SEMINARS IN
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Uric Acid, Evolution and Primitive Cultures

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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.

Hypertension is epidemic in industrialized nations, where it affects nearly 25% of the population, and is the major cause of stroke and congestive heart failure, and the second most common cause of end-stage renal disease.[1] Hypertension is also increasing in prevalence in developing countries, in association with the large-scale epidemics of diabetes and obesity.[2-4] Identifying the cause of primary hypertension has been a central focus of scientific research. Although there is clearly a genetic component, most studies suggest that difference in polygene expression only accounts for 20% to 30% of all hypertension.[5] Thus, emphasis has been placed on environmental factors such as diet (sodium, potassium, and calcium intake), maternal nutrition, stress, and other factors that can alter hormonal or sympathetic nervous system activity that modulates blood pressure. In this article we summarize evidence linking the epidemic of hypertension to uric acid.

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The Uricase Mutation in Human Evolution

Uric acid is a product of purine metabolism that is generated during the enzymatic degradation of xanthine. When the enzyme is xanthine oxidase, both uric acid and superoxide anion are produced, whereas the reaction with xanthine dehydrogenase releases uric acid and the reduced form of nicotinamide-adenine dinucleotide. In most mammals, uric acid is degraded further by the enzyme uricase (also known as urate oxidase) to allantoin. Serum uric acid levels are therefore low (0.5– 2.0 mg/dL) in most mammals. However, during the Miocene epoch (8–20 million years ago) parallel mutations occurred in our hominoid ancestors that first affected the promoter region and later the whole gene, eventually resulting in complete loss of uricase.[6] As a consequence, humans and the Great Apes have higher uric acid levels than most other mammals. In addition, some species of New World monkeys also lost uricase, and many Old World monkeys have lower uricase activity than other mammals,[7] suggesting similar processes in these species. The stepwise loss of uricase may have allowed adaptation to the loss of this important gene because the sudden knockout of uricase in mice is lethal owing to dramatic increases in serum uric acid levels that cause acute urate nephropathy and renal failure.[8] One likely adaptation was a decrease in xanthine oxidase activity because humans have only 1% activity of this enzyme com-

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pared with other mammals.[9] 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.[10] 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.[11] Indeed, uric acid is a strong antioxidant, and accounts for much of the antioxidant activity in plasma.[12] A similar antioxidant hypothesis suggests that the uricase mutation occurred as a consequence of the loss of our ability to synthesize vitamin C.[13] Our ability to synthesize vitamin C was lost approximately 40 to 50 million years ago owing to a mutation in L-gulono-lactone oxidase.[14] 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.[15] 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.[16] In fact, in humans almost all studies show the opposite; higher uric acid levels correlate with an increased risk for death.[17]

We proposed an alternative hypothesis, that the mutation of uricase resulted in increased blood pressure and increased salt sensitivity.[18] 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.[17] 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.[19] Also, hyperuricemia caused renal structural changes that resulted in salt sensitivity.[18] 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.[19-20] Evidence that a similar process may be occurring in humans also is available.[22,23] 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.[17] 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.[24] Thus, diets rich in fatty meats and low in dairy products increase the risk for gout.[25] 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.[26] 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).[27] It is thus of interest that several investigators, including Mohamed himself, noted a strong association of hypertension with gout and/or lead intoxication.[26,28] Indeed, the French physician Huchard[29,30] 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,[31,32] the Middle East,[33] India,[34] China,[35,36] South and Central America,[37-40] the South Pacific,[41] the Australian Aborigine,[42] and in American Indians[43] 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.[2-4]

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.[44-45] Shortly thereafter gout was reported in this population; today both hypertension and gout are more common in African Americans than Caucasians.[46,47] In one study this increased frequency of gout was linked directly with the increased frequency of hypertension.[48] 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.[49-51]

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.[52] In the initial descriptions of Maori health, gout was never seen;[53] 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.[53,54] Australian Aborigines also developed a high frequency of hypertension and obesity after the adaptation of a Western diet.[55] This also is associated with an increased frequency of hyperuricemia.[56] The immigration of Filipinos to the United States also was associated with an increased frequency of hypertension and gout,[57,58] and this was associated with a change in diet from a fish and rice diet to one with a higher content of animal meats.[59] 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.[60]

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.[61]

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.[62,63] 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.[64] Diets high in potassium, such as those observed in most native diets, also are associated with lower blood pressure.[65] 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.[65] 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.[66] 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.[67]

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.[50,51,68,69] 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.[70] 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.[71] 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.[72] It also is interesting that gout is associated with decreased serum levels of 1,25 dihydroxyvitamin D,[73] 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.[69] Recent studies suggest this may be owing to the ingestion of unprocessed cocoa, which contains flavernoids that stimulate nitric oxide production (N. Hollenberg, personal communication). Likewise, exposure to lead[27] 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 (Fig 1).

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.[74] 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.[75] 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

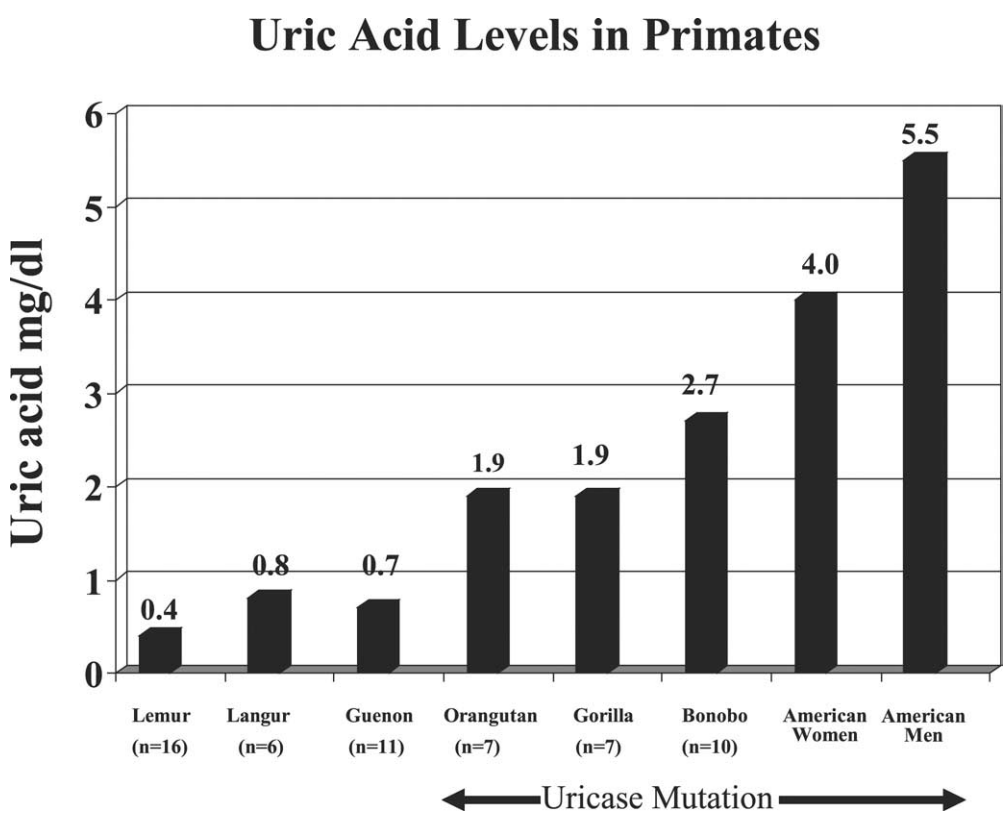

Figure 1 Mean serum uric acid levels of various primates obtained from the San Diego zoo. The values for mean uric acid in American men and women was obtained from the NHANES study.[77]

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.[76] 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[63] or by other components in the diet that may have hypotensive 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.

References

1. American Heart Association: Cardiovascular disease statistics. Available at: www.americanheart.org, 2002
2. Forrester T, Cooper RS, Weatherall D: Emergence of Western diseases in the tropical world: The experience with chronic cardiovascular diseases. Br Med Bull 54:463-473, 1998
3. Singh RB, Suh IL, Singh VP, et al: Hypertension and stroke in Asia: Prevalence, control and strategies in developing countries for prevention. J Hum Hypertens 14:749-763, 2000
4. Seedat YK: Hypertension in developing nations in sub-Saharan Africa. J Hum Hypertens 14:739-747, 2000
5. Danzinger RS: Hypertension in an anthropological and evolutionary paradigm. Hypertension 38:19-22, 2001
6. Oda M, Satta Y, Takenaka O, et al: Loss of urate oxidase activity in hominoids and its evolutionary implications. Mol Biol Evol 19:640-653, 2002
7. Friedman TB, Polanco GE, Appold JC, et al: On the loss of uricolytic activity during primate evolution—I. Silencing of urate oxidase in a hominoid ancestor. Comp Biochem Physiol 81B:653-659, 1985
8. Bradley A, Caskey CT: Hyperuricemia and urate nephropathy in urate oxidase deficient mice. Proc Natl Acad Sci U S A 91:742-746, 1994
9. Xu P, LaVallee P, Hoidal JR: Repressed expression of the human xanthine oxidoreductase gene. J Biol Chem 275:5918-5926, 2000
10. Orowan E: The origin of man. Nature 175:683-684, 1955
11. Ames BN, Cathcart R, Schwiers E, et al: Uric acid provides an antioxidant defense in humans against oxidant- and radical-causing aging and cancer: A hypothesis. Proc Natl Acad Sci U S A 78:6853-6862, 1981
12. Nieto FJ, Iribarren C, Gross MD, et al: Uric acid and serum antioxidant capacity: A reaction to atherosclerosis? Atherosclerosis 148:131-139, 2000
13. Spitsin SV, Scott GS, Mikheeva T, et al: Comparison of uric acid and ascorbic acid in protection against EAE. Free Radic Biol Med 33:1363-1371, 2002
14. Nishikimi M, Fukuyama R, Minoshima S, et al: Cloning and chromosomal mapping of the human nonfunctional gene for L-gulono-lactone oxidase, the enzyme for L-ascorbic acid biosynthesis missing in man. J Biol Chem 269:13685-13688, 1994
15. Pauling L: Evolution and the need for ascorbic acid. Proc Natl Acad Sci U S A 67:1643-1648, 1970
16. Lopez-Torres M, Pererz-Campo R, Rojas C: Maximum life span in vertebrates: Relationship with liver anti-oxidant enzymes, glutathione system, ascorbate, urate, sensitivity to peroxidation, true malondialydehyde, in vivo H2O2, and basal and maximum aerobic capacity. Mech Ageing Dev 70:177-199, 1993
17. Johnson RJ, Kang DH, Feig D, et al: Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 41:1183-1190, 2003
18. Watanabe S, Kang DH, Feng L, et al: Uric acid, hominoid evolution and the pathogenesis of salt-sensitivity. Hypertension 40:355-360, 2002

19. Mazzali M, Hughes J, Kim YG, et al: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 38:1101-1106, 2001
20. Mazzali M, Kanellis J, Han L, et al: Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol 282:F991-F997, 2002
21. 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 41:1287-1293, 2003
22. Feig DI, Johnson RJ: Hyperuricemia in childhood essential hypertension. Hypertension 42:247-252, 2003
23. Feig DI, Nakagawa T, Karumanchi SA, et al: Uric acid, nephron number, and the pathogenesis of essential hypertension. Kidney Int 66:281-287, 2004
24. Johnson RJ, Rideout BA: Uric acid and diet: Insights into the epidemic of cardiovascular disease. N Engl J Med 350:1071-1074, 2004
25. Choi HK, Atkinson K, Karlson EW, et al: Purine-rich foods, dairy intake, and protein intake, and risk of gout in men. N Engl J Med 350:1093-1103, 2004
26. Mahomed FA: On chronic Bright's disease, and its essential symptoms. Lancet I:399-401, 1879
27. Nriagu JO: Saturnine gout among Roman aristocrats. Did lead poisoning contribute to the fall of the Empire. N Engl J Med 308:660-663, 1983
28. Haig A: On uric acid and arterial tension. Br Med J 1:288-291, 1889
29. Huchard H: Arteriolosclerosis: Including its cardiac form. JAMA 53: 1129, 1909
30. Huchard H: Allgemeine Betrachtungen űber die Arteriosklerose. Klin Med Berlin 5:1318-1321, 1909
31. Donnison CP: Blood pressure in the African native. Lancet 1:6-7, 1929
32. Williams AW: Blood pressure of Africans. East Afr Med J 18:109-117, 1941
33. Hudson EH, Young AL: Medical and surgical practice on the Euphrates River. An analysis of two thousand consecutive cases at Deir-Ez-Zor, Syria. Am J Trop Med Hyg 11:297-310, 1931
34. McCay D: Physiological and pathological observations on Wright's method of testing the blood and urine. Lancet 1:1483-1487, 1907
35. Cadbury WW: Blood pressure of normal Cantonese Students. Arch Intern Med 30:362-377, 1922
36. Lowenstein FW: Some epidemiological aspects of blood pressure and its relationship to diet and constitution with particular consideration of the Chinese. Am Heart J 47:874-885, 1954
37. Saunders GM: Blood pressure in Yucatecans. Am J Med Sci 185:843-851, 1933
38. Kean BH: The blood pressure of the Cuna Indians. Am J Trop Med Hyg 24:341-343, 1944
39. Shattuck GC: The possible significance of low blood pressures observed in Guatemalans and in Yucatecans. Am J Trop Med Hyg 17:513-537, 1937
40. Lowenstein FW: Blood-pressure in relation to age and sex in the tropics and subtropics. Lancet 1:389-392, 1961
41. Murrill RI: A blood pressure study of natives of Ponape Island, Eastern Carolines. Hum Biol 20:47-57, 1948
42. Nye LJJ: Blood pressure in the Australian Aborigine with consideration of possible aetiologic factors in hyperpiesia and its relation to civilization. Med J Aust 2:1000-1001, 1937
43. Fleming HC: Medical observations of the Zuni Indians. Contributions from the Museum of the American Indian. New York City, Heinze Foundation, 1924
44. Adams JM: Some racial differences in blood pressure and morbidity in a group of white and colored workers. Am J Med Sci 184:342-350, 1930
45. Saunders GM, Bancroft H: Blood pressure studies on negro and white men and women living in the Virgin Islands of the United States. Am Heart J 23:410-423, 1942
46. Perlman L, Bernstein A, Maslow WC, et al: Gout in a Negro woman: Report of a case. JAMA 151:726-728, 1953
47. Nathan LA, Kubota CK, Turnbull GC: Relative incidence of gout in negro and white males at Cook County Hospital 1944-1952. J Lab Clin Med 42:927, 1953
48. Hochberg MC, Thomas J, Thomas DJ, et al: Racial differences in the incidence of gout. Arthritis Rheum 38:628-632, 1995
49. Cassim B, Mody GM, Deenadayalu VK, et al: Gout in black South Africans: A clinical and genetic study. Ann Rheum Dis 53:759-762, 1994
50. Beighton P, Solomon L, Soskolne CL, et al: Serum uric acid concentrations in an urbanized South African Negro population. Ann Rheum Dis 33:442-445, 1974
51. Beighton P, Daynes G, Soskolne CL: Serum uric acid concentrations in a Xhosa community in the Transkei of Southern Africa. Ann Rheum Dis 35:77-80, 1976
52. Wright-St Clair RE: Early accounts of Maori diet and health. N Z Med J 70:327-331, 1969
53. Lennane GAQ, Rose BS, Isdale IC: Gout in the Maori. Ann Rheum Dis 19:120-125, 1960
54. Rose BS: Gout in the Maoris. Semin Arthritis Rheum 5:121-145, 1975
55. Hoy W, Kelly A, Jacups S, et al: Stemming the tide: Reducing cardiovascular disease and renal failure in Australian Aborigines. Aust N Z J Med 29:480-483, 1999
56. Chin G, Segasothy M: Gouty arthritis in Australian Aborigines. Aust N Z J Med 30:639-640, 2000
57. Decker JL, Lane JJ: Gouty arthritis in Filipinos. N Engl J Med 261:805-806, 1959
58. Decker JL, Lane JJ, Reynolds WE: Hyperuricemia in a male Filipino population. Arthritis Rheum 5:144-155, 1962
59. Healey LA, Skeith MD, Decker JL, et al: Hyperuricemia in Filipinos: Interaction of heredity and environment. Am J Hum Genet 19:81-85, 1967
60. Kagan A, Harriss BR, Winkelstein W, et al: Epidemiologic studies on coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: Demographic, physical, dietary and biochemical characteristics. J Chron Dis 27:345-364, 1974
61. Saile F: Ûber den Einfluβ der vegetarischen Ernährung auf den Blutdruck. Med Klin 25:929-931, 1930
62. Oliver WJ, Cohen EL, Neel JV: Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a "No-salt" culture. Circulation 52:146-151, 1975
63. Prior IAM, Evans JG, Harvey HPB, et al: Sodium intake and blood pressure in two Polynesian populations. N Engl J Med 279:515-520, 1968
64. Elliot P, Stamler J, Nichols R, et al: Intersalt revisited: Further analyses of 24 hour sodium excretion and blood pressure within and across populations. Br Med J 312:1249-1253, 1996
65. Oliver WJ: Primitive Peoples Without Salt: A Perspective for Industrialized Societies. Ann Arbor, Michigan, 1998
66. Wilson WK, Sica DA, Miller SB: Effect of potassium on blood pressure in salt-sensitive and salt-resistant Black adolescents. Hypertension 34: 181-186, 1999
67. Suga S, Phillips MI, Ray PE, et al: Hypokalemia induces renal injury and alterations in intrarenal vasoactive mediators that favor salt-sensitivity. Am J Physiol 281:F620-F629, 2001
68. Tuomilehto J, Zimmet P, Wolf E, et al: Plasma uric acid level and its association with diabetes mellitus and some biological parameters in a biracial population of Fiji. Am J Epidemiol 127:321-336, 1988
69. Hollenberg NK, Martinez G, McCullough M, et al: Aging, acculturation, salt intake, and hypertension in the Kuna of Panama. Hypertension 29:171-176, 1997
70. Chamberlain WP: A study of the systolic blood pressure and the pulse rate of healthy adult males in the Philippines. Philippine J Sci 6:467-482, 1911
71. Sun Z, Zang A, Cade JR: Renal responses to chronic cold exposure. Can J Physiol Pharmacol 81:22-27, 2003
72. Li YC, Kong J, Wei M, et al: 1,25 dihydroxyvitamin D3 is a negative

endocrine regulator of the renin-angiotensin system. J Clin Invest 110:229-238, 2002
73. Takahashi S, Yamamoto T, Moriwaki Y, et al: Decreased serum concentrations of 1,25(OH)2-vitamin D3 in patients with gout. Adv Exp Med Biol 431:57-60, 1998
74. Schlotthauer CV, Bollman JL: Experimental gout in turkeys. Proc Staff Med Mayo Clinic 9:560-561, 1934
75. Laurence DR, Bennett PN: Clinical Pharmacology. Drugs Used in Arterial Hypertension and Angina Pectoris (ed 6). Edinburgh, Churchill Livingstone, 1987, p 505
76. Prior IAM, Rose BS, Harvey HPB, et al: Hyperuricemia, gout, and diabetic abnormality in Polynesian people. Lancet 1:333-338, 1966
77. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality. The NHANES I epidemiologic follow-up study, 1971-1992. JAMA 283: 2404-2410, 2000