



## The uric acid hypothesis: Out with the old, in with the... old

As 2006 draws to a close and the traditional trumpeting of change and renewal begins, it is fitting that this issue contains an article on the rejuvenation of a concept. On page 1059, Drs. Marcelo Heinig and Richard Johnson discuss the hypothesis that serum urate is an independent risk factor for and possibly a primary mediator of cardiovascular disease.

The death knell for this idea tolled about 25 years ago. Asymptomatic hyperuricemia was declared to be benign, its treatment was decried, and serum urate disappeared from the automated metabolic panels. At that time, the evidence seemed to indicate that hyperuricemia was most often the result and not the cause of renal insufficiency and silent hypertensive renal and cardiovascular disease. We had no compelling evidence that its treatment reduced the progression of cardiovascular or renal disease. And we did not know of any pathophysiologic process that could explain why or how urate would likely be any more than an innocent by-product of the damage from hypertension or the effect of medications such as diuretics.

But now the concept is being revived. Some epidemiologic studies have shown serum urate to be an independent risk factor for myocardial infarction and all-cause mortality. It has been shown to trigger a "danger response" in cells. In rats, mild hyperuricemia induces the acute onset of hypertension, which eventually becomes urate-independent and salt-sensitive. It may also promote hypertension in humans: several studies are under way to confirm this, including trials of urate-lowering agents in adolescents with new-onset hypertension. Urate elevation can also elicit endothelial cell dysfunction and promote insulin resistance. In a positive feedback loop, hyperinsulinemia affects the URAT1 renal urate transporter to promote further elevation of serum urate levels. Hyperuricemia is a common component of the metabolic syndrome.

While in 2007 we may not need another marker of cardiovascular risk, a marker that is also a readily treated mediator of disease would be a welcome New Year's gift.

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