

Diseases Linked to Molds

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Diseases Caused by Molds in Humans

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By Peraica, M.; Radic, B.; Lucic, A.; Pavlovic, M. , September 1, 1999

Mycotoxicoses are diseases caused by mycotoxins, i.e. secondary metabolites of molds. Although they occur more frequently in areas with a hot and humid climate, favorable for the growth of molds, they can also be found in temperate zones. Exposure to mycotoxins is mostly by ingestion, but also occurs by the dermal and inhalation routes. Mycotoxicoses often remain unrecognized by medical professionals, except when large numbers of people are involved. The present article reviews outbreaks of mycotoxicoses where the mycotoxic etiology of the disease is supported by mycotoxin analysis or identification of mycotoxin-producing fungi. Epidemiological, clinical and histological findings (when available) in outbreaks of mycotoxicoses resulting from exposure to aflatoxins, ergot, trichothecenes, ochratoxins, 3-nitropropionic acid, zearalenone and fumonisins are discussed.

Introduction

Mycotoxins are secondary metabolites of molds that exert toxic effects on animals and humans. The toxic effect of mycotoxins on animal and human health is referred to as mycotoxicosis, the severity of which depends on the toxicity of the mycotoxin, the extent of exposure, age and nutritional status of the individual and possible synergistic effects of other chemicals to which the individual is exposed. The chemical structures of mycotoxins vary considerably, but they are all relatively low molecular mass organic compounds. The untoward effect of molds and fungi was known already in ancient times. In the seventh and eighth centuries BC the festival "Robigalia" was established to honour the god Robigus, who had to be propitiated in order to protect grain and trees. It was celebrated on 25 April because that was the most likely time for crops to be attacked by rust or mildew.

In the Middle Ages, outbreaks of ergotism caused by ergot alkaloids from *Claviceps purpurea* reached epidemic proportions, mutilating and killing thousands of people in Europe. Ergotism was also known as ignis sacer (sacred fire) or St Anthony's fire, because at the time it was thought that a pilgrimage to the shrine of St. Anthony would bring relief from the intense burning sensation experienced. The victims of ergotism were exposed to lysergic acid diethylamide (LSD), a hallucinogen, produced during the baking of bread made with ergot-contaminated wheat, as well as

to other ergot toxins and hallucinogens, as well as belladonna alkaloids from mandragora apple, which was used to treat ergotism. While ergotism no longer has such important implications for public health, recent reports indicate that outbreaks of human mycotoxicoses are still possible. Some mycotoxicoses have disappeared owing to more rigorous hygiene measures. For example, citreoviridin-related malignant acute cardiac beriberi ("yellow rice disease" or shoshin-kakke disease in Japanese) has not been reported for several decades, following the exclusion of moldy rice from the markets. Citreoviridin is a metabolic product of *Penicillium citreonigrum*, which grows readily on rice during storage after harvest, especially in the colder regions of Japan. Another mycotoxicosis not seen for decades is alimentary toxic aleukia, common in the 1930s and 1940s in the USSR. This disease was caused by trichothecenes produced by *Fusarium* strains on unharvested grain.

General interest in mycotoxins rose in 1960 when a feed-related mycotoxicosis called turkey X disease, which was later proved to be caused by aflatoxins, appeared in farm animals in England. Subsequently it was found that aflatoxins are hepatocarcinogens in animals and humans, and this stimulated research on mycotoxins. There is a long history of the use of certain molds in the production of cheese and salami and in the fermentation of beer and wine. Molds are also used in the production of drugs (antibiotics). The classification of mold metabolites as antibiotics or mycotoxins is based on their toxicity or beneficial effect in treating diseases. Some mold metabolites that were initially considered to be antibiotics (e.g. citrinin) were subsequently found to be highly toxic, and are currently classified as toxins. Ergot alkaloids are still used, *inter alia*, in the treatment of parkinsonism, as prolactin inhibitors, in cerebrovascular insufficiency, migraine treatment, venous insufficiency, thrombosis and embolisms, for the stimulation of cerebral and peripheral metabolism, in uterine stimulation, as a dopaminergic agonist.

The toxic effects of mycotoxins (e.g. ochratoxins, fumonisins, zearalenone, etc.) are mostly known from veterinary practice. Mycotoxicoses, which can occur in both industrialized and developing countries, arise when environmental, social and economic conditions combine with meteorological conditions (humidity, temperature) which favor the growth of molds.

Involvement of mycotoxins in disease causation should be considered in instances when a disease appears in several persons, with no obvious connection to a known etiological agent, such as microorganisms. Given current trade patterns, mycotoxicoses resulting from contaminated food, locally grown or imported, could occur in developing and developed countries alike. Strict control of food and feed and appropriate public health measures are therefore of considerable importance in reducing the risks to human and animal health.

This review covers only the human aspects of the untoward effects of mycotoxins. However, owing to the frequent nonspecific effects of mycotoxin involvement, the results of animal experiments are useful for understanding possible effects on humans. Since review articles and books are available dealing with specific topics such as the chemistry, analytical procedures, metabolism, and economic aspects of mycotoxins (9-18), these aspects of mycotoxin toxicology are not presented here. Mycotoxicoses are usually insufficiently treated in medical textbooks and are not covered in curricula of many medical schools. The aim of this article is to summarize current understanding of the clinical aspects mainly of mycotoxicoses in humans, and to stress the importance of this class of naturally occurring toxins.

Ergot

Ergot is the common name of the sclerotia of fungal species within the genus *Claviceps*, which produce ergot alkaloids. The sclerotium is the dark-coloured, hard fungal mass that replaces the seed or kernel of a plant following infestation. Ergot alkaloids are also secondary metabolites of some strains of *Penicillium*, *Aspergillus* and *Rhizopus* spp.

The ca. 40 ergot alkaloids isolated from *Claviceps* sclerotia can be divided into three groups:

- derivatives of lysergic acid (e.g. ergotamine and ergocristine);
- derivatives of isolysergic acid (e.g. ergotaminine);
- derivatives of dimethylergoline (clavines, e.g. agroclavine).

The source of the ergot strongly influences the type of alkaloids present, as well as the clinical picture of ergotism. *Claviceps purpurea* produces ergotamine-ergocristine alkaloids, which cause the gangrenous form of ergotism because of their vasoconstrictive activity. The initial symptoms are oedema of the legs, with severe pains. Paraesthesias are followed by gangrene at the tendons, with painless demarcation. The last-recorded outbreak of gangrenous ergotism occurred in Ethiopia in 1977-78; 140 persons were affected and the mortality was high (34%).

The other type of ergotism, a convulsive form related to intoxication with clavine alkaloids from *Claviceps fusiformis* was last seen during 1975 in India when 78 persons were affected. It was characterized by gastrointestinal symptoms (nausea, vomiting and giddiness) followed by effects on the central nervous system (drowsiness, prolonged sleepiness, twitching, convulsions, blindness and paralysis). The onset of symptoms occurred 1-48 hours following exposure; there were no fatalities.

Ergotism is extremely rare today, primarily because the normal grain cleaning and milling processes remove most of the ergot so that only very low levels of alkaloids remain in the resultant flours. In addition, the alkaloids that are the causative agents of ergotism are relatively labile and are usually destroyed during baking and cooking.

Aflatoxins

Aflatoxins occur in nuts, cereals and rice under conditions of high humidity and temperature and present a risk to human health that is insufficiently recognized. The two major *Aspergillus* species that produce aflatoxins are *A. flavus*, which produces only B aflatoxins, and *A. parasiticus*, which produces both B and G aflatoxins. Aflatoxins [M.sub.1] and [M.sub.2] are oxidative metabolic products of aflatoxins [B.sub.1] and [B.sub.2] produced by animals following ingestion, and so appear in milk (both animal and human), urine and feces. Aflatoxicol is a reductive metabolite of aflatoxin [B.sub.1].

Aflatoxins are acutely toxic, immunosuppressive, mutagenic, teratogenic and carcinogenic compounds. The main target organ for toxicity and carcinogenicity is the liver. The evaluation of epidemiological and laboratory results carried out in 1987 by the International Agency for Research on Cancer (IARC) found that there is sufficient evidence in humans for the carcinogenicity of naturally occurring mixtures of aflatoxins, which are therefore classified as Group 1 carcinogens, except for aflatoxin [M.sub.1], which is possibly carcinogenic to humans (Group 2B). Several outbreaks of aflatoxicosis have occurred in tropical countries, mostly among adults in rural populations with a poor level of nutrition for whom maize is the staple food. The clinical picture presented by cases indicated acute toxic liver injury, which was confirmed by morphological changes in liver autopsy specimens that were indicative of toxic hepatitis. Mortality rates in the acute phase were 10-60 %. At the end of one year, surviving patients had no jaundice, and most of them had recovered clinically.

A case of attempted suicide with purified aflatoxin [B.sub.1] is reported to have occurred in 1966 in the USA. A young woman ingested a total of 5.5 mg of aflatoxin [B.sub.1] over 2 days and, 6 months later, a total of 35 mg over 2 weeks. Following the first exposure, she was admitted to hospital with a transient, nonpruritic, macular rash, nausea and headache; the second time she reported nausea only. On both occasions, physical, radiological and laboratory examinations were normal and liver biopsies appeared normal by light microscopy. A follow-up examination 14 years later did not reveal any signs or symptoms of disease or lesions. These findings suggest that the hepatotoxicity of aflatoxin [B.sub.1] may be lower in well nourished persons than in experimental animals or that the latent period for turnout formation may exceed 14 years.

Aflatoxins have been detected in the blood of pregnant women, in neonatal umbilical cord blood, and in breast milk in African countries, with significant seasonal variations. Levels of aflatoxins detected in some umbilical cord bloods at birth are among the highest levels ever recorded in human tissue and fluids.

Aflatoxins have been suggested as an etiological factor in encephalopathy and fatty degeneration of viscera, similar to Reye syndrome, which is common in countries with a hot and humid climate. The clinical picture includes enlarged, pale, fatty liver and kidneys and severe cerebral oedema. Aflatoxins have been found in blood during the acute phase of the disease, and in the liver of affected children. However, use of aspirin or phenothiazines is also suspected to be involved in the etiology.

In tropical countries, clinically recognizable jaundice is frequent during the neonatal period. In a large investigation undertaken on 327 Babies with jaundice and 80 matching controls in Nigeria, it was found that the occurrence of glucose-6-phosphate dehydrogenase (G6PD) deficiency together with the presence of aflatoxins in the serum are significant risk factors for the development of neonatal jaundice.

The geographical and seasonal prevalences of aflatoxins in food and of kwashiorkor show a remarkable similarity. In several tropical countries, aflatoxins have been found more frequently and in higher concentration in liver specimens from children with kwashiorkor than in controls. Clinical investigation of aflatoxin elimination in children with kwashiorkor and marasmic kwashiorkor, who were fed an aflatoxin-free diet, proved that aflatoxins in these children are slowly eliminated. In several studies, aflatoxicol was found in the serum, liver, urine and stools of children with kwashiorkor and marasmic kwashiorkor, in contrast to marasmic and control children where this metabolite was not found. It is not clear whether this difference is causally related to kwashiorkor or is a consequence of the disease.

In recent studies, aflatoxins were found in the brain and lungs of children who had died from kwashiorkor and in control children who had died from various other diseases. It was suggested that the presence of aflatoxins in the brains of control children might be due to metabolic imbalance or to a failure in the excretory mechanisms of children with conditions such as measles (which in 25% of cases precedes kwashiorkor), renal failure, pyloric stenosis, gastroenteritis. Aflatoxins in the lungs were found in all children diagnosed to have pneumonia, irrespective of the presence of kwashiorkor. This could be due to a reduced clearing ability of the lungs in pulmonary diseases or to exposure via the respiratory route. In the Philippines, a study of the relationship between the presence of aflatoxin in the serum and urine of children and the outcome of acute lower respiratory infection failed to prove a correlation. However, aflatoxin [B.sub.1] was found in the lungs of one textile and two agricultural workers who died from pulmonary interstitial fibrosis. These individuals were probably occupationally exposed to aflatoxin [B.sub.1] via the respiratory route. Aflatoxin [B.sub.1] was also detected in the lung tissue of a chemical engineer who had worked for 3 months on a method for sterilizing Brazilian peanut meal contaminated with *Aspergillus flavus*, and who died of alveolar cell carcinoma.

In the United Kingdom, it was found that intravenous heroin users can be exposed to aflatoxin [B.sub.1] from samples of heroin on sale. Through intravenous administration, aflatoxin [B.sub.1] bypasses the detoxifying mechanisms of the liver, which results in direct systemic exposure. In the United Kingdom and the Netherlands, analysis of 121 urine samples obtained from heroin addicts revealed a higher proportion of samples contaminated with aflatoxins [B.sub.1], [B.sub.2], [M.sub.1] and [M.sub.2] and aflatoxicol (20%) than those from normal adult volunteers (2%). In addition, aflatoxin [B.sub.1] was found at much lower concentrations in the latter group.

3-Nitropropionic acid 3-Nitropropionic acid (3-NPA) is a secondary metabolite of *Arthrrium* sp., considered to cause a form of acute food-poisoning called "moldy sugarcane poisoning". The

problem occurred during winter (February and March) in 13 provinces of northern China as a consequence of ingesting sugarcane that had been stored for at least two months and which was infested with *Arthrinium* sp. In the period 1972-88, a total of 884 persons were involved in outbreaks, with 88 (10%) fatalities. The main epidemiological feature is the small number of persons in one outbreak (one to five persons), with the victims being mostly children and young people. The incubation period is generally 2-3 hours following the ingestion of moldy sugar-cane, and the main clinical symptoms are vomiting, dystonia, staring to one side, convulsions, carpopedal spasm and coma. Delayed dystonia develops in 10-50 % of patients as a consequence of bilateral symmetric necrosis of the basal ganglia. The development of delayed symptoms can be predicted by abnormality in the basal ganglia on cranial computed tomography (CT) scans. In adults, 3-NPA causes gastrointestinal symptoms; signs of severe encephalopathy are not common.

Ochratoxins

Ochratoxins are secondary metabolites of *Aspergillus* and *Penicillium* strains, found on cereals, coffee and bread, as well as on all kinds of food commodities of animal origin in many countries. The most frequent is ochratoxin A, which is also the most toxic. It has been shown to be nephrotoxic, immunosuppressive, carcinogenic and teratogenic in all experimental animals tested so far.

Acute renal failure in one person, possibly caused by inhalation of ochratoxin A in a granary which had been closed for 2 years, was reported in Italy. The symptoms developed after 24 hours of transitory epigastric tension, respiratory distress, and retrosternal burning. Acute tubular necrosis was found on biopsy, but the blood was not analyzed for ochratoxin A. The presence of the mycotoxin in wheat from the granary was proved qualitatively by thin-layer chromatography.

Owing to the similarity of morphological and functional kidney lesions in ochratoxin A-induced porcine nephropathy and endemic nephropathy, this mycotoxin has been proposed as the causative agent of endemic nephropathy, although the evidence for this is not substantial. This fatal renal disease occurs among rural populations in Croatia, Bosnia and Herzegovina, Yugoslavia, Bulgaria, and Romania, where it has been estimated that about 20,000 people are either suffering from or are suspected to have the disease. There is no acute phase of the illness; the first signs and symptoms of the disease are not specific and include fatigue, headache, loss of body weight and pale skin. A mild low-molecular-mass proteinuria without hypertension but with either aplastic or normochromic anaemia gradually develops over several years. The main features of endemic nephropathy are bilateral, primarily chronic lesions of the renal cortex (tubular degeneration, interstitial fibrosis and hyalinization of the glomeruli). In the advanced stage of the disease, the size and weight of kidneys are remarkably reduced, with diffuse cortical fibrosis, usually without signs of inflammation.

Ochratoxin A is found more frequently and in higher concentrations in the blood of inhabitants from endemic regions than control regions. Many samples of locally produced food and feed collected in the endemic area contained ochratoxin A. It should be emphasized that the grain analyzed had been kept for many months in the inadequate food stores of individual families.

In Tunisia, ochratoxin A has been detected in high concentrations in the blood and food of patients with kidney impairment of unknown etiology. It has also been found in several countries, both in food and feed and in humans.

In endemic regions of Croatia, Bulgaria and Yugoslavia, the incidence of otherwise rare urothelial tumours of the pelvis and ureter is 50, 90 and 100 times greater, respectively, than in nonendemic regions. It has been suggested that ochratoxin A may be the causal agent for both endemic nephropathy and urothelial tumours. IARC classified ochratoxin A as a compound possibly carcinogenic to humans (Group 2B).

Trichothecenes

Trichothecenes are mycotoxins produced mostly by members of the *Fusarium* genus, although other genera (e.g. *Trichoderma*, *Trichothecium*, *Myrothecium* and *Stachybotrys*) are also known to produce these compounds. To date, 148 trichothecenes have been isolated, but only a few have been found to contaminate food and feed. The most frequent contaminants are deoxynivalenol (DON), also known as vomitoxin, nivalenol (NIV), diacetoxyscirpenol (DAS), while T-2 toxin is rarer.

Common manifestations of trichothecene toxicity are depression of immune responses and nausea, sometimes vomiting. The first recognized trichothecene mycotoxicosis was alimentary toxic aleukia in the USSR in 1932; the mortality rate was 60%. In regions where the disease occurred, 54% of grain samples cultured showed the presence of *Fusarium sporotrichoides*, while in those regions where the disease was absent this fungus was found in only 2-8% of samples. The severity of mycotoxicosis was related to the duration of consumption of toxic grain. Such severe trichothecene mycotoxicoses, the consequence of continuous ingestion of toxins, have not been recorded since this outbreak.

In several cases, trichothecene mycotoxicosis was caused by a single ingestion of bread containing toxic flour or rice. In experimental animals, trichothecenes are 40 times more toxic when inhaled than when given orally. Trichothecenes were found in air samples collected during the drying and milling process on farms, in the ventilation systems of private houses and office buildings, and on the walls of houses with high humidity. There are some reports showing trichothecene involvement in the development of "sick building syndrome". The symptoms of airborne toxicosis disappeared when the buildings and ventilation systems were thoroughly cleaned.

Zearalenone Zearalenone (previously known as F-2) is produced mainly by *Fusarium graminearum* and related species, principally in wheat and maize but also in sorghum, barley and compounded feeds. Zearalenone and its derivatives produce estrogenic effects in various animal species (infertility, vulval oedema, vaginal prolapse and mammary hypertrophy in females and feminization of males — atrophy of testes and enlargement of mammary glands).

In Puerto Rico, zearalenone was found in the blood of children with precocious sexual development exposed to contaminated food. Zearalenone was also found together with other *Fusarium* mycotoxins in "scabby grain toxicosis" in China, but the significance of this finding is not clear.

Fumonisin

Fumonisin are mycotoxins produced throughout the world by *Fusarium moniliforme* and related species when they grow in maize. Fumonisin [B.sub.1] and [B.sub.2] are of toxicological significance, while the others (B.sub.3), [B.sub.4], [A.sub.1] and [A.sub.2]) occur in very low concentrations and are less toxic.

In India a single outbreak of acute food-borne disease possibly caused by fumonisin [B.sub.1] has been reported. In the 27 villages involved, the individuals affected were from the poorest social strata, who had consumed maize and sorghum harvested and left in the fields during unseasonable rains. The main features of the disease were transient abdominal pain, borborygmus and diarrhea, which began half an hour to one hour following consumption of unleavened bread prepared from moldy sorghum or moldy maize. Patients recovered fully when the exposure ceased and there were no fatalities. Fumonisin [B.sub.1] was found in much higher concentrations in the maize and sorghum from the affected households than from controls.

Fumonisin [B.sub.1] was found more frequently and in much higher concentrations in maize in regions of Transkei, China and north-east Italy with a higher incidence of oesophageal cancer than

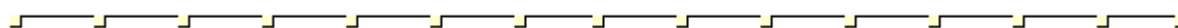
other regions. It was postulated that the high incidence of oesophageal cancer was related to the presence of this mycotoxin in maize, which is a staple food in these regions. The incidence and concentration of aflatoxin [B.sub.1], deoxynivalenol and fumonisins [B.sub.1], [B.sub.2] and [B.sub.3] were recently determined in maize samples from an area of China (Haimen) with a high incidence of primary liver cancer and from an area with a low incidence (Penlai). Aflatoxin [B.sub.1] was found in low concentrations in almost all maize samples from both these areas, but the incidence and concentration of deoxynivalenol and fumonisins were much higher in the samples from the area where the incidence of primary liver cancer was high. The authors put forward the hypothesis that fumonisins, which have known cancer-promoting activity in rat liver, and deoxynivalenol promote the initial lesion caused by aflatoxin [B.sub.1]. An IARC working group classified the toxins from *F. moniliforme* as possibly carcinogenic to humans (Group 2B).

Other Unidentified Mycotoxins

The impact of other mycotoxins on human health was reported in persons occupationally exposed to large amounts of different mycotoxin-producing fungi (farmers, workers in silos, etc.). In such cases, exposure to spores via the respiratory tract seems to be of considerable importance.

In Norway an extensive epidemiological study was undertaken between 1967 and 1991 on 192,417 births to test the hypotheses that perinatal death was associated with parental exposure to pesticides, *Toxoplasma gondii* infection from sheep or pigs, or mycotoxins found in grain. The proportion of late-term abortions (gestational age 16-27 weeks) was higher among farmers. The risk associated with grain farming was higher after the harvest, in seasons with a poor quality harvest and in pregnancies with multiple fetuses, which suggests that mycotoxins in grain induce labour at an early stage of pregnancy.

Pulmonary mycotoxicosis has been reported in ten persons exposed to large quantities of fungal hyphae and spores during the cleaning of silos. The clinical picture developed several hours afterwards, with burning eyes, throat and chest, irritating cough and fever. There was no wheezing, cyanosis or other sign of bronchospasm. In five patients, chest X-rays revealed reticular and fine nodular features compatible with interstitial pneumonitis. Histological study of a lung biopsy from one patient showed a multifocal acute process, with primary involvement of terminal bronchioles containing numbers of various spores. Cultures from lung biopsy material revealed at least five fungal species, including one *Fusarium* and one *Penicillium*. However, blood samples were not checked for the presence of mycotoxins. In contrast with the findings in patients with farmer's lung disease, these patients did not develop positive serological reactions to thermophilic actinomycetes or to extracts of fungi obtained from hay or silage. The patients were followed for periods of 1 to 10 years; they continued their work, avoiding massive re-exposure to fungal dust, and during the observation period there were no further incidents.



Additional Sources of Information:

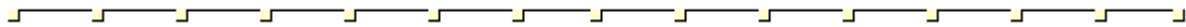
- [Emissions from Mold May Be Culprits in Indoor Air Problems](#)
- [Chronic Stuffy Nose, Nasal Polyps and Fungus](#) — Gabe Mirkin, M.D.
- [Toxic Effects of Some Common Indoor Fungi](#)
- [Diseases Due to Environmental Moulds](#)

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