

## Demolishing the basement membrane hypothesis



Rudy Bilous

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One of the key papers which changed my life was written nearly 37 years ago in 1971. I came across this paper while I was writing my MD thesis on diabetic nephropathy. The title may seem a little obscure but it was a supremely elegant study which looked at the change in renal glomerular basement membrane width in the first few years following a diagnosis of type 1 diabetes.

At the time it was written there was still controversy over whether or not diabetes was primarily a disease of basement membranes in capillary beds. There was a theory that basement membrane thickening preceded the diagnosis of diabetes and underpinned the pathological changes. This paper showed in such an elegant way, that careful measurement of basement membrane width demonstrated complete normality at diagnosis and gradual increases over the first few years of diabetes. Thus, the paper demolished the basement membrane hypothesis and demonstrated conclusively that pathological change was a consequence of the diabetic state.

I was so stimulated by the elegance of the work that I applied for and was successful in being awarded a post-doctoral fellowship at the University of Minnesota working with Doctors Mike Mauer and Mike Steffes who had one of the few laboratories in the world engaged in this kind of renal structural analysis. Six months after my arrival, I met Ruth Østerby herself and developed a close collaborative working relationship which lasted for many years until her retirement. I have continued in this line of research ever since. Finally, in the second year of my fellowship my family doubled with the birth of my son. I can think of few other papers that have been intimately associated with so many personal life changes.



**1** This paper reported an extension of a previously published quantitative electron microscopy study of the glomerular basement membrane in ‘juvenile diabetes’.

**2** The author studied the glomerular basement membrane in three groups of individuals with diabetes aged from 13–34 years all of whom were insulin dependent and compared the results with a control group.

**3** Group 1 comprised seven individuals with recent onset of diabetes. Biopsies of the kidney were taken upon admission to hospital before normalisation of blood sugar levels and again following intensive treatment (with diet and insulin) for approximately one month. Group 2 comprised five

of the cases in group 1 who had another biopsy 1.5–2.5 years later. Group 3 comprised eight people who had a duration of diabetes of 3.5–5 years.

**4** The control group comprised five age-matched individuals with normal fasting glucose levels and OGTTs. They had no history of kidney disease and had normal parameters of kidney function.

**5** All individuals in the study were normotensive and had a serum creatinine within the normal range. All those in whom endogenous creatinine clearance was measured were within the normal range.

**6** Measurements of the basement membrane were obtained from photomontages of cross sections produced from electron micrographs. In total there were 83 glomeruli measured from people with diabetes.

**7** In biopsies from group 3, it was noted that the frequency distribution curves of the glomeruli were significantly different from the

controls ( $P < 0.001$ ).

**8** In biopsies from group 2, a significant increase in basement membrane thickness was also seen compared with group 3 ( $P < 0.005$ ).

**9** In group 1 the thickness of the membrane is identical in the untreated and normalised states.

**10** Because Group 2 is made up of biopsies from people in group 1 in subsequent years, membrane thickness can be compared in these individuals.

**11** There was a highly significant increase in membrane thickness over the first 2 years of diagnosis from normal thickness at onset ( $P < 0.005$ ).

**12** These results support the view that ‘angiopathy develops as a consequence of the metabolic derangement’ and of basement membrane thickening.

Østerby R (1972) Morphometric studies of the peripheral glomerular basement membrane in early juvenile diabetes. 1. Development of initial basement membrane thickening. *Diabetologia* **8**: 84–92

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