

Feature Article

Epigenetics and the Embodiment of Race: Developmental Origins of US Racial Disparities in Cardiovascular Health

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ABSTRACT The relative contribution of genetic and environmental influences to the US black-white disparity in cardiovascular disease (CVD) is hotly debated within the public health, anthropology, and medical communities. In this article, we review evidence for developmental and epigenetic pathways linking early life environments with CVD, and critically evaluate their possible role in the origins of these racial health disparities. African Americans not only suffer from a disproportionate burden of CVD relative to whites, but also have higher rates of the perinatal health disparities now known to be the antecedents of these conditions. There is extensive evidence for a social origin to prematurity and low birth weight in African Americans, reflecting pathways such as the effects of discrimination on maternal stress physiology. In light of the inverse relationship between birth weight and adult CVD, there is now a strong rationale to consider developmental and epigenetic mechanisms as links between early life environmental factors like maternal stress during pregnancy and adult race-based health disparities in diseases like hypertension, diabetes, stroke, and coronary heart disease. The model outlined here builds upon social constructivist perspectives to highlight an important set of mechanisms by which social influences can become embodied, having durable and even transgenerational influences on the most pressing US health disparities. We conclude that environmentally responsive phenotypic plasticity, in combination with the better-studied acute and chronic effects of social-environmental exposures, provides a more parsimonious explanation than genetics for the persistence of CVD disparities between members of socially imposed racial categories. *Am. J. Hum. Biol.* 00:00–00, 2008. © 2008 Wiley-Liss, Inc.

The disproportionate disease and mortality burden of African Americans is among the most challenging of US public health problems. It is now broadly known that an African American man in Harlem is less likely than a man in Bangladesh to survive to the age of 65 (McCord and Freeman, 1990). Nationally, African Americans have an age-adjusted all-cause mortality rate that is 1.5 times that of whites (Keppel et al., 2002), and cardiovascular diseases (CVDs) and their precursor conditions, including hypertension, diabetes, and obesity, contribute heavily to this disparity. The risk of dying from heart disease is 1.3 times higher in African Americans compared to US whites (Mensah et al., 2005), and African Americans are 1.8 times more likely to develop diabetes (CDC, 2007). Hypertension rates are roughly 1.5–2 times higher in African Americans compared to whites (Mensah et al., 2005), and are especially high in certain regions, such as the so-called stroke belt of the American South. In total, nearly half of all African American adults develop some form of CVD, making racial disparities in these conditions one of the most pressing US public health problems today (AHA, 2007).

During the past 15 years, there has been a concerted effort to understand the underlying determinants of racial health disparities (Krieger, 2005; Lillie-Blanton and Laveist, 1996; Williams, 1999), and explanations have tended to align with one of two models that emphasize either social or genetic causes. Researchers who attribute some, or all, of the problem of racial health inequalities to differences in genetic predisposition (Burchard et al., 2003; Hirsch et al., 2006; Risch et al., 2002; Sarich and Miele, 2004; Saunders, 1995) assume that human genetic variation can be differentiated into conventional racial clusters (Allocco et al., 2007; Calafell, 2003; Hinds et al., 2005; Lao et al., 2006; Redon et al., 2006; Rosenberg et al., 2002;

Tang et al., 2005), and that disease-causing alleles are likely to be among those variants that segregate between these groups (Burchard et al., 2003; Risch et al., 2002). Evidence to support this model has recently come from genetic studies of population substructure, in which the analysis of thousands of loci simultaneously has produced clusters of genetic information that can be used to correctly identify individuals' self-described geographic ancestry (Redon et al., 2006; Rosenberg et al., 2002; Tang et al., 2005).

Those who argue that social forces drive racial health disparities point to the importance of factors such as economic disadvantage, psychosocial stress, and institutional and interpersonal discrimination as causes of ill health (Bronfalo et al., 2003; Davidson et al., 2000; Dressler, 1991; Harrell et al., 2003; Jonas and Lando, 2000; Sweet et al., 2007; Troxel et al., 2003; Williams, 1999; Williams and Collins, 1995; Williams and Jackson, 2005; Williams and Neighbors, 2001; Wyatt et al., 2003). Such cultural and structural challenges can impose barriers to healthy lifestyles, limit access to quality medical care, and chronically strain physiological stress systems that are linked to disease (Dressler et al., 2005; Kaplan and Lynch, 2001; Krieger, 2005; Krieger and Davey Smith, 2004; LaVeist, 2005; McEwen, 2001). Together, these social, economic, and contextual factors can have a significant impact on health, and when taken into account, health disparities

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between African Americans and US whites are often diminished (Dressler et al., 2005; McDade et al., 2006; Williams and Collins, 1995).

The debate between these competing models has been described as a “storm” (Krieger, 2005), and mirrors long-standing discussions in anthropology over the meaning of the race concept (Armélagos and Goodman, 1998). As with early theories of racial-genetic determinism, current genetic models of racial health disparities have been criticized on several fronts, including the sampling biases that have been present in studies of population substructure (Serre and Paabo, 2004), and the low percentage of genetic variation that is typically explained by “racial” clusters (e.g. $\sim 4\%$ Rosenberg et al., 2002). This latter criticism is supported by over three decades of research consistently showing between-group genetic differences to be small compared to the genetic variation found within continental regions (Brown and Armélagos, 2001; Goodman, 2000; Jorde and Wooding, 2004; Kittles and Weiss, 2003; Lewontin, 1972; Relethford, 2002). Despite this evidence and the demonstrated importance of social environmental factors for African American health, the tendency for self-identified race to remain a significant predictor of disease outcomes in epidemiological studies, even after lifestyle and SES factors have been adjusted for statistically (Cooper, 1993; Otten et al., 1990; Pappas et al., 1993), continues to be interpreted by some as indirect support for the racial genetic position (Kistka et al., 2007).

As many scholars of health inequality have observed, however, the impact of the social environment on health is multifaceted and challenging to adequately measure and adjust for statistically (Braveman et al., 2005; Kaufman and Cooper, 1999; Smith, 2000). One dimension of this problem is the often low resolution of conventional measures of social, economic, and behavioral determinants of health. More nuanced approaches to quantifying stress and other social, cultural, and material processes related to cardiovascular health are needed, and recent work in biocultural anthropology has made critical contributions to this area of health disparities research (Dressler and Bindon, 2000; Gravlee et al., 2005).

In addition, there is a growing appreciation that environmental influences contribute to adult health disparities by influencing biological processes and responses across the life cycle, with certain ages or developmental stages particularly sensitive to environmental and social influence (Barker, 1994). Building from earlier studies showing that adult mortality is predicted by socioeconomic conditions experienced around the time of birth (Forsdhal, 1977; Kermack et al., 1934), research during the past two decades has now established that early life conditions, such as prenatal undernutrition and stress, or maternal stress during pregnancy, can modify developmental biology in offspring in a fashion that elevates their risk of developing diseases like diabetes, hypertension, and CVD as adults (Barker and Osmond, 1986; Gluckman et al., 2008). Fields including clinical and animal model research, epigenetics, anthropology, public health, sociology, and economics are addressing the evolutionary origins of these developmental responses, their biological bases, and their health and policy implications (e.g. Forrest and Riley, 2004; Geronimus et al., 2006; Graham and Power, 2004; Halfon and Hochstein, 2002; Kuzawa and Pike, 2005; Palloni, 2006). Study of the biological and

developmental mechanisms that underlie these associations is increasingly being pursued under the rubric of the “developmental origins of health and disease” (DOHaD) (see Gluckman and Hanson, 2006), while the public health impacts of early life influences is an important focus of the burgeoning field of “life course epidemiology” (see Kuh and Shlomo, 2004; Smith, 2003).

Long-term impacts of early life undernutrition or stress have been proposed to help explain patterns of adult CVD risk in a variety of ecological, political economic, and cultural settings. To date, much emphasis has been given to the potential role of these processes in transitional populations in which a combination of poor early life nutrition followed by adult weight gain in the same generation could lead to elevated CVD risk (Adair and Prentice, 2004; Benyshek et al., 2001; Gluckman and Hanson, 2005; Kuzawa and Adair, 2003; Prentice and Moore, 2005). Similarly, the tendency for overweight and diabetic women to give birth to overweight, diabetes-prone offspring, operating through intrauterine influences on developmental pathways, has been proposed as an explanation for the high rates of diabetes and metabolic syndrome in populations in South Asia and the American Southwest (Benyshek et al., 2001; Yajnik, 2004).

Although a variety of life course models of cardiovascular epidemiology have been developed (Ben-Shlomo and Kuh, 2002), there has been little systematic evaluation of the potential contribution of developmental and epigenetic responses to early environments to the specific problem of US black-white health disparities in CVD. There is good reason to expect that the DOHaD field will help clarify the origin of these racial health disparities (see also Kuzawa, 2008). African Americans not only have higher rates of CVD as adults, but they also have a higher burden of the antecedent condition of lower birth weight—an early life health disparity believed to trace in part to factors like stress and discrimination experienced by the mother during pregnancy and across her life course (Pike, 2005). Thus, there is a strong rationale to consider a developmental and transgenerational dimension to these racial disparities in cardiovascular health.

This article does not comprehensively review the DOHaD or life-course epidemiology literatures, which have been the subject of extensive recent reviews (Ben-Shlomo and Kuh, 2002; Gluckman and Hanson, 2006; Kuh et al., 2003; Smith, 2003). Nor is this paper intended as a comprehensive review of the causes of racial health disparities or of the full breadth of life-course influences on adult health (for more see Geronimus, 2001; Krieger, 2000; Pollitt et al., 2005; Williams, 2005). Rather, our goal is to evaluate the potential contribution of one specific set of biological pathways to the problem of cardiovascular health disparities between African Americans and US whites: the influence of maternal health and stress during pregnancy on the development of fetal biological systems, which can elevate CVD risk in adult offspring. To this end, we first briefly review evidence for maternal-fetal influences on systems that influence adult CVD risk, and discuss the role of developmental and epigenetic processes as underlying mechanisms. Next, we discuss evidence that these pathways are likely operative in African Americans, and that they help explain US racial disparities in adult CVD. We argue that the embodiment of social and material environments through developmental and epigenetic processes helps explain the persistence of biological

CVD disparities across racial categories that are socially rather than genetically defined (Krieger, 2005).

Controversy remains over the terminology used in scholarly research to describe human biological variation, and a consensus is lacking within anthropology (Gravlee and Sweet, 2008). Given lack of supportive evidence that race is a genetically meaningful concept, some scholars have opted to use terms such as “ethnicity” or “population” to describe geographically or culturally identified groups, while others continue to use the term “race” when referring to the social phenomenon of historically constructed racial categories (AAA, 1998; di Leonardo, 2004; Harrison, 1995; Shanklin, 1994; Weismantel, 1997). Although relevant for understanding disparities in disease, the concept of “ethnicity” traditionally includes a broad set of cultural practices and shared beliefs that define group identity (Gordon, 1964). In this article, we choose to use the term “race” because many of the social forces we discuss as underlying determinants of health disparities, such as discrimination, economic inequalities, or segregated neighborhoods, represent the unique lived reality of race as a socially-defined and *imposed* system in the US. In light of the lack of consensus surrounding terminology, we emphasize that we define race as a socially constructed category that has biological implications, rather than a genetically justified criteria for classifying human variation (AAA, 1998; Cooper and David, 1986).

BACKGROUND

Early environments and adult health

For the past two decades, evidence has been accumulating that stress, prenatal nutrition, and other early life factors can influence risk for adult cardiovascular and metabolic diseases. Starting in the late 1980s, David Barker and colleagues at Southampton University published a series of papers showing that the risk of dying from CVD, or of suffering from conditions that precede CVD like hypertension or diabetes, is higher among individuals who weighed less at birth (Barker, 1994; Barker and Osmond, 1986; Barker et al., 1989). Although studies had previously found evidence for relationships between deprivation during childhood and higher subsequent adult mortality rates (Forsdahl, 1977; Kermack et al., 1934), the Southampton group was the first to link these associations to a biological marker that hinted at possible mechanisms to account for them.

Building from the assumption that a baby born small had been poorly nourished prior to birth, they proposed that these relationships were the outcome of adjustments made by the fetus in response to a compromised intrauterine nutritional environment. They reasoned that a fetus faced with undernutrition would not only slow its growth rate to reduce nutritional requirements, but might also modify the structure and function of organs and systems involved with metabolism and physiology, with effects that could linger into adulthood to influence risk of developing chronic disease. Such durable alterations to developmental biology in response to early environments have been described as developmental “programming” (Dörner, 1975; Lucas, 1991) or “induction” (Bateson, 2001).

The hypothesis that adult metabolism, biology, and disease risk could be “programmed” by prenatal nutrition was greeted with skepticism (Kramer and Joseph, 1996; Paneth et al., 1996). Most early studies merely linked adult

health characteristics with birth weight data recorded in birth records and largely ignored other aspects of the social environment, such as socioeconomic status, that might account for the associations (Kramer and Joseph, 1996; Paneth et al., 1996). Nearly two decades of research have helped push the field beyond this initial skepticism, and DOHaD is now a well-established area of study that lies at the intersection of fields like medicine, public health, and anthropology (Gluckman and Hanson, 2006; Kuzawa and Pike, 2005). Hundreds of human studies have replicated findings of developmental programming, many incorporating longitudinal data on a range of lifestyle and environmental influences that might confound associations with birth size (Adair et al., 2001; Dalziel et al., 2007; Gupta et al., 2007; Huxley et al., 2007; Law et al., 2001; Levitt et al., 2000; Miura et al., 2001; Tian et al., 2006). These studies find that smaller birth size predicts higher blood pressure (reviewed by Adair and Dahly, 2005), insulin resistance and diabetes (Eriksson et al., 2002; Yajnik, 2004), abnormal cholesterol profiles (Kuzawa and Adair, 2003), an “android” or abdominal pattern of fat deposition (Oken and Gillman, 2003), and an elevated risk of suffering or dying from CVD (Huxley et al., 2007; Leon et al., 1998). Conditions experienced during infancy and childhood have also been shown to predict adult biological and health outcomes. Not unlike birth size, small size in infancy is also associated with higher CVD risk in adulthood, while breastfed infants have lower rates of hypertension, obesity, and diabetes as adults (Arenz et al., 2004; Lawlor et al., 2005). There is also evidence that prenatal and postnatal exposures interact to influence adult health. For instance, being born small but then experiencing rapid weight gain during childhood—a marker of later nutritional abundance—predicts the same constellation of adult diseases (Adair and Cole, 2003; Ong, 2006).

Because birth weight reflects both environmental and genetic factors, a relationship between birth weight and adult physiology or disease risk could simply reflect the pleiotropic effects of genes. As one example, insulin regulates fetal growth but also has broad involvement in adult metabolic disease, and pleiotropic genes that influence insulin metabolism could yield a correlation between fetal growth and conditions like insulin resistance or diabetes as a result of genetic rather than developmental processes (Freaty et al., 2007; Hattersley and Tooke, 1999). Although birth weight is fraught with interpretive challenges (Kuzawa and Adair, 2004), multiple observations demonstrate that genetic correlations do not fully explain the associations documented between birth weight and CVD risk in humans.

The first line of evidence is the generally low heritability of birth weight. Although high heritabilities for birth weight are occasionally reported for studies in well-nourished pedigrees (e.g. US/Fels: 0.82, Demerath et al., 2007; 0.59 broad sense, Stern et al., 2000), most studies find that genetic inheritance accounts for only a fraction of the variance in birth weight. Based upon twin registries, heritabilities for birth weight are typically reported in the range 0.2–0.4 (e.g. Baird et al., 2001; Vlietinck et al., 1989; Whitfield et al., 2001), with national birth weight registry studies finding similar estimates (0.31 for birth weight and 0.27 for birth length in all Norwegian births from 1967 to 2004; Lunde et al., 2007). The remaining variance is believed to be determined by maternal influences like nutritional status, exposure to stress, or other factors

influencing blood flow to the endometrial lining or placenta (Gluckman and Hanson, 2004).

Second, in studies of monozygotic twin pairs, the lighter twin has been shown to have elevated risk for adverse changes in body composition and risk for diabetes and hypertension later in life (Bo et al., 2000; IJzerman et al., 2003; Iliadou et al., 2004), demonstrating that genetic correlations do not fully account for the associations with adult disease risk. Finally, observational research on humans is broadly corroborated by animal model research. Animal work in the DOHaD literature has confirmed that factors influencing prenatal nutrition and intrauterine environmental conditions can induce physiologic and metabolic changes in offspring that linger into adulthood (Sinclair et al., 2007; Symonds and Gardner, 2006). For instance, restricting the nutritional intake of pregnant rats, mice, or sheep, or directly restricting blood flow (and thus nutrient transfer) to the fetus, increases postnatal blood pressure, cholesterol, abdominal fat deposition, and diabetes risk in offspring (reviewed by Langley-Evans et al., 2003; McMillen and Robinson, 2005).

Although the wide availability of birth weight data has led to a research emphasis on the role of nutrition as a programming stimulus, maternal psychological stress during pregnancy can lead to a similar constellation of biological changes and disease risk factors in adult offspring, and at times independent of changes in birth weight. The fetus is normally shielded from exposure to stress hormones produced by the mother's body by an enzyme (11- β HSD) that is expressed by the placenta where it converts the active form of the hormone (cortisol in humans) to its inactive form (cortisone). This buffering capacity can be exceeded when the mother is severely stressed, leading to premature or excessive exposure of the fetus to maternal stress hormones. This in turn can contribute to reduced birth size by directly reducing fetal growth rate. Although the pathways are not fully understood, it can also influence the stress hormone-related cascade that triggers parturition, leading to early pregnancy termination (Challis et al., 2005). This fetal exposure to excess cortisol induces a similar suite of biological changes in offspring as are observed with dietary restriction, including an elevation in blood pressure, stress reactivity, abdominal adiposity, insulin resistance, and other precursors of diabetes and CVD (Seckl and Meaney, 2004). Thus, prenatal stress—whether nutritional or psychosocial in origin—shapes a wide range of traits that influence future risk of developing CVD, including how the body manages and distributes glucose and lipids, regulates blood pressure, and responds physiologically to stress.

The mechanisms of phenotypic “memory”—growth, development, and the epigenetic code

The durability of the effects of early environments on multiple biological systems raises the question of what biological mechanisms underlie them: if early environments influence adult biology and health, where in the body are the “memories” of these early experiences stored and maintained? The contributions of several developmental processes have been documented, each corresponding to axes of biological variation independent of one's genotype. The most straightforward involves a change in growth of a tissue or organ as reflected in its size or cell number. As one well-documented example, the kidneys of prenatally

undernourished individuals tend to be smaller and to have fewer nephrons, making them more prone to hypertension and renal failure later in life (Lampl et al., 2002; Luyckx and Brenner, 2005). Similarly, alterations in the number and composition of muscle cells in individuals born lower birth weight could contribute to insulin resistance in adulthood (Jensen et al., 2007), as could changes in the type and number of body fat cells present in different adipose depots (Zhang et al., 2007).

In addition to such modifications in the number of cells present, there is growing evidence that epigenetic changes in the pattern of cellular gene expression are also key to the long-term impacts of early environments (Sinclair et al., 2007; Waterland and Michels, 2007). Although ascribed with numerous meanings since Waddington coined the phrase in 1942 (Waddington, 1942), epigenetics is increasingly being reserved to refer to the study of processes that modify patterns of gene expression without changing the nucleotide sequences of the DNA (Jenuwein and Allis, 2001). The genome is inherited at conception and, other than somatic mutations acquired during cell division, remains unchanged in most body cells across the lifecycle. The “epigenome,” in contrast, is the product of a gradual commitment of cell lineages to more constrained patterns of gene expression. The epigenome is a result, in part, of the genome interacting with the environment, and can be viewed as the molecular basis for cellular differentiation and development over the life-course (Fig. 1).

Unlike the nucleotide bases that form the genetic code, the “epigenetic code” predominantly involves chemical modifications to the structure of the chromatin that scaffolds the DNA within the chromosomes (Berger, 2007). If fully stretched, the chromosomes in a single human cell would be roughly 6 feet in length; thus, a complex process of folding is required to package the complete genome into each cell nucleus where the genes reside and are expressed. In the nucleus, chromosomes must be unwound locally to allow transcription factors to gain access to a gene. How the DNA is packaged within the chromatin influences how easy or difficult a gene is to access and thus, whether and how much it may be expressed in that cell. Epigenetic markings have thus been likened to volume controls for genes, and they play an integral role in the normal process of cellular differentiation. As cells divide, epigenetic markings present in the parent cell are maintained through mitosis and thus heritable to both daughter cells (but see Suzuki and Bird, 2008). Through a complex series of bifurcations at which patterns of gene silencing and amplification are progressively acquired, the single totipotent “stem cell” formed at conception is capable of creating a body with roughly 200 cell types that vary in structure and function, despite the endowment of each of these daughter cells with an identical genome (Reik, 2007).

An important class of mechanisms of epigenetic gene silencing involves localized chemical modifications to the chromatin and its protein constituents, which alter how tightly the DNA is packaged in the region of specific genes. The attachment of an extra methyl group (methylation) to “CpG islands” (regions of DNA rich in cytosine and guanine linked by a phosphodiester bond) within the promoter region of a gene typically impedes expression of that gene in that cell (Berger, 2007). The histone proteins that the DNA fibers are wrapped around can also be modified to alter the tightness of DNA packing, and thus the

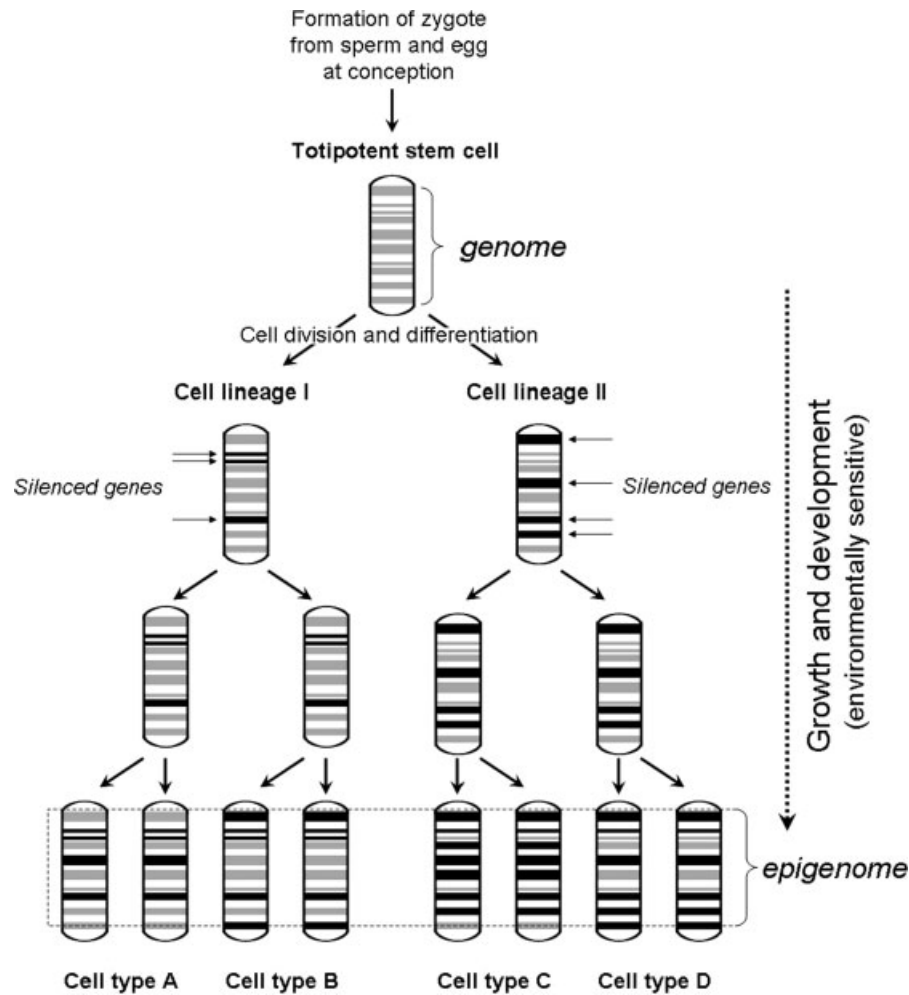


Fig. 1. Schematic illustrating the role of epigenetic gene silencing in the differentiation of an initially totipotent stem cell (the zygote) to “committed” daughter cell lineages. Gray horizontal lines indicate genes capable of being transcribed to produce a protein, whereas black lines are genes that have been silenced by epigenetic modifications (for simplicity, processes that enhance gene expression, such as histone acetylation, are not shown). The pattern of gene silencing is heritable to daughter cells, leading to the eventual commitment of cell lineages to specialized cell types (e.g. neurons, muscle cells) as epigenetic marks are accumulated. The focus of classical genetics on modeling the determinants and evolutionary change in gene frequencies is concerned with the genes inherited at conception (the genome), while epigenetics focuses on the narrower pattern of gene silencing and expression in the cells of specific tissues, organs, and systems (the epigenome). Although epigenetic changes in gene expression are largely regulated themselves by genes, environmental exposures can modify some epigenetic marks in specific cells lines during growth and development, which partly accounts for the durable effects that early environments have on adult biology and disease risk.

accessibility of that stretch of DNA to enzymes and transcription factors. Methylation of the histone generally impedes gene expression, whereas acetylation loosens the chromatin and promotes gene expression. Although more commonly implicated in cancers than CVDs, another epigenetic mechanism involves small noncoding RNA (“micro RNA” or “small RNA”) (Grewal and Elgin, 2007) which are produced in the cell nucleus. Although not transcribed to make proteins themselves, they block transcription and expression of other genes in a gene-specific fashion (RNA interference or “RNAi”), thus providing another way that gene expression can be modified in a durable fashion.

Epigenetics and adult cardiovascular disease risk

Current research is showing how environmental factors can modify epigenetic processes, thereby affecting epi-

netic marks and downstream patterns of gene expression in specific cells and cell lineages (Gluckman et al., 2007a,b; Ho and Tang, 2007; Jirtle and Skinner, 2007; Waterland and Jirtle, 2004; Waterland and Michels, 2007). Recent experimental studies in animal models demonstrate how epigenetic markings in offspring may respond to maternal factors like diet (Lillycrop et al., 2005) and rearing behavior (Weaver et al., 2004). In pregnant rats, protein restriction during gestation reduces methylation of the promoter region of the gene that codes for the glucocorticoid receptor (GR)—the receptor that recognizes and responds to the stress hormone cortisol (a glucocorticoid)—in offspring liver cells. Because methylation impedes access of transcription factors to the gene’s promoter region, the reduced methylation triggered by this dietary intervention increases expression of the GR gene, thus increasing the number of receptors expressed in the liver. This results in an amplification of the liver’s meta-

bolic response to stress hormones, for example increasing expression of the downstream gene product PEPCK—the rate-limiting enzyme in glucose production (gluconeogenesis) (Lillycrop et al., 2007). In this particular animal model, the nutritional experiences of one generation during pregnancy (the pregnant rat dam) influence how the offspring regulate and produce glucose in response to stress as adults. Maternal protein restriction has also been shown to induce hypomethylation of the angiotensinogen receptor gene in the adrenal gland in rat offspring, which likely helps explain why the gene is overexpressed, contributing to the elevated systolic blood pressure seen in these animals (Bogdarina et al., 2007).

In other instances, the effect of early environments can linger beyond adulthood to be passed on to future generations. Such examples of transgenerational epigenetic inheritance can occur through several types of pathways (Gluckman et al., 2007a; Jablonka and Lamb, 1995). Although less often studied, research suggests a more limited but biologically important lingering impact of paternal stress experience on the biological characteristics of offspring (e.g. Drake et al., 2005). These, and related findings in females, suggest that some environmentally induced cytoplasmic elements or epigenetic markings are already present in egg or sperm at conception (Anway et al., 2005; Cropley et al., 2006; Stöger, 2008). In females, provisioning of metabolic and other resources via placenta and lactation opens up additional pathways by which epigenetic settings can be perpetuated across generations. When the establishment of epigenetic markings in offspring cells is sensitive to environmental exposures during the period of direct dependence—i.e. when the “environment” is the maternal phenotype—this can recapitulate a pattern of epigenetic marks in offspring in the absence of direct transfer of those marks through sperm or egg (Drake and Walker, 2004).

One well-documented example of such epigenetic recapitulation is anxiety and rearing style in lactating rats (Diorio and Meaney, 2007; Weaver et al., 2004). Rat pups reared by indulgent mothers exhibit changes in methylation of the GR gene in hippocampal neurons involved in regulating the hypothalamic-pituitary-adrenal (HPA) axis and the stress response. This has the effect of reducing reactivity and anxiety in offspring, and encourages them to adopt a more relaxed and indulgent rearing approach with their own offspring (the grandoffspring). Cross-fostering of pups shows that this effect is not genetic but dependent upon maternal rearing behavior. The effect is also reversed by chemically blocking epigenetic marking, showing that it is not simply a learned behavior (Weaver et al., 2004). This study illustrates how a maternal phenotype can construct a rearing environment that tends to replicate the same phenotype in the next generation, operating not through genes or learning, but through transgenerational recapitulation of epigenetic marking. Indirect evidence for maternal-fetal transfer of epigenetically based alterations in stress (HPA) reactivity has been documented in humans. In holocaust survivors, severity of post traumatic stress disorder (PTSD) symptoms—which influences maternal cortisol production during pregnancy—predict levels of cortisol excretion in postnatal offspring, and Manhattan women who were pregnant during the 9/11 attacks gave birth to offspring who show evidence for alterations in HPA activity in childhood (Yehuda and Bierer, 2008).

The emerging understanding of the epigenetic mechanisms that build the phenotype represents a revolution in biology that is gathering momentum (Baylin and Schuebel, 2007; Kennedy, 2002). Processes such as promoter region methylation reveal why knowing an organism's genotype—the genes inherited by the totipotent zygote at conception—is merely the first frame in the story of how the phenotype is eventually built. Attempts to identify susceptibility genes for diseases involving complex systems and traits have generally had poor results (Cooper and Psaty, 2003). By demonstrating one important way that the impact of a gene on the phenotype can be modified by the environment, this new understanding of epigenetic processes is helping shed light on this issue. By linking maternal experience with fetal biology, this literature is showing how stressors experienced by one generation, such as imbalanced nutrition or psychosocial stress, can perpetuate changed biological settings to offspring, with effects on such functions as glucose metabolism, blood pressure regulation, fat deposition, and the physiologic response to stress.

AN EPIGENETIC MODEL OF BLACK-WHITE DISPARITIES IN CVD

The adult CVDs in which epigenetic and developmental processes play a critical role are the very ones that exhibit the most pronounced disparities across racial groups. As we now review, the following observations suggest that epigenetic and developmental responses contribute to race-based US health disparities: (1) As is true for a wide range of human populations, birth outcomes are important predictors of adult cardiovascular health for African Americans; (2) African American mothers have higher rates of low-birth-weight births than white mothers in the US; (3) this racial disparity in birth outcomes is linked to environmental, and particularly psychosocial, factors, and (4) there is evidence that these patterns can have multi-generational consequences.

Birth weight and adult CVD risk in African Americans

While few large studies have been conducted among diverse US populations, past research shows that the effects of prenatal environments on African American health are generally in agreement with expectations from other populations. Several small US studies have shown that lower birth weight predicts higher blood pressure, elevated cortisol reactivity, and early signs of diabetes in older African American children and adolescents (Covelli, 2006a,b; Li et al., 2001, 2006; Oberg et al., 2007), as well as other related cardiovascular conditions, such as end-stage renal disease, in adults (Fan et al., 2000). Findings from larger, population-based cohort studies have demonstrated the most consistent evidence for the effects of birth weight on subsequent health among African Americans. In the well-characterized Bogalusa Heart Study, birth weight is inversely related to later systolic and diastolic blood pressure in adult African Americans (Donker et al., 1997; Mzayek et al., 2007). Biracial analyses from that study suggest that for some cardiovascular risk factors, such as blood pressure, cholesterol levels, and insulin resistance, birth weight may be a stronger predictor for African Americans than for whites (Donker et al., 1997; Mzayek et al., 2004). Thus, as for other US and global pop-

ulations, and consistent with experimental findings in animal models, lower birth weights predict elevated future adult risk for adverse cardiovascular outcomes in African Americans.

Lower African American birth weight

It is well established that African Americans have lower average birth weights than US whites. National data show that rates of low birth weight (LBW) deliveries are twice as high among African Americans compared to whites, and very LBW births (<1,500 g) are 2.69 times more common among African Americans (CDC, 2005; Keppel et al., 2002). This pattern of racial disparity is true for both main categories of LBW: preterm (Demissie et al., 2001) and small for gestational age (SGA) births (Alexander et al., 1999). The racial disparity in birth outcomes has been documented for several decades and has shown no signs of significant improvement during that time (Demissie et al., 2001; Kramer et al., 2006).

Social origins of African American low birth weight

The association of birth weight with adult CVDs lends urgency to the search for the causes of the lower average birth weights of African Americans compared to other demographic subgroups in the US. As with attempts to explain other health disparities, hypotheses have tended to align with either genetic or environmental explanations. While a genetic cause is a theoretical possibility, there is no evidence that genetic differences between groups explain these inequalities, and, as we discuss below, epidemiologic evidence is difficult to reconcile with this interpretation (see also Pike, 2005).

Because maternal stressors and the passage of stress hormones across the placenta can lead to both preterm birth and fetal growth restriction (Sandman et al., 1997), research has examined the contribution of psychosocial stress to LBW and preterm delivery (PTD) in African Americans. Several epidemiologic studies have found that stressful life conditions and specific measures of psychosocial stress are associated with increased risk for both preterm birth and fetal growth restriction in African American mothers (Giscombe and Lobel, 2005). Exposure to stressful life events among African American mothers is associated with a higher risk for preterm births and lower birth weight (Borders et al., 2007; Dole et al., 2003; Dominguez et al., 2005; Orr et al., 1996; Oths et al., 2001). Additionally, psychological and emotional correlates of stress, such as symptoms of depression and anxiety, have been linked with poorer birth outcomes for African American women (Dole et al., 2003; Mackey and Boyle, 2000; Orr et al., 1996).

Several factors related to racial and economic inequality in US society have also been found to predict adverse birth outcomes. Factors related to socioeconomic status, such as income, education, and access to prenatal care, which tend to be lower among African Americans, are related to birth outcomes for this population in some studies (Giscombe and Lobel, 2005; Wightkin et al., 2007). Exposure to racial discrimination (Collins et al., 2004; Dole et al., 2004; Mustillo et al., 2004), residential segregation (Bell et al., 2006; Grady, 2006), and neighborhood-level poverty (Farley et al., 2006; Reagan and Salsberry, 2005)

have all been linked with higher risk for LBW deliveries. Racial discrimination in particular has been shown to confer a twofold or higher increased risk for poor birth outcomes (Collins et al., 2004; Dole et al., 2003; Mustillo et al., 2004), and in one study that pooled a multiracial sample this accounted for a substantial portion of the observed racial difference in preterm deliveries (Mustillo et al., 2004). Together these findings suggest that social factors, especially those relating to the experience of stress and inequality, contribute to the lower average birth weights in African American pregnancies.

Further evidence for an environmental, rather than genetic, cause of the lower birth weights of African Americans comes from studies of multigenerational trends of birth outcomes. A nongenetic transgenerational influence on fetal growth has long been proposed in the medical community (Ounsted and Ounsted, 1968; Ounsted et al., 1986). Maternal fetal growth rate is among the strongest predictors of offspring fetal growth rate (Morton, 2006; Ramakrishnan et al., 1999), and among survivors of the Dutch Famine winter during WWII, the grandoffspring of pregnant women who experienced the famine had reduced fetal growth (Lumey, 1992). Given evidence for effects of the mother's early life and chronic experiences on the intrauterine environment that she provides offspring, women of the same "race" might be expected to give birth to larger or smaller babies, depending on where they were born and raised. There is in fact good evidence for such differences.

Many studies have compared the birth weights and perinatal health of recent immigrants to the US (who were born overseas) to their racial or ethnic counterparts born in the US (Kleinman et al., 1991). These studies are remarkably consistent in their findings. African American newborns in general have higher rates of LBW, PTD, and neonatal mortality relative to whites in the US. However, these differences are greatly reduced among African American offspring born to foreign-born mothers. In one study of nearly 2.5 million US deliveries, foreign-born women of African ancestry were 25% less likely to give birth to a LBW baby compared to their US-born counterparts, while there was no difference in birth outcome by natality among whites (Acevedo-Garcia et al., 2005). Several other studies report similar findings, showing that foreign-born African Americans giving birth in the US have rates of LBW that are closer to those of US whites than US-born African Americans (Cabral et al., 1990; Forna et al., 2003; Singh and Yu, 1996).

One study of Illinois birth records not only compared birth outcomes in foreign-born and US-born African Americans but also linked these data with information on birth weights across several generations of offspring subsequently born in the US. The patterns present in the first generation were similar to those described above: In contrast to the lower birth weights of US-born African Americans, foreign-born African Americans were found to have a birth weight distribution nearly identical to that of US whites (David and Collins, 1997). However, this equivalence was short lived. Among subsequent generations born in the US, the birth weight distribution of the offspring of African immigrants shifted to lower values (Fig. 2), en route to a convergence with the lower African American mean (Collins et al., 2002). The findings among the European immigrants in this study showed the opposite pattern: their birth weights were originally lower than

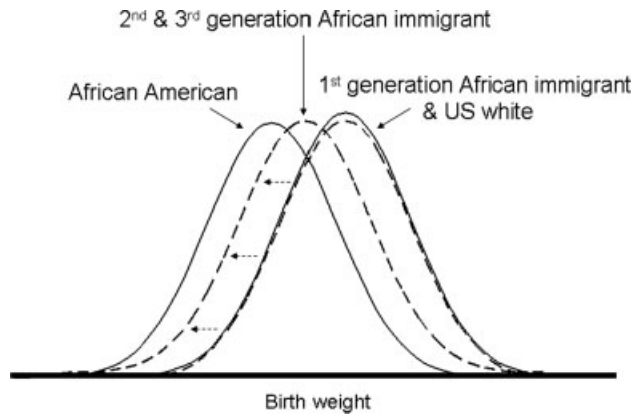


Fig. 2. Schematic illustrating the intergenerational change in birth weight among recent African immigrants to the US. The first generation in the US, born to foreign-born mothers, has a mean birth weight and birth weight distribution comparable to that of US whites. Second and third generations born in the US have lower birth weights, moving closer to the African American mean. Not drawn to scale (after data in Collins et al., 2002; David and Collins, 1997).

the mean for US whites, but increased with each generation born in the US.

It goes without saying that these opposing biological responses were far too rapid to be due to changes in gene frequencies (Boas, 1912). Instead they reveal that living in the United States has different implications for the intrauterine environments that African Americans and whites experience prior to birth as reflected in differences in fetal growth rate, prematurity, and birth weight. Regardless of where populations emigrate from, after several generations the birth weight distribution of later generations comes to resemble that of their US ethnic counterparts. This convergence is strong evidence that the widely documented US racial difference in birth weight is not due to genes (Collins et al., 2002; David and Collins, 2007).

Transgenerational impacts

In addition to the links between maternal stress and the offspring's future health, there are several pathways through which the effects of a stressful intrauterine environment could be perpetuated across generations. The most straight-forward explanation for a perpetuation of risk involves a continuity of environments. Given the persistence of racial institutional discrimination and economic inequality in US society (Blane et al., 1999; Pollitt et al., 2005; Shapiro, 2004; Williams and Collins, 1995), LBW infants are likely to experience many of the same psychosocial stressors as adults that their parents did. Thus women who were themselves born small will likely be at high social-environmental risk for delivering LBW offspring as a result of the perpetuation of a similar social and economic environment.

It is important to note, however, that the "environment" that a fetus experiences is an expression of maternal phenotype. This opens up possibilities for a mother's own stressful prenatal experience, as reflected in her having been born small, to influence the intrauterine developmental environment she provides for the next generation. Hypertension during pregnancy, for instance, elevates

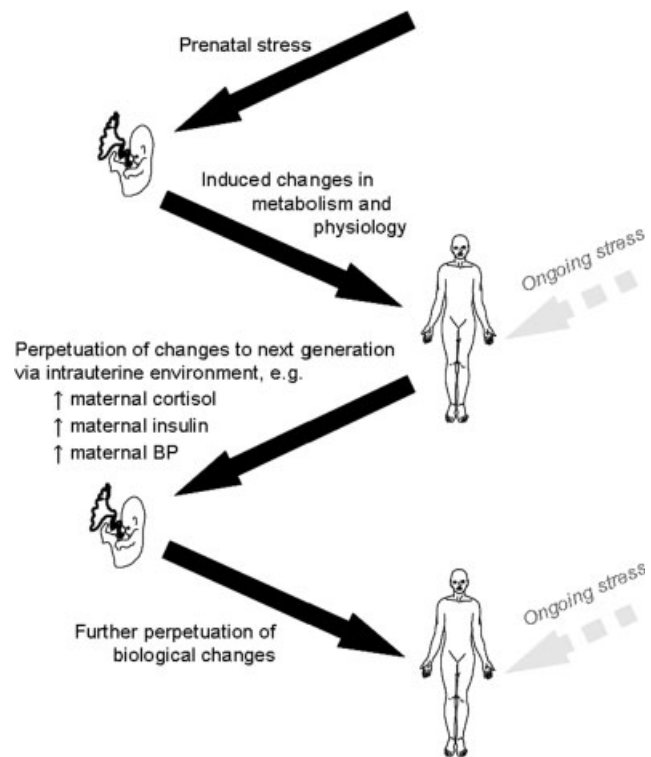


Fig. 3. Model showing the intergenerational transmission of disease states operating through the reciprocal effects of a stressful intrauterine environment on future adult metabolic state, and adult metabolic state (in females) on a stressful intrauterine environment in the next generation. The experience of chronic stress can have both acute and cumulative adverse effects on the present generation, and among women, lingering effects on future generations of offspring operating through durable epigenetic changes (modified after Drake AJ and Walker BR, 2004, *Journal of Endocrinology*, 180(1):1–16. © Society for Endocrinology 2004. Reproduced with permission).

risk for having a preterm birth or LBW delivery by as much as two to three times (Allen et al., 2004; Ananth et al., 1995; Clausson et al., 1998; Graham et al., 2007; McCowan et al., 1996; Ray et al., 2001). Similarly, maternal insulin resistance, hyperinsulinemia, and diabetes during pregnancy can increase passage of glucose and insulin across the placenta, and encourage the development of a similar state of weight gain and metabolic dysregulation in offspring (Dabelea et al., 2000; Lampl and Jeanty, 2004; Pettitt et al., 1987, 1988; Silverman et al., 1995). Heightened stress reactivity not only restricts fetal growth and increases risk for premature delivery, but there is evidence that it can also have direct effects on the development of the fetus's HPA axis (Worthman and Kuzara, 2005). As we discuss in greater detail below, these epigenetic effects are not set in stone, and may be amenable to reversal by intervention. However, these findings suggest that the intrauterine environment experienced by one generation (the mother) can influence the intrauterine environment that she creates for her offspring, in theory helping perpetuate certain biological or metabolic states, albeit in a fading fashion, across multiple matrilineal generations (Fig. 3).

The evidence reviewed above describes the components of a developmental model of US black-white disparities in cardiovascular health. Few US studies with high-quality

birth weight data have had sufficiently large samples across demographic subgroups to empirically test the contribution of birth outcomes to adult racial health disparities. However, a recent analysis of data from the biracial Bogalusa Heart Study cohort has provided strong support for a developmental origin of a key racial health inequality. In this study, the hypertension disparity between US whites and African Americans—one of the most common and widely studied racial health differential—was no longer significant after models adjusted for the effects of birth weight (Cruickshank et al., 2005). This is one of the rare studies to have “explained away” the race disparity in an adult CVD risk factor. No genetic factors have been shown to do this, despite considerable research effort (Cooper and Psaty, 2003).

DISCUSSION

The epigenetic and developmental processes that we review are shedding new light on the health disparities debate. In the current polarized discourse over health inequality, some interpret the inability of adult socioeconomic and behavioral factors to account for racial disparities in disease burden as evidence for underlying genetic differences (e.g. Kistka et al., 2007). This reasoning can be critiqued for ignoring the substantial residual impact of social and environmental factors not captured in the limited measures of these exposures employed in epidemiologic research (Cooper et al., 2003). Evidence for developmental and epigenetic influences on adult health adds a new layer to this critique. As the research reviewed here illustrates, measuring the biological impact of social forces solely at the level of the adult phenotype misses important developmental and epigenetic pathways that likely contribute to racial health inequality. A genetic interpretation of the residual race effect problematically conflates observed biological variation with inferred genetic contributions, and ignores evidence that social factors can have durable life-course and transgenerational effects on health. Whereas group membership and continental race are poor predictors of genetic variation, these same categories are directly related to the social and structural manifestations of inequality that impact the development of responsive biological systems. A wealth of evidence now shows that the social and economic experiences of race have profound influence on adult health and, beginning in childhood, can have effects that are both chronic and cumulative in their impact (Dressler et al., 2005; Geronimus, 2001). The research reviewed here is bolstering this social constructivist perspective by highlighting specific developmental pathways through which these same social factors become embodied during early, critical periods in development, with impacts that extend into adulthood and at times even across generations (Krieger, 2005).

Some may be tempted to interpret these findings as stigmatizing for pregnant women, or shifting blame onto mothers for the long-term health consequences of stressful prenatal environments. The deleterious effects of some maternal behaviors on offspring health, such as smoking or excessive drinking during pregnancy, have long been appreciated (Leary et al., 2006), and indeed, the DOHaD literature broadens the scope of offspring health outcomes that might be adversely affected by such behaviors (e.g. Oken et al., 2008). However, the research reviewed here overwhelmingly points to the importance of factors that

are symptomatic of structural inequality and discrimination rather than choice. The most important predictors of compromised birth outcomes include factors such as self-perceived discrimination, racism, and chronic stress (Giscombe and Lobel, 2005; Mustillo et al., 2004). These experiences are no more the “choice” of the women who experience them than are the many other symptoms of racial discrimination that have been documented in US society, such as African Americans’ lower average incomes (Shapiro, 2004) and reduced job opportunities compared to whites with equivalent qualifications (Pager, 2003).

The emerging epigenetic model of health disparities points to social and economic change as key to addressing racial differences in disease burden, and underscores the need to implement these interventions across the life-course. In particular, this work opens up the possibility for new approaches to encouraging positive health states in future generations. Some sources of social inequality, such as racism, cannot be eliminated by legislation. But societies *can* legislate changes in public spending that benefit pregnant mothers, improve their access to adequate prenatal care and nutrition and help ensure that they are relatively buffered from stress while pregnant and lactating. Although evidence is mixed (Lu et al., 2005), improving access to social support has been found in some studies to reduce rates of LBW among African American women at high risk for adverse pregnancy outcomes (Norbeck et al., 1996). Promotion of breastfeeding, and longer and more secure maternity leave, are additional examples of policies that could have long-term health benefits for future generations, and ease race-based health differentials operating through developmental pathways.

A better understanding of the epidemiology of epigenetic processes will be critical in developing effective interventions (Waterland and Michels, 2007). Although birth weight data are routinely collected in epidemiologic research and are thus widely available for such studies, birth weight is at best a nonspecific indicator of genetic, epigenetic, and other factors. Future research will benefit from incorporation of more nuanced approaches to quantifying stress and other social, cultural and material processes that could influence the nutritional and endocrine characteristics of the prenatal environment. For example, ethnographic approaches to the social and cultural contexts of stress are providing improved insights into the causes and impacts of stress in different communities and demographic subgroups (Dressler and Bindon, 2000; Gravlee et al., 2005), and will have much to add to future work on the developmental origins of adult health disparities.

While we have emphasized the role of the prenatal environment in this review, the impact of stress, nutrition, and other social-environmental exposures on developmental biology are by no means limited to fetal life. Infancy, childhood, and adolescence are all critical developmental windows during which epigenetic modifications in gene expression and tissue and organ function take place. As mentioned earlier, there is evidence that breast feeding confers protection against developing obesity, diabetes, and CVD (Arenz et al., 2004; Lawlor et al., 2005). The quality of the rearing environment and emotional attachment can have lasting effects on reactivity of the stress hormone (HPA) axis (Gunnar, 1998) and are influenced by factors like maternal emotional well-being (Adam et al.,

2004). Rapid weight gain during childhood can increase adult risk for CVDs and exacerbate the impacts of a stressful prenatal environment, suggesting that interventions to limit childhood weight gain could disproportionately benefit the health of individuals born small or exposed to a stressful prenatal environment (Adair and Cole, 2003; Oken and Gillman, 2003). Additionally, brain regions linked to emotional processing and stress reactivity, as well as other aspects of the HPA axis, undergo critical structural development during adolescence (McCormick and Mathews, 2007; Romeo and McEwen, 2006), suggesting that this age is also an important period for programming of the physiologic stress response.

In animal models, this flexibility of the phenotype during later developmental periods has been found to allow for partial or complete reversal of some epigenetic responses to prior stressful environments. Recent animal research has shown that environmental enrichment during adolescence can reverse some of the deleterious effects of early life epigenetic programming (Bredy et al., 2003; Francis et al., 2002; Laviola et al., 2004). Similarly, rat models have shown that injection of neonates with leptin (a body-fat-derived hormone that signals energy status) reverses the adverse metabolic changes triggered by prenatal protein restriction (Gluckman et al., 2007b; Vickers et al., 2005), while orally administered leptin in suckling rats (perhaps mimicking lactation in a well-nourished mother) protects the offspring against developing obesity later in life (Pico et al., 2007). These studies demonstrate the continued flexibility of biological systems into later stages of development, and hold open the possibility that strategies can be developed to modify disease risk and reverse epigenetic influences established prior to birth. Thus, while the social consequences of race can have durable effects on biology and health, we stress that “durable” need not equate with “permanent.”

Epigenetics as a challenge to the concept of genetic race

As emphasized by Boas (1912) a century ago, the contingency of the adult phenotype on environmental conditions experienced during growth and development poses a fundamental challenge to essentialist concepts of race. Current research on developmental and epigenetic contributions to adult health disparities is updating Boas’ argument. Not only are traditional racial categories poor predictors of gene frequencies, a fact that has been appreciated for decades (Brown and Armelagos, 2001; Lewontin, 1972), but developmental and epigenetic processes help to clarify why genes do not determine biological fates in any simple fashion. Genes rarely “determine” phenotypes but instead set the range of outcomes that a biological system may create as it interacts with and responds to the developmental environment (Bogin, 1999; Kuzawa, 2005; West-Eberhard, 2003; Worthman and Kuzara, 2005). Humans inhabit highly variable and socially stratified ecologies; it follows that systems that coordinate adaptation to these realities should come equipped with a capacity to organize in response to local patterns of stress and opportunity (Kuzawa, 2008). The research that we review is demonstrating some of the pathways through which socially defined environmental context can become embodied, contributing to the local perpetuation of linked patterns of early life and adult health disparity.

The model presented here should not be understood as replacing genetic race with an essentialized concept of epigenetic race; instead, it shows how social environments, defined along lines of constructed and socially imposed racial identities, can drive developmental processes, thereby becoming embodied as biological patterns that influence health and disease (Krieger, 2005). Debates about the causes of racial health disparities have traditionally aligned with the poles in the classic model of disease causation, which emphasizes the contrasting disease impacts of inherited genes and the dynamic and culturally shaped environment. The emerging epigenetic and developmental model of chronic disease epidemiology illustrates why this perspective is incomplete, and must be broadened to account for the more durable role that environments have on patterns of biology and health when experienced early in the lifecycle.

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