Biochemical Reviews

Mouldy grain and the aetiology of pellagra: the role of toxic metabolites of *Fusarium*

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In latter years much progress has been made in the elucidation of the chemical structures as well as of the biological and toxicological effects of various secondary metabolites of moulds known as mycotoxins. Of particular interest for countries with damp and temperate climates are the mycotoxins produced by various *Fusarium* species and related field microfungi. These compounds can contaminate cereals and other agricultural products when these are harvested under wet conditions and stored inappropriately. Outbreaks of fatal toxicoses occurred in man and livestock, which have been correlated with the consumption of mouldy grain or its products contaminated with high concentrations of *Fusarium* mycotoxins (Table 1). A particularly tragic outbreak occurred during the Second World War, when famine forced people to eat bread made from mouldy 'overwintered' cereals in the Orenburg district of the U.S.S.R. (Joffe, 1978). Among the various symptoms that followed, the haematological changes, a decrease of the leucocytes in the blood, was so striking that this condition came to be known as 'alimentary toxic aleukia'. Besides the eponymous blood changes, other symptoms included gastrointestinal disorders, haemorrhage, skin lesions, neurological disturbances and sometimes 'septic angina' as a result of decreased immunity. Low nutritional status aggravated the alimentary toxic aleukia, which could be ameliorated to some extent by treatment with B vitamins and vitamin C (Karatygin & Roshnova, 1947). In the mouldy grain, various microfungi have been identified, including *Fusarium poae* and *F. sporotrichioides*, which in cultures (under conditions designed to simulate those to which the 'overwintered' grain was exposed) produce T-2 toxin [4β,15-diacetoxy-8α-(3-methylbutyryloxy)-12,13-epoxytrichothec-9-en-3α-ol] (Fig. 1) and related trichothecenes (Yagen *et al.*, 1977). T-2 toxin has been identified in mouldy maize responsible for an outbreak of 'mouldy corn toxicosis', characterized by haemorrhage, gastrointestinal disorders etc., among cattle in Wisconsin (Bamburg *et al.*, 1968; Hsu *et al.*, 1972). T-2 toxin has been found in bean hulls used as fodder, which caused great losses among horses bred on Hokkaido, the northern island of Japan (Ueno *et al.*, 1972; Ueno, 1977). T-2 toxin was also detected in mouldy brewer's grains included in dairy-cattle feeds in Scotland, which led to the death of 9 out of 115 cows (Petrie *et al.*, 1977).

In experimental animals, T-2 toxin can reproduce lesions similar to those described in alimentary toxic aleukia in man, or in livestock acutely affected by eating mouldy feeds. In long-term experiments, T-2 toxin induced in rats cardiovascular lesions and tumours of the digestive organs and of the brain (Schoental *et al.*, 1979).

Many of the lesions, such as the gastrointestinal and neurological disorders, skin changes, and the excretion by rats of urinary porphyrins after intragastric administration of T-2 toxin (Schoental & Gibbard, 1978), are similar to those described in pellagra.

In her social history of pellagra, Roe (1973) described how the outbreaks of this condition usually occurred among people who had to subsist on spoiled maize. She stressed that the enormous amounts of maize that are produced [in the U.S.A. the more recent production has been reported to be about 5 billion bushels per annum (Lillehoj & Hesseltine, 1977)], are consumed by man and animals without ill effects when the grain is sound.

The cultivation of maize (Indian corn; *Zea mays*) has been developed by the pre-Columbian Indians, who are said not to have suffered from pellagra, because they consumed maize mainly in the form of tortillas; the preparation of the flour included exposure of the grain to slaked lime, which released nicotinic acid from the bound form, and made it utilizable as a vitamin.

The information on how the pre-Columbian Indians prepared their food from corn was obtained by Théophile Roussel (1866), from a thesis of a young Mexican physician, Ismael Salas, presented in Paris, in 1863. '.... Salas emphasized that the principal article of diet of the Mexican peasant was the tortilla

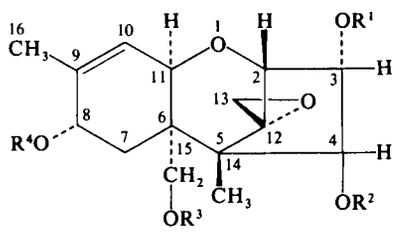

Fig. 1. *Structure of T-2 toxin [4β,15-diacetoxy-8α-(3-methylbutyryloxy)-12,13-epoxytrichotec-9-en-3α-ol], a secondary metabolite of certain Fusarium species*

Key to variable substituents: $R^1 = H$; $R^2 = R^3 = CH_3CO$; $R^4 = (CH_3)_2CHCH_2CO$.

Table 1. *Outbreaks of lethal T-2 mycotoxicoses in man and livestock*

Year	Locality	Species	Material containing T-2 toxin	Disorder known as:	Reference
1942–1943	Orenburg (U.S.S.R.)	Humans	Bread from overwintered grain	Alimentary toxic aleukia	Joffe (1978)
1965–1966	Wisconsin (U.S.A.)	Livestock	Mouldy corn fodder	Haemorrhagic diathesis	Bamburg *et al.* (1968)
1970	Wisconsin (U.S.A.)	Cows	Mouldy corn fodder	Haemorrhagic diathesis	Hsu *et al.* (1972)
1976–1977	Scotland (U.K.)	Dairy cows	Mouldy brewer's grains in fodder	Haemorrhagic diathesis	Petrie *et al.* (1977)
1970	Hokkaido (Japan)	Horses	Mouldy bean-hull fodder	Akakabi-byo (*Fusarium* blight)	Ueno *et al* (1972)
1965–1966	Quebec (Canada), U.S.A. and Belgium	Humans	Beer	'Cobalt-beer' cardiomyopathy	Morin & Daniel (1967); Morin *et al.* (1967)

instead of the corn bread that was eaten so widely in France and Italy by the pellagrins. He said that in the preparation of tortillas the grains of corn are mixed with slaked lime and water in earthenware pots and heated for eighteen hours. At the end of this time, the limewater was drawn off, the corn washed and then pressed in a primitive grindstone till it formed a glutinous paste. This paste was made into round flat cakes which were baked on a heated iron griddle and turned frequently to avoid overcooking ...' (Roe, 1973). This method developed in remote times has been retained by the Mexicans to the present day.

It would be surprising if nicotinic acid, the calcium salt of which is soluble in water, could remain in the corn paste after the corn had been soaked, washed with water and pressed; treatment with alkali could even destroy some of the other B vitamins. Yet the fact remains that pellagra has not been a major problem in Middle America and Mexico among people whose diet consisted mainly of tortillas and fried bean paste.

Following the introduction of maize into other countries, outbreaks of pellagra occasionally occurred in Spain, Italy, France, Egypt etc. The information about this disease came from Dr. Gaspar Casal (1762), who in 1735 began to see patients suffering from 'mal de la rose' (a local synonym of pellagra, based on the red skin lesions) among the very poor Asturian peasants, who '... subsisted chiefly on puchero, a type of corn bread and ferrapas, a sort of corn-meal mush ... with some beans, a little milk, a few sardines or salt cod ...' The disorder included '... skin changes, fluxes of the bowels and severe mental changes ...'. Casal believed that excessive humidity could play an important role in the causation of 'mal de la rosa' (cf. Roe, 1973). It is noteworthy that the Asturias are in the wet north-western part of Spain.

In Italy, outbreaks of pellagra (pella agra) occurred in the 18th and 19th centuries; these usually followed long winters, when the Italian poor lived almost solely on boiled corn meal. According to Marzari, who worked in Treviso in the Italian Alps, '... maize was often picked before it was ripe, it was allowed to become moist and was then stored undried ...' (quoted by Roe, 1973). Guerreschi (1814; quoted by Roe, 1973) suggested, by analogy with ergotism, that pellagra was due to toxins in mouldy corn. Later Ballardini (1845) examined mouldy corn and '... found a greenish discoloration on the grain that came to be known as verderame and that was subsequently found to be due to the fungus *Sporisorium maidis* ...' According to Roe (1973), Ballardini claimed to have reproduced a pellagra-like condition in chickens and in man by feeding such mouldy maize.

Lombroso (1898) described pellagra-like symptoms of variable degrees in young, healthy men, soldiers and workers, given alcoholic extracts from mouldy maize. No such symptoms followed when they were given extracts from sound maize. He observed during the preparation of alcoholic digests from such mouldy maize (imported from Romania) that the alcohol and the grain became increasingly deeper red with time, whereas similar digests from sound maize remained yellowish. The red alcohol-soluble substance was bitter, and was toxic to animals. It is noteworthy in this connection that many *Fusarium* species, including *F. roseum* Link, are reddish, due to the pigment rubrofusarin (5,6-dihydroxy-8-methoxy-2-methylbenzo[*g*]chromen-4-one).

In France, although Théophile Roussel (1866) believed that pellagra was caused by spoiled-corn products, he thought that this disease could develop only in the people who are genetically predisposed.

Outbreaks of pellagra (quoted by Roe, 1973) occurred on the island of Corfu during the years 1858 and 1866, when the grain has been imported from Albania and from other countries: '... the imported corn was sometimes imperfectly ripened and unwholesome ...'. The maize grown locally did not usually produce ill effects.

An outbreak of pellagra occurred in Yucatan, Mexico, in 1882, when locusts destroyed the local Indian corn, and supplies had to be imported from New York: 'The imported corn was brought in the holds of vessels as ballast. By reason of exposure to heat and humidity on the voyage, the corn underwent fermentation and became unfit for food. The constant eating of this spoiled corn led to the slow development of pellagra. The disease was confined to the lower and middle classes, who were obliged to purchase the cheapest corn in the market. The wealthy class escaped as they did not eat the imported corn.'

In the United States, unrecorded cases of pellagra appear to have occurred already in the 19th century, but it was the First National Conference on Pellagra in South Carolina in 1909 that stimulated the interest and investigation into the incidence of this disease. At this Conference a paper was quoted in which Sandwith (1898) reported his observations of pellagra in Egypt, among the poor peasants, the fellaheen, who use 'bad maize' mainly in the form of bread. 'The poor peasants sell their best product at the market and keep the worst to eat at home'. He stressed that eating of corn '... roasted or raw in the green state ...' was less dangerous, as the '... fungus would not have time to grow as it would when corn was stored.' 'It is not good maize or good maize flour which produces pellagra, but the disease for its production requires the habitual use of damaged maize in some form.'

This extensive evidence leaves little doubt that pellagra developed as a result of eating 'spoiled' maize by the very poor, the insane kept in asylums, the inmates of prisons, or when the failure of the normal crops caused famine, and supplies of maize had to be imported by ship under conditions that would be propitious for the growth of moulds and for the production of mycotoxins. Only when people had no choice and little else to eat would they consume such spoiled maize; the effects of its mycotoxins would then be aggravated by the poor nutritional state of the individuals.

Yet, despite all this evidence, vitamin deficiency became the accepted explanation of pellagra and was accepted also by Roe (1973). This was due to the investigations of Goldberger and his co-workers, whose Public Health Reports relevant to pellagra have been collected and reissued by Terris (1964). Goldberger selected for intensive studies two cotton-mill villages in Spartanburg County (South Carolina, U.S.A.), which showed the greatest difference in morbidity from pellagra. 'In the village where pellagra was least frequent, he found that although the villagers who were employed at the mill obtained their basic supplies from a commissary operated by the factory owner, they also had access to certain fresh foods which were sold at an independent grocery' and had good-sized plots for growing vegetables etc. 'The situation was in contrast to that in another village where pellagra was very prevalent. In the latter, the workers and their families were entirely dependent upon the company-owned store at the mill for their food supplies' and very little space was to be found for raising any produce.

This indicated to Goldberger that the supplementary foods must contain some factor(s) that prevent pellagra. As primary requirements in searching for such pellagra-preventive factors, experimental animals were needed in which pellagra-like conditions could be induced.

At about the same time, Chittenden & Underhill (1917) reported the production in dogs of a condition, known as black-tongue, that has some similarities with human pellagra. Black-tongue is characterized by ulcerative inflammation of the mouth and the gastrointestinal tract, some skin lesions and severe nervous symptoms; it is a disease that occurs in dogs given mainly corn bread, and little or no meat. Goldberger (Terris, 1964) reproduced a similar condition by feeding dogs on '... cracker meal, dried peas and cottonseed oil.' This condition could be prevented or ameliorated by supplements of dried brewer's yeast, or liver extracts. Though Goldberger did not identify the pellagra-preventative factors (he died from kidney cancer in 1929), the isolation of nicotinic acid from such liver extracts

drew attention to this compound, which was proved to prevent blacktongue in dogs and to act as a pellagra-preventative factor (Elvehjem *et al.*, 1938).

The fact that dogs fed on meat do not develop blacktongue was explained by its content of tryptophan, which is the course of its metabolism gives rise to nicotinic acid; 60 g of tryptophan will yield 1 g of nicotinic acid.

Yet, though nicotinic acid could ameliorate some of the features of pellagra, it soon became clear that other B vitamins, and possibly also other factors, must be involved.

A pellagra-like condition still occurs in India among communities of the Decca plateau, whose staple food consists of millet (*Sorghum vulgare*), known locally as 'jowar'. Its nicotinic acid content is similar to that in rice (pellagra does not occur among rice eaters), but it contains a high concentration of leucine; the amino acid imbalance was therefore suspected as a possible cause of pellagra (Gopalan & Rao, 1975). During experimental feeding of dogs with 'jowar', supplementation with isoleucine was claimed to prevent the development of blacktongue. It has been reported that in 'jowar' (*Sorghum*) contaminated by *Fusarium incarnatum*, T-2 toxin was detected. Cultures of this *Fusarium* species produced irritant and toxic trichothecenes (Rukmini & Bhat, 1978). This evidence may explain why, among the Indian 'jowar'-eating people, only some develop pellagra.

Pellagra-like conditions occur occasionally among alcoholics. *Fusarium* mycotoxins may also be involved in such cases; sporadic use of *Fusarium sporotrichiella*-contaminated barley, harvested during wet weather, has been found to be responsible for excessive 'gushing' of beer (Gjertsen *et al.*, 1965). It may be significant that it was during 1965–1966 that an outbreak of fatal mouldy-corn toxicosis occurred among livestock in Wisconsin (Table 1) serious enough to stimulate a study into the toxic agent(s) in the mouldy maize. This investigation led to the isolation and identification of the chemical structure of T-2 toxin (Bamburg *et al.*, 1968). It was also during 1965–1966 that fatal cases of cardiomyopathy occurred among heavy beer drinkers in Quebec (Canada), Minnesota and Nebraska (U.S.A.) and Belgium (Morin & Daniel, 1967; Morin *et al.*, 1967; Alexander, 1972). The outbreak in Quebec came to be known as 'cobalt-beer' cardiomyopathy. Later it was suggested that the ill effects of a particular brand of beer were caused by cobalt salts, small quantities of which had been added in order to safeguard the appropriate foaming qualities ('head') of the beer, affected by the use of detergents.

It has been estimated that no more than 8 mg of cobalt sulphate was present in 24 pints of this particular beer, a quantity that would not be expected to have deleterious effects, in view of the medicinal use of tablets each containing 60 mg of cobalt chloride; four such tablets are usually given daily, for the treatment of anaemia, without ill effects (Alexander, 1972; Shaper, 1979). Besides cardiomyopathy, many of the cases showed gastrointestinal lesions, including one perforated duodenal ulcer (Bonenfant *et al.*, 1967), which are not unlike the effects of T-2 toxin (Schoental *et al.*, 1979).

It is now well recognized that cereals can be contaminated by a variety of micro-organisms, of which only some will produce toxic metabolites when the grain is harvested and stored under conditions propitious for the production of the particular mycotoxins. *Aspergillus*, *Penicillium* and *Fusarium* species are among the toxigenic fungi (Lillehoj & Hesseltine, 1977; Scott, 1977).

It could be asked how was it that though spoiled maize had been correlated with the outbreaks of pellagra, the role of the fungi has not been clarified? The main reason appears to have been the failure to isolate the relevant *Fusarium* species. The organisms that were isolated and successfully propagated in cultures were either non-toxic, or when toxic did not reproduce the lesions characteristic of pellagra. Lombroso (1898, pp. 28–29) considered as possibly relevant to pellagra the following micro-organisms: *Aspergillus glaucus*, *Eurotium herbariorum*, *Oidium lactis maidis*, *Penicillium* spp., *Sporisorium maidis*, *Sporotrichum maidis* and various bacteria. Alcoholic extracts from cultures of the micro-organisms that could be isolated did not reproduce the effects caused by alcoholic extracts from mouldy maize. Lombroso stressed that he was unable to isolate *Sporisorium maidis*, which Ballardini (1845) reported as reproducing pellagra-like symptoms; but apparently even Ballardini could not find this fungus consistently in mouldy maize. As for *Sporotrichum maidis*, this organism had been isolated by Garovaglio from maize exposed to stormy weather in 1873 (see Lombroso, 1898, p. 29), but remained a very rare species. Lombroso argued that micro-organisms that are only very rarely found in spoiled maize could not be responsible for a disease so frequent and so widespread as pellagra. Thus he came to believe that the micro-organisms produce toxic ptomaine-like substances only on maize, but not in cultures. He also believed that only some people are genetically predisposed to become affected.

According to Booth (1971, p. 80) *Sporotrichum poae* is a synonym for *Fusarium poae*; Garovaglio's *Sporotrichum maidis* must have been a *Fusarium* species.

In other Italian studies intended to evaluate the contribution of the microflora to the toxicity of mouldy maize, Ceni & Besta (1902) found that alcoholic extracts from spores of *Aspergillus fumigatus* and *A. flavescens* grown at 24–33°C for 5 days were toxic to rabbits, producing convulsions and coma, but the animals that survived longer than 2 days recovered completely.

More recent mycological investigations into the mycoflora of spoiled grains revealed that toxigenic *Fusarium* species can disappear on storage. The survival of micro-organisms depends on the species and on the environmental conditions, on the temperature, the moisture content and on the presence of competing species. Depending on their survival abilities, Pelhate (1969) grouped the various fungi into ephemeral, mesobiotic and persistent types. He showed that *Fusarium roseum* (Lk.) Sn. et H. [known also as *F. culmorum* (W. G. Sm.) Sacc.], *Trichothecium roseum* Link, and other trichothecene-producing species survived better at high humidity and low temperatures. *Fusarium culmorum* survived for only a few months, whereas *Aspergillus fumigatus*, certain *Penicillia* and *Alternaria* are thermotolerant and could survive a few years (Pelhate, 1969).

Comparative growth rates of various species of fungi vary greatly with the temperature. Thus, e.g., on malt agar at 32°C, *Aspergillus fumigatus* will grow 11.6 mm/day, whereas *Fusarium culmorum* will not grow at all (0 mm/day). On the other hand, at 22°C, *A. Fumigatus* grows 9 mm/day and *F. culmorum* 8.5 mm/day (Moreau, 1979, p. 21). The toxigenic *Fusarium* species produce mycotoxins at even lower temperatures, optimally when temperatures fluctuate between 5 and 20°C (Joffe, 1978).

These characteristics of growth and survival of the various fungal species were not known to the pellagra investigators. Unable to isolate and to grow the species, which were relevant for the aetiology of pellagra, they were puzzled by the fact that the extracts from the mouldy maize could reproduce pellagra-like symptoms. It is now known that the trichothecene mycotoxins are relatively stable; no wonder that these persisted long after the disappearance of the micro-organisms that produced them!

Pellagra as mainly trichothecene-mycotoxicosis

In the light of modern mycological and toxicological studies, the aetiology of pellagra and its manifestations become explainable. The effects of mycotoxins are more acute in the malnourished and vitamin-B deficient person, because deficiency of coenzymes would prevent the functioning of some of the enzymes active in the detoxification processes (Schoental, 1976*a*). The variability of response observed among the healthy young men given alcoholic extracts from mouldy maize by Lombroso may have been related to their nutritional status. The

photosensitivity and intolerance of sunlight sometimes experienced by the pellagrins may have been related to disturbances in the porphyrin metabolism, as indicated by the increased urinary coproporphyrin excretion by rats given T-2 toxin (Schoental & Gibbard, 1979). Outbreaks of pellagra usually occurred in the spring, the maize having been stored over the winter in areas with damp and cool weather; such conditions are known to be conducive to the production of trichothecene mycotoxins. And the variability and inconsistencies observed in the many nutritional studies are not surprising, knowing the variability of the amounts of mycotoxins in various batches of maize.

How can the absence of pellagra among the tortilla-eating people be explained? The locally grown maize may have been mostly sound; moreover the treatment with slaked lime would hydrolyse the ester groups present in T-2 toxin and other trichothecenes; the respective hydroxy derivatives are known to be less toxic by a factor of 10 or more. The contamination of the imported maize must have been exceedingly heavy when the outbreak of pellagra did occur in Yucatan.

Although B vitamins can protect to some extent from the more acute toxic effects of xenobiotics (including mycotoxins), they do not prevent the induction of tumours by carcinogens (Schoental, 1976*b*, 1978). It is noteworthy that immigrant Mexicans in the U.S.A. have been found to have lower incidence rates of cancer for all anatomical sites, but not for cancer of the stomach, cervix, liver and gall bladder (Menck *et al.*, 1975). In the aetiology of tumours of these organs, carcinogenic mycotoxins (such as aflatoxins, trichothecenes as well as oestrogenic mycotoxins produced by many *Fusarium* species) could be expected to be involved. It would be of interest to investigate the incidence and localization of tumours among people who suffered from pellagra, but who recovered, owing to the treatment with B-vitamins and good diet, and survived to old age.

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Histamine and histamine H_1- and H_2-receptor antagonists in acute inflammation

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Inflammation is the response of living tissue to injury (Miles & Miles, 1952) and is characterized by a series of local vascular changes and infiltration of leucocytes. The distinction between injury, which comprises the passive changes induced by a noxious agent (examples of which include chemical, physical and microbial challenge) and the subsequent response of the tissue, which is inflammation, is important.

When tissues are exposed to an irritant or are directly injured they respond by attempting to remove the irritation and tissue debris. This response is termed acute inflammation and is a self-limiting process, the tissue soon returning to normal. However, when the body is unable to eliminate the pro-inflammatory stimulus a prolonged inflammatory response known as chronic inflammation develops. Acute and chronic inflammatory responses are defined according to their time course and the nature of the cellular infiltrate, polymorphonuclear leucocytes predominating in acute inflammation and mononuclear leucocytes being the predominant leucocytes involved in chronic inflammation. The virtues and limitations of this long-established but somewhat arbitrary division of inflammatory responses are discussed by Ryan & Majno (1977), who conclude that the division is derived from a sound biological basis and, with some qualification, should be retained.

The purpose of the present review is to consider the role of histamine in acute inflammatory responses and the involvement of histamine receptors in this phenomenon. Readers interested in histamine and chronic inflammation are referred to reviews by Askenase (1977), Bunce *et al.* (1979) and Plaut & Lichtenstein (1979). Other recent reviews on acute inflammation include that of Ryan & Majno (1977), and a series of chapters in the book 'Anti-inflammatory drugs' edited by Vane & Ferreira (1979).