

The argument that the disease cannot be related to pesticides since it does not affect farmers at high altitude to the same extent as farmers at sea level does not prove the point. Farmers at high altitude drink less water than those at low altitude. In addition, the potential role of aristolochic acid or mycotoxins has not been ruled out.

To convince Mr Homes of the validity of his argument, Dr Johnson misinterprets the study by Siriwardhana *et al.* [2]. These investigators evaluated the prevalence of chronic kidney diseases (CKD) in the North Central Province of Sri Lanka. In this region, subjects who consumed < 3 L/day were at a higher risk for developing CKD compared to subjects who consumed more water. This would support Dr. Johnson's conclusion. However, subjects who consumed well water were 7 times more likely to develop CKD when compared with those who did not consume water from wells. This would support my contention that both dehydration and exposure to toxins from well water may be responsible.

In my analysis, I raised the alternative hypothesis that if the water is polluted, those individuals who ingest more water will be more likely to be affected. Sugarcane workers drink more

than 10 L of water/day, and with that they may be ingesting greater amounts of poisons. In the presence of dehydration, the probability of accumulation of these poisons in the kidneys increases proportionately and so does the incidence of kidney disease. The study by Siriwardhana *et al.* [2] supports this hypothesis, which is logical and can be easily tested.

I am sure that if Dr Johnson had adequately informed Mr Holmes of these alternative possibilities, Mr Holmes would certainly have advised him to test all of them before declaring that 'whatever remains, no matter how improbable, must be the truth'.

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# Con: Mesoamerican nephropathy: is the problem dehydration or rehydration?

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## ABSTRACT

In recent years, an increasing number of inhabitants of Central America have developed a form of chronic kidney disease, now named Mesoamerican nephropathy. This disease is characterized by minimal proteinuria, hyperuricemia, hypokalemia and reduced glomerular filtration rate. Histologically the kidneys manifest tubulointerstitial nephritis. The cause(s) of this disease remain unknown. Some have proposed that dehydration, in combination with hyperuricemia, may be primarily responsible for Mesoamerican nephropathy. In this article, I propose the hypothesis that the disease may be largely due to rehydration with large amounts of contaminated water, whereas dehydration would play only a contributing role.

**Keywords:** CKD, epidemiology, hyperuricemia, nephrotoxicity, survival analysis

In recent years, several epidemiological studies have described an epidemic of chronic kidney disease (CKD) affecting primarily young male adults in the geographic region that includes Southeastern Mexico, Guatemala, Belize, El Salvador, Honduras, Nicaragua, Costa Rica and Panama. This condition has been called Mesoamerican nephropathy (MeN) [1–4].

This disease affects primarily young male agricultural workers exposed to very hot conditions. Usually, they present with normal or mildly elevated blood pressure, reduction in estimated glomerular filtration rate (eGFR), non-nephrotic proteinuria, hyperuricemia and hypokalemia. Fischer *et al.* [5] have described

255 patients who were admitted to a hospital in Nicaragua with the diagnosis of acute kidney injury (AKI) related to MeN. These patients manifested fever (55%), mean serum creatinine of 2 mg/dL, hypokalemia (61.3%), hyperuricemia (29.6%), nausea, vomiting, back pain, weakness, leukocytosis, leukocyturia and minimal proteinuria. Kidney biopsies showed acute tubulointerstitial nephritis frequently associated with various degrees of chronicity.

Laws *et al.* [6] evaluated 284 Nicaraguan sugarcane workers performing seven distinct tasks and observed that eGFR decreased during the harvest in seed cutters ( $-8.6 \text{ mL/min/1.737 m}^2$ ), irrigators ( $-7.4 \text{ mL/min/1.73 m}^2$ ) and cane cutters ( $-5.0 \text{ mL/min/1.73 m}^2$ ) as compared with factory workers, suggesting that the disease is at least in part occupational.

The disease does not affect exclusively sugarcane workers, as originally thought, but it also affects miners, construction workers, the fishing industry, port workers and nonworking children [7].

The cause(s) of MeN remains largely unknown, but several hypotheses have been proposed. The most obvious potential cause(s) remains the presence of pesticides or heavy metals, such as cadmium, lead, mercury or arsenic, in the soil or in drinking water. However, to date, there is little evidence for involvement of pesticides or heavy metal poisoning in the MeN region [8]. In one study in Western Nicaragua, low concentrations of arsenic were identified in biological samplings. However, these concentrations were not considered 'excessive' and capable of causing the disease. [9]

In November 2012, the First International Research Workshop on MeN was held in Costa Rica to discuss potential causes of MeN. The workshop established that the cause(s) of MeN remains uncertain. Among the postulated causes were repeated episodes of occupational heat stress and dehydration, in combination with exposure to other nephrotoxic medication, or exposure to inorganic arsenic, leptospirosis or pesticides [2]. Other postulated causes include overuse of non-steroidal anti-inflammatory drugs (NSAIDs) and abuse of alcohol beverages. The unregulated consumption of locally produced alcohol known as *lija* could be another factor. [10]

A potential role of aristolochic acid, a contaminant linked to Chinese herb nephropathy and Balkan endemic nephropathy [11] or mycotoxins (such as ochratoxin A), which has been linked to nephropathy in Tunisia [12], has not been ruled out. Aristolochia is a plant that is common in Central America and its potential use in herbal remedies and even inadvertent contamination of food supplies could be a potential risk for nephropathy.

Murray *et al.* have suggested that the disease could be related to infections, particularly leptospirosis or Hantavirus, but the evidence supporting this hypothesis is inconclusive [13].

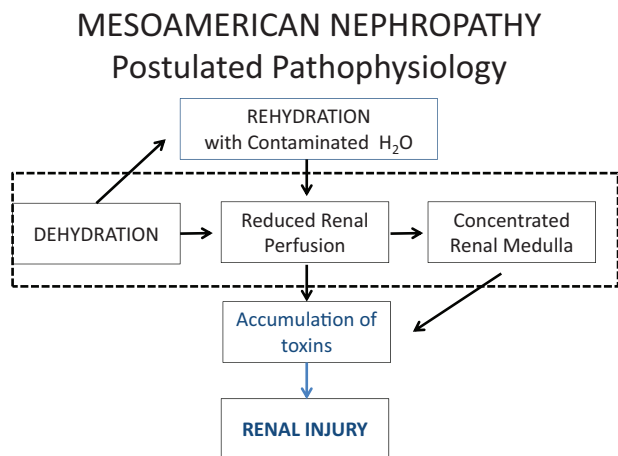
In a recent commentary, Johnson *et al.* proposed that MeN is a 'Dehydration disorder'. These investigators proposed that dehydration coupled with heat stress, rhabdomyolysis and hyperuricemia [14] are likely factors responsible for this epidemic. They suggested that recurrent dehydration may induce renal injury via a fructokinase-dependent mechanism, likely from the generation of endogenous fructose and the polyol pathway [15].

The same group has also postulated that the epidemic of CKD in Mesoamerica may be a consequence of global warming, leading to excessive dehydration [16].

Despite its appeal, the available evidence does not fully support the hypothesis that dehydration and/or hyperuricemia are primary factors responsible for MeN. Here are some of the reasons.

First, the distribution of the disease in regions with the same climatic and working conditions does not appear to be uniform, but localized to some areas and not others. For example, despite similar climatic conditions, the disease is prevalent along the coast of the Pacific Ocean and not the Atlantic Ocean. Global warming should equally affect regions with the same rise in temperature and does not explain the patchy distribution of the disease. In addition, the small increase in temperature over the last 30 years is not adequate to explain the degree and rapidity of this epidemic. Second, although the disease affects predominantly individuals performing hard labor, persons performing ordinary occupations and nonworking children may also be affected. Third, in the report by Laws *et al.*, eGFR decreased during the harvest among irrigators more than among cane cutters despite greater exposure to heat conditions of the latter group. Fourth, hyperuricemia appears to be present in approximately 50% of patients with CKD attributed to MeN, not in all patients, suggesting that uric acid may play a contributing but not an essential role. Moreover, in the study by Fischer *et al.* [5], on admission to the hospital, the average serum uric acid was  $6.1 \pm 1.8 \text{ mg/dL}$ , and it was  $>7.0 \text{ mg/dL}$  only in 29.6%; the average serum creatinine phosphokinase was 138 U/L and only 11.7% of patients had elevated levels; all patients had hypokalemia or normokalemia. All these features are not compatible with heat stroke or rhabdomyolysis.

Fifth, kidney biopsies from patients [17, 18] or animals subjected to severe dehydration or to heat stroke manifest primarily renal tubular necrosis. Tubulointerstitial inflammation appears only in those patients that progress toward chronicity. By contrast, kidney biopsies obtained from patients with AKI caused



**FIGURE 1:** Proposed pathophysiology of MeN. Rehydration with water contaminated by heavy metals, pesticides or other agents, in the context of dehydration and activation of renal concentrating mechanisms, leads to accumulation of toxins within the kidneys and renal tubular-interstitial injury.

by MeN manifest accumulation of leukocytes in the tubules and interstitium, consistent with acute tubulointerstitial nephritis and not with acute tubular necrosis.

For all these reasons, we believe that the available evidence does not support the hypothesis that MeN is caused primarily by global warming, dehydration and hyperuricemia.

I am proposing an alternative hypothesis. Persons working in rural areas of Nicaragua and Meso-America are exposed to very hot and humid climatic conditions. As a consequence, they perspire abundantly and they drink more fluids. Workers in the sugarcane fields may drink close to 8–12 L of water/day. In this environment, even if contaminants of the drinking water do not reach what are ordinarily considered ‘toxic concentrations’, given the enormous amount of fluid intake, workers may end up ingesting on a daily basis substantial quantities of toxic agents (such as heavy metals, pesticides, arsenic or other agents).

Because of the underlying dehydration and the resulting activation of renal concentrating mechanisms, these agents may concentrate in the kidney, achieving toxic levels (Figure 1).

On this basis, rather than (or in addition to) measuring the concentration of toxic agents in the water or soil, this should be done directly in the renal tissue. It may turn out that these agents may accumulate in the kidney even though the concentrations in the soil and drinking water may be within ‘acceptable’ limits.

In support of this hypothesis are the following clinical observations: several toxicological studies have demonstrated the presence of ‘acceptable’ concentrations of heavy metals and arsenic in the soil or water in these areas.

Second, populations with greater probability of developing the disease are those that drink more water. In a cross-sectional study conducted in León, Nicaragua to estimate CKD prevalence, ‘participants who drank 13–52 glasses of water/day had higher odds of CKD’ compared with those who drank 0–4 glasses of water/day [1]. This, of course, does not prove causality and could also be interpreted as suggesting greater dehydration in those who drank more than in those who drank less water.

Another region of the world affected by an epidemic of CKD is the North Central Province of Sri Lanka. In this region, subjects who consumed untreated water in lesser amounts than recommended levels and only from wells of Medawachchiya were at a higher risk for developing CKD compared with subjects who consumed more treated water from alternative sources [19].

This hypothesis does not exclude that other factors may be playing an aggravating or contributing role: dehydration, hyperuricemia, fructose ingestion, NSAIDs, alcohol, etc.

Acceptance of this hypothesis could have enormous public health consequences. Currently, the recommended approach to treating this condition among rural workers is to encourage workers to prevent dehydration by drinking 8–12 L/day of tap water. So far, there is no evidence that this strategy is providing benefits in terms of reduction of incidence and severity of MeN.

While appropriate randomized trials are necessary to confirm this hypothesis, it is advisable to ‘provide workers exposed to the risk of this disease with highly purified drinking water rather than tap water’.

## CONFLICT OF INTEREST STATEMENT

None declared.

(See related articles by Johnson. Pro: Heat stress as a potential etiology of Mesoamerican and Sri Lankan nephropathy: a late night consult with Sherlock Holmes. *Nephrol Dial Transplant* 2017; 32: 598–602; Zoccali. Causal mechanism and component causes in Mesoamerican–Sri Lankan nephropathy: the moderator’s view. *Nephrol Dial Transplant* 2017; 32: 607–610)

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## Opponent's comments

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The heat stress hypothesis is strong because the renal effects of heat (increased body temperature) and dehydration (hyperosmolarity) are clinically, epidemiologically and experimentally consistent with the disease without requiring additional factors. In response to the arguments raised by Dr Campese, the increased frequency of disease along the Pacific coast is consistent with greater mean temperatures in this area (Figure 1) [1]; the reason climate change may partially explain the recent rise in cases is because climate change, while raising mean temperatures slightly, is responsible for the marked increase in heat extremes [2] as we discussed. While not everyone has a high serum uric acid, studies show that the mean uric acid is higher than expected for the kidney function [3] and also strongly correlates with the disease [4]. The fact that some women and children show signs of renal

injury is because there will be a gradient with heat stress exposure from high exposure (fieldwork) to lesser exposure. Heat stress-associated renal disease is also associated with fever, leukocyturia and acute interstitial inflammation that later becomes chronic interstitial fibrosis [5, 6].

The attractive hypothesis by Dr Campese that dehydration increases tubular reabsorption of toxins and thereby could be primarily an augmenting factor remains possible and has been previously suggested [1, 7, 8], but the primary obstacle is that despite extensive screening no specific toxin has been identified. It has been proposed that it may involve the collective effect of multiple toxins that concentrate into the kidney at levels below classically toxic levels [7], which is a difficult hypothesis to test. If it is a toxin, the exposure must be widespread, for the disease in Central America appears clinically similar to the epidemics occurring elsewhere throughout the world.

Nevertheless, I am reminded of an epidemic of renal failure and visceral gout that killed the vast majority of vultures (raptors) in India and Pakistan and was due to the feeding of cattle with a nonsteroidal (diclofenac); in this situation, the combination of dehydration, uricase deficiency and contamination of livestock meat with an NSAID was the root cause of the epidemic [9]. Therefore, I agree with Dr Campese that we should not view the heat stress hypothesis as proven, and we must continue to look for toxins in both the water and food that could augment the effects of dehydration.

Emily Dickinson wrote a poem entitled 'Dwell in Possibility', which we all should. But if we have to dwell in probability, recurrent heat stress is sufficient to explain the epidemic.

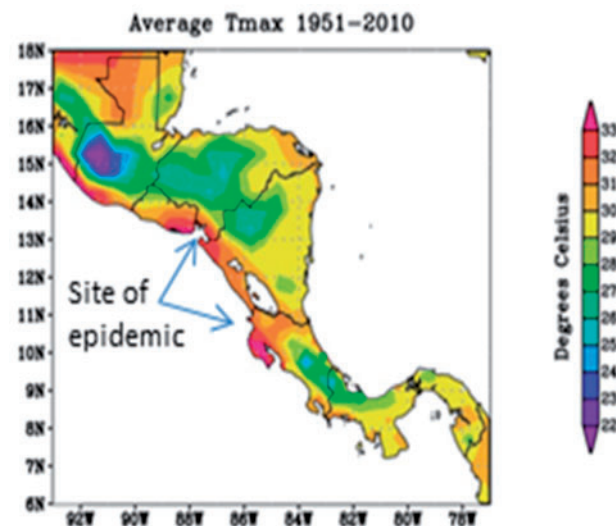


FIGURE 1: Average temperatures (1951–2010) are greatest along the Pacific Coast in Central America and this correlates with the location of MeN. Adapted from Glaser *et al.* [1].

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