Hypertension is epidemic and currently affects 25% of the world’s population and is a major cause of stroke, congestive heart failure, and end-stage renal disease. Interestingly, there is evidence that the increased frequency of hypertension is a recent event in human history and correlates with dietary changes associated with Westernization. In this article, we review the evidence that links uric acid to the cause and epidemiology of hypertension. Specifically, we review the evidence that the mutation of uricase that occurred in the Miocene that resulted in a higher serum uric acid in humans compared with most other mammals may have occurred as a means to increase blood pressure in early hominoids in response to a low-sodium and low-purine diet. We then review the evidence that the epidemic of hypertension that evolved with Westernization was associated with an increase in the intake of red meat with a marked increase in serum uric acid levels. Indeed, gout and hyperuricemia should be considered a part of the obesity, type 2 diabetes, and hypertension epidemic that is occurring worldwide. Although other mechanisms certainly contribute to the pathogenesis of hypertension, the possibility that serum uric acid level may have a major role is suggested by these studies.

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pared with other mammals. It also is possible that alterations in transport mechanisms involved in renal urate excretion may have occurred.

Several hypotheses have been proposed to account for the mutation of uricase in humans and the Great Apes. An early hypothesis was that an increase in serum uric acid level may increase intelligence because it has similarities to other cerebral stimulants, such as caffeine. Perhaps the most favored hypothesis is that the increase in serum uric acid level occurred to provide greater antioxidant activity, and that this may account for the greater longevity of humans and Great Apes compared with most other mammals. Indeed, uric acid is a strong antioxidant, and accounts for much of the antioxidant activity in plasma. A similar antioxidant hypothesis suggests that the uricase mutation occurred as a consequence of the loss of our ability to synthesize vitamin C. Our ability to synthesize vitamin C was lost approximately 40 to 50 million years ago owing to a mutation in L-gulono-lactone oxidase. This mutation may have occurred because the primates of that period were largely fruit-eating and hence were ingesting large quantities of vitamin C, making the mutation harmless. However, later there was a selection advantage for those species that could increase their antioxidants, and this was provided by the uricase mutation.

Although the antioxidant hypothesis remains a viable possibility for why the mutation of uricase persisted, an increased uric acid level is not associated with longevity in any species. In fact, in humans almost all studies show the opposite: higher uric acid levels correlate with an increased risk for death.

We proposed an alternative hypothesis, that the mutation of uricase resulted in increased blood pressure and increased salt sensitivity. We know that our early hominoid ancestors were on a very low sodium diet. It is possible that the rapid evolutionary changes in our species, coupled with the changes in climate during the mid Miocene period, may have favored those individuals who could conserve sodium more effectively. In support of this hypothesis is a large amount of literature showing that uric acid levels correlate with blood pressure levels. Increasing serum uric acid levels in rats (by inhibiting uricase) results in an increase in blood pressure that was particularly evident under low-sodium dietary conditions. Also, hyperuricemia caused renal structural changes that resulted in salt sensitivity. Uric acid induces endothelial dysfunction, leading to an acute salt-resistant increase in blood pressure, followed by uric acid-induced arteriolosclerosis of the renal vasculature, in turn leading to persistent salt-sensitive hypertension. Evidence that a similar process may be occurring in humans also is available. Thus, an increase in serum uric acid level may have a role in the pathogenesis of essential hypertension.

The uricase mutation may have been advantageous to our early hominoid ancestors by helping them to maintain blood pressure levels during environmental stress. But in modern humans there is evidence that the increase in serum uric acid level may predispose them to cardiovascular disease. In part, this new risk could be attributed to changes in sodium intake because early hominoids were eating only 0.5 g/d of salt compared with the 8 to 10 g/d of salt ingested in current American diets. However, another important consideration is the effect of diet on serum uric acid levels because animals lacking uricase do not regulate serum uric acid levels very effectively. Thus, diets rich in fatty meats and low in dairy products increase the risk for gout. In the following section we discuss the possibility that the epidemic of hypertension associated with industrialization may be linked pathogenetically to changes in serum uric acid level that occurred as a consequence of changes in diet, alcohol ingestion, and lead exposure.

### The Anthropology of Blood Pressure and Uric Acid Levels

Hypertension in the absence of obvious renal disease (primary or essential hypertension) was first described in the mid-1800s by Frederick Akbar Mahomed from Guy’s Hospital in London. It was interesting that hypertension was not uncommon in Victorian England, and similarly gout also was rampant, especially among the wealthy, where it was often the subject for caricatures. Part of the epidemic of gout may have been related to the common drinking of fortified wines, especially port, that were heavily contaminated with lead (which is known to increase uric acid levels and cause saturnine gout). It is thus of interest that several investigators, including Mohamed himself, noted a strong association of hypertension with gout and/or lead intoxication. Indeed, the French physician Huchard also reported that the primary causes of arteriolosclerosis, the structural counterpart to hypertension, were gout and hyperuricemia, followed by lead ingestion, with the third most common cause being the indiscretionary eating of large quantities of meat.

Although hypertension was being reported increasingly in Europe, it remained unknown in most other societies. Indeed, early studies in Africa, the Middle East, India, China, South and Central America, the South Pacific, the Australian Aborigine, and in American Indians showed minimal evidence of hypertension before Westernization. However, after exposure to Western culture, a marked increase in the incidence of hypertension and obesity occurred, particularly in association with adaptation of the Western diet.

Although many of these early studies did not report on the relationship of uric acid and gout as it related to Westernization and the increased frequency of hypertension, there are several salient examples in which this was examined. For example, an increased frequency of hypertension in African Americans was first noted in the United States and the Caribbean in the 1930s to 1940s. Shortly thereafter gout was reported in this population; today both hypertension and gout are more common in African Americans than Caucasians. In one study this increased frequency of gout was linked directly with the increased frequency of hypertension. Similarly, gout and hyperuricemia also were rare in Africa until the 1960s and 1970s, when they emerged in urban areas exposed to Western cultures. Again, they were associated with hypertension and obesity.

Other examples include the Maori of New Zealand, who...
were once a lean race that subsided primarily on fish, taro, sweet potato, and fern root. In the initial descriptions of Maori health, gout was never seen; however, with a change to a Western diet of fatty meats and saturated fats, an epidemic of gout along with obesity, type II diabetes, and hypertension was observed. Australian Aborigines also developed a high frequency of hypertension and obesity after the adaptation of a Western diet. This is also associated with an increased frequency of hyperuricemia. The immigration of Filipinos to the United States also was associated with an increased frequency of hypertension and obesity; again associated with an increased intake of animal meats. Studies of immigrant Japanese also show that moving from Japan to Hawaii and then to California was associated with a progressive increase in serum uric acid level and an increased frequency of hypertension and obesity; again associated with an increased intake of animal meats and saturated fats.

These data are consistent with the hypothesis that a change in diet from a traditional wild game, fish, and vegetarian diet to a Westernized diet enriched in fatty meats may be responsible for an increase in serum uric acid level and an increased frequency of hypertension and diabetes. There is an interesting study that shows that vegetarian monks have significantly lower blood pressure levels than monks who eat meat.

**Other Mechanisms Modulating Blood Pressure with Westernization**

It is important to recognize that other mechanisms also likely influence the development of hypertension associated with Westernization. There is considerable evidence that the sodium content in the diet influences blood pressure; cultures ingesting a low-sodium diet have a marked lower frequency of hypertension. A highly positive correlation between sodium intake with blood pressure was found in an international study of over 10,000 individuals in 52 sites throughout the world. Diets high in potassium, such as those observed in most native diets, also are associated with lower blood pressure. In the Yanomamo Amerindians, a low blood pressure society, sodium intake was less than 10 mmol/d whereas potassium intake averaged over 300 mmol/d based on urinary excretion. The mechanism by which potassium diets modulate blood pressure is complex. In salt-sensitive African American adolescents, dietary supplementation with potassium without a change in salt intake resulted in a decrease of diastolic blood pressure. In experimental hypokalemia, in addition to effects of hypokalemia on inhibiting vascular nitric oxide production, low potassium diets also induce renal vasoconstriction and subtle renal injury in association with alterations in intrarenal vasoactive mediators that favor renal sodium retention.

The development of obesity itself also may lead to hypertension. In these epidemiologic studies it is difficult to separate the effects of obesity from hyperuricemia because both commonly are associated.

Many studies also suggest an effect of urbanization or the development of a sedentary lifestyle as being associated with the development of hypertension. There is also a well known tropical temperature effect in which populations in hot climates have lower blood pressures than people living at higher latitudes. This may be related to the effect of heat in inducing vasodilation, and for cold in activating the sympathetic nervous system and renin-angiotensin system to induce vasoconstriction. There also may be a tropical light effect. It recently has been shown that 1,25 dihydroxyvitamin D, which would be increased with chronic light exposure, is a negative regulator of the renin-angiotensin system. It also is interesting that gout is associated with decreased serum levels of 1,25 dihydroxyvitamin D, possibly owing to the low-grade renal injury that is associated with chronic hyperuricemia. It also is possible that Westernization of foods may lead to the removal of certain nutrients that protect against hypertension. For example, the Kuna Indians, who live in a rural environment, develop no hypertension despite a marked intake of sodium. Recent studies suggest this may be owing to the ingestion of unprocessed cocoa, which contains flavonoids that stimulate nitric oxide production. Likewise, exposure to lead or alcohol in Western diets also may underlie the increased prevalence of hypertension in certain populations, although this still could be mediated through the effects of these two agents on serum uric acid levels.

**Studies Relating Uric Acid, Diet, and Hypertension in Other Species**

It is interesting that humans are the only mammalian species that has such a high frequency (25%) of hypertension and arteriolosclerosis. Most studies of primates living in the wild suggest that hypertension and arteriolosclerosis are rare despite the fact that the Great Apes have no functional uricase. This may reflect a diet consisting primarily of fruit and vegetables, and only small amounts of animal protein. As a consequence, serum uric acid levels remain lower in the Great Ape compared with the human living in industrialized society. In contrast to mammals, all birds and most reptiles also lack uricase. In these animals, serum uric acid levels may increase rapidly when eating meat. Turkeys have been reported to develop frank gout after having horse meat put in their feed. It is thus of interest that the domestic turkey, which is fed a diet enriched in protein and high in salt, develops severe hypertension, whereas the wild turkey with its native diet remains normotensive. Although further studies clearly are necessary, it is tempting to speculate that the hypertension may have resulted from a dietary-mediated increase in uric acid coupled with the high sodium load.

**Conclusions**

Although many studies suggest that the change in diet may have led to the epidemic of hypertension by increasing serum...
Uric acid levels, there are some caveats. First, studies of the PukaPuka Indians of the Cook Islands have reported that hyperuricemia is common despite minimal evidence of hypertension. It is possible that any deleterious action of uric acid to raise blood pressure may be countered by the low salt diet of this population or by other components in the diet that may have hypertensive action (such as the raw cocoa ingested by the Kuna Indians) consistent with the hypothesis that hyperuricemia may induce subtle renal injury, resulting in a gradual increase in blood pressure for the same intake of salt. Clearly, more studies are needed to investigate the interesting relationship of uric acid with Westernization of diet and with the development of hypertension.

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