Hypertension in an Anthropological and Evolutionary Paradigm

Robert S. Danziger

“T”he contingent, stochastic nature of genetic evolution [provides a]...historical trail [to help us] to identify genes affecting a trait, understand their origins, and to refine our ability to do genetic screening.”

A renaissance is occurring in the field of molecular evolution. The reframing of questions about pathophysiology and disease in an evolutionary perspective is providing new insights and approaches to treatment. Evolutionary theory has recently been applied to such challenges as neonatal jaundice, otitis media, childhood asthma, allergies, infections such as HIV and sexually transmitted diseases, and cancer (for a review, see Trevathan et al).

During the past several decades, blood pressure has been considered in an evolutionary paradigm. In the present discussion, the current state of this work is summarized. The first portion addresses the question of how blood pressure, in general, and hypertension, in particular, fit into the concept of darwinian selection. The latter portion provides insights into understanding and studying hypertension in the context of evolutionary genetics.

Does Darwinian Selection Apply to Hypertension?

Natural selection reflects the observation made by Charles Darwin that individuals within a breeding population vary in their morphology and behavior and that these features are heritable. Not all members of a population contribute equal numbers of offspring to subsequent generations. There is an increase in the frequency of those traits that promote survival and reproduction from generation to generation. Today, it is understood that the passage of such “traits” is based on the interaction of genes and genotypes with the environment to produce specific phenotypes. Evolution can be observed as change “through time in gene frequencies.” There are 4 primary forces that alter gene frequencies through time. The most important is natural selection; the others are mutation, gene shift (flow), and gene drift (for reviews, see Endler).

For natural selection to occur, 2 basic requirements must be met: the phenotype (1) must heritable (ie, genetically passed from generation to generation) and (2) must be the target of selective forces.

Although there is a significant environmental affect, blood pressure has well-documented major genetic and heritable components. Biometrical strategies used to quantify the relative contributions of genetic and environmental sources of phenotypic variance have consistently shown that 20% to 30% of the interindividual variation in systolic blood pressure is attributable to polygenes. It is generally accepted that genetic influences contribute to the prevailing blood pressure of individuals, as indicated in the similarity of values between first-degree relatives, which is usually described with a correlation coefficient of 0.2 to 0.3. A recurrence risk for hypertensive of =3.5 has been described for affected siblings of hypertensives.

Although blood pressure is heritable, essential hypertension does not follow a clear pattern of inheritance, unlike mendelian forms that result from a single gene defect and are inherited in a simple mendelian manner (for a review, see Hamet et al). This nonmendelian inheritance pattern is postulated to reflect a polygenic etiology of essential hypertension. The association of blood pressure with polymorphisms in multiple genes (eg, atrial natriuretic peptide, endothelin, renin, angiotensin) across races, ethnicities, and gender has been used to support a polygenic cause for essential hypertension (for a review, see Crews and Williams).

There is good evidence that hypertension affects fitness and, therefore, is subject to selective forces. Fitness in a darwinian sense is defined for populations with separate generations as “the expected number of offspring contributed by an individual to the next generation and...is estimated from a particular stage in life to the corresponding stage in the next life cycle.” (“Fitness” is the “probability that a zygote will survive to breed ‘x’ expected number of offspring, given that it does survive.”) Although the major focus of work related to cardiovascular events and pathology associated with hypertension has been in adults past reproductive age, there is abundant evidence across cultures and populations that high blood pressure is associated with both increased fetal and perinatal maternal morbidity and mortality rates. This strongly indicates that hypertension reduces fitness. However, it should be recognized that a reduction in fitness does not absolutely follow, because a trait associated
If Hypertension Reduces Fitness, Why Is It Present?
The persistence of quantitative traits associated with reduced fitness, such as hypertension, has been addressed in various ways in evolutionary theory (eg, altered environment, gene pleiotropisms, and directional selection).

Phenotypes with reduced fitness in a given evolutionary environment may have been originally selected in a more complementary environment. For humans, the physical environment of evolutionary adaptiveness most likely has its roots in the Pleistocene savannah, where "relatives [engaged in] hunting, gathering, mating, raising children, and responding to threats and opportunities provided by neighboring groups." Advances in technology and industry have mitigated the impact of historical agents of selection such as malnutrition, parasites, and infectious diseases during the past 10,000 years in many parts of the world. Now, a number of diseases confronted by medicine workers in technological societies are "diseases of civilization" and reflect differences in evolutionary theory (eg, altered environment, gene pleiotropisms, and directional selection).

The concept that change in evolutionary environment alters fitness is reflected in a related explanation for the persistence of genotypes that reduce fitness. Gene mutations that normally reduce fitness in an environment may have reduced selective force because of the presence of "masking" gene mutations. The presence of a mutation in a gene that is linked to hypertension may lessen the likelihood that mutations in other genes that would normally cause hypertension will have an impact on blood pressure. For example, mutations in the renin or angiotensin gene that normally cause hypertension may not have any effect on blood pressure in the presence of a mutation in the basolateral Na⁺,K⁺-ATPase gene that inhibits its activity.

Gene Pleiotropisms
Phenotypic traits with decreased fitness may be explained in terms of gene pleiotropisms, or genes that contribute to >1 phenotype and are expressed in various tissues with different effects. The major selective force for a particular genotype, which influences multiple traits, may act on a subset of traits or a single trait (ie, an index trait). In other words, a pathological condition associated with a particular allele or alleles of a pleiotropic gene may be only 1 aspect of the associated phenotype. The overall advantage or disadvantage of the allele or alleles may depend on local environments or even its frequency. Pleiotropisms could apply to genes in the renin-angiotensin system, because on the one hand, renin-angiotensin gene polymorphisms associated with increased activity cause hypertension, whereas on the other hand, they may simultaneously reduce developmental renal abnormalities. Thus, the selective force for the "index trait" for angiotensin and renin genes may be renal development rather than blood pressure, thereby favoring polymorphisms with increased activity. There is a genetic linkage of obesity with hypertension, leading to the possibility that throughout evolution in the environments of low caloric availability, a high storage capacity, which is reflected in obesity in contemporary settings of increased food availability, may have been selected. Similarly, primary selective forces to lower perinatal stress may have favored a low birth weight and led to the long-term consequence of the development of hypertension in adulthood.

Directional Selection
Although controversial, directional selection may also be used to explain the evolution of traits such as hypertension. The phenotypic distribution of a complex quantitative phenotype represents a basically adaptive pattern, and extremes are assumed to be disadvantageous. If phenotypes at 1 extreme are more heavily affected than those at the other extreme of a distribution, the mean will move over time in the relatively favored direction. Thus, maximum fitness may be conferred by a compromise between 2 opposing, and possibly unequal, selective forces. Classic examples of this include traits such as brain size and birth weight. It has been hypothesized that a balance between selective forces favoring
larger brain size and those related to maintaining cranial sizes at birth that allow successful delivery underlies the gradual increase in human brain size compared with that in apelike ancestors. In the case of blood pressure, selective forces against hypotension and hypertension may be active. Support for this hypothesis may be provided by the “J curve,” which describes a significant increase in morbidity and mortality rates associated with both low and high blood pressures. If the selective forces against hypotension are greater than those against hypertension, the favored direction may be toward hypertension, and the mean distribution will shift toward higher blood pressures. This reasoning has been invoked to explain the partial skewing of the bell-shaped distribution of blood pressures in the population to the right.

Insights Provided by Evolutionary Theory Into the Pathogenesis of Hypertension

General principles of the molecular evolution pattern of quantitative traits can be applied to blood pressure, in general, and to essential hypertension in particular. The expression of quantitative traits with polygenic inheritance patterns such as hypertension is influenced by both genetic (nature) and environmental (nurture) factors. Needless to say, only genetic differences affect the nature of the offspring. There is ample evidence for the effects of genetic and environmental factors, such as diet and age, on blood pressure. For purposes of analysis, any differences that are not genetic are considered environmental, and it is assumed in many models that genetic and environmental factors act independently and additively. However, the real situation is considerably more complex, because genetic and environmental factors may overlap. For example, a shared environment may exist between relatives, and factors such as diet and activity be transmitted culturally. One of the challenges to understanding the pathogenesis of hypertension is determining the contribution and nature of the interaction between these influences.

Hypertension is defined by James and Baker as the inability of multiple compensatory mechanisms involved in the control of blood pressure to maintain the pressure within appropriate limits. “To the extent that the pathological change of a given regulatory mechanism has a heritable component, high blood pressure that results from it will tend to aggregate in families. However, the pathology that is inherited in one family may not be the same as that inherited in another.”

This also applies to populations that evolve under different circumstances or environments for different durations of time and suggests stronger associations of specific genotypes with hypertension within, as opposed to between, geographical, racial, and ethnic groups. This has been validated by genetic linkage studies of the ACE gene in various groups and subpopulations (for a review, see Corvol and Jeunenaitre’s). A significant correlation of specific ACE polymorphisms with hypertension has been detected only in specific populations (eg, white and Japanese) and families.

The identification of genes and gene patterns that underlie hypertension made possible by the development of new rapid and high-throughput methods of sequencing and genotyping will help in understanding evolutionary aspects of blood pressure determination. With the completion of the Human Genome Project and the data it provides, the value of developments in genetic and molecular evolutionary theory in understanding disease will be increasingly recognized.

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References


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