# FUNGAL NEUROTOXINS

W.L. BRYDEN

Summary

The fungal neurotoxins are briefly reviewed, especially where they have known involvement in human and animal disease. The neurological effects of ergot alkaloids and the tremorgens have been studied in detail as these groups of toxins have often been associated with mycotoxicoses. Other neurotoxic mycotoxins are briefly discussed, but, in most instances, very little research has been carried out on these compounds. Further detailed study of fungal neurotoxins will determine their likely occurrence in the food chain, assist in the delineation of neurological function and may provide a source of compounds with medical application.

## I. INTRODUCTION

Fungi produce an array of biologically active compounds. Some, the antibiotics are used to maintain health and well being, others are highly toxic to higher life forms and are collectively called mycotoxins. The distinction between antibiotics and mycotoxins is one of degree rather than kind. Ingestion of food contaminated with mycotoxins may result in a mycotoxicosis. Mycotoxicoses take many different forms as mycotoxins are a heterogeneous group of secondary metabolites of varying chemical complexity with unique biological properties. The severity of a mycotoxicosis is dependent on the dose and duration of exposure to the toxin and is modified by genetic, physiological and environmental influences.

Mycotoxins have been implicated in disease episodes throughout recorded history but it was the discovery of aflatoxin as the cause of "Turkey X disease" in Great Britain in 1960 (Blount 1961) that prompted the worldwide interest in toxigenic fungi, especially as aflatoxin was subsequently shown to be carcinogenic. Research with aflatoxin has continued since its isolation but there is now increasing interest in delineating the effects of other mycotoxins, their relationship with known diseases and their role in a number of idiopathic diseases.

Mycotoxins have been shown to affect all systems of the body (Kellerman et al. 1988) and the importance of these compounds as hepatotoxins and nephrotoxins has been well documented. The neurotoxicity of mycotoxins, however, is less well appreciated despite the human cases of convulsive ergotism, recorded since the middle ages (Barger 1931) and the established role of mycotoxins in many staggers syndromes of grazing livestock (Cole and Dorner 1986). The evidence establishing the neurotoxicity of mycotoxins is reviewed with particular reference to the ergot alkaloids and fungal tremorgens.

## II. ERGOT ALKALOIDS

Ergotism was the first mycotoxicosis to be recognised and resulted from consumption of the ergot or sclerotium of the fungus of Claviceps purpurea. The disease is due to the effects of alkaloids produced by the fungus that are

Department of Animal Husbandry, University of Sydney, Camden, NSW 2570.

contained within the ergot that develops when the fungus parasitizes the ovary of grass flowers, including those of all important cereal and forage crops. Ergotism and ergot alkaloid chemistry have been the subject of a number of excellent reviews including those by Barger (1931), Bove (1970), Van Rensburg and Altenkirk (1974) and Lorenz (1979).

(a) Ergotism in Man

Detailed descriptions of human ergotism epidemics in Europe appeared in the middle ages and were described as either convulsive or gangrenous. It appears that the epidemics occurred when the population consumed rye bread contaminated with ergot (Barger 1931). In gangrenous ergotism the affected part (usually the foot) became swollen and inflamed (post-ischaemic inflammation) and the patient experienced violent, burning pains which gradually subsided as the limb became numb, turned black (necrosis, gangrene) and became mummified and dry before detachment. To this day gangrenous ergotism is still known as St Anthony's Fire as it was believed that a pilgrimage to the shrine of St Anthony would bring relief from the intense burning sensations (or holy fire). When alleviation of the disease resulted from the trip it was probably due to the removal of ergot from the victim's diet.

An early symptom of convulsive ergotism was tingly sensations or "pins and needles". In addition, itching, numbness of hands and feet, twitching, muscular cramps and sustained spasms and convulsions were described. In severe cases convulsions caused the body to roll into a ball or stretch out straight. Between convulsions many patients suffered little discomfort, displayed voracious appetites and often returned to work in the fields. In fatal episodes of convulsive ergotism postmortem examination revealed bleeding and softening of the brain and lesions of the posterior horn of the spinal column (Barger 1931). Whereas epidemics of gangrenous ergotism were thought to be a sign of divine wrath (hence "holy fire") incidences of convulsive ergotism were the result of bewitchment and many believed the sufferers were possessed by demons. Ergot poisoning has been suggested as the reason for the behaviour of the "bewitched" girls in the Salem village witch trials in Massachusetts, USA in 1692 (Matossian 1982).

There are about 30 species of Claviceps of which C. purpurea is the most studied. It produces a variety of alkaloids with a diversity of biological activities which would account for the descriptions of ergotism seen in man. Interestingly, there are few reports of gangrenous and convulsive ergotism occurring together suggesting a different array of alkaloids are involved in the different disease episodes or a species other than C. purpurea is responsible for convulsive ergotism. C. paspali for instance, causes a neurological disorder in animals but, as discussed later, no pathological changes are noted in affected animals whereas pathological changes are observed in victims of convulsive ergotism.

The ergot alkaloids are indole alkaloids in which the indole group is built into a tetracylic ring system that has been named ergoline (Stoll and Hofmann 1970). The compounds can be divided into four main structural groups: clavine alkaloids, lysergic acids, simple lysergic acid-amides, and peptide alkaloids. The clavine alkaloids are of minor biological importance while the peptides of lysergic acid are the most biologically active.

The various physiological activities of the ergot alkaloids are outlined in Table 1. The peripheral effects involve contraction of smooth muscle including those of blood vessels. It is this effect that results in the occlusion of blood vessels which gives rise to gangrenous ergotism. Ergot alkaloids also induce uterine contractions and reduce postpartum haemorrhage.

However it is only at term that the uterine muscle is more sensitive than other smooth muscles to ergot and therefore these alkaloids cannot be

used to induce abortion. The treatment of migraine with ergot alkaloids has been effective due primarily to the contraction of arteries in the brain. The antiserotonin effect of ergot alkaloids also contributes to the efficacy of these compounding in relieving migraine.

The action of the ergot alkaloids on the central nervous system (CNS) are many (Table 1). Stimulation of the midbrain causes exaggerated tendon reflexes and this would largely explain the severe convulsions observed in convulsive ergotism and the associated hypoglycaemia would contribute to the apparent hunger of the victims. The derivative with the greatest effect on the midbrain is the diethylamide derivative of lysergic acid (LSD). Ergot alkaloids and their derivatives also act on the hypothalmic-pituitary axis to inhibit the secretion of prolactin.

Table 1. Physiological effects of ergot alkaloids (after Stoll and Hofmann (1970)

| Activity | Effect |
|---|---|
| 1. Peripheral effects | Vasoconstriction<br>Uterine contraction |
| 2. Neurohormal action | Serotonin antagonism<br>Adrenergic blockage |
| 3. Central nervous effects | Bulbomedullary components: vomiting, bradycardia, inhibition of the vasomotor centre, and of the baroceptive reflexes<br>Mesodiencephalic components: hyperthermia, hyperglycemia, mydriasis, piloerection, tachypnoea and hyperreflexia |

(b) Ergotism in Animals

Dry gangrene of muzzle, ears, tongue, tail or limbs has been observed in most farm animals (Lorenz 1979) following the ingestion of ergots of C. purpurea. The first signs of ergot ingestion in dairy cows are a drop in feed intake and milk production accompanied by a loss of tractability, the occasional flank tremor (Jang et al. 1987) and finally lameness in the hind limbs followed by gangrene (Woods et al. 1966). Circulating levels of prolactin also drop dramatically. In pigs loss of weight (Bakau et al. 1988) and agalactia (Anderson and Werdin 1977) are the effects noted.

C. purpurea is widespread in Australia but there has been only one report of gangrenous ergotism. Fraser and Dorling (1983) described bilateral hindlimb lameness and gangrene in two Friesian heifers. The outbreak occurred in Western Australian during July after the heifers had consumed meadow hay containing perennial ryegrass seed heads containing the ergots of C. purpurea. Interestingly, cases of ergotsim in cows have been predominantly reported from Europe and occur in the coldest months of the year. The cold weather aggravating the peripheral vasoconstriction of the ergot alkaloids.

Convulsive ergotism or paspalum staggers of grazing ruminants follows the ingestion of paspalum contaminated with ergots of C. paspali. This mycotoxicosis is often encountered in Australia and is discussed under fungal tremorgens.

Recently there has been another form of ergotism described following natural outbreaks of disease in cattle. During January to April 1986, cattle in the Illawarra and Central Tableland areas of NSW were affected by an unidentified syndrome. The syndrome was characterized by hyperthermia, evidenced by increased rectal temperature (41-42°C), increased respiration rate, and excessive salivation (Jessup et al. 1987). Accompanying these signs were obvious behavioural changes in that animals sought shade or water in which to stand, spent less time eating and were more irritable. The clinical signs and behavioural changes were exacerbated by daily temperatures in excess of 35°C. It was shown that the diets being fed were contaminated with ryegrass that had been infected with C. purpurea (Burgess et al. 1986). The syndrome was induced in dairy cows (Jang et al. 1987) and Hereford steers (Ross et al. 1989) by adding ergot from field cases to experimental diets. There was no evidence of gangrene in any cattle. However feeding the ergot to chickens (Bakau and Bryden 1987) produced gangrene of the feet, the lesion most often associated with ergotism of C. purpurea but when chickens were fed ergot and subjected to daily temperatures of 35°C no foot lesions developed. This appears to result from changes in blood flow to the legs of birds subjected to different temperatures while ingesting ergot (Bakau and Bryden 1987). Presumably the high ambient temperature counteracts the vasoconstriction caused by the ergot.

Although much is known about the biological activity of the ergot alkaloids very little is known of their metabolism or excretion. It is generally accepted that they do not accumulate in tissues or appear in milk but there is no conclusive data to substantiate this belief.

## III. FUNGAL TREMORGENS

Compounds that can induce sustained or intermittant tremors in animals are rare but at least 20 mycotoxins have been identified that have this property. Cole (1981) and Cole and Dorner (1986) have reviewed in detail the tremorgenic mycotoxins, including documented field cases. The tremorgens, although produced by unrelated fungi, contain the same basic biologically active indole moiety. The territrems, however, differ entirely from the other tremorgens in that they do not contain nitrogen in their structure (Cole and Dorner 1986) and act on the peripheral not the CNS (Ling et al. 1986).

The known and suspected instances of natural tremorgen intoxication are listed in Table 2. Clinical signs typical of staggers syndromes in cattle and sheep include tremors, incoordination, hyperexcitability and in severe cases ataxia. An affected animal may appear normal until disturbed. Removal of the animal from the intoxicating feed results in rapid recovery with no apparent pathology. Both paspalum staggers and perennial ryegrass staggers (PRGS) have been reported in Australia for many years (Culvenor 1974). PRGS should not be confused with the much more toxic staggers disease, annual ryegrass toxicity in which bacteria carried by plant nematodes produce corynetoxins in cells on the ryegrass (Culvenor and Jago 1985).

The tremorgens do pose a threat to humans as many of the fungi that produce them are ubiquitous contaminants of human food. Cole et al. (1983) have described an apparent natural human tremorgen intoxication from beer....". Approximately four hours after consuming about 30 cc of the contaminated beer, the individual (a physician) became acutely ill with a throbbing frontal headache, feverish feeling, nausea, vomiting, diplopia, weakness and bloody diarrhoea. After 12 hours, handwriting was illegible due to tremor. All symptoms disappeared and no apparent residual effects were noted after 30 hours." The beer had been contaminated with P. crustosum, a known producer of penitrem A. There is a disease in Nigeria known locally as

the 'Ilesha shakes' which has a seasonal occurrence (Wright and Morley 1958). The cause is unknown but cyanogenic glycosides and tremorgens are possibilities.

Table 2. Known and suspected reports of tremorgen intoxication (after Cole and Dorner 1986; Kellerman et al. 1988)

| Intoxication | Species | Suspected or incriminated mycotoxin | Fungus |
|---|---|---|---|
| PS | Cattle, sheep, horses | Paspalitrems | Claviceps paspali |
| PRGS | Cattle, sheep, horses | Lolitrems | Lolium endophyte |
| Corn staggers | Cattle, sheep, horses | Aflatrem; paspalinine | Aspergillus flavus |
| Kweek tremors | Cattle, sheep | ? | Claviceps sp? |
| Mouldy cheese | Dog | Penitrem A | Penicillium crustosum |
| Mouldy walnuts | Dog | Penitrem A | Penicillium crustosum |
| Mouldy bun | Dog | Penitrem A | Penicillium crustosum |
| Mouldy silage | Cattle | Verruculogen/ fumitremorgens | Aspergillus fumigatus |
| Mouldy beer | Man | Penitrems | Penicillium crustosum |
| Bermudagrass tremors | Cattle | ? | Endophyte? |

PS, Paspalum stagger; PRGS, Perrenial ryegrass staggers

Tremorgenic mycotoxins appear to be specific in their biological activity, causing tremor in animals through reversible biochemical changes affecting neurotransmission. It has been suggested that these toxins induce their effects by acting as an antagonist of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the vertebrate central nervous system (Gant et al. 1985). The rapid recovery and the lack of notable lesions in instances of tremorgen intoxication presumably relates to the reversible nature of the lesion and rapid metabolism and excretion of these toxins (Mantle 1986).

## IV. OTHER NEUROTOXIC MYCOTOXINS

There are a number of other mycotoxins where the primary site of action is the nervous system. These and other toxins that exert neurotoxic effects, often secondary to primary effects on other systems, are discussed below.

### (a) Leukoencephalomalacia

Equine leucoencephalomalacia (ELEM) has been recorded in various parts of the world, especially the United States, since last century. The disease occurs in horses and donkeys following the consumption of maize contaminated with Fusarium moniliforme. It is a neurological disease that results in liquefactive necrosis in the white matter of one or both cerebral hemispheres and this lesion is considered pathognomonic for ELEM. Liver involvement is

also seen in some horses (Haschek and Haliburton 1986). F. moniliforme produces a number of mycotoxins but it was only last year that the water soluable compounds, fumonisins, subsequently shown to induce ELEM were isolated (Marasas et al. 1988). One of the compounds, fumonisin B1, is believed to be carcinogenic (Gelderblom et al. 1988).

Only one case of ELEM has been reported in Australia (Robertson-Smith et al. 1985) but the case was not confirmed. Nevertheless, the fungus is found throughout eastern Australia (Burgess et al. 1988) and infects maize especially during wet seasons (Blaney et al. 1986). Isolates of F. moniliforme vary greatly in their toxicity (Marasas et al. 1984) but the toxicity of Australian isolates has not been reported.

(b) Trichothecenes

About 50 metabolites comprise the highly toxic trichothecenes. These mycotoxins are produced by Fusuarium species and both central nervous system lesions and behaviour changes have been noted in animals ingesting them (Marasas et al. 1984).

Deoxynivalenol (DON; vomitoxin) is the most commonly found member of this group and has been found in locally grown wheat and triticale and associated with outbreaks of feed refusal and vomiting in pigs (Moore et al. 1985; Bryden et al. 1987; Tobin 1988). These authors reported levels of DON in feed ingredients of 0.6 to 34 mg/kg. Other trichothecenes also cause feed refusal and emesis in a range of species including ducklings, cats and dogs. The vomiting can be suppressed by prior administration of chloropromazine or metoclopramine, indicating the involvement of the medulla oblongata in this response (Mutsuoka et al. 1979).

T-2 toxin induces neural disturbances in chickens, including impairment of the righting reflex, abnormal positioning of wings, and seizures characterized by loss of normal voluntary motor abilities (Wyatt et al. 1973). In the brains of chickens ingesting T-2 toxin the concentration of dopamine was elevated, that of serotonin unchanged, and epinephrine decreased (Chi et al. 1981).

During the Second World War Russian peasants consumed grain infected with Fusarium. Patients with the resulting toxicosis, 'alimentary toxic aleukia', developed many symptoms including impaired nervous reflexes, meningism, general depression, hyperaesthesia, encephalitis, and cerebral haemorrhages. In some cases delirium, convulsions and paralysis occurred (Joffe 1986). It is likely that a number of mycotoxins were involved in this syndrome, but in particular T-2 toxin.

(c) Diplodiosis

Diplodiosis is a disease usually associated with cattle and results from the ingestion of a neurotoxin produced produced by Diplodia maydis (Kellerman et al. 1988). The syndrome involves lacrimation, salivation and ataxia, with muscle fasciculation, followed by a complete paralysis and death. The fungus is distributed worldwide, but except for one unconfirmed case in cattle grazing maize cobs and stubble in Queensland (Darvell 1964) the disease has only been reported in southern Africa (Kellerman et al. 1988). The neurotoxin has not been isolated and no gross pathological changes are observed in diplodiosis.

(d) Cyclopiazonic acid

Cyclopiazonic acid (CPA) is produced by many aflatoxigenic strains of A. flavus. Interestingly, there is now much evidence to suggest that the original outbreak of "Turkey X disease" may have been a combined toxicosis of aflatoxin and CPA (Cole 1986). Aflatoxin alone does not induce the neurological disturbances observed in the disease but CPA does. This toxin is also produced by species of Penicillium used in cheese manufacture, and has been shown to be toxic to all farm and laboratory animals studied (Dorner et

al. 1985). Although CPA is generally regarded as a liver or kidney toxin Nishie et al. (1985) has found that it has many properties in common with the antipsychotic drugs chlorpromazine and reserprine. It should be noted that these two drugs have entirely different mechanisms of action. Despite the potential health risk of this toxin and the ubiquitous nature of toxic fungi very little is known of its distribution in nature.

(e) Aspergillus clavatus

The fungus A. clavatus has been associated with a neurotoxic tremors syndrome in cattle ingesting mouldy sprouted grain. Kellerman et al. (1988) have described the clinical signs as hypersensitivity, muscle tremors, ataxia, progressive paresis, paralysis and constipation. They noted that the most significant microscopic lesions occurred in the brain and spinal cord. The neurotoxin from this fungus has not been isolated.

(f) Lupinosis

Lupinosis is a mycotoxicosis that has been recorded in Australia for many years and is caused by the ingestion of toxins (phomopsins) produced by the fungus Phomopsis leptostromiformis when it colonises dead lupin plants and stubble. It is recognised primarily as a disease of sheep, especially in Western Australia and the liver is the primary organ affected (Allen 1987). As a result of liver damage, hyperammonaemia may occur and cause degenerative changes in the central nervous system. Affected animals may wander in a disorientated manner, head press or 'star gaze'.

(g) Citreoviridin

Citreoviridin is a neurotoxic metabolite produced by Penicillium sp. In animals it affects the CNS causing paralysis, convulsions and death after cardiac and respiratory failure which are the clinical manifestations of cardiac beriberia in man (Ueno 1974). This disease has been reported in Japan and Asia following the consumption of mouldy rice.

(h) Slaframine and Swainsonine

These alkaloids are produced by the fungus Rhizoctonia leguminicola growing on red clover. Animals ingesting mouldy clover slobber profusely. Slaframine stimulates the salivary glands and pancreas by parasympathetic pathways. Swainsonine, originally isolated from Darling pea, causes neurological dysfunction commonly called 'locoism' or 'pea struck' (Broquist 1985).

## V. CONCLUDING COMMENTS

Acute mycotoxicoses from eating heavily-contaminated food is exceedingly rare in man but occurs from time to time in animals. However, in man and animals it is more likely for low levels of toxin consumption to occur over long periods, perhaps intermittently. Under these circumstances the chronic or insidious effects of these toxins are likely to occur. In this context the immunosuppressive properties of mycotoxins are considered and investigated. It would also seem appropriate to examine the neurological effects of low level mycotoxin ingestion. Perhaps these compounds cause subtle changes in behaviour as occur following exposure to various chemicals. In the foetus and very young, which are particularly susceptible xenobiotics, low level exposure to mycotoxins could result in subtle and permanent neurological changes. This is an area that has received little attention.

The other aspect of fungal neurotoxins that is apparent from this review is that they or their synthetic derivatives are a potential source of drugs for human medicine. Further research with mycotoxins is likely to uncover more compounds not only useful in treating disease but also for exploring the mechanisms of the nervous system.

REFERENCES

ALLEN, J.G. (1987). Proc. Postgraduate Committee in Vet.Sci. No. 103, Veterinary Clinical Toxicology, p.113.

ANDERSON, J.F. and WERDIN, R.E. (1977). J.Am.Vet.Med.Assoc. 170: 1089.

BAKAU, B.J.K. and BRYDEN, W.L. (1987). Proc.Nutr.Soc.Aust. 12: 170.

BAKAU, B.J.K., PEACOCK, A.J., LOVE, R.J. and BRYDEN, W.L. (1988). Proc.Nutr. Soc.Aust. 13: 136.

BARGER, G. (1931). 'Ergot and Ergotism' (Guerney and Jackson:London).

BLANEY, B.J., RAMSAY, M.D. and TYLER, A.L. (1986). Aust.J.Agr.Res. 37: 235.

BLOUNT, W.P. (1961). Turkeys 9: 52.

BOVE, F.J. (1970). 'The Story of Ergot' (Karger: Basel).

BROQUIST, H.P. (1985). Ann.Rev.Nutr. 5: 391.

BRYDEN, W.L., LOVE, R.J. and BURGESS, L.W. (1987). Aust.Vet.J. 64: 225.

BURGESS, L.W., BRYDEN, W.L., JESSUP, R.M., SCRIVENER, C.J. and BARROW, K.D. (1986). Proc.Nutr.Soc.Aust. 11: 120.

BURGESS, L.W., NELSON, P.E., TOUSSOUN, T.A. and FORBES, G.A. (1988).Mycologia 80: 815.

CHI, M.S., EL-HALAWANI, M.E., WEIBEL, P.E. and MIROCHA, C.J. (1981). Poult.Sci. 60: 137.

COLE, R.J. (1981). J.Food.Prot. 44: 715.

COLE, R.J. (1986). Mycotoxin Res. 2: 3.

COLE, R.J. and DORNER, J.W. (1986). In 'Mycotoxins and Phycotoxins', p. 501, editors P.S. Steyn and R. Vleggaar. (Elsevier:Amsterdam).

COLE, R.J., DORNER, J.W., COX, R.H. and RAYMOND, L.W. (1983). J.Agric.Food Chem. 31: 655.

CULVENOR, C.C.J. (1974). Aust.Vet.J. 50: 69.

CULVENOR, C.C.J. and JAGO, M.V. (1985). In 'Trichothecenes and Other Mycotoxins', p. 159, editor J. Lacey (John Wiley & Sons Ltd: Chichester).

DARVELL, P.M. (1964). Queensland Agric.J. 70: 692.

DORNER, J.W., COLE, R.J. and LOMAX, L.G. (1985). In 'Trichothecenes and Other Mycotoxins', p. 529, editor J.Lacey (John Wiley & Sons: Ltd:Chichester).

FRASER, D.M. and DORLING, P.R. (1983). Aust.Vet.J. 60: 303.

GANT, D.B., COLE, R.J., VALDES, J.J., ELDEFRAWI, M.E. and ELDEFRAWI, A.T. (1985). Life Sci. 41: 2207.

GELDERBLOM, W.C.A., JASKIEWICZ, K., MARASAS, W.F.O., THIEL, P.G., HORAK, R.M., VLEGGAAR, R. and KRIEK, N.P.J. (1988). Appl.Environ.Microbiol. 54: 1806.

HASCHEK, W.M. and HALIBURTON, J.C. (1986). In 'Diagnosis of Mycotoxicoses', p. 213, editors J.L. Richard and J.R. Thurston (Martinus Nijhoff Publishers:Boston).

JANG, I.H., Van Der TOL, J., BRYDEN, W.L., McDOWELL, G.H., ROSS, A.D., CHRISTIE, B.M. and BURGESS, L.W. (1987). Proc.Nutr.Soc.Aust. 12: 169.

JESSUP, T.M., DENT, C.H.R., KEMP, J.B., CHRISTIE, B.M., AHRENS,P.J., BURGESS, L.W. and BRYDEN, W.L. (1987). Aust.Vet.J. 65: 353.

JOFFE, A.Z. (1986). 'Fusarium Species: Their Biology and Toxicology' (John Wiley & Sons, New York).

KELLERMAN, T.S., COETZER, J.A.W. and NAUDE, T.W. (1988). 'Plant Poisonings and Mycotoxicoses of Livestock in Southern Africa' (Oxford University Press:Cape Town).

LING, K.H., LION, H.M., FU, T.C., KUO, H., TSAI, M.C. and LIN, M.Y. (1986). Bioactive Mol. 1: 387.

LORENZ, K. (1979). CRC Crit.Rev.Food Sci.Nutr. 11: 311.

MANTLE, P.G. (1986). In 'Mycotoxins and Phycotoxins', p. 399, editors P.S. Steyn and R. Vleggaar (Elsevier:Amsterdam).
MARASAS, W.F., KELLERMAN, T.S., GELDERBLOM, W.C. and COETZER, J.A.(1988) Onderstepoort J.Vet.Res. 55: 197.
MARASAS, W.F.O., NELSON, P.E. and TOUSSOUN, T.A. (1984). 'Toxigenic Fusarium Species; Identity and Mycotoxicology' (The Pennsylvania State University Press:University Park).
MATOSSIAN, M.K. (1982). Am.Scientist 70: 355.
MOORE, C.J., BLANEY, B.J., SPENCER, R.A. and DODMAN, R.L. (1985). Aust.Vet.J. 62: 60.
MUTSUOKA, Y., KUBOTA, K. and UENO, Y. (1979). Toxicol.Appl.Pharmacol. 50: 87.
NISHIE, K., COLE, R.J. and DORNER, J.W. (1985). Food Chem.Toxicol. 23: 831.
ROBERTSON-SMITH, R.G., JEFFCOTT, L.B., FRIEND, S.C.E. and BADCOE, L.M. (1985). Aust.Vet.J. 62: 6.
ROSS, A.D., BRYDEN, W.L., BAKAU, W. and BURGESS, L.W. (1989). Aust.Vet.J. 66: 247.
STOLL, A. and HOFMANN, A. (1970). In 'The Chemistry of the Ergot Alkaloids', p. 267, editor S.W. Pelletier (Van Hostrand Reinhold:New York).
TOBIN, N.F. (1988). Aust.J.Expt.Agric. 28: 107.
UENO, Y. (1974). In 'Mycotoxins', p. 283, editor I.F.H. Purchase (Elsevier:Oxford).
Van RENSBURG, S.J. and ALTENKIRK, B. (1974). In 'Mycotoxins', p. 69, editor I.F.H. Purchase (Elsevier:Amsterdam).
WOODS, A.J., BRADLEY JONES, J. and MANTLE, P.G. (1966). Vet.Rec. 78: 742.
WRIGHT, J. and MORLEY, D.C. (1958). Lancet 1: 871.
WYATT, R.D., COLWELL, W.M., HAMILTON, P.B. and BURMEISTER, H.R. (1973). Appl.Microbiol. 26: 757.