

Editorials

Mold allergy: Some progress made, more needed

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Perhaps more than any other area of our specialty, allergy to molds presents us with a range of uncertainties. Molds are ubiquitous, their spores are airborne in large numbers, and they can clearly elicit sensitizing IgE antibodies. There are several well-defined disorders induced by molds, and we believe that molds can contribute to allergic asthma, though the relationship between sensitization and asthma is less certain for molds than for some other airborne allergens, such as pollens and animal danders. At the same time, many people express concern about the effect of molds on their health, particularly in the context of damp housing. Some of the illnesses attributed by people to molds are very poorly defined, to the extent that they are almost unrecognizable as disease entities in conventional medical terms. This month, the Journal has brought together a set of articles to try to lay out the current state of play and to pose some questions that might form part of a research agenda in this area.

Allergic sensitization to molds and fungi is not a new concept; indeed, it was described by Blackley in the 1860s.¹ Molds and fungi are ubiquitous organisms that serve a critical recycling role in nature. They have complex biochemical pathways that can break down almost all known chemical compounds, yielding basic molecular building blocks but also a range of extremely toxic byproducts. They produce many spores at appropriate times of year, and these can be identified through sampling and counting. In this month's *Images in Allergy* feature, Levetin² has provided us with a series of beautiful images of these complex, beautiful organisms.

Molds and fungi are prolific producers of potentially allergenic proteins. Individual mold and fungal species can each produce 40 or more different proteins that can stimulate IgE production in human beings. There is considerable cross-reactivity between fungi, though the clinical implications of this fact are uncertain. Allergists generally include a number of mold extracts in the battery of airborne allergens that they use in assessing patients with rhinitis or asthma. However, it is clearly impractical to test

Abbreviation used

ABPA: Allergic bronchopulmonary aspergillosis

for all possible allergenic molds, and a sensible balance has to be struck: those molds commonly associated with allergic disease are always to be used for screening, while more extensive testing is warranted in selected patients.

In some parts of the United States and elsewhere, sensitization to *Alternaria* is common and is clearly associated with symptoms. In this issue, Bush and Prochnau³ describe the case of a child who presented with acute severe asthma and turned out on investigation to be strongly sensitized to *Alternaria*. The investigators suggest that this sensitization to *Alternaria* was critical in precipitating acute severe asthma in the child, and they speculate on the potential for this connection to go unrecognized in other cases. Perhaps the most difficult issue noted in this report is the establishing of a causal relationship between exposure to *Alternaria* and symptoms in sensitized individuals. Bush and Prochnau remind us that there is evidence of an association in the literature⁴ but that many unanswered questions remain. Although the management of mold-induced asthma is broadly similar to that of any other form of allergic asthma, Bush and Prochnau provide a useful summary of methods that can be used to minimize mold exposure. They also make the point that none of these methods has been formally assessed in terms of clinical effectiveness. Their conclusion, which forms a recurring theme throughout these articles, is the need for more research to back up the theories that we hold with respect to the role of molds in allergic disease.

Aspergillus fumigatus causes a complex set of clinical conditions, including allergic bronchopulmonary aspergillosis (ABPA). In ABPA the airways are colonized by *Aspergillus*, which excites a variety of immunologic responses. All patients with ABPA develop IgE against the fungus, and most also have precipitating IgG antibodies. IgG precipitins have been widely used to diagnose and monitor ABPA.⁵ This pattern of immunologic response is not typical, as far as we know, of other forms of mold allergy. It is still uncertain why *Aspergillus* has this particular ability to grow in the airways, but presumably it must relate to the organism's growth requirements. It is of course easier to understand why *Aspergillus* can be invasive in immunocompromised patients, though that is a story for another day.

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Another well-defined immunologic condition associated with molds is farmers' lung, in which the patient becomes sensitized to thermophilic actinomycetes. Farmers' lung is a form of extrinsic allergic alveolitis, with typical clinical features of cough, fever, and interstitial infiltrates. The pathogenetic mechanisms include both precipitating IgG antibodies and cell-mediated immunity, and in contrast to ABPA, it does not appear that IgE antibodies play any part.

Anyone who wonders why it has been so difficult to move forward in understanding allergic reactions to fungi should read Esch's article in this issue; it deals with the trials and tribulations of manufacturing standardized allergen extracts from fungi.⁶ Not only are there wide variations between strains of any individual species held in the biobanks, but the same strain can produce supernatants with wildly different compositions, depending on the culture conditions. This, coupled with the relative scarcity of patients in whom to perform biological standardization, has severely hampered drives to produce standardized allergen extracts for use in diagnosis and therapy of mold-induced allergic disease.

At the same time, molds are increasingly blamed for a variety of nonspecific illnesses. Through much of the past 20 years, there has been a vocal campaign by alternative health care practitioners to suggest that *Candida albicans* might be responsible for a range of symptoms, including chronic fatigue, poor concentration, and tiredness.⁷ *C albicans* is a common commensal organism that is usually asymptomatic, but it can cause local irritation of the throat or genital mucosa, especially in diabetic individuals and patients on steroids (topical or systemic). There are also occasional reports of patients whose asthma seems to be driven by inhaled *Candida* antigens.⁸ Like *Aspergillus*, *Candida* can invade the tissues if a patient is immunosuppressed, but there is little or no evidence that it becomes invasive in those whose immune systems are intact. Evidence that *Candida* is responsible for nonspecific illness is thin on the ground, yet there are substantial groups of patients and alternative practitioners who promulgate the concept of *Candida* hypersensitivity.

It is against this background that we have to assess the recent outbreak of attention paid to the black mold, *Stachybotrys chartarum*, which is commonly found in small amounts in damp houses. *Stachybotrys* first came to medical attention when it was blamed for a familial cluster of recurrent influenzalike symptoms.⁹ Little attention was initially paid to this report; subsequently, however, a cluster of 10 cases of acute pulmonary hemorrhage in children in Cleveland, Ohio, was blamed on *Stachybotrys*.¹⁰ Subsequent investigation raised doubts about the causal role of the mold,¹¹ but the concept of toxic mold passed into the literature and is now proving to be a goldmine for litigators. In the first of 2 reviews on the subject, Terr¹² brings us up to date with the story of toxic mold and emphasizes the role of the allergist as an honest evaluator of symptoms and their possible relationship to environmental exposures. Terr explores the difficulty of

assessing the causes of a poorly defined illness and stresses the inappropriateness of epidemiologic studies as a means of determining causality. By virtue of their experience in evaluating patients with complex histories, allergists are in many ways well placed to deal with these complex patients; in the current wave of litigation, we can all expect to see patients with this scenario, and Terr makes a cogent case that we have a responsibility to be objective, not partisan, in our assessments. In the second review, Hossain et al¹³ present the case for the prosecution, with a detailed review of the attributes of *S Chartarum* that make it a potential toxic agent. Importantly, they remind us that *S chartarum* is not common in the indoor or outdoor air but can be found in a variety of soils and cellulose-rich debris. The mold is quite fastidious in its culture requirements, which might explain why it has been difficult to recover from field samples, though cynics might argue that it is difficult to recover because it is not really there in any great concentrations. Critically for their argument, whereas it is quite clear that *S chartarum* can produce a range of toxins, it is less clear that patients are exposed to these in significant concentrations in the real world. Hossain et al mention one isolated case report of pulmonary infection with *S chartarum*. It is not clear how much weight we should give to this, inasmuch as in the first place it is a rare event and in the second place it is clearly not the mechanism by which the nonspecific illnesses might be generated. Whatever the rights and wrongs of the toxic mold story, it is evident that if we want to move forward we will need to improve our methods of assessing environmental sampling.

In our final mold-related paper, Portnoy et al¹⁴ set out a proper scientific basis for measuring exposure to molds. This is an absolute prerequisite for rigorous exploration of the relationship between exposure and disease in this controversial area of medicine.

In summary, allergists and immunologists can expect to see patients with a wide range of conditions in which molds either have been implicated or are suspected as etiologic agents. By understanding the scientific, political, and litigation context better, we should be able to provide a better service to our patients and to those involved in the construction, maintenance, and insurance of buildings and housing projects.

Most editorials and reviews close with an exhortation for more research in the area of interest. Although more research is generally desirable in any area, there can be few other areas of allergy and immunology in which patients and doctors more urgently need and deserve better evidence to support or refute the range of claims currently being made than in the case of molds and diseases. We hope that this collection of articles will serve as a stimulus for research, and the editors would welcome both correspondence and further submissions of original observations in this field.

REFERENCES

1. Blackley C. Experimental researches on the causes of catarrhus aestivus (hay fever or hay asthma). London: Bailliere Tindal & Cox; 1873.

2. Levetin E. An atlas of fungal spores. *J Allergy Clin Immunol* 2004;113:366-8.
3. Bush RK, Prochnau JJ. *Alternaria*-induced asthma: a case study. *J Allergy Clin Immunol* 2004;113:227-34.
4. Bruce CA, Norman PS, Rosenthal RR, Lichtenstein LM. The role of ragweed pollen in autumnal asthma. *J Allergy Clin Immunol* 1977;59:449-59.
5. Malo JM, Longbottom JL, Mitchell J, Hawkins R, Pepys J. Studies in chronic allergic bronchopulmonary aspergillosis. 3. Immunological findings. *Thorax* 1977;32:269-74.
6. Esch RE. Manufacturing and standardizing fungal allergen products. *J Allergy Clin Immunol* 2004;113:210-5.
7. Lacour M, Zunder T, Huber R, Sander A, Daschner F, Frank U. The pathogenetic significance of intestinal *Candida* colonization—a systematic review from an interdisciplinary and environmental medical point of view. *Int J Hyg Environ Health* 2002;205:257-68.
8. Akiyama K, Shida T, Yasueda H, Mita H, Yamamoto T, Yamaguchi H. Atopic asthma caused by *Candida albicans* acid protease: case reports. *Allergy* 1994;49:778-81.
9. Croft WA, Jarvis BC, Yatawara CS. Airborne outbreak of trichothene toxicosis. *Atmospheric Environ* 1986;20:549-52.
10. Etzel RA, Montana E, Sorenson WG et al. Acute pulmonary hemorrhage in infants associated with exposure to *Stachybotrys chartarum* and *Aspergillus versicolor*. *Arch Pediatr Adolesc Med* 1998;152:757-62.
11. Centers for Disease Control and Prevention. Update: pulmonary hemorrhage/hemosiderosis among infants—Cleveland, Ohio, 1993-1996. *JAMA* 2000;283:1951-3.
12. Terr AI. Are indoor molds causing a new disease? *J Allergy Clin Immunol* 2004;113:221-6.
13. Hossain MA, Ahmed MS, Ghannoum MA. Attributes of *Stachybotrys chartarum* and its association with human disease. *J Allergy Clin Immunol* 2004;113:200-8.
14. Portnoy JM, Barnes CS, Kennedy K. Sampling for indoor fungi. *J Allergy Clin Immunol* 2004;113:189-98.