

Epidemics of mold poisoning past and present

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Abstract

Molds are ubiquitous throughout the biosphere of planet earth and cause infectious, allergic, and toxic diseases. Toxic diseases arise from exposure to mycotoxins produced by molds. Throughout history, there have been a number of toxic epidemics associated with exposure to mycotoxins. Acute epidemics of ergotism are caused by consumption of grain infested by fungi of the genus *Claviceps*, which produce the bioactive amine ergotamine that mimics the neurotransmitters norepinephrine, serotonin, and dopamine. Acute aflatoxin outbreaks have occurred from ingestion of corn stored in damp conditions that potentiate growth of the molds of the species *Aspergillus*. Contemporary construction methods that use cellulose substrates such as fiber board and indoor moisture have caused an outbreak of contaminated buildings with *Stachybotrys chartarum*, with the extent of health effects still a subject of debate and ongoing research. This article reviews several of the more prominent epidemics and discusses the nature of the toxins. Two diseases that were leading causes of childhood mortality in England in the 1970s and vanished with changing dietary habits, putrid malignant fever, and slow nervous fever were most likely toxic mold epidemics.

Keywords

Mold, fungi, sick building syndrome, allergy, asthma, poisonings, epidemics, ergotism, ergotamine, trichothecenes, *Stachybotrys*, *Aspergillus*, aflatoxins

Introduction

Molds are ubiquitous throughout the biosphere and cause diseases in humans and other mammals through several mechanisms. Molds produce mycotoxins that can poison humans through ingestion, inhalation, and dermal contact. Mold spores are allergens that can cause asthma and other allergic diseases. Molds are immunogens that can cause hypersensitivity pneumonitis. Molds are microorganisms that can cause infections, particularly in immunocompromised hosts. Throughout recorded history, there have been disease epidemics caused by or suspected of being caused by exposure to mycotoxins. Health problems associated with molds were recognized in biblical times (Heller et al., 2003; Leviticus, 1995). This review will discuss several prominent epidemics associated with mold exposures.

Ergot

Ergot is a genus of fungi *Claviceps* that is a parasite on grain. There are more than 50 known species. The

mycotoxin produced by ergot is known as ergotamine. Related compounds can be produced in variable amounts depending on growing conditions. The toxic mechanism of ergotamine is due to neurotransmitter mimicry. By this, we mean that ergotamine mimics the action of the neurotransmitters dopamine, serotonin, and norepinephrine by binding to their receptors. One of the major effects of ergotamine is vasoconstriction, a property that gives ergotamine and its derivatives efficacy in the treatment of migraine headaches and postpartum hemorrhage. It is also used in the induction of labor.

Ergotism is defined as a toxic syndrome related to the ingestion of ergotamine, which arises from eating

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grain infested with ergot. Peripheral effects of ergotism are hypertension and bradycardia. Vasoconstriction can lead to angina, gangrene, and hemorrhagic skin vesicles and bullae. Infarctions of heart, mesentery, and kidney have been reported in outbreaks of ergotism. Neurological effects include agitation, hallucinations, headaches, miosis, nausea, vomiting, seizures, facial twitching, and stroke. Iatrogenic ergotism can arise from medical mishaps (Bertho et al., 1969).

Epidemics of ergotism have been recorded as long ago as 600 BC in Assyria (Dale, 1906). Epidemics in the middle ages include an outbreak in Quitania, France, in 994 AD. Ergotism is thought to be a cause of an outbreak of illness in Salem, MA, in 1692, in which victims were thought to be witches and were executed (Matossian, 1982).

In Pont Saint Esprit (Bridge of the Holy Spirit) in France, there was an outbreak of illness on 15 August 1151, in which 200 people in a village of 4000 were affected. Victims suffered hallucinations and were described as running crazed in the street. Those afflicted were described as writhing in agony. Vasoconstriction led to the loss of fingers, toes, and in extreme cases hands and feet. The outbreak is attributed to the ingestion of rye flour contaminated with ergot.

Ergotism is sometimes known as St Anthony's fire. St Anthony founded a monastic practice, the Order of Hospitaliers of St Anthony, in Grenoble, France. He advocated ascetic practices including fasting. Victims of ergotism traveled to Grenoble for treatment. It may be that fasting led to the avoidance of eating contaminated grain, with resolution of symptoms (Boucharlat et al., 1977; Kahn, 1998).

Slow nervous fever

Slow Nervous Fever was a disease that occurred in epidemics in England during the period 1650 to 1740. This disease and its association with mycotoxins have been analyzed by Matossian. Clinical manifestations included hot and cold sensations, headaches, dizziness, depression, sensitivity to light and noise, nausea, emesis, rapid pulse, and torpor. The disease progressed to delirium, cold sweats, difficulty swallowing with gulping and choking, and cold extremities. This disease was the leading cause of child mortality during its heyday. It affected families and attacked entire cities. It was more prominent during periods of cold moist weather. There were similar

epidemics described in France and Germany during the same time period. The change from rye to wheat was associated with a decrease in childhood mortality and an increase in population. It is impossible to know at this time what the cause of slow nervous fever is, but the evidence favors mold infestations of rye during cold moist weather.

Putrid malignant fever

Another epidemic analyzed by Matossian (1981) struck England in the period from 1700 to 1750. Like slow nervous fever, this malady struck children. The illness progressed through three phases. The early phase was characterized by headache, dizziness, nausea, emesis, depression, weakness, labored breathing, foul breath, and a peppery sensation in the mouth. This was followed by a middle phase, with emesis of black matter, dark foul-smelling urine, hemorrhagic skin lesions, cold sweats, dysphagia, and esophageal ulcers. The late phase brought bloody diarrhea, intestinal ulcers, ecchymoses, and cold extremities. Putrid malignant fever was associated with warm moist winters, low marshy land, scarcities of food, and, in particular, grain and long sea voyages in wet weather. Children were more likely to be affected than adults. Though the etiology of putrid malignant fever is unknown, insights into its possible origin are given by epidemics of alimentary toxic aleukia in Russia in 1942 and 1947 which have been traced to grain contamination with *Fusarium tricinctum*, a mold that manufactures the trichothecene or T-2 mycotoxins.

Alimentary toxic aleukia also has three phases; with phase one having a peppery sensation in the mouth after eating grains such as wheat, rye, oats, buckwheat, barley, corn, or millet. There is nausea, vomiting, and diarrhea during this early stage. Stage two was an asymptomatic period that could last from 2 to 8 weeks. The final stage manifested fever, hemorrhage, skin lesions, a putrid smell, and neurological effects. Deaths were associated with throat swelling or respiratory effects. Alimentary toxic aleukia struck families, with fatalities more common at the extremes of life. The mortality rate was almost 50% in children less than 10 years of age. Like putrid malignant fever, alimentary toxic aleukia was associated with food shortages and low marsh lands after a mild winter. Both putrid malignant fever and slow nervous fever declined with changes of diet—a switch from potato to grain in the first case and a change from rye to other

grains in the second. In both cases, decline in these illnesses were associated with improvements in childhood mortality and population growth.

Acute aflatoxin poisoning

Aflatoxins are a family of mycotoxins produced by *Aspergillus* species that contaminate grains and other foods. They are potent carcinogens associated with hepatocellular carcinoma (Peraica et al., 1999). Foods susceptible to contamination are grains, tree nuts, peanuts, and oil seeds. Milk from cows whose feed contains aflatoxins can also be contaminated. Acute and chronic aflatoxin poisonings can occur with different manifestations. Acute aflatoxin poisoning occurs when high doses are ingested, which leads to acute hepatic necrosis. Other symptoms include fever, emesis, hemorrhaging, edema, and alterations in digestion and the absorption of nutrients. Acute poisonings can be fatal. Outbreaks of acute aflatoxin poisoning occurred in the eastern and central provinces of Kenya in January to June of 2004 (Nyikal et al., 2004). The epidemic was initially identified as an outbreak of jaundice. The fatality rate was very high. Very high levels of aflatoxin B1 was found in maize stored in damp sheds. Of 31 samples collected in households with victims, 15 had between 20 ppb and 8000 ppb of aflatoxin B1. Of 342 samples collected from maize products for sale in markets, 182 had greater than 20 ppb of aflatoxin B1. In three locations, samples were found with greater than 1000 ppb. The combination of clustering in families with high levels of aflatoxin in food supplies, and illness consistent with acute aflatoxin poisoning, and deaths of animals eating the same foods support the diagnosis of acute aflatoxin poisoning in this epidemic.

A documented epidemic of acute aflatoxicosis occurred in northwest India in 1974 (Krishnamachari et al., 1975a,b). Victims suffered rapidly progressive jaundice, high fevers, emesis, pain, and edema. Hepatomegaly was evidenced on examination. There were 108 fatalities from a total of 397 illnesses. Aflatoxin levels of 0.25 to 15 mg/kg were found on corn. Dogs in the region died from the illness. Pathological features were periportal hepatic fibrosis, bile duct proliferation, and gastrointestinal hemorrhaging. Those who survived the acute poisoning were disease free 10 years later. As similar outbreak in Kenya in 1981 (Ngindu et al., 1982) had 20 hospital admissions, a case fatality rate of 60%, with aflatoxin intake calculated at 38 $\mu\text{g}/\text{kg}$ of body weight in the victims.

One intentional ingestion in a laboratory worker who attempted suicide, has been reported. After ingesting 12 $\mu\text{g}/\text{kg}$ for 2 days, the worker developed a rash, nausea, and headache but recovered without sequel (Willis et al., 1980).

Hurricanes and mold epidemics

Extensive flooding from Hurricane Floyd that hit coastal North Carolina in 1999, Hurricane Rita that hit the gulf coast in 2004, and Hurricane Katrina that hit the Louisiana-Mississippi coast in 2004 led to widespread anecdotal reports of illness related to mold exposures in flooded buildings, but there is a paucity of documentation of the health effects associated with these exposures. An inspection of 112 buildings damaged by flood waters after Hurricanes Rita and Katrina found that mold growth was present in 45% of 112 inspected homes, with heavy mold growth in 17% of homes. Homes with flood levels greater than 6 feet were more likely to be affected. The most common species found were *Aspergillus* and *Penicillium*. Proper respiratory protection was lacking in those exposed, but health effects were not adequately studied (Centers for Disease Control and Prevention [CDC], 2006b).

A study of indoor air of homes flooded in Louisiana by Hurricane Katrina in 2005 found mold spore counts to be double those of non-flooded homes, with *Cladosporium* and *Aspergillus* being the most common species found. *Stachybotrys* species were found in some homes. Endotoxin concentrations did not differ between flooded homes, non-flooded homes, and outdoor air (Solomon et al., 2006).

When Hurricane Floyd hit coastal North Carolina in 1999, there was an increase in hospital admission for asthma. A Centers for Disease Control study of New Orleans firefighters and police officers motivated by reports of an increased number of illnesses after Hurricane Katrina found that upper respiratory symptoms of head and sinus congestion and throat and nasal irritation were very common. Skin rash was reported by 54% of police officers and 49% of firefighters. Neither the etiology nor extent to which mold contributed to these symptoms was determined (CDC, 2006a). After Hurricane Katrina, there was an outbreak of acute respiratory illnesses that increased with time over a 3-week period (Williams et al., 2006), though there is no data on specific etiologies. It can be concluded that flooding after hurricanes leads to visible mold growth in flooded buildings and increases in respiratory and dermal

illnesses, but the extent to which molds contribute to these illnesses has not been adequately assessed.

Stachybotrys chartarum

S. chartarum is a mold that is found in water-damaged homes. It grows on high cellulose and low nitrogen content gypsum board, fiberboard, and other substrates, including compostable pots (Dill et al., 2004). Construction techniques now in use, with large amounts of fiberboard and gypsum board and moisture arising from leaky roofs, water pipes, and condensation, have produced an epidemic of *Stachybotrys* contamination of buildings. While this contamination is not controversial, the extent of the health consequences has the usual naysayers about emerging environmental-related illness. They produced position statements that there is insufficient evidence at this time for an association to be made between mycotoxins and building-related illnesses (Bush et al., 2006; Hardin et al., 2003). A contrary statement documenting the evidence has been produced (Curtis et al., 2004). Anecdotally, chemically sensitive individuals report illnesses related to the odors associated with moldy basements and similar damp environments that are due to volatile mycotoxins, suggesting individual susceptibility may play a role in adverse reactions to airborne mycotoxins.

Hodgson and Dearborn (2002) have pointed out that though human evidence of an association between mycotoxins and human health is anecdotal and based on case reports and series, the standards generally regarded as evidence in environmental medicine are met, including controlled studies in animals, the development of animal models with diseases that parallel the human experience, and studies of the mycotoxins at subcellular levels (Hodgson and Dearborn, 2002 and references therein).

S. chartarum produces the T2 or tricothecene mycotoxins (Holstege et al., 2007) that, when concentrated, produce a deadly cytotoxic syndrome by shutting down protein synthesis. Severe acute poisoning is characterized by multiple organ system failure and necrosis of bowel and airway, bone marrow dysfunction with pancytopenia, and cardiovascular collapse. Severe irritation of the skin, mucous membranes of the oral pharynx and respiratory tract, and conjunctiva occurs, which is somewhat unique among biological toxins relative to chemical toxins. While this devastating toxicity is not seen among inhabitants of moisture-damaged buildings, the presence of

S. chartarum in buildings, sometimes in association with *Aspergillus* species or other molds, has been associated with asthma, hypersensitivity pneumonitis, and the constellation of respiratory and neurological symptoms associated with poorly ventilated buildings (Cooley et al., 1998; Hodgson and Dearborn, 2002; Jarvis et al., 1998; Johanning et al., 1996; Straus and Wilson, 2008, 2009). Tricothecene mycotoxins have been detected in the sera of individuals from contaminated buildings by ELISA assays (Brasel et al., 2004).

A cluster of cases of pulmonary hemorrhagic and hemosiderosis occurred in a hospital nursery in Cleveland during the period November 1994 to January 1995 and was investigated by the Centers for Disease Control. It was concluded that heavy mold growth in the building was responsible for the outbreak (CDC, 1997). This finding was retracted after internal and external reviews of the investigation, which cited the quality of evidence insufficient to conclude an association (CDC, 2000). A growing body of evidence supports that *S. Charatrum* may be the cause of epidemics and isolated cases of pulmonary hemorrhage and hemosiderosis in infant lungs. An updated report did find an association, and infants who relapsed after returning home were more likely to have water damage in their homes (CDC, 2000 update). A case of pulmonary hemorrhage in an infant exposed to *Stachybotrys* has been reported in Delaware (Weiss and Chidekel, 2002). A strain of *S. chartarum* was isolated from the lung of a pulmonary hemorrhage and hemosiderosis patient in Texas, which produced toxins with biological plausibility for producing pulmonary hemorrhage and hemosiderosis (Vesper et al., 2000a). *S. Charatrum* was found in the home of a 1-month-old infant in Kansas City, who developed pulmonary hemorrhage and hemosiderosis (Flappan). The mycotoxin stachylysin is more likely to be found in strains of *S. Charatrum* isolated from homes of children with pulmonary hemorrhage and hemosiderosis than strains from control homes (Vesper et al., 2000b), suggesting a role of this mycotoxin that produces vascular leak in an animal model.

Conclusion

Throughout history, mold infestations have been recognized as a cause of disease epidemics, and in many cases, the causative mycotoxins have been isolated and studied. Though controversy exists about the role mycotoxins play in current disease epidemics

associated with poorly ventilated buildings, sensitivity to indoor air, and airway inflammation and hemorrhage, there is a growing body of evidence that mandates open inquiry into these agents and their role in diseases.

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