

Brenner B M, Meyer TW & Hostetter T H. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N. Engl. J. Med.* 307:652-9, 1982. [Laboratory of Kidney and Electrolyte Physiology and Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA]

This essay addressed three fundamental questions seldom considered explicitly heretofore, namely: Why are humans endowed with many more nephrons than required to preserve the *milieu interieur*? Why do human adults undergo age-related declines in renal blood flow, glomerular filtration rate, and progressive glomerular sclerosis? and: Why is renal disease inexorably progressive? [The SC® indicates that this paper has been cited in more than 865 publications.]

Three Questions in Nephrology

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The novel insight advanced to answer all three questions is that a fundamental mismatch exists between the evolutionary driven design characteristics of the human kidney and the functional burden imposed by modern ad libitum eating habits. Our prior studies led us to believe that sustained rather than intermittent excesses of dietary protein, and perhaps other solutes, impose similarly sustained increases in renal blood flow and glomerular filtration rate, requiring that the glomeruli of the kidney, designed for large meals eaten intermittently, now are burdened more or less continuously and near-maximally. In turn, average pressures and flows in these glomeruli become increased (acquired intraglomerular hypertension) and lead even in healthy adults to progressive glomerular sclerosis and moderate loss of renal function (most apparent after age 60). We hastened to add that the biologic price of this renal adaptation to modern ad libitum feeding is acceptable except in those with preexistent glomerular hypertension and hyperfiltration, i.e., individuals with diabetes mellitus, intrinsic renal disease, or surgical loss of renal mass. In these latter subjects, there is now considerable evidence to indicate that this added hemodynamic burden accelerates the loss of renal function and places many at risk for end-stage renal failure.

T. Addis, in his milestone treatise in 1946, argued from personal clinical experience that reduction in renal "work" by judicious dietary protein restriction was effective in minimizing further loss of renal function in patients with chronic renal insufficiency of diverse etiologies.¹ The "workload" hypothesis subsequently proved erroneous. On the other hand, our work in rodents with surgical loss of renal mass or diabetes as causes of progressive renal injury showed that acquired intraglomerular hypertension is a common abnormality and that its prevention by dietary protein restriction or selected classes of antihypertensive drugs, i.e., angiotensin converting enzyme (ACE) inhibitors, thwarts this tendency to progressive renal damage.^{2,5}

Since we initiated these studies in the early 1980s, the "hyperfiltration theory" has been the subject of intense interest from laboratory and clinical investigators in nephrology and hypertension worldwide. It has been estimated that, by 1985, more than half the abstracts in the chronic renal failure section submitted to the annual meeting of the American Society of Nephrology (which is, in reality, international in scope), dealt with mechanisms of progression of renal disease. From these efforts, the pathways implicated to explain progressive renal injury have expanded to include activation of endogenous vasoactive agents (i.e., angiotensin II, thromboxanes, endothelins, nitric oxide), cytokines and growth factors (i.e., interleukin-1, tumor necrosis factor, insulin-like growth factor-1, epidermal growth factor), excess dietary lipids, and intrarenally generated free radicals, among others. These studies have also motivated the design and execution of many prospective clinical trials of reno-protective strategies such as dietary protein restriction and antihypertensives, particularly ACE inhibitors and calcium channel antagonists. Although firm conclusions are not yet warranted, the preliminary impressions of trials reported thus far largely confirm the successes obtained in animals. Thus, the goal of preventing or at least slowing the otherwise inexorable progression of renal disease may be nearer at hand than many would have predicted even a decade ago.

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