in animals has shown that allogeneic bone marrow transplantation can alter the course of immune mediated disorders such as lupus nephritis and diabetes mellitus.[2,3]

It is interesting to speculate that allogeneic bone marrow transplantation may have a therapeutic role in the management of serious intractable autoimmune disorders.

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Enalapril and metoprolol in diabetic nephropathy

SIR,—Dr S Björck and colleagues conclude that enalapril reduces proteinuria in patients with diabetic nephropathy by a specific action that is independent of its effect on systemic blood pressure, and they assume that the observed antiproteinuric effect of enalapril may be beneficial to the kidneys.[1] This promising finding appears to strengthen previous suggestions for using angiotensin converting enzyme inhibitors as the treatment of choice in diabetic hypertension. Nevertheless, their results should be interpreted with some caution.

Firstly, the reductions in blood pressure achieved by enalapril and metoprolol at the doses applied (with or without frusemide or hydralazine, or both) were not equal in the study. For example, the supine systolic blood pressure decreased from the baseline value by a mean of 22 mm Hg after treatment with enalapril for eight weeks and by only 13 mm Hg with metoprolol. The possibility cannot be excluded that the greater reduction in systemic blood pressure observed in the patients treated with enalapril partly caused the greater antiproteinuric effect of the drug.

Secondly, the treatment with enalapril over eight weeks caused a non-significant, but obvious and continuous, increase in serum creatinine concentration by 7·5%, whereas the concentration remained unchanged in the patients treated with metoprolol. Elevated serum creatinine concentration was a sign of worsening kidney function in these patients, even though the authors did not evaluate the glomerular filtration rate after treatment. Deterioration of renal function has been reported in some patients after the use of angiotensin converting enzyme inhibitors.[2] Enalapril may contribute to decline in renal function in certain vulnerable patients,[2] especially those receiving high doses of loop diuretics.[3]

Thirdly, the finding that treatment with enalapril over only eight weeks increased serum potassium concentration by 9% seems clinically important because such an increase could be life threatening. Regular monitoring of serum potassium concentration might be necessary during the use of angiotensin converting enzyme inhibitors.

If the ultimate aim of antihypertensive treatment is to preserve kidney function in diabetic patients with advanced nephropathy rather than only reducing the amount of proteinuria, the comprehensive results by Björck and colleagues seem to reflect a potentially harmful effect of angiotensin converting enzyme inhibitors in these patients. The benefits of long term use of angiotensin converting enzyme inhibitors compared with other antihypertensive drugs in hypertensive diabetic patients with reduced kidney function are still not clear.[4]

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SIR,—At the end of the study by Dr S Björck and colleagues patients receiving metoprolol and those receiving enalapril had similar mean arterial pressures (102 (SD 11) mm Hg *v* 99 (SD 7) mm Hg), but there was a considerable, albeit not significant, difference between the groups at the start of the study (109 (SD 10) mm Hg *v* 114 (SD 8) mm Hg, p=0·09). Consequently the reduction in mean arterial pressure in the enalapril group was more than twice that in the metoprolol group (15 mm Hg *v* 7 mm Hg).

If the decrement in blood pressure (as well as the final blood pressure) is important in reducing proteinuria then the greater antiproteinuric effects of enalapril can be explained in terms of its antihypertensive effect. Furthermore, metoprolol produced a significant reduction in systolic blood pressure only at eight weeks and did not significantly reduce diastolic pressure, unlike enalapril which significantly reduced systolic and diastolic blood pressure at both four and eight weeks. This suggests that metoprolol may not have been as effective an antihypertensive agent as enalapril, particularly during the first four weeks.

Finally, because of the significant effects on proteinuria of dietary protein restriction in diabetic nephropathy, it is important to establish that dietary protein intake did not change during the study.

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AUTHOR'S REPLY,—As both commentators point out, the baseline blood pressure was higher, although not significantly, in the patients given metropolol. This is an effect of chance in the randomisation procedure. Our goal was to achieve similar blood pressure during treatment with both drug regimens and I believe we succeeded fairly well. Unfortunately, the wrong picture was printed as figure 1 but this error has now been corrected.[1]

Using similar blood pressure control the degree of both albuminuria and proteinuria in the patients given enalapril was less than half of that in the patients given metoprolol. We concluded that this was caused by a pressure-independent antiproteinuric effect of enalapril. Many of the patients still show a reduction in proteinuria after up to 18 months' observation.

Dr Hardy asks about protein intake—there was no change in diet or in protein intake as measured by urinary excretion of nitrogen. Dr Baba and colleagues point out that the serum creatinine concentration rose in the patients given enalapril but not in those given metoprolol. This might reflect haemodynamic changes which led to the reduction in proteinuria. This is probably an early adaptation to the angiotensin converting enzyme inhibitor because, during the next four months, the serum creatinine concentration increased by 11 (SE 9) μmol/l in the patients given metoprolol and decreased 3 (SE 5) μmol/l in those given enalapril.

It is too early to conclude whether enalapril treatment protects kidney function more than metoprolol treatment in the long term. Earlier uncontrolled data that remain to be proved show that angiotensin converting enzyme inhibitors might have a specific renal protective effect.[2] Hyperkalaemia is a complication of angiotensin converting enzyme inhibitor treatment in all patients with renal failure, thus frusemide is the logical first choice in these patients to reduce the risk of hyperkalaemia. The overall reported experience with angiotensin converting enzyme inhibitors in diabetic patients, now covering more than 450 patients, is that the treatment is effective, safe, and well tolerated.[3] The lack of side effects on lipids and metabolic control and a lesser degree of orthostatic hypotension are advantages with these new drugs.

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Node negative breast cancer

SIR,—We accept the comment by Professor R W Blamey and colleagues that the Nottingham prognostic index can define subgroups of patients with operable breast cancer who have different prognoses and that these findings have been validated in Nottingham.[1] This index has, however, not achieved widespread acceptance. It is based on a combination of lymph node stage and size and histological grade of tumour. Lymph node stage in this instance is based on a triple node biopsy (that is, biopsy of a lower axillary node, an apical axillary node, and a node from the internal mammary chain) which is not a common procedure. In addition, while both the Guy's and Nottingham breast units are extremely fortunate to have histopathologists with special skills in classifying breast tumours, tumour grade can be highly observer dependent.[2]

Our review was confined to patients with node negative breast cancer.[3] Knowledge of the state of the patients' axillary nodes clearly depends on adequate dissection. Dissection was routine practice when modified radical mastectomy was the treatment of choice for operable breast cancer. But as Drs Leslie and Maher have pointed out, since the advent of breast conservation techniques, many surgeons no longer dissect the axilla.[4] We feel strongly that, particularly in younger women, knowledge of lymph node state is important to help determine whether adjuvant chemotherapy is indicated.[5]

For patients who have no affected nodes on full axillary dissection it is clearly possible to define prognostic subgroups. Using a combination of tumour size and either histological grade or S-phase fraction measured by flow cytometry three groups of patients with relapse-free survival rates of 95%, 78%, and 52% over five years can be identified.[6] We are currently validating this in a larger group of patients. Both the Guy's and Nottingham prognostic indices can potentially