"Motherless Children Have the Hardest Time": Epigenetic Programming and Early Life Environment

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The Blind Willie Johnson blues song "Motherless Children" highlights the maternal bonds that we all know are critical to emotional and cognitive development. Authors of previous work looking at infant stress response have found that these bonds begin in utero and can be influenced by both maternal and paternal influences and across multiple generations.[1] The observations of Barker et al[2] on the Dutch famine birth cohort of World War II were perhaps the first published observations of this phenomenon.[3] Somehow, we carry the benefits and burdens of our childhoods into our adult lives, with impacts made evident on our behavior and also virtually all organ systems. In a new study published in *Pediatrics*, Lester et al[4] evaluate the potential biological factors that underlie these effects.

Memory at the cellular level must be a key marker of programming. The idea that, during early development, important physiologic parameters can be reset by environmental events, and that this resetting can endure into adulthood, requires cellular memory.

Factors that reflect and contribute to the setting of circadian rhythms may be a form of long-term memory. In that regard, cortisol, which mediates multiple metabolic processes in the body, is a strong candidate to serve as a biomarker of early life programming. Under basal conditions, cortisol, the body's main glucocorticoid hormone, follows a diurnal pattern in the plasma and saliva but also rises in response to stress. The blunting of the characteristic rise of salivary cortisol after an acute stressor may be a biomarker of maladaptive programming. Elegant epigenetic research in mice previously revealed that maternal bonding behaviors altered DNA methylation of the hippocampal glucocorticoid receptor.[5] This altered DNA methylation, in turn, predicts gene expression in the brain.

Lester et al[4] translate that research into humans by applying an acute stressor (the still-face paradigm)[6] and relating the infant's stress response to salivary cortisol rise and history of breastfeeding. The study was conducted in healthy 5-month-old infants, half of whom had been breastfed and half of whom had not, to simulate the mother–infant bond studies conducted in animals. Cortisol reactivity after the still-face stressor was used as an experimental intervention to test infant autonomic regulation. The link between early life environment (eg, maternal–infant bonding and programming of epigenetic regulation of cortisol receptor promotor methylation) may be reflective of the role of epigenetics as a form of cellular memory, providing a mechanism by which early life environment can program health effects that manifest years or even decades later.

Cortisol is a key hormone for neurodevelopment, inflammation, bone health, respiratory health, cardiovascular health, and general metabolism, helping to maintain homeostasis. It should be noted

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that the underlying programming of stress reactivity may not be driven directly by cortisol or the glucocorticoid receptor, but cortisol likely plays a role in the overall mechanism, because cortisol disruption is associated with a variety of complex diseases (obesity, neurodevelopment, bone health, cardiovascular health, etc) related to early life stress. In other words, the change in glucocorticoid receptor methylation may be a direct result of maternal bonding or may be a downstream effect of a linked pathway that ultimately led to this methylation change. Therefore, just changing the DNA methylation marks, even in neurologic tissues, might not make the cortisol response more appropriate, and our efforts should instead be directed at improving parental emotional bonds.

The ability to define biomarkers of early life programming will be key to developing or evaluating interventions designed to reverse maladaptive programming and moving forward toward healthier phenotypes. The article by Lester et al[4] is a key first step in this process because it illustrates methods to identify infants who may be at higher risk for maladaptive stress responses so that we can begin the process of counseling mothers on how to enhance bonding. Advocating for programs used to help parents better identify infant distress cues, engage in physical contact, and provide supportive interactions is a key next step. Several programs have already been developed for high-risk infants, but the fundamental principles apply to all infants, and helping parents understand the long-term benefits will improve compliance and parental and infant satisfaction.

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