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Human Evolution and Chronic Diseases: Genes, Allostasis, and Cut-Points

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Introduction

Many chronic diseases are characterized by a progressive dysfunction in metabolic and/or physiologic systems. Epidemiologically, the incidence and prevalence of these disorders are far greater now than at any time in our evolutionary past. One reason for this increase is the fact that these conditions generally manifest their symptoms in people over 40 years of age, a segment of human populations that has grown disproportionately in modern, industrialized societies where survivorship has increased to six decades and longer for both men and women, particularly over the past century [1]. Determining why genetic variants that lead to or cause chronic conditions such as hypertension, arteriosclerosis, or non-insulin dependent diabetes mellitus perpetuate in human populations continues to be a significant challenge for biomedical science. One important reason for this difficulty is the fact that many chronic diseases are diagnosed from a measurement that exceeds a cut-point in the distribution of a polygenic trait [2]. Their heritability is thus related to the continuously distributed trait for which they represent pathology, such as blood pressure, low-density lipoprotein levels (LDL), fat deposition or serum glucose levels. Because of the polygenic nature of the traits and their allostatic character, the environment also has a major impact on their phenotypic expression and thus also plays a substantial role in whether a measured value falls within a normal or chronic disease range. Finally, combinations and interactions of genes that can produce a disease phenotype may differ across patients. This principle probably also holds true for populations as well. The genetic variants that lead to chronic disease development in one population may be completely different from those that contribute to the same condition in another. The process of chronic disease development is complex. The purpose of this discussion is to briefly explore some conceptual and methodological issues involved in studying the evolution of chronic diseases in humans.

The Persistence of Chronic Disease in Human Evolution

It is incorrect to assume that chronic diseases are only a manifestation of modern Western lifestyles in humans, since whatever genes are responsible for them have likely been with the genus *Homo* since its inception [1]. In fact, allelic variants that can cause chronic disorders in humans are probably evolutionarily older than the appearance of the primates, and may be at least as ancient as the common ancestor of rodents and humans, as artificial selection in rats and mice have created strains that develop genetically based chronic conditions such as spontaneous hypertension, obesity and various cancers that parallel similar conditions in humans [1].

Several well-reasoned theories have been articulated as to why genes that cause chronic diseases exist and perpetuate in humans (mammalian species). These theories focus on two main principles: 1) genotypic adaptations that are rendered maladaptive when there is a substantial environmental change, such as dietary change (thrifty genotype) and 2) tradeoffs within the genome that evolved as a compromise but which ensure survival and reproductive success (antagonistic pleiotrophy) [1]. Some tradeoffs involve natural selection for alleles that are beneficial early in life (prior to and during the reproductive phase of life) but which have detrimental consequences later in life (after reproduction is complete). Others involve genes that have effects in several metabolic or physiological systems (pleiotrophic genes). Selection could occur for an allelic variant that enhances fitness by improving function in one system, but simultaneously, the same variant may contribute the progressive dysfunction of another in which it has influence. One example of antagonistic pleiotrophy might be an allelic variant that is associated with an increased efficiency of dietary cholesterol extraction during early stages of life. This variant may enhance reproductive success by enhancing growth early in life; however, the same variant later in life might contribute to arterial plaque formation and the development of arteriosclerosis [1].

Stress as a Contributor to Chronic Disease Development

Hans Selye [3] educed how stress contributes to chronic disease development. He described a three-stage biological response to stress, the first of which was the initial reaction to noxious environmental stimuli, which involved activation of the hypothalamic-pituitary-adrenal cortical system (releasing the stress hormone cortisol) and the sympathetic adrenal medullary system (releasing the stress hormones epinephrine and norepinephrine). This stage is essentially the "fight or flight" response or "alarm reaction" described much earlier by Walter Cannon [4]. The second stage, the "stage of resistance" was defined by the local adaptive responses of tissue triggered by the hormones released in stage one, and reflected the maintenance of homeostasis in the face of the external environmental stressor(s). The third was a "stage of exhaustion" in which the ability of tissues to resist stress first declined and then failed, ultimately leading to disease. Selye coined the term "general adaptation syndrome" to describe the initiation and ultimate failure of the integrated neuroendocrine and physiological response to stress. From this perspective, chronic diseases develop as an inevitable byproduct of the process of adaptation to stress. Everything from the environment presents a challenge to homeostasis (some large, some small). Over extended periods of time, depending upon the nature and intensity of the environmental stressors, an attrition of bodily processes that maintain the internal milieu occurs. Because homeostatic systems work through negative feedback, symptoms of a chronic disease may not manifest themselves until there is also failure in the compensatory mechanisms of the system. Thus, the process of development of a chronic disease may be long underway while there is still an apparent healthy phenotype.

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Allostasis and Allostatic Load

Allostasis is defined as the ability to achieve stability through change [5]. It is a complimentary concept to homeostasis, in that it describes the behavior of several endocrine and physiological measures that derive their adaptive value from wide variation, rather than maintenance of a range with extremely narrow limits. The releases of stress hormones (epinephrine, norepinephrine, and cortisol) as well as physiological functions the hormones help regulate, such as blood pressure and heart rate are examples of allostatic measures. These traits may actually have several stable set points (as opposed to a single set point in a homeostatic trait), and can change dramatically when environmental conditions warrant.

Chronic diseases develop when there is an excessive allostatic load, meaning that allostatic measures of the body have to vary over the extent of their range with greater frequency, or that they spend longer periods of time at extreme values of their range. As opposed to homeostatic systems, allostatic systems become "diseased" when they either lose their ability to change (generally migrating to values at the extreme of their variation) or lose the ability to regulate their change so that the direction or extent of variation is not appropriate for the environmental stimulus. An example of a stress associated "chronic allostatic condition" is hypertension (high blood pressure) [5].

Biological Evolution and Cultural Change

A factor that has been identified as an important contributor to the development of chronic diseases in humans is the mismatch between the relatively slow pace of human biological evolution compared to the relatively rapid pace of human cultural and lifestyle change [1]. For example, the daily environment experienced by contemporary humans, particularly in urban societies is often characterized by a compartmentalization of activities and social interactions, as well as by rapid change. These conditions differ markedly from the circumstances under which human populations spent the overwhelming majority of their evolutionary time [6]. Several stressful aspects of these urban environments have been described, including but not limited to noise, overcrowding, poor sanitation, and pollution. Urban stressors tend to be compartmentalized into economic, domestic and leisure microenvironments, so they are not continuously experienced by the individual. Thus, the stresses they produce are confronted in a somewhat structured way depending upon the types and patterns of microenvironments experienced. The pattern of microenvironmental experience over the course of a day defines a significant aspect of an individual's lifestyle and varies from person to person. From an evolutionary standpoint, successful adaptation to the evolutionarily recent urban setting hinges to some extent upon the ability to biologically negotiate the stressors specific to the personal mix of microenvironments experienced, which includes the differing people, places and conditions that characterize each setting [6]. Because of the relatively slow pace of evolution, the biological resources available for adapting to these patterned stressful encounters are those that evolved in daily conditions that were characterized by little social compartmentalization and extended intervals of relative calm punctuated by brief periods of excitement. It is the contrast between the relatively rapid cultural change to contemporary dynamic environments (both social and physical) and our slowly evolving physiology that has implicated current urban lifestyles and the biological responses to them in the development of chronic diseases [6]. The way cultural change toward a compartmentalized cosmopolitan environment leads to chronic disease development is probably by increasing allostatic load. That is, when lifestyles become compartmentalized, the amount of time spent in a stressful microenvironment (such as that where wage employment takes place) can be a substantial proportion of the day. In order to adapt to this stress, the allostatic systems of the body adjust themselves to more extreme values. This process, repeated daily for the decades of adult life, could create a heavy allostatic load and chronic disease(s) would ultimately develop.

Biological anthropologists have learned that the cultural change needed to have an impact on allostatic load need not be as drastic as a change from small bands engaging in hunting and gathering to large cosmopolitan urban wage-based societies. Several studies have found that traditionally living populations with varying economic and social systems that incorporate aspects of Western cosmopolitan lifestyles including increasing dietary fat, changing daily activity patterns to a 9 to 5 work routine from a more ecologically driven pattern and altering social organization have a dramatic increase in the incidence of chronic diseases [1,5,7].

Distributional Cut-points and Disease Definitions

As previously noted, many chronic diseases are defined by a measurement that exceeds a cut-point in the distribution of a polygenic trait. When a measured value is higher than the cut-point, the person is considered diseased. Many of the cut-point diseases are diagnosed as excessively high values of allostatic traits (for example, blood pressure (allostatic trait)/ hypertension (chronic condition)). Although the adaptive value of these traits is related to their wide variation, pathology is determined from their population distribution when measurements are taken under "standardized conditions" [5].

There are two problems associated with this type of disease determination. The first concerns deciding what the cut-point value of disease should be. In the case of hypertension, the value might be determined from prospective mortality studies, where disease is determined to occur where statistically, the blood pressure value measured in "standardized conditions" predicts a doubling of the rate of mortality. However, what this means is that as more and larger prospective epidemiological studies are completed, the disease value can and will change [8] Furthermore, because medical associations and/or government appointed expert panels (for example the World Health Organization (WHO) or the Joint National Committee (JNC)) are the governing bodies that determine ultimately what the disease cut-point value should be, it is possible to have conflicting or differing definitions as to what constitutes disease, depending upon which governing body is followed. This has been true for hypertension and hyperlipidemia. Because of the mathematical and political determination of when disease is present in a distribution-related allostatic trait, biological anthropologists studying allelic variation related to the development of disease should be careful and wary of what definition of disease they are using.

The second problem concerns the inability to properly create a "standardized condition" in which to validly measure an allostatic trait. The reason is that for any given individual, any condition can be perceived to be stressful, and as such will cause the allostatic trait to respond by increasing to an extreme value. More than likely, this stress induced value will be above the population distribution "disease" threshold value, and hence a normal, healthy individual will be considered diseased and medically treated when in reality their disease determining measurement is a response to stress. For example, there is now a diagnosis of "white-coat" hypertension, which describes patients whose blood pressure exceeds the hypertension cut-point (say

140/90) only when physicians or medical personnel measure the blood pressure [5,9]. Because standard measurements may not be possible, the probability of disease misclassification in conditions defined by a distributional cut-point in a "standardized measurement" can be large. White coat hypertension has a prevalence of 20-40% in clinical populations [5,9].

Final Thoughts

In general, there is considerable evidence that the development of chronic disease in humans is both a product of long-term evolution and a consequence of adaptation to contemporary cultural and physical environments. Indeed, genetic variants that may contribute the ultimate failure of metabolic and physiological systems are shared by rodents and humans and are thus ancient in our evolutionary tree. Cultural change and an increase in longevity contribute to the observed increased prevalence of chronic diseases in many populations. However, one class of these diseases, those that are determined from "cut-points" in the population distributions of "standardized measurements" of allostatic traits, is improperly defined. This lack of precise definition likely hinders our ability to fully understand their genetic basis.

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