treated do not take into account that the patients were older and that they were treated for too short a time. In growth hormone deficiency, as in Turner's syndrome, there are now studies clearly indicating that the two major factors guaranteeing a more successful treatment outcome are early onset of treatment allowing for longer duration of treatment and a higher dose of growth hormone.[8 9] In growth hormone deficiency, adult height in 121 subjects for males and females was −0.7 SDS compared to mid-parental target height scores −0.6 and −0.4, respectively. Both numbers indicate a much more successful therapeutic outcome, and the children reached adult heights in males of 171.6 +/− 8.2 cm and in females 158.5 +/− 7.1 cm. Total gain in height was 2.4 and 2.7 SDS respectively. The mean duration of treatment was 6.2 years—the duration of treatment was thus twice as long as the French study and the dose of treatment was also twice as much, that is, 0.3 mg/kg/week (0.9 IU/kg/week compared to 0.14 mg/kg/week). Similar conclusions can be drawn from a long term study in Turner's syndrome published by Dutch investigators.[9] These much more robust responses indicate that we should not conclude that growth hormone is ineffective when treatment offered is too late and too little.

We clearly have to hone our diagnostic criteria (evaluate IGF-1 levels) and should avail ourselves of recent advances in molecular endocrinology allowing more refined diagnosis of particular gene defects as causes of short stature.[10–12] In real estate dealings, it is "location, location, location," that counts—in growth hormone therapy it's "duration, duration, duration" that counts. That approach in conjunction with an appropriate growth hormone dose should net more encouraging results while the search for further refinement in diagnostic and therapeutic criteria continues.

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Diabetic nephropathy

New drugs can help to face a growing challenge

Nephropathy and renal failure remain a major complication of diabetes. New drugs have been developed, and clinical trials have established improved methods of preventing progression of nephropathy to end stage renal failure, yet the proportion of patients with diabetic nephropathy on chronic dialysis programmes is rising. In the United States diabetes has become the most common cause of end stage renal failure in patients starting dialysis.[1] In the United Kingdom the figures are progressively increasing. How has this come about?

There are important differences between type 1 and type 2 diabetes. Among white patients in the United Kingdom with type 1 diabetes of 15-30 years' duration, fewer than 20% will have established nephropathy.[2] This is broadly comparable to other European centres, although surveys in the United States show higher numbers and data from Sweden show lower numbers.[2] The prevalence of nephropathy is higher among patients of Asian or African-Caribbean origin. Although the proportion of patients with type 1 diabetes and nephropathy has reduced over the past 20 years, the increasing incidence of type 1 diabetes over this period will increase the absolute numbers of patients reaching end stage renal failure. In addition, patients with type 2 diabetes form a greater proportion of the population having dialysis. Some of these patients have additional pathologies, particularly renovascular disease and renal failure caused by hypertension. In patients with type 2 diabetes nephropathy is closely associated with large vessel disease. The outlook for these patients has improved as a result of interventions to reduce coronary events, notably prescription of lipid lowering treatment, aspirin, β-blockers, angiotensin converting enzyme inhibitors, insulin treatment after myocardial infarction, and, in some of the patients at highest risk, wider use of coronary revascularisation. Thus more of them survive to reach end stage renal failure. The effect of the increasing incidence of type 2 diabetes has not yet been fully felt in the United Kingdom, but this can also be expected to have a major impact. In consequence, an

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active approach to screening for diabetic nephropathy and its management is required.

Microalbuminuria is the first marker of diabetic nephropathy and is also a valuable marker of cardiovascular risk in type 2 diabetes. Albumin specific measurements are required, as measurements of urinary total protein are insufficiently sensitive. Timed overnight collections for the albumin excretion rate are the gold standard but are arduous to carry out in large populations. The ratio of albumin to creatinine is simpler, requiring patients to bring a spot urine sample (which preferably should be passed on rising in the morning) with them to the clinic. The albumin: creatinine ratio measured on such samples relates well to the timed albumin excretion rate.[3] All patients with type 1 and type 2 diabetes are advised to have an annual measurement.[1 4] As the numbers of patients with type 2 diabetes are large this will place a heavy burden on laboratories. For individual patients with type 2 diabetes with proteinuria the risk of cardiovascular death is much greater than that of developing end stage renal failure. Thus the primary emphasis here has to be on dealing with the well known cardiovascular risk factors. Preventing renal failure is an additional issue, especially in patients with greater degrees of proteinuria or declining renal function.

Management of nephropathy centres on aggressive antihypertensive treatment (target blood pressure 130/80 mm Hg) and inhibition of the renin-angiotensin system. Angiotensin converting enzyme inhibitors have an advantage over previous antihypertensive agents.[5] Micropuncture studies show that they reduce intraglomerular pressure over and above their effect on systemic blood pressure. Inhibition of the generation or action of angiotensin II may have additional advantages since angiotensin II has been shown to activate glomerular mesangial cells increasing synthesis of extracellular matrix proteins—actions mediated in part through the release of growth factors such as transforming growth factor β. In patients with microalbuminuria, angiotensin converting enzyme inhibition reduces proteinuria and tends to reduce the rate of decline of the glomerular filtration rate.[6]

Angiotensin II receptor antagonists are a recent addition to the armoury. Since these drugs act at a different point in the renin-angiotensin system they can usefully be combined with angiotensin converting enzyme inhibitors.[7] Recent trials have studied angiotensin II receptor antagonists in type 2 diabetes. In microalbuminuric patients they reduce proteinuria similarly to angiotensin converting enzyme inhibitors. Studied over two years, irbesartan reduced progression from microalbuminuria to established nephropathy.[8] Two major trials in advanced nephropathy have shown a reduction in the rate of progression to end stage renal failure compared with other antihypertensive treatments that do not use angiotensin converting enzyme inhibitors.[9 10] Losartan reduced the risk of doubling of serum concentration of creatinine, end stage renal failure, or death by 16%; irbesartan reduced risk of this composite end point by 20%. This compares with the previous work in type 1 diabetes where captopril reduced risk of doubling serum creatinine by 48%.[5]

Other randomised trials in type 2 diabetes have shown angiotensin converting enzyme inhibitors to reduce cardiovascular events.[11] The studies of angiotensin II receptor antagonists in nephropathy in type 2 diabetes did not show this benefit, perhaps because they were underpowered for the cardiac end point. The diabetic subgroup within the LIFE study, however, with greater patient numbers, shows that losartan reduces cardiovascular morbidity and mortality compared with atenolol despite similar reductions in blood pressure.[12]

In conclusion, epidemiological data identify increased numbers of patients with renal failure caused by diabetic nephropathy. These numbers are likely to increase further. Major trials show that treatment—particularly with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists—prevents progression to end stage renal failure and should be started early. A vigorous approach to screening and treatment is needed.

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Competing interests: The author was an investigator in the irbesartan diabetic nephropathy trial (IDNT) and the MARVAL trial (valsartan). He has attended meetings and lectured on diabetic nephropathy, sometimes with the support of various pharmaceutical companies.

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