The Epigenetic Connection to Black Disparity

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Ta-Nehisi Coates, in his *Atlantic* article "The Case for Reparations,"[1] describes the systematic persecution of blacks in the US not only by white racists, but also through ensconced governmental law. He makes the case for the necessity of passing HR 40 to begin discussion of reparations and the moral and legal deprivations that white America has foisted on blacks for several centuries and that continue to this day.

What Coates does not deal with are the underlying neurobiological consequences of these stressful experiences. New data indicate that environmentally based stressful life events can induce the placement of chemical groups on one's genetic material that have lifelong effects and that can even be transferred across generations. The changes are called epigenetic because they do not affect the DNA sequences that encode genes conveying genetic inheritance of traits, but only affect how easily genes are turned on or off during development and throughout one's life. Life stressors cause the chemical groups (most often a methyl or acetyl group) to be placed on one's DNA and histones (around which DNA is wrapped) and change micro-RNA (mediating DNA messages to alter protein synthesis).[2–5]

Environmentally induced biochemical and behavioral alterations based on epigenetic changes are revealed in animal studies by those induced by early life adversity[6–8] and in the defeat-stress paradigm.[7–9] If a small adult mouse is repeatedly (for 10 days) threatened by a larger mouse that is defending his home cage, the little intruder mouse develops depressive-like behaviors. These changes are associated with decreases in brain-derived neurotrophic factor (BDNF) in the hippocampus and increases in BDNF in the reward area of brain called the nucleus accumbens.[9,10] Prevention of these epigenetic changes ameliorates or prevents the stress-induced behaviors.

The behavioral changes associated with defeat stress are also influenced by the secretion of the inflammatory cytokine interleukin 6 (IL-6) by monocytes in the bone marrow and subsequently tumor necrosis factor α (TNF-α) and IL-1β in brain.[11] Of note, the inflammatory markers IL-1β, IL-6, and TNF-α are often elevated in the blood of depressed and/or traumatized patients. Remarkably, if the IL-6 effects are blocked, the defeated animals do not show the depressive-like behavior. It is also noteworthy that other animals merely witnessing an animal undergoing the stressful experiences will also manifest defeat stress depressive-like behavior.[12] These preclinical observations in rodents are congruent with data in people indicating that witnessing traumatic events happening to others can be sufficient to induce posttraumatic stress disorder (PTSD).

Recently, it has been shown that some epigenetic effects based on adult experiences can be transferred across generations even in the absence of behavioral contact with the offspring.[13–17] This occurs because some epigenetic marks on DNA, histones, and micro-RNA can be preserved and passed to the next generation via the germline (sperm and probably also oocytes).

For example, the offspring of Holocaust survivors have altered biochemistry and behavior.[18] The offspring of women exposed to the Dutch famine of 1944–1945 were smaller at birth and were more susceptible to diabetes, obesity, cardiovascular disease, and other health problems later in life.[19] The grandchildren in the next generation were also unusually smaller at birth or more prone to diabetes and obesity. Remarkably, 6 decades later, scientists found persistent epigenetic changes (less DNA methylation) increasing the production of insulin-like growth factor 2 (IGF-2) from lineages exposed compared to those nonexposed to the Dutch famine.[18] IGF-2 is associated with obesity and could be a mechanism of the persistent vulnerability to obesity in the hunger-exposed lineages. Similarly, a mother's history of maltreatment in her own childhood is also associated with increases in obesity in her offspring, although in this instance it is likely based on changes in utero.[20]

Taken together, these data in animals and humans suggest that the stressors and violence toward the fathers, mothers, and children of black families, experienced directly or witnessed, can leave epigenetic marks on one's genetic material and affect stress reactivity, biochemistry, and behavior, in some instances extending across multiple generations.[5,21] The experience of a woman raped or a man tortured can biochemically and psychically scar not only that person and family, but future generations as well.

These epigenetic effects potentially recurring across generations are not immutable and can be influenced further by other environmental manipulations. For example, if a stressed animal (conditioned to a smell and a shock) is later given a favorable (therapeutic) environmental

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experience—that is, living in an enriched environment—the offspring no longer show the increased reactivity to that smell.[15,22] The message is that epigenetic marks can be long lasting, but are not necessarily permanent or immutable.

The effects of early stress in humans can be remarkably broad. Adults seen in a general medical practice who have experienced adversity in childhood are prone to develop a vast array of medical and psychiatric illnesses.[23] The medical ones include diabetes, asthma, autoimmune diseases, obesity, and cardiovascular diseases (stroke and heart attacks). The psychiatric ones include depression and suicide, among many others. In studies in an international bipolar network, we found that patients with bipolar disorder in the US had more stressors (verbal/emotional, physical, and sexual abuse) in childhood than those in the Netherlands and Germany.[24,25] The history of stressors in childhood was associated with an earlier onset to their bipolar disorder and a more adverse course of illness, as well as a higher incidence of more than 11 medical conditions.[24,26] Not only were the adult patients from the US sicker and had more psychiatric disorders and comorbidities,[25] so did their offspring.[27] Most noteworthy is that the adult patients in the US who had experienced only verbal/emotional abuse (and not physical or sexual abuse) still had an early onset and more severe course of illness.[28] These data are consistent with a large literature showing that even bullying and other forms of verbal abuse can have profound effects not only on behavior but also on brain function and structure. Acts of discrimination would fall under this rubric as well. Thus, not only socioeconomic status, but also the experience of taunts, threats, and discrimination itself can have profound effects on behavior and brain development and structure.

Along with our findings that patients with bipolar disorder from the US experience more stress than those from Europe and have more medical comorbidities related to these stressors, Banks et al[29] reported that older white males (equated for socioeconomic status [SES], health care access, smoking, weight, and other factors) from the US had more medical illnesses of almost every sort than those from Great Britain. Banks et al[29] concluded that white "Americans were sicker than the British." Blacks are even more disadvantaged and are even more prone to an array of medical illnesses than white Americans.[30]

Blacks in the US have almost every medical-related disadvantage that one could imagine. They are overrepresented in the categories of low SES; living in areas at risk for direct or indirect exposure to violence and environmental contaminants; and having high rates of hypertension, diabetes, obesity, heart disease, and asthma, which put them at increased risk of early demise not only from these illnesses but also now from COVID-19. The higher incidence of all of these illnesses is compounded by the poorer treatment of blacks compared to whites.[30] Four centuries of discrimination against black individuals have not only deprived them of economic and social well-being but also fostered an interlocking set of medical factors that affect their risk of illness and their life expectancy. People who have experienced adversity in childhood have been found to have more epigenetic marks in their brain studied on autopsy and also on the DNA in their white cells, and one would postulate that blacks (matched for SES and other factors) would have even more of these epigenetic marks than whites.[18,31–34]

These same adversities of stress and depression can also affect the length of telomeres (which are the ends of each strand of DNA). Their shortening with each cell replication is associated with an increased risk of numerous medical and psychiatric illnesses and is a general index of aging.[35] Stressors and episodes of depression are associated with premature shortening of telomeres, while good life choices such as a good diet, exercise, meditation, and mindfulness are associated with maintenance of longer telomeres.[36] In multiple studies, shorter telomeres have been seen in blacks suffering racial discrimination,[37] and this set of environmentally induced epigenetic changes in telomere length is quite likely another cause of the increased vulnerability to the multiple medical and psychiatric illnesses from which blacks suffer.

At the moment, we do not know how to reverse these epigenetic marks derived from adverse environmental experiences, but preventing them in the first place is within our grasp. Positive environmental experiences, akin to living in an enriched environment in the laboratory studies, have the possibility of removing or preventing the transgenerational transmission of some of the adverse epigenetic marks.[22] Later treatment of defeat-stressed animals with the anti-inflammatory antibiotic minocycline may reverse some stress-induced behaviors,[38] and this remains to be studied in humans. The widely used anticonvulsant valproate, which has epigenetic effects as a histone deacetylase inhibitor, can reopen critical periods of synaptic plasticity, rendering the possibility of allowing new input in adulthood to reverse some effects of earlier experience.[39–41] A host of drugs that have direct effects on epigenetic alterations on DNA and histones are currently being used in cancer therapies in humans,[42] and one can hope that some of these drugs and others will be able to be applied to reversing some of the effects of environmental adversity on neuropsychiatric illnesses in the future. On the level of modifying the effects of traumatic memories in PTSD, neuropsychological interventions alone, such as extinction therapy in the re-consolidation window (which opens up to 1 hour after the active recall of emotional memories), also have been shown to revise traumatic memories and their neural engrams in brain.[43]

We do not know whether the calls by Ta-Nehisi Coates and many others for reparations for the past discrimination against blacks will bear fruit. However, we think knowledge about the neurobiological and behavioral catastrophe emanating from and through the history of the black experience in the US may add emphasis to the discussion. The disparities and the excesses in COVID-19 infections, hospitalizations, and deaths in blacks compared to whites in the US further crystallize and reveal the magnitude and

complexity of the problem. Reparations will not be sufficient to reverse epigenetic marks persisting across generations and the associated wide range of medical illnesses and psychological disadvantages, but the recognition of the interacting and persisting epigenetic assaults to the brain and body wrecked by the history of systematic violence and injustice may place a new light on the justification for reparative action.

In the meantime, some progress could be achieved by ensuring universal access to good medical and psychiatric care so that the profound disparities in health could begin to be addressed in a comprehensive fashion. The multiple and interlocking medical problems of an excess of diabetes, hypertension, obesity, kidney, lung, and cardiovascular disease yielding heart attacks and strokes and a premature loss of life expectancy in blacks will require special attention and new programs that can begin to treat and ultimately prevent this environmentally induced medical disadvantage. Addressing and breaking the transgenerational cycle of medical illnesses needs to involve both adults and children in the current generation.[44]

While the needed medical and public health interventions may not occur in the near future, personal actions can be taken and encouraged.[35,36] It is remarkable that merely adopting positive lifestyle practices is associated with increases in the length of one's telomeres. Treating and preventing depression, minimizing stressors, and engaging in exercise, good diet, meditation, mindfulness, and the practice of loving kindness also may have advantages for all of us.

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