal exposure is nearly ubiquitous. In northern latitudes, outdoor fungal spore levels start low in the spring at a few hundred per cubic meter of air. They rise gradually with rainfall and increasing daily temperatures until they peak in the early fall with high levels approaching 50,000 spores per cubic meter of air. In southern latitudes, airborne fungal levels are nearly continuous, are more dependent on the humidity cycle, and can be somewhat depressed by extreme high temperatures. But, overall airborne spore levels in the tens of thousands of spores per cubic meter of air can be encountered at nearly any time of the year. Fortunately, the fungal taxa that are most abundant in outdoor air (*Cladosporium* and undifferentiated Ascomycetes) are not the fungal taxa to which most atopic individuals are sensitive (*Alternaria* and *Candida*) [48].

## Indoor Fungal Exposure

At this time, there is an accumulating body of evidence that indicates exposure to indoor microbial diversity including fungal diversity might be associated with a lower incidence of atopic disease. However, it is still far from certain whether observed favorable health outcomes are due to exposures to specific microbes or is the important factor exposures to a greater diversity of microbes. On the other hand, the key may be the point in the life of an individual at which exposures occur. Microbial exposures have been associated with protective effects for asthma and atopy [49]. Microorganism-associated molecular patterns through their interaction with elements of the innate immune system might influence overall immune development leading to protective effects for asthma and atopy. Many factors including endotoxin,  $\beta(1-3)$  glucans, and muramic acid from bacteria and fungi have been associated with a reduced risk of allergy and asthma in selected studies. Diversity of microbial (bacterial) exposure has been associated with a reduced asthma risk in farmers' children. Diversity of both fungal and bacterial exposure seemed to have protective effects [50]. Tischer et al. studied the early fungal and bacterial microbiome in house dust from 189 homes with respect to allergic sensitization and wheezing later in childhood. Fungal and bacterial diversity was assessed with

terminal restriction fragment length polymorphism, and information on wheezing outcomes was obtained by parent questionnaires. Specific allergic sensitization was assessed at ages 6 and 10 years. Adjusted logistic regression analyses indicated children with exposure to higher fungal diversity had significantly reduced risk of developing sensitization to aero-allergens at 6 years and ever wheezing until the age of 10 years (adjusted odds ratio (OR) = 0.26 (95% CI 0.10, 0.70) and 0.42 (95% CI 0.18, 0.96), respectively) [51].

The exposure sensitization relationship is clearly a very complex one. Diversity, however, should be distinguished from total fungal load in a structure. Studies repeatedly show that the wrong types of fungal exposure especially in high intensity or chronic events associate with increased asthma and respiratory disease. In a recent study of 196 asthmatic children to examine associations between exposures to household microbes and asthma severity, children were stratified by atopic status. Microbial community structure and concentrations in house dust were determined by using next-generation DNA sequencing and quantitative PCR. Increased asthma severity was significantly associated with an increased concentration of summed allergenic fungal species, high total fungal concentrations, and high bacterial richness [52]. In a birth cohort study of 389 children beginning when they averaged 5 months of age, structured home inspections were performed and children were followed up to the age of 6 years. Specific immunoglobulin E concentrations were determined at 6 years. Moisture damage and mold at an early age in the child's main living areas were associated with the risk of developing physician-diagnosed asthma ever, persistent asthma, and respiratory symptoms. Associations with asthma ever were strongest for moisture damage and with visible mold in the child's bedroom (adjusted odds ratio 4.82 [95% CI 1.29–18.02]) [53].

### Penetration of Outdoor Fungi into the Indoor Environment

It is generally considered that any fungal spores found inside a home should have originated from the outdoor air. Whenever collections to evaluate indoor spore levels are taken, samples should be taken of both indoor and outdoor air. As long as a building is uncontaminated, aerosolization of fungi from growth in the indoors is only minor when compared with the fungal contribution from outdoor air [54]. A study to compare data from indoor and outdoor airborne spore evaluations in relation to seasonal and environmental factors in Kansas City, MO, determined the relationship of indoor fungal spore levels, outdoor ground-level fungal spore levels, and outdoor spore levels at a central collection point. They reported that significant taxa that dominated the total spore level when elevated (*Aspergillus-Penicillium*, *Cladosporium*, and undifferentiated Ascomycetes) were all correlated with mean total spore counts when seen indoors. The indoor taxa typically correlated well

with the outdoor taxa; however, major genera associated with the indoors, such as *Chaetomium* and *Stachybotrys*, were not correlated with outdoor air. The major spore group associated with the indoor environment, *Aspergillus-Penicillium*, was not as strongly correlated with outdoor air as *Cladosporium* and *Alternaria* [55].

### Home Inspection and Allergy Practice

Often, the first association the practicing allergist has with the home assessment/inspection industry is the patient who brings in a story about “black mold” accompanied by a laboratory report with a list of airborne concentrations for common fungi. The laboratory report frequently contains a page of every negative health consequence ever related to fungal exposure. In spite of the many cautionary alarms the allergist might feel, the chief concern is still how can I help this patient. Fortunately, there are many helpful articles in the literature to provide guidance. Horner's paper on interpreting reports from inspections/investigations of indoor mold provides excellent guidance [56]. Basically, allergy (health impact) is not the major reason homes or buildings are inspected for mold. Esthetic concerns and water damage are more common drivers of inspections. All types of fungal spores are commonly found in indoor air. Concern only arises when indoor levels exceed outdoor levels and airborne concentrations can be related to symptoms. There may be evidence of indoor *Cladosporium* growth, but if the patient is not allergic to *Cladosporium*, the concern is for building damage not health.

### Qualifications for Home Inspectors

There are many different overlapping disciplines that provide the background needed to properly evaluate a home or building for fungal problems. However, since most fungal-related medical concerns involve respiratory problems, a person with a background in indoor air quality is typically chosen. There are numerous certifying organizations for indoor air quality including the Indoor Air Quality Association, the American Council for Accredited Certification, and the American Industrial Hygiene Association. A physician who frequently deals with indoor air quality respiratory problems may wish to establish a relationship with one or more certified individuals. A reputable IAQ expert will readily provide information on certification, training, experience, and pricing upon request. Suggestions for the qualifications of an IAQ consultant can be found in Chew et al. [57].

### Indoor Fungal Problems Relate to Water

It has frequently been said “Fungi can eat almost anything, but what they must have to survive is water.” The terms mold problem and wet housing are nearly synonymous. A

**Table 2** These are the minimum topics that should be addressed by an adequate indoor air quality investigation report

|                                                  |                                                                                                                                                                                                                                      |
|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Scope of work                                    | This includes what was investigated and any hypothesis that was tested                                                                                                                                                               |
| Site physical description                        | This includes the address including any portion of the building not evaluated. It also includes details like the address, area description, meteorological values.                                                                   |
| Mechanical review                                | This includes a description of the HVAC systems and any problems with the roof, siding, guttering, downspouts or drainage not covered above.                                                                                         |
| Sample location summary                          | This is a list of the samples taken including where, when, and what.                                                                                                                                                                 |
| Sampling circumstances                           | This includes details like are the windows open, is the heat on, is there activity.                                                                                                                                                  |
| Sampling instruments used                        | This includes details on the instruments like serial numbers, calibration history and general function.                                                                                                                              |
| Summary and interpretation of analytical results | This area includes not only the reports from the analytical laboratory used but also the comments from the report writer that integrate the results from the sampling with the building specifics.                                   |
| Summary of findings                              | This should be a comprehensive narrative that reviews the major findings and draws conclusions about any hypotheses tested.                                                                                                          |
| Recommendations for remediation                  | This area lists the actions the writer believes to be necessary to correct the problems documented in the report. It may describe specific actions or recommend consultation with other professionals such as a structural engineer. |
| Laboratory reports and supporting documents.     | This area is for material that might be informative to the client. Copies or laboratory findings or EPA documents on remediation                                                                                                     |

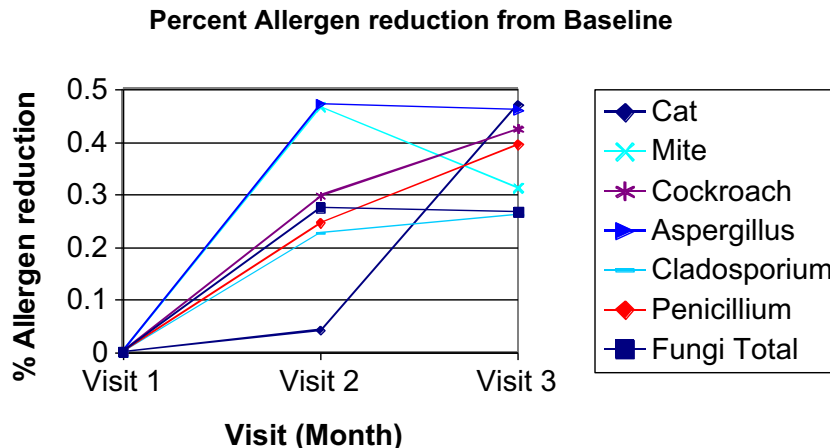
Canadian study of housing found that wet basements and fungi were common [58]. In older homes in Cleveland, conditions leading to moisture and mold problems included water infiltration, rainwater intrusion, poor ventilation, sub slab heating ducts, and moisture in crawlspaces and basements [59]. A Boston public housing study where 20% of the units studied had visible mold revealed similar conditions including leaks from ceilings, walls, radiators, toilets, bathtubs, and sinks and inadequate bathroom ventilation [60]. Another investigation indicated that 43% of occupants of 53 housing unit studies smelled or had seen mold growth, and it was associated with water intrusion and leaks from radiators [61]. The conclusion from these and many other studies is that indoor fungal problems are nearly always related to indoor moisture problems, and the mold problem cannot be remediated as long

as the moisture problem exists. Moisture control is expected to become an increasing problem into the future. Anticipated climate change is expected to increase flooding concerns for very large numbers of homes situated along ocean fronts and coastal rivers. Sea level rise is a very well-documented consequence of climate change that will expose millions of persons to wetter environments. These and other allergy-related factors have been examined in a recent review [62].

### IAQ Inspection Reports

Every inspection of an indoor space for air quality problems should result in a comprehensive report. A listing of laboratory results on a sample taken during an IAQ evaluation is not a sufficient report. If a patient brings just laboratory results, the

**Fig. 2** Dust allergen results including assays for 3 fungi in house dust from 12 families provided cleaning products including bleach-based products and cleaning instructions directed toward reduction of dustborne allergens. Families cleaned for 2 months. The graph indicates the percentage reduction for allergens measured. All allergens were reduced for families using the cleaning regime. Reduction of total fungal allergen measured was significant ( $p < 0.05$ )



allergist should request to see the rest of the report. If there is no full report, the result sheet has little value. The minimum components that should be addressed in an indoor air quality inspection report are contained in Table 2. A further description of the information that should be included in each of these topics can be found in Barnes et al. [63]. The report should be produced by the individual performing the inspection. The interpretation of the report as far as fungal contamination should be made by the inspector and included in the report. That is the person who saw the home and who is in the best position to integrate the inspection information with the laboratory results. It is that person's professional opinion on the house that is most valuable to the health care provider. The report should not contain any health information or health claims regarding the condition of the house. The presence of health claims or health information in the assessment report should be a red flag that the report may not be reliable. It is the responsibility of the person performing the inspection to interpret the results as far as the house is concerned. It is the physicians' responsibility to integrate the information contained in the report with health information collected from the patient (history and sensitivity) and provide medical advice to the patient. The problem of non-concordance between skin or specific IgE testing results and home inspection reports is somewhat akin to the problem of non-concordance between patient history and testing results. However, in the case of fungi in a home, the fungi should be removed for hygienic reasons. It is likely that the wet conditions associated with the fungal presence are related to the reported symptoms even though no specific sensitivities are present [6]. Tips on interpreting properly constructed environmental assessment reports can be found in Barnes et al. [63]. Indeed, the properly constructed report will nearly interpret itself. The physician needs only to add the medical history and testing information to the housing condition information in the report to advise the patient.

## Allergen Avoidance and Remediation

The great thing about remediation for indoor fungal contamination is that a large industry has been built up to provide this service. The remediation itself can be very successful [64]. Many reputable fungal remediation companies guarantee results such that the indoor fungal spore level will be below one-third of the outdoor fungal spore level. Unfortunately, there are some less than reputable remediation firms, but that is true of the construction industry in general. As with any construction project, care must be taken to collect bids from several companies and check references from previous clients. However, the properly executed fungal remediation project will stop fungal-related building deterioration and produce an improvement in the building esthetics.

The plain language summary of the Cochrane study on remediating buildings damaged by dampness and mold for preventing or reducing respiratory tract symptoms, infections, and asthma states that "Repairing houses to remove mold reduced asthma-related symptoms and respiratory infections compared to doing nothing. It also decreased the use of asthma medication in asthmatics" [65]. Work evaluating the impact of cleaning practices on the quality of life of asthmatic children indicated scores for groups provided with cleaning instructions and cleaning products improved during the study. Measured dust allergen levels were decreased 14% overall ( $P < .05$ ) (Fig. 2). Both viable and nonviable airborne spore levels were reduced 18% and 42%, respectively [66, 67].

## Discussion

It is clear that fungal spores and even mycelial fragments are common components found in the air throughout communities in the USA and most areas of the world. The presence of airborne mold by itself either outdoors or indoors does not equate to disease. The key to atopic disease is the presence of IgE antibodies. Sensitivity to fungi is one of the major sensitivities found in atopic populations. When all the factors are present, airborne fungal allergens in either outdoor or indoor environment can trigger symptoms. Numerous studies listed above [52–54, 58–61, 64–66] are consistent with a meta-analysis by Mendell et al. 2011 [68] that supported and expanded the initial Institute of Medicine report from 2004 on damp housing. The consistent message is that moisture and mold in housing are associated with increased respiratory disease, and indoor moisture and mold issues can be successfully remediated. In addition, it is important to distinguish between dampness and mold. A damp environment may also have issues with ventilation and ambient temperature and should be addressed within a given residence.

## Compliance with Ethical Standards

This research does not involve animals or human subjects.

**Conflict of Interest** I am retired from Children's Mercy Hospital where I am a Professor Emeritus at the University of Missouri – Kansas City School of Medicine. I have no conflicts of interest with regard to this manuscript.

**Informed Consent** No informed consent was necessary.

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