Gout: questions that still need to be answered

Knowledge is the small part of ignorance that we arrange and classify.
—Ambrose Bierce

Advances in the latter part of the twentieth century have provided relatively satisfactory basic understanding, clinical classifications, and guidelines for management of hyperuricaemia and clinical gout. However, gout remains a significant public health problem in many populations, and several clinical problems have emerged to challenge clinicians, including the atypical features and increasing prevalence of gout in elderly women, and the frequently aggressive course of cyclosporine-induced gout. Vexing questions remain concerning the pathogenesis of gout. These include the bases for the variability in clinical inflammatory responses to intra-articular urate crystals and monosodium urate deposition in tophi. When the reasons for the lack of development of gout in the majority of patients with persistent hyperuricaemia are determined, we may also understand the basis for the occasional occurrence of gout without chronic hyperuricaemia.

Because each gout patient that the clinician encounters still presents unanswered fundamental questions (table), the following discussion is intended to highlight a few recent observations that point the way to further potentially clinically relevant investigation of several of the significant gaps in our understanding of gout.

URATE DISPOSITION AND DEPOSITION
The species-wide lack of urate oxidase (or uricase, EC 1.7.3.3), which degrades relatively insoluble uric acid to highly soluble allantoin, imposes a relatively narrow balance between uric acid production and tissue deposition in humans. Urate oxidase, which is present in most mammals, was lost in humans and a small number of other species during the course of primate evolution. Thus it may be valuable to determine if this loss somehow confers an evolutionary advantage, for example from the antioxidant properties of uric acid, or some unrecognised biological effect of allantoin.

Recently, targeted disruption of the urate oxidase gene by homologous recombination was demonstrated to generate urate oxidase-deficient mutant mice with a 10-fold increase in both serum and urinary uric acid concentrations, rapidly progressive urate nephropathy, a very high lethality rate in the first weeks of life, and therapeutic responsiveness to allopurinol.

In these groundbreaking studies, which provided the first small animal model of human hyperuricaemia, subcutaneous tophi and articular urate deposition were not detected in homozygotic urate oxidase-deficient mice in the first four weeks of life, despite mean serum urate concentration of 11.0 mg/dl. Thus it will be important to determine if tophi and joint lesions occur later in life in small animal models of hyperuricaemia, and to identify what factors (other than temperature and pH) are critical in regulating tophus formation in vivo. In this regard, it will be important to test further in vivo the relevance of provocative recent findings that suggest urate crystals to be capable of acting as antigens that mediate the production of antibodies which promote de novo uric acid crystallisation. Furthermore, small animal models of hyperuricaemia could prove valuable in further understanding why urate deposition appears to have a predilection for peripheral joints affected by degenerative joint disease.

Heritable factors appear to exert substantial influence on renal handling of urate, and a relative deficit in the renal excretion of uric acid is identified in most patients with primary gout. However, the precise molecular defect(s) in such patients have not been defined. Small animal models of hyperuricaemia should prove particularly advantageous for answering substantial remaining questions about the molecular mechanisms for urate secretion and reabsorption within the nephron, and for developing novel antihyperuricaemia drugs or molecular therapeutic agents. These will probably include molecular delivery of the urate oxidase gene, which may be of particular benefit to hyperuricaemic patients who have the clinically challenging problem of hypersensitivity to uric acid decreasing agents.

GOUTY INFLAMMATION
The activation of cells by monosodium urate crystals is the central event in the pathogenesis of gouty inflammation.
(figure). Recent studies suggest that crystal induced activation of unidentified tyrosine kinases could be critical in several of the induced inflammatory responses, including activation of NADPH oxidase, degranulation, and the induction of inflammatory cytokine gene expression.5–12 The pattern of substrates for the urate crystal induced tyrosine kinase activation in phagocytes is similar to that in cells stimulated by certain other monocrystals. 3 Thus it will be particularly important to discern both the nature of the membrane ligands and signal(s) affected by crystals (figure), and the identities and functions of the pertinent tyrosine kinases and their substrates.

Recently, it has become evident that specific ligand-induced dimerisation is an important step in activation of receptor tyrosine kinases,13 and that tyrosine kinase activation plays a role in Fc receptor mediated phagocytosis.14 In this regard, it is probable that the capacity of naked urate crystals to induce non-specific cross linking of multiple membrane proteins5 is critical to many aspects of crystal induced cell activation. Thus I believe further studies will probably not find a single essential ‘receptor’ for urate crystals on the plasma membrane of most inflammatory cells.

Though monosodium urate crystals induce a plethora of inflammatory mediators and consistently exert potent pro-inflammatory effects experimentally in vitro and in vivo,1 further investigation is needed to explain the absence of clinical inflammation observed often in subcutaneous tophi, and occasionally in joints that bear free intra-articular urate crystals.1 In this regard, the dynamics of neutrophil ingress from the periphery and the local balance between inflammatory and anti-inflammatory mediators are believed to be the critical regulatory factors for gouty inflammation.1 Because characteristic urate crystal induced inflammation is a paradigm for both self limited and readily treated synovitis, it will be valuable to define the clinical relevance of several recent discoveries, including the potential paradoxical contribution of transforming growth factor β15 to both igniting and smothering gouty inflammation, the ability of tumour necrosis factor α to accelerate neutrophil apoptosis,15 and the ability of certain cytokines and urate crystals to modulate expression of the IL-1 receptor antagonist on neutrophils.17 Furthermore, it will be important to identify the pivotal and most clinically significant of the many potential therapeutic effects of colchicine, which include its recently delineated, potent anti-adhesive properties,18 its capacity to inhibit crystal induced neutrophil tyrosine kinase activation,10 12 and its ability to regulate differentially cytokine expression.17

Low density lipoprotein (LDL) binds avidly to monosodium urate crystals and this event can markedly attenuate urate crystal induced phagocyte activation.1 Furthermore, alterations in the surface proteins coating urate crystals, including a dramatic increase in crystal bound LDL, were recently documented during the course of acute gouty inflammation.13 However, further studies are needed because oxidation of LDL lipids, which has been documented in inflammatory fluids, actually renders LDL capable of inducing several proinflammatory cytokines, including the neutrophil chemoattractant IL-8.20 Further advances in understanding how physical changes in the structure and surface coat of urate crystals could regulate crystal-membrane interaction and gouty inflammation in vitro and in vivo also should be facilitated by the advent of atomic force microscopy, which can readily identify microcrystals and resolve their surface constituents in exquisite detail in biological samples.21 22

Conclusion

The pathogenesis of gout poses significant questions that still need to be answered. However, on a broader scale, the most important question about gout may be how we should proceed in sharing our relatively deep understanding of the disease in ways that achieve better recognition by the public and optimal diagnosis and management of all patients with this readily treatable condition.

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