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THE MYCOTOXINS AND HUMAN HEALTH HAZARDS

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Abstract - The general background of the role of mycotoxins in human disease is briefly reviewed. The clinical assessment of individual cases of mycotoxicosis and of epidemics is considered. The acute effects of the ingestion of the aflatoxins and the part that long term exposure may play in human disease, notably cancer, are examined. The necessity for co-operation between chemists, veterinarians, mycologists and physicians in the elucidation of the role of the mycotoxins in human disease is stressed.

The subject has been reviewed recently from a number of aspects (Refs. 1, 2, 3, 4, 5 & 6), and previous IUPAC symposia in Johannesburg in 1969 (Ref. 7) and in Goteborg in 1972 (Ref. 8) covered many problems arising from the exposure of man to the mycotoxins.

The fascinating history of the role which mycotoxins have played in human disease from ergot poisoning in ancient times to the dire warnings of the potential dangers of the aflatoxins in the last decade has impressed the chemist, the agriculturist, the veterinarian, and the experimentalist; but it is now proposed to examine the impact on physicians, both those interested in clinical medicine and in public health administration.

Mycotoxins are fungal metabolites, but in defining their role in medical science a distinction must be made between those metabolites which occur naturally in our environment and those elaborated under laboratory conditions, often in commercial quantities, with which the physician is in close daily contact, namely, the antibiotics. The latter, as we all recognize, have been responsible for a remarkable advance in medicine and perhaps the curative nature of these must be weighed against the toxic and often fatal properties of the others. The benefits of antibiotics are not, however, unattended by risk. The occasionally fatal allergy to penicillin and the aplastic anaemia with a possible risk of leukaemia associated with chloramphenicol are familiar examples. The iatrogenic risks from such fungal metabolites are likely to be recognized readily by the physician and are weighed by him against the benefits of their use, but the naturally-occurring mycotoxins present a wide spectrum of problems, socio-economic, agricultural and veterinary, which are relatively unfamiliar to the physician.

Fungi are ubiquitous, and it perhaps surprises one that the risks from their toxins are not more frequent and widespread, until the very precise requirements for the growth of the fungi and the elaboration of their toxins are appreciated. The acute mycotoxicoses occur sporadically and as far as we know infrequently, and this alone may make diagnosis for the physician difficult and one of exclusion of other viral, bacterial and other causes.

The acute mycotoxicoses form at the moment an ill-defined area of clinical medicine. They are often considered as a collection of strange syndromes such as 'Drunken bread', 'Sassoon Hospital' and Udorn encephalopathy. Exotic labels of this kind are frequently a confession of the lack of precise knowledge. The chronic effects of these toxins in man are even less clearly understood, based as they are on animal data, and the difficulty of interpreting these in human terms.

The major advances in our knowledge of the mycotoxins and human health have arisen from three areas of study: (i) the epidemics associated with cereals, dating from the ancient reports of ergotism to stachybotryotoxicosis in 1931, alimentary toxic aleukia in 1947, and the toxicoses associated with species of *fusaria* in 1956; (ii) the studies in Japan on the contamination of rice, associated with cardiac beriberi and other toxic yellow rice diseases; (iii) the more recent studies on the aflatoxins. Although these were a further example of initial interest being generated by an epidemic, albeit in animals, they are associated with a wide range of substrates. Their remarkable carcinogenic properties made them a focus of increasing concern.

There is evidence that 5 000 years ago Chinese physicians used ergot, and further, that the ancient Greeks, Romans and Arabs were all familiar with its pharmacological properties. The first epidemic of ergotism was reported in 430 BC in Sparta. Epidemics swept through Europe in the Middle Ages, frequently in France, where in 1673 the association with bread poisoning was described by Dodart. In fact, the name of the disease is derived from the French - ergot, a cockspur - which relates to the shape of kernels of contaminated grain. Two centuries later their fungal origin was described by Tulasne, and in 1918 one of the active principles, ergotamine, was isolated. It must be remembered that the dramatic occurrence of epidemics in the Middle Ages of ergotism, with chilling descriptions of gangrene and convulsions, are not merely historic curiosities. The widely reported epidemic in Pont-Saint-Esprit in 1951 (Ref. 9), portrayed in the novel by Fuller (10), contains all the elements of medieval horror. Although the cause has been attributed by some to spraying of an organic phosphorus preparation, litigation relating it to ergot was still under consideration as recently as May 1973 (Ref. 11). Many of the distressing psychiatric and neurological phenomena of that epidemic appeared to be similar to those following the ingestion of fungal metabolites with the properties of lysergic acid diethylamide (LSD). The ability of other fungi, such as the fusaria, to convert lysergic acid containing alkaloids such as ergotamine into LSD (Ref. 12) may explain the variation in symptomatology of different outbreaks of ergotism. Such hazards to human health are nevertheless now rare, but it has been suggested (Ref. 13) that contamination of certain types of pasture is still of economic significance to livestock producers in some areas. With modern marketing and milling methods outbreaks of ergotism became less likely, but the need for continuous surveillance appears to be necessary for in spite of the lengthy history of the problem it has not been solved, only controlled.

The reports of individual health hazards from ergot poisoning are not numerous, which is perhaps surprising in view of its wide use in obstetrics, although this is now decreasing, and for the treatment of migraine. Whereas the acute pain of the latter may provoke massive overdosage, poisoning is more frequently the consequence of extensive use of small doses over many years (Ref. 14). In Africa, idiopathic limb gangrene, with symptoms of ergotism, is seen and has been associated with the ingestion of herbal draughts to facilitate labour (Refs. 15 & 16).

There must be few who are unaware of the dangers of mushroom poisoning. They are perhaps evoked by patients too frequently, and the physician may tend to ignore this suggested aetiology for an acute illness. As the only treatment of poisoning by Amanita phalloides, which carries a 50% mortality, and even of the less severe toxicity associated with the Amanita muscaria, is symptomatic, this may be the correct approach. The symptoms of nausea, vomiting, severe abdominal pain, convulsions and watery diarrhoea are found in diseases with specific treatment and to detect and treat these must be the physician's first duty. Immune anti-phalloidan serum is available commercially, but its efficacy is doubted. Prevention here consists of education, particularly in schools, on the identification of the poisonous varieties.

The mycotoxicosis caused by agents from strains of Stachybotrys atra illustrates the close association between the hazards to both animals and man from these toxins. The first report in 1931 of a fatal haemorrhagic disease of horses indicated that farm workers handling animal fodder also suffered some symptoms of the disease (Ref. 17). Even in areas remote from the focus of animal disease, human cases with skin rashes and haemorrhagic lesions of the mouth and lung were seen among those who used straw for bedding. There have been further outbreaks of animal disease related to this mycotoxin in cattle and hens, and even in zoo animals, but no further reports of a human hazard have appeared (Ref. 18).

The most dramatic epidemics of alimentary toxic aleukia (ATA) occurred in the Soviet Union between 1941 and 1947. The enormous war casualties suffered in some areas were responsible for the autumn harvest being neglected and the grain being left under the winter snow. Near famine conditions dictated that it be used and over 10% of the population of those districts were affected by ATA. The disease was not a new entity, having been reported from Russia since the Nineteenth Century (Refs. 19 & 20). It is a severe disease with a high mortality. The early symptoms relate to the local action of the toxin on the upper intestinal tract and are followed by severe gastroenteritis. A latent period of up to two months of relatively normal activity is overtaken by progressive bone marrow damage. Gross leukopenia, developing into a pancytopenia with dramatic haemorrhagic symptoms, is the final fatal stage of the disease. It should be noted that some early outbreaks were thought to be epidemics of diphtheria or cholera. The exhaustive review by Joffe (19) is fascinating reading, as one is led through all the familiar efforts to incriminate infectious disease and vitamin deficiency until a thorough epidemiological investigation, followed by a major multidisciplinary study, pinpointed the vehicle of the toxin, if not its precise nature. There is indirect evidence (Ref. 21) that ATA is primarily a trichothecene intoxication rather than the steroidal toxin originally suggested by Olifson (22). However, the connexion with the overwintered grain was clear, the lesson for the physician definite, and reports of primary prevention by education and intervention are encouraging.

The history of grain contamination by the fusaria fungi also appears to stem historically from Russia and Siberia, but as recently as 1963 the wheat harvest of western Japan was severely attacked. The human mycotoxicosis, as reported from the suburbs of Tokyo in 1955 and from Hokkaido in 1956, was a typical gastroenteritis. No fatalities were reported. The suggestion that the mycotoxins incriminated are the trichothecenes (Ref. 21) brings it into line with ATA and stachybotryotoxicosis, and there is little from the studies recorded to suggest that there is any marked clinical difference which could not be explained by variations in the amount of mycotoxin ingested. It is considered that although division of these diseases into individual syndromes may be justified by the different fungi involved, it would be more helpful from a clinical standpoint to view them as a single entity.

The confusion of the vitamin B_1 deficient beriberi with the acute cardiac beriberi associated with the penicillium fungi seems now a matter of history. The clinical features of the disease, the epidemiological evidence and laboratory experiments with citreoviridin appeared to separate these cases from those of pure vitamin deficiency. Although these studies contributed much to the knowledge of the possible human exposure to mycotoxins, it was improved techniques of harvesting and storage of rice which prevented further outbreaks (Ref. 23).

The human hazard from the mycotoxin luteoskyrin derived from penicillium Islandicum is perhaps more potential than real. In the recent IARC monograph (Ref. 24) on the evaluation of carcinogenic risk of chemicals to man, a distinguished international group of scientists had to conclude that there was insufficient evidence for an evaluation. This is in marked contrast to the third group, the aflatoxins, where the carcinogenic risk was defined as follows: 'The studies of liver cancer incidence in relation to aflatoxin intake provides circumstantial evidence of a causal relationship.' (Ref. 24).

There have been reports, both individual and epidemic, of the acute effects of aflatoxin in man. The investigation of an epidemic in children in Thailand marshalled impressive evidence incriminating aflatoxin as the toxicological agent (Refs. 25 & 26). Aflatoxin was found not only in the food available to the victims, but in their tissues at autopsy. The lesions at autopsy were similar to those found in monkeys poisoned by the aflatoxins. The clinical history and symptomatology were equated with Reye's syndrome, an idiopathic acute disease in children, which had been reported from a number of countries and associated, with no unequivocal evidence, with a fungal aetiology (Ref. 27). The Thailand reports may serve as a model for the study of an acute mycotoxicosis, but perhaps this standard of investigation is only possible if there is an extensive background of research, both laboratory and epidemiological, on the individual mycotoxin, and a high level of local technology. The recent report of acute aflatoxicosis and association with a localized famine in India, involving nearly 400 persons of whom over 100 died, is still under investigation (Ref. 28). The potential hazards from a chronic exposure to aflatoxin can be summarized briefly. The aflatoxins have been shown to be the most potent hepatocarcinogens known to the experimentalist, unequivocal liver tumours being produced in many animals, including monkeys. The mycotoxin is available in human foodstuffs in those areas where liver cancer is commonly reported and populations in these areas are known to ingest the mycotoxin. Wherever the relationship has been tested by population-based studies the amount of aflatoxin demonstrated in the diet parallels the level of hepatocellular cancer. There are few, if any, naturally occurring carcinogens with such impressive evidence against them.

Although the main route of absorption of the toxins is by ingestion, inhalation of fungi, with a subsequent pulmonary mycotoxicosis, presents a hazard which has been reviewed recently by Emanuel et al. (29). The effects of skin absorption have been noted in the dermatitis associated with the light sensitive agent of pink rot fungus, Sclerotina sclerotiorum (Ref. 30) and, as we have mentioned, with Stachybotryotoxicosis.

The human hazards of acute mycotoxicosis are traditionally linked with epidemics. There appears, on reviewing the literature of these epidemics, to be a communication gap in the clinical appreciation of some of the mycotoxicoses. As the sources of the reports are worldwide, and from countries with a variety of medical facilities, it is not clear whether this gap is due to language, culture, or even politics, but to the physician, epidemics of acute mycotoxicosis do have common clinical features and common treatment problems. It is essential, therefore, that reports of epidemics attempt to establish these similarities rather than to create, as attractive and compelling as the individual local conditions may be to do so, a new syndrome. The non-specific symptomatology is what we would expect from an ingested toxin - a gastroenteritis varying with dose followed by, for example, the specific action on the bone marrow by the mycotoxic agent of ATA.

The only references in medical textbooks to the mycotoxicoses are confined to ergotism and mushroom poisoning and standard textbooks on the mycotoxins are rich in chemical and mycological evidence but offer only brief clinical evaluation. There is little encouragement in this literature for the physician to pursue the subject and I would echo the plea made at your Symposium in 1972 on the Control of Mycotoxins by Goldblatt (13) for a greater awareness of the problem: 'The problem now may be not so much a lack of technical information as ineffective dissemination of existing knowledge.' The clinician, particularly when dealing

with rural communities, must not be content with a diagnosis of a 'non-specific' gastro-enteritis, when the usual laboratory tests for bacterial agents are negative. He must be made aware of the other more sinister symptoms which can be associated with acute myco-toxicosis. The pathologist must be alerted to the autopsy findings of a mycotoxicosis to enable him to set in train the epidemiological studies which may frustrate an epidemic or reveal an individual case of mycotoxicosis.

The standardization of chemical and mycological examinations of specimens involved in the mycotoxicoses is important. International organizations such as the IUPAC play an important role. It is the transfer of this effort to the national level which is, however, vital. The Health Protection Branch of the Canadian Health and Welfare Service, in an attempt to define the relationship of Reye's syndrome to the aflatoxins, has offered a centralized service of analysis to physicians and epidemiologists for specimens of human and vegetable material suspected of aflatoxin contamination. This is to be commended, as the problems of accurate, reproducible methods of analysis for aflatoxin and the associated confirmatory tests are well known, and valuable opportunities are lost in epidemiological studies if the toxicological examinations are incomplete. The field and laboratory methodology of the investigation of such epidemics must be elaborated. The methods for the preservation of material, suspect food or biological specimens, should be studied so that subsequent laboratory analysis can be made for toxins, either those not immediately apparent to the investigator or for confirmation of preliminary analysis.

Sufficient knowledge has now accumulated to enable us to predict the conditions under which major epidemics are likely. These are not primarily medical problems, but agricultural and social. To maintain that the agriculturalist or veterinarian should be alerted to the dangers of a disastrous failure of crops may be fruitless in the aftermath of war, but famine is with us in peace, and emphasis of the possibilities may be timely. Such a warning could also be given with advantage to developing countries or rural communities where conditions for the raising and storage of uncontaminated cereals are marginal.

Is there a health hazard to individuals who may consume occasional high doses under circum-stances in which an epidemic does not develop? Is it possible that epidemics are the tip of the iceberg of large numbers of undetected single cases in the rural environment, particularly in developing countries? The early symptoms of acute mycotoxicosis, as we have noted, are similar to the severe gastroenteritis seen so commonly in tropical countries, particularly in children, and it may be recalled that some of the early epidemics of mycotoxicosis were mis-taken for cholera and diphtheria. As a physician who has spent most of his professional life in close touch with the medical facilities available to rural communities in Africa, I consider that individual cases of acute mycotoxicosis are a distinct possibility in these circumstances. There have been few case reports, but I recall reviewing with Serck-Hanssen (31) material from an autopsy of an African girl who was subsequently found to have consumed cassava heavily contaminated with aflatoxin. There was at that time much interest in Uganda in the aflatoxins, particularly their relation to the high liver cancer incidence in some remote districts. Knowledge of the morphology of the liver pathology found in animal experiments with aflatoxin alerted Serck-Hanssen to the possibility of a mycotoxicosis and this enabled him to initiate the search for the mycotoxin in the girl's home. As few deaths in rural Africa are investigated by autopsy, and fewer still can be followed up by epidemiological studies, we have little idea of the extent of the problem.

The hazards from chronic exposures to mycotoxins are potential rather than documented. The evidence for the involvement of the aflatoxins in the aetiology of liver cancer has been con-sidered strong enough to justify intervention in the food contamination cycle, as the final epidemiological proof of causality. However, it is unlikely that mycotoxins are the sole cause of this cancer, and other factors, such as the part played by hepatitis, must be assessed. As the waste of cereals by fungal contamination and vermin infestation is a major worldwide economic problem, there is ample justification for storage improvement schemes in most rural areas and these alone may go a long way in dealing with these hazards as well as safeguarding precious food supplies.

It is therefore difficult to assess adequately the health hazards to man from mycotoxins. Even with ergotism, which has been known for centuries and which has been dealt with here in greater detail than the other mycotoxic epidemics, we still have no definitive solution, although the incidence of the disease has decreased and can be said to be under control. More knowledge of the natural history of these diseases and their interrelation will enable us to detect individual cases as well as epidemics, and the rapid recruitment of a team of chemists, veterinarians, agriculturalists as well as physicians to investigate these epidemics, large scale natural experiments, will assist us all in answering the many ques-tions affecting our health which are posed by this fascinating branch of science.

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