Mycotoxins

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INTRODUCTION

Mycoses and Mycotoxicoses

Fungi are major plant and insect pathogens, but they are not nearly as important as agents of disease in vertebrates, i.e., the number of medically important fungi is relatively low. Frank growth of fungi on animal hosts produces the diseases collectively called mycoses, while dietary, respiratory, dermal, and other exposures to toxic fungal metabolites produce the diseases collectively called mycotoxicoses.

Mycoses range from merely annoying (e.g., athlete's foot) to life-threatening (e.g., invasive aspergillosis). The fungi that cause mycoses can be divided into two categories, primary pathogens (e.g., *Coccidioides immitis* and *Histoplasma capsulatum*) and opportunistic pathogens (e.g., *Aspergillus fumigatus* and *Candida albicans*). Primary pathogens affect otherwise healthy individuals with normal immune systems. Opportunistic pathogens produce illness by taking advantage of debilitated or immunocompromised hosts. The majority of human mycoses are caused by opportunistic fungi (149, 172, 245, 265). The mechanisms of pathogenesis of both primary and opportunistic fungi are complex, and medical mycologists have devoted considerable research energy trying to identify the factors that distinguish fungal pathogens from saprophytic and commensal species (31, 66). Some infections remain localized, while others progress to systemic infection. For many mycoses, the ordinary portal of entry is through the pulmonary tract, but direct inoculation through skin contact is not uncommon.

In contrast to mycoses, mycotoxicoses are examples of "poisoning by natural means" and thus are analogous to the pathologies caused by exposure to pesticides or heavy metal residues. The symptoms of a mycotoxicosis depend on the type of mycotoxin; the amount and duration of the exposure; the age, health, and sex of the exposed individual; and many poorly understood synergistic effects involving genetics, dietary status, and interactions with other toxic insults. Thus, the severity of mycotoxin poisoning can be compounded by factors such as vitamin deficiency, caloric deprivation, alcohol abuse, and infectious disease status. In turn, mycotoxicoses can heighten vulnerability to microbial diseases, worsen the effects of malnutrition, and interact synergistically with other toxins.

The number of people affected by mycoses and mycotoxicoses is unknown. Although the total number affected is believed to be smaller than the number afflicted with bacterial, protozoan, and viral infections, fungal diseases are nevertheless a serious international health problem. Mycoses caused by opportunistic pathogens are largely diseases of the developed world, usually occurring in patients whose immune systems have been compromised by advanced medical treatment. Mycotoxicoses, in contrast, are more common in underdeveloped nations. One of the characteristics shared by mycoses and mycotoxicoses is that neither category of illness is generally communicable from person to person.

Mycoses are frequently acquired via inhalation of spores from an environmental reservoir or by unusual growth of a

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commensal species that is normally resident on human skin or the gastrointestinal tract. These commensal species become pathogenic in the presence of antibacterial, chemotherapeutic, or immunosuppressant drugs, human immunodeficiency virus infection, in-dwelling catheters, and other predisposing factors (31, 66). The majority of mycotoxicoses, on the other hand, result from eating contaminated foods. Skin contact with mold-infested substrates and inhalation of spore-borne toxins are also important sources of exposure. Except for supportive therapy (e.g., diet, hydration), there are almost no treatments for mycotoxin exposure, although Fink-Gremmels (80) described a few methods for veterinary management of mycotoxicoses, and there is some evidence that some strains of *Lactobacillus* effectively bind dietary mycotoxins (72, 73). Oltipraz, a drug originally used to treat schistosomiasis, has been tested in Chinese populations environmentally exposed to aflatoxin (111).

In plant pathology, many secondary metabolites produced by bacteria and fungi are pathogenicity or virulence factors, i.e., they play a role in causing or exacerbating the plant disease. The phytotoxins made by fungal pathogens of *Cochliobolus (Helminthosporium)* and *Alternaria*, for example, have well-established roles in disease development (287), and several mycotoxins made by *Fusarium* species are important in plant pathogenesis (62). On the other hand, there is relatively little evidence that mycotoxins enhance the ability of fungi to grow in vertebrate hosts. *Aspergillus fumigatus* is case in point. It is the major species associated with aspergillosis and produces gliotoxins (inhibitors of T-cell activation and proliferation as well as macrophage phagocytosis). However, gliotoxin is not known to be produced in significant amounts by *Aspergillus fumigatus* during human disease (265). On the other hand, there are reports that gliotoxin has been associated with infections by *Candida albicans* (230, 231). The ability to grow at human body temperature (37°C) is clearly an important requirement for systemic mycotic infection, but the optimum temperature for the biosynthesis of most mycotoxins is within a more mesophilic range (20 to 30°C). For this and other reasons, the current view is that while some mycotoxins are known pathogenicity factors in plants, their significance in human mycoses is not yet clear.

Definitions, Etymology, and General Principles

It is difficult to define mycotoxin in a few words. All mycotoxins are low-molecular-weight natural products (i.e., small molecules) produced as secondary metabolites by filamentous fungi. These metabolites constitute a toxigenically and chemically heterogeneous assemblage that are grouped together only because the members can cause disease and death in human beings and other vertebrates. Not surprisingly, many mycotoxins display overlapping toxicities to invertebrates, plants, and microorganisms (10).

The term mycotoxin was coined in 1962 in the aftermath of an unusual veterinary crisis near London, England, during which approximately 100,000 turkey poults died (22, 82). When this mysterious turkey X disease was linked to a peanut (groundnut) meal contaminated with secondary metabolites from *Aspergillus flavus* (aflatoxins), it sensitized scientists to the possibility that other occult mold metabolites might be deadly.

Soon, the mycotoxin rubric was extended to include a number of previously known fungal toxins (e.g., the ergot alkaloids), some compounds that had originally been isolated as antibiotics (e.g., patulin), and a number of new secondary metabolites revealed in screens targeted at mycotoxin discovery (e.g., ochratoxin A).

The period between 1960 and 1975 has been termed the mycotoxin gold rush (157) because so many scientists joined the well-funded search for these toxigenic agents. Depending on the definition used, and recognizing that most fungal toxins occur in families of chemically related metabolites,. some 300 to 400 compounds are now recognized as mycotoxins, of which approximately a dozen groups regularly receive attention as threats to human and animal health (49). Mycotoxicoses are the animal diseases caused by mycotoxins; mycotoxicology is the study of mycotoxins (84).

While all mycotoxins are of fungal origin, not all toxic compounds produced by fungi are called mycotoxins. The target and the concentration of the metabolite are both important. Fungal products that are mainly toxic to bacteria (such as penicillin) are usually called antibiotics. Fungal products that are toxic to plants are called phytotoxins by plant pathologists (confusingly, the term phytotoxin can also refer to toxins made by plants; see Graniti [93] for a cogent discussion of the etymology of phytotoxin and its use in plant pathology). Mycotoxins are made by fungi and are toxic to vertebrates and other animal groups in low concentrations. Other low-molecular-weight fungal metabolites such as ethanol that are toxic only in high concentrations are not considered mycotoxins (10). Finally, although mushroom poisons are definitely fungal metabolites that can cause disease and death in humans and other animals, they are rather arbitrarily excluded from discussions of mycotoxicology. Molds (i.e., microfungi) make mycotoxins; mushrooms and other macroscopic fungi make mushroom poisons. The distinction between a mycotoxin and a mushroom poison is based not only on the size of the producing fungus, but also on human intention. Mycotoxin exposure is almost always accidental. In contrast, with the exception of the victims of a few mycologically accomplished murderers, mushroom poisons are usually ingested by amateur mushroom hunters who have collected, cooked, and eaten what was misidentified as a delectable species (184).

Mycotoxins are not only hard to define, they are also challenging to classify. Due to their diverse chemical structures and biosynthetic origins, their myriad biological effects, and their production by a wide number of different fungal species, classification schemes tend to reflect the training of the person doing the categorizing. Clinicians often arrange them by the organ they affect. Thus, mycotoxins can be classified as hepatotoxins, nephrotoxins, neurotoxins, immunotoxins, and so forth. Cell biologists put them into generic groups such as teratogens, mutagens, carcinogens, and allergens. Organic chemists have attempted to classify them by their chemical structures (e.g., lactones, coumarins); biochemists according to their biosynthetic origins (polyketides, amino acid-derived, etc.); physicians by the illnesses they cause (e.g., St. Anthony's fire, stachybotryotoxicosis), and mycologists by the fungi that produce them (e.g., *Aspergillus* toxins, *Penicillium* toxins). None of these classifications is entirely satisfactory. Moreover, as our anthropomorphic focus shifts attention, the same com-

pound may get placed in different cognitive cubbyholes. Aflatoxin, for example, is a hepatotoxic, mutagenic, carcinogenic, difuran-containing, polyketide-derived *Aspergillus* toxin. Zearalenone is a *Fusarium* metabolite with potent estrogenic activity; hence, in addition to being called (probably erroneously) a mycotoxin, it also has been labeled a phytoestrogen, a mycoestrogen, and a growth promotant. For this article, we will eschew classification and simply list the major mycotoxins in alphabetical order by name.

Toxicology and Human Health

Toxicologists tend to concentrate their efforts on hazardous chemicals such as polyaromatic hydrocarbons, heavy metals, and organic pesticides. Because they have devoted less effort to natural products, agriculturalists, chemists, microbiologists, and veterinarians who are often unfamiliar with the basic principles of toxicology have conducted most of the mycotoxin research. There has been a lot of reinventing of the wheel and sometimes an imprecise use of toxicology jargon.

For example, mycotoxicoses, like all toxicological syndromes, can be categorized as acute or chronic. Acute toxicity generally has a rapid onset and an obvious toxic response, while chronic toxicity is characterized by low-dose exposure over a long time period, resulting in cancers and other generally irreversible effects (128). Accepting that it is often difficult to distinguish between acute and chronic effects, many papers on mycotoxicoses blur this basic dichotomy entirely, and it is not always easy to interpret the published data on purported health effects. Almost certainly, the main human and veterinary health burden of mycotoxin exposure is related to chronic exposure (e.g., cancer induction, kidney toxicity, immune suppression). However, the best-known mycotoxin episodes are manifestations of acute effects (e.g., turkey X syndrome, human ergotism, stachybotryotoxicosis).

In order to demonstrate that a disease is a mycotoxicosis, it is necessary to show a dose-response relationship between the mycotoxin and the disease. For human populations, this correlation requires epidemiological studies. Supportive evidence is provided when the characteristic symptoms of a suspected human mycotoxicosis are evoked reproducibly in animal models by exposure to the mycotoxin in question (121). Human exposure to mycotoxins is further determined by environmental or biological monitoring. In environmental monitoring, mycotoxins are measured in food, air, or other samples; in biological monitoring, the presence of residues, adducts, and metabolites is assayed directly in tissues, fluids, and excreta (121).

In general, mycotoxin exposure is more likely to occur in parts of the world where poor methods of food handling and storage are common, where malnutrition is a problem, and where few regulations exist to protect exposed populations. However, even in developed countries, specific subgroups may be vulnerable to mycotoxin exposure. In the United States, for example, Hispanic populations consume more corn products than the rest of the population, and inner city populations are more likely to live in buildings that harbor high levels of molds (5).

Methods for controlling mycotoxins are largely preventive. They include good agricultural practice and sufficient drying of crops after harvest (153). There is considerable on-going research on methods to prevent preharvest contamination of crops. These approaches include developing host resistance through plant breeding and through enhancement of antifungal genes by genetic engineering, use of biocontrol agents, and targeting regulatory genes in mycotoxin development (26). As of now, none of these methods has solved the problem. Because mycotoxins are "natural" contaminants of foods, their formation is often unavoidable. Many efforts to address the mycotoxin problem simply involve the diversion of mycotoxin-contaminated commodities from the food supply through government screening and regulation programs.

There is a vast literature on mycotoxins, and numerous monographs have been published (15, 16, 19, 47, 49, 64, 133, 136, 150, 162, 177, 211, 216, 235, 237, 246, 259, 283, 285, 286). In addition, there are hundreds of review articles and thousands and thousands of papers in the primary literature. Unfortunately, too many publications about mycotoxins consist largely of mind-numbing accumulations of assorted facts: lists of clinical manifestations in different animal species (both exposure tests in laboratories and veterinary diagnoses of mycotoxicoses in agricultural settings), compendia of different toxins found in different foodstuffs, comparisons of assay protocols, tables of international regulations governing mycotoxin levels, and so forth. There is also a significant literature addressing fundamental studies describing organic syntheses, elucidation of biosynthetic pathways, cloning of mycotoxin pathway genes, and other less applied aspects of mycotoxin research.

The scientific quality of the mycotoxin literature is extremely variable. There is a disconcertingly high level of inaccuracy in a few reports, with some authors culling their information from earlier reviews of questionable merit and thereby perpetuating factual errors and discredited hypotheses. Where possible, we will attempt to point out such misinformation. We will focus on those mycotoxins that are known or suspected to cause human disease; on metabolites that are produced by molds that are associated with human food or habitation; and on other topics related directly to human health. Previous reviews on mycotoxins and human health include those by the Council for Agricultural Science and Technology (53), Robens and Richard (215), Beardall and Miller (7), Kuiper-Goodman (145), Fink-Gremmels (80), Peraica et al. (195), Hussein and Brasel (126), and Etzel (76). Because the field of mycotoxin research is so large and so fragmented, and because the criteria for establishing human mycotoxicoses are so elusive, the goal of this article is to give a simple introduction to clinical microbiologists. We will briefly describe what is known about the chemical structure and biosynthesis of the mycotoxin, list the producing fungal species, and give the clinical manifestations and toxicological profiles of the associated mycotoxicoses. In each case, we will refer the reader to selected pertinent papers from the primary literature as well as to other, more comprehensive reviews.

MAJOR MYCOTOXINS

Aflatoxins

The aflatoxins were isolated and characterized after the death of more than 100,000 turkey poults (turkey X disease) was traced to the consumption of a mold-contaminated peanut meal (22, 91). The four major aflatoxins are called B_1, B_2, G_1,
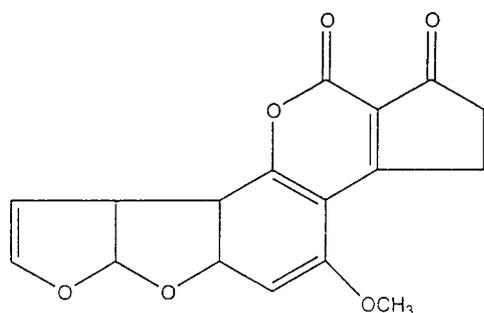
FIG. 1. Aflatoxin B$_1$.

and G$_2$ based on their fluorescence under UV light (blue or green) and relative chromatographic mobility during thin-layer chromatography. Aflatoxin B$_1$ (Fig. 1) is the most potent natural carcinogen known (243) and is usually the major aflatoxin produced by toxigenic strains. It is also the best studied: in a large percentage of the papers published, the term aflatoxin can be construed to mean aflatoxin B$_1$. However, well over a dozen other aflatoxins (e.g., P$_1$. Q$_1$, B$_{2a}$, and G$_{2a}$) have been described, especially as mammalian biotransformation products of the major metabolites (104). The classic book *Aflatoxin: Scientific Background, Control, and Implications*, published in 1969 (91), is still a valuable resource for reviewing the history, chemistry, toxicology, and agricultural implications of aflatoxin research.

Aflatoxins are difuranocoumarin derivatives produced by a polyketide pathway by many strains of *Aspergillus flavus* and *Aspergillus parasiticus*; in particular, *Aspergillus flavus* is a common contaminant in agriculture. *Aspergillus bombycis, Aspergillus ochraceoroseus, Aspergillus nomius*, and *Aspergillus pseudotamari* are also aflatoxin-producing species, but they are encountered less frequently (92, 139, 197). From the mycological perspective, there are great qualitative and quantitative differences in the toxigenic abilities displayed by different strains within each aflatoxigenic species. For example, only about half of *Aspergillus flavus* strains produce aflatoxins (138), while those that do may produce more than 10^6 μg/kg (51).

Many substrates support growth and aflatoxin production by aflatoxigenic molds. Natural contamination of cereals, figs, oilseeds, nuts, tobacco, and a long list of other commodities is a common occurrence (63, 65). Like the genetic ability to make aflatoxin, contamination is highly variable. Sometimes crops become contaminated with aflatoxin in the field before harvest, where it is usually associated with drought stress (65, 137); even more problematic is the fate of crops stored under conditions that favor mold growth. In storage, usually the most important variables are the moisture content of the substrate and the relative humidity of the surroundings (63, 280). Aflatoxin contamination has been linked to increased mortality in farm animals and thus significantly lowers the value of grains as an animal feed and as an export commodity (238). Milk products can also serve as an indirect source of aflatoxin. When cows consume aflatoxin-contaminated feeds, they metabolically biotransform aflatoxin B$_1$ into a hydroxylated form called aflatoxin M$_1$ (267).

Aflatoxin is associated with both toxicity and carcinogenicity

in human and animal populations (70, 186, 193, 232). The diseases caused by aflatoxin consumption are loosely called aflatoxicoses. Acute aflatoxicosis results in death; chronic aflatoxicosis results in cancer, immune suppression, and other "slow" pathological conditions (121). The liver is the primary target organ, with liver damage occurring when poultry, fish, rodents, and nonhuman primates are fed aflatoxin B$_1$. There are substantial differences in species susceptibility. Moreover, within a given species, the magnitude of the response is influenced by age, sex, weight, diet, exposure to infectious agents, and the presence of other mycotoxins and pharmacologically active substances. Thousands of studies on aflatoxin toxicity have been conducted, mostly concerning laboratory models or agriculturally important species (56, 70, 186).

Cytochrome P450 enzymes convert aflatoxins to the reactive 8,9-epoxide form (also referred to as aflatoxin-2,3 epoxide in the older literature), which is capable of binding to both DNA and proteins (70). Mechanistically, it is known that the reactive aflatoxin epoxide binds to the N^7 position of guanines. Moreover, aflatoxin B$_1$-DNA adducts can result in GC to TA transversions. A reactive glutathione *S*-transferase system found in the cytosol and microsomes catalyzes the conjugation of activated aflatoxins with reduced glutathione, leading to the excretion of aflatoxin (208). Variation in the level of the glutathione transferase system as well as variations in the cytochrome P450 system are thought to contribute to the differences observed in interspecies aflatoxin susceptibility (70, 71).

Because of the differences in aflatoxin susceptibility in test animals, it has been difficult to extrapolate the possible effects of aflatoxin to humans, but acute toxicity of aflatoxins in *Homo sapiens* has not been observed very often. It is believed that a 1974 Indian outbreak of hepatitis in which 100 people died may have been due to the consumption of maize that was heavily contaminated with aflatoxin. Some adults may have eaten 2 to 6 mg of aflatoxin in a single day (141). Subsequently, it was calculated that the acute lethal dose for adults is approximately 10 to 20 mg of aflatoxins (200). One anecdotal report refutes this estimate. A woman who had ingested over 40 mg of purified aflatoxin in a suicide attempt was still alive 14 years later. Multiple laboratory tests of her urine and blood, and X-ray, ultrasound, and computerized axial tomography analyses of her abdomen, liver, and spleen all gave normal results (279).

It has been hypothesized that kwashiorkor, a severe malnutrition disease, may be a form of pediatric aflatoxicosis (109). Further early speculations that aflatoxin might be involved in Reye's syndrome, an encephalopathy, and fatty degeneration of the viscera in children and adolescents (102) have not been substantiated. Nevertheless, aflatoxin has achieved some notoriety as a poison. The plot of *The Human Factor*, a spy thriller by Graham Greene (95), revolves around the murder of a central figure whose whiskey was laced with aflatoxin (a toxicologically improbable way to kill someone). Nevertheless, aflatoxin's reputation has a potent poison may explain why it has been adopted for use in bioterrorism. There is substantial evidence that Iraq stockpiled aflatoxin to be delivered in missiles (see section on bioterrorism below).

The data on aflatoxin as a human carcinogen are far more damning than the data implicating it in acute human toxicities.

Exposure to aflatoxins in the diet is considered an important risk factor for the development of primary hepatocellular carcinoma, particularly in individuals already exposed to hepatitis B. In classical epidemiology, several studies have linked liver cancer incidence to estimated aflatoxin consumption in the diet (152, 193, 270). The results of these studies have not been entirely consistent, and quantification of lifetime individual exposure to aflatoxin is extremely difficult. The incidence of liver cancer varies widely from country to country, but it is one of the most common cancers in China, the Philippines, Thailand, and many African countries. The presence of hepatitis B virus infection, an important risk factor for primary liver cancer, complicates many of the epidemiological studies. In one case-control study involving more than 18,000 urine samples collected over 3.5 years in Shanghai, China, aflatoxin exposure alone yielded a relative risk of about 2; hepatitis B virus antigen alone yielded a relative risk of about 5; combined exposure to aflatoxin and hepatitis B yielded a relative risk of about 60 (217). Vaccination against hepatitis B virus is recommended as a more realistic and cost-effective strategy for lowering liver cancer incidence than removing aflatoxin from the diet (111, 112).

In molecular epidemiology, it is possible to demonstrate with more certainty the association between putative carcinogens and specific cancers. Biomonitoring of aflatoxins can be done by analyzing for the presence of aflatoxin metabolites in blood, milk, and urine; moreover, excreted DNA adducts and blood protein adducts can also be monitored (221). The aflatoxin B_1-N^7-guanine adduct represents the most reliable urinary biomarker for aflatoxin exposure but reflects only recent exposure. Numerous studies have shown that carcinogenic potency is highly correlated with the extent of total DNA adducts formed in vivo (69, 70).

Inactivation of the p53 tumor suppressor gene may be important in the development of primary hepatocellular carcinoma. Studies of liver cancer patients in Africa and China have shown that a mutation in the p53 tumor suppressor gene at codon 249 is associated with a G-to-T transversion (23, 122). Mechanistically, it is known that the reactive aflatoxin epoxide binds to the N^7 position of guanines. Moreover, aflatoxin B_1-DNA adducts can result in GC to TA transversions. The specific mutation in codon 249 of the p53 gene has been called the first example of a "carcinogen-specific" biomarker that remains fixed in the tumor tissue (69).

There is also considerable evidence associating aflatoxin with neoplasms in extrahepatic tissues, particularly the lungs. For example, one early epidemiological study of Dutch peanut processing workers exposed to dust contaminated with aflatoxin B_1 showed a correlation between both respiratory cancer and total cancer in the exposed group compared with unexposed cohorts (103). Anecdotal and circumstantial evidence of air-borne aflatoxin exposure leading to cancer has been reported. Deger (59) concluded that dust from scrapings of chromatographic plates from aflatoxin analyses contributed to causing cancer in two young adults. Aflatoxin is a pulmonary carcinogen in experimental animals. The nonhepatic effects of aflatoxin B_1 have been summarized by Coulombe (52).

To recapitulate, there is no other natural product for which the data on human carcinogenicity are so compelling. The International Agency for Research on Cancer has classified aflatoxin B_1 as a group I carcinogen (127).

In developed countries, sufficient amounts of food combined with regulations that monitor aflatoxin levels in these foods protect human populations from significant aflatoxin ingestion. However, in countries where populations are facing starvation or where regulations are either not enforced or nonexistent, routine ingestion of aflatoxin may occur (51). Worldwide, liver cancer incidence rates are 2 to 10 times higher in developing countries than in developed countries (112). Unfortunately, strict limitation of aflatoxin-contaminated food is not always an option. A joint Food and Agriculture Organization/World Health Organization/United Nations Environment Programme Conference report stated that "in developing countries, where food supplies are already limited, drastic legal measure may lead to lack of food and to excessive prices. It must be remembered that people living in these countries cannot exercise the option of starving to death today in order to live a better life tomorrow" (quoted in Henry et al. [112]).

There has been considerable fundamental work on the aflatoxins, especially on their biosynthesis and molecular biology. The first stable step in the biosynthetic pathway is the production of norsolorinic acid, an anthraquinone precursor, by a type II polyketide synthase. An elaborate series of at least 15 postpolyketide synthase steps follows, yielding a series of increasingly toxigenic metabolites (12, 48, 114, 192, 256, 257). Sterigmatocystin, a related dihydrofuran toxin, is a late metabolite in the aflatoxin pathway and is also produced as a final biosynthetic product by a number of species such as *Aspergillus versicolor* and *Aspergillus nidulans*. Sterigmatocystin is both mutagenic and tumorigenic but is less potent than aflatoxin (14). Analysis of the molecular genetics of sterigmatocystin biosynthesis in the genetically tractable species *Aspergillus nidulans* has provided a useful model system. The genes for the sterigmatocystin gene cluster from *Aspergillus nidulans* have been cloned and sequenced (25). Cognate genes for aflatoxin pathway enzymes from *Aspergillus flavus* and *Aspergillus parasiticus* show high sequence similarity to the sterigmatocystin pathway genes (192, 288, 289). The organization of genes in the *Aspergillus flavus, Aspergillus nidulans*, and *Aspergillus parasiticus* sterigmatocystin-aflatoxin pathway has been compared by Cary et al. (34) and Hicks et al. (114).

Finally, it should be mentioned that *Aspergillus oryzae* and *Aspergillus sojae*, species that are widely used in Asian food fermentations such as soy sauce, miso, and sake, are closely related to the aflatoxigenic species *Aspergillus flavus* and *Aspergillus parasiticus*. Although these food fungi have never been shown to produce aflatoxin (276), they contain homologues of several aflatoxin biosynthesis pathway genes (140). Deletions and other genetic defects have led to silencing of the aflatoxin pathway in both *Aspergillus oryzae* and *Aspergillus sojae* (254, 274).

Citrinin

Citrinin (Fig. 2) was first isolated from *Penicillium citrinum* prior to World War II (113); subsequently, it was identified in over a dozen species of *Penicillium* and several species of *Aspergillus* (e.g., *Aspergillus terreus* and *Aspergillus niveus*), including certain strains of *Penicillium camemberti* (used to produce cheese) and *Aspergillus oryzae* (used to produce sake,
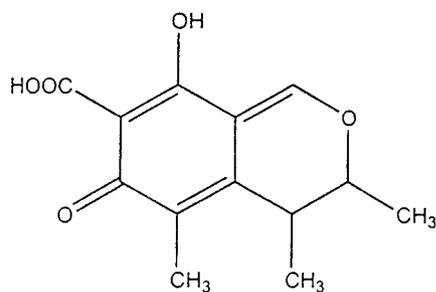
FIG. 2. Citrinin.

FIG. 3. Ergotamine.

miso, and soy sauce) (158). More recently, citrinin has also been isolated from *Monascus ruber* and *Monascus purpureus,* industrial species used to produce red pigments (21).

Citrinin has been associated with yellow rice disease in Japan (222). It has also been implicated as a contributor to porcine nephropathy. Citrinin acts as a nephrotoxin in all animal species tested, but its acute toxicity varies in different species (33). The 50% lethal dose for ducks is 57 mg/kg; for chickens it is 95 mg/kg; and for rabbits it is 134 mg/kg (100). Citrinin can act synergistically with ochratoxin A to depress RNA synthesis in murine kidneys (223). For a review of the early literature, see Krogh (142).

Wheat, oats, rye, corn, barley, and rice have all been reported to contain citrinin (2). With immunoassays, citrinin was detected in certain vegetarian foods colored with *Monascus* pigments (39). Citrinin has also been found in naturally fermented sausages from Italy (4). Although citrinin is regularly associated with human foods, its significance for human health is unknown.

Ergot Alkaloids

The ergot alkaloids are among the most fascinating of fungal metabolites. They are classified as indole alkaloids and are derived from a tetracyclic ergoline ring system. Lysergic acid, a structure common to all ergot alkaloids, was first isolated in 1934. The clavines have ergoline as a basic structure but lack peptide components; the lysergic acid alkaloids include ergotamine and lysergic acid amide (ergine) (11). The structure of ergotamine is shown in Fig. 3.

These compounds are produced as a toxic cocktail of alkaloids in the sclerotia of species of *Claviceps*, which are common pathogens of various grass species. The ingestion of these sclerotia, or ergots, has been associated with diseases since antiquity. An Assyrian tablet dated to 600 B.C.E., referring to a "noxious pustule in the ear of grain," is believed to be an early reference to ergot (120). The human disease acquired by eating cereals infected with ergot sclerotia, usually in the form of bread made from contaminated flour, is called ergotism or St. Anthony's fire. Two forms of ergotism are usually recognized, gangrenous and convulsive. The gangrenous form affects the blood supply to the extremities, while convulsive ergotism affects the central nervous system (11).

Human ergotism was common in Europe in the Middle Ages. For example, a three-volume work entitled *Handbook of Geographical and Historical Pathology* published in London by August Hirch between 1883 and 1886 recorded 132 epidemics
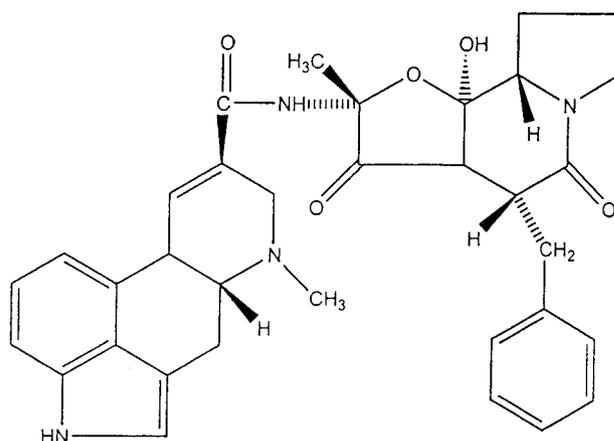
of European ergotism between the 6th and 18th centuries (98). Matossian (170) has suggested that the "slow nervous fever" described by the 18th century English physician Jon Huxham may be another example of human ergotism. Slow nervous fever usually occurred in the summer and fall after a severe winter; Huxham suspected "bad food" as the source of the trouble. Matossian (171) has also postulated that ergot alkaloids may have had a strong influence on fertility trends in England and other European countries during the 17th and 18th centuries.

Modern methods of grain cleaning have almost eliminated ergotism as a human disease. Nevertheless, purported ergot poisoning occurred in the French town of Pont-St.-Esprit in 1951 and was the subject of a full-length book treatment, *The Day of St. Anthony's Fire* (85). Ergotism is still an important veterinarian problem. The principal animals at risk are cattle, sheep, pigs, and chickens. Clinical symptoms of ergotism in animals include gangrene, abortion, convulsions, suppression of lactation, hypersensitivity, and ataxia (154).

Sometimes the line between toxin and drug is defined with the shift of a decimal point or a change in a small chemical moiety. The ergot alkaloids are a case in point. Their myriad actions have long engaged the interest of physicians and pharmacologists. Several ergot alkaloids induce smooth muscle contractions. For centuries it had been observed that grazing on grass infected with ergot caused abortion in pregnant farm animals, so it is not surprising that midwives and others adopted ergot as a folk medicine, using it as both an abortifacient and a drug to accelerate to uterine contractions for women in labor (213). During the 20th century, the famous hallucinogen lysergic acid diethylamide (LSD) was discovered as the result of research with ergot alkaloids conducted at the Sandoz Laboratories in Basel, Switzerland. A chemist named Hofmann combined different amines in peptide linkage with lysergic acid to produce ergobasine (also called ergometrine and ergonovine), the first semisynthetic ergot alkaloid. Then, by varying the amino alcohol constituent, he obtained Methergine, a compound prescribed widely for decades to control hemorrhage after childbirth. Hofmann continued to synthesize new lysergic acid derivatives; the 25th substance in his series was D-lysergic acid diethylamide (LSD-25). In 1943, after ac-
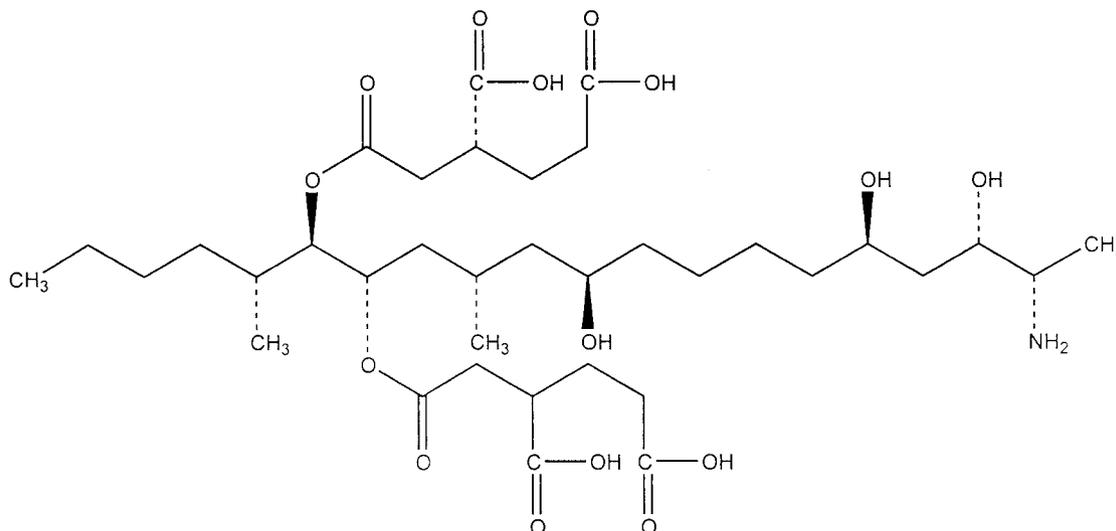
FIG. 4. Fumonisin B_1.

cidentally ingesting some of the compound, he discovered the hallucinogenic properties of this semisynthetic derivative (120). For a while, Sandoz marketed LSD to psychiatrists under the trademark Delysid. It was used unsuccessfully to treat schizophrenia. In a bizarre chapter of American history, the Central Intelligence Agency, under the code name MK-ULTRA, used LSD as a truth serum for interrogating suspected communists (262). More recently, pure ergotamine has been used for the treatment of migraine headaches. Other ergot derivatives are used as prolactin inhibitors, in the treatment of Parkinsonism, and in cases of cerebrovascular insufficiency (11). The therapeutic administration of ergot alkaloids may cause sporadic cases of human ergotism (30).

Finally, it has been hypothesized that the Salem witchcraft affair may have been a form of convulsive ergotism related to consumption of rye infected with *Claviceps* sclerotia (32, 169). Although some historians dispute this hypothesis (242), the epidemiological and clinical data are quite provocative (11). Robin Cook, the author of a number of bestsellers, used the Salem-ergot hypothesis as the basis for a novel in which a young physician isolates *Claviceps* spores from a damp New England cellar, cultures the fungus, and then discovers a new alkaloid with mind- and energy-enhancing properties. Taking a cue from the Central Intelligence Agency, he names his drug Ultra and founds a biotechnology company in order to reap profits from the would-be "billion-dollar molecule." In the end it is discovered that the euphoria-inducing fictional alkaloid has horrifying side effects (50). Cook's novel is our personal favorite example of mycotoxins in popular culture.

Fumonisins

Fumonisins were first described and characterized in 1988 (17, 87). The most abundantly produced member of the family is fumonisin B_1 (Fig. 4). They are thought to be synthesized by condensation of the amino acid alanine into an acetate-derived precursor (250). Fumonisins are produced by a number of *Fusarium* species, notably *Fusarium verticillioides* (formerly *Fusarium moniliforme = Gibberella fujikuroi*), *Fusarium proliferatum,* and *Fusarium nygamai,* as well as *Alternaria alternata* f. sp. *lycopersici* (164, 210). These fungi are taxonomically challenging, with a complex and rapidly changing nomenclature which has perplexed many nonmycologists (and some mycologists, too) (151, 165). The major species of economic importance is *Fusarium verticillioides*, which grows as a corn endophyte in both vegetative and reproductive tissues, often without causing disease symptoms in the plant. However, when weather conditions, insect damage, and the appropriate fungal and plant genotype are present, it can cause seedling blight, stalk rot, and ear rot (185). *Fusarium verticillioides* is present in virtually all corn samples (167, 164). Most strains do not produce the toxin, so the presence of the fungus does not necessarily mean that fumonisin is also present (203). Although it is phytotoxic, fumonisin B_1 is not required for plant pathogenesis (60, 160).

Fumonisins affect animals in different ways by interfering with sphingolipid metabolism (68, 161, 175, 273). They cause leukoencephalomalacia (hole in the head syndrome) in equines (163) and rabbits (27); pulmonary edema and hydrothorax in swine (101); and hepatotoxic and carcinogenic effects (87, 88, 89) and apoptosis in the liver of rats (204). In humans, there is a probable link with esophageal cancer (252). The occurrence of fumonisin B_1 is correlated with the occurrence of a higher incidence of esophageal cancer in regions of Transkei (South Africa), China, and northeast Italy (195). It has been isolated at high levels in corn meal and corn grits, including seven samples from a supermarket in Charleston, S.C., a city which has the highest incidence of esophageal cancer among African-Americans in the United States (252). Several other mycotoxins, nutritional parameters, and other factors have also been implicated in the etiology of human esophageal cancer; see Beardall and Miller (7) for an excellent discussion of the way in which multiple etiological factors are suspected to interact.

A possible case of acute exposure to fumonisin B_1 involved 27 villages in India, where consumption of unleavened bread
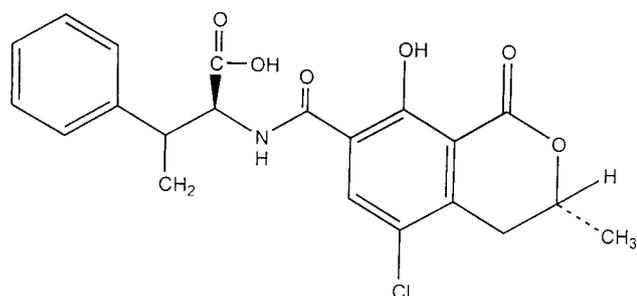
FIG. 5. Ochratoxin A.

made from moldy sorghum or corn caused transient abdominal pain, borborygmus, and diarrhea. All those affected recovered fully (18). Finally, fumonisins can cause neural tube defects in experimental animals and thus may also have a role in human cases. It has been hypothesized that a cluster of anencephaly and spina bifida cases in southern Texas may have been related to fumonisins in corn products (107, 108, 181). The International Agency for Research on Cancer has evaluated the cancer risk of fumonisins to humans and classified them as group 2B (probably carcinogenic) (210).

Unlike most known mycotoxins, which are soluble in organic solvents, fumonisins are hydrophilic. This makes them difficult to study. Usually they are extracted in aqueous methanol or aqueous acetonitrile (20). High-performance liquid chromatography with fluorescent detection is the most widely used analytic method (202). The fumonisin story raises the specter that there may be many other occult but toxic products of fungal metabolism that have not yet been discovered because of their hydrophilic nature.

Ochratoxin

Ochratoxin A (Fig. 5) was discovered as a metabolite of *Aspergillus ochraceus* in 1965 during a large screen of fungal metabolites that was designed specifically to identify new mycotoxins (266). Shortly thereafter, it was isolated from a commercial corn sample in the United States (234) and recognized as a potent nephrotoxin. Members of the ochratoxin family have been found as metabolites of many different species of *Aspergillus*, including *Aspergillus alliaceus*, *Aspergillus auricomus*, *Aspergillus carbonarius*, *Aspergillus glaucus*, *Aspergillus melleus*, and *Aspergillus niger* (1, 6, 46). Because *Aspergillus niger* is used widely in the production of enzymes and citric acid for human consumption, it is important to ensure that industrial strains are nonproducers (105, 255). Although some early reports implicated several *Penicillium* species, it is now thought that *Penicillium verrucosum*, a common contaminant of barley, is the only confirmed ochratoxin producer in this genus (41, 199). Nevertheless, many mycotoxin reviews reiterate erroneous species lists.

As with other mycotoxins, the substrate on which the molds grow as well as the moisture level, temperature, and presence of competitive microflora interact to influence the level of toxin produced. Ochratoxin A has been found in barley, oats, rye, wheat, coffee beans, and other plant products, with barley having a particularly high likelihood of contamination. There is also concern that ochratoxin may be present in certain wines, especially those from grapes contaminated with *Aspergillus carbonarius* (166, 200, 269).

Of the *Aspergillus* toxins, only ochratoxin is potentially as important as the aflatoxins. The kidney is the primary target organ. Ochratoxin A is a nephrotoxin to all animal species studied to date and is most likely toxic to humans, who have the longest half-life for its elimination of any of the species examined (54). In addition to being a nephrotoxin, animal studies indicate that ochratoxin A is a liver toxin, an immune suppressant, a potent teratogen, and a carcinogen (7, 146). Ochratoxin A disturbs cellular physiology in multiple ways, but it seems that the primary effects are associated with the enzymes involved in phenylalanine metabolism, mostly by inhibiting the enzyme involved in the synthesis of the phenylalanine-tRNA complex (28, 166). In addition, it inhibits mitochondrial ATP production (174) and stimulates lipid peroxidation (207).

Ochratoxin has been detected in blood and other animal tissues and in milk, including human milk (166). It is frequently found in pork intended for human consumption (80). Ochratoxin is believed to be responsible for a porcine nephropathy that has been studied intensively in the Scandinavian countries. The disease is endemic in Denmark, where rates of porcine nephropathy and ochratoxin contamination in pig feed are highly correlated (143). In addition, ochratoxin is associated with disease and death in poultry (29, 99).

There has been speculation that ochratoxins are involved in a human disease called endemic Balkan nephropathy (123, 143). This condition is a progressive chronic nephritis that occurs in populations who live in areas bordering the Danube River in parts of Romania, Bulgaria, and the former Yugoslavia. In one Bulgarian study, ochratoxin contamination of food and the presence of ochratoxin in human serum were more common in families with endemic Balkan nephropathy and urinary tract tumors than in unaffected families (35). In addition to ochratoxin poisoning, this curious disease has been attributed to genetic factors, heavy metals, and possible occult infectious agents. The current consensus is that endemic Balkan nephropathy is of unknown etiology, but many mycotoxin reviews list it, without caveat, as an ochratoxicosis.

It has also been hypothesized that the gene for phenylketonuria might occur in relatively high frequency because of a heterozygous advantage against ochratoxin poisoning (284) and that ochratoxin might be a risk factor for testicular cancer (226).

How common is human exposure to ochratoxin? Studies from Canada, Sweden, West Germany, and Yugoslavia detected ochratoxin in human blood and serum (146). Analyses of urine from children in Sierra Leone detected both ochratoxin and aflatoxin throughout the year (135).

Several detailed risk assessments have been conducted for ochratoxin A (146). Given the known human exposure and the abundance of toxicological data from animal studies, the European Union Scientific Committee has recommended that ochratoxin A levels be reduced to below 5 ng/kg of body weight per day (251). In addition, several European countries have proposed individual regulations, with maximum tolerated concentrations varying greatly from country to country (131, 268). The International Agency for Research on Cancer has rated ochratoxin as a possible human carcinogen (category 2B) (7).
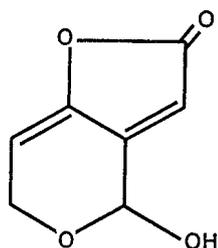
FIG. 6. Patulin.

FIG. 7. T-2 toxin.

In conclusion, it would be prudent for the medical community to pay closer attention to the possibility of ochratoxin toxicity in patients with symptoms of renal pathology (54). Although the role of ochratoxin A in human disease is still speculative, its acute nephrotoxicity, immunosuppressive actions, and teratogenic effects in animal models, coupled with its ability to be carried through the food chain, merit concern.

Patulin

Patulin, 4-hydroxy-4H-furo[3,2c]pyran-2(6H)-one, is produced by many different molds but was first isolated as an antimicrobial active principle during the 1940s from *Penicillium patulum* (later called *Penicillium urticae,* now *Penicillium griseofulvum*). The same metabolite was also isolated from other species and given the names clavacin, claviformin, expansin, mycoin c, and penicidin (45). The chemical structure is shown in Fig. 6. A number of early studies were directed towards harnessing its antibiotic activity. For example, it was tested as both a nose and throat spray for treating the common cold and as an ointment for treating fungal skin infections (44, 45). However, during the 1950s and 1960s, it became apparent that, in addition to its antibacterial, antiviral, and antiprotozoal activity, patulin was toxic to both plants and animals, precluding its clinical use as an antibiotic. During the 1960s, patulin was reclassified as a mycotoxin.

Nowadays, *Penicillium expansum*, the blue mold that causes soft rot of apples, pears, cherries, and other fruits, is recognized as one of the most common offenders in patulin contamination. Patulin is regularly found in unfermented apple juice, although it does not survive the fermentation into cider products (260). Patulin is toxic at high concentration in laboratory settings, but evidence for natural poisoning is indirect and inconclusive. Nevertheless, the Joint Food and Agriculture Organization–World Health Organization Expert Committee on Food Additives has established a provisional maximum tolerable daily intake for patulin of 0.4 mg/kg of body weight per day (260).

Patulin has also played an important role in the study of the classical biochemistry of polyketide biosynthesis. The first cell extract for a fungal polyketide synthase involved studies on a 6-methylsalicylic acid synthase from the species then called *Penicillium urticae* (now *Penicillium griseofulvum*); see Bentley and Bennett (13) for a review.
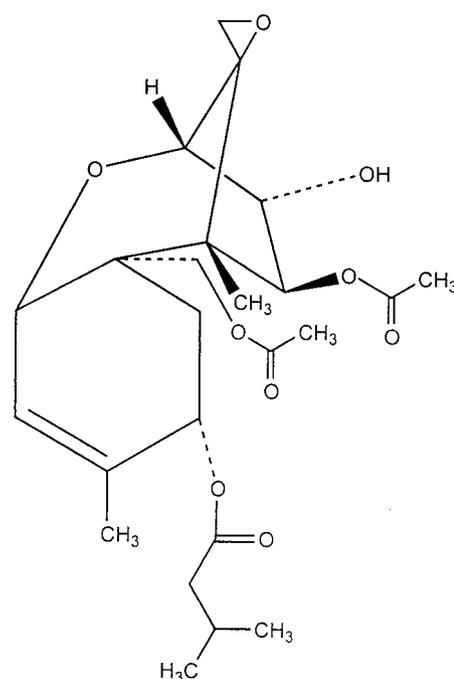
Trichothecenes

The trichothecenes constitute a family of more than sixty sesquiterpenoid metabolites produced by a number of fungal genera, including *Fusarium, Myrothecium, Phomopsis, Stachybotrys*, *Trichoderma*, *Trichothecium*, and others (49, 227, 261). The term trichothecene is derived from trichothecin, which was the one of the first members of the family identified. All trichothecenes contain a common 12,13-epoxytrichothene skeleton and an olefinic bond with various side chain substitutions. They are commonly found as food and feed contaminants, and consumption of these mycotoxins can result in alimentary hemorrhage and vomiting; direct contact causes dermatitis (8, 133, 165).

Trichothecenes are classified as macrocyclic or nonmacrocyclic, depending on the presence of a macrocyclic ester or an ester-ether bridge between C-4 and C-15 (40). The nonmacrocyclic trichothecenes in turn can be subclassified into two groups: type A, which have a hydrogen or ester type side chain at the C-8 position, and include T-2 toxin (Fig. 7), neosolaniol, and diacetoxyscirpenol, while the type B group contain a ketone and include fusarenon-x, nivalenol, and deoxynivalenol (Fig. 8). *Fusarium* is the major genus implicated in producing the nonmacrocyclic trichothecenes. Many members of this genus are significant plant pathogens; their convoluted taxonomy has already been mentioned (165).

The trichothecenes are extremely potent inhibitors of eukaryotic protein synthesis; different trichothecenes interfere with initiation, elongation, and termination stages. Trichodermin was the first trichothecene shown to inhibit peptidyl transferase activity (244, 275). Subsequently, it would appear that while all trichothecenes inhibit peptidyl transferase by binding to the same ribosome-binding site (79), they exert different
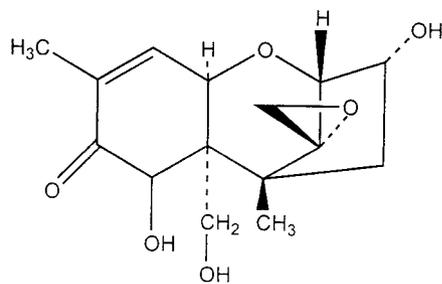
FIG. 8. Deoxynivalenol.

FIG. 9. Satratoxin H.

effects which can be correlated with different functional groups. The 12,13-epoxide group is essential for inhibition of protein synthesis; reduction of the 9,10 double bond reduces toxicity (173).

There is a long history of moldy grain "intoxications" in Japan, where disease in both human beings and farm animals has been attributed to *Fusarium* mycotoxicoses. *Fusarium gra-minearum* (teleomorph *Gibberella zeae*), regularly found on barley, oats, rye, and wheat, is considered the most important plant pathogen in Japan and is believed to be the cause of red mold disease (Akakabi toxicosis) (227, 261). As with all myco-toxins, depending on weather conditions, the growth of tricho-thecene-producing fungi and subsequent production of toxins vary considerably from year to year and from place to place (42).

Diacetoxyscirpenol, deoxynivalenol, and T-2 are the best studied of the trichothecenes produced by *Fusarium* species. Deoxynivalenol is one of the most common mycotoxins found in grains. When ingested in high doses by agricultural animals, it causes nausea, vomiting, and diarrhea; at lower doses, pigs and other farm animals exhibit weight loss and food refusal (218). For this reason, deoxynivalenol is sometimes called vomitoxin or food refusal factor. Although less toxic than many other major trichothecenes, it is the most prevalent and is commonly found in barley, corn, rye, safflower seeds, wheat, and mixed feeds (178).

The symptoms produced by various trichothecenes include effects on almost every major system of the vertebrate body; many of these effects are due to secondary processes that are initiated by often poorly understood metabolic mechanisms related to the inhibition of protein synthesis. A valiant attempt to compile and interpret the data for different trichothecenes, studied in different organisms, administered by different routes, at different doses, at dissimilar intervals, is given by Beasley (8). Of the naturally occurring trichothecenes, T-2 and diacetoxyscirpenol appear to be the most potent in animal studies. In addition to their cytotoxic activity, they have an immunosuppressive effect that results in decreased resistance to infectious microbes (196, 218). They cause a wide range of gastrointestinal, dermatological, and neurologic symptoms; see Trenholm et al. (258) for a summary of 50% lethal dose and other effects in a wide range of experimental and agricultural animals.

It has been hypothesized that T-2 and diacetoxyscirpenol are associated with a human disease called alimentary toxic aleu-kia. The symptoms of the disease include inflammation of the skin, vomiting, and damage to hematopoietic tissues. The acute
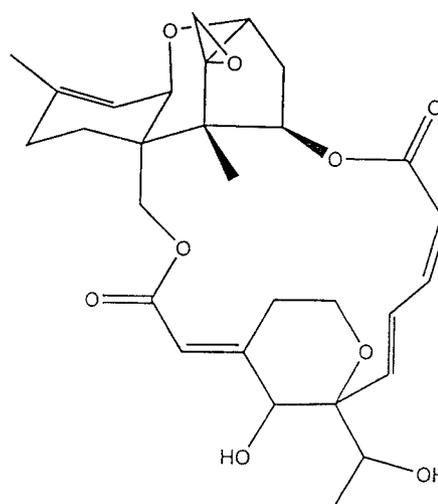
phase is accompanied by necrosis in the oral cavity, bleeding from the nose, mouth, and vagina, and central nervous system disorders. It is possible that alimentary toxic aleukia may some-times have been misdiagnosed as diphtheria or scurvy (171). The Soviet literature contains many reports of disease out-breaks associated with eating moldy grain, some dating back to the 19th century. Alimentary toxic aleukia affected a large population in the Orenburg district of the former U.S.S.R. during World War II. The sick people had eaten overwintered grain colonized with *Fusarium sporotrichioides* and *Fusarium poae* (132, 155).

The work on alimentary toxic aleukia has been reviewed in detail by Joffe (133) and by Beadall and Miller (7). Likewise, Matossian (171) analyzed patterns of weather and mortality from Russian data for 1861 to 1913 and concluded that low April temperatures (taken as a predictor of T-2 toxin in over-wintered and stored grain) were predictive of increased mor-tality the following summer. It has been pointed out that the hypothesis for an alimentary toxic aleukia-trichothecene con-nection would be strengthened if T-2 toxin were actually de-tected in samples of overwintered grain associated with ali-mentary toxic aleukia outbreaks (165) There has been little recent study of alimentary toxic aleukia, but mention of the disease is a fixture of mycotoxin reviews that emphasize human health. More research is needed.

The macrocyclic trichothecenes are produced largely by *My-rothecium*, *Stachybotrys*, and *Trichothecium* species. Glutinosin, a mixture of the macrocyclic trichothecenes verrucarin A and B, was originally identified as an antimicrobial agent (96). Recently, the trichothecenes produced by *Stachybotrys atra* (*Stachybotrys chartarum*) have received the most attention. They include satratoxins (Fig. 9), roridins, verrucarins, and atranones (116).

Stachybotryotoxicosis was first described as an equine dis-ease of high mortality associated with moldy straw and hay. Much of the early work on *Stachybotrys* toxins was published in the Russian literature, focused on horses, and has been well summarized by Forgacs (83). Until recently, human stachybot-ryotoxicosis was considered a rare occupational disease limited
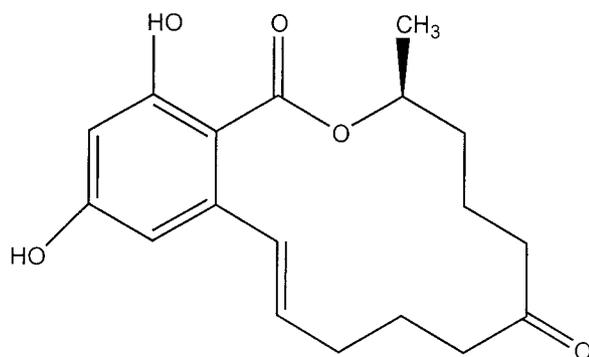
FIG. 10. Zearalenone.

largely to farm workers who handle moldy hay (117). However, it has become apparent that *Stachybotrys* grows well on all sorts of wet building materials with high cellulose content, for example, water-damaged gypsum board, ceiling tiles, wood fiber boards, and even dust-lined air conditioning ducts (55, 188, 189). The presence of *Stachybotrys* has been associated with pulmonary bleeding in infants (36, 77). Although toxic mold was found in the homes of the children with pulmonary bleeding, a cause-and-effect relationship has been difficult to prove (86, 134). Nevertheless, this incident and a few other highly publicized mold cases seem to have precipitated a series of multimillion-dollar law suits against contractors, real estate developers, and insurance companies as well as a great deal of public apprehension about "toxic molds." See the section on sick building syndrome below for more on this aspect of mycotoxicology.

It was suggested that the 10th plague visited on Egypt was a *Stachybotrys* infestation, but since the plague infected grain, not hay, it is more likely that *Aspergillus* or *Penicillium* was the culprit (224).

Many of the genes involved in trichothecene biosynthesis in *Fusarium sporotrichioides* and in *Myrothecium roridum* have been cloned and sequenced (34, 61, 206), and there is also considerable progress in understanding the regulation of the trichothecene gene cluster (253). Homologues of these trichothecene pathway genes have also been reported for *Fusarium graminearum* (24).

Zearalenone

Zearalenone (6-[10-hydroxy-6-oxo-*trans*-1-undecenyl]-B-resorcyclic acid lactone), a secondary metabolite from *Fusarium graminearum* (teleomorph *Gibberella zeae*) was given the trivial name zearalenone as a combination of *G. zeae*, resorcylic acid lactone, -ene (for the presence of the C-1′ to C-2 double bond), and -one, for the C-6′ ketone (263). Almost simultaneously, a second group isolated, crystallized, and studied the metabolic properties of the same compound and named it F-2 (38, 180). Much of the early literature uses zearalenone and F-2 as synonyms; the family of analogues are known as zearalenones and F-2 toxins, respectively. The structure of zearalenone is given in Fig. 10. Perhaps because the original work on these fungal macrolides coincided with the discovery of aflatoxins, chapters on zearalenone have become a regular fixture in monographs on mycotoxins (see, for example, Mirocha and Christensen [179] and Betina [15]). Nevertheless, the word toxin is almost certainly a misnomer because zearalenone, while biologically potent, is hardly toxic; rather, it sufficiently resembles 17β-estradiol, the principal hormone produced by the human ovary, to allow it to bind to estrogen receptors in mammalian target cells (147) Zearalenone is better classified as a nonsteroidal estrogen or mycoestrogen. Sometimes it is called a phytoestrogen. For the structure-activity relationships of zearalenone and its analogues, see Hurd (124) and Shier (233).

The zearalenones are biosynthesized through a polyketide pathway by *Fusarium graminearum*, *Fusarium culmorum*, *Fusarium equiseti*, and *Fusarium crookwellense*. All these species are regular contaminants of cereal crops worldwide (97). An association between moldy grain consumption and hyperestrogenism in swine has been observed since the 1920s; modern work shows that dietary concentrations of zearalenone as low as 1.0 ppm may lead to hyperestrogenic syndromes in pigs; higher concentrations can lead to disrupted conception, abortion, and other problems (148). Reproductive problems have also been observed in cattle and sheep (73).

The reduced form of zearalenone, zearalenol, has increased estrogenic activity. A synthetic commercial formulation called zeranol (Ralgro) has been marketed successfully for use as an anabolic agent for both sheep and cattle (53, 119). In 1989, zeranol was banned by the European Union, but it is still used in other parts of the world (97). Zearalenone has also been used to treat postmenopausal symptoms in women (264), and both zearelanol and zearalenone have been patented as oral contraceptives (115). It has been claimed that the high frequency of early menarche in Puerto Rico might be due to zearalenone and related compounds in the human diet (225); however, studies by the Food and Drug Administration do not support this hypothesis (147).

Recently, endocrine (hormone) disrupters have received a lot of public attention and are widely believed to reduce male fertility in human and wildlife populations (106) but it is not clear how much the zearalenones contribute to the total environmental load of xenoestrogens (233). Sometimes, hormone disrupters are labeled environmental toxicants, further muddying the distinction between a compound that can cause death (toxin) and a compound that has other pharmacological activities.

In summary, the zearalenone family of metabolites illustrates some of the limitations of scientific language. The biological potency of these compounds is high, but the actual toxicity is low. The 50% lethal dose in female rats is greater than 10,000 mg/kg; in female guinea pigs it is 5,000 mg/kg (115), while as little as one μg/kg may create a detectable uterogenic response in female swine. Thus, mycoestrogen is a more appropriate rubric than mycotoxin. Moreover, like the ergot alkaloids, in certain formulations some analogues of these macrolides can be called drugs.

Extensive reviews of Canadian and Scandinavian epidemiological data have concluded that the risk to human populations is minimal. The recommended safe human intake of zearalenone is estimated to be 0.05 μg/kg of body weight per day (147). Zearalenone levels in foodstuffs are not yet regulated anywhere (97). Nevertheless, because of its genuine bi-

ological potency and regular dietary cooccurrence with true mycotoxins such as the fumonisins and trichothecenes, it would not be prudent to ignore the potential of zearalenone to cause adverse health effects.

Other Mycotoxins and Purported Mycotoxicoses

Penicillium roqueforti and *Penicillium camemberti* (=*Penicillium caseicola*), species used to manufacture mold-ripened cheeses, produce a number of toxic metabolites, including penicillin acid, roquefortine, isoflumigaclavines A and B, PR toxin, and cyclopiazonic acid (228).

Several mycotoxins induce tremors as a neurological response in farm animals; most of these fungal tremorgens contain a modified indole moiety and are produced by certain species of *Aspergillus*, *Penicillium*, and *Claviceps*. The tremorgenic mycotoxins include the penitrems, janthitrems, lolitrems, aflatrem, paxilline, paspaline, paspalicine, paspalinine, and paspalitrem A and B (247). *Penicillium crustosum* produces penitrem A, a compound implicated in several cases of canine intoxication and one case of human tremor, vomiting, and bloody diarrhea (53, 118).

Originally isolated from *Penicillium cyclopium* (now *Penicillium aurantiogriseum*), cyclopiazonic acid is an indole tetramic acid. This mycotoxin is a specific inhibitor of calcium-dependent ATPase and induces alterations in ion transport across cell membranes (214). It is produced by many other species of *Penicillium* as well as several species of *Aspergillus*, including *Aspergillus flavus*. Cyclopiazonic acid was isolated from a sample of the ground nut meal that had been implicated in the original turkey X disease and may have contributed to the severity of that early aflatoxicosis. Furthermore, consumption of a kodo millet that was heavily contaminated with molds and contained detectable levels of cyclopiazonic acid produced kuduo poisoning, characterized by giddiness and nausea (209). Finally, some strains of *Penicillium camembertii* involved in the production of gourmet cheese produce cyclopiazonic acid (201).

The yellow rice toxins (citrinin, citreoviridin, luteoskyrin, rugulosin, rubroskyrin, and related compounds) are believed to have exacerbated Shoshin-kakke, a particularly malignant form of beriberi seen in Japan in the early 20th century (222).

A number of rare and obscure diseases have been hypothesized to be possible mycotoxicoses, often on extremely meager evidence. These include Kashin-Beck disease in Russia, mselini joint disease and onylalai in Africa, endemic familial arthritis of Malnad in India, frontoethmoidal encephalomeningocele in Myanmar, sago hemolysis in Papua New Guinea, and deteriorated sugar cane poisoning in China. Descriptions of these conditions and their purported association with exposure to toxigenic fungi have been admirably summarized by Beardall and Miller (7).

SPECIAL TOPICS

The two aspects of mycotoxin research that have received the most coverage in the popular press concern their possible use as agents of chemical warfare and their potential involvement in a variety of building-related disease conditions. Very brief introductions to these topics are given here.

Bioterrorism

Mycotoxins can be used as chemical warfare agents (43). There is considerable evidence that Iraqi scientists developed aflatoxins as part of their bioweapons program during the 1980s. Toxigenic strains of *Aspergillus flavus* and *Aspergillus parasiticus* were cultured, and aflatoxins were extracted to produce over 2,300 liters of concentrated toxin. The majority of this aflatoxin was used to fill warheads; the remainder was stockpiled (248, 290). Aflatoxins seem a curious choice for chemical warfare because the induction of liver cancer is "hardly a knockout punch on the battlefield" (249). Even so, the repugnance caused by the use of chemical and biological weapons is the kind of emotional response that terrorists seek to elicit. Furthermore, if used against ethnic groups such as the Kurds, the long-term physical and psychological results could be devastating. Finally, some experts think aflatoxin might have been selected simply because it was the "pet" toxin of an influential Iraqi scientist (249).

Unlike the aflatoxins, trichothecenes can act immediately upon contact, and exposure to a few milligrams of T-2 is potentially lethal. In 1981, then Secretary of State Alexander Haig of the United States accused the Soviet Union of attacking Hmong tribesman in Laos and Kampuchea with a mysterious new chemical warfare agent, thereby violating the 1972 Biological Weapons Convention. The symptoms exhibited by purported victims included internal hemorrhaging, blistering of the skin, and other clinical responses that are caused by exposure to trichothecenes. Leaf samples from Kampuchea were analyzed by Chester Mirocha of the University of Minnesota, who found nivalenon, deoxynivalenon, and T-2. Furthermore, Mirocha stated that the quantity and proportions of the toxins were unknown in nature and that, based on reports in the scientific literature, these mycotoxins did not occur naturally in Southeast Asia. (We now know that trichothecene-producing fungi do exist in Southeast Asia.) The purported chemical warfare agent came to be known as yellow rain (168).

In a bizarre turn of events, Matthew Meselson of Harvard University produced compelling evidence that yellow rain might have a benign natural explanation. Specks of yellow material found on foliage and other samples of the purported warfare agents from Southeast Asia were composed of plant pollen. The pollen grains were the result of so-called "cleansing flights" (mass defecations) dropped by swarms of wild Asian honeybees (190). Although many government officials tried to dismiss Meselson's explanation as a "great bee caper," the pollen hypothesis was widely accepted. An editorial by John Maddox stated, for example, that the pollen work created "a serious challenge for those who have been arguing that visual observations of 'yellow rain' can be counted as evidence of the use of chemical weapons against embattled populations" (reference 156, p. 207). As one mycologist subsequently quipped, the bee pollen theory "seems too ludicrous not to be true" (reference 182, p. 166).

At the time, several well-written and accessible summaries of the yellow rain controversy appeared in the popular press (see, for example, Pringle [205] and Whiteside [278]). Two books were also published on the subject. The government mycotoxin theory was promulgated in *Yellow Rain* (229), while the opposing position was addressed in *The Yellow Rainmakers*:

Are Chemical Weapons Being Used in Southeast Asia? (78). Although analytical methods were in their infancy during the controversy, they were still sensitive enough to pick up low levels of environmental trichothecene contamination. The government research highlighted, if nothing else, that natural mycotoxicoses were an important health hazard in Southeast Asia (78).

Indoor Air Quality and Sick-Building Syndrome

Associated with dirty air conditioning vents and filters, the dust dislodged during renovations, and the aftermath of water damage to interiors, molds in indoor environments have been implicated in allergies for many years. The most common genera of indoor molds are *Alternaria, Aspergillus*, *Cladosporium*, and *Penicillium* (57, 94, 176). However, several relatively recent events have changed the way in which people view moldy indoor environments and their associated health threats. The first stems from changes in modern, energy-efficient building practices. Many occupants of "tight" new buildings exhibit adverse health effects that are relieved when they leave the building. The condition has come to be called sick-building syndrome. The most prevalent symptoms are irritation of the eyes and respiratory tract, but a large number of other vague complaints have also been reported, including headache and fatigue, skin irritation, nonspecific hypersensitive reaction, and peculiar odor and taste sensations. By stipulated definition, the designation sick-building syndrome means that no specific etiological factor can be identified (75, 90, 191). Among the suspected etiological agents of sick-building syndrome are poor ventilation, office and cleaning supply chemicals, and different forms of microbial contamination. When causal factors can be identified (e.g., as in Legionnaires' disease or asbestos contamination), the appropriate term is supposed to be building-related illness (90, 125, 220). However, in the public imagination, sick-building syndrome is often associated with the presence of toxic molds, especially *Stachybotrys.*

Much of the concern about *Stachybotrys* toxins originated in 1994 with the publication by the Centers for Disease Control of a cluster of eight cases of idiopathic pulmonary hemorrhage among infants in Cleveland, Ohio (36). *Stachybotrys chartarum* was implicated in the outbreak. The mold was found more frequently in the houses of affected babies than in control houses (58). A case-control study identified water damage (leaks and flooding) and smoking as risk factors for developing the infant pulmonary hemorrhage (183). Other evaluations and a second report from the Centers for Disease Control and Prevention were more equivocal and concluded that a cause-and-effect relationship had not been proven (37, 86, 134). Nevertheless, the Committee on Public Health of the American Academy of Pediatrics issued a statement on the toxic effects of indoor molds, alerting pediatricians to the possibility that idiopathic pulmonary hemorrhage may be associated with molds (3). Strains of the fungus isolated from the Cleveland outbreak produced a number of highly toxic macrocyclic trichothecenes (130). *Stachybotrys chartarum* was also shown to produce the hemolysin stachylysin (272). Although there is no method for testing for *Stachybotrys* mycotoxins in humans, PCR methods for evaluating the presence of *Stachybotrys chartarum* have been developed (271).

Without a doubt, fungi, including many toxigenic species, are regularly encountered in damp indoor environments, but there have been relatively few determinations of mycotoxins in these environments (reference 129, p. 49). Because mycotoxins, as currently defined, are not volatile, respiratory exposure is thought to be related to inhalation of mold spores, hyphal fragments, and contaminated dusts. It should be pointed out that almost nothing is known about the toxicity of the myriad volatile compounds produced by fungi.

The early literature on mycotoxins in indoor air has been reviewed by Hendry and Cole (110). It is known that spores in air-borne dust can cause ochratoxin exposure. Significant levels of ochratoxin A were found in dusts from cowsheds in Norway (236) and from a "problem household" in the United States (212). In the latter study, all of the mammals in the affected house (humans, dogs, and guinea pigs) exhibited polyuria, a known symptom of ochratoxicosis in farm animals; the human residents also complained of increased thirst, edema, skin rash, and general lethargy (212). Sterigmatocystin has been isolated from water-damaged wallpaper (187) and from damp carpeting (74). Trichothecenes are found in aerosolized conidia, so inhalation of aerosols containing high spore concentrations is a potential health hazard (241). T-2, diacetoxyscirpenol, roridine A, and T-2 tetraol have been detected in the dust from office ventilation systems (240).

Toxic-mold fears have precipitated a spate of lawsuits. In particular, a Texas case against Farmers Insurance Group has attracted a lot of publicity, and the number of mold damage cases, especially in water-damaged homes, is growing at a rapid rate (9). Unfortunately, much of the evidence is conjectural. Mycotoxins and other microbial products have been implicated as causative agents, but the range of symptoms attributed to toxic molds exceeds what can be explained rationally in terms of toxicological mechanisms (194).

In summary, many occupants of modern, sealed, air-conditioned buildings, especially water-damaged buildings, have reported adverse health effects. No specific microbe or toxin has been identified as the single dominant etiological agent. Exposure to fungi in home and work settings is an increasing area of concern, and the legal climate has led to the development of a new cottage industry in mold abatement. More data are needed before any definite conclusions can be made about the health effects resulting from inhalation of toxigenic mold spores (129).

FOOD SAFETY AND REGULATION

Mycotoxin-producing mold species are extremely common, and they can grow on a wide range of substrates under a wide range of environmental conditions. For agricultural commodities, the severity of crop contamination tends to vary from year to year based on weather and other environmental factors. Aflatoxin, for example, is usually worst during drought years; the plants are weakened and become more susceptible to insect damage and other insults (67). Mycotoxins occur, with varying severity, in agricultural products all around the world. The estimate usually given is that one quarter of the world's crops are contaminated to some extent with mycotoxins (80, 159).

Mycotoxins can enter the food chain in the field, during

storage, or at later points. Mycotoxin problems are exacerbated whenever shipping, handling, and storage practices are conducive to mold growth. The end result is that mycotoxins are commonly found in foods. Kuiper-Goodman (144), a leading figure in the risk assessment field, ranks mycotoxins as the most important chronic dietary risk factor, higher than synthetic contaminants, plant toxins, food additives, or pesticide residues.

The economic consequences of mycotoxin contamination are profound. Crops with large amounts of mycotoxins often have to be destroyed. Alternatively, contaminated crops are sometimes diverted into animal feed. Giving contaminated feeds to susceptible animals can lead to reduced growth rates, illness, and death. Moreover, animals consuming mycotoxin-contaminated feeds can produce meat and milk that contain toxic residues and biotransformation products. Thus, aflatoxins in cattle feed can be metabolized by cows into aflatoxin M_1, which is then secreted in milk (267). Ochratoxin in pig feed can accumulate in porcine tissues (219). Court actions between grain farmers, livestock owners, and feed companies can involve considerable amounts of money. The ability to diagnose and verify mycotoxicoses is an important forensic aspect of the mycotoxin problem (198).

People who have enough to eat normally avoid foods that are heavily contaminated by molds, so it is believed that dietary exposure to acute levels of mycotoxins is rare in developed countries. Nevertheless, many mycotoxins survive processing into flours and meals. When mold-damaged materials are processed into foods and feeds, they may not be detectable without special assay equipment. It is important to have policies in place that ensure that such "hidden" mycotoxins do not pose a significant hazard to human health.

It would require an entirely different review article to do justice to the subject of food safety and the related issues of mycotoxin analysis, regulation, and legal liability. Several national and international organizations and agencies have special committees and commissions that set recommended guidelines, develop standardized assay protocols, and maintain up-to-date information on regulatory statutes. There are also several mycotoxin associations. The web sites for these commissions and organizations are excellent sources for the latest information. See, for example, the Council for Agricultural Science and Technology (www.cast-science.org), the Mycotoxicology Newsletter (www.mycotoxicology.org), the Society for Mycotoxin Research (www.mycotoxin.de), the American Oil Chemists Society Technical Committee on Mycotoxins (www.aocs.org), the Food and Agriculture Organization of the United Nations (www.fao.org), the International Union for Pure and Applied Chemistry Section on Mycotoxins and Phycotoxins (www.iupac.org), the Japanese Association of Mycotoxicology (www.chujo-u.ac.jp/myco/index.html), and the U.S. Food and Drug Administration Committee on Additives and Contaminants (www.fda.gov).

Since it is normally impracticable to prevent the formation of mycotoxins, the food industry has established internal monitoring methods. Similarly, government regulatory agencies survey for the occurrence of mycotoxins in foods and feeds and establish regulatory limits. Guidelines for establishing these limits are based on epidemiological data and extrapolations from animal models, taking into account the inherent uncertainties associated with both types of analysis. Estimations of an appropriate safe dose are usually stated as a tolerable daily intake (144, 145, 239).

Considerable research has been devoted to developing analytical methods for identifying and quantifying mycotoxins in food and feeds. The chemical diversity of mycotoxins and the equally diverse substrates in which they occur pose challenges for analytical chemistry. Each group of compounds and each substrate have different chemical and physical properties, so the methods for the separation of toxins from substrates must be developed on a case-by-case basis. It is, for example, quite a different matter to assay aflatoxin from peanut butter than it is to identify T-2 toxin from corn. Mycotoxins are often produced in trace concentrations, so the sensitivity of the detection systems is also essential. Traditional methods have relied on solvents for clean-up steps and various chromatographic techniques for quantification; more recently, immunogenic assays that can be applied to samples with little or no clean-up have been developed (39). Since mycotoxins are low-molecular-weight haptens, they are nonimmunogenic. Nonetheless, they can be conjugated to a protein carrier, and antibodies against almost all the major mycotoxins are now available. See *Mycotoxin Protocols* (259) and the chapter by Wilson et al. on mycotoxin analytical techniques in *Mycotoxins in Agriculture and Food Safety* (282) and the references cited therein for a good summary of information on equipment, reagents, and procedures for assaying mycotoxins.

Complete elimination of any natural toxicant from foods is an unattainable objective. Therefore, naturally occurring toxins such as mycotoxins are regulated quite differently from food additives (81). The U.S. Food and Drug Administration, the European Union, the Institute of Public Health in Japan, and many other governmental agencies around the world test products for aflatoxins and other mycotoxins and have established guidelines for safe doses, but there is a need for worldwide harmonization of mycotoxin regulations (281). The United States uses one set of guidelines, the European Union uses another, and Japan yet another, and many other guidelines have also been developed. Unfortunately, sometimes the regulatory community seems to be setting limits based more on current analytical capabilities than on realistic health factors (281). The Food and Agriculture Organization of the United Nations has published a series of compendia summarizing worldwide regulations for mycotoxins (81). A modified version of this compendium is presented as an appendix by Weidenborner (277).

SUMMARY

Fungi cause human illness in different ways. Mycoses are the best-known diseases of fungal etiology, but toxic secondary metabolites produced by saprophytic species are also an important health hazard. The term mycotoxin is an artificial rubric used to describe pharmacologically active mold metabolites characterized by vertebrate toxicity. They fall into several chemically unrelated classes, are produced in a strain-specific way, and elicit some complicated and overlapping toxigenic activities in sensitive species that include carcinogenicity, inhibition of protein synthesis, immunosuppression, dermal irritation, and other metabolic perturbations. Mycotoxins usually

enter the body via ingestion of contaminated foods, but inhalation of toxigenic spores and direct dermal contact are also important routes.

It is difficult to prove that a disease is a mycotoxicosis. Molds may be present without producing any toxin. Thus, the demonstration of mold contamination is not the same thing as the demonstration of mycotoxin contamination. Moreover, even when mycotoxins are detected, it is not easy to show that they are the etiological agents in a given veterinary or human health problem. Nevertheless, there is sufficient evidence from animal models and human epidemiological data to conclude that mycotoxins pose an important danger to human and animal health, albeit one that is hard to pin down. The incidence of mycotoxicoses may be more common than suspected. It is easy to attribute the symptoms of acute mycotoxin poisoning to other causes; the opposite is true of etiology. It is not easy to prove that cancer and other chronic conditions are caused by mycotoxin exposure. In summary, in the absence of appropriate investigative criteria and reliable laboratory tests, the mycotoxicoses will remain diagnostically daunting diseases.

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