

## MOLD AND MYCOTOXINS: EFFECTS ON THE NEUROLOGICAL AND IMMUNE SYSTEM IN HUMANS

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### **Introduction:**

The potential harmful effects of exposure to molds in inhabited buildings were recognized in early Biblical times. In the Old Testament (King James Version, Oxford 1888 Edition, King James version, Chapter XIV: Verses 34 thru 47) Leviticus put forth a detailed protocol for the remediation of contaminated structures, including the destruction of dwellings and personal belongings if remediation failed. Presently, it is recognized that water intrusion into buildings leads to amplification of molds (Andersson *et al*, 1997; Gravesen *et al*, 1999; Hodgson *et al*, 1998; Jaakkola *et al*, 2002; Johanning *et al* 1996; Nielsen, 2003; Peltola *et al*, 2001), which often requires remediation.

Fungal fragments occur in indoor air as biocontaminants (Burge, 1990; Gorny *et al*, 2002) Potentially toxic and immunogenic by-products of fungi and molds include mycotoxins (Croft *et al*, 1986; Johanning *et al*, 2002; Nielsen *et al*, 1999; Nieminen *et al*, 2002; Tuomi *et al*, 1998, 2000); 1, 3-alpha-D-glucans (Andersson *et al* 1997), extracellular polysaccharides (EPS) (Duowes, *et al* 1999; Notermans *et al*, 1988; Wouters *et al*, 2000); exodigestive enzymes (Monod, *et al* 2002; and solvents (Claeson *et al*, 2002). In addition, trichothecenes, ochratoxin A, sterigmatocystin, and other mycotoxins have been identified in ventilation duct dust and in the air in buildings where occupants have experienced adverse health effects related to mold exposure (Croft *et al*, 1986; Englehart *et al*, 2003; Jarvis, 2002; Johanning *et al*, 2002; Nieminen *et al*, 2002; Skaug *et al*, 2000; Smoragiewicz *et al*, 1993; Toumi *et al*, 1998). The worst case scenario appears to be repeated episodes of water damage that promote fungal growth and mycotoxin production, followed by drier conditions leading to release of spores and hyphal fragments (Nielsen, 20003).

Occupants of affected structures develop multiple organ symptoms, and have adverse effects of the upper and lower respiratory system, central and peripheral nervous system, skin, gastrointestinal tract, kidneys and urinary tract, connective tissue, and the musculoskeletal system (Anyanwu *et al*, 2003; Croft *et al*, 1986; Johanning *et al*, 1996, Gray *et al*, 2003; Gunnbjornsdottir *et al*, 1998; Hodgson *et al*, 1998; Jaakkola *et al* , 2002; Kilburn, 2002, Savilahti *et al*, 2000) Human illness can result via one or all of the following: 1) mycotic infections (mycoses) (Anaissie *et al*, 2002; Euker *et al*, 2001; Fraser, 1993; Grossi *et al*, 2000); 2) fungal rhinosinusitis (Braun *et al*, 2003; Ponikau *et al*, 1999; Thrasher and Kingdom, 2003); 3) IgE mediated sensitivity and asthma (Barnes *et al*, 2002; Lander *et al*, 2001; Zuriek *et al*, 2002); 4) hypersensitivity pneumonitis and related inflammatory pulmonary diseases (Erkinjuntti-Pekkanene, *et al* 1999; Ojanen, 1992; Patel *et al*, 1999; Sumi *et al*, 1994); 5) Cytotoxicity (Desai *et al*, 2002; Gareis, 1995; Jones *et al*, 2002; Nagata *et al*, 2001; Poapolathep *et al*, 2002); 6) immune suppression/modulation (Berek *et al*, 2002; Bondy and Petska, 2000; Jakab *et al*, 1994); 7) mitochondrial toxicity (Hoehler, *et al* 1997; Niranjana *et al*, 1982; Pace, 1983, 1988; Sajan *et al*, 1997; Wei *et al*, 1984);

8) carcinogenicity (Dominguez-Malagon and tan-Graham, 2001; Schwartz, 2002); 9) nephrotoxicity (Anyanwu *et al*, 2003, Pfohl-leszkowicz, *et al*, 2002); and 10) the formation of nuclear and mitochondrial DNA adducts(Hsieh and Hsieh, 1993; Petkova-Bochatrova, *et al*, 1998; Pfohl-Leszkowicz, *et al*, 1993). Finally, in the infectious state, molds secrete exodigestive enzymes (EDS) that cause tissue destruction, angioinvasion, thrombosis, infarction and other manifestations of mycosis (Ebina *et al*, 1985; Kudo, *et al*, 2002; Kordula *et al*, 2002; Monod *et al*, 2002; Ribes *et al*, 2000; Vesper *et al*, 2000).

The pathological and inflammatory conditions associated with *Stachybotrys chartarum* in infants with pulmonary hemosiderosis have been characterized. *S. chartarum* isolated from the lungs of an affected infant produced a hemolysin (stachylysin), siderophore, and a protease (stachyrase Vesper *et al*, 2000, Kordula *et al* 2002). Stachylysin has also been demonstrated in the serum of adults ill from a building-related exposure (Van Emon, *et al*, 2003). In rodents, its presence has been demonstrated by an immunocytochemical method following installation of *S. chartarum* spores into lungs. The hemolysin increases in concentration from 24 to 72 hours following instillation of spores, indicating that production/release is a relatively slow process (Gregory *et al*, 2003). In addition strains of *S. chartarum* produce different quantities of toxic trichothecenes (Jarvis *et al*, 1998). In an earthworm model Stachylysin increased the permeability of blood vessels, causing leakage through the vessel endothelium and walls (Vesper and Vesper, 2002). Additionally, pathology may result from the interference of pulmonary surfactant synthesis by *S. chartarum* spores and isosatratoxin-F in juvenile mice. Ultrastructural changes in Type II alveolar cells, with condensed mitochondria, increased cytoplasmic rarefaction, and distended lamellar bodies with irregularly shaped lamellae, have been observed following exposure to *S. chartarum* (Mason *et al*, 1998, 2001; McCrae *et al*, 2002; Rand *et al*, 2001). Thus, hemolysins, siderophores and proteases also have an important role in the pathogenesis of mold infections.

Recognizing the complexity of health problems associated with multiple mold exposure, we have previously reported a multi-center investigation of patients with chronic health complaints from exposure to multiple colonies of indoor fungi and molds. We utilized detailed health and environmental history gathering questionnaires, environmental monitoring data, physical examination, pulmonary function testing protocols, routine clinical chemistries, measurements of lymphocyte phenotypic markers (on T, B and NK cells), antibodies to molds, mycotoxins, neuronal antigen antibodies, leukocyte apoptosis, neurocognitive testing, 16 Channel quantitative EEGs (QEEG), nerve conduction studies (NCS), brainstem auditory evoked potentials (BAER), visual evoked responses (VER)

### **Conclusion:**

Forgacs noted in 1962 that mold mycotoxicosis was called “the neglected disease.” The manifestations and disorders in humans caused by molds and mycotoxins continues to be overlooked or unnoticed by many physicians. Each year studies continue to be published throughout the world in medical and scientific literature elucidating and explaining the pathological processes and biomechanisms by which exposure to molds and mycotoxins cause sickness in humans. We have described in this chapter the most recent neuroimmune mechanisms of disease process in humans of molds and mycotoxins. The exact biological and chemical actions through which these mechanisms unfold is not completely understood. However, molds do produce metabolites (mycotoxins, solvents) and antigenic materials (spores, hyphae, extracellular polysaccharides, and enzymes), which are toxic (mycotoxins) and

or cause immunologic responses (antigens). Science and medicine should continue its work in these areas and bring about the much-needed change from the “the neglected disease” to “the accepted disease.”

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