Sick Building Syndrome: is mould the cause?

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Moulds are responsible for diseases in humans through the three pathogenetic mechanisms of infection, allergy, and toxicity. Fungal infection is especially a risk factor for immunodeficient patients, but it occurs in immunocompetent patients as well. Fungal allergy is manifested as bronchial asthma, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis, or allergic fungal sinusitis. Mycotoxicosis is almost exclusively the result of ingestion of mould-contaminated foodstuffs. In each case there is specificity for the etiologic mould. There is controversy regarding the ability of indoor airborne mould spores to cause human disease through non-specific toxicity via the inhalation route. Pulmonary mycotoxicosis is an established, although rare, occupational disease of farmers who inhale enormous quantities of mycotoxins, endotoxins, and other toxic chemicals from contaminated silage. Other conditions attributed to indoor airborne mycotoxin are unproven. These include infantile pulmonary hemosiderosis, epistaxis, ‘toxic encephalopathy’, immune dysregulation and a variety of subjective complaints without objective signs of pathology such as fatigue, headache, dyspnea, gastrointestinal distress, neuromuscular and skeletal complaints, etc. Non-specific irritation from moulds via the inhalation route is also a controversial subject that remains unproven. Published studies alleging an epidemiologic causal relationship are unconvincing.

Keywords moulds, Sick Building Syndrome, mycotoxicity, aeroirritation, fungal illness

Introduction

Sick Building Syndrome (SBS) is a term that has been in use for about the past 25 years. It is particularly applicable to field studies for both clinical and research purposes. It is often used to describe an illness in which building occupants experience acute health effects or discomfort that appear to be linked to the time spent in the building. Usually the specific illness or its cause cannot be identified, although an airborne chemical contaminant is often suspected. The World Health Organization has defined Sick Building Syndrome as an excess of work-related irritations of the skin and mucous membranes and other symptoms, including headache, fatigue, and difficulty concentrating, especially as reported by workers in modern office buildings (http://content.nejm.org/cgi/content/full/328/12/821-R1).

This discussion will address the question of whether or not Sick Building Syndrome can be caused by indoor airborne fungal spores. This is an issue that is currently controversial, so the published medical literature will be used as evidence for and against these controversies.

Sick Building Syndrome will be defined solely for the purpose of this brief review as an illness affecting occupants of a building because of a defect in the building structure or because of its usage. The illness can be either acute or chronic. The cause of the illness is generally ascribed to a micro-organism, chemical fume, or particulate airborne contaminant. The illness

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can arise through any pathogenetic mechanism, usually infection, allergic, toxic, or irritant. There is no restriction as to the number or percentage of occupants affected. Any type of building may be involved. When used in this sense, the term ‘Building-Related Illness’ (BRI) is often applicable.

**Non-controversial issues**

Moulds (fungi) are eukaryotic non-chlorophyll containing micro-organisms that number over 100,000 species and are ubiquitous throughout the earth. It has been estimated that moulds have existed for more than 500 million years and currently occupy 25% of the earth’s biomass. Moulds can be found in any building, and their airborne spores are easily detected indoors as well as outdoors.

Moulds are an established cause of human disease. There are three well-documented pathogenetic mechanisms as there are for other microbial pathogens. These are infection, allergy, and toxicity. Within each category, the corresponding disease states in individual patients are characterized by specificity for the causative fungus. Furthermore, there are well-defined diagnostic clinical criteria that apply to these three mechanisms, so that the specific etiologic fungus can be identified in most cases.

Fungal infections (‘mycoses’) in the immunocompetent host are most often cutaneous or pulmonary and are limited to about 100 known species. There is typically a specific geographic distribution of cases because of environmental conditions favorable to the growth of certain pathogenic moulds. In the immunocompromised (as well as inflammation-suppressed) host the fungal infection is more likely to be systemic, although the portal of entry is often the skin or respiratory tract.

Diagnosis of fungal infection involves identification of the specific mould in the disease (inflamed) tissue.

Fungal allergy has been identified with fewer than 100 species. It is usually expressed as one of four diseases. (i) Mould-allergic bronchial asthma is the most prevalent. It is an atopic disease mediated by IgE antibodies to one or several specific moulds in individual cases. Although mould spores as a cause of asthma in some specifically-sensitized patients has been widely accepted by clinicians for many years, deliberate inhalational exposure of massive quantities of Penicillium chrysogenum spores failed to evoke a response in sensitized subjects [1]. Allergic rhinitis and atopic dermatitis are also atopic diseases, but there is no clearcut evidence that allergenic moulds are involved in the pathogenesis in those patients with demonstrated sensitivities and exposure to the relevant fungi [2]. (ii) Hypersensitivity pneumonitis (HP) [3] is an allergic inflammation of the lung parenchyma from acute exposure to large quantities of a specific mould spore: it is a non-infectious pneumonia caused by a pre-existing hypersensitivity with high-titer specific IgG antibodies or cellular immunity. Chronic HP is characterized by pulmonary restriction leading to interstitial fibrosis that may occur from repeated episodes of acute disease or chronic exposure to lower quantities of the mould spore. This phase of the disease is mediated by delayed-type cellular hypersensitivity to the specific mould. (iii) Allergic Bronchopulmonary Aspergillosis (ABPA) is an allergic response to *Aspergillus fumigatus* and rarely to other species. There is evidence also of colonization of the bronchopulmonary tree with *Aspergillus* hyphae [4] which in turn is probably responsible for sensitizing the patient with the generation of both IgE and IgG antibodies. The disease occurs in some patients with pre-existing atopic asthma or cystic fibrosis. (iv) Allergic fungal sinusitis (AFS) has diverse clinical manifestations [5]. The disease is caused by a limited number of specific fungi. In some forms it may have many of the characteristics of ABPA affecting the paranasal sinuses rather than the lower airways.

The diagnosis of fungal allergy in each of these four instances requires both a compatible clinical expression of disease (history, examination, functional studies, and radiological or laboratory evidence) and an immune response within the patient to the specific mould that is appropriate to the type of allergic disease under consideration, i.e. IgE antibody, IgG antibody, or cellular sensitivity. In ABPA and AFS, there is evidence for both allergy and colonization of the airway and sinuses, respectively, by the specific mould.

Mould toxicity arises through the action of mycotoxins, organic molecules synthesized by the mould. These are often designated as ‘secondary metabolites’ because they are considered unnecessary for the growth or survival of the fungus. Mycotoxins are non-volatile organic compounds of limited molecular size, generally in the 200–500 kD range. Synthesis by the mould is variable and unpredictable to a large extent dependent upon the substrate, either in nature or on laboratory media. Mycotoxins can be found in all forms of the various mould structures including hyphae, spores, etc.

Mycotoxins are, in fact, defined by their effects on experimental animal models [6]. There have been numerous studies in which experimental toxicologists have made a deliberate attempt to induce toxicity, often for the express purpose of pharmaceutical development. A variety of experimental animals and animal
models have been used. These include the intact animal, isolated organ or tissue, and in-vitro biochemical reactions. A number of exposure methods (oral, inhalational, etc.) have been employed, depending upon the experimental purpose.

In contrast, human mycotoxicity is not dependent on such experimental methodology, but rather it is based exclusively on case reports and epidemiologic studies. The evidence from such reports and studies is overwhelming that human mycotoxicity arises almost exclusively through ingestion. Ergotism and aflatoxicosis are examples of such diseases. Others include alimentary toxic aleukia, yellow rice disease, and endemic nephropathy: illnesses caused by eating mouldy foods, especially grains, under conditions of starvation particularly during wartime. One notable exception that does occur through mould inhalation is pulmonary mycotoxicosis [7], sometimes referred to as organic dust toxic syndrome (ODTS) [8]. This is an occupational disease of farmers (Silo Unloader’s Disease) in which mycotoxin concentrations are unknown although undoubtedly massive, because of inhalation of mould spores (as well as bacteria and other microorganisms) within silos that may reach airborne concentrations of $10^{5-10}$ fungal spores/m$^3$. Because of these conditions of exposure, pulmonary mycotoxicosis is likely to be complicated by exposure to bacterial endotoxins and possibly other toxins. By contrast, calculations of airborne Stachybotrys chartarum mycotoxin exposure for humans (not involved in ODTS), based on experimental data in mice, make it extremely unlikely that toxic concentrations would occur within buildings [9], even those severely contaminated by mould from excessive water intrusion or dampness. Thus human mycotoxicosis is overwhelmingly related to ingestion of fungi, with the exception of occupational exposure of farmers to mouldy grains in silos.

### Controversial issues

There are two areas of controversy, both of which involve the mechanisms of mould-related disease. These are: (i) non-specific inhalational toxicity, and (ii) non-specific inhalational irritation. In both cases, the proposed illnesses are claimed to be caused by indoor airborne fungal spores through the actions of mycotoxins. These are listed in Table 1.

#### Nonspecific inhalational toxicity

An epidemiologic study was initiated because of a localized cluster of cases of pulmonary hemosiderosis in very young infants living in water-damaged homes arising from overflowing rain-swollen creeks in Cleveland, Ohio. There was evidence that water intrusion with mould growth had occurred in the homes as a consequence of flooding, and it was proposed that the disease was the result of inhalation of Stachybotrys mycotoxin into the immature lungs of these small children [10]. These studies received considerable attention with widespread media coverage. However a Center for Disease Prevention and Control (CDC) investigation later revealed serious shortcomings in the data suggesting ‘a possible association between acute pulmonary hemorrhage and mould exposure was not proven’ [11].

Cognitive impairment attributed to the reaction of mycotoxins, so-called ‘toxic encephalopathy’, has also been claimed in several published reports [12–15]. The symptoms of this illness are said to include short term memory loss, poor attention span, and difficulty in concentration. These studies of toxic encephalopathy from exposure to inhaled mould spores lack credible evidence for such an association in large part because of patient selection bias. Neuropsychologic data are necessarily subjective in nature. Comparison groups lack validity, being based instead on either estimates of pre-morbid intelligence or normative data. Most importantly, none of these published studies provide measurements of mycotoxin exposure. Thus, there is no credible evidence in these reports that abnormal psychologic testing indicates mycotoxic encephalopathy.

Epistaxis has frequently been claimed to result from exposure to fungi and/or fungal products. Mycotoxicity as a cause of immune dysregulation, either immune deficiency or auto-immunity, is sometimes suggested. However, there have been no published studies of these conditions arising from mycotoxin exposure, so such claims cannot be evaluated for scientific validity. Likewise, there are no publications dealing specifically with a variety of subjective complaints including fatigue, headache, dyspnea, or GI distress allegedly induced by mould or mycotoxin.

#### Nonspecific inhalational irritation

It has been proposed that irritation (‘aero-irritation’) is responsible for human fungal disease. Although irritation has not been clearly defined, it is assumed to comprise symptoms of pruritis and/or hyper-secretion of nasal mucous membranes, conjunctivae or skin.

A review of irritant effects from indoor airborne fungal exposure in homes has recently been published [16]. Although this review is referred to as ‘evidence-based’, careful inspection of the 16 publications [17–32] cited in this review reveals an insufficient basis for such
a claim. One study [25] deals with asthma only and not irritation, and another [31] is a single case report of allergic rhinitis. The 14 remaining publications are all epidemiologic questionnaires which attempt to find significant correlations of symptoms of respiratory mucous membrane irritation with mould (and humidity) exposure. Only one of these [19] includes relevant physical examinations and functional studies to objectively validate the reported symptoms as being consistent with ‘irritation’. Only one [32] of the 14 includes quantitation of airborne mould spores, concluding that on the basis of epidemiologic evidence:

after full remediation in one [moisture-damaged] school, elevated concentrations and increased frequency of indoor air fungi normalized and a significant decrease in prevalence in ten of twelve symptoms studied was observed among school children.

Therefore, this study is the only one of the 16 cited publications in this ‘evidence-based review’ [16] that provides direct experimental evidence of irritant symptomatology and mould exposure.

The presumptive causes of indoor airborne fungal spore irritation – if indeed there is such a phenomenon – include beta (1 →3)-D-glucans, mycotoxins, and microbial volatile organic compounds (mVOC). Glucans are structural cell wall poly-glucose compounds found in all fungi and have been used as surrogate markers of mould presence. mVOC (alcohols, aldehydes, ketones), by-products of microbial metabolism, are volatile and odorous. Although fungal mVOC are generally considered as candidate aeroirritants while glucans and mycotoxins are excluded, not one of the cited studies [16] include measurements of environmental exposure to any of these three mould-related compounds. Douwes [33] likewise has concluded that:

currently available epidemiological data do not permit conclusions to be drawn regarding the presence (or absence) of an association between environmental (1 →3)-beta-D-glucan exposure and specific adverse health effects . . .

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<th>Proposed mechanism</th>
<th>Mycotoxicity</th>
<th>Irritation</th>
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<tr>
<td>Exposure route</td>
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<td>Inhalation</td>
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<tr>
<td>Mould specificity</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Proposed illness(es)</td>
<td>Pulmonary hemosiderosis ‘Toxic encephalopathy’</td>
<td>Mucus membrane and/or ocular irritation</td>
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Discussion

Moulds are microorganisms that are constantly and abundantly present within the human environment and capable of causing disease through infection, allergic reactions, or toxic processes. Recently, proposals have been put forward to suggest additional clinical conditions, most often attributed to mycotoxins from indoor mould-contaminated sources. As such, these proposed illnesses would fit within the rubric of Sick Building Syndrome or Building-related Illness.

This brief review outlines the established mould-related pathogenic mechanisms and the corresponding fungal diseases of humans. It also focuses on the recent controversial proposals for human diseases caused by moulds, citing the shortcomings and inconsistencies of relevant published literature, and in some cases even the absence of any supporting publications.

Many of the proposed mould-related illnesses are subjective ones without defined objective physical (including those detectable by imaging studies) or biochemical abnormalities. These include cognitive difficulties, headache, abdominal distress, fatigue, sleep disturbance, anxiety, and other symptoms. Although this pattern of symptomatology has been attributed in the past by some to a variety of environmental factors including infectious and toxic agents, it is generally considered to be a manifestation of psychopathology [34].

Definitive research on the causative role of environmental moulds in disease is a daunting challenge. Deliberate exposure using defined quantities of agents and objective measurements of responses in order to reproduce a putative disease in humans under appropriately controlled conditions would be an ideal goal were it not for the obvious danger inherent in this approach. Therefore, epidemiologic research is recognized as a first step in defining the problem. Many such studies have already been completed and published, but the vast majority of them depend upon non-validated questionnaires to obtain both the clinical data and estimates of mould or mycotoxin exposure. The large numbers of subjects in some of these studies does not correct for the lack of objectivity. In some studies, subjective ‘dampness’ is a surrogate for mould exposure without considering whether a humid indoor environment in itself might be responsible for some or all of the symptomatology [35]. Furthermore, such an environment is likely to involve excessive exposure to
multiple and interacting chemical and biological agents [36].

The only human disease currently recognized as one caused by mycotoxin inhalation is pulmonary mycotoxicosis (ODTS). This disease occurs when massive airborne mycotoxin exposure is present under unusual occupational conditions. On the other hand, exposure to mycotoxins from damp and/or water-damaged building interiors has been postulated to cause both respiratory and non-respiratory effects in the occupants of such buildings. It is extremely unlikely that mycotoxin exposure under these conditions would reach levels approaching those estimated to occur in ODTS. In this case, epidemiologic studies and animal models are cited as supporting evidence of a relationship between mould exposure and the clinical symptomatology. In addition to the deficiencies of epidemiological research in this area that was mentioned above, the absence of dependable measurement of mycotoxin exposure is critical. In laboratory animal studies, on the other hand, delivery of precise quantities of defined mycotoxins to the tracheobronchial tree and precisely quantified observed effects can be achieved [37]. To date, the relationship of these effects (e.g. localized inflammatory response) to the clinical observations of the human inhabitants of water-damaged buildings remains speculative.

Further research is clearly needed to define those illnesses caused by or related to moulds and to refine diagnostic processes and disease management for clinicians. Additional epidemiologic studies are necessary, but these should be designed to better address more focused questions and to include more objective clinical and exposure data using appropriate controls. Results should then be more relevant in the design of appropriate animal models.

Conflict of interest: The author has served as an expert medical witness in litigation involving claims of mould-related injury.

References


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