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HUMAN LONGEVITY: NATURE VS. NURTURE—FACT OR FICTION

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In order to be longevous, "select long-lived parents, and particularly long-lived mothers."—RAYMOND PEARL [1, p57]

Introduction

Some 50 years later, the papers written by the biologist Raymond Pearl still stand as classics in the study of human longevity [1–6]. By attempting to explain how individuals become longevous, Pearl was addressing a question that virtually everyone ponders once old enough to comprehend their own mortality. Traditionally, factors that might influence how long we live have been divided into two general categories: heredity (nature) and environment (nurture). The perceived importance of heredity often depends on one's scientific discipline, and views range from seeing heredity as a primary determinant to considering it no more than a minor contributor

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to human longevity. Despite a rapidly expanding knowledge base in the biomedical sciences and emphatic claims made about the heritability of longevity, the relative importance of nature versus nurture in determining duration of life remains unresolved. If desire could determine truth, the hope that longevity can be continuously increased through lifestyle modifications and manipulation of the environment within which we live would make nurture the easy winner.

Measuring Heritability

With the exception of monozygotic twins, every human possesses an assemblage of genes that differs from that of any other human—past or present. Traits like eye color or blood type are heritable because they are genetically transmitted from parent to offspring. The trait of interest in this discussion is human longevity or duration of life. Humans die at virtually every age of the known life span, and they live in a wider diversity of environments than any other species. Deaths caused by genetic diseases are known to exist. However, there are also causes of death (e.g., accidents, homicide) that almost certainly have little to do (directly) with the genetic makeup of the individuals who die. Scientists interested in human aging want to know how much of the observed duration of life is genetically determined and how much is environmentally influenced. However, the biometricians and geneticists who have developed the theory and methods for estimating heritability do not estimate the heritability of a trait in categorical genetic terms. Instead, they estimate the proportion of the variation in the observed distribution of a trait that can be attributed to either genetic or environmental sources.

Although the initial question concerning the heritability of human longevity seems simple enough, the approach to answering it is complicated by a scale of measurement—variance—that can be difficult to visualize and interpret. And there are additional complications that are central to understanding the disputes that arise over the issue of heritability. Most of the remaining discussion within this section will be a distillation of information contained within three papers that are highly recommended reading for anyone interested in pursuing the concept of heritability in greater detail. The Kempthorne paper is a sharply worded commentary by a prestigious biostatistician on the relevance of heritability measures for making a causal connection between race and IQ—a scathing criticism of the scientific approach used by the advocates of both nature and nurture [7]. A substitution of the word "longevity" for "IQ" in the Kempthorne paper will provide an equally appropriate portrayal of the misuse and abuse of heritability that has been applied to human longevity. One of the Jacquard papers deals explicitly with the issue of human longevity, while the other paper by Jac-

quard provides an excellent discussion of the genetic assumptions and subsequent mathematical consequences that affect the estimation of heritability more generally [8–9].

A major source of confusion about heritability stems from the fact that it has a colloquial meaning that differs from the restrictive definitions linked to the methods used to estimate it. In fact, population geneticists apply the term heritability to three interrelated concepts, referred to as biometric heritability, broad sense heritability, and narrow sense heritability [9]. *Biometric heritability* is estimated by the slope of a regression line where a quantitative character like the longevity of offspring is regressed on to functions of that character measured for the parents [see 10, pp134–38 for details and an example]. This measure of heritability was originally intended to provide an empirical estimate for the predictability of phenotypic resemblance between parents and offspring—the greater the phenotypic resemblance, the higher the biometric heritability. Biometric heritability has been a valuable tool in breeding programs used to improve domestic plants and animals. It was not intended to provide an explanation, genetic or otherwise, for the observed degree of resemblance between individuals within a single generation of a population [9]. As such, the concept of biometric heritability cannot be used to resolve the nature versus nurture debates on human longevity.

In its simplest and most often used form, the calculation of *broad sense heritability* permits the variation of a phenotypic character observed within a specified population and environment to be partitioned into genetic and environmental components. Heritability in the broad sense (also referred to as the coefficient of genetic determination) is then estimated as the genetic variance of the character being studied divided by the total variance observed for that character [9]. The critical element of this approach is the estimation of the component for genetic variance. In order to accomplish this estimation, two strong assumptions are normally made: (1) the independence of genotype and environment is assumed (i.e., no preference of a particular genotype for a particular environment; in other words, no genetic-environmental interaction); (2) the genetic and environmental components of variance are assumed to be additive (i.e., environmental effects do not depend on the genotype of the individuals) [8]. These assumptions cannot be met for most human cohorts. For example, the documented survival advantage of individuals that carry the gene for sickle cell anemia in environments where malaria is endemic would violate the independence assumption [11].

At the cost of increased mathematical complexity, the model for heritability in the broad sense can be made more realistic by the addition of a term for the interaction of genotype and environment. Unfortunately, the addition of an interaction term means that the system of equations used to estimate the parameters for this more realistic model have more un-

knowns than equations—a condition that requires even more numeric constraints be imposed on the equations (hence, assumptions) in order to arrive at a solution [9]. Typically, the comparison of data for monozygotic and dizygotic twins are used to estimate broad sense heritability [e.g., see 12 for an application to the heritability of longevity]. No matter how meticulously conducted, studies that measure broad sense heritability must: (1) be interpreted within the context of the restrictive assumptions required to derive the estimate; (2) emphasize that heritability refers to the contribution that genes make to the observed variation of a character (e.g., longevity)—not the importance of genetic factors in determining the character itself; and (3) emphasize that an estimate of heritability applies only to the population and environment under study [9]. Other populations and environments may give rise to completely different estimates of heritability in the broad sense. In other words, estimates of heritability in the broad sense cannot be generalized across population subgroups, geographic boundaries or time periods. Jacquard made an even bolder assertion when he declared that "broad heritability . . . can only be defined by making unrealistic assumptions [and] . . . one can wonder why so much trouble is taken to measure a parameter linked to a concept which is usually not definable" [9, p474].

Whereas heritability in the broad sense deals with genotypes, *heritability in the narrow sense* attempts to partition genetic variability into the contributions made by individual genes [9]. In order to be realistic, heritability in the narrow sense must accommodate the interaction of alleles at the same genetic locus (dominance), as well as the interaction of genes located at different loci (epistasis, linkage). The result is a genetic variance that has an additive component where the genetic effect on the distribution of a character under study is equal to the sum of the effects contributed by individual genes, and a non-additive component that is made up of all the various kinds of effects arising from gene interactions. In order to simplify the mathematics, the interaction terms are often ignored and heritability in the narrow sense is interpreted as a measure of the variation in a character that can be attributed to additive genetic effects [9, 13]. It can be shown that the formula used to calculate heritability in the narrow sense can be expressed as a function of the frequency of genes that are presumed to affect the character of interest in the population under study [7–9]. This dependence on gene frequencies can lead to the surprising result that estimates of heritability can be effectively zero for traits (i.e., rare recessive traits) that are known to be genetically determined [9, p473].

Although the measures of heritability developed by statistical and agricultural geneticists form a gradation of focus that ranges from phenotypic variation (biometric heritability), to genotypic variation (broad sense heritability), to individual genetic segregation and recombination (narrow sense heritability), none of the measures can be used legitimately to make

inferences about the heritability of longevity in the colloquial sense desired by researchers who study aging. Even when used in the sense intended by geneticists, these measures cannot be used to draw meaningful conclusions about the heritability of the variation in longevity observed in other populations, environments, or time periods.

It should be emphasized that the concept of heritability and the measures that arose from it have proven to be extremely useful tools for plant and animal breeders. They have been used to design breeding programs that have led to such things as greater milk production, higher protein to fat ratios in meat, enhanced crop yields, increased egg production, improved food utilization, increased resistance to infectious and parasitic diseases—in other words, significant improvements in economic value of plants and animals used for agricultural production. The heritability concepts developed by agricultural geneticists are not compatible with a colloquial notion of heritability that focuses on the genetic transmission of a specified trait rather than its genetic variation in a population. The time-tested concepts of population genetics should not be applied to problems for which they were not designed. Confusing these genetic concepts with heritability in the colloquial sense can easily lead to inappropriate claims and misleading interpretations about the heritability of human longevity—especially when presented for public consumption.

Luminaries like Karl Pearson and Raymond Pearl have attempted to quantify nature versus nurture for duration of life [5, 14]. Other notable attempts to estimate the heritability of longevity have also been made [see 8, 15, 16 for reviews of this literature]. None of these efforts to estimate the heritability of longevity have escaped the limitations imposed by the methods of estimation. A summary conclusion made by Jacquard for one of these studies may be used to summarize the results of virtually every study that has attempted to estimate the heritability of longevity: "environmental factors are so important as regards duration of life that genetic factors seem insignificant in comparison" [8, p310]. Jacquard himself would probably be the first to point out that he should have written "as regards the distribution of duration of life," rather than refer to the trait itself.

The logic of population genetics makes it clear that statements like "longevity is moderately heritable" [12], or that environment is more important than genes in determining longevity, must be interpreted with caution. The distribution of individual life spans in a specified population and environment may be "moderately heritable," but this conclusion tells us next to nothing about the contribution that genes may or may not make to the life span of an individual. Instead, these statements indicate that environmentally induced mortality has a larger impact than genetic factors on the variation in attained age observed within the population under study—an indication that the environment remains a hostile place. As humans continue to move toward a world where environmentally influenced mortality

diminishes, the balance between environmental and genetic components of variance must inevitably shift toward the genetic compartment. If and when this shift occurs, the logic used to criticize claims that "longevity is moderately heritable"can also be used to criticize claims that "longevity is largely heritable." Once again, heritability refers to the distribution of longevity in a population, not the specific genetic determinism of longevity itself.

Low values of heritability have been used as scientific evidence that the life span of humans and the life expectancy of human populations have no upper limits that are either imposed or even significantly influenced by genetic factors [12]. Even if the conclusion is correct, the biomathematics of heritability reveals that the logic used to arrive at this conclusion is unjustified. What follows are a variety of perspectives suggesting that genes may play a more influential role in human longevity than many would like to think. Advocating the importance of genetics to human longevity carries with it a message of pessimism and optimism in equal measure. On the one hand, this position supports the view that genetically influenced upper limits to human longevity do exist [17]. On the other hand, this position also supports the belief that scientific progress in understanding genes will continue to provide opportunities to modify these upper limits [18, 19].

A Demographic Perspective

How long someone is biologically capable of living is a theoretical attribute of an individual that can be neither observed nor estimated with precision. Thus, before the relative importance of factors that might influence longevity can be revealed, it is necessary to determine why individuals die, what they die from, and why some people appear destined to die young while others are able to live a century or more. Although death is a uniquely individual phenomenon, much of our current understanding about death and its causes has come from the study of populations.

Life expectancy is a summary statistic for a population that estimates the average time yet to be lived by individuals of a specified age (typically from birth). Dramatic increases in life expectancy during the 20th century and the more recent declines in death rates that have been observed at older ages have caused researchers to ask how much higher life expectancy can rise [20–23]. The distinction between measures of longevity for individuals (life span) and populations (life expectancy) has begun to blur as researchers debate the question of how high the life expectancy for human populations can rise. As such, an investigation of the forces that influence the life span of individuals and the life expectancy of populations is a logical step toward understanding the determinants of human longevity.

Anthropologists estimate that our earliest ancestors lived on average only about 18 years, and that by the time of the Roman empire, life expectancy had not risen much beyond 22 years [24]. From the time of Caesar to the

start of the 20th century, life expectancy at birth doubled to 45 years. As humans approach the dawn of a new millennium, average life expectancy for females in some parts of the world now exceeds 80 years. The primary causes for this spectacular rise in life expectancy include a combination of improved sanitation, better housing and living conditions, the discovery and widespread use of antibiotics, and other advances in medical technology [25, 26].

Peeling away the layers of an onion provides an effective image for explaining the transition from the primary causes of death in the past to those that dominate the present. As one layer of an onion is peeled away, another layer is revealed below it. In this analogy, the outer layer of the onion represents the infectious and parasitic diseases that killed the vast majority of our ancestors and, prior to the 18th century, restricted life expectancy at birth to less than 30 years. At least in the developed world, modified living conditions and the introduction of antibiotics that can be used to combat infectious and parasitic diseases have permitted the next layer of the onion to be revealed—a layer dominated by such chronic disorders as cardiovascular disease and cancer. Contrary to popular perception, the rising death toll from heart disease and cancer signals a great biomedical victory against infectious diseases rather than the negative health consequences of decadent lifestyles and environmental degradation.

The life expectancy revolution of the 20th century brought forth profound changes in the demography and health status of humans. Not only has age at death been redistributed from the young to the old, but for the first time the world is experiencing explosive population growth and unprecedented population aging [27]. Furthermore, the rapid rise of life expectancy in modern times clearly documents a dramatic shift in the major causes of human mortality. As evidenced by ongoing debates over health insurance, Social Security, and Medicare, anything that changes the health status and age structure of a population will have profound societal consequences that touch the lives of virtually everyone. Whether this dramatic shift in what humans die from has any relevance to judging the relative balance between environmental and hereditary determinants of individual longevity will be an important issue in the future.

An Evolutionary Perspective

A hereditary basis for longevity cannot be discussed without the conceptual framework provided by evolutionary biology. At the heart of evolutionary biology is the concept of natural selection, whereby the frequencies of genes in a population are determined by the differential survival and reproductive success of individuals that carry alternative forms of the genes—alternative forms created initially by mutation events. In order to win in the evolutionary game of life, an individual must survive long enough

to reproduce in a world that is normally so hostile that most individuals die before they are able to attain the age of sexual maturity. These two factors, natural selection and a hostile environment, provide the necessary ingredients for the evolutionary explanations for why individuals grow old and die.

A hostile environment provides a gauntlet of mortality forces that has made early reproduction (relative to potential life span) a necessary component of the life history strategy for most organisms. Delaying reproduction increases the probability that death will occur before one's genes can be passed on to the next generation. As a consequence, much of the genetic machinery of a sexually reproducing organism is devoted to processes of growth and development that occur between fertilization and sexual maturity. Physiological constraints on how early in the potential life span sexual maturity can occur, coupled with an age-related increase in the probability of death (from causes that are often unrelated to the aging process), defines an age window for a species within which reproduction occurs (referred to as the reproductive period). The existence of a circumscribed reproductive period also establishes well-defined pre-reproductive and post-reproductive periods within the potential life span of sexually reproducing organisms.

The ability of natural selection to influence gene frequencies differs dramatically among the three biologically meaningful partitions of the life span. Selection is highly effective during the pre-reproductive period because any variant of a gene (allele) that adversely affects an organism's ability to survive long enough to reproduce would be at a severe disadvantage. Conversely, natural selection has little or no influence on alleles whose harmful or beneficial consequences are restricted to the post-reproductive period, because these genes have already been propagated. Finally, natural selection follows an age-gradient of declining effectiveness during the reproductive period that is inversely proportional to cumulative reproductive success. This theory leads to the prediction that a biometric estimate for the heritability of longevity should increase for offspring born to longer-lived parents—a prediction that has been supported by a recent analysis of human data [28].

Restricting the influence of natural selection to only a portion of the potential life span has led evolutionary biologists to speculate on why harmful genes can persist in a population and how senescence (aging) might have arisen. George Williams, a renowned evolutionary biologist, has argued that it should be possible for alleles with harmful effects (when expressed late in life) to accumulate in a population if they enhance survival and reproductive success early in life [29]. The late Nobel laureate, Sir Peter Medawar, described the post-reproductive period of the life span as a "genetic dustbin" for the expression of genes whose harmful effects during this period are beyond the reach of natural selection [30]. Under nor-

mal survival conditions (i.e., a hostile environment), the harmful effects of these genes would not be observed because most animals either die before or shortly after reproducing—typically from causes unrelated to aging (e.g., accidents, infectious and parasitic disease, predation). Thomas Kirkwood has noted that immortality of the individual would not even be desirable evolutionarily if the physiological costs required for such extended survival were not translated into greater reproductive output [31]. Thus, evolutionary biologists link senescence to reproduction and conclude that senescence may simply be an inadvertent consequence of survival extended into the post-reproductive period. It is in this region of the life span where the harmful consequences of deleterious genes can be expressed without compromising early survival or reproduction.

The mutation accumulation hypothesis of Medawar and the antagonistic pleiotropy hypothesis of Williams have been presented in the evolution literature as competing models [29, 30, 32, 33]. Attempts have been made to determine which of the two models is correct [34]. There has, however, been an emerging consensus over the years that the genetic mechanisms proposed by both models have played a role in the evolution of senescence [35–38]. Some researchers have argued that the models of Williams and Medawar, other evolution-based models, and mechanism-based models of aging from other disciplines are both complementary and consistent with an aging process that is a product of multiple interacting biological processes [17, 29, 30, 39–49].

A Semantic Diversion

Evolution theory implies that natural selection could not give rise to genes designed for either the programmed death or immortality of an individual because selection is either weak or nonexistent at the ages when these phenomena would presumably occur. Instead of genes designed either to kill at predetermined ages (death genes) or to produce long-lived organisms (longevity genes), evolution has given rise to an alternative strategy for perpetuating life—a strategy based on reproductive fitness rather than an avoidance of death. The persistent hope that death genes or longevity genes exist is perpetuated when researchers working with species less complex than humans are reported in the media as having found aging or longevity assurance genes [e.g., 50–52]. Because all organisms share a common genetic heritage, such findings are often construed to mean that scientists will eventually be able to modify the aging process by manipulating the same or similar genes in humans. Semantics are important in science. Genes that perform functions that may be correlated with longevity should not be labeled as either death or longevity genes, since these are functions that, according to evolutionary theory, could not have arisen from the action of natural selection.

A Biodemographic Perspective

Some contemporary researchers have focused their work on what has become known as the biodemography of aging—an application of biological reasoning to the study of age-related patterns of mortality within and between species that has origins dating back to the pioneering work of Gompertz and Pearl [17, 39, 40, 53–55]. A central premise of this biodemographic approach is that the evolution theories used to explain the senescence of individuals can be extended to make predictions about age patterns of mortality in populations [17]. Because evolution theory is grounded in genetics [56–58], biodemographic predictions involve temporal patterns of mortality that apply primarily to causes of death that Medawar described as being "in some degree influenced by heredity" [30, p4]. Although gene-environment interactions guarantee inexact boundaries, this line of reasoning suggests that causes of death may be partitioned into genetic (intrinsic) and non-genetic (extrinsic) categories [40]. The importance of partitioning mortality into its intrinsic and extrinsic components has been recognized by scientists from a variety of disciplines for over a century [59–62]. In order to incorporate an expanding biomedical awareness of the pathogenesis and molecular etiology of disease, we have suggested that intrinsic diseases and disorders can be further partitioned into a heritable (germ line) component and a category of genetic diseases that arise from the accumulation of genetic (somatic) damage that individuals acquire during their lifetime [40–42, 44–47, 63–66]. Another category of genetic diseases that may be important are those that arise from genetic damage that accumulates in aging sperm and ova cells, a phenomenon that has been associated with parental age at conception [67, 68].

Although individuals within a sexually reproducing population are responding to the same evolutionary pressures, genetic heterogeneity among individuals and the influence of personal behaviors on the expression of intrinsic mortality will inevitably lead to a distribution of intrinsic-related deaths across the age structure. In other words, a population is comprised of individuals with a wide range of inherent and acquired intrinsic-mortality risks that inevitably leads to early mortality for some and late mortality for others. The schedule of age-specific death rates for a population that results from intrinsic causes is referred to as an intrinsic mortality signature and is predicted by biodemographic theory to be as characteristic of a species as the morphological traits traditionally used by taxonomists [17].

An unintended experiment involving strains of laboratory mice from studies conducted at Argonne National Laboratory over several decades allowed us to conduct an empirical test for the existence of an intrinsic mortality signature [17]. Mortality from infectious disease (i.e., extrinsic mortality) was common in the early experiments but became nearly nonexistent after improved animal husbandry practices were implemented in

later studies. As anticipated, mice from the early studies died (from all causes of death combined) at significantly younger ages than their genetically identical counterparts in the later studies. However, when intrinsic causes of death were used as a basis for comparison, statistically significant differences in the age pattern of mortality could not be detected between the two time periods. These results were interpreted as being consistent with the prediction that species possess an intrinsic mortality signature [17]. Mortality data from humans and beagles suggest that intrinsic mortality signatures exist for these species as well, although we have suggested that the intrinsic mortality signature for humans has been modified through the ability of medical technology to "manufacture" survival time [17, 19].

The existence of an intrinsic mortality signature has considerable relevance to the genetics of longevity, as well as to the question of upper limits to life expectancy. An intrinsic mortality signature that is stable over time suggests that individuals of a sexually reproducing species inherit a genetic legacy from their ancestors that translates into a predictable age pattern of mortality. This mortality pattern reflects a biology that has been molded over evolutionary time by environmental conditions that have consistently precluded survival into the post-reproductive period for most members of the population. If an intrinsic mortality signature exists, then lower limits to age-specific death rates must also exist. Imagine a population completely protected from extrinsic causes of death but denied access to any medical intervention that might influence (i.e., postpone the age of death) intrinsic disease processes—the goal for most control groups in studies involving laboratory animals. Assuming the population is representative of the species from which it came, the life expectancy for this hypothetical population is an estimate of the upper limit for the average life span of individuals within this species—an upper limit imposed by the intrinsic mortality signature.

An intrinsic mortality signature that reflects the inherent genetic heterogeneity within a population of sexually reproducing organisms means that regardless of how well individuals are protected from the environment, some individuals will inevitably die young while others will have the biological potential to survive to old age. In other words, individuals are born with what might be considered "longevity fuel tanks" of varying size (genetic constitution), and the longevity for some individuals will be limited even if they have control over the gas pedal (environment and behavior) and use this control wisely. The relative importance of the genotype (genetic constitution) in affecting longevity depends on the contribution that intrinsic mortality makes to total mortality.

Given the current state of biomedical knowledge, any classification of mortality can be subjected to criticism. Even if that knowledge were perfect, the application of a mortality classification to humans would still be subject to criticism because the cause of death information on a death certificate

is rarely determined by pathologic examination. In practice, the partitioning of mortality is based on an identification of causes of death that are judged to be extrinsic [17, 40]. Applying this approach to mortality data for the United States in 1990, intrinsic mortality has been shown to range from approximately 15 percent of total mortality around the age of sexual maturity, climbing rapidly thereafter to 75 to 80 percent among the elderly. This implies that intrinsic mortality is a significant contributor to mortality in a developed country like the United States. It must be emphasized, however, that our definition of intrinsic mortality includes not only causes of death that are genetic in the classical sense (germ line), but also includes causes of death that are assumed to arise from genetic damage that accumulates within somatic cells after conception.

When researchers interested in heritability partition variance into genetic and environmental components, the variation in attained age associated with genetic damage that is accumulated over a lifetime would be placed within the environmental component. Given the historical use for the measures of heritability, this inevitable assignment to the environmental compartment is both logical and appropriate. However, if the goal is to assess the influence of genetic factors on human longevity—heritability in the colloquial sense—then there is a growing body of scientific evidence that implies the variation attributed to genetic damage that is accumulated could be justifiably placed within the genetic compartment. Such a decision would have the obvious consequence of increasing the statistically defined estimate of heritability for human longevity.

A Genetic Perspective: Inherited Effects

McKusick's 10th edition of the *Mendelian Inheritance in Man* encompasses two volumes and 2,000 pages of text describing genetic disorders and diseases [63]. In the two years since the previous edition, 869 new entries were added. As techniques for DNA sequencing have improved and become more automated, there has been a dramatic acceleration in the identification of genes by researchers involved in the Human Genome Project. Thus, biomedical knowledge of the human genome has entered a phase of rapid and probably prolonged growth.

This rapid growth in the identification of human genes has required a huge investment of resources—time, people, and money. An even bigger investment will be required to determine the structure and function of the products that are produced by the genes being identified. Knowledge of function is required in order to reveal the possible role that genes play in causing human diseases and disorders. Knowledge of function and structure is required to distinguish between normal and abnormal variants of a gene. The largest task of all will be to understand how different genes interact with each other and the environment in order to produce the bio-

logical effects that we observe at the level of individuals. Despite the enormity of these challenges, progress will be made—progress that will not only reveal more genes involved in human disease, but also ways to intervene in the disease processes. Given that disease, death, and longevity are intimately interwoven, any increase found for the genetic basis of disease must also lead to increasing estimates for the heritability of longevity—in the colloquial as well as the classical sense.

Genetic Perspective: Accumulated Genetic Damage

Without the energy provided by mitochondria, multicellular life would not be possible. In the process of creating stored energy that can be used for work by the cell, mitochondria produce molecules called free radicals. Metabolic free radicals are considered a significant (but not the only) source of damage to DNA that occurs thousands of times every day in every cell [69, 70]. Fortunately, the vast majority of this damage is repaired with great efficiency. However, the complex surveillance mechanisms that exist within cells to maintain the functional integrity of DNA are not perfect [71–73]. The result of this biological imperfection is that unrepaired damage to DNA begins to accumulate over time, beginning with the first cell formed by the union of egg and sperm [74].

An accumulation of genetic damage caused by free radicals has been implicated as a potentially major force influencing the aging process, further enhancing the prominent position that the free radical hypothesis of aging already holds in the scientific community [45–47, 70, 74, 75]. This subcomponent of intrinsic mortality is consistent with the disposable soma theory in evolution, which views the imperfect maintenance of the soma (body) as an inevitable consequence of the physiological investment in reproduction that an organism must make in an environment characterized by high mortality pressures from extrinsic causes of death [43]. Accumulated genetic damage in different organs and tissues provides a plausible mechanism for Cutler and Semsei's disdifferentiative hypothesis of aging, which posits the loss of gene regulation as a mechanism that links cancer and aging [44]. Under this paradigm, cancer occurs when genes regulating cell growth and differentiation become damaged. Accumulated genetic damage also provides a potential link between the disdifferentiative hypothesis of aging and the antagonistic pleiotropy theory of senescence [29, 44].

Williams suggested that deleterious effects (i.e., intrinsic diseases) associated with genes expressed after the "period of maximum reproductive probability" could arise from the action of natural selection, if these same genes are involved in processes that confer reproductive advantages early in life [29, p410]. It would appear that Williams envisioned a normal gene that has an abnormal effect when expressed late in life—a feature that would distinguish these genes from the harmful alleles in the germ line

that Medawar predicted would accumulate within the post-reproductive period over evolutionary time [30]. Genes linked to Alzheimer's disease have properties that are consistent with the notion of antagonistic pleiotropy, but researchers have not been successful in finding other genes that behave this way. Genes responsible for cancer (oncogenes) are known to play important roles in the regulation of cell growth and differentiation early in life. They accomplish this regulation by encoding the proteins that regulate the expression of genes involved in growth and differentiation. If accumulated damage caused by free radicals disrupted the balance (relative abundance) of regulatory proteins, then the genes they regulate could be expressed at temporally inappropriate (e.g., post-reproductive) periods of the life span. Damage caused in this way would be consistent with the concept of gene disregulation proposed by Cutler and Semsei and could produce an effect indistinguishable from that envisioned by Williams [29, 44].

When human survival extends well beyond the end of the reproductive period, as it has in modern times, we have predicted that the causes of intrinsic mortality will shift from inherited lethal disorders toward diseases caused by unrepaired or partially repaired genetic damage that is accumulated within somatic cells during the course of living [17, 40]. In other words, we are predicting a shift occurs from diseases that conform to the predictions of Medawar to diseases that conform to the predictions of Williams [29, 30, 44]. Diseases that fall into this latter category may include many forms of cancer. For example, the p53 gene is normally responsible for triggering a series of biochemical events that lead to programmed cell death (apoptosis). There is a growing consensus among researchers that many forms of cancer may be caused when free radical damage to the p53 gene prevents apoptosis and permits abnormal cell growth to occur [77–79]. Although these somatic diseases are genetic, they are not heritable in the strict sense [40]. However, the metabolic pathways that generate the free radicals and the imperfect mechanisms of DNA maintenance and repair that permit this damage to accumulate are probably heritable in the strict sense. As population aging accelerates and the already unprecedented proportion of the population that survives into the post-reproductive period of the life span grows even larger, the diseases caused by genetic damage that accumulates over the course of a lifetime will have a progressively larger impact on health and longevity. Acknowledging the genetic liabilities of oxidative metabolism does not diminish the importance of behavior and environment, it simply gives greater clarity to the biomedical challenges posed by the heritability of human longevity.

Discussion

The literature on heritability is primarily quantitative and evolved from statistical requirements in animal and plant breeding and selection for ge-

netic improvement. When the concept of heritability is applied to an issue like race and IQ, the rhetoric becomes sharp and full of strong emotions. By comparison, the historic literature on the heritability of longevity comes across as scholarly and motivated by intellectual curiosity. Today, population aging has a significant impact on issues of national importance—the solvency of the Social Security trust funds, retirement age, Medicare benefits, hospital and health insurance, long-term health care, physician-assisted suicide, and medical costs in general [27]. As progressively larger segments of the population survive to increasingly older ages, issues revolving around aging and human longevity will dominate national debates over public policy. Central to these debates will be questions about limits to human life expectancy, the biomedical and social consequences of approaching and exceeding those limits, and the ethics of using the technology of science to alter the human life span. Research on human longevity is no longer simply a quaint topic for scholarly research and conjecture.

The attained age or duration of life that is achieved by individuals would have societal significance even if perfect health could be maintained until the last day of life. The implications of attained age become profoundly important when a potentially significant portion of the time spent prior to the last day of life is spent in various states of poor health. It is the health consequences at the end of life that makes the question of whether limits on human longevity exist a hotly debated topic, and it is the relative mutability of these potential limits that makes the heritability of longevity a critical issue. The factors that influence the longevity of individuals are only partially understood even in a broad sense today, and they may never be fully identifiable given that every individual is a unique genetic entity experiencing an equally unique personal environment. Imperfect knowledge imposes a degree of irreducible uncertainty on researchers, who must use surrogate measures derived from populations (e.g., death rates, life expectancy, maximum life span, variation in attained age) in order to study human longevity and the forces that influence it.

Some demographers have predicted that the life expectancy for human populations either does not have an upper limit, or the limits are so high that life expectancies at birth in excess of 100 years are not only attainable but likely to be achieved in the near future [21, 80–82]. If achieved, life expectancies of this magnitude would have societal implications that defy comprehension. Although the mathematical approaches used to arrive at these conclusions differ, they are all based on biological assumptions (both implicit and explicit) that are relevant to the colloquial sense of heritability discussed in this paper. Even though diseases of genetic origin are acknowledged to exist, it is assumed by those who predict large increases in life expectancy over the coming decades that either these diseases play only a minor role in determining human longevity, or that they can be successfully eliminated through breakthroughs in biomedical technology.

We have presented an alternative perspective in this paper. The measures of heritability developed by geneticists to monitor their progress in improving plants and animals for agricultural use do not provide estimates of the contribution made by genetic factors to attributes like IQ and longevity—heritability in the colloquial sense. As such, the low values observed for these measures in studies of human longevity cannot be used to justify the claim that genetic factors play no more than a minor role in determining human longevity [12]. We expect that the massive undertaking collectively known as the Human Genome Project will continue to reveal genes that are involved in human disease, and that many of these genes will involve biological processes that are correlated with the longevity of individuals and, hence, the life expectancy of populations. The future will reveal how many of these genes are embedded within the gene pool of our species, and how many are the result of genetic damage that is accumulated within the somatic cells of the body over the course of a lifetime.

Journals are filled with examples of abnormal genes causing diseases and disorders that had not previously been attributed to biological causes. There is growing evidence to suggest that genetic damage (that may be only partially stochastic in where it occurs) within somatic cells caused by metabolically derived free radicals may be an important cause of human disease—particularly among individuals who have survived to the post-reproductive period of the life span. Although the variation in attained age attributed to these diseases would not fall within the genetic component of a classical definition of heritability, these diseases and their mortality consequences are as predictably "heritable" for a population as the phenotypic effect of a gene present at fertilization is for an individual. In our research, we have attempted to capture the mortality consequences of all genetic factors (both inherited and acquired) into a cause of death category referred to as intrinsic mortality. Our biodemographic analysis of age patterns of mortality for different species have revealed that intrinsic causes of death may be both a significant and a consistent source of mortality.

Genes do not exist within a vacuum. Instead, they exist within a hierarchy of environments that span all the levels of biological organization, ranging from the macro-environment outside the organism to the micro-environment surrounding a specific gene. It is known that gene-environment interactions occur at every one of these levels of biological organization. From this perspective, the nature versus nurture question is more fiction than fact. It will never be possible to totally disentangle genetic effects from the environments that give them meaning. This also means that for any character of biological interest, there will be plenty of room for endless debates between the supporters of environment and the advocates of genes.

Our reason for writing this paper was not to make an argument for the genetic determinism of human longevity, nor was it our intent to suggest that genetic effects are beyond the reach of biomedical intervention. Our

objective was to explore the possibility that genetic factors may play a significantly greater role in determining human longevity than the current consensus would appear to suggest. Much of the basis for this argument comes from a growing sense of the costs that accrue from the benefits of a symbiotic relationship with mitochondria that permitted eukaryotic cells and, by extension, humans to exist. Genetic damage that is accumulated during a lifetime and its subsequent effects on health and longevity may be an unavoidable cost of the inherited metabolic pathways that produce the energy required to create and sustain life. This cost may become a heavy burden as progressively larger segments of the human population are ushered further into the post-reproductive period of the life span, where the effects of this genetic legacy on health and quality of life are most keenly manifested. Since all mitochondria come from our mothers, perhaps Raymond Pearl was prophetic when he declared that in order to be longevous, "select long-lived parents, and particularly long-lived mothers" [1]. However, to be fair to men, recent data suggests that long-lived fathers may be just as important as long-lived mothers in determining the longevity of their offspring [83].

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