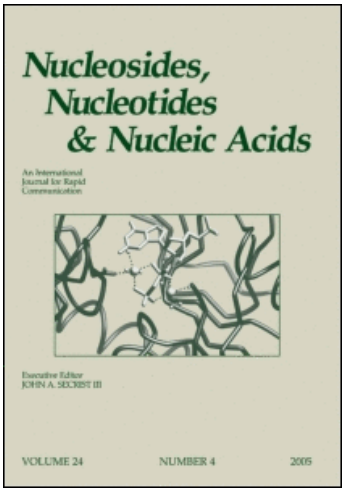

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Uric Acid and Renal Disease

J. Stewart Cameron[a]
[a] Renal Unit, Guy's Hospital, Guy's King's and St. Thomas' Medical School, King's College, London, UK

To cite this Article Cameron, J. Stewart(2006) 'Uric Acid and Renal Disease', Nucleosides, Nucleotides and Nucleic Acids, 25: 9, 1055 — 1064
To link to this Article: DOI: 10.1080/15257770600890954
URL: http://dx.doi.org/10.1080/15257770600890954

Nucleosides, Nucleotides, and Nucleic Acids, 25:1055–1064, 2006

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770600890954

Taylor & Francis
Taylor & Francis Group

URIC ACID AND RENAL DISEASE

J. Stewart Cameron □ *Renal Unit, Guy's Hospital, Guy's King's and St. Thomas' Medical School, King's College, London, UK*

□ *The interrelationship between uric acid and renal disease is reviewed in a historical context. Four phases can be distinguished—the descriptions of uric acid stones and gravel in the eighteenth century, of chronically scarred kidneys containing urate crystals in the nineteenth, the appearance of the syndrome of acute urate nephropathy following tumour lysis in the mid twentieth century, and finally the realization that soluble urate affects both systemic and glomerular blood vessels, and may play a role in both hypertension and chronic renal damage.*

Keywords Uric acid; Renal disease; Urate nephropathy; Tumor lysis syndrome; Hyperuricaemia; Uric acid stones

INTRODUCTION

A relationship between uric acid/urate and kidney disease has been long established, but many questions still remain unanswered and new data and ideas have created a resurgence of interest in uric acid as a potential major player in renal damage.[1–3] I would like to review briefly developments in this area in a historical context. Since the first observation of "lithic acid" (uric acid) as the major component of some renal stones in the latter half of the eighteenth century by the Swedish chemist Carl William Scheele (1742–1786), renal disease and uric acid have been intertwined. In addition it has been known for a century that the kidney is the major route of removal of purines from the body, in particular the major bulk metabolite, uric acid/urate.

CURRENT STATUS OF HANDLING OF URATE BY THE HUMAN AND MAMMALIAN KIDNEY

By the 1970s it had become clear, principally from studies of intact humans and animals, and micropuncture studies of mammalian renal tubular fluid, that urate is filtered almost freely with bulk transfer of urate

Address correspondence to J. Stewart Cameron, Elm Bank, Melmerby, Cumbria, CA10 1HB, UK. E-mail: jstewart.cameron2@btopenworld.com

throughout the proximal tubule from lumen into the blood amounting in adult humans to reabsorption of about 90% of filtered urate.[3,4] There appeared to be only minor addition of urate to tubular fluid later in the nephron, probably without further reabsorption.[4] From 1950 it had been known both on a genetic basis in occasional humans, but also under extreme study conditions in normal subjects, that secretion of urate was present but masked, probably by the predominant reabsorption under normal circumstances. A large amount of effort was put into attempts to identify more precisely the sequence and sites of tubular events principally using pharmacological agents,[5] but it is clear now that much of this information was misleading. This is particularly true with regard to the effect of pyrazinamide, which is now known to be a major substrate for reabsorption, as well as having a minor effect inhibiting some urate secretory channels.

In the past 15 years major advances in our understanding these processes have occurred.[3,4,6] First through studies of vesicles prepared from basolateral and tubular (brush border) membranes derived from renal tubular cells, and within the past 5 years from identification and sequencing of genes for transporters and ion channels with varying specificity and affinity for urate. These exchangers and channels have a differential distribution on the apical (brush border) and basolateral surfaces of the functionally polarised tubular cells, principally in the early segments of the proximal tubule. Current knowledge, still undergoing development, is summarized in Figure 1.

The complexity of the handing of urate may arise in part from inheritance of transporters important in removal of urate in ancestral birds and

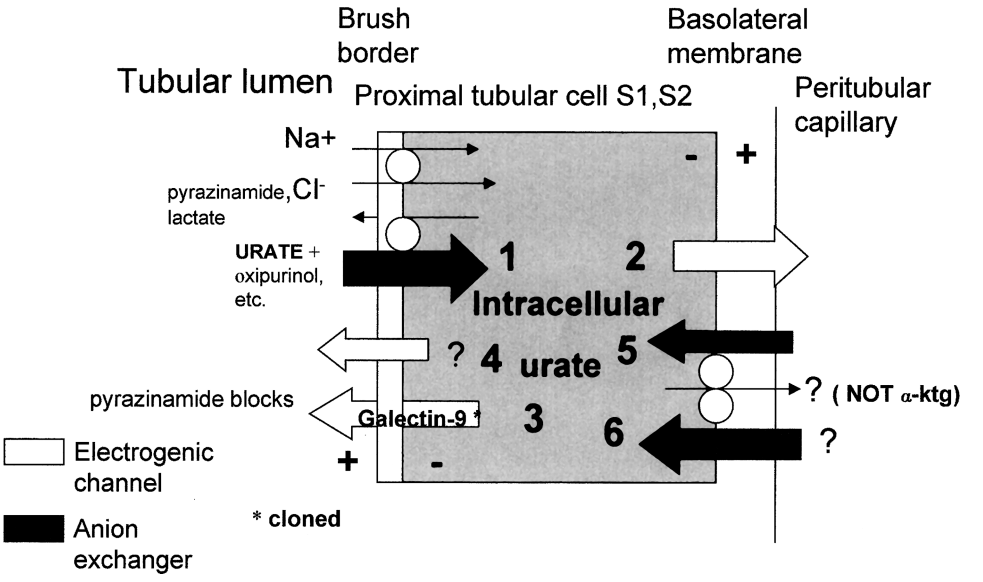

FIGURE 1

reptiles (in whom it is the major final product of nitrogen metabolism), as well as transporters specific to mammals which result in reabsorption. The loss of uricase activity some 8 million years ago rendered primates uniquely vulnerable to accumulation of urate in body fluids, despite loss of much activity in the final step of the urate-producing pathway, xanthine oxidreductase (XOR) around the same time.

The bulk of filtered urate is reabsorbed through an apical brush border sodium-coupled anion exchanger now known as URAT-1.[7] This corresponds to the high-affinity exchanger of Roch-Ramel and colleagues' apical membrane vesicles.[8] The genetic absence of this transporter in the pig leads to net secretion of urate at all concentrations in the blood, which suggest that the low-affinity exchanger (which may be one of the family of organic acid transporters[9]) has only a low flux. These exchangers are confined to the proximal tubule, almost entirely to the first two segments. Several voltage-dependent secretory anion channels seem to be present also, including one cloned from the pig (OATv1)[10] but another channel, apparently present along most of the nephron, is the UAT described by Abramson and colleagues.[11] This urate transport is one aspect of the polyfunctional molecule galectin-9. In addition other channels (of which the multi-drug resistance protein 4 is only one example), have some affinity for urate and promote its efflux from the cell.[12,13]

Much less is known about urate transport into and out of the renal tubular cells at the basolateral membrane, especially in humans.[3] Certainly a high capacity voltage-dependent exporting mechanismss are present, probably again multiple, but their nature is unknown as yet. Urate is imported into the tubular cell in mammals principally through the anion exchangers OAT-1 and OAT-3, as in many cells throughout the body,[9] but its activity in humans remains uncertain. Of course intracellular urate derived from reabsorption could be resecreted into the tubular fluid without ever entering the plasma.

One consequence of the presence of URAT-1 is that the human renal proximal tubular cell is exposed to a greater concentration of urate than any other cell in the body, especially given that only modest amounts of XOR are present only in human liver and gut epithelium, unlike its ubiquitous presence in all other mammalian tissues.[14] Mutations in URAT-1 account for most—if not all—human inherited hypouricaemias arising from hyperuricosuria—a state resembling that present normally in the pig kidney. Gain-of-function mutations/polymorphisms in this gene *might* play a role in hyperuricemia as well, but none have yet been described, despite a search for this phenomenon. It is more likely that most "classical" human gout is associated with alterations in one or more of the "minor" voltage-dependent secretory channels. This is probably true also in FJHN/MCKD complex of disorders,[2] in which the expression of the pathology

(abnormal intracellular traffic of uromodulin) appears to be confined to the thick ascending limb of Henle's loop,[2] at a site where no urate reabsorption occurs so far as we are aware, although some secretion probably is to be found there.

URIC ACID STONES

Historically, as noted above the first stage of relating renal pathology to urate/uric acid was the finding of stones predominantly made of these substances. Many such individuals with stones have clinical gout (a few with over production and overexcretion of urate) and even today the relative risk of urate stone formation is 2.2 in gouty as compared with nongouty populations.[15] However, many more individuals simply suffer from "idiopathic" urate lithiasis with normal plasma and urine urate concentrations. The association of this with a hot climate is explained by concentrated urine, but urine pH also is crucial, as demonstrated by states of intestinal bicarbonate loss (e.g., inflammatory bowel disease).

It has been known since at least 1962 that both groups of gouty and nongouty urate stone formers share a characteristic: their urine pH throughout the whole 24 hours of the day is low (<5.5) unlike the diurnal variation and generally higher pH of normal individuals.[16,17] This in turn makes precipitation of uric acid, rather than urate, much more likely. We still lack a satisfactory explanation for this persistent aciduria—it has been known for 40 years that in response to acid loading, gouty, and idiopathic uric acid stone formers excrete less ammonium than normals, but we still do not know why this is: there is no systemic resting acidosis. Little work has been done on this topic for some time.[16,17] Ammonia is formed in the renal tubule almost exclusively from glutamate, and the purine nucleotide cycles play little or no part in the kidney, unlike other tissues such as muscle.

PARENCHYMATOUS KIDNEY DISEASE AS A RESULT OF URATE/URIC ACID

Todd, in 1849, gave the first detailed description of diffuse renal involvement in gout, and soon it was realized that gouty patients often developed a crystal-related nephropathy, with frequent renal failure. During the subsequent century this was defined further as characterised by medullary deposits of urate/uric acid, associated with interstitial damage, tubular atrophy, and vascular degeneration.[18–20] In the later twentieth century the proinflammatory potential of urate/uric acid crystals was described, with endocytosis of crystals into macrophages and platelets followed by release of multiple inflammatory mediators from the participating cells. However, just as a central role for urate/uric acid crystals was defined within

joints, urate-associated nephropathy diminished greatly in incidence and severity,[21–23] leaving only a few gouty sub-groups suffering nephropathy with any regularity: those with partial HPRT deficiency[2] and urate overproduction showing increased excretion of urate on a low purine diet, those with lead poisoning, or those suffering familial dominantly inherited gout associated with abnormal trafficking of uromodulin in the thick ascending limb (FJHN/MCKD).[2] The latter two groups show normal total (absolute) urate excretion on a low purine diet, even though there a major reduction in the factional excretion of filtered urate seems to be a central event in both conditions.

Some of this improvement in the renal outlook for those suffering classical gout was undoubtedly followed introduction of uricosuric agents from the 1940s onward, and especially allopurinol from 1965, but this does not seem to provide the whole explanation. For example, when renal function of gouty patients whose urate remained high (when treated only with long-term colchicine) is compared with that of age-related controls, generally normal levels are found—albeit within the lower half of the normal range of GFR.[24,25] Some doubted the specificity of the changes seen in the kidney and their relation to the urate deposits- primary associated vascular disease seemed a principal cause.[21,22] Nevertheless, interstitial changes were prominent also and seemed not to be associated with infection. Today renal failure from chronic urate deposition is rare, and finding it raises a suspicion of the presence of either lead intoxication, FJHN/MCKD or partial HPRT deficiency.[3]

ACUTE URIC ACID RELATED NEPHROPATHY

Occasional patients with myeloid tumours such as leukaemias spontaneously develop an acute renal failure with prominent deposition of uric acid in the renal tubules, but the incidence of this "tumour lysis" syndrome[26] rose greatly and came into prominence about 1950, when such patients began to be treated with cytotoxic agents. Massive cellular breakdown occurred as a result, with huge loads of urate traversing the kidney. The intratubular pH is finally adjusted in the distal nephron, beginning in the cortical collecting duct, from which the pH steadily falls as the tubules traverse the medulla. In addition, as with urea the concentration of urate in the medulla is much higher than in the cortex, as part of the osmolar concentrating gradient present in the medulla.[27] Thus uric acid rather than urate is present within the collecting duct at low pH, which strongly favours its precipitation as a slurry, which then obstructs the tubules and loads the urine with crystals.

This acute, uric acid, intratubular deposition was compared in sharp contrast by some to the chronic, interstitial deposition of urate noted in

classical gout.[28] However, it became evident that some of the interstitial urate in chronic disease might arise also within the tubule as uric acid, with lysis of the tubular wall and translocation of the crystals and modulation to urate in response to differing pH.[29,30]

Conventionally, patients undergoing or likely to develop the tumour lysis syndrome have been treated with fluid infusions, sometimes alkalinisation, and allopurinol. This regime has its own disadvantages, since xanthine is of course even more insoluble than uric acid at physiological pH, and may coprecipitate with uric acid the active metabolite of allopurinol, oxipurinol. However since 1970 fungal urate oxidase has been available also, albeit allergenic and poorly available.[31] Now the enzyme gene has been expressed in yeast cultures, and a nonallergic, a readily-available preparation is on the market and undergoing extensive trials[32] as well as in resistant chronic gout.[33]

SOLUBLE URATE AS A RENAL AND VASCULAR TOXIN

For more than century a possible role of uric acid in cardiovascular disease has been debated,[34–36] largely because of major statistical associations present in both retrospective (and now prospective) studies between plasma urate concentrations and a variety of indicators of vasculopathy, and more recently the so-called "metabolic syndrome" (see Nakagawa, unpublished article). These include clinically myocardial infarction and vascular disease in general, truncal obesity and hypertension; and chemically, hypertriglyceridaemia, and hypercholesterolaemia. There has been disagreement whether urate emerged from these studies as an independent variable predicting vascular disease, however: until recently most observers felt that it did not.

There has been disagreement also about how the raised urate concentrations might come about: greater purine intake is an obvious possibility, urate production might be increased from ischaemia in vasculopathy,[37] and/or the fractional excretion of filtered urate reduced, for example by lactate. Recently, however, it has been realised that insulin has a major influence on renal tubular handling of urate,[38,39] and thus, the high plasma insulin concentrations of insulin-resistant states may decrease FEurate: this could be the central and early event leading to the many consequences of the metabolic syndrome, including hyperuricaemia[40] (see Nakagawa, unpublished article).

However, as well as renal damage from associated vascular disease, the possibility arises that urate in solution is directly toxic to the kidney or the intrarenal vasculature. Studies from the laboratory of Dr. Richard Johnson have examined this possibility. Rats treated with the uricase inhibitor oxonate in large doses develop a severe urate nephropathy; but if smaller doses are given chronically a state of stable persistent hyperuricaemia can

be obtained. In such rats, Johnson et al. have shown that an afferent arteriolopathy occurs,[41] which can be reversed by reducing the plasma urate concentration using allopurinol or benzodiarone, and also by ACE inhibition. They have confirmed previous studies that soluble urate induces proliferation in arteriolar smooth muscle cells in culture,[42] again reversible by ACE inhibition. When hyperuricaemia is superimposed on a model of kidney damage induced by 5/6 nephrectomy,[43] renal vascular lesions are increased, proteinuria is enhanced, and on glomerular arteriolar micropuncture arteriolar hypertension is increased as well as renal vascular resistance:[44] all these are reversed by lowering the urate concentrations. These results strongly suggest a direct role for soluble urate in inducing renal damage.[45]

However, we must note the differences in urate metabolism in rat and man. In the rat XOR is ubiquitous and strong: in humans it is weak and localised to liver and gut,[14] so that the majority of cells (including vascular endothelium and smooth muscle) cannot synthesise urate. Humans lack the promoter for uricase and so their cells are bathed in a plasma containing 300–400 umol/l of urate. In the rat, the plasma concentration of urate is less than half this. Thus, human cells have a very low intracellular urate, but are bathed in a plasma with a high concentration, whereas in complete contrast rat cells contain considerable amounts of urate, and lie in plasma deficient in it. The exception is the human proximal tubular cell, which bears the high-affinity urate exchanger URAT-1 (see above), and thus contains high concentrations of urate.

We can of course make some predictions from this work in rats to test whether the hypothesis that soluble urate is damaging to the kidney may hold in humans also. First, deficiency in XOR and absence of urate should be protective. However, this spontaneous "knockout" state in humans is rare and no conclusions can be drawn clinically. In addition, such patients develop xanthine crystalluria and stones, and hence, may sustain renal damage.

Second, chronic hyperuricaemia from other metabolic causes should lead to renal damage; however the scanty data from rare conditions such as fructose-induced chronic hyperuricaemia or glycogen storage disease type I do not support this suggestion.

Third, symptomless hyperuricaemia and gouty hyperuricaemia should be associated with chronic and progressive renal damage. As noted above, there are many problems in interpreting renal function in these states, particularly in gouty individuals in whom crystal-induced damage, obstruction, infection and vascular disease are variably present. In general, renal function in classical gouty patients is within the lower range of normal when corrected for age[24,25]—an equivocal result. However in the inherited familial gouty nephropathic patients (FJHN/MCKD) whose feurate is

particularly reduced, hyperuricaemia precedes all other manifestations of the disease,[46] and later slow evolution of renal failure is common.

Fourth, urate concentrations should correlate with—and above all predict—progression of renal diseases. Obviously a raised urate concentration measures overall renal function, so such data cannot be conclusive, but in an immunological form of renal disease (IgA nephropathy),[47,48] and following renal transplantation,[49] urate concentrations correlate with rates of progression to renal failure.

Fifth, lowering of urate concentrations should protect against renal failure or its progression in hyperuricaemic states. Here, we are hampered by studies lacking power or precision.[50,51] However the best of a number of small studies which measured true GFR showed a decline in renal function over 2 years in gouty patients treated with colchicine alone, compared with a similar group whose urate concentration was reduced additionally using allopurinol.[52] There is some suggestion also that renal function can be stabilized in gouty patients whose renal function already has fallen, using benzbromarone.[53] In addition early treatment using allopurinol may avert the slow renal failure of FJHN/MCKD,[54] although this is contested by others[55] whose data, however, deal with treatment begun after renal damage had occurred.

CONCLUSIONS

Thus, experimental evidence in rats and some clinical data suggest that soluble urate may be a factor in progressive renal damage, whether mediated directly or through renal vascular damage, or both. However, the bottom line is that we very much need adequately powered, prospective controlled studies of plasma urate reduction in hyperuricaemic patients with and without gout, and in idiopathic renal disease, to determine whether this is true in man.

REFERENCES

1. Johnson, R.J.; Cameron, J.S. (Eds) Uric acid in cardiovascular and renal disease. *Seminars in Nephrology* **2005**, 25, 1–166.
2. Cameron, J.S.; Simmonds, H.A. Hereditary hyperuricemia and renal disease. *Seminars in Nephrology,* **2005**, 25, 9–18.
3. Cameron, J.S.; Simmonds, J.S. Uric acid and the kidney. In *Oxford Textbook of Clinical Nephrology*, 3rd edition. Davison, A., Cameron, J.S., Grünfeld, J.P. et al. (Eds.) Oxford University Press, Oxford, **2005**, vol 2, pp. 1059–1073.
4. Weiner, I. Urate transport in the nephron. *Am. J. Physiol.* **1979**, 237, F85–F92.
5. Diamond, H.S. Interpretation of pharmacologic manipulation of urate transport in man. *Nephron* **1989**, 51, 1–5.
6. Rafey, M.A.; Lipkowitz, M.S.; Leal-Pinto, E.; Abramson, R.G. Uric acid transport. *Current Opinion in Nephrology and Hypertension* **2003**, 12, 511–516.
7. Enomoto, A.; Kimura, H.; Chairongdua, A.; Shigeta, Y.; Jutabha, P.; Cha, S.H.; Hosyamada, M.; Takeda, M.; Sekine, T.; Igarashi, T.; Matsuo, H.; Kikuchi, Y.; Oda, T.; Ichida, K.; Hosoya, T.;

Shimokata, K.; Niwa, T.; Kanai, Y.; Endou, H. Molecular identification of a renal urate-anion exchanger that regulates bood urate levels. *Nature* **2002**, 417, 447–452.
8. Roch-Ramel, F.; Guisan, B.; Diezi, J. Effect of uricosuric and anti-uricosuric agents on urate transport in human brush-border membrane vesicles. *Journal of Experimental Pharmacology and Therapeutics* **1997**, 280, 839–845.
9. Sekine, T.; Cha, S.H.; Endou, H. The multispecific organic ion transporter (OAT) family. *European Journal of Physiology* **2000**, 440, 337–350.
10. Jutabha, P.; Kanai, Y.; Hosoyamada, M.; Chairongdua, A.; Kim do, K.; Iribe, Y.; Babu, E.; Kim, J.Y.; Anzai, N. Identification of a novel voltage-driven organ ion transporter present at apical membrane of renal proximal tubule. *Journal of Biological Chemistry* **2003**, 278, 27930–27938.
11. Lipkowitz, M.S.; Leal-Pinto, E.; Cohen, B.E.; Abramson, R.G. Galectin 9 is the sugar-regulated urate transporter/channel UAT. *Glycoconjugate Journal* **2004**, 19, 491–498.
12. Hagos, Y.; Stein, D.; Ugele, B.; Burckhardt, G.; Bahn, A. Human renal organic ion transporter 4 (hOAT4) operates as an asymmetrical organic ion /OH' or anion Cl' exchanger. *Kidney and Blood Pressure Research* **2004**, 27, 267–423.
13. Van Aubel, R.A.; Smeets, P.H.; van den Heuvel, J.J.; Russel, F.G. Human organic ion transporter MRP4 (ABCC4) is an efflux pump for the urine end metabolite urate with multiple allosteric binding sites. *Am. J. Physiol.- Renal Fluid Electrolyte Physiol.* **2005**, 288, F327–F333.
14. Kooij, A.; Schijns, M.; Fredricks, W.M.; Van Noorden, C.J.; James, J. Distribution of xanthine oxidoreductase activity in human tissues—a histochemical and biochemical study. *Virchows Archiv, B.; Cell Pathology including Molecular Pathology* **1992**, 63, 17–23.
15. Kramer, H.J.; Choi, H.K.; Atkinson, K.; Stampfer, M.; Curhan, G.C. The association between gout and nephrolithiasis in men: the Health Professionals' follow-up study. *Kidney International* **2003**, 64, 1022–1026.
16. Kamel, K.S.; Cheema-Dhadli, S.; Halperin, M.L. Studies on the pathophysiology of the low urine pH in patients with uric acid stones. *Kidney International* **2002**, 61, 988–994.
17. Sakhaee, K.; Adams-Huet, B.; Moe, O.W.; Pak, C.Y.K. Pathophysiologic basis for normouricsuric acid nephrolithiasis. *Kidney International* **2002**, 62, 971–979.
18. Mohr, P. Urate deposition in tissues. In *Urate Deposition in Man and its Clinical Consequences*. Gresser, U. and Zöllner, N. (Ed.), Springer-Verlag, Berlin **1991**, pp. 24–27.
19. Talbott, J.H.; Terplan, K.L. The kidney in gout. *Medicine (Baltimore)* **1960**, 39, 405–467.
20. Barlow, K.A.; Beilin, L.J. Renal disease in primary gout. *Quarterly Journal of Medicine* **1968**, 37, 79–96.
21. Beck, L.H. Requiem for gouty nephropathy. *Kidney International* **1986**, 30, 280–287.
22. Nickeleit, V.; Mihatsch, M.J. Uric acid nephropathy and end stage renal disease- review of a non-disease. *Nephrology Dialysis Transplantation* **1997**, 12, 1832–1838.
23. Ifudu, O.; Tan, C.C.; Dulin, A.L.; Delano, B.G.; Friedman, E.A. Gouty arthritis in end-stage renal disease: clinical course and rarity of new cases. *American Journal of Kidney Diseases* **1994**, 23, 347–351.
24. Berger, L.; Yu, T.-F. Renal function in gout. IV An analysis of 524 gouty subjects including long-term follow-up studies. *American Journal of Medicine* **1975**, 59, 695–613.
25. Gibson, T.; Highton, J.; Potter, C.; Simmonds, H.A. Renal impairment and gout. *Annals of the Rheumatic Diseases* **1980**, 39, 417–423.
26. Jones, D.P.; Mahmoud, H.; Chesney, R.W. Tumor lysis syndrome: pathogenesis and management. *Pediatric Nephrology* **1995**, 9, 206–212.
27. Cannon, P.J.; Symchych, P.S.; Demartini, F.E. The distribution of urate in human and primate kidney. *Proceedings of the Society for Experimental Biology and Medicine* **1968**, 129, 278–284.
28. Emmerson, B.T.; Row, P.G. An evaluation of the pathogenesis of the gouty kidney. *Kidney International* **1975**, 8, 65–71.
29. Brown, J.; Mallory, G.K. Renal changes in gout. *New England Journal of Medicine* **1950**, 243, 325–329.
30. Farebrother, D.A.; Hatfield, P.; Simmonds, H.A.; Cameron, J.S.; Jones, A.S.; Cadenhead, A. Experimental crystal nephropathy (one year study in the pig). *Clinical Nephrology* **1975**, 4, 243–250.
31. Potaux, L.; Aparicio, M.; Maurel, C.; Ruedas, M.E.; Martin-Dupont, C. [Uricolytic therapy. Value of urate oxidase in the treatment of hyperuricaemia] Nouvelle Presse Médicale **1975**, 4, 1109–1112 (in French).
32. De Bont, J.M.; Pieters, R. Management of hyperuricaemia with rasburicase: review. *Nucleosides, Nucleotides and Nucleic Acids* **2003**, 23, 1431–1440.

33. Vogt, B. Urate oxidase (rasburicase) for treatment of severe tophaceous gout. *Nephrology Dialysis Transplantation* **2005**, 20, 431–433.
34. Johnson, R.J.; Kivlighn, S.D.; Kim, Y.-G.; Suga, S.; Fogo, A. Reappraisal of the pathogenesis and consequences of hyperuricemia in hypertension, cardiovascular disease, and renal disease. *American Journal of Kidney Diseases* **1999**, 33, 225–234.
35. Johnson, R.J.; Tuttle, K.R. Much ado about nothing, or much to do about something ? The continuing controversy over the role of uric acid in cardiovascular disease. *Hypertension* **2001**, 35, E10.
36. Waring, W.S.; Webb, D.J.; Maxwell, S.R.J. Uric acid as a risk for cardiovascular disease. *Quarterly Journal of Medicine* **2000**, 93, 707–713.
37. Messerli, F.H.; Frohlich, E.D.; Dreslinski, G.R.; Suraez, D.H.; Aristomuno, G.G. Serum uric acid in essential hypertension: an indicator of renal vascular involvement. *American Journal of Medicine* **1980**, 93, 817–821.
38. Muscelli, E.; Natali, A.; Bianchi, S.; Bigazzi, R.; Glavan, A.Q.; Sironi, A.M.; Frascerra, S.; Ciociaro, D.; Ferriannini, E. Effect of insulin on renal sodium and uric acid handling in essential hypertension. *American Journal of Hypertension* **1996**, 9, 746–352.
39. Quinones, G.A.;et al. Effect of insulin on uric acid excretion in humans. *American Journal of Physiology* **1995**, 268, E1–E5.
40. Facchini, F.; Chen, Y.-D.; Hollenbeck, C.B.; Reaven, G.M. Relationship between resistance to insulin-mediated glucose concentration uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA* **1991**, 266, 3008–3011.
41. Mazzali, M.; Kanellis, J.; Han, L.; Feng, L.; Xia, Y.Y.; Chen, Q.; Kang, D.H.; Gordon, K.L.; Wtabnabe, S.; Nakagawa, T.; Lan, H.Y.; Johnson, R.J. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood-pressure independent mechanism. *American Journal of Physiology* **2002**,, F991–F997.
42. Rao, G.N.; Corson, M.A.; Berk, B.C. Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain. *Journal of Biological Chemistry* **1991**, 266, 8604–8608.
43. Kang, D.-H.; Nakgawa, T.; Feng, L.;et al. A role for uric acid in the progression of renal disease. *Journal of the American Society of Nephrology* **2002**, 13, 2888–2997.
44. Sanchez-Lozada, L.G.; Tapia, E.; Santamaria, J.; Avila Casado, C.; Soto, V.; Nepomuceno, T.; Rodriguez-Iturbe, B. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney International* **2005**, 67, 237–247.
45. Kang, D.-H.; Nakagawa, T. Uric acid and chronic renal disease: possible implication of hyperuricemia in progression of renal disease. *Seminars in Nephrology* **2005**, 25, 43–49.
46. McBride, M.B.;et al. Presymtomatic detection of familial juvenile hyperuricaemic nephropathy in children. *Pediatric Nephrology* **1998**, 12, 359–364.
47. Syrjanen, J.; Mustonen, J.; Pasternack, A. Hypertriglyceridemia and hyperuricaemia are risk factors for progression of IgA nephropathy. *Nephrology Dialysis Transplantation* **2000**, 15, 34–42.
48. Ohno, I.; Hosya, T.; Gomi, H.; Ichida, K.; Okabe, H.; Hikita, M. Serum uric acid and renal prognosis in patients with IgA nephropathy. *Nephron* **2001**, 87, 333–339.
49. Gerhardt, U.; Grobe Huttmann, M.; Hohage, H. Influence of hyperglycemia and hyperuricemia on long-term transplant survival in kidney transplant patients. *Clinical Transplantation* **1999**, 13, 375–379.
50. Fessel, W.J. Renal outcomes of gout and hyperuricemia. *American Journal of Medicine* **1979**, 67, 74–82.
51. Rosenfeld, J.B. Effect of long-term allopurinol administration on serial GFR in normotensive and hypertensive hyperuricemic subjects. *Advances in Experimental Medicine & Biology* **1974**, 41, 581–596.
52. Gibson, T.; Rodgers, V.; Potter, C.; Simmonds, H.A. Allopurinol treatment and its effect on renal function in gout: a controlled study. *Annals of the Rheumatic Diseases* **1982**, 41, 59–65.
53. Perez-Ruiz, F.; Calobozo, M.; Herrero-Beites, A.M.; Garcia-Erauskin, G.; Pijoan, J.I. Improvement in renal function in patients with chronic gout after proper control of hyperuricemia and gouty bouts. *Nephron* **2000**, 86, 287–291.
54. Fairbanks, L.; Cameron, J.S.; Venkat Raman, G.; Rigden, S.P.; Rees, L.; Van't Hoff, W.; Mansell, M.; Pattison, J.; Goldsmith, D.J.; Simmonds, H.A. Early treatment with allopurinol in familial juvenile hyperuricaemic nephropathy (FJHN) ameliorates the long-term progression of the renal disease. *Quarterly Journal of Medicine* **2002**, 95, 597–607.
55. Miranda, M.E.; Puig, J.G.; Mateos, F.A.; Herranz, I.; Martinez Ara, J.; Berrocal, T.; Proieto, C.; Picazo, M.L. The influence of allopurinol on renal deterioration in familial nephropathy. *Advances in Experimental Medicine and Biology* **1994**, 370, 61–64.