On uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka

To the Editor: We read with great interest the above article,[1] in which the authors had accrued data from a population survey of chronic kidney disease (CKD) in a rural population in Sri Lanka. Our experience in Singapore in the 1970s[2] was very similar to the Sri Lankan study in which Lim *et al.*[2] conducted a community survey of the population. The prevalence of proteinuric CKD was also low, i.e., 0.63%.

For 1983, our Renal Registry recorded about 40% of uncertain etiology; these were mainly patients with proteinuric CKD with bilateral contracted kidneys, probably due to mesangial proliferative glomerulonephritis (GN) or reflux nephropathy. We also documented low-molecular-weight proteinuria in these patients.[3]

The Hygiene Hypothesis proposes that early and frequent exposure to bacterial and other antigens occurring in less developed or developing countries leads to a T-helper-1 phenotype response that predisposes to mesangial proliferative GN.[4] Singapore and the surrounding Asian countries all had a high prevalence of mesangial proliferative GN in the 1970s. This would explain the similarity in the uncertain or unknown etiology pattern of proteinuric CKD between rural Sri Lanka and non-urbanized Singapore in the 1970s.

On the basis of our local experience, we would suggest that this group of patients in Sri Lanka could be in the same category as our 40% of unknown causes of end-stage renal failure in the 1970s in Singapore, where the majority probably had mesangial proliferative GN. We postulate that the Sri Lankan farmers could have had exposure to an infective rather than a toxic etiology based on the Hygiene Hypothesis.

1. Athuraliya NTC, Abeysekera TDJ, Amerasinghe PH *et al.* Uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka. *Kidney Int* 2011; **80**: 1212–1221.
2. Lim CH, Woo KT, Chan YW *et al.* 1975 Health Survey: prevalence of urinary abnormalities in the population. *J Med Assoc Thailand* 1978; **61**: 229.
3. Woo KT, Lau YK, Lee GSL *et al.* Pattern of proteinuria in IgA nephritis by SDS-PAGE: clinical significance. *Clin Nephrol* 1991; **36**: 6–11.
4. Hurtado A, Johnson RJ. Hygiene hypothesis and prevalence of glomerulonephritis. *Kidney Int* 2005; **68**: S62–S67.

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The Authors Reply: We are happy that our paper[1] has generated interest among other scientists.[2] Certainly, the topic of chronic kidney disease with uncertain etiology (CKDu) is gaining wider attention in the region and worthy of looking at multiple factors that may be responsible.

In the letter written by Woo *et al.*,[2] paragraph 4 lacks clarity, in the light of the content given in paragraph 2. For instance, the 40% end-stage renal failure was in 1983 and not in the 1970s. Furthermore, we believe that the notion of mesangial proliferative glomerular nephritis of patients reported in the registry of 1983 is not well supported. The relevance of the reference[3] that refers to immunoglobulin (Ig)A nephropathy and membranoproliferative glomerular nephritis is not clear either.

Although the hygiene hypothesis is indeed an interesting suggestion, the histopathology of kidneys of patients with CKDu in Sri Lanka indicates a tubulointerstitial disease with negative immunofluorescence for IgG, IgM, and complement 3 as described in the paper.[1,3] Therefore, we are more inclined to favor a toxic etiology given the current observations.

1. Athuraliya NTC, Abeysekera TDJ, Amerasinghe PH *et al.* Uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka. *Kidney Int* 2011; **80**: 1212–1221.
2. Woo K-T, Choong HL, Tan HB *et al.* On uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka. *Kidney Int* 2012; **81**: 1277.
3. Nanayakkara S, Komiya T, Ratnatunga N *et al.* Tubulointerstitial damage as the major pathological lesion in endemic chronic kidney disease among farmers in North Central Province of Sri Lanka. *Environ Health Prev Med*; doi:10.1007/s12199-011-0243-9.

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The more or less 'pristine' renal allograft biopsy

To the Editor: The study of Naesens *et al.*[1] presents compelling evidence that with routine pathological evaluation of renal allograft biopsies pathologists are often unable to detect ongoing immunological injury that is likely responsible for the 'inevitable destiny' of renal allografts (i.e., chronic failure).[2] The challenge to morphologists is indeed formidable, considering the multitude of possible pathways of injury: specific and nonspecific, acute and chronic, infectious, hemodynamic, mechanical, toxic, etc.