SIR,—I was very saddened to hear of two doctors being found guilty of manslaughter following the inadvertent intrathecal administration of a drug (vincristine) intended for intravenous injection.[1] This error has occurred before in Britain, with equally tragic results, one patient being paralysed from the neck down. Although the numbers of patients involved is small, the consequences for the patients and doctors involved and health authorities paying the financial costs are so great that action must surely be taken to prevent this situation recurring.

What is needed is a physical method to prevent intravenous treatment from being given intrathecally. The problem could be solved by the development of a syringe solely for intrathecal injection with a new non-Luer lock connection. This would be available only from a pharmacy where intrathecal injections are prepared. To use this syringe would require the parallel development of either fitting lumbar puncture needles that fit non-Luer locks or new injection filters, as are usually placed between the lumbar puncture needle and the syringe, with a Luer lock fitting at the outward (lumbar puncture needle) port and a new non-Luer lock fitting at the inward port. This simple, although initially costly, development would undoubtedly save lives, careers, and money in the long run.

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1 Dyer C. Doctors convicted of manslaughter. *BMJ* 1991;**303**: 1157. (9 November.)

ACE inhibition and diabetic nephropathy

SIR,—Dr Elisabeth R Mathieson and colleagues have provided further evidence of the therapeutic potential of angiotensin converting enzyme inhibition in delaying the development of overt diabetic nephropathy, in this case in normotensive insulin dependent diabetic patients with microalbuminuria.[1]

While the currently accepted definition of microalbuminuria (30-300 mg/24 h) encompasses an albumin excretion rate ranging from the upper limit of normal to the level usually detectable as a persistently positive result on dip stick testing, most studies on the prognostic importance of microalbuminuria for diabetic nephropathy found that the best discrimination between those who did and did not progress was an albumin excretion rate some two to three times higher than the upper limit of normal.[2-4] An update of the Steno studies 1 and 2 also found that strict glycaemic control by means of continuous subcutaneous insulin infusion was effective in preventing progression to diabetic nephropathy in patients with an albumin excretion rate between 100 and 300 mg/24 h when compared with conventional insulin treatment[5]; in patients with microalbuminuria in the lower range (30-99 mg/24 h) no significant progression occurred in either group.

Although the patients in the captopril and control groups studied by Dr Mathiesen and colleagues were matched for albumin excretion rate,[1] table II shows that 14 of the control group (61%) had an initial albumin excretion rate $\geq$100 mg/24 h, compared with only six of the captopril group (29%). Although those treated with captopril undoubtedly derived benefit, a greater proportion of the control group might have been expected to progress to diabetic nephropathy because they had a higher baseline excretion, although analysis of covariance showed that this imbalance did not affect the observed difference between the two groups. It is worth noting, however, that six of the seven control patients who progressed to diabetic nephropathy were from the subgroup of 14 who had a baseline albumin excretion rate $\geq$100 mg/24 h. Conversely, only one of the nine control patients with an initial albumin excretion rate <100 mg/24 h progressed to diabetic nephropathy compared with none of the 15 equivalent patients in the captopril group.

Statistical analysis (Fisher's exact test) of the whole group shows a significant benefit of treatment with captopril on progression ($p<0.01$). Although the number of patients is small, analysis according to the baseline albumin excretion rate indicates that those patients with a rate $\geq$100 mg/24 h show benefit from treatment that just fails to reach significance ($p=0.07$), whereas there is clearly no benefit in the group with an initial rate <100 mg/24 h ($p=0.375$). This may represent the length of follow up as patients with low level microalbuminuria are presumably likely to progress to the higher level if followed up for a sufficient time.

Therapeutic intervention at this later stage of microalbuminuria—that is, at 100-300 mg/24 h—seems to be sufficiently early in the course of the disease to delay the development of diabetic nephropathy considerably and maybe even prevent it. Given that none of the possible treatments—for example, strict glycaemic control, low protein diet, converting enzyme inhibition—are without hazard, is it not time for all such studies to differentiate clearly between patients with low and high level microalbuminuria?

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1 Mathiesen ER, Hommel E, Giese J, Parving H-H. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. *BMJ* 1991;**303**:81-7. (13 July.)
2 Viberti GC, Jarrett RJ, Mahmud U, Hill RD, Argyropoulos A, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982;i: 1430-2.
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4 Mathiesen ER, Oxenboll B, Johansen K, Svendsen PA, Deckert T. Incipient nephropathy in type 1 (insulin-dependent) diabetes. *Diabetologia* 1984;**26**:406-10.
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SIR,—Dr Elisabeth R Mathiesen and colleagues provide evidence that treating normotensive diabetic patients with microalbuminuria with captopril and thiazide diuretic may arrest the progression of renal pathophysiology.[1] They are uncertain, however, whether their encouraging result was due to a reduction in glomerular capillary pressure or to improved selectivity of glomerular filtration. Deeper analysis of their data, not available in the published study, might have helped to evaluate the outcome with respect to these hypotheses.

The authors attempted to reduce diastolic blood pressure in all treated patients by 5 mm Hg with the indirect goal of reducing glomerular capillary pressure. Though they state that they failed to meet their intervention objective, half of their subjects in the treatment arm did have a reduction in diastolic blood pressure of at least the target amount over the four years (table II). A comparison between patients who did and did not respond to treatment would provide insight into the need for control of diastolic blood pressure (and concomitant control of glomerular capillary pressure) to achieve the desired outcome.

The alternative hypothesis, that the protective effect of captopril was due to its direct influence on filtration selectivity, could have been evaluated by looking for a dose-response relation between the drug treatment and the change in albuminuria. Though the authors describe their procedure for titrating the dose of captopril (and bendrofluazide, when needed) to reduce diastolic blood pressure by 5 mm Hg, no information is provided on how much medication was required for each of the patients who met the treatment goal. Consequently, the reader is unable to assess whether the renal sparing effect is proportional to the dose of captopril itself.

Research in animal models to explore the mechanism of albuminuria has yielded inconclusive results.[2,3] Consequently, I hope that re-evaluation of the data by Dr Mathiesen and colleagues may help to elucidate the pathophysiology and guide future treatment.

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1 Mathiesen ER, Hommel E, Giese J, Parving H-H. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. *BMJ* 1991;**303**:81-7. (13 July.)
2 Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 1986;**77**:1993-2000.
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SIR,—In a four year prospective study Elisabeth R Mathiesen and colleagues found that captopril significantly reduced urinary albumin excretion in normotensive insulin dependent diabetic patients with microalbuminuria whereas an increase occurred in the untreated group.[1] This was found even though the arterial blood pressure "remained constant throughout the four years, with no difference between the groups." As possible explanations for the antiproteinuric effect of captopril the authors discuss various mechanisms essentially unrelated to reduction of systemic blood pressure.

Though no significant difference in blood pressure between the two groups was found, the authors do not include the change in blood pressure in each group in their discussion. As can be calculated (paired Student's *t* test) from the detailed information in the paper, the systolic blood pressure in the group treated with captopril fell by 6 mm Hg ($p<0.03$, 95% confidence interval 1 to 11 mm Hg) and the diastolic blood pressure fell by 6 mm Hg ($p<0.001$, 2 to 10 mm Hg). No significant changes were seen in the control group. The difference (unpaired *t* test) in the reduction in diastolic blood pressure between the groups was 6 mm Hg ($p=0.07$, −1 to 12 mm Hg).

In the total population of patients (treated and untreated) blood pressure increased in 13 patients, 12 of whom also had an increase in urinary albumin excretion. Blood pressure fell or remained unchanged in 31 patients, of whom 21 also had a reduction in urinary albumin excretion. In the captopril group a significant correlation can be calculated between the reduction in urinary albumin excretion (log (excretion at follow up)−log (excretion at baseline)) and reduction in systolic blood pressure ($r=0.54$, $p<0.02$). Similar correlations exist in the group of pooled patients ($r=0.59$, $p<0.0001$) and in the control group ($r=0.58$, $p<0.01$).

It is unjustified to exclude a decrease in systolic blood pressure as the most obvious reason for the observed antiproteinuric effect of captopril.

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1 Mathiesen ER, Hommel E, Giese J, Parving H-H. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. *BMJ* 1991;**303**:81-7. (13 July.)