INDOOR DISEASES RELATED TO MICROBIAL CELL WALL COMPONENTS

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Abstract

Investigations have been performed in a number of indoor environments where symptoms had been reported. The environmental measures comprised airborne endotoxin and (1→3)-ß-D-glucan, and the effects were evaluated using a modification of the organic dust questionnaire and measurements of airway responsiveness. Level of (1→3)-ß-D-glucan were around 1 ng/m^3 when no symptoms were reported. Levels above 20 ng/mg^3 were always associated with extended symptoms. Endotoxin levels were low and below those predicted to cause airways inflammation, caused by the (1→3)-ß-D-glucan exposure or by other mold components for which (1→3)-ß-D-glucan is a marker. The term "sick building" syndrome should be abolished and the symptoms observed be related to the relevant disease entities.

Background

During the last decades, a variety of non-specific symptoms of general as well as local nature has been reported by persons in office buildings as well as living quarters (sick buildings). Symptom prevalences up to 60% and more have been reported. The symptoms generally comprise an irritation of the eyes and upper airways and dry cough, suggestive of an inflammatory response. A small proportion of subjects experience traditional allergic reactions and in addition, there are often complaints of headache, excessive tiredness and skin irritation.

While it was initially believed that the causative agents were of a physical and chemical nature, there is now accumulating evidence that a large proportion of the cases reported are related to exposure to microbial agents. This presentation will describe the conditions required for microbial growth indoors, review field studies on the relation between disease indoors and microbial growth and describe the particular diseases involved.

Microbes indoor

Under normal conditions, the number of microbes indoors is about the same or less than outdoors. Air conditioning units may lower the number by up to about 50%, provided that doors and windows remain closed [54]. Apart from extraordinary events, such as storing mouldy materials indoors or keeping garbage for extended periods of time, the major reason for increased numbers of microorganisms indoors is dampness.

Reasons for humidity indoors are inadequate isolation against rain or ground dampness, leaking water pipes or reservoirs, activities of inhabitants, and remaining humidity in newly constructed building materials.

A number of studies has now been published in which the indoor air flora of microbes has been well characterized and the conditions under which growth occurs determined [8,20,29]. The most common microbial contamination in humid buildings is moulds which grow at relative humidities around 70% and above. Leaking water pipes, condensation behind walls in wet spaces like bathrooms and shower cabins are potential areas for mould growth. Once a colony is established, mould spores can be found at the particular site for long periods, probably decades or decennia, if they are not exposed to sunlight or currents of fresh air.

Another common microorganism indoors is Gram-negative bacteria. They are ubiquitous in our environment and grow in pools of stagnant water such as in reservoirs of humidifiers or water tanks [41]. High levels of endotoxin are present in sewage water, mainly owing to the growth of naturally occurring Gram-negatives such as *Enterobacter* and *Klebsiella*.

The presence of Gram-negative bacteria in the environment has been known for a long time but it was not until the development of the Limulus lysate assay that a proper assessment of the quantities of endotoxin in the environment could be made. In 1973, it was reported that bacterial endotoxin was present in drinking water [16]. A few years later, Jorgensen *et al* [24] and Levin and Bang [28] determined the amount of endotoxin in drinking water and waste water. Another environment in which endotoxins were detected was different organic dusts. These are defined as particles of animal, vegetable and microbial origin [46]. Regardless of their origin, organic dusts are always contaminated with microbes - bacteria or molds.

Epidemiological evidence

Mould and dampness

Microorganisms are ubiquitous in man's environment and at lower exposure levels are usually tolerated without adverse reactions. When the level increases, however, effects in terms of inflammation and sensitization appear. The first recorded observation of ill effects related to indoor environments is found in the Bible, where a caution against what was probably mould in houses is found in the book of Leviticus [3,50]. Reactions to moulds were first reported by Floyer [21], who described a asthmatic reaction after inhalation of moulds. About 150

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years later, Blackley [4] described his own reactions after inhaling *Penicillium* spores. Medical problems related to humid buildings were first described by van Leeuwen [27], who suggested that the asthma symptoms which were prevalent in humid areas in Holland, were related to the observed presence of moulds indoors.

During the last 15 years, more than 20 large studies have revealed an association between dampness or mould growth indoors and respiratory symptoms among children and adults [1,5-7,9-15,22-26,29-35,40,53,55-59,64-65]. Table 1 presents a review of the different studies with some important study characteristics.

Studies on Specific Substances

Background

Microorganisms contain a large number of potentially toxic and allergenic substances. During growth, moulds generate volatile organic compounds such as geosmin and different sulphur compounds which cause a typical musty smell. These have been measured in indoor environments. Mycotoxin has been measured in a few studies. (1→3)-ß-D-glucan is a polyglucose compound which is present in the cell wall of molds, and certain bacteria and plants. Ergosterol is a cell membrane component that is specific to fungi. Quantitative analysis of ergosterol has been used in indoor environments and higher levels have been found in damp buildings [Miller, personal communication].

Mycotoxins

Mycotoxins are biologically the most potent of agents in moulds and mycotoxin contamination has been demonstrated in homes containing *Aspergillus fumigatus* [38]. *Stachybotrus atra* is a hydrophilic mould that can produce highly toxic macrocyclic trichothecenes.

Mycotoxin producing fungi are not uncommon in residential buildings. Smith *et al* [52] determined mycotoxins in 83 fungal isolated from damp buildings in Edinburgh. In 47% of the samples, evidence of cytotoxic materials was present. In a study of 52 Canadian homes, evidence of *Aspergillus fumigatus* mycotoxin production was found in three of the homes. Trichothecene mycotoxins have also been found in ventilation systems of buildings where occupants reported a series of symptoms probably related to neurogenic effects [2].

Haemhorragic pneumonia among children has been associated with mould exposure at home. The mycotoxin from *Strachybothrus atra* is likely to be the causative agent [18,19].

Endotoxin

Endotoxin is a lipopolysaccharide compound with important inflammatogenic properties. From an environmental point of view, one can distinguish between lipopolysaccharide and bacterial endotoxin. The former is a chemical product that is obtained through extraction techniques and is a pure substance with only trace amount of proteins. In nature, the lipopolysaccharide on the outer wall of Gram-negative bacteria is present together with whole bacterial cells or fragments thereof, in the form of particles which also contain protein and other cell constituents - endotoxin.

In an epidemic of drinking-water mediated fever, Muittari *et al* [39] reported that the amount of endotoxin found in the water in the homes of families affected by the disease was 0.2-1.2 g/ml. Repeated outbreaks of fever were reported from a printing factory with contaminated humidifiers [41]. There was an abundant growth of Pseudomonas in the humidifier water and airborne endotoxin levels ranged from 0.13 to 0.39 $\mu g/m^3$. Of fifty workers examined, twenty reported symptoms of work related fever and influenza like symptoms. Teeuw *et al* [60] surveyed 1355 employees working in 19 governmental offices in the Netherlands. Gram-negative bacteria were found in higher numbers in buildings with problems where the endotoxin concentration was also higher (0.25 $\mu g/m^3$ vs 0.05) in buildings without problems. The source of the Gram-negative bacteria was contaminated water in humidifiers. There is some controversy regarding the presence of endotoxin in ordinary house dust. Using a vacuum sampling method Michel *et al* [36] have demonstrated a relation between the clinical severity of asthma and endotoxin whereas significant amounts of endotoxin have not been found when sampling airborne dust indoors [Rylander unpublished].

(1→3)-ß-D-Glucan

Several studies have investigated the relation between exposure to airborne (1→3)-ß-D-glucan and the extent of symptoms in indoor environments. One study demonstrated a relation between the amount of airborne (1→3)-ß-D-glucan and the extent of nasal irritation and hoarseness [42]. There was also a relation between endotoxin levels and symptoms of cough and itchy eyes. A subsequent study examined daycare centers, a post office and some houses [43]. A relation was found between the extent of irritation in the throat and the amount of airborne (1→3)-ß-D-glucan. Another study comprised a day care center before and after renovation [48]. Airborne levels of glucan were 11.4 ng/m^3 before the renovation and 1.3 afterwards. Airway responsiveness was measured in 12 of the employees and 9 of these had an increased value before the renovation as compared to 2 afterwards. Two of the employees developed a clinical allergy during the course of the study. This is an unusual event in a population of adults and could be related to the indoor air (1→3)-ß-D-glucan exposure.

A case study in Switzerland comprised a clinical investigation of two boys living in a house with severe mould problems due to faulty ground drainage. Airborne glucan levels of ranged from 5 to 106 ng/m^3 with an

average of 46 [45]. The boys developed cough, wheezing and tiredness after about 6 months living in the house and one of them also became sensitized to house dust mite. They moved out of the house and the symptoms disappeared. About a year later, the parents developed airways inflammation and they also had to move out of the house.

The relations found in epidemiological studies as described above, do not necessarily indicate causal relationships and challenge studies with pure substances have to be made. In a pilot study, where subjects were exposed to an aerosol of pure endotoxin or (1→3)-ß-D-glucan, an increase in the intensity of symptoms of stuffy nose was found after both exposures, while increased headache and skin problems were caused by (1→3)-ß-D-glucan [44]. In a following challenge study, (1→3)-ß-D-glucan exposure caused an increase in nose and throat irritation and in airway responsiveness [49].

Symptomatology and Diseases

Rationale

The symptoms reported in the different studies, comprise a variety of non-specific symptoms such as irritation in the eyes, nose, congested nose and cough, skin problems, tiredness and headache. The symptoms profile is remarkably similar in the different studies reported.

The exposure indoors can be looked upon as another location of organic dusts. These are aerosols of a vegetable, animal and microbial origin [46]. It has recently been proposed that the symptoms in indoor environments express the same diseases that are found in organic dust environments [47]. These symptoms mainly reflect a non-specific airways inflammation and that, in a minority of cases, a classical IgE mediated sensitization can develop against an indoor air antigen such as house dust mite or moulds. Against this background, there are four different disease entities that can be related to indoor air exposure.

The Diseases

Toxic pneumonitis (inhalation fever, organic dust toxic syndrome) is characterized by an increase in body temperature, shivering and muscular and joint pains, symptoms resembling influenza. The disease is short-lived and the symptoms have disappeared within a few days [63]. Toxic pneumonitis occurs mainly in connection with humidifiers. It may also appear after very dusty work such as cleaning of shelves, sweeping dirty floors, and changing wall-to-wall carpets. The number of cases in an exposed population can be high.

Airways inflammation develops slowly over a period of time and can be present in different stages of severity. It is characterized by irritation in the airways, stuffy or swollen nose with an increased airway responsiveness and cough. This develops into a sputum producing cough after prolonged exposure. The proportion of persons affected can be large. Airways inflammation is often accompanied by systemic symptoms in terms of headache, fatigue and joint pains. It is likely that several of these are caused by inflammatory mediators, produced in the lung after inhalation and distributed to different parts of the body via the blood [17,37].

Hypersensitivity pneumonitis (allergic alveolitis, granulomatous pneumonitis) is a special inflammatory disease that may develop after prolonged exposure to organic dust. This disease was first described among farmers - hence the name farmer's lung. It appears in many different kinds of environments where exposure to organic dusts take place. The disease is characterized by a lymphocyte infiltration which may proceed to granulomas and even fibrosis. Agents that cause hypersensitivity pneumonitis probably do so by influencing the reactivity of T cell lymphocytes [51]. The most widely recognized causative agent is moulds. Case studies of the disease in home environments have been reported.

Asthma, rhinitis and conjunctivitis are diseases which require repeated exposures to a specific agent. In some particularly reactive individuals, this exposure with time induces a strong response to much lower amounts of the agent than normally. Asthma is characterized by variable airflow limitation with accompanying subjective symptoms of shortness of breath. Important from a clinical point of view, is the chronic inflammation which develops in the airways, probably as a result of several acute reactions with corresponding release of inflammatory mediators. In a given population, the number of individuals who develop asthma is small even if incidence figures could be high in conditions of elevated exposure such as in industrial settings.

Relation to Microbes

Several studies demonstrate an association between airborne endotoxin and toxic pneumonitis and this effect has also been reproduced with the pure agent. From investigations on organic dusts in occupational environments there is evidence for a relation between endotoxin exposure and airways inflammation. Hypersensitivity pneumonitis and asthma have not been related to endotoxin.

The majority of the studies reviewed demonstrates that reported presence of water damage or mould growth in the dwellings was associated with an increased risk for symptoms of airways inflammation among children as well as adults. Regarding viable moulds or bacteria, the relationship is less clear.

Sampling for viable microorganisms can, however, not be considered as a precise quantitative method due to a variety of technical reasons. This conclusion is in

agreement with a study by Verhoeff *et al.*, [61] who found a large variability over time and poor reproducability of bacterial procoagulates in indoor air. This is not unexpected as it is likely that the effects are caused by substances active also after the death of the organism.

The data from the epidemiological evidence for a relation between airways inflammation and dampness/moulds in buildings show several of the criteria required for causality such as consistency, biological plausibility and temporarility.

Regarding diseases and risk groups, no symptoms of toxic pneumonitis or hypersensitivity pneumonitis were reported in the investigations. Airways inflammation was the most prevalent disease. Several studies reported the presence of asthma but as this is a disease with a prolonged onset, one would require longitudinal studies to assess the risk. As the data stand now, one can only conclude that symptoms of asthma were present and that they were more frequent among those in buildings with moulds. If the underlaying reason is an aggravation of the inflammation in asthma or the causation of asthma due to dampness or moulds remains obscure. The results from a Dutch study [62], demonstrated an increased risk for persons with a higher level of IgE as compared to a group with a lower level. This supports the hypothesis of an aggravation of an existing inflammation caused by asthma. In experimental studies it has been reported that the effect of inhaled bacterial endotoxin and (1→3)-ß-D-glucan caused more pronounced effects among persons with a history of atopy [48].

Conclusion and Recommendation

This review of the risk for disease in indoor environments and the relation to microbial growth demonstrates that airways inflammation is the most common disease. Some data suggest that it is more widespread among persons with a preexisting atopy or asthmatic inflammation in the airways. A relation between the extent of airways inflammation and dampness/mould growth has been found in most of the studies.

The review has not dealt with other possible causes of disease indoors, nor tried to rank the different potential agents that may cause airways inflammation or asthma. It is a general impression from the material reviewed, however, that dampness and mould growth are major factors both for airways inflammation and aggravation of the inflammation in asthma. Some studies also show that keeping of furred pets is a major risk factor, even if the data are not consistent. Environmental tobacco smoke is often cited as an important risk factor but this risk appears to be relatively minor compared to dampness and moulds.

From a public health point of view, renovating damp or mouldy houses with the aim to exterminate living as well as dead mould colonies, even if they are hidden in the interior of the building, has a high priority. It is also important to maintain the water reservoir in humidifiers to prevent growth of Gram-negative bacteria with an ensuing contamination of the water with endotoxin.

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Table 1. Overview of structure of studies on dampness/mould and disease

	Population		Dampness/mould		Effects	
Author	**Children**	**Adults**	**Reported**	**Measured**	**Reported**	**Measured**
Melia *et al* -82	191			X	X	
Burr *et al* -85		144	X		X	
Strachan -88	881				X	X
Andrae *et al* -88	?		X		X	
Strachan & Sanders-89	1000		X	X	X	
Strachan -90	88		X	X	X	X
Wagemaekers *et al* -89	190	328		X	X	
Brunekreef *et al* -89	4625		X	X		X
Platt *et al* -89	1169		X		X	X
Dijkstra *et al* -90	1051		X		X	X
Dales *et al* -91a		14779	X		X	
Dales *et al* 91b	13495		X		X	
Brunekreef-92a		6436	X		X	
Brunkreef-92b	4395		X		X	X
Harrison-92		1338		X	X	
Jaakkola *et al* -93	2568		X		X	
Spengler *et al* -94	12842		X		X	
Strachan & Carey -95	763		X		X	
Verhoeff *et al* -95	516		X	X	X	X
Cuijpers *et al* -95	470		X		X	X
Li & Hsu -96a	1370		X		X	
Li *et al* -96b	1370	612	X		X	