British Journal of Psychiatry (1985), **146**, 115–119

Annotation

Fusarial Mycotoxins and Behaviour: Possible Implications for Psychiatric Disorder

R. SCHOENTAL

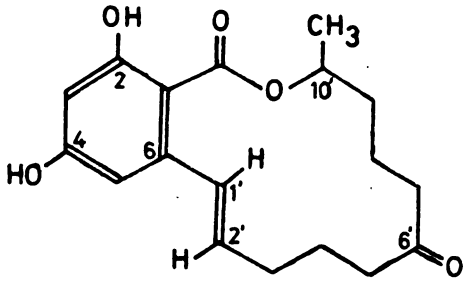
Summary: Man and animals are sporadically exposed to mycotoxins (the secondary metabolites of moulds), which include those produced in damp and cool environment by the almost ubiquitous soil-microfungi, the *Fusaria.* Perinatal exposure to the mycotoxins may cause damage to many organs, including the CNS and those which are targets for oestrogenic agents. Depending on the levels of the mycotoxins and the time of their action, the effects may manifest themselves as neonatal abnormalities, or as neurological and behavioural anomalies and chronic disorders later in life. The relationship between the anatomical and behavioural development of individuals and their perinatal exposure to fusarial mycotoxins requires further investigation.

Fusarial mycotoxins and their biological effects

Dampness, lack of ventilation, and a high moisture content of their substrate are among the conditions conducive to the growth of moulds. Almost 100,000 species have been described, but only some are toxigenic, i.e. able to produce deleterious secondary metabolites, known as mycotoxins; this is usually under specific conditions. Individual species of moulds differ widely in their requirements for growth and survival, and in their resistance to interspecies competition.

In the British Isles, as in other temperate countries, *Fusaria,* the soil microfungi and their spores are almost ubiquitous (Booth, 1971). Certain among the *Fusarium* species can produce oestrogenic substances, zearalenone and related resorcylic acid lactones (Mirocha *et al,* 1977). They can also produce trichothecenes, e.g. T-2 toxin which is an irritant, immunosuppressive and carcinogenic agent (Bamburg & Strong, 1971; Schoental *et al,* 1979; Ueno, 1980). Zearalenone, though not steriodal in its structure (Figure 1) is oestrogenic; in target organs, it binds to the same receptors as oestradiol-17ß, and it affects the hormonal balance in the body. Its presence in high concentrations in mouldy feeds is known to cause outbreaks of hyperoestrogenism in livestock. The first reported outbreak of vulvovaginitis, testicular atrophy, and sterility in pigs occurred in the mid-western states of North America in 1926, when as a result of unusually cold and wet weather during the harvest, maize became mouldy (McNutt *et al,* 1928) and contaminated mainly with *Fusarium graminearum (Gibberella zeae),* a zearalenone producer (Stob *et al,* 1962).

Perinatal exposure to oestrogenic agents during the period of the development of sex organs could affect genital morphology, reproductive functions, and sexual and other behaviour during later life, as demonstrated in rats (Soulairac & Soulairac, 1974; Vannier & Raynaud, 1980). Similar effects have been produced using zearalenone (Schoental, 1982; 1983b; Schoental, in preparation). Various other outbreaks of feed-related disorders in livestock in different countries have usually been correlated with highly unseasonal weather conditions, described as 'historical' by meteorologists (Lamb, 1964; Ludlam, 1971).

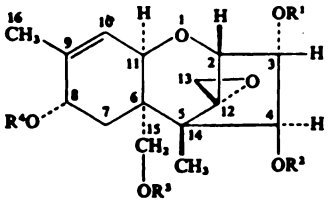


ZEARALENONE

FIG. 1 Structure of zearalenone. [6-(10'-hydroxy-6'-oxo-trans-1-undecenyl)-β-resorcylic acid lactone].

Agricultural products used for human consumption are usually of better quality, and seldom give rise to large-scale outbreaks which are recognisable as acute or subacute mycotoxicoses. However, in the past, such outbreaks did occur sporadically as a result of famine, war, or other cataclysmic disasters, when man had no choice but to consume foodstuffs which were visibly mouldy, as in the outbreak of 'alimentary toxic aleukia' (ATA) in the USSR during World War 2 (Nesterov, 1948; Mayer, 1953; Joffe, 1978). The moulds responsible

https://doi.org/10.1192/bjp.146.2.115 Published online by Cambridge University Press



T-2 Toxin: $R^1 = H$; $R^2 = R^3 = CH_3CO$; $R^4 = (CH_3)_2CHCH_2CO$

FIG. 2 Structure of T-2 toxin. [4β,15-diacetoxy-8α-(3-methylbutyryloxy)-12,13-epoxy-trichotec-9-en-3β-ol], a secondary metabolite of certain *Fusarium* species.

for ATA have been identified as mainly *Fusarium poae* and *F. sporotrichioides*, which under appropriate conditions can produce both T-2 toxin and related trichothecenes (Yagen *et al*, 1977; Joffe, 1978). T-2 toxin (Figure 2) is very toxic to a variety of animal species (LD_{50} in rats approx. 4 mg/kg body weight), immunosuppressive, irritant, and cytotoxic to many cell types; it causes haemorrhages and both acute and chronic lesions (including tumours) in the alimentary tract, the brain, and certain other organs (Schoental *et al*, 1979; Schoental, 1981a,b,c; Ueno, 1980).

In the course of experiments in which white rats were exposed perinatally to both, zearalenone and T-2 toxin, those that survived were kept without further treatment; among the males, some were exceedingly aggressive, and one was muricidal (Schoental, 1982). This aggressive behaviour remained constant during their adult life, till they were killed after a year or so. The lesions found at autopsy were mainly enlarged and haemorrhagic pituitaries, though the muricidal rat also had a Leyding cell tumour of the right testicle. Also, testicular atrophy and other sex organ lesions have been observed in livestock consuming mouldy fodder containing zearalenone.

The combination of a general cytotoxic agent and an oestrogenic one, acting at the time of the development of the target organs, appears to have long-lasting behavioural effects, and to be more effective in inducing chronic lesions than each of these substances acting separately (Schoental, in preparation). The secondary metabolites of *Fusaria* do not appear to require specific liver enzymes for activation, and would be expected to produce similar effects in many animal species, including man.

Both CNS lesions and behavioural changes have been described in the USA in horses (Wilson *et al*, 1973), poultry (Wyatt *et al*, 1973), and other livestock, and the same has been reported from Japan, Hungary, and South Africa as a result of consumption of mouldy fodder contaminated by *Fusarium* or *Stachybotrys spp.* producing toxic trichothecenes (Schneider *et al*, 1979; Ueno, 1980).

Experimentally, neural disturbances have been reproduced in chicken which were given T-2 toxin in their diet; they showed impairment of the righting reflex, abnormal positioning of wings, and seizures characterised by loss of normal voluntary motor abilities (Wyatt *et al*, 1973). In their brains, the concentration of dopamine was elevated, that of serotonine unchanged, and epinephrine decreased (Chi *et al*, 1981).

In pigs, vomiting follows exposure to mouldy fodder contaminated by T-2 toxin or by other trichothecenes, one of which (deoxynivalenol, also known as vomitoxin or food refusal factor) frequently contaminates maize and other cereals. If such cereals are used for alcoholic fermentation, the trichothecenes would mainly remain in alcoholic beverages such as beer (Payen *et al*, 1983), excessive drinking of which is known to cause vomiting.

Ducklings, cats, and dogs also vomit after trichothecenes, even when the substances are administered by subcutaneous injections. The vomiting can be suppressed by prior administration of chlorpromazine or metaclopramine, indicating the involvement of the medulla oblongata in this response (Matsuoka *et al*, 1979).

Clinical and neurological disorders caused by mouldy cereals

Much evidence was accumulated about the possible effects of fusarial mycotoxins on man from the observations of doctors who attended the patients in the Russian grain belt, where large-scale outbreaks used to occur of seasonal disorders. These were originally suspected to be due to infections, but were eventually traced to the consumption of unwholesome cereals in food, as indicated by the name 'alimentary toxic aleukia' (ATA). This is now the accepted designation of a syndrome (known also as 'septic agina', 'panmyelotoxicosis', etc.), which is caused by the consumption of bread made from over-wintered, mouldy grain, contaminated by toxigenic species of *Fusarium* and other microfungi and by their mycotoxins. The syndrome was particularly severe in under-nourished people in rural areas, and was compared to the effects of radiation (Mayer, 1953). ATA consists of four stages: a period of between three and nine days of acute gastro-intestinal tract disorder, followed by about two weeks to two months of apparent improvement, during which the development of leukopenia, thrombocytopenia,

https://doi.org/10.1192/bjp.146.2.115 Published online by Cambridge University Press

haemorrhage, and depressed immunity are followed by the third stage of acute, often fatal infections of the throat, lungs, etc. Among those who survived this stage, recovery was slow, even in less serious cases (Nesterov, 1948; Mayer, 1953; Joffe, 1978).

In patients with ATA, impaired nervous reflexes, meningism, general depression, hyperaesthesia, encephalitis, cerebral haemorrhages, and destructive lesions of some neurons and sympathetic ganglia have been reported. Sometimes delirium, convulsions, and paralysis have occurred (Serafimov, 1946; Kholodenko, 1947; Mayer, 1953; Joffe, 1978).

The Russian psychiatrists observed that some of their patients suffering from ATA (now known to be an acute or subacute form of fusarial mycotoxicosis) sometimes showed opposite signs and symptoms—either a tendency to somnolence or asomnia, either psychomotor excitement or anergia, apathy, etc. The extent of the disordered states varied greatly among the individual patients, some of whom experienced vivid visual and aural hallucinations.

It would seem not unreasonable to expect that when exposure to mycotoxins occurs perinatally, the striking visual and aural experiences may have their counterparts in lesions of the respective areas of the developing brain and other organs. In later life, this could well result in specific abilities or disabilities, and in personalities that differ from the 'normal' in various respects. Recent experimental work has made it clear that the patterns of adult behaviour may indeed be predetermined during the perinatal period.

Season of birth and the incidence of serious neurological abnormalities in humans

It may be significant that epidemiological studies have indicated that the risk of serious neonatal abnormalities of the CNS such as anencephaly, Down's, Turner's, and Klinefelter's syndromes, as well as chromosomal aberrations in the newborn, is related to the season of birth and higher among those born during the winter or spring months (McKeown & Record, 1951; Laurence *et al*, 1968; Jongbloet, 1970; Anon, 1983). However, no satisfactory explanation has been formulated for these phenomena.

The risk of developing schizophrenia has also and more consistently been reported to be related to the season of birth, and to be higher among those born in the winter and spring months. The incidence of schizophrenia is known to vary also with age and sex; its aetiology, however, remains mainly unknown (Hare, 1978). "The damage might be due to nutritional deficiency, viral infection, or other obstetrical problems" (Pulver *et al*, 1981). In their study of the cases of schizophrenia first diagnosed during the period 1 January, 1969 to 31 December, 1971, among white residents of Monroe Country, New York, the highest incidence of schizophrenia occurred among the 24 year-olds, who were born about 1946. In New York State during 1947, the weather conditions have been reported by Ludlum (1971) to have included "extreme precipitation" and "extreme snowfall"; that year is also memorable for exceptionally heavy snowfalls and cold weather in Great Britain. Such conditions favour the survival of the cryophilic *Fusaria*, and the production of high levels of their secondary metabolites—zearalenone and the trichothecenes (Joffe, 1978; Mirocha *et al*, 1977).

The foetus and the very young, who are particularly susceptible to the effects of xenobiotics during the stages of development and active growth, could suffer damage when exposed to mycotoxins, derived from contaminated food or drinks (such as alcoholic ones) ingested by their mothers (foetal alcohol syndrome), or present in the milk of cows consuming mouldy fodder. As the levels of mycotoxins depend on the weather conditions, they vary greatly from year to year, from month to month, from day to day, and from one locality to another. It is therefore not surprising that inconsistent and often contradictory results have been obtained in epidemiological studies, in which the local weather conditions (and the possibility of exposure to mycotoxins) have not been taken into consideration.

As mycotoxins have been shown to contaminate alcoholic beverages occasionally, when the grain used for fermentation might have been mouldy (Schoental, 1981c; Payen *et al*, 1983; Haikara, 1983), they may play a role in the aetiology of Wernicke Korsakoff encephalopathy of adults, which includes gastrointestinal disorders, and is usually correlated with excessive consumption of alcoholic beverages and thiamine deficiency (Anon, 1979).

However, additional factors—genetic, nutritional, environmental (e.g. damp homes), and social—have also to be taken into consideration (Gann, 1975). Their interaction may determine who will remain 'normal' and who will suffer damage of some extent, the repair of which may give the individual either specific abilities or disabilities, or lead to abnormal, and even criminal behaviour. In the past, man was aware of the deleterious effects of moulds, which were con-

https://doi.org/10.1192/bjp.146.2.115 Published online by Cambridge University Press

sidered 'unclean' in the Pentateuch, and laws were promulgated on how to deal with the contaminated environment (Schoental, 1980; Schoental, 1984).

Modern man in his air-conditioned dwelling, consuming food treated with pesticides, seldom comes across growing moulds, and remains unaware of the possibility that he may be exposed to the hazards of mycotoxins. Yet many mycotoxins, once formed, will remain in food long after the moulds have disappeared, as they are mostly resistant to the action of pesticidal chemicals, cooking, baking, fermentation, etc. When food is contaminated by the irritant and very toxic trichothecenes, indigestion, stomach pain, vomiting, diarrhoea, salivation, and headache may soon follow, and would draw attention to the food ingested, but the presence of the almost non-toxic oestrogenic zearalenone would remain unrecognised. The insiduous effects of a large intake of zearalenone might become apparent only much later, when the connection with the past exposure would not be readily traceable. Outbreaks of precocious development of sex organs among very young children that occurred in the past five years in Puerto Rico appear related to excessive intake of zearalenone and its derivatives, which were detected in the blood of some of the affected children (Sáenz de Rodriquez, 1984).

Transitory aggressive or otherwise changed behaviour is known to result from exposure to various drugs or toxic materials, but very little attention has as yet been given to exposure to the 'natural' mycotoxins. As the effects of toxic substances are usually more prominent when acting perinatally, the birth-date of the individual and the then prevailing weather conditions may be a useful indication as to whether detailed investigations are warranted into the involvement of mycotoxins in the neurological and psychiatric characteristics of the criminal—and possibly also of the saint and the genius (Lombroso, 1891; Schoental, 1983a, 1984a).

References

Anon (1979) Wernicke's encephalopathy. *British Medical Journal*, **3**, 291–292.

—— (1983) Seasonality, Down's syndrome and anencephaly. *Lancet*, **1**, 1312–1313.

Bamburg, J. R. & Strong, F. M. (1971) 12,13-epoxytrichothecenes. In *Microbial Toxins. A Comprehensive Treatise, Algal and Fungal Toxins* (eds. S. Kadis, A. Ciegler & S. J. Ajl). Vol 7. London: Academic Press.

Booth, C. (1971) *The genus Fusarium*. Kew: Commonwealth Mycological Institute.

Chi, M. S., El-Halawani, M. E., Weibel, P. E. & Mirocha, C. J. (1981) Effects of T-2 toxin on brain catecholamines and selected blood components in growing chickens. *Poultry Science*, **60**, 137–141.

Gunn, J. (1975) Psychiatric aspects of violence and violent offenders. *Forensic Science*, **5**, 219–227.

Haikara, A. (1983) Malt and beer from barley artificially contaminated with *Fusarium* in the field. *European Brewing Convention Congress Proceedings*, 401–408.

Hare, E. H. (1978) Variations in the seasonal distribution of births of psychotic patients in England and Wales. *British Journal of Psychiatry*, **132**, 155–158.

Joffe, A. Z. (1978) *Fusarium poae* and *F. sporotrichioides* as principal causal agents of alimentary toxic aleukia. In *Mycotoxic Fungi, Mycotocins, Mycotoxicoses. An Encyclopedic Handbook* (eds. T. D. Wyllie & L. G. Morehouse). New York: Marcel Dekker.

Jongbloet, P. H. (1970) Chromosomal aberrations and month of birth. *Lancet*, **2**, 1317–1318.

Kholodenko, M. I. (1947) Changes in the nervous system in toxic alimentary aleukia (so-called "septic angina"). *Nevropatologiia i Psykhiatriia*, **16**:4, 67–68.

Lamb, H. H. (1964) *The English Climate. Calendar of Historic Weather Events since 1500*, appendix 2. London: English University Press.

Laurence, K. M., Carter, C. O. & David, P. A. (1968) Major central nervous system malformations in South Wales. 1. Incidence, local variations and geographical factors. *British Journal of Preventive & Social Medicine*, **22**, 146–160 and 212–222.

Lombroso, C. (1891) *Man of Genius*. London: Walter Scott.

Ludlum, D. M. (1971) *Weather Record Book. The outstanding events 1871–1970*. Princeton: Weatherwise Inc.

McKeown, T. & Record, R. G. (1951) Seasonal trends in congenital malformations of the central nervous system. *Lancet*, **i**, 192–196.

McNutt, S. R., Purwin, P. & Murray, C. (1928) Vulvovaginitis in swine. Preliminary report. *Journal of the American Veterinary Medical Association*, **73**, 484–492.

Matsuoka, Y., Kubota, K. & Ueno, Y. (1979) General pharmacological studies of fusarenon-X, a trichothecene mycotoxin from *Fusarium* species. *Toxicology & Applied Pharmacology*, **50**, 87–94.

Mayer, C. F. (1953) Endemic panmycolotoxicosis in the Russian grain belt. *The Military Surgeon*, **113**, 173–189 and 295–315.

Mirocha, C. J., Pathre, S. V. & Christensen, C. M. (1977) Zearalenone. In *Mycotoxins in Human and Animal Health* (eds. J. V. Rodricks, G. W. Hesseltine & M. A. Mehlman) Park Forest South, Illinois: Pathotox Publications.

Nesterov, V. C. (1948) The clinical course of septic angina. *Klinicheskaia Meditsina*, **26**:7, 34–41.

Payen, J., Girard, T., Gaillardin, M. & Lafont, P. (1983) About contamination of beers by mycotoxins. *Microbiologie-Aliments-Nutrition*, **1**, 143–146.

Pulver, A. E., Sawyer, J. W. & Childs, B. (1981) The association between season of birth and the risk for schizophrenia. *American Journal of Epidemiology*, **114**, 735–749.

Sáenz de Rodriguez, C. A. (1984) Environmental hormone contamination in Puerto Rico. *New England Journal of Medicine*, **310**, 1741–1742.

Schneider, D. J., Marasas, W. F. O., Kuys, J. C. O., Kriek, N. P. J. & Schalkwyk, van G. C. (1979) A field outbreak of suspected stachybotryotoxicosis in sheep. *Journal of the South African Veterinary Association*, **50**, 73–81.

Schoental, R. (1980) A corner of history. Moses and mycotoxins. *Preventive Medicine*, **9**, 159–161.

https://doi.org/10.1192/bjp.146.2.115 Published online by Cambridge University Press

—— (1981a) Relationships of *Fusarium* toxins to tumours and other disorders in livestock. *Journal of Veterinary Pharmacology and Therapeutics*, **4**, 1–6.
—— (1981b) Carcinogenic mycotoxins. In *Dietary Influences on Cancer, Traditional and Modern* (eds. R. Schoental & T. A. Connors). Boca Raton: CRC Press.
—— (1981c) Carcinogenic contaminants of food, *ibid.*
—— (1982) Behavioural and other effects of secondary metabolites of certain *Fusarium* species. In *Behavioral Models and the Analysis of Drug Action* (eds. M. Y. Spiegelstein & A. Levy) Amsterdam: Elsevier.
—— (1983a) Mozart's illnesses and death. *Journal of the Royal Society of Medicine*, **76**, 1079, and idem. (1984a) *ibid.*, **77**, 157.
—— (1983b) Health hazards of secondary metabolites of *Fusarium*. *Microbiologie-Aliments-Nutrition*, **1**, 101–107.
—— (1984) Mycotoxins and the Bible. *Perspectives in Biology*, **28**, in press.
—— Joffe, A. Z. & Yagen, B. (1979) Cardiovascular lesions and various tumours found in rats given T-2 toxin, a trichothecene metabolite of *Fusarium* species. *Cancer Research*, **39**, 2179–2189.
Serafimov, B. N. (1946) Psychiatric symptomatology in alimentary toxic aleukia (septic angina). *Nevropatologiia i Psykhiatriia*, **15**:6, 50–54.
Soulairac, M.-L. & Soulairac, A. (1974) Conséquences de l'oestrogenisation post-natale sur le comportement sexuel et le tractus génital du rat mâle adulte. *Journal de Physiologie, Paris*, **68**, 19B–20B.
Stob, M., Baldwin, R. S., Tuite, J., Andrews, F. N. & Gillette, K. G. (1962) Isolation of an anabolic, uterotropic compound from corn infected with *Gibberella zeae*. *Nature*, **196**, 1318.
Ueno, Y. (1980) Trichothecene mycotoxins. Mycology, chemistry and toxicology. *Advances in Nutrition Research*, **3**, 301–353.
Utian, W. H. (1973) Comparative trial of P.1496, a new non-steroidal oestrogen. *British Medical Journal*, **i**, 579–581.
Vannier, B. & Raynaud, J. P. (1980) Long-term effects of prenatal oestrogen treatment on genital morphology and reproductive function in the rat. *Journal of Reproduction and Fertility*, **59**, 43–49.
Wilson, B. J., Maronpot, R. R. & Hildebrandt, P. K. (1973) Equine leukoencephalomalacia. *Journal of the American Veterinary Medical Association*, **163**, 1293–5.
Wyatt, R. D., Colwell, W. M., Hamilton, P. B. & Burmeister, H. R. (1973) Neural disturbances in chickens caused by dietary T-2 toxin. *Applied Microbiology*, **26**, 757–761.
Yagen, B., Joffe, A. Z., Horn, P., Mor, N. & Lutsky, I. I. (1977) Toxins from a strain involved in ATA. In *Mycotoxins in Human and Animal Health* (eds. J. V. Rodricks, G. W. Hesseltine & M. A. Mehlman. Forest Park South, Illinois, Pathotox Publications.

R. Schoental, PhD. DSc. *Affiliated to Department of Pathology, Royal Veterinary College, University of London, Royal College Street, London NW1 0TU*

(Received 31 July; revised 10 September 1984)

https://doi.org/10.1192/bjp.146.2.115 Published online by Cambridge University Press