Aspergillus: Biology and Industrial Applications

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Aspergilli are important agents of disease among both domestic and wild animals. The growth and copious sporulation of several *Aspergillus* species on hay, stored grain, bedding, litter, and composting plant material in the animals' normal environment ensures frequent exposure to these agents and to feeds colonized by them. These molds cause disease both by infection and by intoxication. Infection caused by aspergilli (aspergillosis) occurs regularly in poultry, young calves, mature cows, occasionally in mature horses, and also affects exotic and wild avian species. Occasional infections may be expected to occur in most animal species. The development of aspergillosis in all these animals may be the sequela of either inhaled or ingested organisms colonizing surfaces of respiratory or enteric structures and progressing by erosion, macrophage carriage, vascular dissemination, or other means to other organ systems including brain, abdominal viscera, and the gravid uterus. With the exception of young broiler chickens, where aspergillosis may involve a very high percent of the flock, infection rates in animal groups rarely exceed 5–10% of the group. However, the ubiquitous nature of the agents, chiefly *Aspergillus fumigatus*, ensures wide involvement of separate animal groups, which results in significant economic losses. De-
tailed information on the more prominent forms of aspergillosis in animals is given below.

The second form of animal disease caused by aspergilli are mycotoxicoses. Several Aspergillus species contain mycotoxigenic strains that cause diseases of the liver, kidney, enteric, and other organs. Some of these toxins have very broad consequences, causing suppression of immunologic mechanisms, teratogenic effects, and carcinogenesis. In virtually all cases of Aspergillus-induced mycotoxicosis, the toxigenic fungi colonize standing or stored feed materials such as corn, cottonseed, peanuts, or cereal grains, all of which are prominent animal feed concentrates. When conditions of moisture and feed substrate are compatible with fungal growth, prodigious growth of the toxigenic fungi ensues with elaboration of toxic secondary metabolites, the mycotoxins, into the feed stuff. The mycotoxins generally affect specific target organs or systems such as liver, kidney, thymus, skin, enteric mucosa, bone marrow, gut-associated lymph tissue, etc. When high doses of toxin are consumed, acute clinical episodes with distinct symptomatology generally ensue. However, when low levels of toxin intake occur, the clinical effects are less distinctive, often obscure, and may include such protean manifestations as reduced rate of growth by young animals, reduced production of milk or eggs, and increased susceptibility to infectious diseases. Mycotoxin production is often a regional problem and has definite seasonal peaks wherein the crops of one year may be considerably more involved than those of other years. These fluctuations are caused by varying conditions of drought, wetness during harvest, or insect damage, making crops differentially susceptible to fungal invasion. In any year, the storage of inadequately dried grain or the use of leaking grain storage facilities create conditions conducive to fungal growth and toxin elaboration. Even bagged commercial feeds, when allowed to become wet, may create minienvironments that foster mycotoxin formation.

The mycotoxins generally are heat resistant so they survive many feed processing actions such as pelleting. They are nonantigenic so they do not promote acquired immunity in exposed animals. Because of their severe consequences on the health of human consumers, legal surveillance has been established for some mycotoxins, notably aflatoxin in the USA. These regulations limit the movement, use, detoxification, and resale across state or international lines of feedstuffs known to be contaminated beyond certain established limits. Their occurrence in commercial feeds creates special diagnostic and forensic needs to establish mycotoxins as the cause of an animal disease outbreak. Credible incrimination can only be made by the demonstration of the toxin in feed or in tissues and body fluids of affected animals. Isolation of potentially toxigenic fungi from suspect feeds is not sufficient evidence for incriminating the feed because the isolated fungal strain may not be toxigenic, the feed substrate may not have supported toxin formation, or the environmental conditions may not have provided opportunity for toxin elaboration. There is no substitute for chemical identification of a mycotoxin in the feed that is of a type and in sufficient quantity...
to cause the disease observed in affected animals. Detailed information on specific mycotoxics of *Aspergillus* origin is given below.

10.1 ANIMAL INFECTIONS CAUSED BY ASPERGILLI

10.1.1 Sources of Infection
The surroundings of both domestic and wild animals are endowed with dead and often decaying vegetation in the form of feed, bedding, litter, and standing forage. Some fungal colonization of these materials is inevitable but when they become moist from natural precipitation, or from fecal and urine contamination, or from spillage around waterers, fungal growth and sporulation can be prodigious. Movement of hay, bedding, or litter inside animal housing units creates substantial aerosols that provide ample opportunity for respiratory exposure (Austwick and Venn 1968). *Aspergillus* conidia are usually under the 5 μm diameter that permits deep inspiration and deposition in bronchioles and pulmonary alveolae of all animals and in air sacs of avian species. Thus infection rates in stabled cattle and horses or housed poultry are usually substantially greater than in their free ranging counterparts. Some *A. fumigatus* strains produce an abundance of elastase, which acts as a virulence factor in infected tissue (Kothary et al. 1984).

10.1.2 Infecting Flora
*Aspergillus fumigatus* is by far the most frequent agent of aspergillosis in animals (Ainsworth and Austwick 1973). Other species are frequently reported from surveys of tissues of cattle (Richard et al. 1970; Knudtson and Kirkbride 1992), poultry (Ainsworth and Austwick 1973), and horses (Cook et al. 1968). Several of these have been found as pathogens in lungs, air sacs, gutteral pouches, intestines, and bovine placentas. Prominent among these other pathogenic species are *A. flavus* and *A. nidulans*.

10.1.3 Avian Aspergillosis
Avian aspergillosis is seen most frequently in young broiler chickens, turkey pouls, older breeding turkeys that are housed on built-up litter, and exotic birds held in captivity such as raptors and penguins. At one time aspergillosis accounted for 10% of all losses in broiler chicks. Many of these birds were infected in the hatchery where *A. fumigatus* in incubators grew through the porous egg shells, sporulated in the air cell of the egg, and created massive aerosols when the shell was broken. The present day hatchery practice of fumigating the incubators has substantially reduced this phase of infection, which is called “brooder pneumonia.” Built-up litter in turkey houses is a major source of *A. fumigatus* infection for breeding turkeys. Exotic birds held in captivity are often stressed due to artificial rearing conditions, climate, and other conditions that do not match the birds’ native surroundings.
Predisposition to avian aspergillosis includes the bird's age; young birds are generally more prone to clinical infection. Some mycotoxins impair immunological responses and resistance mechanisms when consumed by poultry and other animals; T-2 toxin, produced by various *Fusarium* species, impairs phagocytosis in rabbits and makes them more susceptible to invasive aspergillosis (Niyo et al. 1988).

Avian aspergillosis is usually seen as a respiratory infection (pneumon-icomyositis; airsacculitis). *A. fumigatus*, or occasionally other fungi, colonize the mucosal surfaces of the respiratory tract and also the serosal surfaces of the unique avian air sacs, resulting in mycotic airsacculitis. Primary infection of the eye and gut mucosa may occur and metastatic infection of the abdominal viscera and brain are frequent sequela. Experimental aerosol infections of turkey pouls with *A. fumigatus* have shown that the organisms can be cultured from the peripheral blood and brain within minutes after cessation of aerosol exposure (Richard et al. 1981). Presumably the fungus is carried within macrophages to these locations.

The symptomatology of avian aspergillosis is varied and indistinct. Prominent among the signs are unthriftiness, anorexia, depressed attitude, dyspnea, and sometimes diarrhea and death. In more chronic cases the wings droop and there are signs of respiratory distress, including coughing and open mouth breathing. Loss of righting reflex or torticollis may accompany central nervous system infection.

Important lesions at necropsy include caseous plaques in the air sacs and bronchioles and areas of caseation necrosis in the lungs and parenchymatous organs of the abdomen. If the infectious foci are exposed to aeration as in pulmonary bullae and air sacs, the organism usually sporulates and the lesion is covered with blue gray powdery material that are conidia formed in situ. In these cases the entire conidial head of the organism can be seen in diagnostic microscopy preparations (Figure 10–1). Pathologic features of aspergillosis include suppuration to caseation necrosis of affected tissue and the presence of narrow, (approximately 3 μm), septate, hyaline hyphae with parallel sides (Figure 10–2). There is a tendency for the mycelial elements to satellite around vascular structures.

Control of avian aspergillosis is largely dependent on removal of heavily laden infectious sources from the birds' environment. Removal of built-up litter, prevention of moisture around waterers that promote fungal growth and sporulation and fumigation of hatchery incubators are important considerations. Therapy for aspergillosis is rarely instituted in birds, with the exception of valuable exotic individuals where amphotericin B and 5-fluorocytosine have been used (Redig 1986; Speller 1980).

### 10.1.4 Mycotic Abortion

Mycotic abortion in cattle is an economically important disease to both the dairy industry and beef industry throughout the world. Two surveys have shown that mycotic abortion was the most frequent cause of diagnosed abortion in stabled eastern dairy cattle (Hubbert et al. 1973) and the second most prevalent cause of diagnosed abortion in western range cattle (Kirk-
Aspergillus fumigatus is the most common agent of this disease, accounting for approximately 75% of all cases (Ainsworth and Austwick 1973; Knudtson and Kirkbride 1992). In mycotic abortion caused by *A. fumigatus*, the cow is symptomless until abortion occurs. After aborting, the cow clears the infection and returns to effective breeding status. Within an affected herd, abortion may occur in 5–10% of the pregnant cows.

The pathogenesis of bovine mycotic abortion appears to involve exposure to a substantial source of the fungus in moldy hay or bedding. From either source, large quantities of fungal spores or mycelial elements are taken in by inhalation and ingestion. When pregnant cows in their third trimester of gestation are exposed they are particularly susceptible to infection.

The fungal elements penetrate from the lung or though the intestinal mucosa, gain access to the vascular supply of the placenta and colonize there, causing mycotic placentitis. The affected placental cotyledons are necrosed and if sufficient numbers are destroyed the fetus is aborted. When only a few cotyledons are involved, placentation may continue but the fungus grows across the placenta and invades the amniotic fluid and tissues of the calf. At birth, such a calf often has skin lesions or internal organs with foci of aspergillosis. Ascending infection through the vaginal canal has not proven to be an effective route of exposure but either inhalation of
conidia or ingestion of conidia and mycelial elements have proven to be effective routes of infection (Pier et al. 1972, 1983). In all cases of mycotic abortion caused by *A. fumigatus*, there is demonstrable mycotic placentitis. When examined microscopically, scrapings or sections from necrotic cotyledons on the aborted placenta usually reveal an abundance of slender (3 μm), branching, septate, hyaline mycelia similar to those of avian aspergillosis (see Figure 10–3). While cultural examination of placental scrapings is necessary to identify the causative agent, microscopic demonstration of branching mycelial forms in placental tissue is necessary to assure that the agent is present as a tissue-invading pathogen rather than a contaminant from the cow's environment.

Predisposition to mycotic abortion involves third-trimester pregnancy and an abundant source of *A. fumigatus* (or other causative fungi) on the hay or bedding of the cow. Agents that disrupt intestinal mucosal integrity and facilitate colonization and invasion by fungal mycelia are thought to facilitate the disease. Intestinal ulcers, caused by bovine virus diarrhea virus, and migrating helminth larvae that carry fungal elements from the gut lumen into surrounding tissues, are considered to be factors of predisposition. It is probable that strains of *A. fumigatus* that are elastase producers would be more effective in invading and causing necrosis of the placental tissues.
10.1 Animal Infections Caused by Aspergilli

Control of mycotic abortion involves removing moldy hay, bedding, or other prominent sources of conidia and mycelial elements. Control of migrating helminth larvae and viral agents of intestinal erosions are also suggested.

10.1.5 Enteric Infections
Young calves and other newborn animals occasionally develop foci of *Aspergillus* or other mycotic infections in the intestinal mucosa. The infections occur in neonatal animals up to approximately one month of age. In calves, mucosal ulcerations caused by bovine virus diarrhea virus as well as other agents affecting mucosal integrity (e.g., cryptosporidia, coccidia, migrating helminth larvae, etc.) predispose to fungal invasion. Some calves are born with aspergillosis of skin, lungs, and intestine because they are survivors of slowly developing cases of mycotic placentitis (see Section 10.1.4) that permit elements of *A. fumigatus* to grow across the placenta and colonize the amniotic fluid and fetus. In these instances, insufficient placental necrosis allows the pregnancy to progress to term but the fetus is infected in utero.

10.1.6 Other Animal Infections
Another prominent focus of *Aspergillus* infection in animals is equine gutteral pouch mycosis (Cook et al. 1968). The gutteral pouch is a blind diverticulum of the equine eustachian tube. Affected horses develop swellings
about the face, protrusion behind the mandible (the pouch’s location), dysphagia, dyspnea, and very often acute epistaxis, which is sometimes life threatening. The infecting fungi, chiefly *A. fumigatus* and *A. nidulans*, gain access to the gutteral pouch via aerosols of conidia from hay or bedding and colonize the mucosal epithelium causing necrosis (Figure 10–4). The necrosis may extend to adjacent structures, including the major vasculature in the area, resulting in severe nasal hemorrhage. Treatment is by surgical invasion, cautery, and irrigation of the affected pouch with fungicidal preparations (Greet 1987).

### 10.2 Mycotoxicoses of *Aspergillus* Origin

Most mycotoxins that affect animals are produced by toxigenic fungi that colonize feed products, elaborate their toxins into the feed substrate, and elicit disease when the animal ingests the contaminated material. There are several prominent mycotoxins produced by aspergilli that cause adverse effects on animal health (Pier 1981; Richard and Thurston 1986). These toxins are considered in detail below.
10.2.1 Aflatoxicosis

The aflatoxins are a closely related group of mycotoxins that are produced by toxigenic strains of *Aspergillus flavus*, and *A. parasiticus*. (Recent information indicates that some strains of *A. nomius* may also be aflatoxigenic. Kurtzman et al. 1987). Aflatoxin B₁ is the most biologically active form of aflatoxin. Most animals, including humans, are susceptible to the effects of aflatoxin, although some are more susceptible to its action than others (Table 10-1). In general, the young of each animal species are more susceptible than the mature.

The main target organ for aflatoxin is the liver; the thymus of young animals is also an important target organ. Acute aflatoxicosis in all animal species is typified by hepatic necrosis, coagulopathy (associated with liver injury), serosal, and mucosal hemorrhage, icterus, and often death. Animals dying with acute aflatoxin poisoning often have extensive hemorrhages and free blood in the intestinal lumen. The urine may be dark with bile pigments. At lesser dose rates, affected animals develop yellow, fibrotic livers with

<table>
<thead>
<tr>
<th>TABLE 10-1</th>
<th>Dose-Related Effects of Aflatoxin on Animals¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single oral dose, LD₅₀ (mg/kg body weight)</td>
<td></td>
</tr>
<tr>
<td>Duckling</td>
<td>0.4</td>
</tr>
<tr>
<td>Pig</td>
<td>0.6</td>
</tr>
<tr>
<td>Turkey</td>
<td>1.4</td>
</tr>
<tr>
<td>Sheep</td>
<td>2.0</td>
</tr>
<tr>
<td>Chick</td>
<td>6.5</td>
</tr>
<tr>
<td>Rat</td>
<td>5.5–17.9</td>
</tr>
<tr>
<td>Acute hepatitis and coagulopathy (Daily dose in mg/kg body weight per day²)</td>
<td></td>
</tr>
<tr>
<td>Calf</td>
<td>0.2–0.5</td>
</tr>
<tr>
<td>Pig</td>
<td>0.1–0.2</td>
</tr>
<tr>
<td>Broiler chicken</td>
<td>0.2–0.4</td>
</tr>
<tr>
<td>Decreased growth rate (mg/kg per day)</td>
<td></td>
</tr>
<tr>
<td>Calf</td>
<td>0.1–0.2</td>
</tr>
<tr>
<td>Pig</td>
<td>0.1</td>
</tr>
<tr>
<td>Turkey</td>
<td>0.2</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>0.02</td>
</tr>
<tr>
<td>Impaired immunogenesis (mg/kg per day)</td>
<td></td>
</tr>
<tr>
<td>Turkey poult</td>
<td>0.01</td>
</tr>
<tr>
<td>Pig</td>
<td>0.07</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>0.04</td>
</tr>
</tbody>
</table>

¹ Adapted, in part, from Pier (1981).
² Mg/kg body weight per day × 25 = approximate feed level in parts per million.
fatty changes in the hepatocytes and bile duct hyperplasia being evident in histopathologic preparations. The gall bladder is usually distended with dilute bile. These animals have high prothrombin times and their sera contain above-normal levels of liver-related enzymes and bile pigments; their growth rates are retarded and cell-mediated immune functions are impaired. Affected animals generally have an unthrifty appearance and are more susceptible to many infections than normal animals.

Aflatoxin is well established as a carcinogen in some laboratory animals, trout, and higher vertebrates that develop hepatic carcinomas after exposure to aflatoxin over long periods of time (Hsieh et al. 1977; Sinhuber et al. 1977; Peers and Linsell 1973). However, the relationship of aflatoxin to human liver cancer is somewhat problematic due to conflicting evidence among several epidemiologic studies and the lack of consideration in some of these studies of other risk factors involved in liver cancer such as hepatitis B virus. In light of the problems with determining past exposure to aflatoxins in a human population and the conflicting evidence regarding the probable etiologic relationship of aflatoxin to primary liver cancer in humans (Campbell et al. 1990), this aspect of aflatoxicosis remains questionable. Nevertheless, the International Agency for Research on Cancer (IARC) has classified aflatoxin B1 as a probable human carcinogen (IARC 1987). Recent developments in methods of immunoassay for aflatoxin and related substances at the macromolecular level may help clarify this question (Garner 1989). Carcinogenesis has not been a problem in food-producing animals, possibly due to their relatively short life span. Teratogenic and mutagenic activities also have been ascribed to aflatoxin (Hayes 1981).

Among the economically significant effects of aflatoxin on domestic animals, in addition to death loss, are those of reduced rate of growth, the impairment of immunogenesis, and native resistance mechanisms. The rate of growth and feed efficiency of young growing animals are important to economic production of market animals; both criteria are substantially depressed by aflatoxin levels below those needed to produce clinical illness. Thus, economic effects are present without overt clinical disease. Immunosuppression and reduction of native defense mechanisms are also produced by relatively low levels of aflatoxin. Both aflatoxin B1 and M1 cause thymic aplasia in young animals; the cortical layer of thymocytes are depleted or absent. Reduced lymphokine production, reduce macrophage activity, impaired development of delayed cutaneous hypersensitivity, impaired graft versus host activity, and a reduction in the C3 level of complement have all been reported for aflatoxin-treated animals. The effects of aflatoxin on immunosuppression have been shown to cross the most complex of placentas and affect the unborn fetus. These are very important actions in animal populations that rely on vaccination and acquired immunity for their resistance to common diseases. Because the immunosuppressive effects can occur at levels below those needed for overt clinical disease, the livestock producer often sees the signs of the infectious disease
10.2 Mycotoxicoses of Aspergillus Origin

rather than the signs of the mycotoxicosis that predisposed the animals to
infection (Pier 1986).

Because of the suspected carcinogenicity of aflatoxin for humans, the
Food and Drug Administration (FDA) has developed a surveillance system
and action levels for aflatoxin in various commodities. In general, FDA
action levels are 20 ppb for feed commodities in interstate commerce; how­
ever, certain commodities used for animal feed have been eased to 300 ppb
(e.g., cottonseed meal used in feed and feed corn used for finishing beef
cattle). Because there is approximately a 14,000:1 ratio between aflatoxin
feed content and the detectable residue in meat, these have been deemed
safe levels for animal consumption relative to the human food chain. Milk,
however, has a narrower feed-to-residue ratio, approximating 200:1; for this
reason animal feeds used for dairy cattle have more stringent require­
ments. Market milk is under continued surveillance and aflatoxin residues in milk
must be below 0.5 ppb.

Aflatoxin has probably always been with us and will continue to be with
us as an environmental contaminant. Because of its potent biological effects,
however, we must be aware of its presence and control its level in human
and animal feeds. There are a number of chemical tests that can be used
to monitor its presence in feed, milk, and other foods to ensure the safety
of human and animal health. When a feed or food is suspected of aflatoxin
content, it should be either destroyed or tested to ensure safe levels before
it is consumed. The tests are inexpensive; the consequences of aflatoxicosis
are not.

10.2.2 Ochratoxicosis

Ochratoxins are a group of secondary metabolites produced by a number
of species of both Aspergillus and Penicillium. Aspergillus ochraceus (A.
alliaceus) and Penicillium viridicatum are the major producers, but six other
aspergilli and five other penicillia are known to produce them (A. alliaceus,
A. melleus, A. ostianus, A. petrakii, A. sclerotiorum, and A. sulphureus; P.
commune, P. cyclopium, P. purpurescens, and P. variabile) (Krogh 1977;
Richard and Cole 1989). Ochratoxin A is the most biologically active of the
ochratoxin group and is carcinogenic. Its major target organ is the kidney,
where it causes necrosis of the tubular epithelium. In more advanced stages
the glomerulus and interstitial tissues of the kidney are affected. Signs of
intoxication are typical of tubular nephritis, including polyuria, polydipsia,
and the shedding of tubular casts in the urine. Affected kidneys are usually
enlarged and pale in chronically affected animals. In addition to the effect
on the kidney, poultry may show central nervous system effects, including
tremors, flailing movements, and loss of righting reflex. At lesser intake
levels the signs of ochratoxicosis in poultry are less dramatic but, never­
theless, economically important, including reduced growth rate, reduced egg
production, and poor shell quality. Ochratoxin A also affects the gut of
intoxicated animals, causing enteritis and extensive necrosis of gut-associated lymph tissue. This latter action substantially diminishes the animals antibody-producing ability, resulting in a different type of immunosuppression than that seen with aflatoxin. As with many mycotoxins, lower levels of intake than those associated with overt clinical disease cause diminished growth rate and feed efficiency. Ochratoxin A has been suggested as a causative agent in the insidiously fatal human disease, Balkan endemic nephropathy; but definitive proof of this association remains to be demonstrated. Teratogenic effects have been reported for Ochratoxin A with malformations of the skull, vertebrae, and ribs occurring in treated mice (Hayes 1981).

Ochratoxin and aflatoxin illustrate the interesting geographical variation typical of mycotoxicoses. Ochratoxin A occurs naturally in corn, barley, oats, and wheat. It is a prominent mycotoxin in Canada, Denmark, and Yugoslavia; it is infrequently found in the United States and Central America. Aflatoxin, on the other hand, rarely occurs on native products in Canada and Yugoslavia but is a very prominent mycotoxin in the United States and Central America.

Dose response relationships of ochratoxin and other selected mycotoxins of Aspergillus origin are summarized in Table 10-2.

10.2.3 Other Mycotoxins of Aspergillus Origin

10.2.3.1 Cyclopiazonic Acid. At least eight fungal species in the genera Aspergillus and Penicillium produce the mycotoxin cyclopiazonic acid (CPA). Among the aspergilli are A. flavus, A. versicolor, and A. oryzae. The major effects of CPA given orally to laboratory animals include fatty changes and hepatic cell necrosis in the liver, necrosis and other degenerative changes of the kidney tubules, enteritis, and death at high dose levels. (Central nervous dysfunction has been reported following intraperitoneal injection of CPA but this has not been observed following normal routes of administration.) Aflatoxin and CPA coexist in some samples of stored corn, and some stains of A. flavus coproduce aflatoxin and CPA (Gallagher et al. 1978). Interesting interactions have been demonstrated between aflatoxin and CPA when given to guinea pigs. Significant extra reduction in growth rates, increased hepatic cell changes, and lethality were observed when the mycotoxins were administered together; however, the usual immunosuppressive effects of aflatoxin were counteracted by the presence of CPA (Pier et al. 1989).

10.2.3.2 Gliotoxin. Gliotoxin is produced by fungi of several genera including Aspergillus, Penicillium, and Gliocladium. Among the aspergilli, A. fumigatus, A. chevalieri, and A. terreus are known producers. This interesting
mycotoxin has antiviral activity but its toxicity precludes its use as a therapeutic agent. Administration to a variety of laboratory animals causes death but histopathologic lesions have not been described. Gliotoxin interferes with macrophage function and acts as a hematopoetic inhibitor. Gliotoxin is unusual among the mycotoxins in that it can be produced in vivo, and there is some evidence that it may act as a virulence factor for *A. fumigatus* (Richard et al. 1989).

10.2.3.3 Citreoviridin. A potential mycotoxin of domestic animals, citreoviridin occurs on corn and possibly on other feeds. While produced primarily by *Penicillium* species it is also produced by *A. terreus* (Frenck and Gehrken 1980). Citreoviridin is a neurotoxin; experimental toxicity includes ascending paralysis, residual lameness, and muscular atrophy.

10.2.3.4 Oxalic Acid. A questionable mycotoxin by some standards, oxalic acid is produced in abundance by *Aspergillus niger* and several other organisms growing in silage cap and other feeds. This metabolite causes

### TABLE 10–2  Dose-Related Effects of Ochratoxin A, Cyclopiazonic Acid, Gliotoxin, Citreoviridin, Patulin, and Penicillic Acid

<table>
<thead>
<tr>
<th>Mycotoxin</th>
<th>Animal</th>
<th>Route</th>
<th>Effect</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ochratoxin A</td>
<td>Chick</td>
<td>Single oral dose LD₅₀</td>
<td>Reduced rate of gain, coagulopathy</td>
<td>2.0–3.6 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Broiler</td>
<td>Reduced rate of gain, coagulopathy</td>
<td>0.5 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Broiler</td>
<td>Acute disease and death</td>
<td></td>
<td>4–16 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pig</td>
<td>Chronic nephropathy</td>
<td></td>
<td>0.2 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pig</td>
<td>Acute fatal enteritis</td>
<td></td>
<td>1.0 mg/kg</td>
</tr>
<tr>
<td>Cyclopiazonic acid</td>
<td>Rat</td>
<td>Single oral dose LD₅₀; male</td>
<td></td>
<td>36 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Guinea pig</td>
<td>Liver pathology, reduced growth rate</td>
<td></td>
<td>2.2 mg/kg</td>
</tr>
<tr>
<td>Gliotoxin</td>
<td>Mouse</td>
<td>Approximate oral LD₅₀</td>
<td>Lethality</td>
<td>2.5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Hamster</td>
<td></td>
<td>Lethality</td>
<td>2.5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Turkey poult</td>
<td></td>
<td>Lethality</td>
<td>7.5 mg/kg</td>
</tr>
<tr>
<td>Citreoviridin</td>
<td>Mouse</td>
<td>Oral LD₅₀</td>
<td></td>
<td>29 mg/kg</td>
</tr>
<tr>
<td>Patulin</td>
<td>Mouse</td>
<td>Oral LD₅₀</td>
<td></td>
<td>35 mg/kg</td>
</tr>
<tr>
<td>Penicillic acid</td>
<td>Mouse</td>
<td>Oral LD₅₀</td>
<td></td>
<td>600 mg/kg</td>
</tr>
</tbody>
</table>

1 Adapted, in part, from Pier (1981), Wyllie and Moorehouse (1978).
2 Daily dose in mg/kg.
appreciable animal disease due to altered calcium metabolism and deposition of oxalate crystals in the kidney tubules, causing a mechanical nephritis (Pier 1981; Smith and Moss 1985).

10.2.3.5 Patulin. Patulin is a mycotoxic compound produced by a number of *Penicillium* species as well as by *Aspergillus clavatus*, *A. giganteus*, and *A. terreus*. Patulin occurs naturally on bruised apples and in apple juice prepared from them as well as in certain other fruit products (Richard and Cole 1989). Its occurrence in animal feeds is not well substantiated (Pier 1981). Major effects of toxin consumption are gastritis and nausea in humans, and pulmonary and cerebral edema in laboratory animals, which may also have congestion of major internal organs (Wylie and Moorehouse 1978). Teratogenic effects have been reported in chickens (Hayes 1981). Along with its mycotoxic properties, patulin has antibiotic activity (antiviral); similar to gliotoxin, this antibiotic property has not been utilized pharmacologically because of its concomitant toxicity. The toxin is moderately heat stable but sulfur dioxide and vitamin B1 react with and inactivate patulin in juices.

10.2.3.6 Penicillic Acid. Another mycotoxin of relatively minor importance in animals is penicillic acid. Produced largely by *Penicillium* species, it is also produced by a number of aspergilli in the *A. ochraceus* group (= Section *Circumdati*) (*A. alliaceus*, *A. melleus*, *A. ochraceus*, *A. ostianus*, *A. quercinus*, *A. sclerotiorum*, and *A. sulphureus*). Penicillic acid is produced under storage conditions of grains and foods and often occurs in conjunction with ochratoxin A. Effects of penicillic acid administration in laboratory animals include necrosis of liver, kidney, and thyroid tissues. Penicillic acid can be carcinogenic but has also been found to have some antitumor and antibiotic properties, including activity against bacteria, fungi, and viruses (Wyllie and Moorehouse 1978).

10.2.3.7 Sterigmatocystin. Sterigmatocystin is a mycotoxin that appears to have little importance in naturally occurring human or animal disease. Its known effects are confined to laboratory animals following experimental exposure. It is a precursor in the biosynthetic pathway for the formation of aflatoxin (Bhatnagar et al. 1989). Like aflatoxin, it is hepatotoxic and carcinogenic (Purchase and Van der Watt 1970). Several species of *Aspergillus* are capable of producing sterigmatocystin, most notably *A. flavus* and *A. parasiticus*. Because few species of fungi accumulate this mycotoxin, it does not occur frequently in food but has been found in green coffee, moldy wheat, and some Dutch cheeses (Richard and Cole 1989).

10.3 CONCLUSION

The aspergilli continue to be important agents of animal diseases through either infection (aspergillosis) or intoxication (mycotoxicosis). While they
rarely cause infection in high percentages of animal populations, their frequency in the animals' environment ensures their occurrence as opportunist pathogens in economically significant numbers of livestock and poultry.

The mycotoxicosis, however, may affect very high percentages of an animal population when the conditions favor mycotoxin production in feeds. The mycotoxins of Aspergillus origin as well as those of other fungal genera (chiefly Penicillium and Fusarium) are a broad, fascinating, and economically important group of biologically active compounds. They have important ramifications in agriculture and food technology. Some cause major losses worldwide; others are very geographically limited. For comprehensive reviews of the major classical mycotoxins the reader is referred to Goldblatt (1969), Purchase (1974), Rodricks et al. (1977), and Wyllie and Moorehouse (1978). Compendiums of more recent findings on specific mycotoxins may be found in Betina (1989), Lacey (1985), Natori et al. (1989), and Steyn and Vleggar (1986).

REFERENCES


