CORRESPONDENCE

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- *No letter should be more than 400 words.*
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- *Because we receive many more letters than we can publish we may shorten those we do print, particularly when we receive several on the same subject.*

Human insulin

SIR,—The issues relating to diabetic patients' experiences with human insulin are complex and the prospect of their being made the subject of legal action is distressing. It is all the more important therefore to disentangle two separate questions that are becoming muddled.

The problem addressed by Professor Arthur Teuscher and his colleagues concerns different responses to porcine and human insulin.[1,2] Their findings are indeed hard to explain, but what they do not do is cast doubt on genetically engineered human insulin for the simple reason that the human insulin used in their study[2] was not genetically engineered.

The formulations used contained the so called semisynthetic insulin, in which one amino acid out of 51 (at residue B30) of porcine pancreatic insulin is replaced chemically to make human insulin. Many commentators, including Ms Clare Dyer, writing in the news section,[3] have made this error, which was compounded in Ms Dyer's case by her reference to "genetically engineered 'human' insulin" with quotation marks used pejoratively.

The second problem, the subject of a few isolated case reports (which regrettably led to a misleading note in the usually reliable *Drug and Therapeutics Bulletin*[4]), concerns the apparent ability of some patients to distinguish between human insulins made by the two manufacturing processes (semisynthetic and genetically engineered). This is even more difficult to explain as the drug substances in each case are identical and cannot be distinguished by any biological or physicochemical test system.

So can we get the ground rules straight? The first question is, Do some diabetic patients react differently to the two different chemical substances, porcine insulin and human insulin—albeit they have 98% homology—irrespective of the mode of manufacture? The second question is, Do some diabetic patients react differently to human insulin prepared by different manufacturing processes, the end products of which are identical according to all known test procedures?

S L JEFFCOATE

National Institute for Biological Standards and Control,
South Mimms,
Hertfordshire EN6 3QG

1 Egger M, Davey Smith G, Imhoof H, Teuscher A. Risk of severe hypoglycaemia in insulin treated diabetic patients transferred to human insulin: a case control study. *BMJ* 1991;**303**:617-21. (14 September.)
2 Egger M, Davey Smith G, Teuscher AU, Teuscher A. Influence of human insulin on symptoms and awareness of hypoglycaemia: a randomised double blind crossover trial. *BMJ* 1991;**303**:622-6. (14 September.)
3 Dyer C. A case against human insulin? *BMJ* 1991;**303**:601. (14 September.)
4 Novo human insulin—the same but different. *Drug Ther Bull* 1990;**28**(6):24.

SIR,—The two papers by Dr Matthias Egger and colleagues on the risk of hypoglycaemia associated with treatment with human insulin[1,2] reopen a debate that British doctors with diabetic patients had hoped was closed. I acknowledge that there may be a difference in the features of hypoglycaemia induced by porcine and human insulin, but what is more clear is how exceedingly tight glycaemic control was in their patients.

In their crossover trial they report mean preprandial blood glucose concentrations recorded by their patients of between 7·2 and 8·6 mmol/l. There is no proof that such tight control will prevent specific microvascular complications and certainly no evidence to show that established tissue damage can be reversed. Some of their patients actually had proliferative retinopathy or nephropathy, or both.

Severe hypoglycaemia is at worst lethal and at best embarrassing, and doctors should do their best to educate their patients, particularly those with hypoglycaemic unawareness, to avoid it. This means setting realistic targets for self measured preprandial blood glucose concentrations tailored to the circumstances of the individual patient. If doctors are not sure that their patients have enough knowledge and confidence to achieve this the target preprandial blood concentrations must be raised to safe levels, usually above 10 mmol/l.

Our concern therefore should not be to seek to prove or refute potentially litigious differences between porcine and human insulin with respect to hypoglycaemic awareness but to make sure that our patients are aware of not only the various causes and manifestations of hypoglycaemia (including the neuroglycopenic sign of denial of its existence) but also the likelihood of these features changing in one person over time. They and their relatives or friends should be aware of the immediate treatments[3] and should be able to find expert advice locally for help and to restore confidence.

Diabetes care is not simply about reducing high blood glucose concentrations. After all, why does the British Diabetic Association call its magazine *Balance*?

DAVID M MATTHEWS

Stonehouse Hospital,
Stonehouse ML9 3NT

1 Egger M, Davey Smith G, Imhoof H, Teuscher A. Risk of severe hypoglycaemia in insulin treated diabetic patients transferred to human insulin: a case-control study. *BMJ* 1991;**303**:617-21. (14 September.)
2 Egger M, Davey Smith G, Teuscher AV, Teuscher A. Influence of human insulin on symptoms and awareness of hypoglycaemia: a randomised double blind crossover trial. *BMJ* 1991;**303**:622-6. (14 September.)
3 Matthews DM, Patrick AW, Collier A, Kellett HA, MacIntyre CCA, Steel JM, *et al*. Awareness and use of glucagon in diabetics treated with insulin. *BMJ* 1986;**293**:367-8.

SIR,—The important question not answered by Matthias Egger and colleagues' report on patients treated with human insulin is whether or not unconsciousness develops more frequently during treatment with human insulin.[1] The first paper suggests an alteration of symptoms without unconsciousness; the second still leaves doubt because two different groups of patients were studied. What both of these papers show clearly is that problems from hypoglycaemia are common in people using animal insulins—a serious problem well known to diabetic physicians practising long before the era of human insulins. What is also certain is that we must take seriously those patients who experience problems with human insulins and change them back to insulins of animal origin; as the authors suggest, conversion from animal to human insulin must be advised for only the most carefully considered reasons (and these are few).

Where does this leave insulin manufacture? It looks as if animal (chiefly porcine) insulins will have to remain available indefinitely. It would also help if manufacturers distinguished more clearly which insulins are human and which are of animal origin (at present names like Velosulin and Insulatard are the same for human and porcine insulins). Perhaps in the longer term these problems will accelerate the development of insulin analogues with new properties and durations of action, none of which will carry either an "animal" or a "human" label.

P J WATKINS

Diabetic Department,
King's College Hospital,
London SE5 9RS

1 Egger M, Davey Smith G, Imhoof H, Teuscher A. Risk of severe hypoglycaemia in insulin treated diabetic patients transferred to human insulin: a case control study. *BMJ* 1991;**303**:617-21. (14 September.)
2 Egger M, Davey Smith G, Teuscher AU, Teuscher A. Influence of human insulin on symptoms and awareness of hypoglycaemia: a randomised double blind crossover trial. *BMJ* 1991;**303**:622-6. (14 September.)

SIR,—It is puzzling that the debate about insulin-induced hypoglycaemic symptoms and the species of insulin seems to have been confined to the European continent.[1-3] The issue is now being considered by solicitors in the United Kingdom, and claims may possibly be brought against the main manufacturers of insulins.[4] In the United States, the "land of litigation," the problem does not seem to exist, or if it does it is of little consequence and not reported.[5] Why should there be such a transatlantic difference?

There is no obvious answer. Counterregulatory hormone responses to hypoglycaemia can be influenced by preceding glycaemic control,[6] but the paper by Matthias Egger and colleagues suggests that it was neuroglycopenic symptoms rather than adrenergic symptoms that were more common in those patients receiving human insulins.[2] There is no reason to believe that American diabetic patients have different glycaemic control from that of their European counterparts.