SUID-AFRIKAANSE MEDIESE TYDSKRIF

SOUTH AFRICAN MEDICAL JOURNAL

Kaapstad, 11 Desember 1974 Deel 48 : No. 60 : Volume 48 Cape Town, 11 December 1974

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Aflatoxin and Primary Liver Cancer

The remarkable propensity of growing fungi to synthesise biologically active organic compounds has been extensively exploited in the pharmaceutical industry. Numerous incidental metabolites, which do not necessarily exhibit antimicrobial activity, are also produced, and many of these are extremely toxic to mammalian tissue. Some of these toxic compounds have also been demonstrated to be carcinogenic in experimental systems. Of major importance in this regard is a group of carcinogenic toxins produced by the ubiquitous *Aspergillus flavus*, and known as aflatoxins, of which aflatoxin B_1 is an exceptionally potent specific liver carcinogen.

The discovery of aflatoxin B_1 more than a decade ago was the culmination of considerable speculation on the cause of the extraordinary occurrence of liver cancer in Africa. At the time the late A. G. Oettlé[1] stated: 'In the field of the mycotoxicoses there is sufficient evidence to justify a substantial investment in research to obtain the information necessary for an informed decision. If this hypothesis be confirmed, it will involve considerable expenditure but also a tremendous reward—the prevention of one of the commonest cancers in Africa'.

As might have been anticipated, a flurry of studies, using a variety of different approaches, commenced in various parts of Africa. Some showed a statistical correlation between the cultivation of groundnuts, apparently a selective medium for aflatoxin production, and the occurrence of primary liver cancer,[2] while others showed that the disease was more common in geographical areas conducive to fungal growth on foodstuffs.[3] Several random surveys[4,5] showed that aflatoxin was commonly present in stored grains in localities where the disease was frequently encountered.

The enormous implications of these loose associations clearly necessitated a more precise scientific approach, such as the demonstration of a dose-response relationship. Thus three independent teams, working in Thailand, Kenya and Mozambique, commenced measuring the actual intake of aflatoxin by various populations and concurrently assessed the liver cancer rate of the observed population. A paper in this issue by Van Rensburg *et al.* reports the initial results of the joint South African-Mozambican team obtained in the highest known liver cancer area in the world. Their data suggest that approximately 1 male in every 40 households will die of primary liver cancer. They have also established an enormous average aflatoxin intake — 15 μg per day by adults—in the area studied. By means of pooling these data with similar studies elsewhere, a statistical association between the level of aflatoxin intake and the liver cancer rate has been demonstrated.

If populations are indeed exposed to such heavily contaminated foodstuffs, it seems reasonable to anticipate considerable medical consequences, particularly damage to the liver, from the toxic action of these compounds.

Isolated instances of 'toxic hepatitis' have been reported in patients where circumstantial evidence indicated that fungal metabolites were the cause.[6,7] A study of liver pathology in Mozambique[8] provides additional supporting data to relate factors of pathogenesis for primary liver cancer in the Blacks to an environmental exogenous toxic substance. A total of 158 cases was diagnosed as toxic liver damage and characteristically exhibited a clear non-staining cytoplasm, cytoplasmic hyalinisation, ballooning degeneration, nuclei of variable sizes and single-cell necrosis. The absence of cellular infiltration served as the main difference between viral hepatitis, but in addition the toxic damage exhibited less cholestasis, the sinusoids were clearly demarcated and wider and hyperplastic areas were sometimes present. Posthepatic cirrhosis was observed to follow some cases of toxic liver damage and, in 3 cases, primary liver cancer. In a collateral experimental study involving the administration of mycotoxin to rats, a remarkably similar sequence of pathological events was observed. The possibility thus exists that, in that country, mycotoxins may be an important cause of liver disease.

Somewhat convincing are the studies on the association between aflatoxin and encephalopathy and fatty degeneration of the viscera (EFDV) or Reye's syndrome, a disease commonly seen in children in Thailand. A total of 179 cases[9,10] which were confirmed at autopsy or by biopsy were characterised by the abrupt onset of coma or convulsions, fever, respiratory distress, vomiting and death within 72 hours. Abnormal laboratory findings included: elevated serum transaminases and free fatty acids, prolonged prothrombin times, decreased carbon dioxide con-

tent, cholesterol and triglyceride values. Autopsies revealed cerebral oedema and neuronal degeneration, fatty degeneration of the liver, kidneys and heart and generalised lymphocytolysis. Again circumstantial evidence suggested that aflatoxin B_1 might be the aetiological agent in the disease and it was postulated that the syndrome results from acute toxic hepatitis occurring in patients with subclinical hepatic disease. Experimental studies in monkeys revealed a striking similarity between the clinical signs and pathological findings following the administration of aflatoxin B_1.[11]

In a later study, autopsy material from 23 fatal cases was obtained for aflatoxin analyses.[12] Aflatoxin was detected chemically in the tissue of 22 of the 23 children, with levels reaching 93 μg/kg in liver, 123 μg/kg in stool and 127 μg/kg in the stomach. Only trace amounts of aflatoxin were detected in control children who died of diseases unrelated to EFDV, a fact which reflects a common low level ingestion of aflatoxin previously suggested by the presence of aflatoxin in some market foods. Furthermore, the seasonal variation and geographical distribution in the occurrence of the disease paralleled the seasonal variations of aflatoxin levels found in food. Aflatoxin is also known to have been detected in Russia in 3 patients with Reye's syndrome. All 3 exhibited the typical pathology of the disease, but in addition 2 children exhibited bile duct proliferation and hyperplastic nodules in the liver. The latter lesions particularly are readily induced in a variety of experimental animals by aflatoxin.

'Seek and you shall find' seems to have been the experience of the small band of mycotoxin enthusiasts. Caution must be exercised to ensure that their positive results do not lead to an excessively biased approach to relevant problems. Experience in the sphere of geographical pathology shows that a complex interaction of noxious agents may operate to produce a net result such as primary liver cancer. Cells undergoing repeated regenerative cycles are well known to have an increased susceptibility to chemical carcinogens, and in the case of aflatoxin, experimental postnecrotic cirrhosis has a remarkable synergistic effect on the pathogenesis of induced tumours.[13] A systematic study of the occurrence and nature of liver insults in the harsh tropical environment of Mozambique may provide illuminating information. Also of importance in the area with the highest liver cancer rate in the world, are the critical factors in the Black environment and culture which determine the enormous intake of mycotoxin. The next communication of the joint Portuguese-South African team in this *Journal* will describe some of these, and it is hoped that their observations will ultimately assist in reducing the incidence of liver cancer.

What is the real risk of exposure to aflatoxin of the westernised South African population? Existing legislation stipulates that all food sold for consumption must be free of aflatoxin. Theoretically, this means that all producers should regularly analyse their products by means of a rather elegant chemical technique using thin-layer chromatography. In practice, it is reasonable to assume that only those products containing constituents which are known to be liable to contamination will be examined. The groundnut clearly leads the field as far as a selective medium for the fungus is concerned. Groundnuts sold intact by large producers are invariably free of aflatoxin, but problems have been experienced with processed products such as peanut butter, resulting in stringent controls by the Department of Health which now render the product relatively safe.

Technological difficulties make the legislative stipulation of 'no aflatoxin' somewhat unrealistic. Enforcement of the law is under some circumstances handicapped by this unreasonable requirement. To obviate this difficulty, the Department of Health has given notice permitting a maximum level of 20 μg/kg aflatoxin, of which only 5 μg/kg may be aflatoxin B_1 (*Government Gazette,* 30 May 1974). If the dose-effect line published in this issue is valid, the intake of such a level may be expected to increase the liver cancer rate in the westernised population by 10-fold. Naturally such a situation will not arise, owing to a varied diet and dilution factors. However, such levels in staple foods such as maize will be intolerable, and a watchful eye will have to be kept on new tendencies in intensive agricultural techniques involving earlier harvesting and higher moisture contents of grains—factors which could escalate the mycotoxin problem.

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