Lesson of the Week

Unnecessary insulin treatment for diabetes

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The indications for starting treatment with insulin have been described often, but there has been little or no debate about when insulin should be stopped. Many patients have indications, such as ketoacidosis or bad control despite adequate treatment with diet and tablets, which are unequivocal and point to a life-long requirement for insulin. In others the need for insulin is less certain. The policies on treatment used in this borderline area—and a borderline is inevitable, whatever criteria are used for diabetic control—undoubtedly vary from clinic to clinic and country to country. One common assumption underlying the choice of whether to treat with insulin is that it is a "life sentence." This creates a psychological barrier for the doctor and the patient and may postpone treatment that is really needed. Once started insulin treatment is hard to stop: "it is easier to continue a treatment than to reassess it."[1]

We report on seven patients in whom insulin treatment was either unnecessary or actually harmful, and suggest how to decide whether insulin treatment is necessary.

Case reports

The patients were seen at this hospital and at City Hospital, Nottingham. Their ages ranged from 33 to 70 years, the duration of diabetes from six months to 22 years, and the insulin dose from 20 to 88 units daily. The clinical details are summarised in the table. All had been treated with highly purified porcine insulins. Insulin was withdrawn during hospital admission in six patients and in one as an outpatient. Control of the diabetes was assessed by five blood glucose measurements each day, using a glucose oxidase method. Insulin secretory reserve was tested after insulin withdrawal in four patients by measuring the fasting C-peptide and the response to 1 mg intravenous glucagon.[2]

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Insulin treatment does not always imply insulin dependence

Case 1—A man aged 33 had an eight-year history of diabetes and had received insulin for seven years. His father and brother also had diabetes, and the brother was treated with insulin. Control over the diabetes appeared to deteriorate as the insulin dose was increased in stages from 22 to 52 units daily. On his second admission to hospital his blood glucose concentrations varied between 12 and 17 mmol/l (216-306 mg/100 ml) (figure). When insulin was withdrawn the blood glucose concentration fell into the range 7-9 mmol/l (126-162 mg/100 ml), and his complaints of fatigue, irritability, and headache resolved completely.

Case 2—A 48-year-old Pakistani man was diagnosed as a diabetic during treatment for pulmonary tuberculosis and was treated with insulin to avoid possible drug interactions between oral hypoglycaemics and antituberculous agents. Subsequent control was poor, and he excreted 50-100 g of glucose daily in his urine. No improvement was seen when the insulin dose was increased from 16 to 36 units daily. Three years after diagnosis he attended with a normal blood glucose and a 24-hour glucose concentration of 9 g. It emerged that his insulin syringe was broken, and that he had received no treatment at all for 48 hours. On admission his blood glucose concentration remained between 5 and 9 mmol/l (90-162 mg/100 ml) on diet alone, and he has maintained this level of control for 16 months as an outpatient.

Case 3—A 66-year-old woman had developed diabetes 22 years previously, when she was 60% overweight. Her control remained poor despite many adjustments of the insulin dosage. When insulin was withdrawn after 19 years of treatment, from a dose of 52 units daily, her control improved and symptoms of intermittent hunger, dizziness, and malaise disappeared.

Case 4—A 70-year-old retired consultant physician presented in hyperosmolar coma with a blood glucose concentration of 36 mmol/l (649 mg/100 ml). He had remained in apparent good control over four years of insulin treatment. On admission

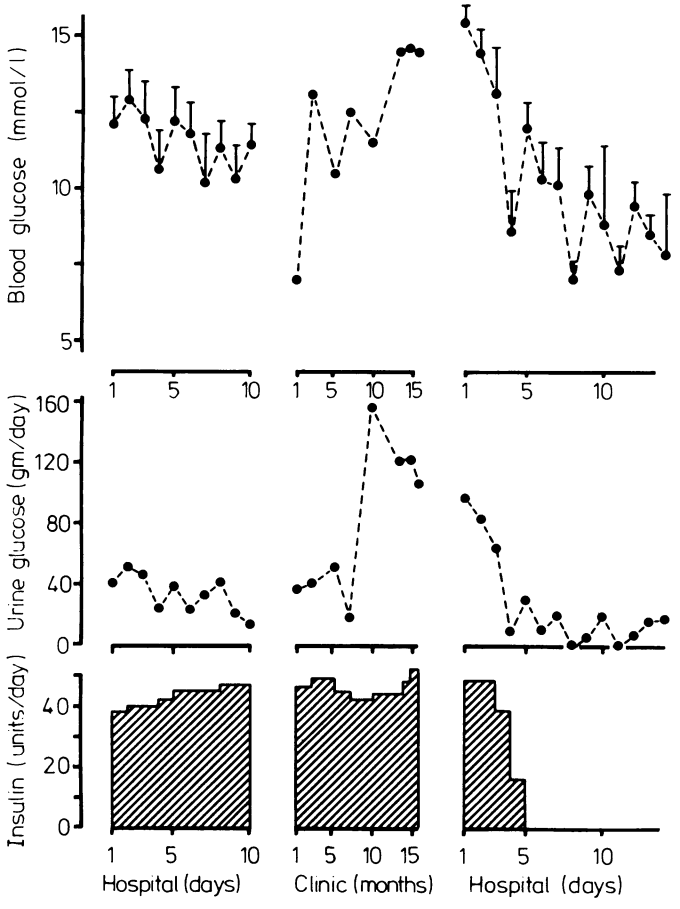
Clinical data on seven patients with diabetes

	Case No						
	1	2	3	4	5	6	7
Age (years) and sex	33 M	48 M	66 F	70 M	53 M	68 F	45 M
No of years of insulin treatment	7	3	19	4	1	11	2
Daily dose of insulin (units/kg)	0·8	0·5	0·8	0·5	1·3	0·9	0·3
Weight (kg) (ideal body weight)	67 (64)	73 (64)	78 (63)	81 (58)	70 (67)	69 (58)	61 (72)
Fasting C-peptide/response to glucagon (nmol/l)	0·37/0·48	0·48/0·99	—	0·76/1·40	—	—	0·30/0·48
Follow-up (months)	16	16	13	14	19	9	8

Ideal body weight was calculated according to Natvig.[3] Normal range of fasting C-peptide: 0·25–0·63 nmol/l, rising to 0·86–1·88 nmol/l after glucagon.[4]
Conversion: SI to traditional units—C-peptide: 1 nmol/l ≈ 0·148 units of insulin/l.

blood glucose concentrations were in the range 3-4·5 mmol/l (54-81 mg/100 ml), and rose to 5-9 mmol/l (90-162 mg/100 ml) when insulin was withdrawn. During insulin treatment he had had many often atypical symptoms of hypoglycaemia, including irritability, lethargy, and depression. In a subsequent letter of thanks he wrote that he now felt "mentally reborn, full of spirits, energy, and pleasure" in his work.

Case 5—A West Indian man aged 53 was admitted in hyperosmolar coma with a blood glucose concentration of 61 mmol/l



Case 2. The blood glucose concentration is shown as the mean ± SEM of five measurements each day during two periods in hospital. Insulin was stopped during the second period. The patient attended the clinic eight times in the interval, and the blood glucose concentration at each visit is shown. Glucose excretion (g/24 h) and insulin dose are also given.

Conversion: SI to traditional units—Blood glucose: 1 mmol/l ≈ 18 mg/100 ml.

(1099 mg/100 ml) and discharged on 88 units of insulin daily. He remained well and in good control during six months of follow-up but complained of intermittent nocturnal hypoglycaemia. Taking glibenclamide 5 mg daily he had no glycosuria, and blood glucose concentrations measured in the clinic have remained in the range 3-8 mmol/l (54-144 mg/100 ml) during 19 months of follow-up.

Case 6—A moderately obese woman aged 68, whose sister, mother, and maternal grandmother had insulin-treated diabetes, was found to have diabetes during an episode of pneumonia. While taking insulin she had frequent symptoms of sweating, anxiety, headache, and dizziness, and on more than one occasion had been accused of being drunk. She was transferred from 60 units of insulin daily to glibenclamide 10 mg daily with no change in control. "Life has changed 100% for the better," was her comment.

Case 7—A 45-year-old man presented with asymptomatic hyperglycaemia and a skin abscess. Insulin was started because of the infection and initial poor control, and subsequent clinic blood glucose concentrations were from 4 to 8 mmol/l (72-144 mg/100 ml). Equally good control was achieved with diet alone.

Discussion

Our study is a reminder that insulin treatment does not always imply insulin dependence. The classification of diabetes into insulin dependent (type I) and non-insulin dependent (type II) is justified on genetic and epidemiological grounds,[5] but the clinical distinction may not be clear cut, and most older patients graduate to insulin only after a trial of diet and oral agents. Unnecessary insulin treatment may reflect misuse of such alternatives—for example, incorrect diet—but our experience suggests that the usual reason is that insulin is continued when the original indication no longer applies. Thus two of our patients presented in hyperosmolar coma, usually not an indication for long-term insulin treatment,[6] two had infections, one was considered unsuitable for oral hypoglycaemics because of treatment for tuberculosis, and another started insulin at a time when oral agents were not widely available.

Excessive insulin doses are surprisingly well tolerated by many patients. This may be more apparent than real, since chronic recurrent hypoglycaemia may pass unrecognised because episodes occur during sleep or because symptoms are atypical or so usual that the patient considers them a normal part of life.[7] Possibly also patients may become less sensitive to insulin, since hyperinsulinaemia can down-regulate the affinity of the insulin receptors.[8] These considerations may help to explain why in case 5, for example, the patient was able to take 88 units of insulin daily with minimal symptoms of hypoglycaemia.

Three of our patients had better control without insulin and four had equally good control. The paradox of bad control induced by excessive doses of insulin, first described by Somogyi, is conventionally explained in terms of counter-regulatory hormones produced in response to hypoglycaemia.[9] Another factor of potential importance in patients with significant residual β-cell function is that insulin secretion is suppressed after episodes of hypoglycaemia, an effect possibly mediated by adrenaline,[10] and this may aggravate hyperglycaemia when food is taken to combat hypoglycaemic symptoms.[11]

To establish that insulin treatment is unnecessary depends on clinical suspicion. The history may give a clue if it shows that the patient has not had an adequate trial of alternative treatment. Recurrent hypoglycaemia should always suggest overtreatment, which should also be considered if poor control fails to respond to increasing doses of insulin. Paradoxically, apparent "near-perfect" control, such as that seen in four of our patients, should arouse suspicion, since this degree of control is often extremely difficult to achieve in truly insulin-deficient patients. Insulin dependence is not established by long duration of diabetes, or by the use of large doses of insulin; the duration of diabetes in our patients ranged up to 22 years, and the dose up to 88 units per day. Wells reported good diabetic control in a series of patients from Singapore after the withdrawal of insulin in dosages up to 720 units a day.[12] A strong family history of diabetes, as given in cases 1 and 6 in our series, may help to identify families in which the variant of type II diabetes known as "maturity-onset type diabetes of young people" is transmitted as an autosomal dominant trait.[13] Finally, since the need for insulin treatment is related to a failure of production of endogenous insulin, in theory a test of secretory reserve such as the glucagon test[2] would be valuable, but in the event two patients in our series have done well despite a "deficient" C-peptide response. In contrast, Mahler found that a hypoglycaemic response to the tolbutamide test identified eight of 15 insulin-treated patients in his series who did not require insulin.[14]

All our patients were well nine months after insulin was stopped. Freedom from injections and from symptoms of hypoglycaemia has given them an enormous psychological boost. There is no doubt also that they are complying more

enthusiastically with other aspects of their diabetic regimen. The practical point we emphasise is not so much that insulin may sometimes do harm, but that stopping it can be highly beneficial. We have shown that equally good, or better, control could be achieved without insulin, and there can be no justification for a treatment that is not necessary. Elective insulin treatment may benefit some patients who are not strictly insulin dependent, but we hope that our observations will draw attention to the need for a flexible critical approach to their management.

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Conference Report

Recession and health in Scotland

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Little can be better for focusing the mind on the problem of economic inequality and health than arriving in a frozen and murky Glaswegian dawn from the fleshpots of Bloomsbury. For just as Texas has the biggest of everything, so Scotland has the worst of everything, and where better than Glasgow in November 1981 to debate the issue of unemployment and health? Accordingly the Scottish National Party and the W P Neill Trust sponsored a conference entitled "Unemployment and Health—the Scottish Perspective." All of the speakers were academics, but politicians attended and wanted a "straight answer" to what they saw as a "straight and politically very important question": Does unemployment damage health? What they got, however, was an answer so tortuous that it led at least one man to storm out in frustration.

Time-series analysis and all that

Only one man speaking at the conference had sufficient data to begin to answer the question, and that man was the now famous Professor Harvey Brenner from Johns Hopkins University. He presented the results of a preliminary analysis of how unemployment and other economic, social, and environmental factors have affected mortality in postwar Scotland. His results have since been widely reported and misreported.

Brenner's Scottish study is the latest in a long line. He began with a mathematical model that attempted to describe the inverse relation between the rate of employment in New York State from 1914 to 1967 and the rate of first admissions to mental hospitals.[1] He then extended his model to other psychopathological conditions in the United States[2] and then on to cardiovascular mortality.[3] Later, in 1979, he published a study on mortality and the national economy in England and Wales from 1936 to 1976.[4] This was severely criticised,[5] and then defended by Brenner.[6] The sad truth is that these time-series analyses are beyond the comprehension of most doctors (and most of those at the conference). Also, as Dr Steve Engleman, who had been specially imported from the department of community medicine in Edinburgh to criticise the model, said, the analyses are "inherently difficult" and a little tinkering with the "regressions" can do wonders. So most of those at the conference were in the same predicament as mechanically ignorant people deciding whether to buy from a second-hand car salesman. The general mood of the conference seemed to be that Brenner's model—particularly his new model of Scotland—was worth buying.

Although the mathematical complexities of Brenner's model are hard to follow, the general scheme is quite comprehensible. He starts from the premise (with which almost everybody would agree) that income—both national and individual—is the main determinant of mortality: rich people live longer than poor people. Brenner has been concerned, however, to break down this relation further and discover which economic variables have the most powerful influence on mortality. How, for instance, does a recession affect mortality?

And here a very important point must be made: Brenner's model does not permit conclusions specifically about the unemployed. He is using unemployment as a "marker" of recession,

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