

Letters to the Editor

ADRENALINE RESPONSE TO HYPOGLYCAEMIA AND INSULIN SPECIES

SIR,—Patients with longstanding insulin-dependent diabetes may lose awareness of hypoglycaemia. This is thought to be due in part to a deficient adrenaline response<sup>1</sup> and is associated with a risk of sudden and profound neuroglycopenia. Some doctors and patients believe that a change to human from beef or pork insulin may cause hypoglycaemic unawareness. However, most studies of changes in insulin species have been retrospective and on few patients, comparing biological potency and counter-regulation rather than awareness.<sup>2-6</sup> Furthermore, the complaints about loss of warning signs have often come from patients who, besides a switch to human insulin, have had other major changes in regimen such as the introduction of home blood glucose monitoring or a switch from twice to four times daily insulin. A major change in regimen is important because the glucose threshold at which adrenaline secretion is triggered is strongly influenced by metabolic control.<sup>7,8</sup> The following case suggests that the species of insulin can affect hypoglycaemic warning and adrenaline release independently of blood glucose control.

A 32-year-old man had diabetes diagnosed in 1980. He was put on twice-daily porcine soluble and NPH insulins and after a year he had a haemoglobin A<sub>1</sub> (HbA<sub>1</sub>) of 8.2% on a daily insulin dose of 0.42 U/kg. In 1982 he began to have hypoglycaemic attacks without warning symptoms, and because of erratic home blood glucose profiles he was put on four times daily porcine insulin, soluble, before meals and lente at night. Control remained good between 1982 and 1985 (HbA<sub>1</sub> 7.3–10.8%) but frequent severe and unheralded attacks of hypoglycaemia continued on a total daily insulin dose of 0.66 U/kg. In a further attempt at stabilisation he was changed from porcine lente to bovine ultralente at night, but without any obvious effect. The patient lived alone and his physician (R. B. T.) was advised several times that “something must be done or he will be found dead at home”.

In August, 1986, after bovine ultralente was discontinued, he was changed to human ultralente in equivalent doses which led to yet more severe hypoglycaemic attacks. Shortly after changing to human insulin (November, 1986) adrenaline secretion in response to hypoglycaemia was first measured (table) and reached a peak of only 0.97 nmol/l after blood glucose had been “clamped” at 2.5 mmol/l for 30 min. Despite the obviously defective counter-regulation, the patient was started on continuous subcutaneous human insulin infusion (CSII) at his own request in August, 1987.

INSULIN REGIMEN, BLOOD GLUCOSE CONTROL, AND ADRENALINE RESPONSE TO HYPOGLYCAEMIC CLAMPS

Date	Insulin regimen (and daily dose in U/kg)	HbA <sub>1</sub> (%)	Adrenaline levels (nmol/l) during hypoglycaemic hyperinsulinaemic clamps at blood glucose (mmol/l) of:*		
			4.5	2.5	2.0
1982	Pork ‘Velosulin’ + ‘Insulatard’ × 2 (0.55)	9.8	..	..	..
1983	Pork velosulin × 3 + insulatard (0.55)	7.6	..	..	..
1984	Pork velosulin × 3 + insulatard (0.54)	7.3	..	..	..
1985	‘Actrapid’ × 3 + beef ‘Ultratard’ (0.66)	8.6	..	..	..
Nov, 1986	Actrapid × 3 + human ultratard (0.72)	8.8	0.67	0.97	..
1987	CSII (human velosulin) (0.54)	6.9	..	..	..
Aug, 1988	CSII (0.55)	8.1	0.39	0.84	2.38
Jan, 1989	Beef soluble × 3 + protamine zinc (0.47)	8.3	0.49	1.93	5.48

\*Adrenaline first measured in November, 1986.

For the first 7 months on CSII there were no serious reactions and the HbA<sub>1</sub> averaged 6.9%. In May, 1988, he had his most severe and prolonged reaction to date, and a further hypoglycaemic clamp was done in August (HbA<sub>1</sub> 8.1%) when again (see table) there was a very poor adrenaline response after 60 min at a blood glucose of 2.5 mmol/l. Reducing blood glucose to 2 mmol/l produced a peak adrenaline of 2.38 nmol/l but without the typical symptoms or physiological changes of hypoglycaemia. It was thought unsafe to continue CSII, and in September he was changed to beef insulin (CP Pharmaceuticals), 4 units of soluble before each meal and 18 units of protamine zinc at night, a total daily dose of 0.47 U/kg.

This regimen produced much more consistent control and, after 4 months, no serious hypoglycaemic reactions. A hypoglycaemic clamp was repeated in January, 1989 (HbA<sub>1</sub> 8.3%) and showed a doubling of adrenaline levels over those recorded 5 months earlier. Nevertheless, even after 30 min at a blood glucose of 2 mmol/l with an adrenaline concentration of 5.48 nmol/l, hypoglycaemic symptoms were conspicuous by their absence although there were changes in heart rate and blood pressure.

This case does not prove that human insulin causes hypoglycaemic unawareness or that beef insulin restores it. Nevertheless it does suggest that adrenaline secretion in response to hypoglycaemia may be affected by the species of insulin. We intend to study more cases but for the present we agree with Dr Alexander (June 21, p 156) that “the opinions of people who are experiencing difficulties with human insulin should be respected . . . and if necessary their insulin changed back to the pork or beef that had previously suited them”.

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1. Heller SR, Macdonald IA, Herbert M, Tattersall RB. Influence of the sympathetic nervous system on hypoglycaemic warning symptoms. *Lancet* 1987; ii: 359–63.  
2. Schluter KJ, Petersem L-G, Sontheimer J, Enzmann F, Kerp L. Different counter-regulatory responses to human insulin (recombinant DNA) and purified pork insulin. *Diabetes Care* 1982; 5 (suppl 2): 78–81.  
3. Rosak C, Althoff P-H, Enzmann F, Schoffling K. Comparative studies on intermediary metabolism and hormonal counter-regulation following human insulin (recombinant DNA) and purified pork insulin in man. *Diabetes Care* 1982; 5 (suppl 2): 82–89.  
4. Landgraf-Leurs MMC, Brugelmann I, Kammerer S, Lorenz R, Landgraf R. Counter-regulatory hormone release after human and porcine insulin in healthy subjects and patients with pituitary disorders. *Klin Wochenschr* 1984; 62: 659–68.  
5. Muller-Esch G, Ball P, Bekemeyer U, et al. Comparative study of hormonal counter-regulation during GCIIS-guided insulin hypoglycaemia tests using human insulin (recombinant DNA) and pork insulin. *Diabetes Res* 1985; 2: 121–25.  
6. Fernandez RP, Casanueva FF, Devesa J, Cabezas-Cerrato J. Metabolic and hormonal parameters after insulin-induced hypoglycaemia in man: comparison between biosynthetic human insulin and purified pork insulin. *Horm Metab Res* 1965; 17: 351–54.  
7. Simonson DC, Tamborlane WV, De Fronzo RA, Sherwin RS. Intensive insulin therapy reduces the counter-regulatory hormone responses to hypoglycaemia in patients with type 1 diabetes. *Ann Intern Med* 1985; 103: 184–90.  
8. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycaemic thresholds for counter-regulatory hormone release. *Diabetes* 1988; 37: 901–07.

DUODENAL ULCER RELAPSE AFTER ERADICATION OF CAMPYLOBACTER PYLORI

SIR,—Professor Lam (Feb 18 p 384) criticises our study. We wish to reply.

Eradication of *Campylobacter pylori* in our patients was associated with a much longer remission of healed duodenal ulcers and the apparent rate of healing was also higher. The apparent ulcer-healing rate at follow-up endoscopy was low in our patient group in which *C. pylori* was not eradicated (CP+ve patients), irrespective of the therapy. Our Table II shows healing in 44/72 (61%) CP+ve patients. Since 27/44 (61%) of these healed ulcers relapsed before 3 months, we cannot see why it is difficult to understand our suggestion that others probably relapsed before the first follow-up 2 weeks after therapy ended. Even if the argument is not substantiated, it is not unreasonable. The failure rates at 12 months were the same for both cimetidine (46/50, 92%) and colloidal

bismuth subcitrate (CBS) (19/22, 86%). We agree that our patients are unique, as Lam says, since all patients are unique.

Every effort was taken to keep the trial blind. Follow-up was timed 2 weeks after therapy ceased (so that mouth-staining would not be seen by the endoscopist) and communication was avoided between the clinician and the patient before gastroscopy. More importantly the pathologist and microbiologist were independent; they had no knowledge of the therapy and neither the clinician nor the patient knew of the presence or absence of bacteria. Thus we do not agree that the title is misleading.

Lam mentions that our definition of ulcer relapse includes "any recurrence of ulcer symptoms". This is almost correct—our patients were treated as in normal practice. If they complained of symptoms requiring therapy, they were considered to have relapsed and usually (32/43, 74%) an ulcer was found on gastroscopy. We thought it unreasonable to call such patients "successfully treated" if they had a recurrence of symptoms but did not have an ulcer crater at endoscopy.

We agree that "bismuth not cimetidine is associated with clearance of campylobacter", but if Lam really believes we did not "safeguard against investigator or patient bias", we suggest he considers the following. There is no way to demonstrate CBS therapy on histology or microbiology, unless Lam thinks that the absence of gastritis and campylobacter, only seen with CBS therapy, causes observer bias. All bias can thus be eliminated by considering only the group of patients treated with CBS. This shows 22 CP+ve patients, 10 (45%) healed at follow-up and 3 (14%) still healed at 12 months; compare this with 24 CP-ve patients, 22 (92%) healed and 17 (71%) still healed at 12 months.

Tinidazole was not intended to "differentiate cimetidine and bismuth", nor for that matter was our study. If Lam is interested in tinidazole, he should examine our results for CBS with or without tinidazole, which show an improvement with tinidazole. We were investigating the effect of the eradication of *C. pylori*, not the effect of cimetidine, CBS, or tinidazole per se—our results should be viewed from this aspect.

The distribution of campylobacter is patchy, as stated by Lam, but only at a microscopic level and, with improved methods, we rarely have contradictory results. In this series no CP+ve patient gave negative histological findings and culture without treatment and only 1 patient gave two successive negative biopsy specimens followed by a *C. pylori* positive culture (probably a true re-infection). The series includes about 450 biopsies on 100 patients. Under these circumstances we consider "eradication" a correct and justified term.

Our work was designed to show the effect of the eradication of *C. pylori* on duodenal ulcer relapse. It was never intended as a drug trial. Cimetidine is an ulcer-healing agent but will not eradicate *C. pylori*. Our results suggest that eradication of *C. pylori* is associated with a dramatic reduction in the relapse of healed ulcers.

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## TRENDS IN LYMPHOMA DIAGNOSIS

SIR,—Your Feb 4 editorial (p 249) erroneously suggests that lymphomatoid granulomatosis, midline granuloma, angioimmunoblastic lymphadenopathy (AILD), histiocytic medullary reticulosis (HMR), and mycosis fungoides are related, and that the skin lesions seen in these conditions are similar. In fact, all these conditions are very different clinically and pathologically, except for lymphomatoid granulomatosis and polymorphic reticulosis (midline granuloma).

Lymphomatoid granulomatosis and polymorphic reticulosis are similar if not identical.<sup>1</sup> They are angiocentric and angiodescriptive lymphoproliferative lesions which may evolve into a more monomorphic picture of angiocentric lymphoma. Despite their polymorphous cellular composition, they are held to be neoplastic diseases by virtue of their ability to metastasise, aberrant T-cell

immunophenotype, and the T-cell receptor gene rearrangements.<sup>1-3</sup> The lesions tend to affect extranodal sites such as the upper respiratory tract, lung, and skin, and synchronous or metachronous involvement of more than one of these sites may occur.<sup>1,3</sup> They differ histologically from mycosis fungoides in the prominent vascular invasion, frequent necrosis, more deeply located dermal infiltrate, infrequent epidermal invasion, and rarity of cerebriform cells.<sup>3</sup> Your editorial equates midline granuloma with polymorphic reticulosis but "midline granuloma" refers to a progressive, necrotising lesion affecting the nose and adjacent structures, and a wide variety of diseases can produce that clinical picture, including infection, vasculitis, and angiocentric lymphoproliferative lesions.<sup>2,4</sup> On the other hand, "polymorphic reticulosis" is a purely histological designation.

AILD is an altogether different entity clinically and histologically,<sup>5</sup> and morphologically and cytologically it is distinct from either lymphomatoid granulomatosis and mycosis fungoides. Many cases reported as AILD may really be peripheral T-cell lymphoma (immunoblastic lymphadenopathy-like T-cell lymphoma).<sup>5</sup>

Although Scott and Robb-Smith did not label HMR as malignant in their original description, Robb-Smith subsequently considered it a proliferation of malignant and actively phagocytic histiocytes.<sup>6</sup> Immunohistochemical and genotypic studies have shown that most malignant "histiocytic" proliferations are T or B cell malignancies.<sup>7</sup> Malignant true histiocytic diseases do exist but most cases satisfying the diagnostic criteria of HMR are probably large-cell lymphomas, such as anaplastic Ki-1 or peripheral T-cell lymphoma, associated with reactive haemophagocytic syndrome.<sup>8,9</sup> Angiocentric lymphoproliferative lesions, as in the case reported by Whittaker and colleagues,<sup>10</sup> are also not uncommonly complicated by the haemophagocytic syndrome.<sup>1,3</sup> What has been reported as HMR has probably included reactive haemophagocytic syndrome as well, especially in reports before the description of this benign syndrome.

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1. Lipford EH, Margolick JB, Longo DL, et al. Angiocentric immunoproliferative lesions: a clinicopathologic spectrum of post-thymic T-cell proliferations. *Blood* 1988; 72: 1674-81.
2. Chan JKC, Ng CS, Lau WH, et al. Most nasal/nasopharyngeal lymphomas are T-cell neoplasms. *Am J Surg Pathol* 1987; 11: 418-29.
3. Chan JKC, Ng CS, Ngan KC, et al. Angiocentric T-cell lymphoma of the skin, an aggressive lymphoma distinct from mycosis fungoides. *Am J Surg Pathol* 1988; 12: 861-76.
4. Costa J, Delacretaz F. The midline granuloma syndrome. *Pathol Annu* 1986; 21: 159-71.
5. Nathwani BN, Brynes RK. Reactive immunoblastic proliferations. *Semin Diag Pathol* 1988; 5: 317-28.
6. Robb-Smith AHT, Taylor CR. Lymph node biopsy. London: Miller Heyden, 1981: 137-39.
7. Weiss LM, Trela MJ, Cleary ML. Frequent immunoglobulin and T-cell receptor rearrangement in 'histiocytic' neoplasms. *Am J Pathol* 1985; 121: 369-73.
8. Chan JKC, Ng CS, Hui PK, et al. Anaplastic large cell Ki-1 lymphoma, delineation of two morphological types. *Histopathology* (in press).
9. Chan JKC, Ng CS, Law CK, et al. Reactive haemophagocytic syndrome, a study of 7 fatal cases. *Pathology* 1987; 19: 43-50.
10. Whittaker S, Foroni L, Luzzatto L, et al. Lymphatoid granulomatosis: evidence of a clonal T-cell origin and an association with lethal midline granuloma. *Quart J Med* 1988; 68: 645-55.

## ROUTINE CORONARY ANGIOGRAPHY FOR EFFORT ANGINA

SIR,—The decision to perform coronary angiography in patients with non-disabling effort angina is often based on the results of an exercise test. We question the validity of this approach.

In a retrospective analysis 434 patients who had a history of angina at the time of an exercise test which was positive for pain or ST segment changes were followed up for up to 9 years. A conservative management policy was used—ie, coronary angiography was offered to patients with disabling angina with bypass surgery for those with multiple vessel coronary artery obstruction. We found that coronary angiography had been done in