

Hyperuricemia and Gout

New Insights into Pathogenesis and Treatment

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Abstract

Over the past decade, significant advances have been made regarding the pathogenesis, clinical implications, and treatment of hyperuricemia. While physicians have understood for at least a century that uric acid causes gout, we are now beginning to address the question of why hyperuricemia exists and the mechanisms by which uric acid acts to stimulate inflammation. This review focuses on (1) previously unknown biological roles of uric acid; (2) why the loss of the uricase gene and resultant hyperuricemia may have provided an evolutionary advantage to primates and, in particular, to humans; (3) the molecular effects of uric acid on inflammatory cells; and (4) novel antihyperuricemic agents currently under study.

The history of our understanding of gout parallels the history of scientific knowledge. The first written reference to gout dates to 2600 BC, when Egyptians first described podagra, or gouty arthritis, usually of the big toe, and today understood as uric acid arthropathy. By 400 BC, Hippocrates had jotted down his aphorisms on gout. The

first person to describe tophi was Galen, around 200 AD; however, the term “gout” (from the Latin “gutta,” for a drop of liquid) was probably coined by Randolphus of Bocking, around 1200 AD. In 1679, Anton von Leeuwenhoek, the inventor of the microscope, first saw urate crystals, but it would be several hundred years before the great English physician Alfred Garrod affirmed that urate was “the cause of gouty inflammation.” In 1931, Garrod’s son Archibald, author of the first clinical genetics textbook, declared gout an “inborn error of metabolism.” By 1961, McCarty and Hollander had initiated the use of the polarizing microscope, helpful in the study of crystals.¹ Since 1970, however, the field of gout (with a few notable exceptions, such as the works of Terkeltaub^{2,3} and Shumacher,^{4,5} for example) has been surprisingly fallow.

If we examine the history of gout treatment, a similar pattern of acceleration in development is seen, then senescence. Colchicine, originally isolated from the autumn crocus, was first used for gout as early as 500 B.C. (not as an antiinflammatory, but as a purgative, leveraging the drug’s well-known capacity to induce diarrhea). Colchicine subsequently fell out of favor, in part due to Hippocrates’ lack of enthusiasm, but was revived in the 1700s (in the interim, in the 1600s, Henry VIII’s court physician Andrew Boorde confidently recommended the wearing of dog skin hose as a cure for gout). By 1877, the use of high-dose salicylates had come into favor. The midpoint of the 20th century was perhaps the golden age of gout therapy, with the introduction, in rapid succession, of ACTH (1948, adrenocorticotropic hormone), prednisone (1955), and allopurinol and indomethacin (1963). From the Cold War until the end of the 20th century, there were no more significant advances in gout therapy.¹

Possibly, the roadblock in the advancement of hyperuricemia and gout indicated an arrival at an epistemological dead end; the *what* of gout was fairly well understood and therapy was fairly standardized (if not always adequate).

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However, in these first few years of the 21st century, the understanding and treatment of gout and hyperuricemia has begun to advance once more. Now the attention has turned to the *why* and *how* of gout, and the answers, if only preliminary, are provocative. In reviewing the recent advances in hyperuricemia and gout, we will address four distinct questions: (1) Why do mammals have *any* uric acid? (2) Why do we (humans) have *a lot* of uric acid? (3) Why do some of us have *too much* uric acid, and (4) *How* does uric acid act to cause inflammatory events?

Why Do We Have Any Uric Acid?

Uric acid is a breakdown product of purines (ATP, GTP, and nucleic acids), and excretion of uric acid permits the required removal of nitrogenous wastes from the body. However, the ubiquity of uric acid as an excretion strategy suggests the possibility that its presence may provide an additional advantage. Recently, the research group of Kenneth Rock has offered data that suggests that uric acid may, surprisingly, play an essential role in immunity.⁶

In order to examine uric acid's possible role in immunity, it is helpful, first, to review the concepts of vaccines and adjuvants. It has been long appreciated that vaccination of an organism with antigen alone is likely to induce tolerance rather than an immune response. In order to generate an immune response, the antigen must be injected in the presence of an adjuvant. A number of adjuvants have been recognized, including *mycobacterium*, lipopolysaccharide, and so forth, but until relatively recently, the mechanism by which adjuvants helped stimulate an immune response was not appreciated. It is now known that many adjuvants act via ligation of Toll-like receptors (TLRs). These receptors represent a primitive but elegant part of the immune system, in that they recognize structural regions of molecules found in bacterial but not mammalian cells—so-called pathogen associated molecular patterns.⁷ Thus, the immune system has the capacity to recognize foreign antigens that it has never encountered before. While the initial evolutionary role of TLRs was undoubtedly to aid in innate immunity, these receptors now play a role in providing an adjuvant signal to antigen-presenting cells.

An antigen-presenting cell (APC; e.g., dendritic cells, macrophages, B cells) that samples an antigen in the setting of TLR activation will not only present antigen on an MHC molecule, but also upregulate a number of so-called costimulatory molecules, such as CD86. The costimulatory molecules provide a second signal that, in coordination with the antigen-bound MHC molecule, induces a full T-cell response. In the absence of a second signal, the antigen presentation event may be recognized as spurious by the T cell, resulting in a tolerizing rather than a stimulating effect.

One adjuvant that enhances T-cell activation is mammalian cytosol from dying or damaged cells. However, the specific cytosolic element(s) permitting a full immune response remained a mystery. In 2003, Shi and colleagues

decided to try to identify the active component. After irradiating mouse fibroblasts, isolating the cytosol, and injecting the cytosol into mice along with an antigen of interest (in this case, the gp120 surface antigen of the HIV virus), they isolated T cells from the mice and measured their ability to respond to gp120. Using this approach, Shi and coworkers confirmed that addition of cytosol from the irradiated cells served as an adjuvant, converting a minimal immune response into a boisterous one. With that result in hand, they fractionated the cytosol through multiple column chromatographies, testing the ability of each fraction to serve as an adjuvant. This process was repeated with each subsequent "positive" fraction, until they purified the adjuvant function to homogeneity and demonstrated that only two molecules in the cytosol served as adjuvants. One adjuvant was a high molecular weight molecule, not yet identified. The second was uric acid.⁶

To confirm that uric acid was indeed an endogenous adjuvant, they performed a series of additional experiments. For example, they demonstrated that the adjuvant effect of the putative urate fraction was abrogated by the addition of uricase. Moreover, they demonstrated that exogenously added uric acid could substitute for the cytosol as an adjuvant. Interestingly, the minimum concentrations of urate required to serve as adjuvant were greater than 7.0 mg/dL, and uric acid only served as an adjuvant in crystalline form. This requirement for crystalline uric acid may serve as a fail-safe mechanism to prevent immune response activation in the presence of low concentrations of urate.

To understand why evolution might select for endogenous antigens, we must next review the concept of the "danger signal." In the 1990s, Matzinger postulated that cells damaged by trauma or viral infection might need a way to signal to the immune system, either to elicit a response to the infecting entity or to signal a need to clean up necrotic cellular debris.⁸⁻¹⁰ Matzinger coined the term "danger signal" for the molecules that could serve these functions, but their identity remained unknown, at least until now. Why would uric acid serve in this capacity? One possibility is that programmed cell death initiates an active process of purine degradation, leading to high urate production (it is just such a process that occurs during tumor lysis syndrome). Thus, local uric acid levels may rise precipitously in a dying cell, and uric acid may, therefore, be an ideal candidate to serve as the danger signal (Fig. 1).

If this line of investigation is correct, it suggests that uric acid may play a profound role in the immune system and, indeed, in the survival of mammalian species. The question then arises, is there any functional evidence that this model may be correct? To date, only a few animal models have been used to investigate the possible role of urate in immunity, and, in what may be the most convincing, Hu and associates employed a mouse model of immunologic tumor rejection to test a putative role of urate. They observed that lowering uric acid levels with either allopurinol or uricase led to

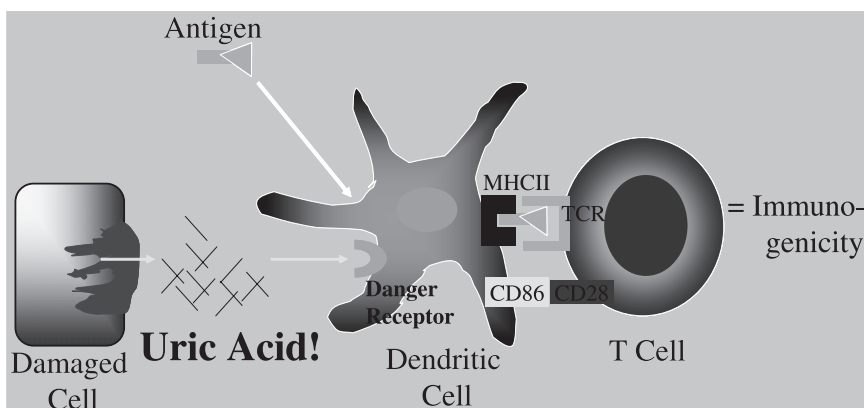


Figure 1 Uric acid is the danger signal that acts as endogenous adjuvant when tissue is injured during immune presentation.

delayed tumor rejection. Conversely, treatment of the tumor mice with uric acid enhanced the rate of tumor rejection.¹¹ In another animal model, Shi and colleagues demonstrated a possible role for urate in the development of diabetes.¹²

Why Do Humans and Other Primates Have So Much Uric Acid?

In contrast to most mammals, whose serum urate levels are typically below 2 mg/dL, primates (including humans, great apes, and some New World monkeys) tend to have serum urates in the range of 6 to 7 mg/dL, owing to a lack of uricase. Why has this loss of uricase occurred? To suggest an answer to this question, we must turn to the work of nephrologist Richard Johnson and to an examination of genetic anthropology. As it turns out, the loss of the uricase gene in primates occurred during the Miocene era, roughly 10 to 22 million years ago. However, an examination of our primate cousins indicates that the loss of uricase happened not once, but several times, and by several different mutations. In gibbons, the loss of uricase occurred earliest (about 22 million years ago) via a 13 base pair deletion in the gene, whereas in all other primates, a mutation in codon 33 eliminated uricase about 18 million years ago (Fig. 2).¹³ Additional mutations followed, exclusively affecting humans, gorillas, and chimps, and by several different mutations. In gibbons, the loss of uricase

occurred repeatedly and by different mechanisms during the same era suggests that it may have conferred a survival advantage during that period.¹⁴

Watanabe and coworkers suggest what special advantage the loss of uricase might have provided. They note that during the Miocene era, our ancestors were mainly limited to a vegetarian diet of fruits and grasses, a diet particularly low in sodium. It is possible, Johnson suggests, that this low-salt diet led to what might be called an era of hypotensive crisis. Johnson further hypothesizes that the loss of uricase and the accumulation of uric acid might somehow have compensated for the problem of hypotension. If this were the case, why did the loss of uricase not occur in other mammals as well? The answer may be because primates and monkeys are unique in spending a significant part of their time as bipeds, and, therefore, are more heavily dependent upon blood pressure to maintain cerebral perfusion.

To test this hypothesis in an animal model, Johnson's group placed rats on a very low-sodium diet. Even in these quadrupeds, the loss of sodium led to a significant drop in blood pressure. The investigators then treated the animals with oxonic acid, a uricase inhibitor, and the rats' blood pressure returned to normal or higher than normal levels. Moreover, this increase in blood pressure could be abrogated by concurrent treatment with allopurinol (Fig. 3). Thus, in

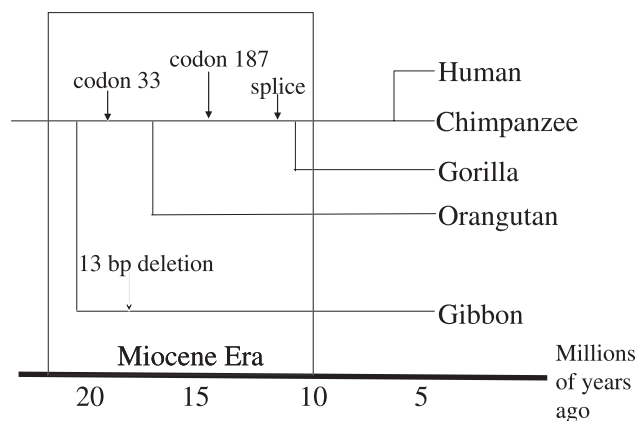


Figure 2 The loss of the uricase gene happened differently in different primates, but all in the same era.

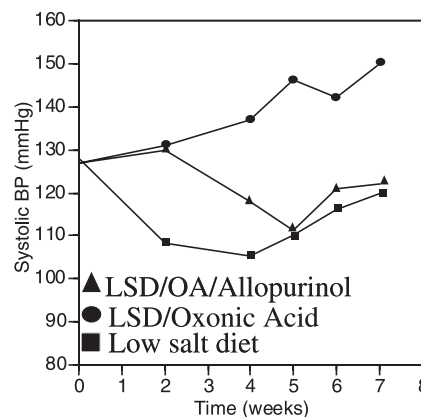


Figure 3 Could increased serum urate levels correct hypotension?

rodents, at least, low-salt hypotension may be compensated by increases in uric acid.¹⁵

How might urate act to raise blood pressure? Johnson's group and others have identified multiple possible mechanisms. Among these are stimulation of the rennin-angiotensin axis; inhibition of neuronal nitric oxide synthase, with resultant effects on vascular tone; induction of renal microvascular disease, including smooth muscle proliferation, especially of the afferent arteriole; and induction of renal interstitial inflammation and tubular injury.¹⁶⁻¹⁹

Given these observations, the long-appreciated association between hyperuricemia and hypertension begins to take on an appearance of cause-and-effect.²⁰ The question logically follows: might lowering serum urate provide a therapy for essential hypertension? Johnson's group performed a small, open-label proof of principle study to test that hypothesis. They enrolled five adolescents with documented essential hypertension, all with serum urates of 6.0 mg/dL or above, in a 10-week trial. For the first 4 weeks, all of the patients received allopurinol, 200 mg BID. The remaining 6 weeks were a washout period. Blood pressure was measured before the administration of allopurinol, at the end of the four-week treatment course, and at the end of the washout period. After 4 weeks of allopurinol therapy, all five patients demonstrated lowered blood pressure, with four of the five in the normal range. After the washout period, all five had significant increases of their blood pressures back toward their initial starting values.²¹ A larger blinded study is ongoing. These data suggest that urate can positively regulate human blood pressure, and that interventions to lower urate may be of value. Whether these results would apply to individuals with long-established hypertension or to people with "normal" serum urate values are questions that deserve answers.

Why Do Some Human Beings Have Too Much Uric Acid?

While most humans have "normal" uric acid levels in the 4 to 7 mg/dL range, physicians know that many patients have serum uric acid levels that are higher, and it is these levels that tend to increase the risk for gouty attacks, tophi, or both. The reasons for "gout-level" hyperuricemia are various and complex. However, it is important that we consider them, as the incidence of gout appears to be on the rise. Indeed, several epidemiologic studies indicate a doubling of the rate of gout in the past several decades.^{22,23} One reason may be our dietary habits and the "obesity epidemic" in the United States. It has long been appreciated that both high-purine diets and obesity are associated with gout, but few rigorous studies have been performed. Recently, Choi and associates have rigorously investigated these questions, and their results are both expected and, to some extent, new. They confirm, for example, that increased meat intake is associated with a higher relative risk for both hyperuricemia and gout, whereas the ingestion of high-purine vegetables has a much less significant effect. Equally interesting is the fact

that dairy intake is independently correlated with a lower risk for hyperuricemia and gout.^{24,25}

Another long-appreciated cause of hyperuricemia and gout is alcohol intake, but, again, prior studies have been limited. Choi's group also addressed this question in a 12-year prospective study of more than 47,000 males, confirming that alcohol intake is proportional to gout risk. Beer appeared to be the most significant offender, followed by hard spirits; the increasing predilection to beer consumption in the United States may, therefore, contribute to the rise in gout. Interestingly, the investigators found that wine provided the least risk, and that consumption of moderate amounts of wine (range of 2 to 4 drinks/week) provided no risk at all.²⁶ While these studies need to be duplicated, clinicians treating patients may wish to consider the relative benignity of wine compared with other alcoholic drinks when recommending lifestyle changes.

Not all causes of hyperuricemia are extrinsic, however, and several recent advances have shed light on the ways in which the kidneys handle or fail to handle uric acid.²⁷ Renal urate handling has long been understood to be a multistep process: glomerular filtration of urate is followed by proximal tubule resorption of 99% of the filtered load, then resecretion of approximately 50% of the resorptate. Another resorption step occurs before the urinary urate is finally excreted. While relatively little is known about the resecretion step (the cause of the defect in many uric acid "underexcretors"), much more information is accumulating regarding the protein responsible for the initial proximal tubule urate resorption. In particular, renal physiologists and geneticists have identified the gene, and the transporter protein involved: URAT1.²⁸ This protein is the target for most uricosuric drugs, including probenecid, sulfapyrazone, benzbromarone, and high-dose salicylates, as well as minor uricosurics, such as losartan.²⁹ Other transporter proteins, including UAT1, have also been identified though their importance is not well appreciated.³⁰

Less progress has been made to date on understanding why some individuals overproduce uric acid. It is well known that hereditary hyperactivity of the purine synthesis enzyme PRPP (5-phospho-D-ribosyl-1-pyrophosphate) synthase can lead to hyperuricemia, as can partial deficiency of HGPR (hypoxanthine-guanine phosphoribosyl) transferase, the rate-limiting step in the purine salvage pathway. However, little or no new research has addressed the mechanisms of uric acid overproduction.

How Does Hyperuricemia Lead to an Inflammatory Response to Urate Crystals?

The acute or chronic presence (alone or simultaneously) of serum urate levels at concentrations above the solubility point of uric acid (approximately 7.0 mg/dL) may eventually result in the formation of uric acid crystals in the joints or elsewhere. Crystal formation results in inflammation, and some of the mechanisms in this process have been well

appreciated. In a joint, the presence of crystals stimulates a two-pronged inflammatory signal. The activation of complement results in the generation of chemoattractants, such as C5a, which activates and attracts bloodstream neutrophils. However, neutrophil ingress will be denied by the vasculature unless vascular endothelial cells are first activated by cytokines generated by macrophages lining the synovium, such as IL-1, TNF- α and IL-6. Recent studies have provided insights into the mechanisms through which uric acid crystals activate macrophages, in particular, the role of the NALP3 (NACHT, LRR and pyrin domain-containing protein) inflammasome.

Inflammasomes are structures that mediate the generation of IL-1,³¹ a cytokine that is initially synthesized as a pro-molecule and needs to be cleaved in order to be activated. The enzyme that provides the cleavage function is caspase-1. In turn, caspase-1 function depends upon its alignment with one of several potential scaffolding complexes; it is these complexes that are known as inflammasomes.³² Most inflammasomes consist of several molecules and usually include one of several molecules from the NALP family. Mutations in several NALP proteins have been associated with a number of different autoimmune diseases, autoinflammatory diseases, or both. For example, mutations in NALP1 have been shown to be associated with autoimmune vitiligo in conjunction with a number of different systemic autoimmune diseases.³³ In contrast, mutations that lead to hyperactivity of NALP3 have been identified as the etiologies of diseases such as familial cold autoinflammatory syndrome and neonatal onset multisystem inflammatory disease. Thus, inflammasomes play critical roles in the regulation of inflammation. Recently, Martinon and colleagues have demonstrated the ability of uric acid to stimulate the macrophage NALP3 inflammasome, leading to IL-1 production.³⁴ Moreover, macrophage TNF production in response to uric acid appears to be secondary to NALP3 activation and IL-1 generation. While controversy exists as to whether or not uric acid activates NALP3 via

Toll-like receptors (specifically, TLR2 and 4), it appears that MyD88, the molecule that transmits TLR signals intracellularly, plays an important role in both activating the NALP3 inflammasome and in signaling a secondary autohumoral response to secreted IL-1 (Fig. 4).³⁴⁻³⁶

Exposure of inflammatory cells to uric acid crystals additionally activates a number of other intracellular signaling molecules, including MAP kinases and NF- κ B, with resultant secretion of proinflammatory cytokines such as IL-8.³⁷

How Do We Treat, or Better, Prevent Hyperuricemia and Gout?

As noted at the beginning of this review, the therapy of gout has advanced little in the past half-century. Acute gouty arthritis is most commonly treated with nonsteroidal antiinflammatory drugs (NSAIDs), steroids, or colchicine. Some of these agents—colchicine, in particular—are also useful as prophylactic against gouty attacks. Lowering uric acid to prevent gouty attacks has primarily been accomplished with allopurinol although probenecid may be used in primary urate under-excreters with intact renal function and no history of nephrolithiasis. However, new and alternative therapies are needed, particularly since contraindications for many of the above therapies include diabetes, renal insufficiency, and gastrointestinal pathology, all of which are common in patients with gout.

Two new gout therapies are being evaluated in clinical trials. Febuxostat is a nonpurine xanthine oxidase inhibitor, and, as such, its basic mechanism of action mimics that of allopurinol. However, where allopurinol is accompanied by significant hypersensitivity, febuxostat does not appear to cross-react with allopurinol. Moreover, since febuxostat is metabolized by the liver but not renally excreted (allopurinol relies on the kidney for its excretion), febuxostat may prove safe in patients with renal failure; data is not yet available.³⁸ In terms of efficacy, febuxostat at 80 mg/day has been shown to be superior to allopurinol 300 mg/day for urate lowering.³⁹ As rheumatologists know, however, doses of allopurinol as

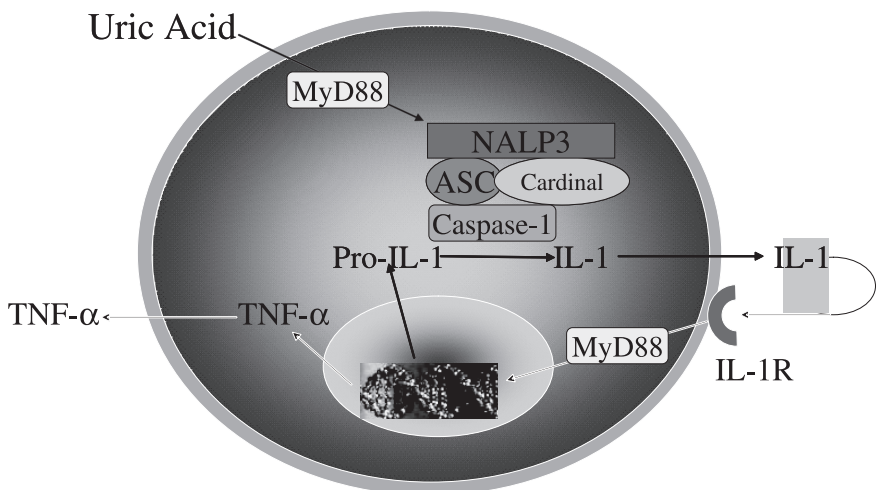


Figure 4 The NALP3 Inflammasome: macrophage generation of IL-1 for cellular secretion.

high as 800 mg/day may be safe and efficacious in appropriate patients, so the relative efficacy of these agents has yet to be established.

Another urate-lowering strategy is to infuse uricase, which enzymatically digests both soluble serum urate and insoluble uric acid deposits. Uricase treatment has been attempted as far back as the 1960s,⁴⁰ and a recombinant bacterial uricase (rasburicase) has already been approved by the FDA (Food and Drug Administration) for prophylaxis of tumor lysis syndrome.⁴¹ In individual cases, rasburicase has been reported to be effective in the management of gout.⁴² However, bacterial uricase is highly immunogenic, sometimes poorly tolerated, and has a short half-life. To attempt to overcome these limitations, a pegylated uricase has been formulated and is in clinical testing. Studies suggest that a single intravenous (IV) infusion of pegylated uricase may persist for many weeks and can be highly effective in lowering serum urate to near-zero levels.⁴³ Assuming that the agent proves safe and effective, at issue will be its expense and inconvenience. Pegylated uricase might be particularly useful in patients who fail other therapies or in patients with massive tophaceous accumulation, in whom uricase treatment may provide a rapid “debulking” of total body urate stores. Is also an intriguing question as to whether or not pegylated uricase might serve as an induction therapy to reduce urate stores and permit subsequent, easier management with more traditional therapies.

Possibly the most fruitful area for current investigation, however, would involve interference directed at the recently elucidated signaling pathways that govern macrophage responses to urate crystals. These would include the possibility of inhibiting caspase-1 (caspase-1 inhibitors having already been in trial for rheumatoid arthritis),⁴⁴ NALP3 (in this regard, it is interesting to note that colchicine has been shown to inhibit NALP3), and MyD88.³⁴ Indeed, the role of the NALP3 inflammasome in IL-1 stimulation suggests the possibility that direct inhibition of IL-1, for example, using the IL-1 receptor antagonist anakinra might be beneficial in gout. To provide an initial assessment of the possible utility of this approach, Tschopp and coworkers have treated the acute attacks of 10 gout patients with anakinra in an uncontrolled, open-label study and noted at least 50%-100% improvement in all 10 patients within no more than three days.⁴⁵

In summary, after a pause in activity, the field of gout and hyperuricemia is burgeoning again. Recent evidence indicates that uric acid is not just an end-product to be excreted, but rather, may play an important role in cellular immunity and even have made it possible for primates to stand on two feet. Despite the fact that uric acid may confer several biological advantages, many humans nevertheless have too much of it, and suffer diseases such as gout (and perhaps hypertension) as a consequence. While treatments for gout and hyperuricemia have not evolved further over the last sixty years, our understanding of how uric acid leads

to an acute inflammatory response is increasing, and new urate-lowering therapies are on the horizon that ultimately should lead to better-tailored therapies for acute and chronic gout.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed in the manuscript, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References

1. Nuki G, Simkin PA. A concise history of gout and hyperuricemia and their treatment. *Arthritis Res Ther*. 2006;(8 Suppl 1):S1.
2. Terkeltaub RA, Ginsberg MH. The inflammatory reaction to crystals. *Rheum Dis Clin North Am*. 1988;14(2):353-64.
3. Terkeltaub R. Gout in 2006: The perfect storm. *Bull NYU Hosp Jt Dis*. 2006;64(1-2):82-6.
4. Schumacher HR Jr. Pathology of crystal deposition diseases. *Rheum Dis Clin North Am*. 1988;14(2):269-88.
5. Schumacher HR Jr. Crystal deposition disease. *Curr Opin Rheumatol*. 1997;9(3):251-2.
6. Shi Y, Evans JE, Rock KL. Molecular identification of a danger signal that alerts the immune system to dying cells. *Nature*. 2003;425(6957):516-21.
7. Janeway CA, Jr. Medzhitov R. Innate immune recognition. *Annu Rev Immunol* 2002;20:197-216.
8. Gallucci S, Matzinger P. Danger signals: SOS to the immune system. *Curr Opin Immunol*. 2001;13(1):114-9.
9. Skoberne M, Beignon AS, Bhardwaj N. Danger signals: A time and space continuum. *Trends Mol Med*. 2004;10(6):251-7.
10. Andrews NW. Membrane repair and immunological danger. *EMBO Rep* 2005;6(9):826-30.
11. Hu DE, Moore AM, Thomsen LL, Brindle KM. Uric acid promotes tumor immune rejection. *Cancer Res*. 2004;64(15):5059-62.
12. Shi Y, Galusha SA, Rock KL. Cutting edge: Elimination of an endogenous adjuvant reduces the activation of CD8 T lymphocytes to transplanted cells and in an autoimmune diabetes model. *J Immunol*. 2006;176(7):3905-8.
13. Wu XW, Muzny DM, Lee CC, Caskey CT. Two independent mutational events in the loss of urate oxidase during hominoid evolution. *J Mol Evol*. 1992;34(1):78-84.
14. Watanabe S, Kang DH, Feng L, et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension*. 2002;40(3):355-60.
15. Mazzali M, Hughes J, Kim YG, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension*. 2001;38(5):1101-6.
16. Feig DI, Nakagawa T, Karumanchi SA, et al. Hypothesis: Uric acid, nephron number, and the pathogenesis of essential hypertension. *Kidney Int*. 2004;66(1):281-7.
17. Feig DI, Rodriguez-Iturbe B, Nakagawa T, Johnson RJ. Nephron number, uric acid, and renal microvascular disease in the pathogenesis of essential hypertension. *Hypertension*. 2006;48(1):25-6.
18. Kanellis J, Watanabe S, Li JH, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular

- smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension*. 2003;41(6):1287-93.
19. Sanchez-Lozada LG, Tapia E, Avila-Casado C, et al. Mild hyperuricemia induces glomerular hypertension in normal rats. *Am J Physiol Renal Physiol*. 2002;283(5):F1105-10.
 20. Feig DI, Mazzali M, Kang DH, et al. Serum uric acid: A risk factor and a target for treatment? *J Am Soc Nephrol*. 2006;17(4 Suppl 2):S69-73.
 21. Feig DI, Johnson RJ. The role of uric acid in pediatric hypertension. *J Ren Nutr*. 2007;17(1):79-83.
 22. Arromdee E, Michet CJ, Crowson CS, et al. Epidemiology of gout: Is the incidence rising? *J Rheumatol*. 2002;29(11):2403-6.
 23. Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. *J Rheumatol*. 2004;31(8):1582-7.
 24. Choi HK, Atkinson K, Karlson EW, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med*. 2004;350(11):1093-103.
 25. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: The Third National Health and Nutrition Examination Survey. *Arthritis Rheum*. 2005;52(1):283-9.
 26. Choi HK, Atkinson K, Karlson EW, et al. Alcohol intake and risk of incident gout in men: A prospective study. *Lancet*. 2004;363(9417):1277-81.
 27. Terkeltaub R, Bushinsky DA, Becker MA. Recent developments in our understanding of the renal basis of hyperuricemia and the development of novel antihyperuricemic therapeutics. *Arthritis Res Ther*. 2006;(8 Suppl 1):S4.
 28. Enomoto A, Kimura H, Chairoungdua A, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature*. 2002;417(6887):447-52.
 29. Hatch M, Freel RW, Shahinfar S, Vaziri ND. Effects of the specific angiotensin II receptor antagonist losartan on urate homeostasis and intestinal urate transport. *J Pharmacol Exp Ther*. 1996;276(1):187-93.
 30. Lipkowitz MS, Leal-Pinto E, Rappoport JZ, et al. Functional reconstitution, membrane targeting, genomic structure, and chromosomal localization of a human urate transporter. *J Clin Invest*. 2001;107(9):1103-15.
 31. Ogura Y, Sutterwala FS, Flavell RA. The inflammasome: First line of the immune response to cell stress. *Cell*. 2006;126(4):659-62.
 32. Martinon F, Burns K, Tschopp J. The inflammasome: A molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell*. 2002;10(2):417-26.
 33. Jin Y, Mailloux CM, Gowan K, et al. NALP1 in vitiligo-associated multiple autoimmune disease. *N Engl J Med*. 2007;356(12):1216-25.
 34. Martinon F, Petrilli V, Mayor A, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. 2006;440(7081):237-41.
 35. Liu-Bryan R, Scott P, Sydlaske A, et al. Innate immunity conferred by Toll-like receptors 2 and 4 and myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal-induced inflammation. *Arthritis Rheum*. 2005;52(9):2936-46.
 36. Chen CJ, Shi Y, Hearn A, et al. MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. *J Clin Invest* 2006;116(8):2262-71.
 37. Liu R, O'Connell M, Johnson K, et al. Extracellular signal-regulated kinase 1/extracellular signal-regulated kinase 2 mitogen-activated protein kinase signaling and activation of activator protein 1 and nuclear factor kappaB transcription factors play central roles in interleukin-8 expression stimulated by monosodium urate monohydrate and calcium pyrophosphate crystals in monocytic cells. *Arthritis Rheum*. 2000;43(5):1145-55.
 38. Schumacher HR Jr. Febuxostat: A non-purine, selective inhibitor of xanthine oxidase for the management of hyperuricaemia in patients with gout. *Expert Opin Investig Drug*. 2005;14(7):893-903.
 39. Becker MA, Schumacher HR, Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005;353(23):2450-61.
 40. Royer R, Vindel J, Lamarche M, Kissel P. [Modalities of purine excretion during enzyme treatment of gout and other hyperuricemic conditions with urate oxidase]. *Presse Med*. 1968;76(49):2325-7.
 41. Rampello E, Fricia T, Malaguarnera M. The management of tumor lysis syndrome. *Nat Clin Pract Oncol*. 2006;3(8):438-47.
 42. Richette P, Bardin T. Successful treatment with rasburicase of a tophaceous gout in a patient allergic to allopurinol. *Nat Clin Pract Rheumatol*. 2006;2(6):338-42; quiz 343.
 43. Sundry JS, Ganson NJ, Kelly SJ, et al. Pharmacokinetics and pharmacodynamics of intravenous PEGylated recombinant mammalian urate oxidase in patients with refractory gout. *Arthritis Rheum*. 2007;56(3):1021-8.
 44. Randle JC, Harding MW, Ku G, et al. ICE/Caspase-1 inhibitors as novel anti-inflammatory drugs. *Expert Opin Investig Drugs*. 2001;10(7):1207-9.
 45. So A, De Smedt T, Revaz S, Tschopp J. A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res Ther*. 2007;9(2):R28.