- ² Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one: I: survival, causes of death and complications. *Diabetologia* 1978;**14**:363-70.
- ³ Mogensen CE. Early functional and morphologic vascular renal consequences of the diabetic state. *Diabetologia* 1979;**17**:71-6.
- ⁴ Steno Study Group. Effect of 6 months of strict metabolic control on eye and kidney function in insulin dependent diabetics with background retinopathy. *Lancet* 1982;*i*:121-4.
- ⁵ 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.
- ⁶ Mogensen CE, Vittinghas E. Urinary albumin excretion during exercise in juvenile diabetes: a provocation test for early abnormalities. *Scand J Clin Lab Invest* 1975;**35**:295-300.
- ⁷ Viberti GC, Jarrett RJ, McCartney M, Keen H. Increased glomerular permeability to albumin induced by exercise in diabetic subjects. *Diabetologia* 1978;**14**:293-300.
- ⁸ Huttunen N-P, Kaar M-L, Puukari R, Akerblom HK. Exercise induced proteinuria in children and adolescents with type 1 (insulin dependent) diabetes. *Diabetologia* 1981;**21**:495-7.
- ⁹ Koivisto VA, Huttunen N-P, Vierikko P. Continuous subcutaneous insulin infusion corrects exercise induced albuminuria in juvenile diabetes. *Br Med J* 1981;**282**:778-9.
- ¹⁰ Barratt TM, McLaine PN, Soothill JF. Albumin excretion as a measure of glomerular dysfunction in children. *Arch Dis Child* 1970;**45**:496-501.
- ¹¹ Houser M. Assessment of proteinuria using random urine samples. *J Pediatr* 1984;**104**:845-8.
- ¹² Woo J, Floyd M, Cannon DC, Kahan B. Radioimmunoassay for urinary albumin. *Clin Chem* 1978;**24(a)**:1464-7.
- ¹³ Davies AG, Postlethwaite RJ, Price DA, Burn LJ, Houlton CA, Fielding BA. Urinary albumin excretion in school children. *Arch Dis Child* 1984;**59**:625-30.

Correspondence to Dr I G Jefferson, Department of Paediatrics, John Radcliffe Hospital, Oxford OX3 9DU.

Received 11 December 1984

Commentary

V MATTI VEHASKARI

Washington University School of Medicine,
St Louis, USA

Paediatricians may not always be aware that nearly half of all diabetic children will eventually develop diabetic nephropathy. Once present, it defies all treatment progressing almost without exception to end stage renal disease. Diabetic nephropathy is rarely seen in paediatric practice because the first clinical sign of it, proteinuria, is not evident until the duration of juvenile diabetes mellitus exceeds 10 years.

The issue of diabetic nephropathy is, however, brought much closer to those caring for diabetic children by the recent findings indicating that subtle renal functional changes may be present from the very onset of diabetes. In adult diabetics, the presence of two early abnormalities seems well established. Firstly, there is an increase in the

glomerular filtration rate. Since the total number of glomeruli does not increase, some or all glomeruli must be hyperfiltrating. Secondly, although the urinary total protein excretion may be within normal limits, small increases in albumin excretion can often be documented. This 'microalbuminuria' has been shown to occur in some patients only with physical exercise, while in others even the baseline albumin excretion is slightly increased.

Two reports in this issue of the *Archives* extend these observations to the paediatric age range. Davies *et al* show that approximately one half of their diabetic children had increased glomerular filtration rates and that resting urinary albumin excretion was increased in 13 of the 83 subjects. In contrast, Jefferson *et al* were unable to confirm the increase in baseline albumin excretion in their smaller group of children, but they showed an abnormally high excretion in response to controlled exercise in 10 of 40 children.

Based mainly on experimental work, a tentative hypothesis has been put forward to explain the development of diabetic nephropathy. According to the hypothesis, hyperglycaemia or some other aspect of the metabolic disorder leads initially, perhaps via a hormonal mediator, to intrarenal haemodynamic changes and hence to an increased glomerular filtration rate. The accompanying increase in albumin excretion may result from the same haemodynamic changes. At a single nephron level, longstanding hyperfiltration is detrimental to the glomeruli, leading to gradual glomerular sclerosis and destruction; the onset of this phase is marked by the appearance of clinical nephropathy with heavy proteinuria followed by a steady decline in renal function.

The hypothesis immediately raises two important questions regarding the clinical studies. Are the patients with the subtle abnormalities the same ones who later develop diabetic nephropathy? And if so, can the progression be prevented by early intervention, for example by strict metabolic control or other manoeuvre that might abate the hyperfiltration? Preliminary data on adult diabetics suggest that resting microalbuminuria is indeed a predictor of diabetic nephropathy: similar information on exercise induced microalbuminuria is not available. Short term treatment with continuous subcutaneous insulin infusion brings both resting and exercise induced microalbuminuria towards normal, but the proof that this has anything to do with successful prevention of diabetic nephropathy must await the results of long term intervention studies. Whether the supranormal glomerular filtration rate is decreased by switching from conventional insulin treatment to continuous infusion is not clear.

In support of the hyperfiltration theory, a fascinating case report describes a diabetic with unilateral renal artery stenosis that prevented hyperfiltration from occurring in the affected kidney; at necropsy, diabetic nephropathy was found only in the opposite kidney. The lack of correlation between glomerular filtration rate and albumin excretion reported by Davies *et al*, on the other hand, is not entirely consistent with the hypothesis. Moreover, it is a common clinical experience that some diabetics with poor metabolic control never develop nephropathy while others with good balance seem destined for renal failure; clearly, hyperglycaemia cannot be the only factor. Thus, the interpretation of the clinical data in light of the hyperfiltration theory must be done with caution.

Even from a practical point of view, there would be many problems in trying to apply the new information to routine care. Identifying patients who are at risk of developing diabetic nephropathy is not as simple as might be understood from some reports. The relation between resting and exercise induced microalbuminuria in predicting diabetic

nephropathy is unclear. When dealing with borderline or minimally increased albumin excretion rates, the accepted normal range becomes important; ideally, one should utilise age and sex related values from the same laboratory recognising the logarithmic distribution of urinary protein excretion. Many patients would be difficult to classify because of fluctuations in the microalbuminuria with some values falling in the normal range, and most importantly, there is no proved effective intervention currently available for the at risk group. Screening of all diabetic children for microalbuminuria seems therefore premature.

Nevertheless, the emerging concept of diabetes and the kidney is an exciting one and shall with further research undoubtedly lead to modifications in the treatment of juvenile diabetes. If glomerular hyperfiltration does become the villain that has to be suppressed to prevent diabetic nephropathy, new innovative approaches could evolve from studies on experimental diabetes; for example hyperfiltration in animals can be reduced by low protein diet or by surgical constriction of renal blood vessels.