methylene blue therapy in paediatric cases of encephalopathy in which the child has in all probability ingested unripe ackee fruit.

Methylene blue is cheap, safe, and available at most specialist centres since it is widely used in the treatment of methaemoglobinaemia. Intervention with methylene blue, perhaps in combination with riboflavin to promote new flavoprotein synthesis, in early presentation of endemic encephalopathy offers an opportunity to prevent mortality.

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1 Meda HA, Diallo B, Buchet J-P, et al. Epidemic of fatal encephalopathy in preschool children in Burkina Faso and consumption of unripe ackee (*Bligha sapida*) fruit. *Lancet* 1999; **353:** 536–40.
2 Ikeda Y, Tanaka K. Selective inactivation of various acyl-CoA dehydrogenases by (methylenecyclopropyl) acetyl-CoA. *Biochem Biophys Acta* 1990; **1038:** 216–21.
3 Küpfer A, Aeschlimann C, Wermut B, Cerny T. Prophylaxis and reversal of ifosfamide encephalopathy and methylene-blue. *Lancet* 1994; **343:** 763–64.
4 Küpfer A, Aeschlimann C, Cerny T. Methylene blue and the neurotoxic mechanisms of ifosfamide encephalopathy. *Eur J Clin Pharmacol* 1996; **50:** 249–52.
5 Aeschlimann C, Küpfer A, Schefer H, Cerny T. Comparative pharmacokinetics of oral and intravenous ifosfamide/mesna/methylene blue therapy. *Drug Metabol Dispos* 1998; **26:** 883–90.

Sir—Honoré Meda and colleagues[1] report an epidemic of encephalopathy in Burkina Faso. Since 1986, each year between February and June, in Tanguieta hospital in the north of Bénin, West Africa, we have noted ten to 15 unexplained deaths among children aged 3–7 years, which present striking similarities with the epidemic encephalopathy in these workers' report. Typically, the children were admitted in coma, often with convulsions, but without fever. Parents usually reported that their child went to sleep normally, woke up early, cried, convulsed, and went into coma. Most of these children died within 48 h, despite anticonvulsant, antibiotic, antimalarial, or corticosteroid drugs.

In 1991, when glycaemia testing became available in the hospital, we discovered that such children had hypoglycaemia (mean 0·34 g/L), some very severe (<0·10 g/L). Children who arrived within 2–3 h of onset of the symptoms and received intravenous glucose survived.

In 1996, we undertook an epidemiological investigation in the district. We found that most cases originated from the commune of Cotiakou (24 cases in a population of 7056 inhabitants over 2 years; crude attack rate 170 per 100 000 inhabitants per year). The adults in this commune did not know the origin of the disease, but emphasised that its occurrence was a recent event. Some village elders suspected the fruits of the faux acajou tree to be the cause. We identified these fruit as ackee (*Blighia sapida*).[2] Some people regarded ackee as toxic, some only if unripe, and others attributed toxicity specifically to a thin layer of the yellow part of the fruit's stone. We were also informed that fishermen in north Benin and in north Togo use ackee as a poison to kill fish.

In all other communes of the district the disease was entirely unknown. Yet, in 1997 we discovered another cluster in an adjacent district in the commune of Wansoukou: 40 cases had occurred in 1 year, in a population of 4500 (crude attack rate 889 per 100 000 inhabitants per year). It was among the most important causes of mortality in children. Hemoglucotest and nasogatric tubes were supplied to the health centres in the affected area, and staff were trained to recognise the syndrome, and administer sugar. On the assumption that ackee fruit was responsible, the village elders in Wansoukou decided to forbid its consumption, and in 1998 only five cases of the disease were reported.

The Burkina Faso study[1] indicates that unripe ackee fruit is toxic and confirms data from Jamaica.[3,4] However, we remain puzzled because many affected, children have no history of consuming ackee. Moreover, in other regions of Bénin, ackee fruit is widely consumed, but people do not know of any toxicity, and the syndrome is never reported by hospital staff. We thus remain suspicious of whether other causes may not be involved. We are worried because many health workers in West Africa diagnose similar cases as non-febrile cerebral malaria, and administer quinine, which may induce further hypoglycaemia.

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2 Goodwin LG. Plant poisons. In: Manson-Bahr PEC, Bell DR, eds. Manson's tropical diseases. London: Balliére Tindall, 1996: 516–24.
3 Scott HH. On the "vomiting sickness" of Jamaica. *Ann Trop Med Parasitol* 1916; **10:** 1–63.
4 Tanaka K, Kean EA, Johnson B. Jamaica vomiting sickness. Biochemical investigation of two cases. *N Engl J Med* 1976; **295:** 461–67.

Sir—Honoré Meda and colleagues[1] describe deaths of several young children in the West African country of Burkina Faso associated with severe hypoglycaemia and vomiting, which seems to have been caused by eating the arrilli of unripe ackee fruit. Ackee poisoning was first described in Jamaica, where it was common before the danger of eating unripe fruit became widely known. However, there has been one report of poisoning in the Côte d'Ivoire,[1] which is adjacent to Burkina Faso. Ackee poisoning might also occur in other neighbouring African countries. Education about the danger of eating unripe ackee fruit is therefore a priority.

Ackee fruit contain hypoglycin (L(R,S)-2-amino-3-methylenecyclopropylpropionic acid and its γ-glytamyl aster). Their metabolite methylenecyclopropylacetyl-coenzyme A (MCPA-CoA) irreversibly inactivates several flavoprotein acyl-CoA dehydrogenases by forming covalent complexes with their flavin prosthetic groups. This complex formation inhibits the oxidation of long-chain fatty acids and the metabolism of several aminoacids, including leucine and isoleucine, leading to inhibition of glyconeogenesis with severe hypoglycaemia, and isovaleric and 2–methylbutyric acidaemia. Since fatty acids cannot be oxidised and glucose is not replaced or ingested, hypoglycaemia follows as the body runs out of glucose.[2,3] Consequently, ackee poisoning is exacerbated by malnutrition,[3] particularly when there is a food shortage due to drought.[2] Some, but not all, patients with ackee poisoning have recovered when treated promptly with glucose.[4] Dehydration, acidosis, and elecrolyte disturbances may also require attention.

Laboratory studies of hypoglycin poisoning in animals strongly suggest that administration of riboflavin and glycine may also be useful in human ackee poisoning.[3] These compounds have the advantages that they are chemically stable, water soluble, readily available, inexpensive, non-toxic, and can be given intravenously or rectally.

Isovaleryl-CoA and 2-methylbutyryl-CoA accumulate when the metabolism of leucine and isoleucine is inhibited by MCPA-CoA. These metabolites and MCPA-CoA are converted to their acylglycine esters by glycine N-acylase and excreted, which limits toxic effects. The hydrolysis of isovaleryl-CoA to isovaleric and 2-methylbutyric acids by acyl-CoA hydrolase is also limited, which decreases the acidaemia.[5]

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1 Meda HA, Diallo B, Buchet J-P, et al. Epidemic of fatal encephalopathy in preschool children in Burkina Faso and consumption of unripe ackee (*Blighia sapida*) fruit. *Lancet* 1999; **353:** 536–40.
2 Founge S, Nako Y, Declume C. Etude expérimental de la toxicité des arilles de *Blighia sapida* (*Sapindaceae*) en rapport avec l'intoxication des enfants de Katiola (Côte-d'Ivoire). *Ann Pharm Fr* 1986; **44:** 509–15.
3 Sherratt HSA. Jamaican vomiting sickness. In: de Wolff FA, ed. Handbook of clinical neurology, Vol 65: intoxications of the nervous system, part II. Amsterdam: Elsevier Science, 1995: 79–113.
4 Stuart KL. Vomiting sickness of Jamaica. In: Kean EA, ed. Hypoglycin. New York: Academic Press, 1975: 39–44.
5 Sherratt HSA, Al-Bassam SS. Glycine in ackee poisoning. *Lancet* 1976; ii: 1243.

Preoperative fasting

Sir—Bruno Simini in his March 13 commentary[1] questions the rules of preoperative fasting and recommends that anaesthetists prescribe clear liquids for gastrointestinal motility. Preoperative fasting is necessary to reduce the risk of pulmonary aspiration. This risk depends not only of gastric content volume but also on lower oesophaegeal sphincter competence and gastric tone. Drinking before surgery could affect some of these three components, but has never been evaluated in the field of anaesthesia.

Moreover, even if stress has no effect on the gastric emptying of 50 mL water,[2] it is wrong to say that stress does not delay gastric emptying.[3] Maes and colleagues[4] tested gastric emptying of 150 mL milk in healthy children and adults. They report that the variability of the emptying results was remarkably large, with gastric half emptying time varying between 40 min and 240 min. During the 2 h before surgery patients are exposed not only to stress but also to pain, premedication, ambient temperature changes, and manipulations, all of which could affect their gastric emptying, but have not been evaluated. A large proportion of our patients have diseases or conditions that affect their oesophageal, gastric, or pyloric function in even a small way (people with diabetes, smokers, obese people, elderly people, and children).

Fasting guidelines should provide safety limits wide enough to cover the larger population of patients; there are, so far, no evidence-based data to recommend any change of institutional guidelines, particularly when the risk is so high and benefit so low. The benefit on postoperative nausea of drinking in the immediate preoperative period is not certain, and in Smith and colleagues' study[5] some patients fasted for liquids for more than 15 h. In such a case intravenous hydration would presumably procure the same benefit.

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1 Simini B. Preoperative fasting. *Lancet* 1999; **353:** 862.
2 Lydon A, McGinley J, Cooke T, Duggan PF, Shorten GD. Effect of anxiety on the rate of gastric emptying of liquids. *Br J Anaesth* 1998; **81:** 522–25.
3 Fone DR, Horowitz M, Maddox A, Akkermans LM, Read NW, Dent J. Gastroduodenal mortality during the delayed gastric emptying induced by cold stress. *Gastroenterology* 1990; *98:* 1155–61.
4 Maes BD, Ghoos YF, Geypens BJ, Hiele MI, Rutgeerts PJ. Relation between gastric emptying rate and energy intake in children compared with adults. *Gut* 1995; **36:** 183–88.
5 Smith AFm Vallance H, Slater RM. Shorter preoperative fluid fast reduce postoperative emesis. *BMJ* 1997; **314:** 1486.

Ageing eyes retain their mystery

Sir—In Kathryn Senior's March 6 news item (p 818),[1] she records developments that aim to uncover the mechanism for the formation of age-related macular degeneration (ARMD), and points out the necessity for further epidemiological studies on the environmental and genetic risk factors involved in ARMD. Although emphasis must be maintained on the pursuit of eventual treatments, in the absence of an effective treatment for ARMD, Alan Bird of Moorfields Eye Hospital (London, UK), who she quotes, is right to argue for the allocation of greater resources for population-based studies aimed at elucidating potential risk factors in the development of ARMD. Too often, scarce health-care resources have been targeted towards the cure of vision loss and blindness due to ARMD, and have failed to provide funding for the pursuit of public health and preventive ophthalmological initiatives. Perhaps now in view of the urgency affecting the rising tide of age-related blindness, it is time for epidemiology to play a leading part in providing answers to the plight of persons affected with ARMD and other age-related eye disease, such as cataract.

One strategy, which might achieve rapid results in the elucidation of potential risk factors for ARMD, is for highly sensitive measurements of possible environmental and biological processes to be taken. Such an approach, which focuses on small in-vivo changes to the retina during the development of ARMD in relation to minute environmental or biological changes or exposures, could well illuminate promising preventive or treatment pathways in a more immediate time frame than by use of traditional exposure measurements. By identifying single or multiple risk factors of even the slightest magnitude (either protective or causative) subsequent efforts could then be directed towards understanding and hopefully rectifying underlying biological mechanisms associated with ARMD.

A lack of creativity in the study design and sensitivity of the techniques in epidemiological studies to evaluate the risk factors for ARMD could well translate into years, if not decades, of unrealised clinical potential for the provision of an effective means of delaying or halting the visual loss in patients with ARMD. Clearly, if ARMD could be successfully prevented through potential lifestyle modifications to smoking status, diet, and exercise, then this is important information that should reside within the public domain, where it would have the added effect of reducing the demands for costly and currently unsuccessful ophthalmic care for patients with ARMD.

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1 Senior K. Ageing eyes retain their mystery. *Lancet* 1999; **353:** 818.