lating insulin preparations used in interpreting data of insulin biogenesis.

Yours sincerely,
J. G. Devlin

References

1. Drell DW, Notkins AL (1987) Multiple immunological abnormalities in patients with Type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 30: 132-143
2. Devlin JG, Maguire O, Parameswaran V, Blake PJ (1979) Insulin immunology: humoral and cellular aspects in mono-component insulin treated patients. *Postgrad Med J* 55 [Suppl 2]: 14-18

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More on the role of insulin in the treatment of diabetic ketoacidosis

Dear Sir,

Jakobsen et al. [1] have provided valuable experimental support for the postulate that insulin plays a pathogenetic role in two of the complications resulting from the treatment of diabetic ketoacidosis (DKA)-namely the adult respiratory distress syndrome (ARDS) or its more benign counterpart, a widening of the A-a O₂ gradient, and cerebral oedema, usually "benign" and very rarely fatal [2, 3].

Insulin has previously been shown to result in a large decrease in plasma volume and a reduction in the plasma albumin pool when administered intravenously to diabetic patients who were not ill [4]. Furthermore, insulin is known to be capable of decreasing renal sodium excretion by enhancing sodium reabsorption in the diluting segment of the distal nephron [5] and resulting in major fluid and sodium retention in previously uncontrolled diabetic patients [6] - so called "insulin oedema".

It is evident that most adults [7] and probably, children [8] develop subclinical or "benign" cerebral oedema [3] during the course of therapy for DKA.

We have previously described ARDS developing during the treatment of severe DKA [2, 9]. One of the survivors in our most recent series [9] had his insulin therapy inadvertently delayed for some 3 h after admission. It was this serendipitous occurrence which suggested insulin as a possible pathogenetic factor in ARDS as well as cerebral oedema developing the treatment of DKA.

An additional piece of supporting clinical information derives from the review by Arem and Zoghbi [10] describing 8 patients with massive insulin overdoses. Two of their eight cases plus an additional two cases from their literature review demonstrated ARDS. Furthermore, we have recently treated an elderly woman who had fatal hypoglycaemia secondary to the use of chlorpropamide who developed ARDS shortly after admission to the hospital.

Yours sincerely,
R. Matz

References

1. Jakobsen J, Knudsen GM, Juhler M (1987) Cation permeability of the blood-brain barrier in streptozotocin-diabetic rats. *Diabetologia* 30: 409-413

2. Carroll P, Matz R (1982) Adult respiratory distress syndrome complicating severely uncontrolled diabetes mellitus: report of nine cases and a review of the literature. *Diabetes Care* 5: 574-580
3. Matz R, Carroll P (1982) Cerebral edema and diabetic ketoacidosis. *Ann Intern Med* 97: 141-142
4. Gunderson HJG, Christensen NJ (1977) Intravenous insulin causing loss of intravascular water and albumin and increased adrenergic nervous activity in diabetics. *Diabetes* 26: 551-557
5. DeFronzo RA (1981) The effects of insulin on renal sodium metabolism: a review with clinical implications. *Diabetologia* 21: 165-171
6. Blumenthal SA (1975) Observations on sodium retention accompanying insulin treatment of diabetes mellitus. *Diabetes* 24: 645-649
7. Fein IA, Rackow EC, Sprung CL, Grodman R (1982) Relation of colloid osmotic pressure to arterial hypoxemia and cerebral edema during crystalloid volume loading of patients with diabetic ketoacidosis. *Ann Intern Med* 96: 570-575
8. Krane EJ, Rockoff MA, Wallman JK, Wolfsdorf JI (1985) Subclinical brain swelling in children during treatment of diabetic ketoacidosis. *N Engl J Med* 312: 1147-1151
9. Carroll P, Feinstein S, Nierenberg S, Matz R (1986) The adult respiratory distress syndrome complicating diabetic ketoacidosis. *Cardiovascular Reviews and Reports* 7: 801-803
10. Arem R, Zoghbi W (1985) Insulin overdose in eight patients: Insulin pharmacokinetics and review of the literature. *Medicine* 64: 332-332

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More on the evidence for a specific heart disease of Type 1 (insulin-dependent) diabetes

Dear Sir,

We were most interested in the ensuing correspondence on this subject [1] following our paper describing the abnormalities of cardiac function in asymptomatic diabetic patients [2]. In commenting on our study, Dr. Harrower claims that neither the demonstration of abnormal ventricular function during dynamic exercise nor the presence of histological changes detected by endomyocardial biopsy support the concept of a specific heart disease in diabetes [1]. We would appreciate the opportunity to comment further.

Dr. Harrower has recently reported a study of 9 patients at the time of diagnosis of diabetes, only 5 of whom showed a change in the left ventricular ejection fraction following improvement of glycaemic control [3]. The mean resting left ventricular ejection fraction did not change. Despite the small number of patients (a criticism which he levels at our histological studies), this is consistent with the concept that the resting left ventricular ejection fraction may be influenced by hyperglycaemia.

In citing the effects of glycaemic control on left ventricular function, Dr Harrower appears however, to be unfamiliar with other publications on this topic. Goldwit et al. studied ventricular function by radionuclide ventriculography in 10 Type 1 (insulin-dependent) diabetic patients with a mean duration of diabetes of 7 years [4]. Their subjects were selected because diabetic complications were absent and it was considered unlikely that the specific heart disease of diabetes could have developed because of the relatively short duration of diabetes. Blood glucose was varied using a glucose clamp technique, and the resting left ventricular ejection fraction appeared to vary with the blood glucose; the resting left ventricular ejection

fraction was higher during hyperglycaemia. The response to dynamic exercise was similar to that of a non-diabetic control group and was unrelated to blood glucose concentration. Thus while the resting left ventricular ejection fraction may be related to prevailing blood glucose, the response to *dynamic* exercise appeared to be independent of glycaemia. Furthermore, Goldwit et al. demonstrated that the response of the ejection fraction to hyperglycaemia or dynamic exercise was not affected by 6–25 weeks of improved glycaemic control [4]. In a previous study [5] we showed that the response to dynamic exercise was normal in a group of young Type 1 diabetic patients with diabetes of short duration. In our recent study [2] we chose to examine the cardiac response to dynamic exercise which is apparently unaffected by hyperglycaemia.

Other studies have shown that the response of the left ventricular ejection fraction to dynamic exercise is abnormal in patients with longstanding diabetes [6, 7] and this was confirmed by our own investigation [2]. Two recent reports have suggested that the responses to dynamic exercise may be more abnormal in diabetic patients with advanced retinopathy [8] and autonomic neuropathy [9]. The abnormalities provoked by dynamic exercise were consistent, and were associated with the coexistence of microvascular disease.

In our study we performed endomyocardial biopsy and documented the presence of fibrosis, small vessel changes, and basement membrane thickening [2]. The sampling problems inherent with endomyocardial biopsy coupled with the small number and size of specimens, may explain why histological changes were not found in all patients. The right ventricle was biopsied because of the greater safety of the procedure compared with left ventricular biopsy. Dr. Harrower [1] states that these histological changes have been reported previously. Fischer et al. [10] obtained ventricular biopsies from diabetic patients during coronary artery bypass grafting, and observed myocardial fibrosis and basement membrane thickening. All of these patients had severe coronary heart disease unlike the asymptomatic diabetic patients in our study. None of our patients had coronary heart disease demonstrable by coronary arteriography, and none had hypertension, so no obvious pathophysiological explanation can be advanced for these histological changes except that they are a direct consequence of long-standing diabetes.

By demonstrating abnormalities of left ventricular function on exercise in diabetic patients with normal coronary arteries, and by showing histological changes in the hearts of several of these patients, we believe that our study provides substantial support for the concept of a specific heart disease in diabetes.

Yours sincerely,

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References

1. Harrower ADB (1987) More on the question of a specific heart disease in diabetes. *Diabetologia* 30: 195
2. Fisher BM, Gillen G, Lindop GBM, Dargie HJ, Frier BM (1986) Cardiac function and coronary arteriography in asymptomatic Type 1 (insulin-dependent) diabetic patients: evidence for a specific diabetic heart disease. *Diabetologia* 29: 706–712
3. Harrower ADB, Small DR, Railton R (1986) Variability of left ventricular function at diagnosis and after treatment in insulin-dependent diabetes. *Diabetes Res* 3: 149–152
4. Goldwit RS, Borer JS, Javanovic LG, Prexler AJ, Hochreiter CA, Devereux RD, Peterson CM (1985) Relation of hemoglobin A₁ and blood glucose to cardiac function in diabetes mellitus. *Am J Cardiol* 56: 642–646
5. Fisher BM, Gillen G, Ong-Tone L, Dargie HJ, Frier BM (1985) Cardiac function and insulin-dependent diabetes: radionuclide ventriculography in young diabetics. *Diabetic Med* 2: 251–256
6. Vered Z, Battler A, Segal P, Liberman D, Yershalmi Y, Berszin M, Neufeld HN (1984) Exercise-induced left ventricular dysfunction in young men with asymptomatic diabetes mellitus (Diabetic cardiomyopathy). *Am J Cardiol* 54: 633–637
7. Mildenerberger RR, Bar-Shlomo B, Druck MN, Jablonsky G, Morch JE, Hilton JD, Kenshole AB, Forbath N, McLaughlin PR (1984) Clinically unrecognized ventricular dysfunction in young diabetic patients. *J Am Coll Cardiol* 4: 234–238
8. Margomato A, Gerundini P, Vicedomini G, Gilardi MC, Pozza G, Fazio F (1986) Abnormal cardiovascular response to exercise in young asymptomatic patients with retinopathy. *Am Heart J* 112: 554–560
9. Zola B, Kahn JK, Juni JE, Vinik AI (1986) Abnormal cardiac function in diabetic patients with autonomic neuropathy in the absence of ischemic heart disease. *J Clin Endocrinol Metab* 63: 208–214
10. Fischer VW, Barner HB, Larose LS (1984) Pathomorphologic aspects of muscular tissue in diabetes mellitus. *Hum Pathol* 15: 1127–1136

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Erratum

Diabetologia, Volume 30, Number 7, July 1987, p. 554A

The following abstract was misprinted in the July and Abstracts issues of the journal. The correct version should read:

352. Combined therapy with sulphonylurea (gliclazide) and insulin for Type 1 (insulin-dependent) diabetic patients: one year follow-up

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We have recently described that the association of gliclazide (SU) for six months to the usual insulin treatment (INS) in Type 1 (insulin-dependent) diabetic patients was accompanied by a manifold improvement of diabetes control. To evaluate the persistence of such effects, we continued the study for six more months. The same dose of SU

(160 mg/24 h) was left in association with INS in 8 Type 1 diabetic volunteers and plasma glucose, other intermediate metabolites, C-peptide (CPR), glucagon (IRG) and growth hormone (GH) were measured in basal conditions and after arginine challenge (ATT). Moreover, the insulin need, HbA_{1c}, and the erythrocyte filtration index were evaluated. At the end of the 12-month trial, the plasma glucose values were maintained at the 6-month levels (mean: 12.10 ± 2.21 at time 0 vs 9.28 ± 1.77 at 6 months vs 9.56 ± 1.60 mmol/l at 12 months and the CPR was still increased (delta area: -0.14 at time 0 vs 0.93 at 6 months vs 1.18 ng/ml at 12 months. Growth hormone and IRG values were similar to those obtained at 6 months. Insulin need and HbA_{1c} were significantly decreased. Red cell deformability was improved. In conclusion, the association of SU to INS in Type 1 diabetic patients induced metabolic, hormonal and haemorheological improvements, and a reduction of insulin need, which persisted after 12 months.