Big Problems from Little Kidneys

A review of: Keller G, Zimmer G, Mall G, Ritz E, Amann K 2003 Nephron number in patients with hypertension N Engl J Med 348:102–108

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DEVELOPMENT OF THE human kidney begins at about 5 weeks fetal age when the ureteric bud, an outpouching of the nephric duct, grows into the metanephric mesenchyme and begins to branch. Iterative interactions between each new branch tip and the adjacent mesenchyme generate the nephrons of each kidney. At birth, this crop of nephrons hangs like fruit on branches of the arborized collecting system and constitutes the individual's nephron endowment for life. Occasionally, when the process goes awry, neonates may be born with obvious hypoplasia (1:400) or aplasia (1:3600) of at least one kidney (1, 2). Very rarely, children are born with hereditary syndromes (e.g., renal-coloboma syndrome) in which congenital bilateral nephron deficit is associated with progressive renal insufficiency (1, 3).

While our medical paradigms easily accommodate these developmental "errors", we tend to accept as "normal" the wide variance in nephron number (0.3 to 2.0 million nephrons per kidney) reported from autopsies of adults who die from non-renal causes (4, 5). Yet, since 1988, Brenner and colleagues have challenged this notion, proposing that "normal" humans born at the lower end of the nephron endowment scale are predisposed to "essential" hypertension (6). They hypothesized that signals driving compensatory hypertrophy of the few overworked nephrons cause glomerulosclerosis and a cycle of subtle, slowly progressive renal dysfunction (7). Their hypothesis is supported by studies showing lower nephron number in inbred hypertensive rats compared to normotensive control strains (8) and showing that longevity of transplanted rat kidneys was influenced by allograft nephron number (9). However, it has been understandably difficult to gather evidence that suboptimal nephron endowment has any clinical consequence for the "normal" human population.

In this context, the recent article by Keller *et al.* (10) is important. The authors used a careful, well-validated method for measuring whole-kidney nephron number in autopsies on 10 German subjects with clear evidence of primary hypertension vs 10 control subjects, closely matched for gender, age, height and weight. The subjects were less than 60 years old, after which glomerular obsolescence might confound the issue. On average, the hypertensive subjects had 46.6% fewer nephrons per kidney than controls. The kidneys of hypertensive subjects also had larger glomeruli (glomerular volume = 233% of controls) – enough compensatory hypertrophy to restore total glomerular volume per kidney to baseline. As predicted by Brenner's hypothesis linking suboptimal nephron number, compensatory glomerular hypertrophy and progressive glomerular damage, there was also more glomerulosclerosis in the affected kidneys (5.5% vs. 0%).

Although their patient sample was small, the observations by Keller *et al.* provide clear support for Brenner's hypothesis and demand our attention. Children born with fewer nephrons may not only be at greater risk for essential hypertension but presumably have less renal reserve to contend with diabetes, glomerulonephritis and other acquired nephropathies later in life. Recently it was shown that low birth weight (<2.5 kg) is associated with a 13% reduction in nephron number (11). Perhaps even more significant is the observation in rodents that nephron number is reduced (20%) by moderate maternal vitamin A deficiency (12). If this observation is translatable to humans in developing countries such as India (population = 1 billion), where up to 20% of pregnant women are vitamin A deficient, the public health implications of a nutritional cause for suboptimal nephron endowment are staggering.

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