

# Moulds and asthma: time for indoor climate change?

Ashley Woodcock

## Effect of controlling mould in houses on respiratory health

The spectre of indoor moulds as a contributor to respiratory disease keeps raising its fruiting body and just won't go away. Numerous studies support a circumstantial and temporal link between high mould exposure and worse symptoms in susceptible individuals. However, it seems that the majority of respiratory physicians (at least in Europe) are at best non-believers. They are reluctant to consider moulds as important in patients with respiratory symptoms, rarely make specific enquiry, and almost never make attempts to reduce mould exposure. This contrasts with enthusiasm bordering on evangelism from some experts in the USA where huge litigation raises the stakes, with over 10 000 cases pending and multi-million settlements already routine.<sup>1</sup> In the past we have been hindered by profound ignorance of the biology of these important environmental contaminants. What do we know about indoor moulds, and how are they implicated in respiratory diseases, and specifically asthma? Should we be trying to reduce mould exposure for specific patients or the whole population and, if so, how?

Evidence for outdoor mould exposure and exacerbations of asthma is strong. For example, *Alternaria* is the dominant allergen in the mid west USA with strong temporal relationships between exposure and asthma severity. There are huge airborne spore counts (1000 times grass pollen counts) on peak days, associated with immediate worsening in sensitised subjects<sup>2-5</sup> and increased asthma deaths.<sup>6</sup>

However, assessing indoor mould exposure and relating exposure to worse respiratory disease is a much more complex issue. A range of mould species is undoubtedly associated with serious respiratory disease including infection (sinus and pulmonary) and allergy (allergic bronchopulmonary aspergillosis). In addition, there is strong evidence for a link between severe asthma and indoor mould sensitisation.<sup>7</sup> But it has been unclear whether this association is an epiphenomenon reflecting worse non-specific atopy, or whether specific avoidance or treatment for fungi might be beneficial. Several confounding issues

prevent an immediate conclusion: skin prick test solutions for moulds are crude, vary by manufacturer and may be non-specific,<sup>8</sup> and severe asthma could be a reflection of a severe reaction to environmental mould exposure or require colonisation of the airways (or skin). Novel and sensitive molecular methods may now help resolve this, since they identify apparently frequent fungal colonisation of sputum. This will avoid the need for culture and identification (which is highly skilled, selects fungi by their culture characteristics and may distort patterns of true exposure). A new acronym has recently been proposed for severe asthma with fungal sensitisation (SAFS); anecdotal responses to antifungal therapy have been observed, and a double-blind randomised controlled trial of itraconazole is nearing completion.

The fungal kingdom is thought to contain over a million species, of which about 80 000 have been named and about 600 species cause some form of human disease. In contrast, most infectious diseases of plants are fungal in origin. To date, very few airborne genera i.e. *Alternaria*, *Aspergillus*, *Cladosporium*, *Botrytis* and *Penicillium* have been implicated in allergic asthma, and a few more in extrinsic allergic alveolitis. A number of factors may make these species respiratory allergens. First, fungi such as *Aspergillus* and *Penicillium* have a spore size (~5 µm) within the respirable range, unlike other fungi which have much larger spores. Second, some fungi such as *Aspergillus fumigatus* which is capable of growth at 37°C can germinate and colonise the sinuses and airways, unlike *Aspergillus clavatus*, for example (the cause of malt workers' lung), which barely survives at 37°C. Third, most fungal allergens fall into specific protein types, although a few key ones are unique to a species. *A. fumigatus* is best explored and over 60 allergens are described with a wide range of biological effects.<sup>9</sup> Proteases may be important in fungal antigen penetration of the airway mucosa but could also have a broader role in permitting sensitisation to other non-protease environmental allergens (such as cat or dog proteins).<sup>10</sup> Importantly, pre-formed allergen may be inhaled on the

surface of hyphal fragments. Fourth, non-allergic mechanisms could act in parallel or independently. Glucan is a pro-inflammatory component of fungal cell walls<sup>11</sup> and fungi also produce a range of volatile fungal mycotoxins, the importance of which we do not know with respect to respiratory disease.

Remarkably, we still do not understand what actually constitutes airborne mould exposure and where it comes from. The public and physicians alike consider indoor mould as that black (and virtually indestructible) rind in the shower, or where there is water penetration onto walls and ceiling often in low income households. However, there may be other important sources of mould. We have recently cultured a large range of moulds in pillows,<sup>12</sup> together with volatile mycotoxins detected in low concentrations by mass spectrometry. The mould flora varied with type of pillow (synthetic vs feather). With the recent almost universal trend towards synthetic quilts and pillows, direct inhalation from bedding may be an important exposure in the context of allergy or infection in, for example, immunosuppressed patients. There is even evidence to suggest that *Trichophyton* nail infection can exacerbate asthma, which improves with specific treatment.<sup>13-14</sup> New techniques of exposure assessment using nasal samplers<sup>15</sup> and silent ion charged plates,<sup>16</sup> together with multiplex technology for measuring multiple allergens simultaneously,<sup>1</sup> provide hope for some future clarification of exposure. However, it is likely to be horrendously complex and, as a result, contentious.

In the absence of data on individual exposure, can we make any recommendations on control measures targeted at indoor moulds and improved health outcomes? Well, dampness is bad for asthma<sup>17-19</sup> but good for mould growth. In this issue of *Thorax*, Burr and colleagues<sup>20</sup> have examined asthma control after reducing dampness and removing mould in a randomised controlled trial in patients in South Wales with visible indoor mould in their homes (see page 767). Patients were randomised to either a simple intervention (mould removal plus fungicide applied to visible mould plus loft fan to promote ventilation) or control. At the end of the study the intervention group had lower humidity and about half the visible mould of the controls at 12 months (40% vs 78%). Unexpectedly, there was a trend for less improvement in peak expiratory flow variability in the intervention group than in the control group, but there were significant improvements in symptoms and reduced medication use. This is an important study, but it must be interpreted with caution. There are many potential

confounders, including reduction in passive smoke or mite allergen exposure, which could explain the improvement in respiratory symptoms. These types of study are extremely difficult, expensive and time consuming, but also virtually impossible to blind. Patient reporting bias could explain the soft positive outcomes, especially in conjunction with the low follow-up rate (6 months ~55%, 12 months ~75%). Even if the study is accepted as supporting mould control, we do not know which component of mould control is effective (removal, or fungicide, or increased ventilation, or perhaps all three combined). Or perhaps improving ventilation and reducing humidity is a good thing for respiratory health whatever the mechanism?

The answer to this question has been the subject of a truly landmark study from New Zealand<sup>21</sup> which studied 1350 non-insulated homes with low income families. The houses were generally stand-alone wooden homes on piles, with heating of a living room only. Two-thirds of homes had damp and three-quarters had visible mould. The homes had at least one household member with respiratory symptoms in the last year or a history of asthma, pneumonia or chest infections. Homes were randomised to have ceiling insulation installed, draught stopping around windows and doors, and moisture impenetrable barriers fitted below the floors (cost £700/house) or to control. Over 12 months there were substantial (of the order of 50%) improvements in self-rated health, wheezing and reduced time off work and school in the intervention group, with fewer visits to GP and hospital. Visible mould was reduced by 50%. Again it is impossible to fully blind this study, but it was single blind and the size of the study and the size of improvements for a mix of

hard and soft outcomes give it great weight. Essentially, the authors have identified an important and cost effective public health intervention. Whether it works by reducing mould exposure or whether mould is a bystander of housing quality is an open question.

So there is the challenge for any society with a social conscience. The New Zealand study needs to be reproduced around the world, accounting for local housing conditions and climate, to see if the results are transferable. In New Zealand the intervention not only improves respiratory health in a vulnerable part of society, it actually saves them money. Overall heating costs went down by 20%, and that can't be bad for that other big environmental challenge—outdoor climate change!

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## Vitamin D and asthma

# Maternal diet vs lack of exposure to sunlight as the cause of the epidemic of asthma, allergies and other autoimmune diseases

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## Role of vitamin D deficiency in allergic and autoimmune diseases

**A**sthma is occurring in epidemic proportions with more than 300 million affected subjects worldwide. In almost

all cases the disease has its onset in early childhood, with 80–90% of all cases initially being diagnosed before the age of 6 years.<sup>1,2</sup>

It was not always so. In the early 1970s the prevalences of asthma and allergy were roughly half of what they are today, and although the onset of the asthma epidemic started insidiously and cannot be precisely documented, it has several interesting and important features that have defied a unified explanation until now. There is clearly a North/South equatorial gradient with Western industrialised countries furthest away from the equator (New Zealand, Australia, the UK) having the highest prevalence worldwide. There is also a clear urban/rural gradient among poorer Third World countries, and a First (industrialised) World/Third World gradient with the lowest asthma prevalence occurring in rural areas in Third World societies. A very important feature of the epidemic is that it is not only asthma that has increased. A host of