Early Functional and Morphologic Vascular Renal Consequences of the Diabetic State

Dear Sir,

We read with interest the review article on Early Functional and Morphologic Vascular Renal Consequence of the Diabetic State (Diabetologia (1979) 17: 71–79) by Dr. Mogensen and his colleagues, but would like to comment in particular upon albumin excretion where the studies at Guy's Hospital have yielded a number of differences from those at Århus.

In contrast to Dr. Mogensen's findings we have shown [1] that mean urinary albumin excretion can be elevated under ordinary conditions of life and during conventional treatment in clinically non-proteinuric insulin-dependent diabetics with duration of disease ranging from 6 months to 39 years. This was also true for each group when the patients were divided into duration categories 0–10, 11–20, 21–39 years. Interestingly enough the group with the longest duration of disease had the smallest proportion of patients with subclinically elevated albuminuria; we speculated that this could be due to the deliberate exclusion of patients with clinical proteinuria and/or premature mortality of proteinuric patients. We have extended these observations to another 30 insulin-dependent diabetics and confirmed our original findings.

In a recent publication [2] we have suggested that, although the evidence is based on prevalence studies, Mogensen's studies would support the view of an abrupt passage from normal excretion of albumin to clinically overt proteinuria, whereas our findings would support the view of a gradual increase of albumin excretion until the appearance of manifest albuminuria. This is an important difference in considering the natural history of diabetic renal disease and also in view of the fact that subclinically elevated albuminuria can be promptly reduced by optimal glycaemic control [1]. While the Århus workers [3] have shown a reduction in albumin excretion when insulin

treatment is commenced in previously untreated patients and an increase in albumin excretion when insulin is withdrawn for some days, in our study [1] conventional blood glucose regulation was compared with optimal blood glucose control achieved by continuous subcutaneous insulin infusion (CSII). During CSII the total daily insulin dose remained unaltered in 3 patients, was reduced in 2 and was increased only in the other 2 in comparison with the daily insulin dose during conventional treatment. This suggests that our diabetics were not insufficiently treated during their conventional insulin regimen. We concluded that a change in the quality of glycaemic control can reduce the elevated capillary *glomerular* permeability to albumin, in that β_2 -microglobulin excretion (an index of tubular function) was normal both during conventional and optimal blood glucose control.

Under stress situations (e. g. physical exercise) the urinary albumin excretion becomes exaggerated even in those patients who have normal albuminuria [4, 5]. Patients with elevated resting albuminuria show higher mean absolute values after exercise, but we found [5] that the increment above baseline was not different from that of patients with normal resting albuminuria. Moreover, in our admittedly small series of 16 patients we did not find any correlation between exercise-induced albuminuria and duration of diabetes. The finding in our study [5] that the urinary excretion of β_2 -microglobulin does not increase during exercise led us to conclude that the exaggerated exercise albuminuria is due to an increased glomerular permeability. This agrees with recent findings of Mogensen et al. [6] but is at variance with the findings of Poortmans et al. [7]. As to the effect of insulin on renal albumin excretion in a recent controlled study McKay and Viberti were unable to confirm Mogensen's data (Fig. 1).

Fig. 1. Urinary albumin excretion (log scale) in 5 insulin-dependent diabetics (identified by different symbols) before insulin and after IV injection of 8–10 U of Actrapid. Both pre and post-insulin periods lasted 75 min. At the beginning of each period 200 ml of water were given by mouth. Patients $\square$ and $\blacktriangle$ were given glucose IV concurrently in order to keep blood glucose constant. Four patients also performed, in random order, a saline (0.15 mol/l) control study in which exactly the same protocol was used (right panel). No statistically significant differences were seen between pre and post injection periods either with insulin or with saline.

Finally, we would like to comment on the causes of the high GFR in diabetic patients. Mogensen's discussion of this (p. 72–73) contains a number of statements which must be questioned in the light of recent developments in the study of glomerular ultrafiltration dynamics. Although no direct data are available for man, filtration equilibrium (FE) has been shown to exist in the Munich-Wistar rat [8] and at least one primate species [9]. Filtration equilibrium is said to exist when ultrafiltration pressure (transcapillary hydraulic pressure gradient minus plasma oncotic pressure) falls to zero before the end of the glomerular capillary is reached, due to progressive haemoconcentration by abstraction of filtrate. Thus, filtration stops at some point along the length of the capillary. Since GFR is the arithmetical product of mean ultrafiltration pressure ($\overline{\text{Puf}}$), glomerular surface area (S) and a term representing the conductivity of the membrane (k), it is clear that under conditions of FE an increase in S or k or both cannot produce any further increase in GFR or filtration fraction (FF); this can *only* be achieved by an increase in $\overline{\text{Puf}}$. Even if FE does not strictly obtain in the human, a large increase in S would only lead to a small increment in GFR unless the degree of disequilibrium were very large, which is improbable. Furthermore, such a relationship would be highly non-linear, which is inconsistent with the finding that: 'a close correlation has been found between individual values of GFR and absolute filtration areas in short-term diabetics'.

How then to account for the observations of Mogensen et al.? The only hypothesis which adequately explains an increase in GFR and FF is that $\overline{\text{Puf}}$ is increased in the diabetic patient, and that this increase is proportionately greater than any associated increase in renal plasma flow. This requires an increase in efferent, and a decrease in afferent, arteriolar resistance. This will lead not only to increased $\overline{\text{Puf}}$ but also to increased *distending*

pressure. If the glomerular capillaries are compliant (as seems likely from their ultrastructure) an increase in capillary surface area would be expected, approximately proportional to the increase in pressure (and therefore to the increase in GFR).

The observation that GFR correlated with increased kidney size and weight [10] in diabetic patients is most interesting and perhaps throws further light on the nature of the process involved. The great bulk of kidney mass is tubules, glomeruli contributing but a small proportion of the total. We therefore infer that there is a proportionality between *tubular mass* and *glomerular function* in diabetes. There is growing evidence that glomerular haemodynamics are under the control of the tubule via a feedback loop operating at the point of approximation of the early distal tubule and the glomerular arterioles (macula densa and juxta-glomerular apparatus). Thus, control of GFR is mediated by changes in renal plasma flow (with proportionate changes in $\overline{\text{Puf}}$); the glomeruli are normally operating far below their maximal functional capacity to the extent that GFR can be greatly elevated above normal values simply by increasing renal plasma flow – no *structural* change is necessary.

We would, therefore, suggest the following scheme to account for the increased GFR of the diabetic patient:

- 1) Increased glucose delivery to the tubule leads to tubular hypertrophy in order to meet the increased need for glucose reabsorption.
- 2) Since glucose and sodium reabsorption in the proximal tubule are in part coupled, the obligate increase in sodium reabsorption accompanying the increase in glucose reabsorption requires that GFR increases to maintain glomerulotubular balance for salt and water – a prime requisite for survival.
- 3) The necessary increase in GFR is achieved, through tubulo-glomerular feedback, by an increase in efferent arteriolar resistance and a decrease in

afferent arteriolar resistance leading to increased $\overline{P_{uf}}$ and an increase in GFR out of proportion to any increase in glomerular plasma flow, i. e. an increase in FF.

4) The increased distending pressure causes a secondary, passive increase in glomerular surface area which, for reasons given above, does not directly contribute to the increase in GFR and FF.

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