Is There a Pathogenetic Role for Uric Acid in Hypertension and Cardiovascular and Renal Disease?

Richard J. Johnson, Duk-Hee Kang, Daniel Feig, Salah Kivlighn, John Kanellis, Susumu Watanabe, Katherine R. Tuttle, Bernardo Rodriguez-Iturbe, Jaime Herrera-Acosta, Marilda Mazzali

Abstract—Hyperuricemia is associated with hypertension, vascular disease, renal disease, and cardiovascular events. In this report, we review the epidemiologic evidence and potential mechanisms for this association. We also summarize experimental studies that demonstrate that uric acid is not inert but may have both beneficial functions (acting as an antioxidant) as well as detrimental actions (to stimulate vascular smooth muscle cell proliferation and induce endothelial dysfunction). A recently developed experimental model of mild hyperuricemia also provides the first provocative evidence that uric acid may have a pathogenic role in the development of hypertension, vascular disease, and renal disease. Thus, it is time to reevaluate the role of uric acid as a risk factor for cardiovascular disease and hypertension and to design human studies to address this controversy.  

Key Words: antioxidants ■ hypertension, essential ■ cardiovascular diseases ■ renin-angiotensin system ■ vascular diseases ■ renal disease

Uric acid, a product of purine metabolism, is degraded in most mammals by the hepatic enzyme, urate oxidase (uricase), to allantoin, which is freely excreted in the urine. However, during the Miocene epoch (20 to 5 million years ago), 2 parallel but distinct mutations occurred in early hominoids that rendered the uricase gene nonfunctional.1 As a consequence, humans and the great apes have higher uric acid levels (>2 mg/dL) compared with most mammals (<2 mg/dL).

Uric acid levels also vary significantly within humans as the result of factors that increase generation (such as high purine or protein diets, alcohol consumption, conditions with high cell turnover, or enzymatic defects in purine metabolism) or decrease excretion. A reduction in glomerular filtration rate (GFR) increases serum uric acid, although a significant compensatory increase in gastrointestinal excretion occurs.2 Hyperuricemia also may result from increased net tubular absorption. After filtration, uric acid undergoes both reabsorption and secretion in the proximal tubule, and this process is mediated by a urate/anion exchanger and a voltage-sensitive urate channel.3,4 Organic anions such as lactate decrease urate secretion by competing for urate through the organic anion transporter, whereas several substances, including probenaciacid and benziodarone, have opposite effects.5 Hyperuricemia is usually defined as >6.5 or 7.0 mg/dL in men and >6.0 mg/dL in women.

Hyperuricemia Is Increased in Subjects at Cardiovascular Risk

Serum uric acid is frequently elevated in subjects at cardiovascular risk (Table 1).6–15 Uric acid is higher in men and postmenopausal women because estrogen is uricosuric.8 In subjects with obesity, insulin resistance, and dyslipidemia (“the metabolic syndrome”), hyperuricemia frequently occurs because insulin stimulates sodium and urate reabsorption in the proximal tubule.8 Uric acid is increased in subjects with renal disease as the result of reduction in GFR and renal urate excretion. Diuretics, such as thiazides, increase serum uric acid by stimulating both sodium and urate reabsorption in the proximal tubule. Alcohol intake results in elevated uric acid levels due to increased urate generation (from increased adenine nucleotide turnover) and decreased excretion (due to lactate blocking tubular transport of urate).14,15

Uric acid is also commonly associated with hypertension. It is present in 25% of untreated hypertensive subjects, in 50% of subjects taking diuretics, and in >75% of subjects with malignant hypertension.9 The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate reabsorption.10 Hypertension also results in microvascular disease, and this can lead to local tissue ischemia.11 In addition to the release of lactate that blocks urate secretion in the proximal tubule, ischemia...
also results in increased uric acid synthesis. With ischemia, ATP is degraded to adenine and xanthine, and there is also increased generation of xanthine oxidase. The increased availability of substrate (xanthine) and enzyme (xanthine oxidase) results in increased uric acid generation as well as oxidant ($O_2^-$) formation. The finding that ischemia results in an increase in uric acid levels may also account for why uric acid is increased in preeclampsia and congestive heart failure. Other factors may also contribute to why uric acid is associated with hypertension, including alcohol abuse, lead intoxication, obesity and insulin resistance, and diuretic use.

The observation that an elevated uric acid is associated with subjects at cardiovascular risk may account for why hyperuricemia predicts the development of cardiovascular disease in the general population (Table 2), in subjects with hypertension (Table 3), and in subjects with preexisting cardiovascular disease (Table 4). Hyperuricemia also predicts stroke in diabetic and nondiabetic subjects and predicts the development of hypertension and renal disease in the general population. In these studies, uric acid may be simply “marking” subjects at increased cardiovascular and renal risk. Consistent with this hypothesis, many studies have found that uric acid is not an independent risk factor for cardiovascular disease after controlling for these other risk factors (Tables 2 through 4). Hyperuricemia is therefore considered benign unless associated with gout or kidney stones.

Nevertheless, some studies find uric acid predictive for the development of cardiovascular disease, hypertension, and renal disease despite controlling for associated risk factors. This raises the possibility that uric acid may have a pathogenic role in hypertension and cardiovascular disease. Indeed, recently soluble uric acid has been recognized to not be inert but rather to have several biological actions that could either be beneficial or detrimental to humans. We now review these studies and provide an interpretation for how they may relate to human disease.

**Uric Acid as an Antioxidant: A Protective Factor in Cardiovascular Disease?**

An important observation was that uric acid may function as an antioxidant, and possibly one of the most important antioxidants in plasma. Urate (the soluble form of uric acid in the blood) can scavenge superoxide, hydroxyl radical, and singlet oxygen and can chelate transition metals. Peroxynitrite is a particularly toxic product formed by the reaction of superoxide anion with nitric oxide that can injure cells by nitrosylating the tyrosine residues (nitrotyrosine formation) of proteins. Uric acid can also block this reaction.

Recently, Hink et al reported that uric acid may also prevent the degradation of extracellular superoxide dismutase (SOD3), an enzyme critical in maintaining endothelial and vascular function. SOD3 is an extracellular enzyme that catalyzes the reaction of superoxide anion ($O_2^-$) to hydrogen peroxide ($H_2O_2$). The removal of $O_2^-$ by SOD3 prevents the reaction and inactivation by $O_2^+$ of the important endothelial vasodilator, nitric oxide (NO). SOD3, by removing $O_2^+$, therefore helps to maintain NO levels and maintain endothelial function.

Normally, SOD3 is inactivated in the presence of $H_2O_2$, suggesting a feedback inactivation of the enzyme. However, uric acid blocks SOD inactivation by $H_2O_2$ by regenerating SOD3 with the production of a urate radical. This latter radical, although potentially a pro-oxidant, has been found to be markedly less reactive than classic oxidants and can be rapidly regenerated back to urate in the presence of ascorbate.

Ames et al hypothesized that the uricase mutation occurred during early hominoid evolution because the antioxidant action of uric may have provided an evolutionary advantage and that this may account for the greater longevity of humans and the great apes compared with most other primates. The increase in serum uric acid in subjects with cardiovascular disease might therefore reflect a compensatory mechanism to counter the oxidative stress that occurs in these conditions. However, this does not readily explain why higher uric acid levels in patients with cardiovascular disease are generally associated with worse outcomes (Tables 3 and 4).

**Is Uric Acid a Mediator of Hypertension and Renal Disease?**

Uric Acid, Endothelial Dysfunction, and Impaired Nitric Oxide Production

Endothelial dysfunction, local oxidant generation, elevated circulating cytokines, and a proinflammatory state are com-

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**TABLE 1. Uric Acid Is Increased in Groups at Cardiovascular Risk**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal women and men</td>
<td>Estrogen is uricosuric</td>
</tr>
<tr>
<td>African Americans</td>
<td>Unknown</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Decrease in GFR increases uric acid levels</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Volume contraction promotes urate reabsorption</td>
</tr>
<tr>
<td>Obesity/insulin resistance</td>
<td>Insulin increases sodium reabsorption and is tightly linked to urate reabsorption</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Urate reabsorption increased in setting of increased renal vascular resistance; microvascular disease predisposes to tissue ischemia that leads to increased urate generation (from adenosine breakdown) and reduced excretion (due to lactate competing with urate transporter in the proximal tubule); some hyperuricemic hypertension may be due to alcohol ingestion or lead intoxication</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>Increases urate generation, decreases urate excretion</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate.
mon in patients with cardiovascular disease. Endothelial dysfunction is often demonstrated by showing an impaired NO release in response to acetylcholine, which results in impaired endothelium-dependent vasodilation. Oxidants may cause endothelial dysfunction by reacting with and removing the NO. The observation that xanthine oxidase generates oxidants and uric acid in settings of tissue ischemia potentially explains why uric acid is associated with endothelial dysfunction and oxidative stress in conditions such as heart failure and diabetes. Hyperuricemia is also associated with the activation of circulating platelets, which also may reflect endothelial dysfunction. Allopurinol, which inhibits xanthine oxidase and hence blocks both uric acid and oxidant formation, can reverse the impaired endothelial NO production in both heart failure and type 2 diabetes. Allopurinol has also been reported to reduce cardiovascular complications after coronary artery bypass and in patients with dilated cardiomyopathy. Although the beneficial effects correlate with the lowering of uric acid in some of these studies, most authorities have hypothesized that the beneficial effect of allopurinol is to reduce oxidative stress.

Uric acid may contribute to endothelial dysfunction. Waring et al have reported that uric acid infusion in healthy humans resulted in impaired acetylcholine-induced vasodilation in the forearm, thereby documenting impaired endothelial NO release. Serum uric acid and serum nitric oxide levels also vary during the day in a reciprocal pattern, suggesting a pattern of physiological regulation. Recent studies in experimental animal models have also found that mild hyperuricemia inhibits the nitric oxide system in the kidney (see below).

The mechanism by which uric acid impairs endothelial function is not known. However, whereas uric acid is con-
sidered an antioxidant, it is also pro-oxidative under certain conditions, especially when other antioxidants are at a low level.74,75

Uric Acid, Vascular Smooth Muscle Cell Proliferation, and Inflammation

Uric acid also stimulates rat vascular smooth muscle cell proliferation in vitro.76–79 Vascular smooth muscle cells do not express a receptor for uric acid but rather have organic anion transporters that allow urate uptake.80 Once inside the vascular smooth muscle cell, uric acid activates specific mitogen activated protein kinases (Erk1/2) with the de novo induction of cyclooxygenase-2 (COX-2), local thromboxane formation, and with upregulation of platelet-derived growth factor A (PDGF A) and C-chain and PDGF-α receptor mRNA76–79 (Figure). The uric acid–induced cell proliferation can be inhibited by blocking any member of this pathway.76–79

Soluble uric acid also is proinflammatory. Uric acid stimulates synthesis of monocyte chemoattractant protein-1 (MCP-1) in rat vascular smooth muscle cells by activating p38 MAP kinase and the nuclear transcription factors, NF-κB and AP-1.81 MCP-1 is a chemokine that is important in vascular disease and atherosclerosis.82 Soluble uric acid also stimulates human mononuclear cells to produce interleukin-1β, interleukin-6, and tumor necrosis factor (TNF)-α.83 Infusion of uric acid into mice also leads to a marked increase in circulating TNF-α levels.84 Thus, in experimental and in vitro systems, uric acid appears to have the ability to induce inflammatory and vascular mechanisms that may contribute to rather than protect against the development of cardiovascular disease.

Experimental Models: Hypertension in Hyperuricemic Rats

Recently, mild hyperuricemia was developed in rats through the use of a uricase inhibitor (oxonic acid). Unlike previous hyperuricemic models,85,86 this model was associated with no urate crystal deposition in the kidney and relatively preserved renal function.87 A remarkable observation, now documented by two different laboratories, was that systemic hypertension developed in hyperuricemic rats after several weeks.77,78,87,88

<table>
<thead>
<tr>
<th>Study</th>
<th>Length of Follow-Up, y</th>
<th>Univariate Correlation with Events</th>
<th>Independent Predictor in Multivariate Analyses</th>
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<tbody>
<tr>
<td>Hypertension Detection Follow-Up Program Cooperative Research Group 198516</td>
<td>5</td>
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<td>Yes</td>
</tr>
<tr>
<td></td>
<td>198717</td>
<td>5†</td>
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<tr>
<td>Work site 199818</td>
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<tr>
<td>PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) 200019</td>
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<td>Yes</td>
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<tr>
<td>European Working Party on High BP in the Elderly 199140</td>
<td>3</td>
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<td>No</td>
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<tr>
<td>SHEP (Systolic Hypertension in the Elderly Program)* 200141</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Syst-China* 200142</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Syst-Eur* 200243</td>
<td>2</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Patients with isolated systolic hypertension; †subanalysis of patients on thiazides.

TABLE 4. Hyperuricemia Predicts Cardiovascular Events in Patients With Pre-Existing Cardiovascular Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Univariate Correlation With Events</th>
<th>Independent Predictor in Multivariate Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project Research Group, 197644</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>French Canadian Study, 197345</td>
<td>No</td>
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</tr>
<tr>
<td>Atherogene Study, 200246</td>
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<td>Yes</td>
</tr>
<tr>
<td>The Heart Institute of Spokane, 200247</td>
<td>Yes</td>
<td>Yes</td>
</tr>
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</table>
Pathway for uric acid–mediated vascular smooth muscle cell proliferation. Uric acid is posited to enter into vascular smooth muscle cells through an anion exchanger/transporter (OAT), where it alters intracellular redox, activates mitogen activated protein kinases (ERK1/2 and p38), COX-2, and nuclear transcription factors (NFκB and AP-1), leading to synthesis of thromboxane (TXA2), PDGF and PDSF receptors, and MCP-1.

Hyperuricemic rats were also shown to have salt sensitivity (that is, a greater increase in blood pressure for the same sodium load compared with normal rats).78 An explanation for the mechanism comes from studies in other experimental models that have shown that salt sensitivity may result from preglomerular vascular disease.89 Experimental models associated with preglomerular vascular disease have renal ischemia, leading to the infiltration of leukocytes into the interstitial tissue that generate local oxidants, altering the balance of local vasoregulatory factors favoring vasoconstriction, and resulting in a reduction in sodium excretion, a shift in pressure natriuresis, and an increase in blood pressure. Elements of this pathway have been demonstrated in a variety of animal models, and the salt sensitivity can be prevented or ameliorated by interrupting this pathway.89

Consistent with this pathway of salt sensitivity, chronically hyperuricemic rats have thickening and hypercellularity of the afferent arteriole of the glomerulus, with inward hypertrophic vascular remodeling, leading to an increase in medial thickness and a reduction in lumen diameter.78 The arteriolopathy occurs independent of blood pressure, although it is dependent on the renin-angiotensin system.77 In concert with the development of preglomerular vascular disease, rats manifest subtle tubulointerstitial inflammation and fibrosis.78 Once these renal changes develop, salt sensitivity can be shown. At this point, the kidney is driving salt sensitivity because correction of the elevated uric acid level is no longer protective.78

Experimental Hyperuricemia and Renal Injury

Renal injury also occurs in hyperuricemic rats, consisting of afferent arteriolopathy, mild tubulointerstitial fibrosis, glomerular hypertrophy, and eventually, glomerulosclerosis and albuminuria.90 Micropuncture studies document that this is associated with an increase in glomerular hydrostatic pressure.88 The renal changes are prevented if serum uric acid is maintained in the normal range with allopurinol.88,90

Experimental hyperuricemia also accelerated injury in established models of renal disease. Hyperuricemia exacerbates cyclosporine nephropathy in rats, resulting in worse tubulo-interstitial injury and arteriolar hyalinosis with increased renin and a greater loss of macula densa NOS1 and renal NOS3 expression.91 Hyperuricemia also accelerated progression in the remnant kidney model and resulted in higher blood pressure, more proteinuria, worse renal function, and more glomerulosclerosis and tubulo-interstitial fibrosis.79 These rats also had severe vasculopathy, involving the interlobular artery and afferent arteriole with de novo expression of COX-2 in the blood vessels and increased renal renin expression. The renal changes were significantly improved by reducing uric acid levels with allopurinol.

Do the Experimental Studies Provide New Insights?

The observation that hyperuricemic animals have salt sensitivity and increased blood pressure provide an additional mechanism to explain why the uricase mutation occurred in early hominoid evolution. Thus, the uricase mutation may have provided an evolutionary advantage to early hominoids by maintaining blood pressure under the low sodium dietary conditions of that period.78

The observation that experimental hyperuricemia causes hypertension, intrarenal vascular disease, renal disease, and vascular inflammation in rats may also provide the long-sought pathogenic mechanism by which uric acid could cause cardiovascular disease in humans.

Is there evidence that uric acid causes hypertension in humans? Epidemiological studies show a continuous relation of serum uric acid with blood pressure that is stronger in younger subjects with some dampening over time,19,20,92 which is consistent with the experimental studies that demonstrate that once sufficient renal injury occurs that animals develop salt-sensitive hypertension regardless of the uric acid levels.78 Hyperuricemia is also an independent risk factor for predicting the development of hypertension (Table 5).51,52 To date, no studies have examined whether lowering uric acid will reduce blood pressure in hypertensive humans, but it should be noted that the above studies suggest that lowering uric acid would be more effective at preventing rather than treating hypertension, for once the intrarenal vascular disease develops, the hypertension would then be expected to be driven by the kidney. Hyperuricemia also correlates with

<table>
<thead>
<tr>
<th>TABLE 5. Hyperuricemia Predicts the Development of Hypertension</th>
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<tr>
<td><em>Shown to independently predict the development of hypertension.</em></td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israeli Ischemic Heart Study, 1972</td>
<td>70</td>
</tr>
<tr>
<td>Kaiser Permanente Medical Care Program, 1990</td>
<td>71</td>
</tr>
<tr>
<td>Olivetti Heart Study, 1993</td>
<td>72</td>
</tr>
</tbody>
</table>

*Shown to independently predict the development of hypertension.
plasma renin activity,\textsuperscript{93,94} and renal renin expression is also increased in hyperuricemic rats.\textsuperscript{97}

Does uric acid cause renal disease in humans? Patients with gout frequently have renal dysfunction (25\% to 40\% of cases), with histologic injury in the majority.\textsuperscript{95} The renal lesion consists of variable degrees of arteriolosclerosis, glomerulosclerosis, and interstitial fibrosis, often with focal deposition of urate crystals in the outer medulla.\textsuperscript{95} Many authorities have ascribed the renal lesion to coexistent hypertension or aging-associated renal disease.\textsuperscript{96} However, this type of analysis cannot account for all of the renal injury observed.\textsuperscript{97}

Recently, an elevated uric acid has been reported to predict the development of renal insufficiency in individuals with normal renal function.\textsuperscript{55} Uric acid is an independent predictor for progression in IgA nephropathy.\textsuperscript{98,99} Hyperuricemia also correlates with the development of renal dysfunction in type II diabetes\textsuperscript{100} and independently predicts progression in renal transplant patients on cyclosporine (Al-Uzri AY, Prather JC, Norman DJ, Gloconda S, and de Mattos AM. Hyperuricemia as a risk factor for renal allograft loss, American Transplant Congress, 2002, abstract). In contrast, it remains unclear if uric acid is a risk factor for progression in subjects with established renal disease. Although experimental studies suggest uric acid may act as a risk factor for progression,\textsuperscript{79} in the MDRD study, uric acid was not found to be a risk factor.\textsuperscript{101} Furthermore, whereas some studies report an improvement in renal function with the lowering of uric acid in gouty subjects,\textsuperscript{102,103} others have not been able to confirm these findings.\textsuperscript{104}

How about the role of uric acid in mediating the systemic inflammatory response and endothelial dysfunction in humans? As discussed earlier, uric acid infusion into humans causes endothelial dysfunction,\textsuperscript{72} and allopurinol improves endothelial dysfunction in subjects with congestive heart failure or diabetes.\textsuperscript{65,67} Uric acid also stimulates the production of cytokines from leukocytes and chemokines from vascular smooth muscle cells. This suggests a potential role for uric acid or for xanthine oxidase in mediating the systemic inflammatory response that is linked to cardiovascular events.

Finally, these studies may provide insights into why uric acid is not always found to be an independent risk factor for cardiovascular events. Thus, if uric acid caused cardiovascular disease as a consequence of causing hypertension or renal disease, then it would not be expected to be independent of these latter variables when evaluated as risk factors for cardiovascular events. Furthermore, in the SHEP trial, in which diuretics were shown to reduce cardiovascular mortality rates in the elderly, a recent subanalysis showed that the cardioprotection was lost in those treated patients in whom uric acid levels increased.\textsuperscript{61} It is therefore of interest that many studies that failed to show uric acid to be an independent risk factor for cardiovascular events found that the association of uric acid with cardiovascular events was attenuated by either the presence of hypertension or the use of diuretics.\textsuperscript{22,30,31,34,44}

Another reason why uric acid may not always be an independent risk factor for cardiovascular events could be that the beneficial antioxidant actions of uric acid may partially counter its potential detrimental effects. It is of interest that almost all studies examining the relation of uric acid levels with cardiovascular events show a J-shaped curve with the nadir of risk being in the second quartile.\textsuperscript{20–25,28,29,39,43,44} Although speculative, it is possible that the increased risk for the lowest quartile reflects the decreased plasma antioxidant activity, whereas the increased risk at higher levels reflects the role of uric acid in inducing vascular disease and hypertension.

In conclusion, recent evidence supports a role for uric acid as a true cardiovascular risk factor, particularly for the development of hypertension and renal disease. Studies need to be performed in humans to prove or disprove this possibility before lowering uric acid is routinely recommended. Given that hyperuricemia causes glomerular vascular disease in rats, one might posit that it may be easier to show a role for uric acid in hypertension by designing preventive trials as opposed to treatment trials. However, it is possible that treating hyperuricemia may be effective in lowering blood pressure when the hyperuricemia has not been present for a long period (such as in children with hypertension and in patients given short-term treatment with cyclosporine or diuretics) or when subjects are given a low salt diet (which would remove the renal injury–dependent mechanism).

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References


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