Letters to the Editor

MOTORNEURONE DISEASE ON GUAM: POSSIBLE ROLE OF A FOOD NEUROTOXIN

SIR,—Guam and certain other Marianas islands of the Western Pacific form a geographical isolate with a very high incidence of amyotrophic lateral sclerosis (ALS) and a clinical variant, parkinsonism-dementia (ALS-PD).[1] Thirty years of investigation have resulted in a detailed description of the clinical, epidemiological, and neuropathological features of ALS-PD, but the cause remains unknown. An environmental agent is considered likely because incidence rates have fallen as the island has become westernised.[2]

Whiting[3] and Dr F. R. Fosberg have suggested that Guam motorneurone disease might be related to the consumption of the seeds of the false sago palm (*Cycas circinalis*). This idea stimulated research on cycasin, a potent hepatotoxic and carcinogenic component of the cycad seed, and interest in cycasin became so intense that little attention was given to the potential importance of another toxic component in *C circinalis* seed, β-N-methylamino-L-alanine (L-BMAA or α-amino-β-methylaminopropionic acid).[4] Prolonged intoxication of rodents with D,L-BMAA did not produce a motorneurone disease,[5] although Dastur[6] reported that a single macaque fed cycasin-free flour (BMAA content unknown) developed Betz and anterior horn cell degeneration.

Our preliminary studies show that repeated oral administration of L-BMAA (0·81 mmol/kg daily) to male cynomolgus monkeys (*Macaca fascicularis*) induces a degenerative motor-system disease. Within 8 weeks of intoxication, a pair of animals showed signs of pyramidal dysfunction, limb weakness, atrophy, upper-extremity tremor and wrist drop, bradykinesia and behavioural changes, conduction deficits in central and peripheral motor pathways, and neuropathological changes highlighted by degeneration and/or chromatolysis of giant Betz cells in motor cortex and of lower motor neurones. No such abnormalities occurred in two controls.

These observations suggest that L-BMAA and chemically related neurotoxic compounds deserve serious consideration as potential causative agents of motorneurone diseases in Guam and elsewhere. Dr L. T. Kurland (whose discussion is gratefully acknowledged) has stated that clarification of the aetiology of ALS-PD in the Western Pacific foci can be expected to have widespread repercussions on understanding of the aetiology not only of ALS but also of Parkinson and Alzheimer diseases.

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UREA HYDROLYSIS IN PATIENTS WITH CAMPYLOBACTER PYLORIDIS INFECTION

SIR,—The urease of *Campylobacter pyloridis* has been attracting interest, mainly as a means of rapid diagnosis.[1-3] However, no one has yet asked how much urea is hydrolysed and what clinical effects this hydrolysis might have. Urea is broken down to carbon dioxide and ammonia; might this explain some of the symptoms of gastritis, especially flatulence?[4]

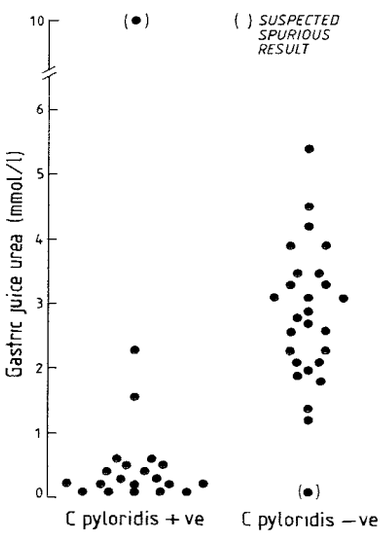
The gastric juice of 48 consecutive patients, after an overnight fast and with no medication on the day of the test, was aspirated from the body of the stomach at the beginning of the endoscopy. The juice was refrigerated and the urea was measured in a Beckman series II analyser. The results of culture and histological studies were not revealed until all 48 samples had been analysed. The patients were attending a research gastroscopy clinic where it was normal practice to do biopsies and cultures to exclude *C pyloridis* infection. Most of them had duodenal ulcer or non-ulcer dyspepsia. Patients with *C pyloridis* infection were treated with antibiotics plus bismuth subcitrate tablets and were followed up 2 weeks after treatment.

21 patients had *C pyloridis* infection on culture and/or histological grounds. After removal of 2 outliers which were probably errors (1 *C pyloridis* positive case had a gastric juice urea level three times the blood urea, and 1 negative case had no gastric juice urea and may have drunk water before the test), the urea concentration was 0·45±0·55 (SD) mmol/l in the patients with *C pyloridis* infection and 2·9±0·98 mmol/l in uninfected patients ($p<0·001$). In the patients with *C pyloridis* the gastric juice ammonium concentration was also high (up to 50 mmol/l) but it did not correlate so well with the culture results (34±16 mmol/l in *C pyloridis* positives, 11±5 mmol/l in *C pyloridis* negatives; $p<0·001$).

These findings could offer a simple method for diagnosing *C pyloridis* infection in patients who vomit, have nasogastric tubes in situ, or in whom gastroscopy and/or gastric biopsy is contraindicated. A gastric juice sample from a fasting patient which contains less than 1 mmol/l of urea will be indicative of *C pyloridis* infection (figure). If no urea is detectable the diagnosis will be certain.

Studies of urea hydrolysis in man have often given conflicting results. Urease was wrongly assumed to be localised to the colon[5-8] and people with *C pyloridis* infection (gastric mucosal urease) may have been included as both subjects and controls.

Whether urea hydrolysis could explain the flatulence of some ulcer patients is debatable. The amount of urea hydrolysed in patients with *C pyloridis* is as yet unknown but if it equals the sum of that contained in the salivary, gastric, and part of the duodenal secretion (total 4500 ml fluid per day[9] or 11·25 mmol urea per day), it is enough to produce about 280 ml CO_2 at body temperature. In



Gastric juice urea levels in patients with or without evidence of *C pyloridis* infection.

addition, the juxtamucosal site of *C pyloridis* exposes large volumes of plasma to urease, producing about 120 ml of CO_2 for each litre of plasma cleared of urea (plasma urea 5 mmol/l), a possible source of intestinal gas.

This situation mimics that of ruminants where mucosa-associated bacteria in the foregut hydrolyse urea from the blood plasma in a process called urea recycling.[10] We believe that urea recycling is also present in patients with *C pyloridis* infection, perhaps suggesting a bovine origin for the new organism. In addition, the ammonia produced may not be benign, especially in people who cannot tolerate an increased ammonia load (cirrhosis) or those in whom the urea supply is increased (uraemia).

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VERY-LOW-DOSE CYTARABINE FOR MYELODYSPLASTIC SYNDROMES AND ACUTE MYELOID LEUKAEMIA IN THE ELDERLY

SIR,—Following the demonstration in vitro that subcytotoxic doses of cytarabine induce terminal maturation of human myeloid leukaemic cells[1] there have been many attempts to treat myelodysplastic syndromes, and acute myeloid leukaemia (AML) with low-dose regimens of this drug often with encouraging results.[2–5] There has been no consensus on dose, duration of therapy, or route (continuous intravenous infusion[3] or twice daily subcutaneous injection). One group has claimed that bone-marrow improvement does not usually occur until 750 mg of the drug has been given.[5] However, even doses as low as 10 mg/m^2 twice daily for 14 days may cause severe bone-marrow suppression, and some patients have died of bleeding or infection.[4]

In our series of twenty-two patients treated with low-dose cytarabine (10–20 mg twice daily for 2–3 weeks) five patients, all treated for 3 weeks, responded well with normal or improved blood counts, reduced transfusion requirements, and decreased marrow blasts percentage for 6–16 months.[6] Of those who did not improve, five died of infections or bleeding associated with treatment and three died of rapidly progressive leukaemia. Of the nine who survived the treatment without benefit to their disease, three needed platelet transfusions and two had severe infections during the treatment.

In view of the toxicity of cytarabine at these doses, we have since treated eight patients at an even lower dose of 5 mg (3 mg/m^2) twice daily for 21 days (see table). The patients were treated as outpatients. Six improved, and three have had a complete response. During the treatment, peripheral blood counts fell in all patients. Only three required platelet support; two have had infections during treatment. One of the patients had not improved and had had recurrent severe infections when given 10 mg twice daily, but has achieved a sustained improvement on 5 mg twice daily. Four of the six patients who improved continue on regular courses of cytarabine. Two have stopped treatment, after 9 and 6 months, and have maintained their improvement for 4 months so far. Our impression is that this "ultra-low"-dose regimen is both safer than conventional low-dose cytarabine and at least as effective.

Encouraged by the low toxicity of these doses, we have now started to treat patients with refractory sideroblastic anaemia with evidence of trilineage dysplasia but without neutropenia or thrombocytopenia with the same regimen, to see whether marrow function will improve sufficiently to reduce transfusion requirements. So far eight courses have been given to three patients. None of the patients has had a decrease in percentage of ringed sideroblasts in the marrow after treatment. It is too early to evaluate improvement but these patients have required no platelet support and have not had infections during treatment.

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CLINICAL DETAILS, LABORATORY FINDINGS, AND OUTCOME

Patient (age, sex)	Disease*	Marrow blasts (%)		Neutrophils (10^9/l)		Platelets (10^9/l)		No of courses	Time since 1st treatment (mo)	Outcome†
		A	B	A	B	A	B			
1 (60, F)	RAEB	10	7	1·7	2·7	39	77	6	13	Good response
2 (78, F)	RAEB-AML	30	4	0·7	3·2	235	298	4	10	Complete response
3 (65, F)	RAEBt	22	2	0·3	3·1	68	252	7	13	Complete response
4 (75, M)	RAEB-AML	30	9	0·6	0·4	153	197	7	13	Good response
5 (68, M)	AML	32	14	0·5	2·8	89	106	3	5	Good response
6 (74, M)	AML	90	3	0·3	3·1	73	147	2	2	Complete response
7 (82, M)	RAEB	16	12	0·5	0·5	16	17	1	2	No improvement
8 (85, M)	RAEB	5	NT	14·8	9·7	554	328	1	7	No reduction in transfusion requirement

A = pre-treatment; B = post-treatment (minimum values for marrow blasts, maximum for neutrophil and platelet counts).
*RAEB = refractory anaemia with excess of blasts; RAEBt = RAEB in transformation; AML in dysplastic marrow in patient 6; RAEB with red cell aplasia in patient 8. †Complete response = marrow blasts less than 5% with or without dysplastic features, and normal blood count; good response = improvement in marrow blast percentage and/or cytopenia sustained for several months.
NT = not tested.