Letters to the Editor

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Mycotoxins and Building-Related Illness

To the Editor: Building-related illnesses include a variety of recognized disease entities that are characterized by objective clinical findings potentially related to specific exposures in the indoor environment.[1] Examples include allergic rhinitis, asthma, hypersensitivity pneumonitis, Legionnaire's disease, and humidifier fever.[2–4] A number of microorganisms, including many species of bacteria and fungi, are well established as potential etiologic agents of building-related illnesses; these illnesses may be classified as being allergic, infectious, or related to a toxic or inflammatory reaction.[5] The recent article by Hodgson et al (Hodgson MJ, Morey P, Leung W, et al. Building-associated pulmonary disease from exposure to *Stachybotrys chartarum* and *Aspergillus versicolor*. *J Occup Environ Med.* 1998;40:241–249) addresses the issue of whether exposure to mycotoxins in an indoor environment is related to illness among building occupants. We agree with the authors that this is an important public health issue, but we disagree with the authors' conclusions that a "mycotoxin-induced effect is the most likely explanation" of the health problems discussed in the article.

We recognize the difficulties of performing adequate clinical and epidemiologic evaluations of large groups of people, particularly in a setting such as that described by Hodgson et al. However, because of the lack of objective evidence supporting an increased prevalence of pulmonary illness among building occupants, the lack of any information demonstrating actual exposure to mycotoxins, and the limited evidence from the literature suggesting that mycotoxins are related to illness in the indoor environment, in our opinion the authors' conclusion that a mycotoxin-induced effect is the most likely explanation for the observed pulmonary findings among building occupants in this study should be questioned.

Published accounts concerning human health effects related to potential exposure to mycotoxins have been case reports involving agricultural settings and/or the ingestion of contaminated foodstuffs.[6–9] The relevance of these case reports to fungal growth in the indoor environment is unclear. *Stachybotrys chartarum*, one of the fungi identified by Hodgson et al, is one of many fungi that produces a class of mycotoxins called trichothecenes.[10,11] Reports of stachybotryotoxicosis (mycotoxicosis related to *Stachybotrys* exposure), occurring in animals and humans, have come primarily from Eastern Europe and Russia, in areas where stachybotryotoxicosis was enzootic in horses.[10,12] Human illnesses were reported to include dermatitis, bloody rhinitis, cough, and severe upper respiratory tract irritation. Cases of stachybotryotoxicosis related to occupational exposure have been reported to occur among workers at farms, cottonseed oil plants, grain elevators, and facilities used for reprocessing moldy grain, malt grain–processing facilities, textile mills using plant fibers, and bindertwine factories.[10] In those reports, the illnesses were characterized as a "general intoxication," including a variety of chest and upper respiratory tract symptoms and fever, as well as dermatitis and (in some cases) leukopenia. Recovery was reported to be rapid after cessation of exposure, and re-exposure resulted in much more serious sequelae.[10] These cases of mycotoxicosis, concerning persons in agricultural or industrial environments, may have involved exposures to fungi and their products in concentrations that can be assumed to be much higher than those experienced by persons in most indoor environments.

Several studies are frequently cited (by Hodgson et al and other investigators) as evidence that adverse health effects or symptoms are related to indoor exposure to mycotoxins.[13-16] None of these studies provide any objective evidence of clinical illness clearly related to mycotoxin exposure. One cited study[16] reported findings from a group of persons working in a water-damaged office building contaminated by *Stachybotrys*. The primary finding was that, compared with workers in another building, persons in the building contaminated with *Stachybotrys* reported an increased prevalence of lower respiratory tract, dermatologic, eye, and constitutional ("flu-like") symptoms. Also, there were statistically significant differences between work locations in results of tests for white blood cell count, the proportion of mature T-lymphocyte cells (CD3%), and natural killer cell count. However, persons working in the most heavily contaminated areas (basements) had elevated cell counts and percentages, compared with those working on another floor of the same building. In addition, the clinical significance of the reported laboratory differences (such as CD3% of 75.66, 72.9, and 73.65 among controls, ground-floor occupants, and basement occupants, respectively) is unclear. Antibody testing of occupants of the problem building revealed no evidence of increased exposure to any specific fungi. No exposure to mycotoxin was demonstrated.

In another cited study,[14] five occupants of a home reported a variety of symptoms, including cold and flu symptoms, sore throats, diarrhea, headaches, dermatitis, patches of hair loss, and fatigue. The clinical descriptions of the illnesses were incomplete, and no medical diagnostic information was presented. In the home, a cold-air return duct and an area of wood fiberboard were contaminated with

Stachybotrys. When the mold was cleaned up, the family members' symptoms reportedly resolved. The authors inferred that mycotoxins from the mold were responsible for the symptoms. Even if some or all of the reported symptoms were related to the occupants' presence in the home, it is just as reasonable to infer that an allergenic response to the fungi (or some other [unidentified] factor[s]) were responsible for some or all of the reported symptoms.

In 1994, an investigation of 10 cases of acute pulmonary hemorrhage and hemosiderosis among infants was reported.[17,18] A case-control study determined that case patients were more likely to be male, more likely to have a close relative who also coughed up blood while living in the same home, and more likely to live in a home in which a guardian reported water damage during the six-month period preceding the illness.[19] Air sampling revealed that the quantity of fungus, including *Stachybotrys atra* (*chartarum*), was higher in the homes of the case infants than in those of controls.[18] No systematic evaluation of water damage in these homes was reported. The air sampling was done using an "aggressive" sampling strategy (purposely stirring up potential contaminants in the homes),[20] which is unlikely to be representative of actual exposures to fungi. The investigators presented limited evidence indicating the presence of mycotoxins in ceiling tiles and wall coverings.

In the current study, Hodgson et al have limited ability to "describe the spectrum of disease" among occupants of the subject buildings. The use of several undefined case definitions makes interpretation of the reported symptoms and pulmonary function tests difficult. Lack of data concerning comparison groups also limits interpretation and raises the question of whether the comparison groups were appropriate. The authors report that 17 of 47 self-selected individuals had some clinical evidence of pulmonary disease, but they do not report results of similar testing among "unexposed" office workers. The authors compare symptoms among occupants of the building of concern with those of occupants of other buildings but do not provide adequate information to compare response rate, demographic factors, smoking status, or job duties between the occupants of the study and comparison buildings. These factors are known to influence the prevalence of reported symptoms among building occupants.[21,22] In addition, without some means of assessing exposure at the level of the individual or groups of individuals, we have no way of knowing whether the reported symptoms are related to mycotoxin exposure. The results of this study's limited antibody testing add no support to the hypothesis that the building's occupants had biologically significant exposure to fungi.

It is our personal opinion that there is currently no clear evidence documenting that mycotoxins cause health effects among building occupants. The presence of excessive fungal growth in a building is an indicator of inadequate building design, construction, and/or maintenance. The basis for, timing of, and extent of the remediation of a contaminated building are beyond the scope of this discussion; important factors to consider regarding remediation would include the extent of building contamination, the fungal biodiversity, and the frequency and severity of documented health effects among building occupants. Persons who have symptoms potentially related to an indoor environment should be clinically evaluated and, if indicated, removed from exposure to the offending agent(s) until that exposure is reduced or eliminated. If fungal exposure is thought to be a factor, close follow-up with the treating clinician and others will likely be needed as there are currently no "acceptable" limits of fungal growth in the indoor environment;[23] given that fungi are ubiquitous, all potential sources of fungal exposure (including the home) would also need to be evaluated. It is clear that health problems potentially related to the indoor environment, including those potentially associated with exposure to fungi or fungal products, need further evaluation using appropriate environmental, medical, and epidemiologic tools.[24]

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References

1. Kreiss K. The sick building syndrome: where is the epidemiologic basis? *Am J Public Health*. 1990;80:1172–1173.
2. Hoffman RE, Wood RC, Kreiss K. Building-related asthma in Denver office workers. *Am J Public Health*. 1993;83:89–93.
3. Rose C. Hypersensitivity pneumonitis. In: Harber P, Schenker MB, Balmes JR, eds. *Occupational and Environmental Medicine*. St. Louis, MO: Mosby-Year Book, Inc.; 1996:201–215.
4. Menzies D, Bourbeau J. Building-related illnesses. *N Engl J Med*. 1997;337:1524–1531.
5. Burrell R. Microbiological agents as health risks in indoor air. *Environ Health Perspect*. 1991;95:29–34.
6. Drobotko DV. *Stachybotryotoxicosis: A New Disease of Horses and Humans*. [Report presented at the Academy of Science, USSR.] January 12–16, 1942.
7. Austwick PKC. Mycotoxins. *Br Med Bull*. 1975;31:222–229.
8. Bhat RV, Ramakrishna Y, Beedu SR, Munshi KL. Outbreak of trichothecene mycotoxicosis associated with consumption of mould-damaged wheat products in Kashmir Valley, India. *Lancet*. 1989;1:35–37.
9. Wang Z, Peng J, Tong Z. Human toxicosis caused by moldy rice contaminated with Fusarium and T-2 toxin. *Biomed Environ Sci*. 1993;6:65–70.
10. Forgacs J. Stachybotryotoxicosis. In: Kadis S, Ciegler A, Ajl S, eds. *Microbial Toxins*, vol. 8. New York: Academic Press; 1972:95–128.
11. Ueno Y. The toxicology of mycotoxins. *Crit Rev Toxicol*. 1985;14:99–132.
12. Bata A, Harrach B, Ujszaszi K, Kis-Tamas A, Lasztity R. Macrocyclic tricothecene toxins produced by *Stachybotrys atra* strains isolated in middle Europe. *Appl Environ Microbiol*. 1985;49:678–681.
13. Flannigan B, Miller JD. Health implications of fungi in indoor environments– an overview. In: Samson R, Flannigan B, Flannigan M, Graveson S, eds. *Health Implications of Fungi in Indoor Environments*. Amsterdam: Elsevier; 1994:3–28.

14. Croft WA, Jarvis BB, Yatawara CS. Airborne outbreak of tricothecene toxicosis. *Atmospher Environ.* 1986;20:549–552.
15. Auger PL, Gourdeau P, Miller JD. Clinical experience with patients suffering from a chronic fatigue-like syndrome and repeated upper respiratory infections in relation to airborne molds. *Am J Ind Med.* 1994;25:41–42.
16. Johanning E, Biagini R, Hull D, Morey P, Jarvis B, Landsbergis P. Health and immunology study following exposure to toxigenic fungi (*Stachybotrys chartarum*) in a water-damaged office environment. *Int Arch Occup Environ Health.* 1996;68:207–218.
17. Centers for Disease Control. Acute pulmonary hemorrhage/hemosiderosis among infants—Cleveland, January 1993–November 1994. *MMWR.* 1994;43:881–883.
18. Centers for Disease Control and Prevention. Update: pulmonary hemorrhage/hemosiderosis among infants—Cleveland, Ohio, 1993–1996. *MMWR.* 1997;46:33–35.
19. Montana E, Etzel RA, Allan T, Horgan TE, Dearborn DG. Environmental risk factors associated with pediatric idiopathic pulmonary hemorrhage and hemosiderosis in a Cleveland community. *Pediatrics.* 1997;99:E5.
20. NIOSH. *Hazard Evaluation and Technical Assistance Report.* [HETA 95–0160–2671.] Cincinnati, OH: Centers for Disease Control and Prevention, National Center for Environmental Health, US Department of Health and Human Services, Public Health Service; 1996.
21. Mendell MJ. Non-specific symptoms in office workers: a review and summary of the literature. *Indoor Air.* 1993;3:227–236.
22. Nelson NA, Kaufman JD, Burt J, Karr C. Health symptoms and the work environment in four nonproblem United States office buildings. *Scand J Work Environ Health.* 1995;21:51–59.
23. Verhoeff AP, Burge HA. Health risk assessment of fungi in home environments. *Ann Allergy Asthma Immunol.* 1997;78:544–556.
24. Mendell MJ, Fine L. Building ventilation and symptoms—where do we go from here? *Am J Public Health.* 1994;84:345–348.

The Authors Reply: We appreciate the opportunity to respond to the comments of Drs Page and Trout about our recent outbreak investigation. We are relieved that they consider this a major public health issue, although we are unsure whether they mean moisture in the built environment, the potential adverse health effects of mycotoxin exposure in buildings, or something else. They do appear to recognize the constraints that physicians and epidemiologists encounter as they manage patients with disease in an environment that requires negotiations with employers for access, negotiations with employers and insurers for cost reimbursement, and negotiations with patients around disease, a very different situation from that encountered in NIOSH hazard evaluations.

There is ample evidence that moisture in buildings is associated with disease. One formal study attempt estimated that the etiologic fraction of asthma attributable to moisture in the home was at least 25%.[1] For reasons outlined in the manuscript, many researchers believe a major portion of that problem is unrelated to type I allergy, at least in residential airways symptoms. The recent report on NIOSH investigations identified an association of moisture and respiratory symptoms[2] in the workplace. Although it is tempting to implicate type I allergy, the few attempts to document an association have either failed[3,4] or suggested that the explained fraction is trivially small.[5] Over 25% of asthma reported to the occupational disease surveillance activities in Departments of Health in Massachusetts and Connecticut now represent building-related asthma. The problem is encountered by practicing physicians far more frequently than the peer-reviewed literature implies, where in a single outbreak,[6] asthma was attributed to below-grade moisture incursion in a municipal building.

Most scientists recognize that case reports and outbreak investigations cannot provide generalizable knowledge, as the population to which they may be extrapolated is controversial. The purpose of such reports is generally to make the medical and scientific community aware of discussions, theories, and concerns they should be aware of, could keep their eyes open for, and perhaps recognize again if encountered elsewhere. The first systematic evidence on immunological effects of moisture will appear soon,[7] although even that paper raises far more questions than it answers. The exciting work on airborne dust exposure, mycotoxins, and mechanistic implications in Dr Dearborne's laboratory in Cleveland is well known to scientists who follow the field and is likely to address some of Dr Trout's concerns. These provide exciting models of how scientists might investigate both outbreaks or clusters and exposure.

Our own investigation was conducted under severe constraints. Although we were initially invited in at the request of several judges, funding for the project (approximately $12,000) came from the administration and the workers' compensation carrier. Four phases were laid out as fairly standard approaches to epidemics, including interviews with suspected "index cases," a questionnaire survey, a clinical medical screening protocol, and a formal case-control study. As part of the work, we (the local physicians, the insurer, and the administration) agreed upon a set of management criteria for patients that were disseminated to employees and their physicians. On the basis of the initial medical interviews, the increased prevalence of symptoms in the questionnaire survey, and obvious physiologic abnormalities in the screening protocol, we were convinced that something was worth investigating. The insurance carrier was unwilling to fund a cross-sectional study using rhinometry before and after work or nasal smears for eosinophils. By the time our negotiations with the insurer, institutional review board clearance, and logistical constraints were resolved, many employees/patients were removed from work, three months after our first visit. As reported in the manuscript, at least one possible reason for the negative results in the case-control study may be that exposure had stopped for many of the subjects. Doing investigations such as this out of state poses some problems for clinicians.

We considered type I allergy an unlikely explanation for the lung function abnormalities because of the lack of association between immunoglobulin E (IgE) antibodies and either symp-

toms or physiologic changes. Lynch et al described an outbreak of hypersensitivity pneumonitis in which only 10% of subjects had abnormal chest x-rays, data of which we were unaware when we did this study and wrote the manuscript.[8] We considered hypersensitivity pneumonitis an unlikely event because of the lack of association between IgG antibodies and either symptoms or physiologic changes. Don Milton has recently suggested that an endotoxin itself might be an explanation; we found no source of water aerosol and consider airborne endotoxins an unlikely phenomenon in this outbreak. Either of these are legitimate hypotheses, though with less evidence, in our view.

At present, NIOSH building investigations generally do not attempt to identify, as they have at least sometimes in the past, objective measures of disease, as at least markers of group differences, including physiologic testing such as spirometry or single-breath carbon-monoxide diffusing capacities[9] or immunologic markers.[10,11] Cooperation between the NIOSH Health Hazard Evaluation team, with greater field epidemiology flexibility and laboratory depth, and local practitioners, who may have access to patients with convincing evidence of poorly characterized disease and emerging syndromes, may lead us all to characterize occupational disease more effectively. This may require rethinking the specific roles we each play, identifying legal constraints that might impede information flow and sharing, and addressing issues of respect for the different strengths we bring to problems. Dr Trout has willingly recently participated in such a mixed investigational venture, with exciting productivity for both sides.

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References

1. Cooper K, Demby S, Hodgson M. Moisture and lung disease. population-attributable risk calculations. In: J Woods, D Grimsrud, N Boschi, eds. *Healthy Buildings 97/Indoor Air Quality 97*, vol.1. 1997;213–218.
2. Sieber K, Stayner LT, Malkin R, et al. The NIOSH Indoor Environments Evaluation Experience: part three—associations between environmental factors and self-reported health conditions. *Appl Occup Environ Hygiene.* 1996;11:1387–1392.
3. Menzies R, Tamblyn R, Comtois P, et al. Case-control study of microenvironmental exposure to aero-allergens as a cause of respiratory symptoms—part of the SBS complex. Presented at: *IAQ92: Environments for People*, ASHRAE, Atlanta, 1992:201–210.
4. Apter A, Hodgson M, Lueng W-Y, Pichnarcik L. Nasal symptoms in the "Sick Building Syndrome." [Abstract.] *Ann Allergy Asthma Immunol.* 1997;78:152.
5. Menzies D, Nunes F, Comtois P, Hanley JA, Pasztor J. Aeroallergens and work-related respiratory symptoms among office workers. *J Allergy Clin Immunol.* 1998;101:38–44.
6. Hoffman RD, Wood RC, Kreiss K. Building-related asthma in Denver Office Workers. *Am J Publ Health.* 1993;843:89–93.
7. Dales R, Miller D, White J, Dulberg C, Lazarovits A. The influence of residential fungal contamination on peripheral blood lymphocyte populations in children. *Arch Environ Health*, in press.
8. Lynch DA, Way D, Rose CS, King TE Jr. Hypersensitivity pneumonitis: sensitivity of high-resolution CT in a population-based study. *AJR Am J Roentgenol.* 1992;159: 469–472.
9. Hodgson MJ, Morey P, Attfield M, Fink JN, Sorensen W, Visvesvara G. Pulmonary disease in an office building: single-breath carbon-monoxide diffusing capacity as a cross-sectional field tool. *Arch Environ Health.* 1985;40:96–101.
10. Hodgson MJ, Morey PR, Simon J, Waters T, Fink JN. Acute and chronic hypersensitivity pneumonitis from the same source. *Am J Epidemiol.* 1987;125:631–638.
11. Johnanning E, Biagini R, Hull D, Morey P, Jarvis B, Landsbergis P. Health and immunology study following exposure to toxigenic fungi (*Stachybotrys chartarum*) in a water-damaged office environment. *Int Arch Occup Environ Health.* 1996;68:207–218.