An Evolutionary Perspective on Salt, Hypertension, and Human Genetic Variability

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Natural selection for electrolyte conservation has likely been the norm throughout human evolutionary history. However, the current patterns of excessive dietary salt intake create the potential for salt overload. Under these conditions, hypertension may be considered an expected pathological response to an evolutionarily new constraint. The transatlantic Middle Passage may have created a genetic bottleneck for salt conservation in African-Americans. Although the initial consequences of this important historical event probably constricted genetic variability and further magnified the potential for salt-sensitive hypertension, the Middle Passage undoubtedly also served as a more generalized major source of environmental stress and may have stimulated subsequent hereditary diversity in the survivors of this holocaust and their descendants. Accelerated rates of mutation, genetic recombination, and transposable genetic elements in conjunction with enhanced opportunities for gene flow, new selective pressures, and drift have all contributed to the tremendous heterogeneity of contemporary African-Americans. It is unlikely that a single genetic event, even of the severity of the Middle Passage, can account comprehensively for the apparent susceptibility of this macroethnic group to high blood pressure and hypertension. (Hypertension 1991;17[suppl I]:I-129–I-132)

Dietary salt overload has long been thought to precipitate and sustain hypertension; however, few studies have assessed the relation of these two variables within the larger framework of human evolutionary history. The vantage of modern evolutionary theory provides a longitudinal population perspective; when applied to the problem of salt and hypertension, it can potentially provide depth, insight, and integrative clarity to an array of biomedical and epidemiological observations. The objectives of this paper are threefold: 1) to provide an overview of salt intake during our species' evolutionary history, 2) to propose specific evolutionary mechanisms that, once activated, may have created a foundation for current group differences in susceptibility to hypertension, and 3) to assess known historical events for their potential influence on existing patterns of group variations in hypertension.

In this last objective, specific reference will be made to the hypothesis presented by Wilson and Grim on selection for salt conservation among African-Americans.

Salt and Natural Selection in Human Prehistory

The earliest molecular and fossil evidence of human evolution comes from Africa. It is from the tropical biomes of eastern and southern Africa that waves of Homo species are thought to have migrated to the Middle East, Asia, Eastern and Central Europe, and later Western Europe. A majority of paleoanthropologists, Old World archaeologists, and molecular biologists with expertise in the study of human origins concur that anatomically modern Homo sapiens evolved first in Africa and from there migrated, outcompeting and replacing other existing groups or significantly admixing with them, or both. Studies of modern human diversity in mitochondrial DNA, a good index of recent human origins, suggests that all of modern humanity likely evolved from a shared ancestor who lived between 200,000 and 40,000 years ago or 10,000 to 2,000 generations in the past. In an evolutionary context, this is a relatively short period of time; it is also a brief period relative to the 4 million years that hominids have walked erect on Earth. The primary occupation of our species during the vast duration of our residence here has been gathering plant products and hunting animal game. Under the nomadic conditions necessitated by the gathering and hunting occupational niche, the production and use of supplemental salt for food preservation and flavor enhancement assumed little, if any, role in the diets of early humans. Even when groups of these early African hominids began to migrate to other tropical regions of the world and later to formerly glaciated areas, there would have been little impetus for supplemental

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point of view, the "empty set" in this paradigm is occupied by those individuals who appear to maintain a high salt tolerance. In other words, the unexpected group, under the modern conditions of excessive salt intake, are those humans who do not develop the pathology of hypertension. From the perspective of population biology, these latter individuals would be the most promising for study because they have a high probability of evidencing important and successful adaptations to the new selective pressures imposed by consistently elevated dietary salt intakes.

Population Variation in Susceptibility to Hypertension

Diversity among humans is the raw material upon which natural selection acts; indeed, without this variability, natural selection, the primary force in evolution, would have little potency. Diversity within and between groups of humans frequently reflects the consequences of evolution. Whereas evolution is expressed at the level of the population, the target of natural selection is the phenotype, which is the expression of an individual's genetic blueprint (the genotype) and the environment. Hypertension, like many other complex disease states, exhibits broad variation in the magnitude of association between the phenotype and the genotype. It is not possible at this time to quantify the specific genetic component of hypertension in our species. However, it remains clear that one's hereditary background plays an important role in disease susceptibility and expression. Since an assortment of electrolyte-conserving mechanisms may have been established during the earliest periods of human evolution and would have retained high adaptive value until very recently in our history, it is likely that a diversity of adaptive (conserving) mechanisms of varying degrees of effectiveness continue to be expressed among modern humans. Divergent patterns of response to salt overload at both the individual and group levels of assessment may reflect an uneven distribution of the more effective electrolyte-conserving mechanisms across the human species. This uneven distribution of effective conserving mechanisms may account, in part, for the observations by some of significant group differences in sensitivity to salt overload.

A number of evolutionary forces may have inadvertently contributed to this uneven pattern of physiological response. Traditionally, we look to mutation, genetic recombination, genetic drift, gene flow, and natural selection as the primary agents that may mold a group's genetic structure. Variation within a group is promoted by cytophysiological, developmental, ecological, and demographic factors, including such variables as mosaicism of the local environment (the Ludwig effect), geographic variation of the environment and gene flow, inverse assortive mating (i.e., heterogamy, the nonrandom pairing of individuals with dissimilar phenotypes), heterosis (the superior biological fitness of the heterozygote), a change of selection pressure over time, and inefficient natural selection.

With the advent of agriculture as the dominant mode of subsistence 10,000 years ago, the initial stimulus for salt production and use may have been food preservation. Agriculture requires a settled population, which facilitates greater population densities. However, agriculture is a more precarious means of obtaining subsistence than is gathering and hunting. Under these conditions, food preservation became an important behavioral response to the new selective pressures of dietary uncertainty associated with agriculture. In the absence of opportunities for natural cold storage, or perhaps as an adjunct, the application of salt in food processing and the ingestion of nondiscretionary intakes assumed greater importance in the human diet, although supplementary (i.e., discretionary) salt use may still have remained minimal.

In this context, the modern American diet appears evolutionarily anomalous, particularly with regard to discretionary salt intakes. Some research suggests that the salt levels ingested by Americans are at least 10-20 times the minimal level compatible with human health. Given the pathological consequences associated with salt overload and toxicity, the sequelae of hypertension may be thought of as normal or expected responses to an abnormal environmental constraint, dietary salt overload. From an ecological point of view, the "empty set" in this paradigm is
An Evolutionary Evaluation of the Wilson and Grim Hypothesis

Genetic diversity appears to be constrained within a group when we observe uniformity of physiological response to a particular environmental constraint that is known, in other groups, to elicit a range of responses. In the presence of regular salt overload, a high proportion of African-Americans appear to evidence hypertension. This high frequency in susceptibility and its likely correlation with salt exposure suggests the past influence of significant and effective natural selection for electrolyte conservation. The hypothesis proposed by Wilson and Grim points to the experience of the Middle Passage as such an event in African-American history. Intense selection for electrolyte conservation may have produced a bottleneck effect on the preexisting genetic variability, as depicted in the upper part of Figure 1. Although we may debate the uniformity of this selection pressure for electrolyte (especially sodium) conservation during this tragic period in human history, there is no argument that this event represents a condition of extremely high environmental stress.

A consensus of the available literature on the Middle Passage suggests that the major stress-inducing constraints faced by captive Africans included 1) crowding and severely restricted movement for protracted periods (i.e., immobilization stress), 2) temperature extremes, particularly intense thermal stress during rough seas and heavy rains when conveyances were shut and tarpaulins were thrown over the gratings (i.e., acute heat stress), 3) complete cultural alienation and extreme psychological stress, including despondency, anorexia, and the "fixed melancholy" syndrome symptomatic of shock, and 4) increased exposure to communicable diseases, particularly smallpox and dysentery (the "bloody flux"), with the greatly enhanced potential for electrolyte depletion. Eyewitness reports of the conditions prevalent on the majority of slave ships suggests that the easy contamination and potential for infection provided by the close proximity to diseased and dead fellow captives and to blood- and mucus-covered decks, the excessive heat generated by the tight packing of human cargo under conditions of clearly inadequate ventilation, the high rates of starvation (often self-imposed), and restricted fluid intakes could all provide ample survival advantage for individuals with superior electrolyte-conserving mechanisms. Furthermore, there is evidence that many of these stresses continued once slave-loaded ships harbored in ports in the Western Hemisphere and during the seasoning process in the Caribbean.

Many researchers have noted that, under conditions of environmental stress, the occurrence of certain genetic events is accelerated. Many types of stress appear to produce the molecular effect of intensive modification of DNA bases. The rate at which stress-induced molecular lesions occur may overwhelm the usual mechanisms of repair and restoration. The excision repair of DNA damaged in the gap-related opposite sites of both strands seems to trigger a burst of recombinations and point mutations such that the rate of genetic recombination increases, the potential for mutation increases substantially, and the presence of mobile (i.e., transferable) genetic elements increases. Behavioral stress has also been shown to induce sister chromatid exchanges. Stresses, including those characterizing the Middle Passage, clearly appear capable of producing, at the molecular level, a new spectrum of combination variation.

At the level of the phenotype, environmental stress can produce obvious physiological changes in cellular biology, including a depletion of brain norepinephrine and dopamine, increased renal sympathetic nerve activity, and decreased urinary sodium excretion. Many of these stress-facilitated phenotypic effects may be of sufficient magnitude to alter an individual's biological fitness. In addition to these generalized phenotypic effects, research on acute heat exposure suggests that thermosensitivity is genetically linked with spontaneous hypertension. Under conditions of severe physical and biological stress, phenotypic and genotypic variability tend to be high, especially for quantitative traits important in determining survival.

Without question, the stresses of the transatlantic Middle Passage represented a severe selective constraint on the Africans transported to slavery in the Americas. Yet, new evidence on the molecular, ge-
ngetic, and biochemical effects of stress suggest that the very presence of this major constraint may have accelerated the subsequent accumulation of genetic diversity in the descendants of survivors. In addition to an increased rate of recombination, mutation, and transposable genetic elements, the survivors of this transatlantic holocaust and their offspring were subsequently exposed to new biotic and abiotic selective pressures in the American environment, to opportunities for gene flow with non-Africans, and frequently to the social conditions (i.e., isolation) for significant genetic drift. As depicted in the lower half of Figure 1, these new ecological factors may have further magnified the genetic variability of contemporary African-Americans.

It is unlikely that the intense selective pressure for electrolyte conservation proposed by Wilson and Grim, although a significant constraint during the Middle Passage, can be shown to have persisted as a consistent feature of the more recent post-Middle Passage environments of African-Americans. Once the survivors were deposited in the Americas, they faced a diversity of new physical and biological challenges in various ecological settings. Under these nonuniform conditions, the descendants of these Africans not only survived but continued to evolve. The result has been an expansion of their collective genetic variability after the Middle Passage rather than a continued constriction of heterogeneity. With respect to hypertension studies among African-Americans, their history suggests that, although they have been subject to often severe diversity-constricting events, they have also been exposed to diversity-expanding phenomena as well. As such, it is unlikely that any single genetic event can be relied on to account for this group's current apparent susceptibility to high blood pressure and essential hypertension. Rather, the phenotypic and genotypic diversity that characterizes this sociological construct suggests that the Middle Passage was, more likely, a prelude to an expansion in subsequent variation within this highly heterogeneous macroethnic group.
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