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Of sick turkeys, kwashiorkor, malaria, perinatal mortality, heroin addicts and food poisoning: research on the influence of aflatoxins on child health in the tropics

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Similarities between the geographical and climatic prevalences of kwashiorkor and of exposure to dietary aflatoxins, and between the biochemical, metabolic and immunological derangements in kwashiorkor and those in animals exposed to aflatoxins, prompted investigation of the associations between kwashiorkor and aflatoxins. Studies in Africa in the 1980s indicated a role for these toxins in the pathogenesis of the disease. Paediatric cases of kwashiorkor are less prone to severe *Plasmodium falciparum* malaria than normal children. In mice infected with *P. berghei*, aflatoxin exposure inhibits parasite growth and ameliorates morbidity. Aflatoxins occur in $\leq 40\%$ of samples of breast milk from tropical Africa, usually as low concentrations of the relatively non-toxic derivatives of aflatoxin B_1 (AFB_1) but sometimes as high concentrations of the very toxic AFB_1. This could explain kwashiorkor in breast-fed babies. Aflatoxin exposure occurs in $\geq 30\%$ of pregnancies in tropical Africa and the toxins are often in cord blood, sometimes at extremely high concentrations. Aflatoxins are now incriminated in neonatal jaundice and there is circumstantial evidence that they cause perinatal death and reduced birthweight. Aflatoxin-induced immunosuppresion may explain the aggressive behaviour of HIV infection in Africa. There are similarities between observations on HIV cases in Africa and those on heroin addicts in Europe, where 'street' heroin is frequently contaminated with aflatoxin. Aflatoxins were found in 20% of random urine samples from heroin addicts in the U.K. and the Netherlands. Aflatoxins have also been incriminated in episodes of food poisoning which have been associated with serious morbidity and mortality, particularly among young children.

The initial stimulus to the work summarized in this paper was a luxuriant growth of mould on my best suit in the rainy season in western Nigeria in the early 1960s. The cause was a failed electric heater in my cupboard, installed to prevent mould growth in the excessive humidity. The thought occurred that, if cloth could sustain such heavy mould growth, local foods would provide a much better substrate. The idea was born of possible associations between mould contamination of food and kwashiorkor, a 'nutritional' disease of obscure pathogenesis prevalent during the rainy season in developing countries in the tropics. This idea was given impetus by events in the United Kingdom and elsewhere between 1960 and 1962, which led to the discovery of a group of mould toxins—aflatoxins—which have potent biological effects.

It is necessary to introduce readers to (or to remind them of) some of the salient facts about aflatoxins and kwashiorkor separately, before describing the associations which have been established between them and the improbable bedfellows in the title of this paper.

AFLATOXINS

In the spring and summer of 1960 a mysterious disease killed over 100 000 turkeys in the

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south and east of England. It was termed turkey 'X' disease but also affected ducklings and pheasants. At about the same time there were reports from East Africa of a disease with heavy mortality in ducklings, and inspection of a shipment of commercially raised trout in the U.S.A. revealed that most had hepatomas. Animal deaths on this scale proved a great stimulus to research, and veterinarians, pathologists, microbiologists and mycologists, as well as organic, analytical and physical chemists, in industry and academia pooled their resources in a multi-disciplinary approach to research which achieved one of the most important and rapid advances in environmental toxicology.

It was soon realised that turkey 'X' disease was food-related, because a change of diet reduced morbidity and mortality and the disease was not transmissible. The common factor in the feed of all affected animals was Brazilian groundnut meal contaminated by the mould *Aspergillus flavus* and containing a toxic substance which, in 1962, was named 'aflatoxin' because it was derived from this mould (A-flavus-toxin) (Blount, 1983). Within a year, four major toxins had been identified, characterized and designated AFB_1 and AFB_2 (after their blue fluorescence in ultraviolet light) and AFG_1 and AFG_2 (after their green fluorescence). Cows fed AFB_1 and AFB_2 excreted aflatoxins in their milk with similar to but weaker biological effects than their parent compounds; the excreted toxins, so-called milk (M) aflatoxins, were designated AFM_1 and AFM_2, respectively. Since these early discoveries, knowledge of aflatoxins has grown enormously and some 20 different aflatoxins have now been discovered and characterized.

Fungi of the *A. flavus* group occur worldwide but their toxin-producing potential is dependent upon the relative humidity and temperature surrounding the natural substrate. Fungal growth and toxin production is maximal at a mean temperature of 27°C and a relative humidity of between 80% and 90% (Goldblatt, 1969). Where environmental conditions favour toxin production, commodities are often heavily contaminated with aflatoxins.

Aflatoxins (AFB_1 in particular) are toxic to plants, micro-organisms, cells in culture, farm, domestic and laboratory animals, and humans. Species sensitivity varies but no totally refractory species has been identified. The biological effects of aflatoxins include carcinogenicity, teratogenicity and mutagenicity.

The metabolic effects of aflatoxins include: inhibition of DNA, RNA and protein synthesis; reduction in miscellaneous enzyme activities; depression of glucose metabolism; inhibition of lipid synthesis, including that of phospholipids, free fatty acids, triglycerides and cholesterol and its esters; and depression of clotting-factor synthesis (Bushby and Wogan, 1981). Aflatoxins tend to block steroid binding sites in the tissues. They are also potently immunosuppressive, as shown by (1) reduced host resistance to a wide range of bacteria, viruses and fungi; (2) depressed complement activity; and (3) impaired cell-mediated immunity (Richard *et al.*, 1978). The liver is the main target for toxicity and pathological changes include fatty infiltration, biliary proliferation and toxic necrosis in acute severe poisoning.

KWASHIORKOR

In the early 1930s, Cicely Williams described a 'new' disease which she had encountered in children in the Gold Coast (now Ghana). Her previous paediatric experience in Britain had not prepared her for these miserable, oedematous children, usually with discoloured, desquamating scalded-looking skin who often distressed their medical attendants by dying suddenly and unexpectedly in spite of competent, caring attention. The condition was known locally as 'kwashiorkor', the vernacular name for the disease among the Ga people. Dr Williams attached this name to the disease and expressed the opinion that it was associated with a maize (corn) diet (Williams, 1933).

Reports of the disease (under a vast array of different names) subsequently flooded in from other countries in Africa, Asia and South and Central America, and stimulated decades of research, by an army of research workers, to determine its aetiology and pathogenesis. The

most popular and persistent theory to arise was that kwashiorkor is caused by dietary protein deficiency with relative calorie excess. By 1980, however, nutritionists agreed that the theory of protein malnutrition did not accord with the facts and was untenable, and conceded that the cause of kwashiorkor remained obscure (Coward and Lunn, 1981). Amongst the puzzling epidemiological features of kwashiorkor the following are noteworthy: (1) the disease really is 'tropical', being limited to warm, humid countries; (2) it is seasonal, occurring mainly during the rainy season, and never features in nutritional disasters associated with drought; (3) over-feeding on starchy foods and kwashiorkor go hand-in-hand in many areas; and (4), perhaps most peculiar of all, the disease sometimes occurs in babies who are entirely breast-fed, a circumstance not explainable by any nutritional theory (Trowell *et al.*, 1954).

There are no characteristic biological, biochemical or pathological changes in marasmus, the commonest form of childhood malnutrition in the tropics, which occurs when food intake is inadequate to meet basic needs. This is in marked contrast to kwashiorkor, in which there are many characteristic derangements of function and structure including hypoproteinaemia, depressed enzyme and lipid synthesis, derangement of water, electrolyte and glucose metabolism, increases in plasma levels of some hormones, and depression of immune functions (particularly of cell-mediated immunity, which is characteristic of the disease). Fatty infiltration of the liver is constant and characteristic and can reach grotesque proportions (Alleyne *et al.*, 1977).

SIMILARITIES BETWEEN KWASHIORKOR AND AFLATOXINS

There are remarkable similarities in the geographical and climatic factors that influence the prevalence of kwashiorkor and aflatoxin exposure, and remarkable similarities also in the biochemical and metabolic derangements observed in kwashiorkor and those in controlled studies of animals exposed to aflatoxins. These similarities, and findings in animals that young age and malnutrition increase susceptibility to aflatoxins, as do certain specific vitamin (e.g. vitamin A) and trace-metal (e.g. zinc) deficiencies, and that protein supplementation of the diets of aflatoxin-exposed animals ameliorates the toxicity, gave impetus to clinical and epidemiological studies to explore possible associations between kwashiorkor and aflatoxins.

Studies on Kwashiorkor and Aflatoxins

Starting in 1980, controlled investigations were undertaken on children with kwashiorkor, marasmus, marasmic kwashiorkor and on normally nourished children (Wellcome Trust Working Party, 1970) to detect evidence of aflatoxin exposure. Initial, major, clinical epidemiological studies were undertaken in Sudan (Hendrickse *et al.*, 1982) and were followed by similar studies in other African countries. These studies were complemented by analysis of autopsy liver samples, from children dying of kwashiorkor, for their aflatoxin content (Lamplugh and Hendrickse, 1982), and aflatoxin analysis of human breast milk in African countries (Coulter *et al.*, 1984; Lamplugh *et al.*, 1988; Maxwell *et al.*, 1989). These investigations established that: (1) aflatoxins could be detected significantly more frequently and at higher mean concentrations in the sera of children with kwashiorkor than in those of marasmic or healthy children; (2) aflatoxicol, a reduction metabolite of aflatoxin B_1 (AFB_1), is frequently present in the sera of children with kwashiorkor, but never in healthy or marasmic children; (3) AFB_1 and/or aflatoxicol was present in kwashiorkor autopsy liver samples (i.e. in all 57 examined) but could not be detected in the livers of any children who died of other causes; (4) the metabolism of aflatoxins in children with kwashiorkor, particularly as it relates to the transformation of AFB_1 to its less toxic derivatives such as AFM_1, and urinary excretion of aflatoxins were impaired compared with those in other nutritional groups (Hendrickse, 1985); and (5) aflatoxins were found in $\geq 30\%$ of samples of breast milk from Sudan, Ghana, Nigeria and Kenya; although these usually

occurred as small amounts of the relatively non-toxic AFM_1, large amounts of the very toxic parent compound, AFB_1, were sometimes found.

These findings, although not 'scientific proof' of a causal role for aflatoxins in kwashiorkor, provide rational explanations for all the mysterious features of kwashiorkor which have defied explanation for more than 50 years. The occurrence of kwashiorkor in breast-fed babies is demystified by the detection of toxic amounts of AFB_1 in human breast milk, as is the paradox of kwashiorkor and overfeeding going hand-in-hand (the more aflatoxin-contaminated food eaten, the greater the toxicity). The seasonal and geographical incidence of kwashiorkor are as would be expected if aflatoxins were implicated. The biochemical and immunological derangements in kwashiorkor bear an uncanny resemblance to findings in laboratory, farm and domestic animals exposed to aflatoxins. The ability of aflatoxins to block steroid-binding sites in tissues provides the only plausible explanation for elevated hormone levels in children in whom all other metabolic functions are severely depressed.

Aflatoxin-excretion studies in children with kwashiorkor and marasmic kwashiorkor, fed on aflatoxin-free food from the time of their admission to hospital, revealed that they excreted aflatoxins, mainly in their stools, for up to 9 and 6 days, respectively. The total quantity of aflatoxins excreted by these children indicated that they were harbouring up to 4 μg aflatoxins/kg body weight when admitted to hospital (De Vries *et al.*, 1990).

KWASHIORKOR AND MALARIA

Notwithstanding the immunosuppression that invariably occurs in kwashiorkor, children with the disease are much less susceptible to severe *Plasmodium falciparum* malaria than are normal children (Hendrickse *et al.*, 1971). Cerebral malaria has seldom, if ever, been reported in kwashiorkor (Eddington and Gilles, 1976).

A possible explanation for this anomalous situation is that aflatoxins might retard the growth and development of the malarial parasite in these children. Experiments were done to compare the responses to a standard infecting dose of *Plasmodium bergei* in mice on a standard laboratory diet with or without aflatoxin contamination. These studies showed persistently lower parasite densities in the peripheral blood of AFB_1-fed mice than in that of mice not exposed to the aflatoxin, all of which succumbed to *P. bergei* infection before any of the aflatoxin-fed mice died (Hendrickse *et al.*, 1986).

These observations may endorse the wisdom of a Nigerian mother who, many years ago, refused my advice to wean her infant on Guinea corn (nutritious and seldom aflatoxin-affected) and preferred maize or cassava (less nutritious and often aflatoxin-contaminated). When asked the reason for her choice, she replied that Guinea corn was more likely to cause fever and possibly death than were the other foods!

PRENATAL EXPOSURE TO AFLATOXIN

The detection of aflatoxin in breast milk prompted the study of aflatoxin exposure in pregnancy in Africa, with special reference to the effects on the foetus and newborn. Controlled experiments in pigs have established that prenatal and continuing postnatal aflatoxin exposure (in breast milk) causes thymolymphatic atrophy and depression of immunity, damages liver structure and function, reduces viability and impairs nutrition and growth (Pier *et al.*, 1985).

The most serious and prevalent problems affecting newborns in the tropics include foetal malnutrition and low birthweight, infections, jaundice of obscure causes and generally poor viability. Given these facts, the need to determine the effects of aflatoxin exposure in pregnancy on newborn health and survival becomes self-apparent.

Studies in Kenya, Nigeria, Ghana and Zambia have revealed frequent, significant, foetal exposure to aflatoxins during pregnancy.

Levels of aflatoxins detected in some cord bloods at birth are amongst the highest levels ever recorded in human tissue and fluid (Lamplugh *et al.*, 1988; Maxwell *et al.*, 1989).

Resources were inadequate to provide expert monitoring of newborns and to ensure adequate follow-up of cases in Africa. In consequence, data on the effects of aflatoxin exposure in pregnancy are incomplete, but the following observations are noteworthy.

In Kenya, the mean birthweight of the offspring of women exposed to aflatoxins prenatally was lower than that of those who had not been similarly exposed (De Vries *et al.*, 1989). Three unexplained stillbirths were recorded in pregnancies in which maternal and cord blood at birth showed aflatoxins. In Nigeria, a baby who died of obscure causes in the perinatal period showed aflatoxins M_1 and M_2 in amounts ranging from 487–11 462 pg/g in autopsy specimens of liver, kidney, lung and brain.

Neonatal jaundice (NNJ) of obscure cause is a major problem in many tropical developing countries. Recently, detailed, controlled, collaborative studies by University College Hospital, Ibadan and the Liverpool School of Tropical Medicine, on 327 jaundiced infants and 80 of their mothers and controls, revealed that glucose-6-phosphate dehydrogenase (G6PD) deficiency and the presence of any aflatoxin in serum are significant risk factors for NNJ. The risk associated with G6PD deficiency has long been recognised, but aflatoxins have not previously been identified as a risk factor in newborn jaundice (Sodeinde *et al.*, 1995).

A major concern about prenatal aflatoxin exposure relates to damage to the thymolymphatic system causing immunosuppression, as occurs in piglets exposed prenatally to aflatoxins. There is particular concern about the possibility that aflatoxins may be a contributory factor in the aggressive behaviour of congenital human immunodeficiency virus (HIV) infection in African infants. Evidence now exists that acquired immune deficiency syndrome (AIDS) occurs more frequently and develops more rapidly in African infants than could be predicted from experience recorded in the Western world, except perhaps in Western infants born to intravenous heroin users who are HIV-positive.

AFLATOXIN EXPOSURE IN HEROIN ADDICTS

Needle sharing by heroin addicts is a special risk factor for acquiring HIV infection, but does not explain why intravenous heroin users are more prone to develop clinical AIDS than others infected with HIV.

Heroin is a plant product from tropical and sub-tropical countries, clandestinely processed, packaged and distributed in conditions which favour mould contamination and toxin formation. The possibility that intravenous heroin users may be exposed to aflatoxins was investigated.

The Merseyside Police Drug Squad were approached for assistance and co-operated by supplying 13 samples of 'street' heroin for analysis. Street heroin is notorious for impurities added by dealers to 'stretch' their supply. This proved to be the case with most samples, which were very difficult to 'clean up' and analyse. There were four relatively pure heroin samples which, on analysis, yielded AFB_1 in concentrations of 1.63, 4.31, 5.23 and 30.82 nmol/kg (Hendrickse and Maxwell, 1989).

Random urine samples were obtained from 60 heroin addicts in Amsterdam, 61 in Merseyside and 12 in London, and from 99 normal adult male volunteers of similar age who served as controls. The results of aflatoxin analysis on these urines were as follows: 27 (20%) of the heroin abusers showed aflatoxins B_1, B_2, M_1, M_2 and aflatoxicol in their urine, in quantities which ranged from 0.73–29.09 nmol/litre, whereas only two of the control urines showed any aflatoxin, and then only 0.13 and 0.24 nmol AFB_2/litre (Hendrickse *et al.*, 1989).

These findings reveal a hitherto unsuspected group of people who are exposed regularly or intermittently to intravenous aflatoxins. There is an important difference between this kind of exposure and dietary exposure. In-

gested aflatoxins, after absorption from the gut, pass through the liver, where some or all are detoxified, whereas, when injected intravenously, aflatoxins bypass the liver and this results in direct systemic exposure to the toxins, presumably with increased toxicity.

FOOD POISONING

We were asked to assist in finding the cause of a food-poisoning episode in South–east Asia which affected 19 individuals, aged 2–74 years (median = 8 years), who fell ill within hours of eating rice noodles. Jaundice occurred within 48 h of onset of symptoms in 17 who had clinical and biochemical evidence of hepatitis. Fourteen patients deteriorated rapidly and died of liver failure and, in seven cases, superadded renal failure. Bacterial, viral and fungal infection were excluded by microbiological screening of blood, urine and faeces.

Autopsy samples of organs from 10 of the deceased (fresh frozen and formal-saline preserved) were sent to the Liverpool School of Tropical Medicine (LSTM) for aflatoxin analysis by high-performance liquid chromatography. Aflatoxins (mainly AFB_1) in high concentrations were detected in all liver samples and in 21 of 38 other organ samples. The presence of aflatoxins was confirmed by ELISA (Hendrickse, 1991).

COMMENT

In medicine, interest in aflatoxin has centred on its role in the pathogenesis of primary liver cancer in adults and episodes of acute poisoning and possible associations with Reyes syndrome in children.

The studies summarized in this paper have broken much new ground. Associations between aflatoxins and kwashiorkor, initially dismissed as unjustified and absurd by eminent nutritionists and prestigious, national, research-grant-awarding bodies, are now a focus of international interest and gaining credence. The subsequent discovery of (1) widespread and often severe aflatoxin contamination of breast milk, (2) aflatoxin exposure in pregnancy and in neonates, (3) the interactions between aflatoxins and *P. bergei*, and (4) aflatoxins in heroin and in the urines of heroin addicts are findings not previously recorded in the world literature.

It is quite likely that the work in Sudan which started the chain of events recorded here would not have got off the ground but for the generosity of the lay supporters of Oxfam, who granted £18 000 for aflatoxin studies when the medical-scientific establishment was unwilling to assist.

If any of the associations between aflatoxins and disease in childhood revealed by these studies are confirmed by future studies, then sickness and death associated with aflatoxin exposure would assume enormous proportions and these toxins would be incriminated as among the most pernicious environmental hazards to which many populations are exposed.

There are scientific, ethical and humanitarian grounds for the continued exploration of the effects of aflatoxins on child health by the LSTM, which nurtured these studies which have contributed so much 'new' knowledge in this field.

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