

# Genesis and evolution of diabetic nephropathy

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The kidney disease of diabetes has a devastating effect on survival, particularly evident in diabetics of youthful onset and therefore mainly, though not exclusively, in the insulin-dependent patient.<sup>1,2</sup> The development of intermittent proteinuria in the young, insulin-dependent diabetic, which becomes continuous after 15 years or so of diabetes and which is followed a few years later by the steady, apparently irreversible progression to terminal renal failure, is so commonplace that it can almost be regarded as the natural history of diabetes.<sup>3</sup> However, this is an inadequate and misleading paradigm. Recent clinical observations and experimental findings<sup>4</sup> justify a more optimistic view and demand a more active approach, not only to diabetic nephropathy but also to the whole spectrum of the so-called specific complications of diabetes mellitus.

Demonstrable renal abnormality occurs very early in the course of diabetes—in the first months, weeks, or even days after a well-defined clinical onset of the disease. The three phenomena which have attracted most attention in this early phase are hyperfiltration—that is, a raised glomerular filtration rate (GFR),<sup>5</sup> microproteinuria expressed by increased urinary albumin excretion,<sup>6,7</sup> and generalised kidney enlargement.<sup>8</sup> All these changes have been documented in spontaneous diabetes in man and in experimental diabetes in animals. Their pathogenesis, their interrelations, and their possible roles in the later development of clinical nephropathy and renal failure in diabetes have been the subject of intense research and debate. Some pieces of the puzzle fit together but others are still missing (Table).

## *Renal abnormalities in diabetes mellitus*

<i>Phase 1: Functional</i>	<i>Phase 2: Structural</i>	<i>Phase 3: Clinical</i>
Hyperperfusion	Basement membrane thickening	Macroproteinuria.
Microproteinuria	Mesangial expansion	High blood pressure
Nephromegaly	Glomerular arteriolar change	Decline in glomerular function
		Progressive renal failure

In general, there is progression from one phase to the next. Determinants of the rate of progression are poorly understood. Transition from phase 2 to phase 3 occurs only in approximately one third. Phase 1 is reversible, phase 3 (at present) is not. Reversibility of phase 2 is unknown.

## *Microproteinuria*

Our interest in the mechanisms and evolution of diabetic kidney disease was prompted by observations on urinary albumin excretion rates in newly detected glucose-intolerant and diabetic people after a diagnostic survey for diabetes in the town of Bedford in 1962.<sup>9</sup> As part of a long-term, prospective study of a cohort of these newly-found hyperglycaemic subjects a specific and sensitive radioimmunoassay for human urinary albumin was developed,<sup>10</sup> on the assumption that sequential measurement of urinary albumin excretion rates would provide a sensitive detector of the onset and rate of evolution of diabetic kidney disease. However, the newly detected hyperglycaemic subjects showed significantly increased urinary albumin excretion compared with normoglycaemic subjects even at the time of diagnosis,<sup>11</sup> though the increase was well below the threshold of sensitivity of standard tests for proteinuria. The degree of "microalbuminuria" was positively correlated with the degree of glucose intolerance, and it was independently correlated with the level of arterial pressure.

We proposed that the excessive microproteinuria was the urinary counterpart of the thickened glomerular basement membrane which characterises diabetic nephropathy morphologically and is thought to be responsible for the abnormal permeability to macromolecules such as plasma albumin. It seemed likely that measuring the albumin excretion would provide a highly convenient and ethically acceptable substitute for repeated renal biopsy to follow the natural history of diabetic nephropathy from its earliest stages.

These suppositions have proved almost entirely false. It was shown in a series of elegant studies<sup>12</sup> that no measurable thickening of the glomerular basement membrane occurred for the first year or two after diagnosis of insulin-dependent diabetes. Nevertheless, significant microproteinuria could be demonstrated during this very early phase<sup>7,13</sup> and it could be provoked by inducing diabetes in rats with streptozotocin.<sup>14</sup> It was also shown that the rate of urinary albumin excretion in man could be rapidly influenced by the degree of metabolic control of the diabetes.<sup>15</sup> In our own studies in a group of insulin-

dependent diabetics with microproteinuria, the near normalisation of glycaemia, obtained by the use of continuous subcutaneous insulin infusion (CSII),<sup>16</sup> led to a prompt fall of urinary albumin excretion rates towards or even into the normal range.<sup>17</sup> In another group of insulin-dependent patients whose urinary albumin excretion at rest was in the normal range, exercise induced an increase considerably above normal and this "unmasked" proteinuria was also corrected by CSII.<sup>18</sup> Tubular function was very unlikely to be implicated in this fall in urinary albumin excretion as urinary  $\beta_2$ -microglobulin excretion, a good index of tubular function,<sup>19</sup> did not alter. The speed with which the abnormal albumin excretion was normalised virtually precluded structural "recovery" of basement membrane thickening as a feasible mechanism and suggested the search for some functional explanation for the variation in glomerular permeability. Although the basement membrane is not thickened early in diabetes, it is increased in quantity as a result of the enlargement of the glomerular tuft and elongation of glomerular capillary loops<sup>20 21</sup> as part, and perhaps a disproportionately large part, of the general renal hypertrophy. It is difficult, however, to ascribe the increased proteinuria to this increase in basement membrane,<sup>22</sup> let alone to countenance prompt regression of the latter to explain the fall in the albumin excretion rate. The dissociation of the renal hypertrophy from other renal haemodynamic responses to metabolic perturbations (see below) further detracts from the "structural" explanation and favours the "functional."

#### *Nephromegaly*

Renal hypertrophy is to be found early in spontaneous diabetes in man,<sup>8</sup> perhaps affecting the glomerular tufts disproportionately,<sup>20</sup> and in the rat made diabetic experimentally; in the latter<sup>23</sup> the degree of nephromegaly is related to the level of hyperglycaemia,<sup>24</sup> and glomerular hypertrophy outpaces overall renal enlargement.<sup>25</sup> In the experimental animal, the development of nephromegaly may be inhibited by strict control of the blood glucose concentration,<sup>23 26</sup> and in man it can be reduced by effective treatment.<sup>8</sup> As in the case of compensatory renal hypertrophy that occurs after unilateral nephrectomy, diabetes first induces cellular hypertrophy and then cellular hyperplasia,<sup>27</sup> but in some other respects the processes differ. Unilateral nephrectomy in the diabetic animal accelerates the morphological glomerular changes of diabetes in the remaining kidney, probably by way of altered glomerular haemodynamics, namely increased glomerular blood flow and intraglomerular capillary pressure.<sup>28</sup>

#### *Hyperperfusion*

The early and sometimes very striking increase in the glomerular filtration rate (GFR) found in early diabetics of all ages was first noted in diabetic children,<sup>29</sup> and has subsequently been abundantly confirmed.<sup>5 30</sup> GFR is dependent on renal plasma flow, on the pressure gradient across the glomerular barrier, and on the surface area and permeability characteristics of the barrier itself. Though initially disputed, it now appears to be agreed that in insulin-dependent diabetes renal plasma flow is increased along with the raised GFR<sup>31 32</sup> and so probably contributes to it; how direct this relation is remains questionable.

There is experimental evidence in animals of an increase also in the pressure gradient across the capillary membrane, though observations are scanty and it is not yet clear whether the raised pressure gradient is attributable to an increased intraglomerular capillary pressure, a lowered Bowman space/tubular pressure, or to both.<sup>33 34</sup> The filtration surface is also increased due to hypertrophy, though this may not necessarily affect the GFR. If the progressive increase in the plasma protein concentration that occurs as the blood traverses the capillary ultimately balances the hydrostatic filtration pressure, so that filtration ceases before the distal end of the capillary is reached, then further capillary elongation or dilatation per se would not increase filtration.<sup>35</sup> As to the permeability characteristics of the glomerular barrier itself and the hormonal and metabolic factors which affect it in diabetes, there is at present little solid information.

#### *Mechanism of renal hyperfunction*

The prompt reversal of the early renal dysfunction of diabetes which can be achieved by greatly improving metabolic control suggests a causal role for one or more of the related circulating substrates, metabolites, or hormones which characterise the uncontrolled diabetic state—for example, hyperglycaemia, raised fatty acids, abnormalities of ketones and aminoacids, insulinopaenia, raised concentrations of glucagon, growth hormone and catecholamines. Several of these factors have been studied experimentally in man. Raised blood glucose concentrations both in normal subjects and in well controlled diabetics led to a significant increase in GFR and renal plasma flow. The infusion of glucagon into moderately controlled insulin-dependent patients had a similar effect.<sup>32 36</sup> Conversely, insulin infusion in the insulin-dependent patients evoked a fall of the raised GFR and renal plasma flow, though not to normal levels; these effects appeared to be related to the fall in the blood glucose concentration as they were prevented by a

simultaneous glucose infusion. Relatively brief intravenous infusion of growth hormone in normal subjects had no effect on the GFR though repeated intramuscular injections for four days increased it.<sup>37 38</sup> At least part of the increased filtration rate is independent of renal hypertrophy, as Christiansen *et al*<sup>32</sup> found that the imposition of strict metabolic control in nine newly diagnosed insulin-dependent diabetics led within one week to a mean 17% reduction in the raised GFR without significant reduction in the size of the enlarged kidneys. Renal hypertrophy may, however, account for the failure of the GFR to fall completely to normal in the relatively short term.

#### *The transition to clinical nephropathy*

The link, if any, between the early phenomena described above and the ultimate development of heavier proteinuria followed by progressive impairment of renal function remains speculative. A plausible hypothesis invokes a cumulative damaging effect of prolonged hyperfiltration on the structural integrity of the glomerular capillary wall and the mesangium.<sup>4</sup> Such progressive damage, probably attributable to hyperfiltration, was demonstrated experimentally. In rats, removal of the right kidney coupled with infarction of approximately five-sixths of the other by means of arterial ligation led initially to a large increase in single nephron GFR in the remaining parenchyma, followed by proteinuria, deposition of macromolecules and mesangial expansion.<sup>39</sup> Later, there was a progressive decline of residual function. The increased filtration drive was generated by increased glomerular plasma flow and transglomerular filtration pressure. Alteration in permeability and selectivity of the glomerular filtration barrier may also contribute to the proteinuria and the subsequent progressive glomerular destruction and failure. Applied to man, however, this hypothesis leaves unexplained the fact that, although all diabetics are theoretically subject to this long-term hyperfiltration, only one in three insulin-dependent diabetics will develop renal failure. However, in practice a proportion of such diabetics, even when imperfectly controlled, are found to have a normal GFR (unpublished observations). In addition, factors in the renal interstitium and vasculature may be crucial determinants.<sup>40 41</sup>

#### *Progression of renal failure*

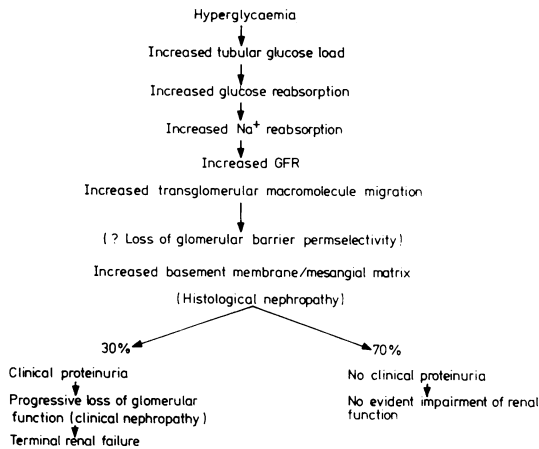
About one-third of patients who develop insulin-dependent diabetes before the age of 30 years will develop clinically demonstrable proteinuria after having the disease for about 20 years (though with wide variability about this mean). The prognostic import of the appearance of clinical proteinuria

(> 0.5 g/24 h) is grave, cohort studies suggesting a mean survival of approximately seven further years.<sup>1 2</sup> The rate of progression to renal failure varies considerably from patient to patient but for any individual it is strikingly linear.<sup>42</sup> The rate of decline has been asserted to correlate with the initial arterial pressure<sup>43</sup> though this has not been a universal experience.<sup>44 45</sup> In one large unselected group of patients with clinically evident diabetes, the mean arterial pressure in those with proteinuria was significantly higher than in those without proteinuria,<sup>46</sup> however, the arterial pressure of the group as a whole differed little, if at all, from that of large samples of the general non-diabetic population after allowing for the effects of age and sex. This suggested that the chance occurrence of a raised blood pressure in a diabetic might determine more rapid or more severe evolution of nephropathy. Nevertheless it is unquestionable that once nephropathy is established in the diabetic it will itself raise arterial pressure, which may then accelerate the decline in renal function. The rate of deterioration of function in such patients may be significantly slowed by vigorous and effective treatment of hypertension.<sup>47 48</sup>

Little else appears to affect the rate of the inexorable downhill course.

Disappointingly, the institution of "tight" metabolic control of diabetes with CSII, resulting in marked improvement in prevailing levels of glycaemia throughout the day and night, was found not to slow the rate of progression in six diabetics with nephropathy over a period of six months.<sup>45</sup> It appears that although metabolic disorder may well initiate nephropathy it plays little, if any, part in determining the rate of decline in renal function, at least once a fall in GFR has become apparent. At this stage, the remaining functional nephrons may be subject to conditions similar to those of the residual kidney in the experiments by Brenner referred to above,<sup>39</sup> namely intense hyperperfusion which itself damages and then destroys the glomeruli. Perhaps radical changes in the composition of the diet and reduction of solute load might slow the rate of decline in the human diabetic, as in the experimental animal.

The concept of feedback regulation of glomerular dynamics by tubular events<sup>49</sup> is relevant to the functional derangement of the diabetic kidney. Hyperglycaemia leads to an increased filtered load of glucose and hence to increased tubular reabsorption of glucose. There will be an associated increase in sodium reabsorption since the proximal tubular reabsorption of glucose and sodium are to some extent coupled, possibly related in hyperglycaemia, to reduced tubular reabsorption of phosphate.<sup>22 50</sup> The known close relation between sodium



*A hypothetical scheme relating the early "metabolically sensitive" changes in the diabetic kidney to the late irreversible structural changes.*

reabsorption and GFR suggests that the former may have an important role in regulating glomerular filtration, probably by way of some humoral regulator(s). A simplified hypothesis summarising such a sequence is illustrated in the Figure. Normalisation of glycaemia by vigorous treatment would rapidly arrest the surfeit of tubular glucose and the associated increased sodium reabsorption, thereby reducing the tubuloglomerular signal and restoring a normal GFR. The nature of this putative tubuloglomerular signal is obscure but is currently being investigated. Whether the early variations in urinary albumin excretion rate which appear to parallel changes in GFR can be attributed simply to alterations in glomerular haemodynamics or whether some metabolic effect on the permselectivity of the glomerular barrier is also involved is at present obscure. The charge characteristics of the barrier, an important determinant of permselectivity,<sup>51</sup> depend upon the local secretion of sialoproteins, a function which could be critically influenced by metabolic status—for example, the normal repulsion of the negatively charged albumin particle may be reduced, resulting in increased penetration of albumin into and through the barrier. There is some experimental evidence of diminished sialoprotein content of the diabetic kidney<sup>52 53</sup> though this mechanism may be more important in determining the heavier proteinuria of the later stages when nephropathy is clinically evident.

The clinical attack upon diabetic nephropathy is thus still confronted by problems and paradoxes. How are the early phenomena, characterised by hyperfunction and reversibility with metabolic correction, related to the late abnormalities

characterised by hypofunction and apparent unresponsiveness to tight diabetic control? What distinguishes those diabetics with the early phenomena who go on to clinical proteinuria and renal failure from those who do not? At what point in the evolution of nephropathy does its course become uninfluenced by the correction of the metabolic abnormality? What are the minimal levels of metabolic control which might confer some protection upon the patient? Are there other non-metabolic measures, perhaps pharmacological, which might delay the progression of renal disease? Apart from blood pressure control, might there be other ways to slow the erosion of renal function during the terminal progression to renal failure? Though the prospect for longer term dialysis and renal transplantation for diabetics in renal failure has improved considerably, it remains a formidable undertaking, and the prevention of kidney damage and the conservation of renal function must be a major priority in the care of the diabetic.

We acknowledge the valued support for some of the studies described from the Wellcome Trust, the Medical Research Council, the National Medical Research Foundation and the British Diabetic Association. We are also particularly grateful for the skilled technical assistance we have received from Mr D MacIntosh and Ms Andrea Collins and to the many diabetic patients who have patiently and enthusiastically co-operated in our research.

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