Microalbuminuria: How intraglomerular haemodynamic forces came to the fore

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'The world of nephrology was radically changed by this paper which introduced the revolutionary concept that intraglomerular haemodynamic forces were a key element of injury and promoted the progression of capillary damage.'

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In the late 1970s I observed that microalbuminuria in people with type 1 diabetes could be reversed quickly – in a matter of days – by a dramatic improvement of glycaemic control using a continuous subcutaneous insulin infusion system (Viberti et al, 1979). I did not have the faintest idea of what this meant or how it came about. Particularly surprising was the speed of the change at a time when, in our understanding, microalbuminuria was regarded as the functional counterpart of glomerular basement membrane thickness – a process of extracellular matrix deposition whose metabolic rates were measured in years. It was in the midst of this confusion that, in March 1981, I came across a research paper which, almost by magic, lifted the fog surrounding my observation. This paper transformed forever my thinking about the nature of glomerular disease in diabetes and indeed, in general, changed people's understanding of the mechanisms of chronic glomerular diseases and opened up therapeutic avenues which have proved highly successful in the treatment and prevention of end-stage renal failure.

This 1981 *Kidney International* paper from Thomas Hostetter and colleagues (Hostetter et al, 1981) demonstrated by direct measurement (using the micropuncture of superficial glomeruli in the Munich-Wistar rat) that the glomerular hyperfiltration of the moderately hyperglycaemic diabetic animal (a model closely resembling the condition in humans) was due in significant part to an elevation, by approximately 10 mmHg, of the pressure within the glomerulus. Tom went on to postulate that the glomerular hypertension (rather than the increase in glomerular plasma flow, the other major determinant of hyperfiltration) was the key mechanism for the initiation and progression of diabetic and, for that matter, other glomerulopathies (Hostetter et al, 1982). Importantly, from my perspective, it was a mechanism which could acutely modulate glomerular filtration of protein and albuminuria. It was subsequently shown that tight control of hyperglycaemia by insulin could indeed change glomerular haemodynamics and lower intraglomerular pressure (Hostetter et al, 1983).

Applying the animal model

At the time Tom Hostetter was working in Professor Barry Brenner's laboratory at the Brigham and Women's Hospital in Boston, Massachusetts. Barry Brenner, the senior author on the 1981 *Kidney International* paper, had been instrumental a few years earlier, in the careful and systematic description of the physiologic determinants of glomerular ultrafiltration (Brenner and Humes, 1977). I realised that Barry's laboratory was the place to go if I wanted to further my understanding of diabetic kidney diseases. I was able to visit in the summer of 1981 and watched Tom perform all the direct measurements of glomerular haemodynamics using a servo-null transducer system connected with the micropipette which, under the microscope, he had inserted into the rat superficial glomerulus. In the many meetings we had we reasoned that if his construct (derived from a rather odd animal model with visible glomeruli on the cortex surface) was correct and translatable to humans, the person with diabetes who had developed microalbuminuria, under observational conditions, would have to progress to clinical, heavy proteinuria and overt renal disease. And indeed in 1982 (Viberti et al, 1982) I was able to show, by reassessing a cohort of patients who had been painstakingly monitored and followed up over several years by Professor Harry Keen, that in type 1 diabetes microalbuminuria was a predictor of diabetic nephropathy.

I remember my time spent with Tom in Barry Brenner's laboratory as one of the most learning-intensive and exciting periods of my scientific career. Tom was not only a superb teacher of renal pathophysiology but became a friend and our friendship has lasted to this

day.

The implications of Tom Hostetter's discovery were far reaching. It followed that if it were possible to manipulate and normalise intraglomerular pressure the progression of diabetic kidney disease (which in those days was considered inevitable) would be delayed, maybe stopped, or even reversed.

In the space of a few years Barry Brenner's group went on to show, in the animal model, that inhibition of the renin–angiotensin system resulted in the correction of glomerular hypertension and that this manoeuvre prevented diabetic kidney disease (Zatz et al, 1986). The translation of these findings to the human model is one of the success stories of modern medicine. Nowadays angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the cornerstone for the treatment of diabetic nephropathy. Diabetic kidney disease is no longer a sentence of early death, disease remission is a reality for some patients, while disease regression and primary prevention are the object of intensive current investigation.

The importance of the 1981 *Kidney International* paper extended well beyond diabetes – it has been successfully applied to the management of many other chronic glomerular diseases. Tom's model of the hypothetical role of glomerular hypertension in the initiation and progression of diabetic nephropathy has become a classic (Hostetter et al, 1982). It has inspired a whole generation of researchers and has changed our understanding and treatment of chronic renal diseases for good.

Two decades later it continues to inform the work of my group, which is now concerned with the molecular effects of mechanical forces in different glomerular cell types in the attempt to discover new reversible molecular mediators of renal damage in diabetes.

The world of nephrology, which in 1981 was steeped in the realm of inflammation and immunology, was radically changed by this paper which introduced the revolutionary concept that intraglomerular haemodynamic forces were a key element of injury and promoted the progression of capillary damage. To use a soundbite much in fashion these days: it was a real paradigm-shift. Or was it? Interestingly, but perhaps not surprisingly in science, recent cellular and molecular studies, including our own, indicate that, in a variety of renal cell types, mechanical forces are potent inducers of inflammation (Gruden et al, 2005).

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