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Continued overleaf

Chronic kidney disease of unknown aetiology in the North Central Province of Sri Lanka: trying to unravel the mystery

The 'battle' over establishing the cause of chronic kidney disease of unknown aetiology (CKDu) in the North Central Province (NCP), the seat of Sri Lanka's ancient civilisation, has been highlighted in many newspapers, television and radio programmes in recent years. Whilst impartiality in media reports sounds good in principle, and is appropriate for many subjects, it can misrepresent science unless genuine equipoise exists [1]. Because media reports about science can affect an individual's health and environment, the media also have a duty by the public to report science accurately, in a manner that fairly represents the weight of evidence. To enable this, scientists must take responsibility in allowing high quality evidence to develop over time, come to a consensus and make statements with a good degree of certainty.

Ever since CKDu became an issue in the NCP, many experts have worked to both investigate and treat patients as well as to identify associated risk factors and possibly its cause. In 2008, the World Health Organisation together with the Epidemiology Unit of the Ministry of Healthcare and Nutrition developed a draft research proposal to provide a framework for a programme of research activities, the main aim of which was to estimate the prevalence and identify the determinant(s) of CKDu. This research programme discouraged other scientists exploring the issue to the detriment of scientific enquiry and the wellbeing of residents in the NCP. As we approach the end of 2011, there is still little scientific evidence of the determinants of kidney disease or its aetiology.

Given the widespread discussion and debate in the media recently, it is timely that the available, credible, scientific evidence on CKDu (published in peer reviewed journals) is collated and analysed, and the difficulties faced in establishing causality are discussed.

Bibliographic computerised searches using the Ovid search engine located 12 articles on CKDu published in peer-reviewed scientific journals. In 2009, Athuraliya *et al* described CKDu patients as being predominantly young males from low socio-economic farming communities; patients presented with non-specific symptoms, mild proteinuria and had bilateral echogenic small kidneys on ultrasound examination [2]. However, this year, the same group reported the occurrence of proteinuric-chronic kidney disease in the NCP to be strongly associated with an age over 60 years and farming; specific risk factors were not identified in 87% of the patients [3]. A possible association between CKDu and exposure to organophosphate pesticides was reported in 2006 [4]. A later study found evidence of clustering suggesting an environmental aetiology, and reported that a family history of renal disease, using ayurvedic medications and snakebite were significant predictors of

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CKDu (5); being a farmer, using pesticides and drinking well water were also associated with CKDu [5]. Nanayakkara *et al* reported evidence of familial clustering of patients suggestive of a polygenic inheritance pattern comparable to that associated with multifactorial diseases [6]. They also demonstrated that renal tubular damage occurred at a very early stage of CKDu [6]. Another recent study found that hypertension, diabetes mellitus, urinary tract infections, drinking well water in the fields, smoking and pesticide spraying were significantly associated with microalbuminuria [7]; pesticide spraying appeared less common in patients with CKDu, and this may have been due to a selection bias where patients with CKDu may not have been involved in recent spraying activity due to ill health.

From the time an environmental aetiology was first suggested several investigators have attempted to identify the agent(s) responsible with a particular focus on medical and geomedical studies. Much attention has been drawn to cadmium (Cd). In 2008, Bandara *et al* provided evidence of NCP residents being exposed to high levels of Cd from reservoir water, irrigated rice, lotus rhizomes, freshwater fish and milk from cows reared in Cd-contaminated pastures [8]. In 2010, they claimed that dietary Cd was the cause of CKDu [9]. Their findings have been challenged; Chandrajith *et al* [10] reported that the Cd content in water sources and rice from affected regions was much lower than the levels found by Bandara *et al* [8, 9], and also showed that urinary Cd excretion was low in both CKDu patients and asymptomatic individuals from endemic and non-endemic (Kandy) areas. Nanayakkara *et al* too demonstrated low urinary Cd excretion in both CKDu patients and their unaffected relatives compared to Japanese controls [6]. More recently, Chandrajith *et al* investigating water sources in CKDu affected regions found moderate to high levels of fluoride (F1) in the water [10]. They also found evidence of a very low Na⁺:Ca²⁺ ratio in water in these regions compared to water in non-endemic regions (Huruluwewa and Wellawaya), and suggested that renal tubular damage due to F1 was dependent on the low Na⁺:Ca²⁺ ratio in drinking water [11]. A study investigating food samples, cultivated and consumed by people in regions where CKDu is prevalent, for ochratoxin A, found levels to be below the statutory maximum, and concluded that the toxin was unlikely to be a potential risk factor [12]. However, a more recent study has detected higher rates of urinary ochratoxins in CKDu patients in the NCP and their unaffected relatives than in Japanese controls, suggesting that exposure to the toxin may be common in the region [13].

Epidemiologically, establishing causality is difficult. Sir Bradford Hill outlined the minimum conditions that are required to establish causality, and these form the basis of modern epidemiologic research [14]. The conditions are:

- 1) Temporal relationship: the causative factor or agent must necessarily always precede the outcome.
- 2) Strength of the association: the strength or the size of the association is measured by appropriate statistical tests (relative risks, odds ratios and *p*-values). The larger the risk estimate or smaller the *p*-value, the greater the evidence for causality provided that other conditions are also fulfilled. The strength of the association is also dependent on the epidemiological study design used, with randomized controlled trials and cohort studies providing the strongest evidence, and cross sectional studies providing the weakest.
- 3) Dose response relationship: an increase in the amount of exposure should increase the risk or vice versa. If a dose-response relationship is present, it is strong evidence for a causal relationship. However, the absence of a dose-response relationship does not rule out a causal relationship, because

a threshold may exist above which a relationship may develop. If a specific factor is the cause of a disease, the incidence of the disease should decline when exposure to the factor is reduced or eliminated.

- 4) Consistency: The association is consistent when results are replicated in studies in different settings using different methods. Hence, numerous experiments have to be done before meaningful statements can be made about the causal relationship between two or more factors.
- 5) Plausibility: The association should agree with currently accepted understanding of pathological processes. There needs to be some theoretical basis for causality either in humans or in animals. However, research that disagrees with established theory is not necessarily false; it may, in fact, force a reconsideration of accepted beliefs and principles.
- 6) Consideration of alternate explanations: To establish causality, it is not only necessary to determine an association, but equally important is to rule out other explanations. It is always necessary to consider multiple hypotheses before making conclusions about the causal relationship between any two items.
- 7) Experiment: The condition should be modifiable (prevented or ameliorated) by an appropriate experimental regimen.
- 8) Specificity: Specificity is established when a single putative cause produces a specific effect. This is considered by some to be the weakest of all the criteria and may not be applicable to diseases of multifactorial origin. When specificity of an association is found, it provides additional support for a causal relationship but the absence of specificity in no way negates a causal relationship.
- 9) Coherence: The association should be compatible with existing theory and knowledge. As with plausibility, research that disagrees with established theory and knowledge are not automatically false. They may, in fact, force a reconsideration of accepted beliefs and principles.

The *minimum* criteria listed above makes it daunting to establish the cause of CKDu in the NCP of Sri Lanka; research done to date does not come even close to fulfilling these criteria. Mere associations, though encouraging, should not be considered to be of causal importance without documented evidence of proof. We advocate caution by the scientific community and the media when using such assertions that impact on policy, the livelihoods of the farming community and the economy of the country without scientific validity and biological plausibility.

The cause of CKDu is likely to be multifactorial. At this point in time there is insufficient evidence to pinpoint a cause(s). Both the wellbeing of residents of the NCP

and the enormous drain on health system resources and the economy demand that resolving the issue is a national priority. Well designed and adequately powered studies into CKDu should be strongly encouraged and adequately funded.

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A R Wickremasinghe, Department of Public Health, Faculty of Medicine, University of Kelaniya, Sri Lanka, **R J Peiris-John**, Section of Epidemiology and Biostatistics, School of Population Health, Faculty of Medical and Health Sciences, University of Auckland, New Zealand, **K P Wanigasuriya**, Department of Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka.

Correspondence: ARW, e-mail <arwicks@sltnet.lk>. Competing interests: none declared.