study. The observation that low catecholamine increments to exercise were confined to patients with signs of cardiac autonomic neuropathy proves that employed tests adequately identified autonomic neuropathy. The observation that patients with normal cardiac autonomic neuropathy tests showed normal catecholamine increments to exercise fits well with the observation of Cavan et al. that young and uncomplicated Type 1 (insulin-dependent) diabetic patients have normal to increased increments in noradrenaline to exercise.

Cavan et al. suggested that the reduced renin response to exercise in Type 1 diabetic patients was related to an inadequate age-matching and/or the occurrence of diabetic complications. However, it is unlikely that age, nephropathy, and retinopathy were of major importance for the impaired renin response. The patient material has been re-evaluated. In keeping with the results in the whole patient material, a selected strictly aged-matched patient sub-group (14 patients aged 19 to 36 years; mean 30 ± 1 years) also showed low increments in renin activity during exercise (2.0 ± 0.5 nmol·l^{-1}·h^{-1} vs 3.7 ± 0.5 nmol·l^{-1}·h^{-1}; $p < 0.05$) compared with control subjects. An influence of diabetes duration is unlikely since there were no significant correlations between the duration of diabetes and renin values. Moreover, 11 patients without albuminuria (albumin in urine < 0.02 g/l) showed as low renin at 80% of maximal exercise as the 12 patients with nephropathy (2.4 ± 0.7 nmol·l^{-1}·h^{-1} vs 2.7 ± 0.5 nmol·l^{-1}·h^{-1}; NS) clearly indicating that diabetic patients without nephropathy also had significantly ($p < 0.05$) lower renin values at 80% of maximal exercise compared with the control subjects. Regarding retinopathy, there was a tendency though not significant for patients with retinopathy ($n = 9$) to show lower renin values at 80% of maximal exercise (2.0 ± 0.3 nmol·l^{-1}·h^{-1} vs 3.0 ± 0.7 l^{-1}·h^{-1}; NS) than patients without. However, patients both with and without retinopathy showed lower renin values at 80% of maximal exercise than control subjects ($p < 0.01$ and $p < 0.05$, respectively). The influence of diabetic control was difficult to assess. As expected, blood glucose values were higher in patients than in control subjects but the metabolic control was not particularly bad; postprandial blood glucose prior to exercise was 9.8 ± 0.8 mmol/l in the patients.

In conclusion, Type 1 diabetic patients demonstrated lower increments in renin during exercise than control subjects and the deviation was unrelated to the presence of cardiac autonomic neuropathy, disturbances in circulatory catecholamines, nephropathy, retinopathy, age, and the duration of diabetes. Whether the disturbed renin response is related to hyperglycaemia or is an intrinsic feature of Type 1 diabetes has to be elucidated.

Yours sincerely,
G. Sundkvist on behalf of my coauthors

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Evidence for lactate production by human adipose tissue in vivo

Dear Sir,

We are pleased that measurements of interstitial fluid lactate in human adipose tissue [1] confirm our finding [2], based on arteriovenous differences, that adipose tissue is a net producer of lactate in vivo. However, we find some of the comments made by Dr. Jansson and colleagues rather misleading. They describe our preparation as one of 'skin and an unknown amount of the abdominal fat'. Since both groups are studying the same adipose depot, the metabolic contribution of skin seems likely to be similar in the two preparations. We have summarised evidence that this contribution is, in fact, small [2]. Jansson et al. discuss an 'apparent difference in lactate concentration between the interstitial water and the epigastric vein'. The concentrations reported in our paper were of lactate in whole blood. Since human plasma lactate concentrations are about 40% higher than those in whole blood [3], the results are actually in very good agreement. Finally, our work is apparently criticised for lack of measurement of blood flow, although the same applies, of course, to the microdialysis measurements. We have now added the measurement of adipose tissue blood flow to our studies, and have thus been able to quantitate substrate exchanges in human adipose tissue after ingestion of a meal [4]. It is perhaps worth pointing out that a complete study of this sort requires measurement of lipoprotein triacylglycerol exchange, unfortunately not yet possible by the microdialysis technique.

Yours sincerely,
K. N. Frayn and S. W. Coppack

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Response from the authors

Dear Sir,

We are certainly familiar with the study by Frayn et al. [1] and their promising technique in measuring arteriovenous differences over the abdominal subcutaneous wall. However, one advantage with the microdialysis technique as compared to a-v measurements is that the interstitial fluid of the subcutaneous tissue reflects fat cell metabolism without the contamination of skin lactate production. We are also aware of the fact that the blood lactate is lower than plasma lactate. However, lactate production in adipose tissue averages ~1 μmol/100 g tissue which is a high production rate. In contrast, Frayn et al. stated that the lactate production in the adipose tissue is low. Thus, even though the plasma lactate levels in our study [2] and that of Frayn et al. [1] seem to be comparable the conclusions are obviously different since the lactate concentration in the extracellular water indicates that adipose tissue is an important source of production [2]. In our article we also clearly state that distinct quantifications cannot be made since the blood flow was not measured. [2] However, we have now added blood flow measurements to the microdialysis procedure which will allow more precise information. Since we have not measured lipoprotein exchange we cannot comment on the results referred to by Drs. Frayn and Coppack. However, the microdialysis technique certainly allows measurements of fairly large molecules.

Yours sincerely,
P.-A. Jansson, U. Smith and P. Lönnroth

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Immunotherapy in pre-Type 1 diabetes mellitus

Dear Sir,

During the past decade a large body of data has accumulated implicating autoimmunity in the pathogenesis of Type 1 diabetes. This has prompted research trials of immunotherapy to prevent ongoing Beta-cell destruction [1–3]. However, the effectiveness of immunotherapy initiated after the onset of clinical diabetes is limited by the extent of Beta-cell destruction which has occurred by this stage [4]. The ability to predict Type 1 diabetes in the pre-clinical stage by the combination of genetic (HLA typing), immunological (islet and insulin autoantibodies) and metabolic (first phase insulin secretion to intravenous glucose) markers, sets the scene for therapeutic intervention during the evolution of the autoimmune disease process when Beta-cell destruction is only partial [5–7]. Trials of potential therapies in this pre-clinical stage have been initiated in the USA, West Germany, Italy and New Zealand. Despite the potential to prevent a disease that may have considerable morbidity and mortality, therapeutic trials in pre-diabetic patients must be carefully controlled because the sensitivity, specificity and precision of the predictive markers are still not properly established. Such trials should therefore include randomization as well as placebo blinding where applicable. They should only be undertaken with informed consent and with oversight of Human Committees by investigators with experience in assessing the predictive markers of Type 1 diabetes and the potential therapies to be employed. Therapies aimed at the prevention of Type 1 diabetes should not be administered until control trials establish their efficacy and safety.

Yours sincerely,
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