Mycotoxicoses of Importance to the Bovine Practitioner

by
Paul T. Cardeilhac, D.V.M., Ph.D.
Department of Veterinary Science
University of Florida
Gainesville, Florida

Introduction

Diseases of cattle caused by molds and fungi have a long history in veterinary medicine. Many diseases result from the growth of molds in the animal, and they are called mycoses. These have been roughly divided into Dermatomycoses such as Trichophytosis of cattle, and deep (systemic) mycoses such as actinomycosis. Increased interest and training in medical mycology have yielded great advances in this area of disease. The conditions are frequently complications of the use of antibiotics. The most fascinating aspect of mycology to the toxicologist is the field of mycotoxicosis. This is the study of the mycotoxins produced during various phases of mold growth whether it occurs within the animal or on feed which will be consumed by the animal.

Mycotoxins are only one of a host of biologically active compounds produced by molds. Antibiotics and hallucinogens (LSD, etc.) are the best known of these biologically active compounds derived from mold metabolites, but many others are known. It is difficult to distinguish a mycotoxin from an antibiotic, another mold metabolite with potent biological activity, which is used for its beneficial effects. Agents which are considered mycotoxins today may be utilized in the treatment of disease in the future.

Aflatoxin

Aflatoxin has been used to describe a dozen or more individual toxic metabolites produced by several molds which are usually classified under genus *Aspergillus* or *Penicillium*. An individual member of this troup of compounds has been found to be the most potent carcinogen known to man. Rats consuming feed containing 15 parts per billion of aflatoxin B, have developed hepatomas in significant numbers.[1] The importance of these toxins to domestic animals in the southeastern United States has been known for some time before the causal agent was characterized.[2] Sufficient research support and scientific talent were focused on the problem to identify and characterize the toxic agents after a severe poisoning of turkey poults (100,000 killed), ducklings, pigs, and calves in England. Brazilian peanut meal contaminated with aflatoxins was present in the feed of all affected animals.[3]

The outbreak in calves was of interest because the first assigned cause was senecio (ragwort) poisoning. This conclusion was made because of liver damage, and symptoms were similar to those of seneciosis. Members of the Central Veterinary Laboratory in England demonstrated that none of the toxic alkaloids usually found in senecio were present in the meal, but aflatoxins were present in the peanut meal component of the feed.[3] The world-wide occurrence of aflatoxin was illustrated by the discovery by the Central Veterinary Laboratory that peanuts or peanut meal from 13 producing countries contained aflatoxins.

In a series of feeding trials conducted on cattle, several aspects of the clinical pathology and excretion of aflatoxin were determined.[3] Early weaned bull calves receiving feed containing 0.22 to 0.44 ppm aflatoxin B_1 had no clinical signs of toxicity, but weight-gain was depressed because of the reduced feed intake and the presence of aflatoxin. Weaned calves five to eight weeks of age are given feed containing 2.2 ppm aflatoxin showed decreased feed intake and weight gain after one month, clinical signs of unthriftiness after 10-12 weeks, and terminal symptoms after 16 weeks or more.

Two year old feedlot animals were given concentrate rations containing 0.22, 0.44, and 0.66 ppm aflatoxin for 20 weeks. No significant effect on the performance in those animals was detected, but "mild" liver lesions were

observed in the high dose level. The feedlot animal would appear to be highly resistant to aflatoxin poisoning, but field cases have been reported where the animals showed marked loss of weight, and death. In other tests steers were placed on rations containing 0.1, 0.3, 0.7, and 1.0 ppm aflatoxin B_1. Animals fed 0.7 and 1.0 ppm had reduced weight gains, decreased feed efficiencies, and enlarged kidneys and livers.

Dairy cows seem to be resistant to the toxin, but first-calf heifers were found to show clinical symptoms after 7 months on concentrate rations containing 2.4 ppm aflatoxin B_1. Milk production is affected in cows with significant drops in milk yield observed after 20 to 53 days on concentrate rations containing 2.7 ppm aflatoxin. Milk from cows fed aflatoxin have been found to contain aflatoxin or toxic metabolites. Sufficient aflatoxin or metabolites has been found in the fat and liver of a calf, fed a ration with 2.2 ppm aflatoxin, to produce liver damage and death in ducklings. In addition to the milk, aflatoxin is mainly excreted in the feces with little or none in the urine. The most characteristic lesions in cattle is reported to be liver damage. Gross lesions found were visceral edema, ascites, and pallor and mottling of the liver. Severe fibrosis is a usual finding in cattle. Enlarged hepatic cells, enlarged nuclei and bile duct proliferation are characteristic of the disease in cattle.

The sequence of lesions in calves was described as follows: (1) one month; mild ductal hyperplasia; (2) second and third month; increased ductal cell hyperplasia and centrolobular degeneration of the hepatic cells; (3) fourth month; central necrosis of hepatic cells, marked bile duct proliferation and occlusion of the centrolobular veins. There is no specific treatment for aflatoxicosis except to prevent the disease or remove the source of contaminated feed. Supportive treatment for liver disease would be indicated in acute cases.

Ergotism and "Fescue foot"

Ergotism was the first recognized mycotoxicosis. *Claviceps purpurea (Ergot)* is usually the cause of the disease and attacks the seedheads of certain pasture grasses and cereal grains. In Florida, Paspalum ergot (*Claviceps paspali*) has been found to attack Argentine Bahia grass, Dallis grass and brown-seed paspalum.[4] Although toxic symptoms of Ergotism have been associated with ergot since the sixteenth century, the six toxic lyseric acid derivatives which will produce the disease, were not isolated until the 1930's.

In Florida, ergot appears on grass early in the summer usually after a rainy season.[4] After infection, the seed is replaced by a mass of spores covered with a white, sweet, sticky material that attracts certain insects. The insects spread the infection through a field under moist conditions. Spore production soon stops, usually by late summer, and a resting body or sclerotium is formed. The sclerotium is a small sphere with a light brown outer layer surrounding a hard white internal material and contains the toxic alkaloids.

Symptoms occur in two forms, acute and chronic. In Florida, the acute form is most often observed; while other workers rarely find the acute form.[5] In the acute disease excitability, nervousness, incoordination, paralysis of the limbs and tongue, disturbances of the gastro-intestinal tract, abrupt excitation, twitching of shoulder and rump muscles, and death may occur.[4, 6] Acute symptoms are reported to appear after five days if pasturing on heavily parasitized Dallis grass. In chronic poisoning, abortion and gangrene of the extremities (which may later drop off) are the usual signs.

Animals which are suffering acute ergot poisoning should be removed from the source of the poison, handled with a minimum of excitement and given constant access to drinking water. Lameness before the onset of gangrene can be treated with heat. Temperatures lower than 75° F appear to aggravate ergotism.[7] Gangrene cannot be reversed; otherwise animals on a good quality ration free from ergot recover in about one to two weeks.

A disease of cattle which produces lameness, gangrene, and sloughing of extremities similar to ergotism is fescue toxicity usually called "fescue foot". Extracts of toxic hay have been found to produce the disease in animals, and because of the similarity to ergotism, alkaloids of fescue have been suspected of causing the disease.[5] The sporadic and seasonal nature of "fescue foot" indicated that it might be a mycotoxin.[8] Toxins have been produced by molds which were isolated from fescue.[8] The cause of the disease, which may seriously limit the future use of fescue grass, could be a mycotoxin.

Moldy Feed Toxicosis

Under the right condition, cereal grains and other feeds or fibers will become parasitized by molds. The problem is world-wide, and as a result several hundred mold metabolites have been isolated. Many of these metabolites have proved to be toxic to animals. Although the agents are well characterized, little is known about the diseases they produce. A list of some mycotoxins is given in Table 1.

One of the more important problems of moldy feed toxicosis in cattle is called *Aspergillustoxicosis.*[9] This term covers several species of Aspergillus molds and a number of toxins in addition to aflatoxin which has been described.

TABLE I. SOME POSSIBLE RELATIONSHIP OF SOME MOLDS AND MYCOTOXINS TO ANIMAL DISEASES (10-16)

MOLDS	TOXINS	DISEASES RELATED TO MOLD
Alternaria tenius	Tenuazonic acid	Inhibits human and animal tumors, retards protein synthesis in liver cells
Aspergillus flavis	Aspergillic acid	Moldy corn poisoning
A. Flavis	Aspertoxin	Moldy corn poisoning
A. flavis	Kojic acid	Moldy corn poisoning
A. flavis	Tremorgenic substance	Moldy corn poisoning
A. flavis	B-Nitropropionic acid	Moldy corn poisoning
A. flavis	A. flavis Endotoxin	Moldy corn poisoning
A. fumigatus	Fumagillin	Hyperkeratosis
A. fumigatus	Gliotoxin	Hyperkeratosis, "Facial eczema"
A. fumigatus	Helvolic acid	Hyperkeratosis
A. ochraceus	Ochratoxin A	Moldy corn poisoning
A. terreus	Terreic acid	Yellow rice toxicosis
Cladosporium epiphium	Epicladosporic acid	Alimentary toxic aleukia of man (cattle seem resistant)
C. fagi	Fagicladosporic acid	Alimentary toxic aleukia of man (cattle seem resistant)
Fuserium tricinctum	Diacetoxyscirpenol (unguidin)	Moldy corn poisoning
F. scirpi	Diacetoxyscirpenol	Moldy corn poisoning
F. tricimctum	T-2 Toxin	Hyperkeratosis
F. graminerum	2-carulenone (F-2, estrogenic metabolite)	Decreased fertility in dairy cattle, causes vulva-vaginitis in swine
F. graminerum	uncharacterized	Emesis and refusal of food in swine
Helminthosporium oryzae	Ophiobolin A	Toxic to mice; occurs as pathogen of cereals; grasses and other plants thus presents a potential hazard to cattle
H. zizaniae	Ophiobolin A	
H. Ophiobolus	Ophiobolin A	
H. oryzae	Ophiobolin B	Same as ophiobolin A, but more toxic–LD_{50} 4.4mg/kg
H. zizaniae	Ophiobolin B	Same as ophiobolin A, but more toxic–LD_{50} 4.4mg/kg
H. ophiobolus	Ophiobolin B	Same as ophiobolin A, but more toxic–LD_{50} 4.4mg/kg
Penicillium rubrum	Rubratoxin B	Moldy corn toxicosis
P. cyclopium	Cyclopiazonic acid	Moldy corn toxicosis
P. viridicatum	unknown	Mold nephrosis of swine
P. urticae	Patulin	Mass death of cows that consumed malt feed contaminated with this mold has been reported
P. toxicarium	unknown	Ascending paralysis, respiratory and circulatory disturbances
P. Citreoviride	Citreovirdin	Paralysis and death by action on motor ganglia, hemorrhages, liver and kidney damage
P. citrinum	Citrinum	Kidney damage (renal tubules)
Pithomyces chartaram	Sporidesmin	"Facial eczema"
Sporodesmium bakeri	Sporidesmin	"Facial eczema"
Trichoderma viride	Trichodermin	Moldy corn poisoning
T. roseum	Trichothecin rosololactone	Moldy corn poisoning

Bovine hyperkeratosis or X-disease in cattle has been induced by feeding pelleted feed, pasture, timothy hay, and various feeds or fodders.[9] Early clinical signs were reported to be listlessness, depression, lachaymation, salivation, emaciation, diarrhea, low plasma vitamin A level, dry skin, and raised areas around the face. The disease progresses to hyperkeratosis with liver damage, kidney damage, and ulceration of the mouth and abomasum.

Mycologic examination of feed causing field outbreaks of X-disease yielded at least three toxigenic Aspergillus molds, *A. chevalieri, A clavatus,* and *A. fumigatus.* These fungi were shown to be toxic, and it can be concluded that they may be the source of mycotoxins which may induce a hyperkeratosislike syndrome in cattle. Aspergillustoxicosis can be induced experimentally at any time, but conditions are best during the winter months.

Stachybotryotoxicosis is a condition resulting from a mycotoxin produced by toxigenic strains of *Stachybotrys atca.*[9] The horse is more sensitive to the toxin than the bovine, but outbreaks have been reported in cattle. The mold has been found on hay, straw, and grain. Some of the clinical signs are depression and lachrymation. After six days the animal may show anorexia, watery stool; by nine days an agranulocytosis becomes apparent and progressively worsens. No specific treatment is available for any of these intoxications, but in all cases the animal or the mold-contaminated material should be removed.

Summary

The development of knowledge about mycotoxins has stimulated intense research in this area of toxicology. One can be certain that many new toxins will be found and new and old diseases of cattle which are caused by mycotoxins will be discovered. Full utilization of animal feeds will require an understanding of the following facts about mycotoxins: (1) identification of molds which produce toxins, (2) conditions necessary for toxin production, (3) a detailed understanding of the clinical pathology produced by individual toxins and mixtures of toxins, (4) methods to prevent mycotoxin contamination of feeds, (5) sensitive and accurate methods for the detection of mycotoxins, and (6) methods for the removal or detoxification of mycotoxins from contaminated feed. *(continued on pg. 25)*

Microscopic: "Lung-marked smooth muscle hypertrophy and hyperplasia of small airways and vessels" . . . "Scattered stromal thickening with chronic inflammatory cells and eosinophils" . . . "several foci of pneumonia and many neutrophils in stroma and aveali."

Diagnosis: Pneumonitis and bronchitis, allergic, with eosinophils and smooth muscle hyperplasia and hypertrophy" . . . "Pneumonia, focal" . . . "It is a new type of cattle lung disease to the pathologist."

Discussion:

1. Is there some component in the commercial spray used which subsequently caused an allergic reaction?
2. Is it possible that the affected individuals harbored a small number of lungworms (Dictyocaulus spp.) or migrating Ascaris lumbricoides larvae which were killed by the spray and which subsequently set up the allergic type response in the lung tissue?
3. If either No. 1 or No. 2 is true, why did the condition subsequently appear in the individuals in the herd which were in no way exposed to the "fogging?" Did an "opportunistic" unidentified virus or bacteria "take over"?

If any of you have the answer and/or have experienced similar outbreaks, I'd be glad to hear from you!

Addendum: During the past summer, and by telephone conversation with veterinarians, four other similar herd outbreaks have been reported, all with the same "fogging" history.

It behooves us, therefore, in the best interest of our clients to remind them to follow the manufacturer's directions closely in the control of face flies. A "fogger" held near the muzzle of a restrained animal may be an invitation to similar disaster!

(Mycotoxicoses, contd. from pg. 20)

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"If I could live my life all over again, I would become a veterinarian."
Paul Getty