MICROBIAL CONTAMINATION OF INDOOR AIR #6227

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The literature of ca. 10 years ago placed modest emphasis on fungi in relation to bacteria and viruses in indoor air (1,2). Viruses are almost entirely spread by personal contact and no obvious changes in building design or management can alter this (2,3). Many types of bacteria have been reported in indoor air, sometimes in high concentrations. Most of these are normal species associated with skin and nasal-pharyngeal surfaces. There is no direct evidence that the presence of these bacteria in office/residential indoor air contribute to disease (4). However, elevated concentrations of bacteria are normally a sign of poor ventilation (see 5).

Indoor air exposure to Legionella and the endotoxin-containing bacteria is hazardous. However, the management of these bioaerosols in indoor air is well-defined and they rarely pose a health risk (6,7,8). In the last five years, fungi have come to be seen as quantitatively the most important bioaerosols with respect to health in indoor air. This paper will briefly review aspects of microbial problems in buildings. Recent findings regarding the biomedical aspects of fungal contamination of indoor air will be considered with a perspective on the normal mycoflora of indoor air.

BACTERIA

Legionella

The bacterium that cause Legionaires' disease and Pontiac fever is ubiquitous in water but only poses risk when growth occurs in domestic water heating systems and cooling towers near HVAC air intakes (6,9,10). The disease is characterized by flu symptoms ranging to severe illness leading to death in some individuals. It appears that individual susceptibility (co-morbidity, age) is somewhat more important than exposure in determining the outcome . Legionnaires' disease has been suggested to be "an unnecessary risk" because proper maintenance of cooling towers, plumbing and domestic water heating systems eliminates significant exposure to the bacterium (6). However, a 1988 estimate has Legionella causing 5,000-7,000 deaths per year in the U.S.A. (11).

Bacterial endotoxins

Endotoxins are lipopolysaccharides that are present in the cell membrane of gram negative bacteria. Endotoxins are present in a variety of plant materials and dusts from bacterial contamination. Extensive bacterial growth in HVAC humidifiers and cooling towers has been reported. This can lead to airborne contamination by endotoxin and endotoxicosis (12,13). However, proper maintenance of the HVAC system completely eliminates the risk (8). It is not clear how common this is because, although endotoxin measurements are not difficult, they are not often done. The increased use of steam injection humidification would work to decrease endotoxicosis in buildings (14).

Occupational exposures to endotoxin occur in animal confinement facilities, sewage treatment plants and in the handling of cotton dusts. This leads to chest tightness, mild fever as well as a complex variety of immunological changes (see following; 8,12).

Other bacteria

A number of species of bacteria not considered above have been reported from humidifiers including Pseudomonas aeruginosa, Flavobacterium, Acinetobacter species, and Alcaligenes species (15). In one report, the latter species was aerosolized at 1.5×10^4 $CFUm^{-3}$ with no health complaints from the building occupants (4,16).

Regardless of bacteria sourced from humidifiers, most bacteria in indoor air are those shed from skin and oral-nasal pharyngeal cavities. Numerous species have been reported from indoor air especially Micrococcus, Flavobacterium and Staphylococcus (16). S. epidermidis shed from skin flakes is reported as usually abundant in indoor air (4). People emit very large numbers of particles containing bacteria: 400,000/min sitting at a desk and 45,000,000/min during exercise (17).

In office buildings, numbers of viable bacteria have been reported to be in the 10^3 $CFUm^{-3}$ range (5,16,18). However, the numbers of viable bacteria may represent less than 1% of the total number of cells present in air (18). As noted above, the majority of reports indicate that gram positive bacteria are most common in air. Gram negative species containing endotoxin may become an appreciable fraction of the airborne bacterial flora (4,19). Hence, sometimes exposure to bacterial endotoxin may exceed threshold levels.

Mouilleseaux and Squinazi (Laboratoire d'Hygiène de la Ville de Paris; 5) developed a guideline for general air quality as follows:

$$IQ = \frac{CO}{5} + \frac{CO_2}{1{,}000} + \frac{CFUm^{-3}\ \text{bacteria}}{1{,}000}.$$

With respect to bacterial counts, this reflects the likelihood that high counts reflect poor sanitation and/or inadequate ventilation. This guideline echoes a remark made in a presentation to ASHRAE in 1904: "substances and impurities that cannot be estimated from the presence of carbonic acid (CO_2), as for instance an excessive amount of vapor of water, sickly odors from respiratory organs, unclean teeth, perspiration, the presence of microbes due to various conditions, stuffy air from dusty carpets and draperies, and many other factors combined, will in most cases cause greater discomfort and ill-health (cited in 14). Note that the Mouilleseaux and Squinazi IQ formula does not include filamentous fungi.

FUNGI

The normal indoor air mycoflora is identical to that of outdoor air. This is intuitively as it should be and indeed, this has been demonstrated in residential housing in the U.S.A. and Canada (20,21). Data from investigations conducted in 1988-89 in buildings belonging to the Canadian government demonstrated that the mean $CFUm^{-3}$ from 162 air samples was ca. 40. A similar value (38.3 $CFUm^{-3}$) was obtained in 1989-90 (Miller, unpublished data). The species involved were almost entirely phylloplane fungi: Cladosporium cladosporioides, C. herbarum, Alternaria alternata and non sporulating types which were primarily mushroom spores (14).

These fungi constitute >90% of airborne spores except during periods of snow cover when the airborne mycoflora is negligible. Soil fungi such as Aspergillus and Penicillium normally constitute only a few percent of spores in outdoor air samples (4,20,22).

Data from April 1990 to July 1992 are shown in figure 1 using the same method as Nathanson & Miller (14). This figure summarizes 346 samples from buildings from several cities in eastern Canada. These samples were primarily taken for audit reasons i.e. buildings not associated with microbial air quality problems. Phylloplane fungi are plotted on the Y axis (CFU m^{-3}), filamentous fungi, primarily Aspergillus and Penicillium species appear on the X axis (CFU m^{-3}), and relative proportion is shown on the Z axis. These data provide clear evidence that the indoor air mycoflora of Canadian office buildings is qualitatively similar and quantitatively lower than that of outdoor air.

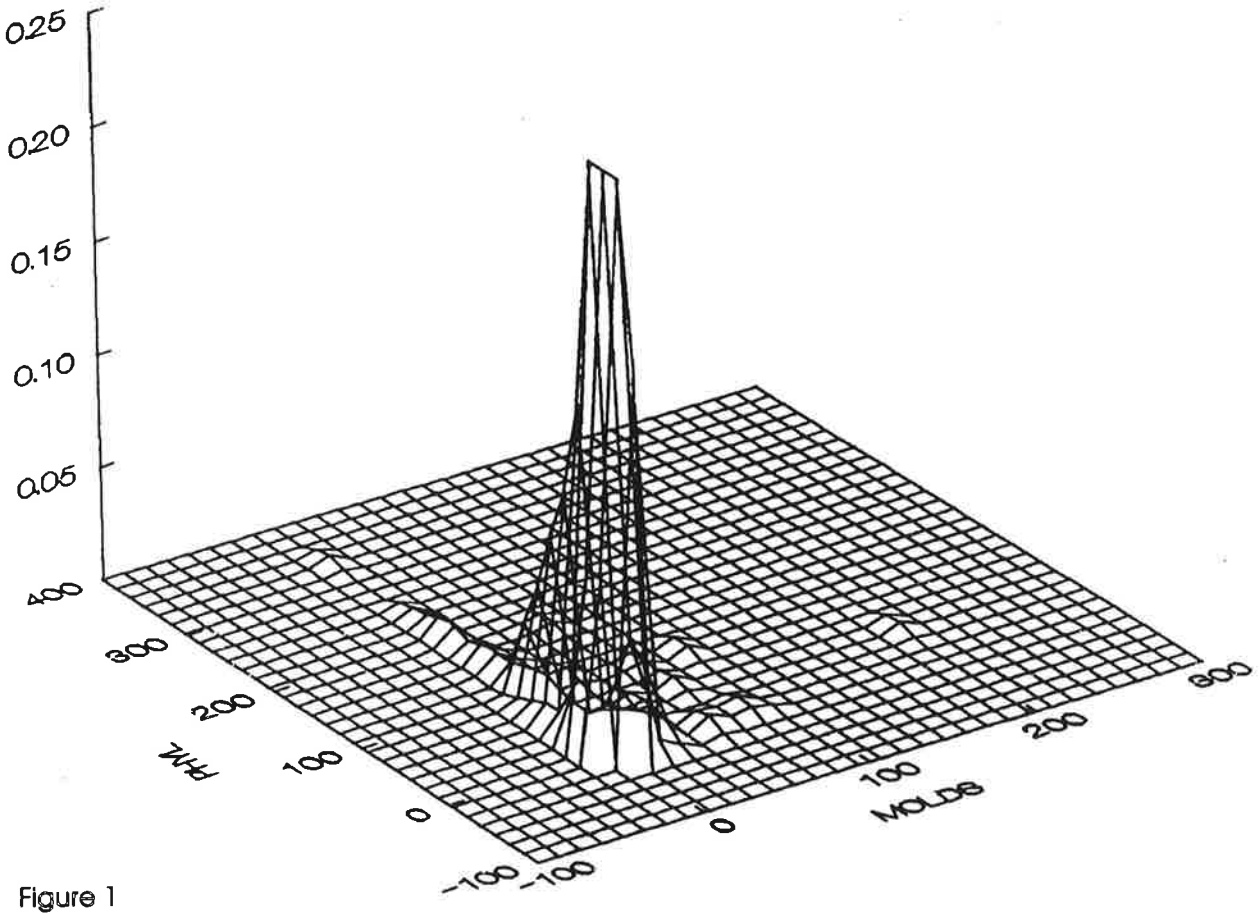

Figure 1

Data from several recent studies of molds in dust have demonstrated that slightly to strongly xerophilic species can form an appreciable percentage of the population. These include a variety of toxigenic species including Penicillium auranteogriseum, Aspergillus versicolor, etc. This has resulted in the identification of a group of "indoor molds" that have been reported in buildings in several parts of the world including Canada, the U.K., The Netherlands, and Japan (4,20,23). This important fact has been overlooked because of the historical use of media that primarily allow the growth of hydrophillic species including malt extract-glucose and Sabouraud dextrose agars (4,22).

These fungi have been demonstrated to grow on various building surfaces at material water activities appropriate to the species involved. For example, hydrophillic species including some phylloplane types will grow where materials are very wet. More xerophillic species will appear away from the point source of water. Similarly, drying of a wet area will result in a succession of species towards the xerophillic species. A detailed discussion of the issues involved can be found in Flannigan (4).

In my experience, health or comfort complaints from building occupants invariably result when the indoor air mycoflora deviates from the picture presented in figure 1. That is airborne counts of phylloplane species greatly exceed normal values (data up the Y axis) or the proportion of non phylloplane molds increases (points up the X axis). The following section will explore evidence that supports this practical observation.

CONSEQUENCES OF INHALATION EXPOSURE OF MOLDS FOR HUMAN HEALTH

Well-characterized hazards

Inhalation exposure to the spores of fungi can cause a variety of well-characterized problems including disease, hypersensitivity pneumonitis and allergy. Pathogenic species include various aspergilli including Aspergillus fumigatus, Histoplasma and Cryptococcus. In urban environments, pigeon and bat droppings can be a problem in air intakes and even in ducts. This is unusual, but cases of these diseases from building-related exposure are known (22,24). Hypersensitivity pneumonitis is a syndrome caused by inhalation of large concentrations of dusts containing organic matter including fungal spores. The gas-exchange tissue of the lung undergoes T-lymphocyte mediated inflammation. Very high concentrations of spores are considered to be required to induce acute symptoms. Although this is primarily a hazard of agriculture, hypersensitivity pneumonitis has been reported in individuals exposed in a home (7,22).

Exposure to fungal propagules probably always induces allergy (allergic rhinitis and asthma). It becomes a question of exposure in terms of time and quantity. The responses to fungal allergens by pulmonary macrophage and other cells are mediated by genes. This provides a basis for the apparent distribution of sensitive individuals i.e. atopy (25,26). There are serious problems with the diagnosis of allergy, especially to non phylloplane molds (22,27). A fairly large percentage of the population (10-15%) are known to be allergic to the common phylloplane molds Cladosporium and Alternaria (26). Test allergens can be purchased for perhaps 30 species of fungi. In most cases where a fungus is growing in a building or HVAC system, the appropriate test allergen is not available. This means that any allergy will most likely not be correctly diagnosed. Allergy is not always an outcome of hazardous exposure to fungi (7,22).

Mycotoxicosis

From the 1970's a subset of individuals with apparent hypersensitivity pneumonitis from exposure to fungal spores particularly from the aerobic zone of silos was recognized. The patients did not show the characteristic immunological reactions of this disease, but there was serious lung damage. This was described as "pulmonary mycotoxicosis". Concurrent with the identification of pulmonary mycotoxicosis, the importance of avoiding inhalation of spores of A. flavus/parasiticus was realized. The spores of these and other toxigenic molds have been shown to contain high to extremely high concentrations of the mixtures of mycotoxins produced by the species. A number of studies have been done showing the elevated risk of liver cancer from inhalation of spores and dusts containing aflatoxin. The most recent studies have largely

eliminated the problem of ingestion exposure as a confounding variable (22,28). Recently, the inhalation exposure of aflatoxins has been confirmed by molecular dosimetry (29).

Studies of the agricultural and occupational inhalation exposure to the spores of Stachybotrys atra done in Russia and France concluded that this induced mycotoxicosis (7,22,30,31).

There are three other kinds of data that support the notion that exposure to toxigenic molds as opposed to phylloplane molds represents a significant health issue. The first piece of information concerns the results of studies of the presence of viable mold spores in lung tissue from autopsies in Japan. Penicillium and Aspergillus spores were the dominant genera isolated from tissue of individuals with normal lungs (51.2% and 27.9%, respectively). In contrast, viable Cladosporium spores were found in only 2.3% of samples from normal lungs. The data from lung tissue with various pathologies were similar. Remarkably, all of the dominant species of Aspergillus and Penicillium isolated were toxigenic (32). Most mycotoxins are macrophage inhibiters (28). It appears that the spores of toxigenic molds remain protected until the toxins leach into the blood and lymph. Inhalation exposure to at least one class of mycotoxin, trichothecenes, is considerably more hazardous (20-50x) than intravenous exposure in terms of LD_{50} in several animal models (22).

The effects of chronic exposure to mycotoxins such as aflatoxin, ochratoxin, fumonisin and the trichothecenes are thought to be quite important on human populations. The first three toxins are considered to result in increased cancers in several parts of the world (33,34). Inhalation leading to systemic exposure to all of these compounds result in immune suppression. Ingestion exposure to trichothecenes results in altered mucosal immune function by interfering with the regulation of development, differentiation, and homing of IgA-producing cells. Resistance to bacterial, viral and fungal pathogens is greatly reduced after trichothecene exposure in several animal models. The LD_{50} of Salmonella typhimurium was reduced by 10,000 times in mice fed a diet containing 1 μg/g deoxynivalenol. Ochratoxin inhibits killer cell activity and allows increased growth of transplanted tumour cells in mice (35). Patulin reduced the microbicidal activity of mouse peritoneal macrophages in vitro (36). Oral exposure to the trichothecene T-2 increased the sensitivity of mice to i.p. injections of endotoxin (37).

The last piece of data that supports the theory that chronic exposure to toxigenic molds is of special interest comes from recent epidemiological studies. Studies of the respiratory health of 4,100 children from six cities in the northeast U.S.A. were recently published. These demonstrated that the presence of mold and dampness in the homes were correlated to several respiratory symptoms as well as a number of non-respiratory symptoms. The effect is of similar dimension to parental smoking. Further studies appear to show that the correlation lies with non-phylloplane molds (22,38). A much larger study of ca. 15,000 children from 30 communities in Canada came to similar conclusions. In this study however, the data demonstrated that allergy was not a key factor. The authors concluded that a non-allergenic mechanism was involved (39,40).

These epidemiological results suggest that mold exposure is an important effector of public health. They also strongly suggest that mildly xerophillic, toxigenic penicillia and aspergilli that can dominate the dust mycoflora need to be considered as a more likely "cause" than the phylloplane molds.

Mold volatiles have been suggested as contributing to the health effects (7,28,41). Volatiles of Paecilomyces varioti have been demonstrated to be cytotoxic (42). The principal volatile of molds, ethanol, has been detected in indoor air in an analysis of volatile organic compounds by

GC-MS. The room was found to have significant fungal contamination (Walkinshaw & Miller, unpublished data). It is not known whether fungal volatiles contribute to any health effects as detected in the above-noted epidemiological studies.

Regardless of mycotoxins, fungal spores contain another class of low-molecular weight compounds, β-1,3-glucans. These have been recently shown to have a number of effects on pulmonary macrophages that are in some respects comparable to those elicited by bacterial endotoxin (43). Inhalation exposure to the spores of the mildly xerophillic, toxigenic "indoor molds" will entail: (a) exposure to allergens, (b) exposure to β-1,3-glucans and (c) exposure to the toxic metabolites (mycotoxins) of the fungi involved. The following section will discuss what could be expected from inhalation exposure to spores of toxigenic molds.

FUNGAL SPORES AND THE PULMONARY MACROPHAGE

The inhalation of particulate matter occurs approximately according to figure 2 (after 44). A relatively high percentage of particles enter the gas exchange tissue of the lungs. Pulmonary alveolar macrophages (PAM) are primarily responsible for the clearance of insoluble particles. The population of these cells is maintained in a steady state although it will increase with increased exposure to particles including fungal spores, bacterial cells, plant materials, insect parts and excreta. At high particle burdens of inert or biological particles, alveolar cells become overloaded and the particles are not cleared (45).

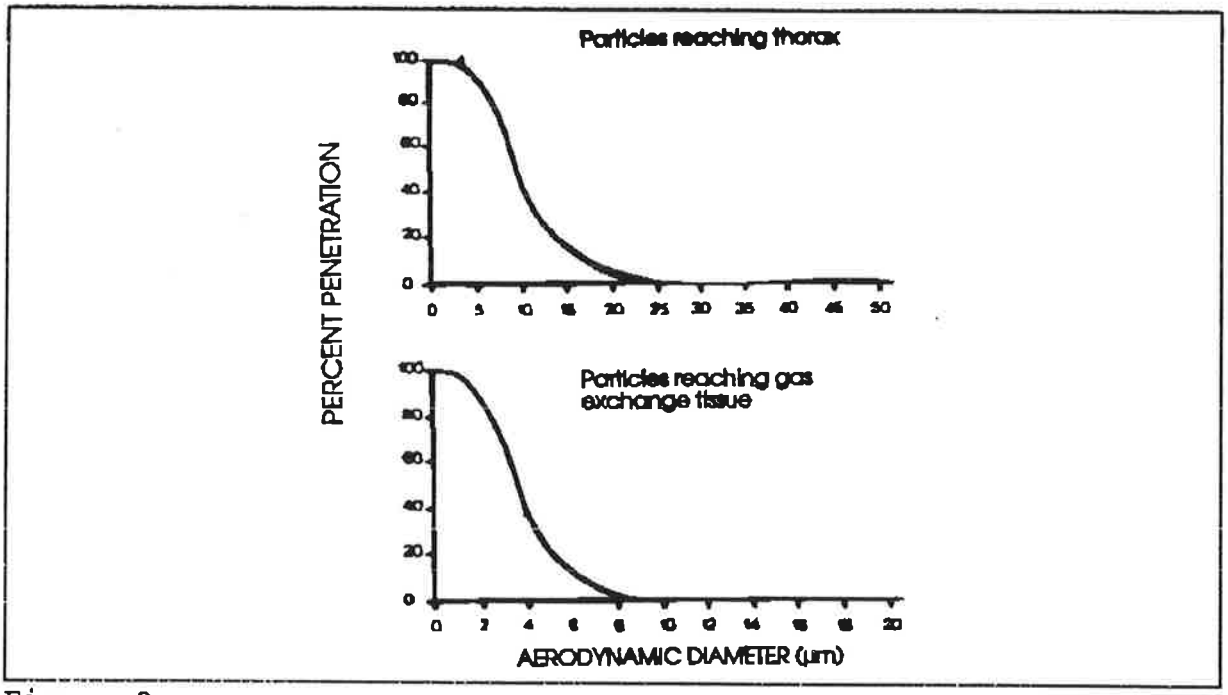

Figure 2

As noted above, fungal spores contain allergens, β-1,3-glucans and, in toxigenic species, various low molecular weight compounds called mycotoxins. The biological responses to this mixture will be multifactorial and much more complex than the "simplistic antigen-antibody-complement-mediated process" generally invoked (25). Figure 3 illustrates the complex cascade of events that can operate in normal PAM (25).

PAM and immune system response to β-1,3-glucans is only partially understood. It appears that exposure causes inflammation reactions in lymphocytes affecting lymphocyte mitogenicity,

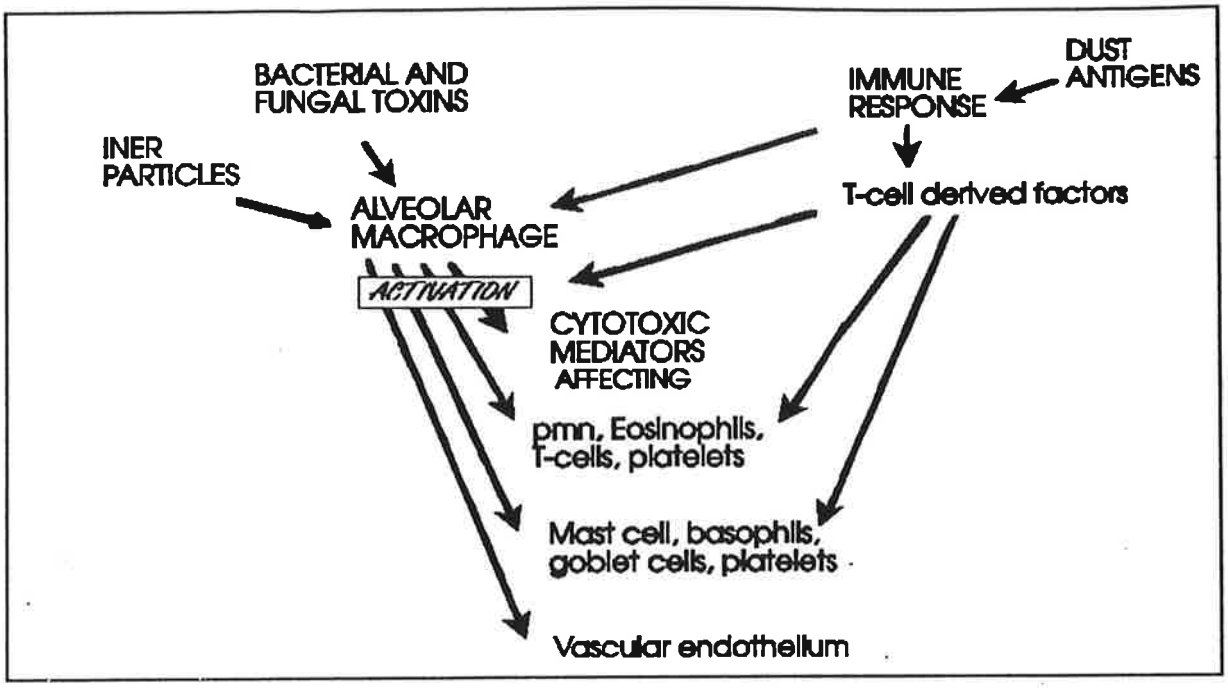

Figure 3

affects interleukin I secretion (via T-cells) and stimulates bacterial and tumour defence. Fungal glucan decreases phagocytosis and decreases PAM numbers (43).

As noted above, systemic exposure to fungal toxins has an array of effects on humans and animals. Additional to the toxic and immunological effects noted above, systemic exposure has been reported to affect PAM. Small oral doses of aflatoxin reduced phagocytosis of A. fumigatus spores in rabbit alveolar macrophages (46). From in vitro experiments, the deposition of these toxins in the lung predicts other effects on PAM. Patulin interferes with transcription in RNA synthesis and causes breaks in DNA strands. It is toxic and carcinogenic in rats. Patulin inhibited phagocytosis in alveolar macrophage cells at 10^{-7} M possibly by interfering with the cell membrane (47). Penicillic acid is toxic, carcinogenic in rats and is cytotoxic, inhibiting mitosis. Phagocytosis in alveolar macrophages is inhibited at 10^{-5} M; the mechanism is unresolved (48).

The trichothecene T-2 was shown to affect phagocytosis of Staphylococcus aureus at 10^{-7} M. Macrophage inactivation was found to be due to the lymphocyte mediators as opposed to the mitogens. Macrophage activation was inhibited by T-2 toxin as was the production of macrophage monokines such as interleukin I. Trichothecenes such as T-2 are potent inhibiters of peptidyl transferase and this property explained the toxicity to alveolar macrophage cells (47).

CONCLUSION

Holt (25) and Stober et al. (45) discuss the complex "cascade" of events that are triggered by inhalation of biotic and abiotic particles that can be present in indoor air and occupational settings. Many "indoor molds" are toxigenic fungi, the spores of which contain complex mixtures of low molecular weight toxins (e.g. Penicillium species, 49). The inhalation of spores of toxigenic fungi containing allergens, β-1,3-glucan and low molecular weight toxins would interfere with normal macrophage functioning and a variety of effects on immune function would ensue (figure 3).

Flannigan (4) pointed out that no clear association has been made between objective mold measures and wheeze and asthma symptoms. However, from the two large epidemiology studies carried out in the U.S.A. and Canada discussed above, two facts remain. A variety of respiratory and non respiratory symptoms have been linked to the presence of mold and dampness. The Canadian studies indicate that a non allergenic mechanism is important. Increased exposure to fungal spores in air have been shown to be linked to sick building symptoms unrelated to strictly respiratory symptoms including tiredness and headache (43). The cascade of immunological effects described by Holt (25) is also linked to central nervous system function.

Unusual exposure to fungal spores alone and in combination with biotic and abiotic factors can be expected to promote viral and bacterial disease and decrease general well-being. There is much research underway to clarify these complex issues. I have no doubt that the facts available now justify action to keep airborne mycoflora to the norm defined in figure 1 i.e. the indoor mycoflora should be qualitatively the same and quantitatively lower compared to that outdoors.

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