

Estimation of the net acid load of the diet of ancestral preagricultural *Homo sapiens* and their hominid ancestors¹⁻³

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ABSTRACT

Background: Natural selection has had <1% of hominid evolutionary time to eliminate the inevitable maladaptations consequent to the profound transformation of the human diet resulting from the inventions of agriculture and animal husbandry.

Objective: The objective was to estimate the net systemic load of acid (net endogenous acid production; NEAP) from retrojected ancestral preagricultural diets and to compare it with that of contemporary diets, which are characterized by an imbalance of nutrient precursors of hydrogen and bicarbonate ions that induces a lifelong, low-grade, pathogenically significant systemic metabolic acidosis.

Design: Using established computational methods, we computed NEAP for a large number of retrojected ancestral preagricultural diets and compared them with computed and measured values for typical American diets.

Results: The mean (\pm SD) NEAP for 159 retrojected preagricultural diets was -88 ± 82 mEq/d; 87% were net base-producing. The computational model predicted NEAP for the average American diet (as recorded in the third National Health and Nutrition Examination Survey) as 48 mEq/d, within a few percentage points of published measured values for free-living Americans; the model, therefore, was not biased toward generating negative NEAP values. The historical shift from negative to positive NEAP was accounted for by the displacement of high-bicarbonate-yielding plant foods in the ancestral diet by cereal grains and energy-dense, nutrient-poor foods in the contemporary diet—neither of which are net base-producing.

Conclusions: The findings suggest that diet-induced metabolic acidosis and its sequelae in humans eating contemporary diets reflect a mismatch between the nutrient composition of the diet and genetically determined nutritional requirements for optimal systemic acid-base status. *Am J Clin Nutr* 2002;76:1308–16.

KEY WORDS Nutrition, evolution, acid base, dietary net acid load, protein, cereal grains, energy-dense, nutrient-poor foods

INTRODUCTION

The nutritional requirements of *Homo sapiens*—the only extant species of the 5–7-million-year-old hominid family and its most recently evolved member (<200 000 y old)—were established by natural selection during millions of years in which its hominid ancestors, including earlier *Homo* species, consumed foods exclusively from a menu of wild animals and uncultivated plants (1–3). The profound transformation of the ancestral diet 10 000 y ago resulting from the inventions of agriculture and animal husbandry

and, more recently, by industrial-scale food production and distribution technologies has provided natural selection an enormous challenge to eliminate the inevitable resulting maladaptations but has afforded it too little time—<1% of hominid evolutionary time—to do so (1, 3–6).

In comparison with the diet habitually ingested by preagricultural *Homo sapiens* living in the Upper Paleolithic period (40 000–10 000 y ago), the diet of contemporary *Homo sapiens* is rich in saturated fat, simple sugars, sodium, and chloride and poor in fiber, magnesium, and potassium (1, 2). These and numerous other postagricultural dietary compositional changes have been implicated as risk factors in the pathogenesis of “diseases of civilization,” including atherosclerosis, hypertension, type 2 diabetes, osteoporosis, and certain types of cancer (7–13).

One characteristic of the contemporary human diet for which no quantitative comparison has been made with the inferred ancestral preagricultural diet is its imbalance of nutrient precursors of hydrogen and bicarbonate ions, resulting in the body’s net production of noncarbonic acid, ranging over an order of magnitude from 10 to 150 mEq/d among diets (14–17). Although multiple homeostatic mechanisms operate to mitigate the resulting deviations in systemic acid-base equilibrium, on average, blood acidity remains increased and plasma bicarbonate concentrations decreased in proportion to the magnitude of the daily net acid load (15, 16). Increasing evidence has been adduced that suggests that such persisting, albeit low-grade, acidosis, and the relentless operation of responding homeostatic mechanisms, result in numerous injurious effects on the body, including dissolution of bone, muscle wasting, kidney stone formation, and damage to the kidney (18–23).

In this article we report estimates of net endogenous acid production (NEAP)—the net acid load of the diet—for 159 retrojected prehistoric preagricultural diets of *Homo sapiens* and their hominid ancestors. In contrast with the characteristically net acid-producing contemporary diet, most such retrojected ancestral diets were net base-producing, and we detail the characteristics that made them so.

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TABLE 1

Estimation of net endogenous acid production (NEAP) from 2 prototypical ancestral, preagricultural Paleolithic diets and an average contemporary human diet

| Food group | Energy content <i>kJ/100 g edible portion</i> | Daily energy intake <i>% of total (kJ)</i> | Potential yield | | Unmeasured anion | | Endogenous production rate | | | NEAP ¹ <i>mEq/d</i> | Protein intake <i>g/d</i> |
|---|--|---|-------------------------------------|------------------------------------|-------------------------------|------------------------|-------------------------------|------------------------------|------------------------------|-----------------------------------|------------------------------|
| | | | Sulfuric acid <i>mEq/1000 kJ</i> | Bicar-bonate <i>mEq/1000 kJ</i> | Content <i>mEq/1000 kJ</i> | Intake <i>mEq/d</i> | Sulfuric acid <i>mEq/d</i> | Organic acid <i>mEq/d</i> | Bicar-bonate <i>mEq/d</i> | | |
| <i>Paleolithic diet (animal-to-plant energy ratio = 35%:65%; animal-fat energy = 26% of animal-food energy)</i> | | | | | | | | | | | |
| Meat (n = 9) | 559 | 35.0 (4393) | 17.5 | 2.2 | 1.0 | 4.2 | 77.1 | 0.6 | 9.8 | — | 178 |
| Nuts (n = 10) | 2418 | 10.8 (1360) | 2.1 | 2.9 | 6.7 | 9.1 | 2.9 | 1.4 | 4.0 | — | 7 |
| Leafy greens (n = 5) | 93 | 10.8 (1360) | 5.8 | 67.7 | 122.5 | 166.6 | 7.9 | 25.0 | 92.0 | — | 30 |
| Vegetable fruit (n = 6) ² | 73 | 10.8 (1360) | 2.7 | 49.8 | 86.2 | 117.3 | 3.7 | 17.6 | 67.8 | — | 24 |
| Tubers (n = 3) | 393 | 10.8 (1360) | 1.4 | 16.0 | 22.6 | 30.7 | 1.9 | 4.6 | 21.8 | — | 6 |
| Roots (n = 5) | 109 | 10.8 (1360) | 1.6 | 38.8 | 60.6 | 82.4 | 2.2 | 12.4 | 52.7 | — | 10 |
| Fruit (n = 15) | 277 | 10.8 (1360) | 0.7 | 19.6 | 29.0 | 39.4 | 1.0 | 5.9 | 26.6 | — | 5 |
| Total (n = 53) | — | 100 (12552) | — | — | — | 450 | 97 | 100 ³ | 275 | -78 | 258 |
| <i>Paleolithic diet (animal-to-plant energy ratio = 55%:45%; animal-fat energy = 53% of animal-food energy)</i> | | | | | | | | | | | |
| Meat (n = 9) | 559 | 35.0 (4393) | 17.5 | 2.2 | 1.0 | 4.2 | 77.1 | 0.6 | 9.8 | — | 178 |
| Animal fat (additional) ⁴ | — | 20.0 (2510) | — | — | — | — | — | — | — | — | — |
| Nuts (n = 10) | 2418 | 7.5 (941) | 2.1 | 2.9 | 6.7 | 6.3 | 2.0 | 0.9 | 2.8 | — | 5 |
| Leafy greens (n = 5) | 93 | 7.5 (941) | 5.8 | 67.7 | 122.5 | 115.3 | 5.5 | 17.3 | 63.7 | — | 21 |
| Vegetable fruit (n = 6) ² | 73 | 7.5 (941) | 2.7 | 49.8 | 86.2 | 81.2 | 2.5 | 12.2 | 46.9 | — | 16 |
| Tubers (n = 3) | 393 | 7.5 (941) | 1.4 | 16.0 | 22.6 | 21.2 | 1.3 | 3.2 | 15.1 | — | 4 |
| Roots (n = 5) | 109 | 7.5 (941) | 1.6 | 38.8 | 60.6 | 57.0 | 1.5 | 8.6 | 36.5 | — | 7 |
| Fruit (n = 15) | 277 | 7.5 (941) | 0.7 | 19.6 | 29.0 | 27.3 | 0.7 | 4.1 | 18.4 | — | 3 |
| Total (n = 53) | — | 100 (12552) | — | — | — | 313 | 91 | 80 ³ | 193 | -23 | 234 |
| <i>Average US diet</i> | | | | | | | | | | | |
| Meat (n = 9) | 559 | 9.2 (830) | 17.5 | 2.2 | 1.0 | 0.8 | 14.6 | 0.1 | 1.9 | — | 34 |
| Cheese (n = 4) | 1301 | 4.0 (358) | 7.1 | -3.8 | 3.7 | 1.3 | 2.6 | 0.2 | -1.4 | — | 6 |
| Milk and yogurt (n = 3) | 249 | 6.9 (615) | 5.5 | 4.7 | 24.7 | 15.2 | 3.4 | 2.3 | 2.9 | — | 10 |
| Eggs (n = 1) | 612 | 1.9 (168) | 12.1 | -4.4 | -6.6 | -1.1 | 2.0 | -0.2 | -0.7 | — | 3 |
| Grains (n = 5) | 1496 | 27.4 (2464) | 3.4 | -2.3 | -1.3 | -3.2 | 8.5 | -0.5 | -5.8 | — | 15 |
| Nuts (n = 10) | 2418 | 4.5 (401) | 2.1 | 2.9 | 6.7 | 2.7 | 0.9 | 0.4 | 1.2 | — | 2 |
| Beans (n = 6) | 1081 | 1.0 (93) | 5.1 | 18.3 | 30.3 | 2.8 | 0.5 | 0.4 | 1.7 | — | 2 |
| Vegetables (n = 19) ⁵ | 138 | 5.1 (455) | 3.0 | 46.3 | 79.0 | 35.9 | 1.4 | 5.4 | 21.1 | — | 5 |
| Fruit (n = 15) | 277 | 4.5 (405) | 0.7 | 19.6 | 29.0 | 11.7 | 0.3 | 1.8 | 7.9 | — | 1 |
| EDNP foods ⁶ | — | 35.6 (3194) | — | — | — | — | — | — | — | — | — |
| Total (n = 72) | — | 100 (8983) | — | — | — | 66 | 34 | 43 ³ | 29 | 48 | 78 |

¹NEAP equals the sum of the endogenous production rates of sulfuric and organic acids minus that of bicarbonate; see Methods for details of the computational model.

²Fruit commonly referred to as vegetables (tomatoes, pumpkin, zucchini, cucumbers, eggplant, and okra).

³Computed as 32.9 + Σ(0.15 × food group unmeasured anion intake); from reference 36.

⁴See text for explanation.

⁵Combined food group of roots; tubers, leafy green vegetables, and vegetable fruit.

⁶Energy-dense, nutrient-poor foods (eg, separated fats, refined sugars, and vegetable oils).

METHODS

The effects of diet on acid-base metabolism in humans are sufficiently well established to permit quantitative estimations of NEAP from knowledge of the types of foods and their amounts consumed (14, 24–26). Likewise, considerable progress has been made in retrojecting the types of foods and the boundary limits on their amounts consumed by ancestral preagricultural humans and their hominid ancestors (1, 2, 27). Accordingly, it is possible to estimate NEAP for inferred ancestral preagricultural diets.

Strategies for diet selection

In estimating NEAP for the ancestral hominid diet, we initially followed the guidelines of Eaton and Konner (1) regarding which food groups were habitually ingested by preagricultural *Homo sapiens* living in the Upper Paleolithic Period, the ratio of animal to plant foods consumed, and total dietary energy intake. Their retrojected diet contained (by wt) 35% lean meats (wild game) and 65%

plant foods, for a total energy intake of 12 552 kJ/d (3000 kcal/d) (1). From the reported energy content per gram of wild game [5.90 kJ/g (1.41 kcal/g)] and plants [5.40 kJ/g (1.29 kcal/g)] (1), it was calculated that game made up 37% and plants made up 63% of the total daily energy intake in the Paleolithic diet.

However, there is no consensus among paleoanthropologists as to the norm of animal-to-plant subsistence ratios for preagricultural *Homo sapiens* or their hominid ancestors (28–34). It has been argued that plant foods dominated the diet throughout the longer period of human evolution (28, 35), that hominids did not become successful hunters of large game until the Middle to Upper Paleolithic Period (34), and that the evolutionarily late big-game hunter-gatherer phase of human experience little affected long-established human nutrient requirements (32). We take no position on the different interpretations. Rather, in computing NEAP for the presumed ancestral preagricultural diet, we initially targeted a diet containing 35% of energy as meat and 65% as plant food (Table 1), approximating Eaton and



TABLE 2

Effect of the ratio of animal-food energy intake to plant-food energy intake (animal-to-plant energy ratio) on net endogenous acid production (NEAP) for ancestral preagricultural Paleolithic diets with different animal-food fat densities and equal distribution of plant-food energy among plant-food groups

| Animal-to-plant energy ratio ¹ | Animal fat content % of animal energy | Endogenous production rate | | | NEAP ² mEq/d | Protein intake g/d |
|--|--|----------------------------|--------------|-------------|----------------------------|-----------------------|
| | | Sulfuric acid | Organic acid | Bicarbonate | | |
| <i>Paleolithic diet (animal-fat content = 26% of animal-food energy)</i> | | | | | | |
| 35%:65% | 26 | 97 | 100 | 275 | -78 | 258 |
| 30%:70% | 26 | 87 | 105 | 294 | -101 | 239 |
| 25%:75% | 26 | 78 | 110 | 313 | -125 | 220 |
| 20%:80% | 26 | 68 | 115 | 332 | -148 | 201 |
| 15%:85% | 26 | 59 | 121 | 351 | -171 | 182 |
| 10%:90% | 26 | 49 | 126 | 369 | -195 | 163 |
| 5%:95% | 26 | 40 | 131 | 388 | -218 | 143 |
| <i>Paleolithic diet (animal-fat content = 46%–63% of animal-food energy)</i> | | | | | | |
| 60%:40% | 57 | 89 | 75 | 173 | -9 | 227 |
| 55%:45% | 46 | 102 | 80 | 195 | -13 | 259 |
| 55%:45% | 53 | 91 | 80 | 193 | -23 | 234 |
| 50%:50% | 56 | 81 | 85 | 212 | -46 | 214 |
| 50%:50% | 63 | 70 | 85 | 211 | -56 | 189 |
| 45%:55% | 59 | 72 | 90 | 231 | -70 | 195 |
| 40%:60% | 53 | 91 | 80 | 193 | -23 | 234 |
| 35%:65% | 47 | 75 | 100 | 272 | -97 | 208 |
| 30%:70% | 51 | 65 | 105 | 291 | -121 | 189 |
| 25%:75% | 56 | 56 | 110 | 310 | -144 | 169 |
| 20%:80% | 48 | 55 | 115 | 330 | -160 | 170 |
| 20%:80% | 56 | 50 | 115 | 329 | -164 | 160 |
| 15%:85% | 56 | 45 | 120 | 349 | -183 | 151 |
| 10%:90% | 48 | 42 | 126 | 369 | -201 | 147 |
| 5%:95% | 51 | 36 | 131 | 388 | -222 | 135 |

¹Percentages of daily energy intake.

²The sum of the endogenous production rates of sulfuric and organic acids minus that of bicarbonate; see Methods for details of the computational model.

Konner's proposed subsistence ratio (1, 2). Then, for comparative purposes, we recalculated NEAP for diets with descending ratios of animal-food energy intakes to plant-food energy intakes (animal-to-plant energy ratios) of from 35% of energy as meat and 65% as plant food (35%:65%) to 5%:95% (**Table 2**).

If the animal foods in the Paleolithic diet were lean, as expected for wild game flesh, diets with animal-to-plant energy ratios > 35%:65% would have been intolerable because total protein intakes would have exceeded the body's ability to prevent serious toxicity from nitrogenous metabolites (37). Diets with animal-to-plant energy ratios as high (or as low) as 65%:35%, however, have been tolerated by many historically observed hunter-gatherer societies, presumably because the animal foods consumed had a lower protein-to-fat ratio (ie, higher fat density) than lean meat (27, 33). Therefore, we also estimated NEAP for diets with animal-to-plant energy ratios up to 60%:40%, incorporating substantially higher animal fat densities (46–63% compared with 26% of animal-food energy as fat) (Tables 1 and 2).

For a fixed daily energy intake and any selected animal protein intake, increasing the fat energy content of the animal food (eg, 46–63% compared with 26% of the animal food's energy content) influences the computation of NEAP by reducing the fraction of the daily energy available for plant-food consumption. Accordingly, to quantify the effect of increasing animal fat density we assigned the desired preempting fat energy as "animal fat additional" and subtracted that energy value from the amount allotted for plant-food consumption (Table 1).

In apportioning plant-food energy among plant-food categories for a given animal-to-plant energy ratio, we adopted 2 strategies. In the first strategy, all the plant foods in the database (see below)

were segregated into 6 categories, and plant-food energy was apportioned equally among them. With this strategy we examined the effects of variations of differences in animal-to-plant energy ratios ($n = 22$ scenarios) (Tables 1 and 2). In the second strategy, all the plant foods in the database were segregated into 4 categories, and plant-food energy was apportioned variably among them. With this strategy we examined the effects of different plant-food distributions; each food group was apportioned as 100%, 67%, 50%, 33%, 17%, and 0% of total plant-food energy, for a total of 38 plant-food distribution scenarios (**Table 3**). We ran the computational model for these 38 distribution ratios for each of 4 animal-to-plant food and animal fat density combinations, generating a total of 152 additional ancestral preagricultural diet scenarios (Table 3) over and above the 22 with equal apportionments among the plant-food categories (Tables 1 and 2). The 2 strategies combined thus generated 175 hypothetical ancestral preagricultural diet scenarios. For all calculations, unless otherwise specified, the combined energy intake from animal and plant foods was maintained at 12 552 kJ/d (3000 kcal/d).

Diet database

For the primary data, we assembled a nutrient database of 53 food items from among the major food groups most likely to have been consumed by Paleolithic humans: 9 lean meats (including 4 wild game meats) and 44 plant foods assigned either to 6 groups (roots, nuts, tubers, fruit, leafy green vegetables, and vegetable fruit) or to 4 groups (roots and tubers, leafy green vegetables, nuts, and fruit) depending on which of the 2 diet-selection strategies were being implemented (see above). When used, the category



TABLE 3

Effect of different plant-food energy distributions on net endogenous acid production (NEAP) for preagricultural Paleolithic diets with different ratios of animal-food energy intake to plant-food energy intake (A/P) and different animal-food fat densities (AFD)

| Plant-food group ² | NEAP ¹ | | | |
|--|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| | A:P = 50%:50%; AFD = 56% | A:P = 35%:65%; AFD = 55% | A:P = 35%:65%; AFD = 26% | A:P = 20%:80%; AFD = 46% |
| | <i>mEq/d</i> | | | |
| 100% fruit | -35 | -89 | -64 | -140 |
| 67% fruit, 33% leafy greens | -84 | -152 | — | -218 |
| 67% fruit, 33% roots and tubers | -39 | -93 | -68 | -146 |
| 67% fruit, 33% nuts | 7 | -33 | -8 | -72 |
| 50% fruit, 50% roots and tubers | -40 | -95 | -70 | -148 |
| 50% fruit, 50% nuts | 28 | -6 | 19 | -38 |
| 50% fruit, 25% leafy greens, 25% roots and tubers | -74 | -140 | -114 | -203 |
| 50% fruit, 25% leafy greens, 25% nuts | -40 | -95 | -70 | -148 |
| 50% fruit, 25% roots and tubers, 25% nuts | -6 | -51 | -25 | -93 |
| 50% fruit, 17% each leafy greens, roots and tubers, nuts | -40 | -95 | -70 | -148 |
| 100% roots and tubers | -45 | -102 | -77 | -156 |
| 67% roots and tubers, 3% leafy greens | -91 | -161 | -136 | -229 |
| 67% roots and tubers, 33% nuts | 1 | -42 | -17 | -83 |
| 50% roots and tubers, 50% nuts | 23 | -12 | 13 | -46 |
| 67% roots and tubers, 33% fruit | -42 | -98 | -72 | -151 |
| 50% roots and tubers, 25% leafy greens, 25% fruit | -77 | -143 | -118 | -207 |
| 50% roots and tubers, 25% fruit, 25% nuts | -8 | -54 | -29 | -97 |
| 50% roots and tubers, 25% leafy greens, 25% nuts | -45 | -101 | -76 | -156 |
| 50% roots and tubers, 17% each leafy greens, fruit, nuts | -43 | -99 | -74 | -153 |
| 100% leafy greens | — | — | — | — |
| 67% leafy greens, 33% fruit | -133 | -216 | — | -296 |
| 67% leafy greens, 33% roots and tubers | -136 | -220 | — | -302 |
| 67% leafy greens, 33% nuts | -90 | -160 | — | -228 |
| 50% leafy greens, 50% fruit | -108 | -184 | — | -257 |
| 50% leafy greens, 50% roots and tubers | -114 | -190 | — | -265 |
| 50% leafy greens, 50% nuts | -45 | -101 | — | -155 |
| 50% leafy greens, 25% fruit, 25% roots and tubers | -111 | -187 | — | -261 |
| 50% leafy greens, 25% fruit, 25% nuts | -77 | -142 | — | -206 |
| 50% leafy greens, 25% roots and tubers, 25% nuts | -79 | -146 | — | -210 |
| 50% leafy greens, 17% each fruit, roots and tubers, nuts | -89 | -158 | — | -226 |
| 100% nuts | 92 | 77 | 102 | 64 |
| 67% nuts, 33% leafy greens | 1 | -41 | -16 | -82 |
| 67% nuts, 33% fruit | 50 | 22 | 47 | -4 |
| 67% nuts, 33% roots and tubers | 46 | 18 | 43 | -9 |
| 50% nuts, 25% leafy greens, 25% fruit | -8 | -53 | -28 | -97 |
| 50% nuts, 25% leafy greens, 25% roots and tubers | -11 | -57 | -31 | -101 |
| 50% nuts, 25% fruit, 25% roots and tubers | 26 | -9 | 16 | -42 |
| 50% nuts, 17% each leafy greens, fruit, roots and tubers | 2 | -40 | -14 | -80 |

¹Missing values are for diet scenarios in which the total protein intake exceeded the metabolic tolerance, ie, $\geq 275/d$.

²*Fruit* means fruit and vegetable fruit (see footnotes to Table 1) and “leafy greens” means leafy green vegetables.

“vegetable fruit” included fruit that is more commonly referred to as a vegetable, such as tomatoes, pumpkin, zucchini, cucumbers, eggplant, and okra. Cereal grains and legumes were excluded because of their late (mostly postagricultural) incorporation into the human diet (38–40). Eligible food items were selected if included in McCance and Widdowson’s *The Composition of Foods* (41), the major nutrient database reporting values for all the inorganic cations and anions required to compute NEAP (see below). The components of NEAP were first calculated for individual food items and then were averaged by food group (Tables 1 and 3).

Because McCance and Widdowson’s database includes one game meat only (deer), we added 3 additional game meats (buffalo, wild rabbit, and antelope) from the US Department of Agriculture’s *Nutrient Database for Standard Reference* (42), assuming a chloride content of 67% of sodium content (in mmol), which

corresponds to that of deer and is similar to that of 5 lean cuts of diverse domestic meats (62%) (41).

The complete nutrient composition profiles necessary for computing net acid load, including the content of chloride and the sulfur-containing amino acids, were unavailable for wild plant foods. Although the protein content and the content of certain minerals in some comparable wild and cultivated plant-food groups differ (43), the magnitude of these differences is too small to have a major effect on the net acid load from these food groups.

Computing NEAP for the contemporary diet required expanding the database to include dairy foods, eggs, cereal grains, and a food group of energy-dense, nutrient-poor (EDNP) foods (eg, separated fats, refined sugars, and vegetable oils) (44), the latter of which were considered protein- and mineral-free for purposes of computing NEAP (Table 1).

Basis for the computational model

On a daily basis, NEAP can be computed from the sum of the production rates of sulfuric acid (resulting from the metabolism of dietary sulfur-containing amino acids) and organic acids (resulting from incomplete combustion of carbohydrate and fat) minus that of bicarbonate (resulting from the combustion of dietary organic acid salts of potassium and magnesium) (14), all of which can be computed from the nutrient composition of individual foods. Sulfuric acid and bicarbonate yields can be determined individually for each food item in the diet, the former from the sulfur content calculated from cystine and methionine (42) and the latter with use of the method of Remer and Manz (25), which is based on each item's content of major inorganic cations and anions and published data on the average fractional intestinal absorption of each of nutrient. The difference between the major inorganic cation and anion contents (in mEq, corrected for intestinal absorption), typically a positive value, reflects the amount of unmeasured organic acid salts available to the body for metabolism to bicarbonate and hence reflects the potential systemic bicarbonate (base) load from the food item. Rates of sulfuric acid and bicarbonate production for the entire diet can then be calculated either as the sum of the values for the individual foods or, after assignment of the individual foods to food groups, as the sum of the average values for the food groups. We used the latter procedure in the present analysis (Table 1). A single value for organic acid production for the entire diet can be computed from the total unmeasured anion content of the diet, as per the method of Kleinman and Lemann (36).

Details of the computational model

Computations were based on the model of Remer and Manz (24, 25), which was validated by measuring steady state renal net acid excretion rates (RNAEs) in subjects consuming different protein intakes (24). RNAE correlates linearly and positively with independently measured NEAP ($r = 0.94$), with a mean difference (measured NEAP – measured RNAE) of -1 ± 12 mEq/d (14). The absolute differences between computed NEAP and NEAP estimated from RNAE were similarly small (3–11 mEq/d) (24). We refined the model slightly, as described above, to account for differences in the sulfur content of proteins among foods and for the effect of the diet's unmeasured anion content on endogenous organic acid production contributing to NEAP (36). Remer and Manz assumed that there was no difference in the sulfur content among food proteins and that body organic acid production was independent of diet composition.

The potential sulfuric acid yield from a food item's protein content (in g/100 g edible portion) was calculated assuming that the fractional intestinal absorption of protein is 0.75 (24, 25) and that there was complete metabolism of the intestinally absorbed protein's cystine and methionine sulfur content to sulfuric acid. Factoring by the energy content per 100 g edible portion, the result (expressed in mEq/1000 kJ) is referred to as the food item's potential sulfuric acid yield (Table 1). The cystine and methionine contents were obtained from the US Department of Agriculture database (42).

The potential bicarbonate yield from a food item's organic acid salts was computed from that food item's major inorganic ion composition as follows:

$$0.95 \times [\text{Na}^+] + 0.80 \times [\text{K}^+] + 0.25 \\ \times [\text{Ca}^{2+}] + 0.32 \times [\text{Mg}^{2+}] \\ - 0.95 \times [\text{Cl}^-] - 0.63 \times [\text{P}_i] \quad (1)$$

where the coefficients indicate average fractional intestinal absorption of the ion, ion concentrations are in mEq/100 g edible

portion, and the valence of inorganic phosphorus (P_i) is taken as 1.8 (24, 25). Factoring by energy content per 100 g edible portion, the result, expressed in mEq/1000 kJ, is referred to as the food item's potential bicarbonate yield (Table 1).

The fraction of endogenous organic acid production that contributes to NEAP is quantifiable as the daily urinary excretion rate of organic anions (14). Organic anions that are not excreted yield bicarbonate on metabolism, which back-titrate the protons released during organic acid generation and, hence, do not contribute to NEAP. Because organic anion excretion (mEq/d) is predictable from the unmeasured anion content (mEq/d) of the diet (36), it is possible to estimate endogenous organic acid production from the composition of the diet:

$$\text{Diet organic anion excretion} = 32.9 + 0.15 \\ \times \text{diet unmeasured anion content} \quad (2)$$

where the unmeasured anion content is taken as $\text{Na}^+ + \text{K}^+ + \text{Ca}^{2+} + \text{Mg}^{2+} - \text{Cl}^- - \text{P}_i$, each expressed as mEq/d, with the valence of P_i taken as 1.8. An equivalent procedure is to allot 15% of the value of each diet food item as its contribution to systemic organic acid production, sum the contributions of the individual items, and add 32.9. When the diet is defined by food group (eg, meat or fruit), the computation is performed with the unmeasured anion content of each food group averaged over a representative sample of food items in each group, which is the method we used in the present analysis (Table 1).

RESULTS

Scenarios with equal distributions of plant-food energy among plant-food groups

For a preagricultural diet consisting of 35% meat and 65% plant foods and an animal-food fat density of 26%, the computational model yielded a negative NEAP value: -78 mEq/d (Table 1). This net base load of the aggregate diet reflected bicarbonate production rates exceeding the sum of sulfuric and organic acid production rates from 5 of the 6 plant-food groups (vegetable fruit, tubers, roots, leafy green vegetables, and fruit). The sixth plant-food group, nuts, was essentially acid-base neutral. Meat was the only net acid-producing food group. When meat was incrementally reduced from 35% to 5% of total energy, bicarbonate production rates increasingly predominated, and NEAP progressively decreased to -218 mEq/d (Table 2).

Similarly, for a preagricultural diet consisting of 55% meat and 45% plant foods and an animal-food fat density of 53%, the computational model yielded a negative NEAP value: -23 mEq/d (Table 1). When meat was incrementally reduced from 55% to 5% of total energy, bicarbonate production rates again increasingly predominated, and NEAP progressively decreased to -222 mEq/d (Table 2). The highest NEAP observed in any scenario was -9 mEq/d, when the animal-to-plant energy ratio was 60%:40% at an animal fat density of 57% (Table 2).

Scenarios with unequal distributions of plant-food energy among plant-food groups

The computations for these additional 152 diet scenarios are summarized in Table 3. Fifteen scenarios (11%) were rejected because their corresponding protein intakes exceeded physiologic limits (>275 g/d). Although some of the remaining 137 scenarios are likely nonrepresentative of major ancestral subsistence scenarios, we believe the range of scenarios will encompass the



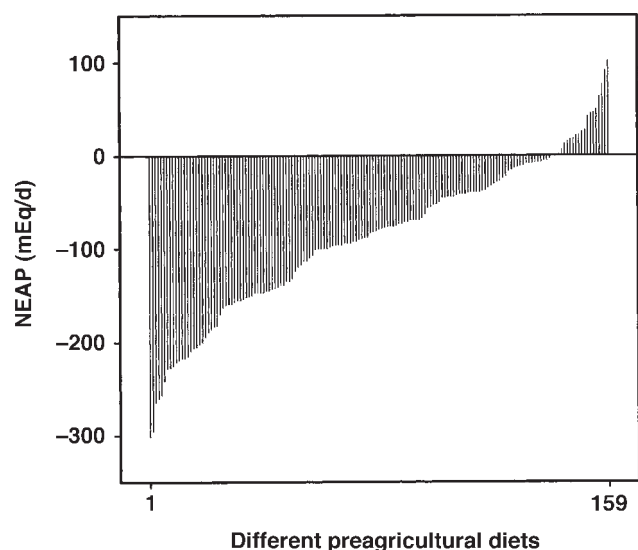


FIGURE 1. Effect of 159 different retrojected ancestral preagricultural diets on net endogenous acid production (NEAP). Each vertical bar represents a different diet, shown in ascending order of NEAP. The mean (\pm SD) NEAP for the 159 retrojected preagricultural diets was -88 ± 82 mEq/d. Details of the composition of the diets are summarized in Tables 2 and 3.

possibilities. The results show that the vast majority of possible ancestral preagricultural diets (117 of 137, or 85%) are net base-producing, although the magnitudes of net base yields vary widely. Of the 20 scenarios that yielded net acid-producing diets, 90% (18/20) were those with high proportions of nuts among the plant foods ($\geq 50\%$ of plant-food energy), particularly when total plant-food energy was restricted by higher animal-to-plant energy ratios. It seems unlikely that ancestral hominid diets consisting predominantly of meat and nuts played a dominant role in conditioning the genetic makeup of modern humans. Although a small percentage of retrojected diets are net acid-producing, the overall average NEAP among the 137 diets was -82 mEq/d, adding further weight to the likelihood that ancestral preagricultural diets were net base-producing on average.

Combined results of all preagricultural scenarios

Combining the results of the 2 diet-selection strategies yielded 159 (22 + 137) hypothetical ancestral preagricultural diets within acceptable total protein tolerances (Tables 2 and 3). Of these, 87% (139/159) were net base-producing by the computational model (**Figure 1**). Thus, in contrast with the known positive NEAP for contemporary diets (14–17, 24, 36), the vast majority (87%) of retrojected ancestral preagricultural diets were net base-producing. The mean (\pm SD) NEAP for all 159 diets computed was -88 ± 82 mEq/d.

Application of the computational model to modern preagricultural hunter-gatherer and primitive nongrain horticultural societies

Considerable information has been published on the dietary patterns of modern hunter-gatherer societies, so it seemed reasonable to try to apply the computational model in selected cases, in particular to see whether a net base-producing diet might even be a possibility as a habitual diet for any such society. As we began to do that, we quickly discovered that most of the information in

the literature was not specific enough to define a diet for each society that together incorporated all 3 components needed to estimate NEAP: 1) animal-to-plant energy ratio, 2) animal-fat energy density, and 3) distribution of plant-food energies among plant-food groups. It was necessary to make numerous guesses and to define a variety of menus for each society to incorporate likely variations in those components, which essentially duplicated the strategies we used, described above, to encompass the range of possible ancestral preagricultural diets. Nevertheless, in surveying the literature, we noted that the descriptions of diets of many hunter-gatherer societies can be matched to the net base-producing diet scenarios listed in Table 3 and thus serve as precedent for habitual consumption of net base-producing diets by ancestral humans. These included the !Kade San (45, 46) and the Western Desert Australian Aborigine (47). Likewise, the descriptions of diets of many primitive horticultural societies, such as the Kitavans in the Trobriand Islands (48), who habitually consume mostly tubers and fruit and other nongrain plant foods, and the Yanomamo of the Amazon Forest (49), who cultivate plantains (a type of banana) and hunt wild game, can be matched to the net base-producing diet scenarios listed in Table 3.

Testing for bias in the computational model

To test whether the computational model is biased toward generating negative NEAP values, we applied the model to an average American diet, which is known to be net acid-producing (16, 17, 36). The diet consisted of average amounts of each of the 10 food groups consumed by Americans, as reported in the third National Health and Nutrition Examination Survey (NHANES III) (44, 50), the most recent of these US surveys (Table 1). For a reported average daily energy intake of 8983 kJ (2147 kcal), the model yielded a NEAP value of 48 mEq/d (Table 1), a value remarkably similar to the average NEAP of free-living healthy American adults as estimated from their renal net acid excretion rates: 49 ± 18 mEq/d (17) and 43 ± 19 mEq/d (51). The computational model is therefore not biased toward negative NEAP values and closely predicts the observed average value of the substantial positive net acid load from the American diet.

DISCUSSION

These findings suggest that in making the transition, $\approx 10,000$ y ago, from a preagricultural hunter-gatherer diet to the modern agricultural-based diet, the human species crossed the neutral zone with respect to NEAP, switching from net base to net acid production. That change was due entirely to a reduction in endogenous bicarbonate production rates (Table 1). Although both sulfuric acid and organic acid production rates are lower in the contemporary diet than in the preagricultural diet, bicarbonate production rates are disproportionately lower (Tables 1 and 2), thereby tipping the balance from net base to net acid production. This overriding reduction in bicarbonate production is due to the displacement of base-rich plant-food groups (roots, tubers, leafy green vegetables, vegetable fruit, and fruit) by cereal grains and EDNP foods (eg, refined sugars and separated fats), neither of which food group is net base-producing; therefore, neither of which could contribute to counterbalancing the acid produced from net acid-producing animal food groups in the contemporary diet (meat, cheese, milk and yogurt, and eggs) (Table 1). Indeed, cereal grains themselves are net acid-producing and alone accounted

for 38% of the acid load yielded by the combined net acid-producing food groups in the contemporary diet (Table 1).

The quantitative net acid-producing effect of substituting cereal grains for other plant-food groups can be particularly appreciated by applying the computational model to the 2 prototypical preagricultural diets outlined in Table 1 in the circumstance in which cereal grains are substituted as the only plant food. In the first diet (animal-to-plant energy ratio: 35%:65%; animal-food energy: 26%), the substitution resulted in an increase in NEAP from -78 to 147 mEq/d. In the second diet (animal-to-plant energy ratio: 55%/45%; animal-food energy: 53%), the substitution resulted in an increase in NEAP from -23 to 132 mEq/d. That is, in both cases, substituting cereal grains for the other plant-food groups in the preagricultural diet converts the diet from a net base-producing to a net acid-producing one.


The computational model also permitted us to examine the effect of removing cereal grains from the contemporary diet. On the basis of the NHANES III survey (Table 1), apportioning cereal-grain energy to the 4 nongrain plant-food groups (nuts, beans, vegetables, and fruit), in proportion to their relative energy contributions to the diet, would decrease NEAP in the contemporary diet from 48 to -4 mEq/d, a value similar to the neutral point but would not convert the diet to a decidedly net base-producing one. That is, eliminating cereal grains alone and proportionately increasing the remaining plant foods is not sufficient to convert the contemporary diet to a substantial net base-producing one. This finding highlights the fact that it is the combined effect of substituting cereal grains and EDNP foods for nongrain plant-food groups that accounts for the transition from a substantial net base-producing diet to a net acid-producing one in the switch from a pre- to a postagricultural diet. Apportioning cereal grain and EDNP food group energies in the contemporary diet to the 4 nongrain plant-food groups in the diet, again in proportion to their relative energy contributions to the diet, converts the diet from a net acid- to a substantial net base-producing one, decreasing NEAP from 48 to -53 mEq/d; the latter value falls well within the range of estimated values for preagricultural diets, as shown in Table 2.

It should be emphasized that, for the contemporary diet, both the neutralizing effect of replacing cereal grains with nongrain plant-food groups and the net base-producing effect of replacing both cereal grains and EDNP foods with nongrain plant-food groups were computed without changing the amounts of the net acid-producing animal foods in the diet (meat, cheese, milk and yogurt, and eggs). Indeed, animal food intake could increase considerably under these circumstances without conversion of the diet to a net acid-producing one.

If a net base-producing diet was the norm throughout most of hominid evolution, it can be assumed that human metabolic machinery and integrated organ physiology is genetically adapted to an endogenous net base load on average (1–3). Thus, in considering the lifelong effect of the habitual ingestion of contemporary diets, it may be necessary to consider not only the negative effects incurred by their imposed chronic net acid load but also the potential positive effects no longer realized because of their failure to supply a chronic net base load.

Heretofore, the potential biological benefits from a lifelong dietary net base load and its attendant systemic metabolic alkalizing effects have not been considered by paleoanthropologists, nutritionists, physiologists, or clinicians. Extrapolating from the limited current knowledge of the metabolic and physiologic effects of base loading, testable potential benefits of a chronic net base-producing diet for which plausible mechanistic rationales can be given include preventing and treating osteoporosis (52), age-related

muscle wasting (22), calcium nephrolithiasis (17, 53, 54), and sodium chloride-sensitive hypertension (55); improving exercise performance (56); treating infertility (57, 58); and slowing the progression of age-related and disease-related chronic renal insufficiency (16, 18, 59).

Because the steady state plasma bicarbonate concentration is a continuous inverse function of NEAP over a broad range of positive and negative values (16, 36, 56, 60), the findings in the present study also suggest, from an evolutionary perspective, that a mild systemic metabolic alkalosis resulting from chronic dietary net base loading is the natural and optimal systemic acid-base state of humans. To our knowledge there have been no measurements of systemic acid-base equilibrium in modern hunter-gatherers living in the wild. Denton (61) summarized the preliminary studies of MacFarlane et al of a New Guinean hunter-gatherer tribal group living in “the primitive feral condition,” noting that “urine pH of adults was usually between 7.5 and 9.0 because of potassium bicarbonate and carbonate excretion.” Such high urine pH values are difficult to achieve, except with large mild alkalosis-producing bicarbonate inputs. 

REFERENCES

1. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med* 1985;312:283–9.
2. Eaton SB, Eaton SB III, Konner MJ. Paleolithic nutrition revisited. In: Trevathan WR, Smith EO, McKenna JJ, eds. *Evolutionary medicine*. New York: Oxford University Press, Inc, 1999:313–32.
3. Neel JV. When some fine old genes meet a ‘new’ environment. In: Simopoulos AP, ed. *Evolutionary aspects of nutrition and health: diet, exercise, genetics and chronic disease*. Basel, Switzerland: S Karger, 1999:1–15.
4. Cavalli-Sforza LL. Human evolution and nutrition. In: Walcher DN, Kretchmer N, eds. *Food nutrition and evolution: food as an environmental factor in the genesis of human variability*. New York: Masson, 1981:1–7.
5. Eaton SB, Cordain L. Evolutionary aspects of diet: old genes, new fuels. *Nutritional changes since agriculture*. *World Rev Nutr Diet* 1997;81:26–37.
6. Cordain L. Cereal grains: humanity’s double-edged sword. In: Simopoulos AP, ed. *Evolutionary aspects of nutrition and health: diet, exercise, genetics and chronic disease*. Basel, Switzerland: S Karger, 1999:19–73.
7. Eaton SB, Konner M, Shostak M. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. *Am J Med* 1988; 84:739–49.
8. Committee on Diet and Health, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Diet and health: implications for reducing chronic disease risk*. Washington, DC: National Academy Press, 1989.
9. World Health Organization. *Diet, nutrition, and the prevention of chronic diseases: report of a WHO Study Group*. Geneva: World Health Organization, 1990.
10. American Institute for Cancer Research. *Food, nutrition and the prevention of cancer: a global perspective*. Washington, DC: World Cancer Research Fund, American Institute for Cancer Research, 1997.
11. Simopoulos AP. *Evolutionary aspects of nutrition and health: diet, exercise, genetics and chronic disease*. Basel, Switzerland: S Karger, 1999.
12. Trevathan WR, Smith EO, McKenna JJ. *Evolutionary medicine*. New York: Oxford University Press, 1999.
13. Brand-Miller JC, Colagiuri S. Evolutionary aspects of diet and insulin resistance. In: Simopoulos AP, ed. *Evolutionary aspects of nutrition and health: diet, exercise, genetics and chronic disease*. Basel, Switzerland: S Karger, 1999:74–105.

14. Lennon EJ, Lemann J Jr, Litzow JR. The effect of diet and stool composition on the net external acid balance of normal subjects. *J Clin Invest* 1966;45:1601–7.
15. Kurtz I, Maher T, Hulter HN, Schambelan M, Sebastian A. Effect of diet on plasma acid-base composition in normal humans. *Kidney Int* 1983;24:670–80.
16. Frassetto L, Morris RC Jr, Sebastian A. Effect of age on blood acid-base composition in adult humans: role of age-related renal functional decline. *Am J Physiol* 1996;271:1114–22.
17. Lemann J Jr. Relationship between urinary calcium and net acid excretion as determined by dietary protein and potassium: a review. *Nephron* 1999;81(suppl):18–25.
18. Alpern RJ, Sakhae S. The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. *Am J Kidney Dis* 1997;29:291–302.
19. Osther PJ, Bollerslev J, Hansen AB, Engel K, Kildeberg P. Pathophysiology of incomplete renal tubular acidosis in recurrent renal stone formers: evidence of disturbed calcium, bone and citrate metabolism. *Urol Res* 1993;21:169–73.
20. Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris RC Jr. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994;330:1776–81.
21. Frassetto L, Morris RC Jr, Todd K, Sebastian A. Chronic low-grade metabolic acidosis in normal adult humans: pathophysiology and consequences. In: Paoletti R, Crosignani P, Kenemans P, Wenger N, Jackson A, eds. *Women's health and menopause*. London: Kluwer Academic Publishers, 1999:15–23.
22. Frassetto L, Morris RC Jr, Sebastian A. Potassium bicarbonate reduces urinary nitrogen excretion in postmenopausal women. *J Clin Endocrinol Metab* 1997;82:254–9.
23. New S, Macdonald HM, Grubb DA, Reid DM. Positive association between net endogenous noncarbonic acid production (NEAP) and bone health: further support for the importance of the skeleton to acid-base balance. Madrid: IBMS/ECTS, 2001 (abstr).
24. Remer T, Manz F. Estimation of the renal net acid excretion by adults consuming diets containing variable amounts of protein. *Am J Clin Nutr* 1994;59:1356–61.
25. Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. *J Am Diet Assoc* 1995;95:791–7.
26. Frassetto LA, Todd KM, Morris RC Jr, Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. *Am J Clin Nutr* 1998;68:576–83.
27. Cordain L, Brand-Miller J, Eaton SB, Mann N, Holt SHA, Speth JD. Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. *Am J Clin Nutr* 2000;71:682–92.
28. Gordon KD. Evolutionary perspectives on human diet. In: Johnston FE, ed. *Nutritional anthropology*. New York: Alan R Liss, Inc, 1987:3–39.
29. Speth JD. Early hominid hunting and scavenging: the role of meat as an energy source. *J Hum Evol* 1989;18:329–43.
30. Wrangham RW, Jones JH, Laden G, Pilbeam D, Conklin-Brittain N. The raw and the stolen. Cooking and the ecology of human origins. *Curr Anthropol* 1999;40:567–94.
31. O'Connell JF, Hawkes K, Blurton Jones NG. Grandmothering and the evolution of *Homo erectus*. *J Hum Evol* 1999;36:461–85.
32. Milton K. Hunter-gatherer diets—a different perspective. *Am J Clin Nutr* 2000;71:665–7 (editorial).
33. Mann N. Dietary lean red meat and human evolution. *Eur J Nutr* 2000;39:71–9.
34. Cordain L, Brand Miller J, Eaton SB, Mann N. Reply to SC Cunnane. *Am J Clin Nutr* 2000;72:1585–6 (letter).
35. Milton K. Back to basics: why foods of wild primates have relevance for modern human health. *Nutrition* 2000;16:480–3.
36. Kleinman JG, Lemann J Jr. Acid production. In: Maxwell MH, Kleeman CR, Narins RG, eds. *Clinical disorders of fluid and electrolyte metabolism*. New York: McGraw Hill, 1987:159–73.
37. Rudman D, DiFulco TJ, Galambos JT, Smith RB III, Salam AA, Warren WD. Maximal rates of excretion and synthesis of urea in normal and cirrhotic subjects. *J Clin Invest* 1973;52:2241–9.
38. O'Dea K. Traditional diet and food preferences of Australian aboriginal hunter-gatherers. *Philos Trans R Soc Lond B Biol Sci* 1991;334:233–41.
39. Harlan JR. In: Anderson PC, ed. *Prehistoire de l'agriculture. Nouvelles approches experimentales et ethnographiques*. (Wild grass seed harvesting and implications for domestication.) Paris: Centre National de la Recherche Scientifique, 1992:21–7 (in French).
40. Cordain L. The late role of grains and legumes in the human diet, and biochemical evidence of their evolutionary discordance. 1999. Internet: <http://www.beyondveg.com/cordain-l/grains-leg/grains-legumes-1a.shtml> (accessed 27 August 2002).
41. Holland B, Welch AA, Unwin ID, Buss DH, Paul AA, Southgate DAT. McCance and Widdowson's the composition of foods. 5th rev ed. Cambridge, United Kingdom: The Royal Society of Chemistry and Ministry of Agriculture, Fisheries and Food, 1991.
42. US Department of Agriculture, Agricultural Research Service. USDA nutrient database for standard reference, release 13. 2000. Internet: <http://www.nal.usda.gov/fnic/foodcomp/index.html> (accessed 26 August 2002).
43. Milton K. Nutritional characteristics of wild primate foods: do the diets of our closest living relatives have lessons for us? *Nutrition* 1999;15:488–98.
44. Kant AK. Consumption of energy-dense, nutrient-poor foods by adult Americans: nutritional and health implications. The third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr* 2000;72:929–36.
45. Tanaka J. Subsistence ecology of Central Kalahari San. In: Lee RB, DeVore I, eds. *Kalahari hunter-gatherers*. Cambridge, United Kingdom: Harvard University Press, 1976:98–119.
46. Woodburn J. An introduction to Hadza ecology. In: Lee RB, DeVore I, eds. *Man the hunter*. Chicago: Aldine Publishing Co, 1968:49–55.
47. Gould RA. Behavior and adaptation. In: Gould RA, ed. *Living archaeology*. Cambridge, United Kingdom: Cambridge University Press, 1980:48–87.
48. Lindeberg S, Berntorp E, Nilsson-Ehle P, Terent A, Vessby B. Age relations of cardiovascular risk factors in a traditional Melanesian society: the Kitava Study. *Am J Clin Nutr* 1997;66:845–52.
49. Chagnon NA. *Yanomamo: the fierce people*. New York: Holt, Rinehart, and Winston, Inc, 1968.
50. Smit E, Nieto FJ, Crespo CJ, Mitchell P. Estimates of animal and plant protein intake in US adults: results from the Third National Health and Nutrition Examination Survey, 1988–1991. *J Am Diet Assoc* 1999;99:813–20.
51. Frassetto LA, Nash E, Morris RC Jr, Sebastian A. Comparative effects of potassium chloride and bicarbonate on thiazide-induced reduction in urinary calcium excretion. *Kidney Int* 2000;58:748–52.
52. Bushinsky DA. Metabolic alkalosis decreases bone calcium efflux by suppressing osteoclasts and stimulating osteoblasts. *Am J Physiol* 1996;271:F216–22.
53. Lemann J Jr. Pathogenesis of idiopathic hypercalciuria and nephrolithiasis. In: Coe FL, Favus MJ, eds. *Disorders of bone and mineral metabolism*. New York: Raven Press, 1992:685–706.
54. Lemann J Jr, Gray RW, Pleuss JA. Potassium bicarbonate, but not sodium bicarbonate, reduces urinary calcium excretion and improves calcium balance in healthy men. *Kidney Int* 1989;35:688–95.
55. Morris RC Jr, Sebastian A, Forman A, Tanaka M, Schmidlin O. Normotensive salt sensitivity: effects of race and dietary potassium. *Hypertension* 1999;33:18–23.

56. McNaughton L, Backx K, Palmer G, Strange N. Effects of chronic bicarbonate ingestion on the performance of high-intensity work. *Eur J Appl Physiol Occup Physiol* 1999;80:333–6.
57. Maas DH, Storey BT, Mastroianni L Jr. Hydrogen ion and carbon dioxide content of the oviductal fluid of the rhesus monkey (*Macaca mulatta*). *Fertil Steril* 1977;28:981–5.
58. Chen Y, Cann MJ, Litvin TN, et al. Soluble adenylyl cyclase as an evolutionarily conserved bicarbonate sensor. *Science* 2000;289:625–8.
59. Nath KA, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. *J Clin Invest* 1985;76:667–75.
60. Van Goidsenhoven GMT, Gray OV, Price AV, Sanderson PH. The effect of prolonged administration of large doses of sodium bicarbonate in man. *Clin Sci* 1954;13:383–401.
61. Denton D. *The hunger for salt*. New York: Springer-Verlag, 1962.

