survival, although to a lesser degree. Treatment may still be affecting the ischemia reperfusion phase even though given after reperfusion, because this is not just a short-lived injury that occurs immediately after reperfusion but instead an inflammatory process that can continue for some time.[9] Alternatively, C5a could be involved in other pathways that lead to graft injury, and of particular interest is its potential to augment the alloimmune response. In the report by Gueler *et al.*[4] blocking the C5a receptor prevents graft rejection and reduces the recipient's response to donor in a mixed lymphocyte reaction. This could be due to nonspecific effect of C5a on tissue injury in the reperfusion phase. Blockade of the C5a receptor reduces tissue injury, thereby limiting the supply of antigen, altering the maturation of antigen-presenting cells, and therefore decreasing the alloresponse. That treatment was required only for 6 d after transplantation to prolong survival to 12 wk supports this explanation.

Other published results support a more specific role for complement, in particular the anaphylotoxins, in the development of both B cell[10] and T cell immunity.[11] The generation of C5a locally at the site of interaction between antigen-presenting cells and T cells provides a survival signal for T cells[12] and is required for development of effector functions.[13] This is a significant effect and is sufficient to modify the survival of murine cardiac allografts.[14] In the study by Gueler *et al.*,[4] blocking C5a receptor signaling at a time when an allo-specific T cell response is developing is sufficient to prevent later rejection. The mechanism by which T cell reactivity remains suppressed is not known.

In conclusion, whatever its mode of action, C5a is clearly important in transplantation and represents a potential new target for therapy. Most of the data to support this statement so far have been generated in rodent transplant models. The challenge is to translate these findings into clinical practice. It has not always been easy to make the transition between rodent and clinical transplantation, but complement inhibition may be one area where this will prove successful.

DISCLOSURES

None

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See related article, "Complement 5a Receptor Inhibition Improves Renal Allograft Survival," on pages 2302–2312.

Uric Acid Levels Increase Risk for New-Onset Kidney Disease

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Despite our best efforts, the past decade has seen little progress in the treatment of chronic kidney disease (CKD). The mainstay of

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therapy continues to be controlling BP, blocking the renin-angiotensin system, and, for the patient with diabetes, tight control of blood sugar. Even with optimal therapy, we tend to retard, not to halt, the progression of kidney disease. Thus, the identification of novel risk factors and new treatments for CKD should remain a major goal of medical research.

Although the fields of genomics, proteomics, and metabolomics provide a novel way to search for new risk factors, in some cases, "old" risk factors are reemerging. One such risk factor is uric acid. For years, uric acid was considered a possible cause for the CKD observed in patients with gout. Indeed, both biopsy and autopsy studies confirm the presence of focal urate crystal deposition in the deeper regions of the cortex and medulla of patients with gout, often in association with arteriolosclerosis, glomerulosclerosis, and tubulointerstitial fibrosis.[1] "Gouty nephropathy" was the name given to the disease, and it was also thought to occur in some patients with asymptomatic hyperuricemia; however, many authors subsequently proposed that the renal lesions in patients with gout were due to other causes, such as hypertension or aging-related disease, and, besides, it was difficult to attribute focal crystal deposition as a cause for a disease that was diffusely present throughout the kidney. Thus, a "requiem" for gouty nephropathy was held, and, as a cause of kidney disease, uric acid was removed from the textbooks.[2]

There were other compelling reasons to view uric acid as a false risk factor for kidney disease. One reason is that uric acid is primarily excreted by the kidney. As GFR falls, there is both an increase in the fractional urinary excretion of uric acid and increased enteric excretion, but these processes do not fully compensate and serum uric acid levels rise. In patients initiating dialysis, approximately 50% have hyperuricemia[3]; therefore, CKD may be more likely a cause of hyperuricemia than the reverse. Furthermore, whereas uric acid crystals are known to be proinflammatory, soluble uric acid is an antioxidant that may be important in blocking aging and cancer-associated oxidative stress.[4] Certainly, it would be difficult to consider an antioxidant as a risk factor for renal disease when oxidative stress seems to be such an important driving force for cardiovascular and renal disease.

A series of new experimental studies have challenged the paradigm that uric acid is either harmless or even beneficial in CKD. Although uric acid is indeed an antioxidant in the extracellular setting, recent studies suggested that once uric acid enters a cell, it can cause oxidative stress, stimulate inflammatory mediators, cause endothelial dysfunction, and activate the local renin-angiotensin system.[5–8] Raising uric acid in rats by blocking the degradative enzyme uricase also causes hypertension, which is mediated initially by stimulation of the renin-angiotensin system and inhibition of the bioavailability of endothelial nitric oxide.[9] Importantly, raising uric acid also caused *de novo* renal disease as well as accelerated existing renal disease.[9,10] Micropuncture studies further showed that hyperuricemic rats develop preglomerular arteriolar disease that alters renal autoregulation, resulting in the combination of systemic and glomerular hypertension with renal vasoconstriction.[11,12] Finally, none of these studies implicated urate crystals.

Clinical studies are now "relooking" at the relationship of uric acid with the development of CKD. For example, Iseki *et al.*[13] followed 6403 adults in the Okinawa General Health Maintenance Association and found that a uric acid of ≥8.0 mg/dl conferred a 2.9-fold risk in men and a 10.4-fold risk in women for developing elevated creatinine after controlling for multiple risk factors. In another study of 13,338 adults from the Atherosclerosis Risks in Communities and the Cardiovascular Health Study, a change in 1 mg/dl uric acid was independently associated with a 7 to 11% increased risk for developing CKD.[14] Alternatively, a study by Chonchol *et al.*[15] could not confirm this association.

In this issue of *JASN*, Obermayr *et al.*[16] report the results of a study on uric acid levels as a predictor of new-onset kidney disease in 21,457 healthy volunteers from the Vienna Health Screening Project followed for a period of 7 yr. The volunteers were stratified into three groups: Those with normal uric acid levels (<7.0 mg/dl), modestly elevated uric acid levels (7.0 to 8.9 mg/dl), and markedly elevated uric acid levels (≥9.0 mg/dl). CKD was defined as a GFR <60 ml/min per 1.73 m^2 calculated using the Modification of Diet in Renal Disease (MDRD) formula. After adjustment for multiple risk factors, uric acid levels remained an independent risk factor for CKD in both men and women with a risk of 1.74 (95% confidence interval 1.45 to 2.09) and for 3.12 (95% confidence interval 2.29 to 4.25), respectively. The risks were greater in those with elevated BP. Interestingly, there was no relationship with proteinuria.

How should we interpret these data? First, one must recognize that independence does not necessarily equate with causality. For example, a risk factor could be independent and not causal if the true causal risk were not considered in the analysis. For example, if ischemia or oxidative stress were causal in CKD, then uric acid might be found to be an independent risk factor in these analyses, because uric acid levels rise in these settings and because these variables were not considered in the analysis. Likewise, a risk factor may not be independent but could still be causal. For example, if uric acid causes hypertension and this were the mechanism by which it caused kidney disease, then if both hypertension and uric acid are considered in a multivariable analysis, it is possible that uric acid would not be independent of hypertension as a cause of kidney disease. This is all the more relevant because recent experimental and clinical studies suggested uric acid is a cause of hypertension, especially in younger patients.[17,18]

The best way to evaluate the role of uric acid in the pathogenesis of CKD is to determine whether lowering uric acid slows renal progression. At least one recent trial involving a small number of patients did just that.[19] In that study, 54 patients with hyperuricemia and CKD were treated with allopurinol or usual therapy for 1 yr. In patients receiving allopurinol, only 16% showed progression of renal disease (defined as a rise

in creatinine level of ≥40%), whereas progression was observed in 46% of the control subjects ($P = 0.015$). Although the study is of interest, it was only a small sample size, and clearly more studies are needed before one can make a final conclusion. In addition, allopurinol can be associated with significant toxicities, including the Stevens-Johnson syndrome.

In conclusion, although the concept that uric acid might have a role in kidney disease once suffered a requiem, it has undergone a revival and seems deserving of additional study. If indeed it represents a remediable target for intervention, then a new chapter in the treatment of kidney diseases may result.

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DISCLOSURES

R.J.J. is listed as an inventor on several patent applications related to the lowering of uric acid as a means to prevent or treat cardiovascular and renal diseases. None of these applications has been officially patented, and none has been licensed.

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See related article, "Elevated Uric Acid Increases the Risk for Kidney Disease," on pages 2407–2413.