NATIONAL SCIENTIFIC COUNCIL ON THE DEVELOPING CHILD

Early Experiences Can Alter Gene Expression and Affect Long-Term Development

WORKING PAPER 10

Center on the Developing Child HARVARD UNIVERSITY

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The National Scientific Council on the Developing Child, housed at the Center on the Developing Child at Harvard University, is a multi-disciplinary collaboration designed to bring the science of early childhood and early brain development to bear on public decision-making. Established in 2003, the Council is committed to an evidence-based approach to building broad-based public will that transcends political partisanship and recognizes the complementary responsibilities of family, community, workplace, and government to promote the well-being of all young children. For more information, go to www.developingchild.net.

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The Issue

NEW SCIENTIFIC RESEARCH SHOWS THAT ENVIRONMENTAL INFLUENCES CAN ACTUALLY AFFECT whether and how genes are expressed. Thus, the old ideas that genes are "set in stone" or that they alone determine development have been disproven. In fact, scientists have discovered that early experiences can determine how genes are turned on and off and even whether some are expressed at all.[1,2,3] Therefore, the experiences children have early in life—and the environments in which they have them—shape their developing brain architecture and strongly affect whether they grow up to be healthy, productive members of society. This growing scientific evidence supports the need for society to re-examine the way it thinks about the circumstances and experiences to which young children are exposed.

The approximately 23,000 genes that children inherit from their parents form what is called the "structural genome." Scientists liken the structural genome to the hardware of a computer—both determine the boundaries of what's possible, but neither works without an operating system to tell it what to do. In the genome, that operating system is called the epigenome.[4] Like the software in an operating system, the epigenome determines which functions the genetic "hardware" does and does not perform.[5] This system is built over time as positive experiences, such as exposure to rich learning opportunities, or negative influences, such as environmental toxins or stressful life circumstances, leave a chemical "signature" on the genes. These signatures can be temporary or permanent, and both types affect how easily the genes are switched on or off. For example, even though identical twins have the same structural genomes, their different experiences result in different epigenomes.[6] These differing experiences leave signatures on the epigenome that cause some genes to be expressed differently. This explains why genetically identical twins, though similar in many ways, can exhibit different behaviors, skills, health, and achievement in both school and, later, in the workplace.

The field of epigenetics is relatively new and at the cutting-edge of the biological sciences. To date, scientists have found that *temporary* epigenetic chemical modifications control when and where most of our genes are turned on and off. This, however, is not the entire story. Certain experiences can also cause *enduring* epigenetic modifications in hundreds of genes that have already been identified, and the list is growing.[7,8] Increasing evidence shows that experience-driven, chemical modifications of these latter genes appear to play particularly key roles in brain and behavioral development. This new knowledge has motivated scientists to look more closely at the factors that shape the epigenome and to study whether interventions can reverse these modifications when negative changes occur.

Nutritional status, exposure to toxins and drugs, and the experiences of interacting with varied environments can all modify an individual's epigenome.[9] Epigenetic instructions that change how and when certain genes are turned on or off can cause temporary or enduring health problems. Moreover, research in both animals and humans shows that some epigenetic changes that occur in the fetus during pregnancy can be passed on to later generations, affecting the health and welfare of children, grandchildren, and their descendents.[10,11,12] For example, turning on genes that increase cell growth, while at the same time switching off genes that suppress cell growth, has been shown to cause cancer.[13,14] Repetitive, highly stressful experiences can cause epigenetic changes that damage the systems that manage one's response to adversity later in life.[2,3,15] On the other hand, supportive environments and rich learning experiences generate positive epigenetic

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signatures that *activate* genetic potential.[16] In this second case, the stimulation that occurs in the brain through active use of learning and memory circuits can result in epigenetic changes that establish a foundation for more effective learning capacities in the future.[17,18]

As we get older, new experiences can continue to change our epigenome. However, science tells us that the chemical signatures imprinted on our genes during fetal and infant development can have significant influences on brain architecture that last a lifetime. Stated simply, the discovery of the epigenome provides an explanation, at the molecular level, for why and how early positive and negative experiences can have lifelong impacts.[2,3,19,20]

Policymakers can use this knowledge to inform decisions about the allocation of resources for interventions that affect the life circumstances of young children—knowing that effective interventions can literally alter how children's genes work and, thereby, have long-lasting effects on their mental and physical health, learning, and behavior. In this respect, the epigenome is the crucial link between the external environments that shape our experiences and the genes that guide our development.

What Science Tells Us

OVER THE PAST 50 YEARS, EXTENSIVE RESEARCH has demonstrated that the healthy development of all organs, including the brain, depends on how much and when certain genes are expressed. When scientists say that genes are "expressed," they are referring to whether they are turned on or off—essentially whether and when genes are activated to do certain tasks. Research has shown that there are many non-inherited environmental factors and experiences that have the power to chemically mark genes and control their functions. These influences create a new genetic landscape, which scientists call the epigenome. Some of these experiences lead to chemical modifications that change the expression of genes temporarily, while increasing numbers have been discovered that leave chemical signatures that result in an enduring change in gene expression.

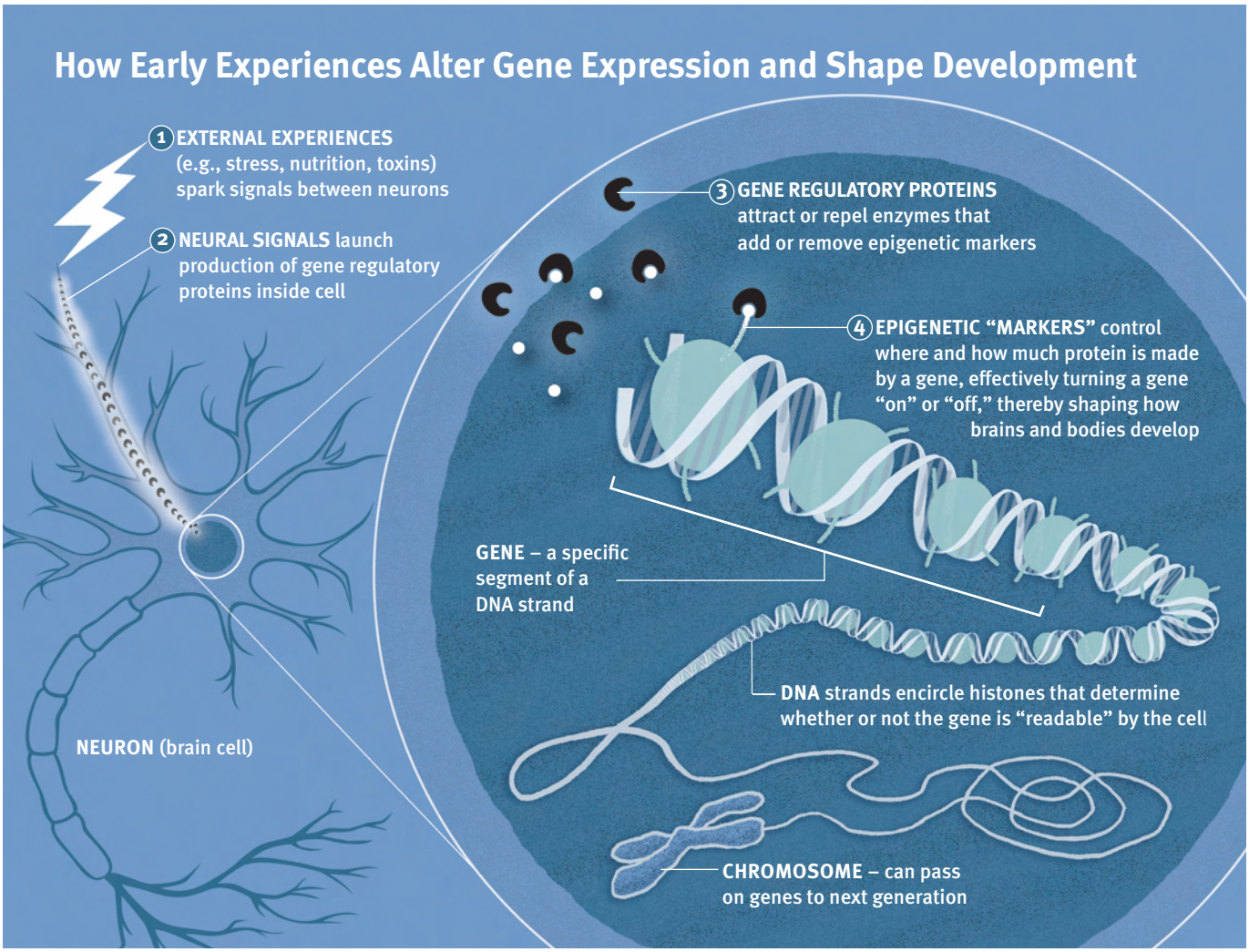
Early prenatal or postnatal experiences and exposures influence long-term outcomes by chemically altering the structure of genes. Known as *epigenetic* modification (from the Greek root *epi*, meaning upon or over), these chemical signatures are written on top of the gene without actually altering the genetic code itself.[21] Instead, the signatures attract or repel other chemicals that help the genes produce the proteins that are the building blocks our brains and bodies need to develop. Research tells us that some genes can only be modified epigenetically during certain periods of development, defined as *critical periods* of modification, while other genes are open to alterations throughout life.[2,3,22,23,24,25]

Epigenetic modification typically occurs in cells that comprise organ systems, thereby influencing how these structures develop and function. Experiences that change the epigenome early in life, when the specialized cells of organs such as the brain, heart, or kidneys are first developing, can have a powerful impact on physical and mental health for a lifetime.[26] We are also learning from new scientific discoveries in both animals and humans that environmental factors, such as certain drugs or the nutritional status of the mother, have the potential to cause epigenetic changes to genes in egg or sperm cells in the fetus. When such changes occur, this new chemical signature of the DNA is enduring and can be inherited by future generations.[27,28,29]

The brain is particularly responsive to experiences and environments during early development, which influences how well or poorly its architecture matures and functions. We know from extensive research that the physiological activity created by experience is powerful in shaping brain architecture and actually changes the chemistry that encodes the genes in brain cells.[30] Put simply, the brain adapts to the experiences it has. Certain types of adaptations result in healthy systems, such as effective learning and memory, and other adaptations lead to the development of unhealthy systems, such as setting a stress response activation level too high

or too low. The physiological activity caused by positive mastery experiences can lead to epigenetic changes that control the expression of genes in brain cells that are essential for successful learning.[17,18,31] In a parallel fashion, exposure to damaging levels of stress early in life can lead to long-lasting epigenetic changes in brain cells that direct how our bodies respond to adversity throughout the lifespan.[32] In short, early experiences cause epigenetic adaptations in the brain that influence whether, when, and how genes build the capacity for future skills to develop.

Modification of the epigenome caused by stress during fetal and child development affects how well or poorly we respond to stress as adults and can result in increased risk of adult disease. Some of our genes provide instructions for how our bodies respond to stress, and research has shown that these genes are clearly subject to epigenetic modification. For example, research in animals has shown that stressful experiences to which the pregnant mother is exposed, or to which the offspring is exposed soon after birth, can produce epigenetic changes that chemically modify the receptor in the brain that controls the stress hormone cortisol and, therefore, determines the body's response to threat (the fight-or-flight response).[19,33,34] Healthy stress responses are characterized by an elevation in blood cortisol followed by a return to baseline to avoid a highly activated state for a prolonged period of time. If young children or pregnant mothers experience toxic stress—as a result of serious adversity (such as chronic neglect, abuse, or exposure to violence) in the absence of protective relationships—persistent epigenetic changes can result.[32] These modifications have been shown to cause prolonged stress responses, which can be likened to revving a car engine for long periods of time. Excessive stress has been correlated with changes in brain architecture and chemistry as well as animal behaviors that resemble anxiety and depression in



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humans.[35,36,37,38,39,40] Human studies have found connections between highly stressful experiences in children and increased risk for later mental illnesses, including generalized anxiety disorder and major depressive disorder.[41,42,43] Atypical stress responses over a lifetime can also result in increased risk for physical ailments, such as asthma, hypertension, heart disease and diabetes.[29,32,41,42,43,44,45,46,47,48]

In addition to adverse experiences, a wide variety of chemicals, nutrients, and drugs are also capable of modifying the epigenome for long-lasting effects on gene expression. Epigenetic modification caused by exposure to toxic substances can either turn genes off or on, and both conditions have been linked to increased risk for mental and physical illnesses. Certain dietary supplements (such as excessive amounts of folic acid, choline, or vitamin B_{12}) and chemicals (such as bisphenol A, or BPA, which is found in some plasticware) can turn genes off.[1,8,49,50] Some genes that can be turned on by heavy metals, such as cadmium, nickel, and lead, have been linked to the cellular over-activity that results in an increased risk for certain kinds of cancer.[28,51,52] Many organs, including the brain, are most vulnerable to the influence of these substances on gene expression during the period of fetal and infant development, when basic organ systems are being built. These resulting differences in gene expression, in turn, can lead to fundamental changes in brain architecture and the biological systems that govern how well we function later in life.

Recent research demonstrates that even after the epigenome has been modified, there may be ways to alter it again that actually can reverse negative changes and restore functioning. Experiments in animals have shown that certain types of epigenetic modifications that were thought to be permanent can be reversed under certain conditions.[35,53] Most recently, researchers found that stressful experiences during early postnatal development resulted in epigenetic modification that caused exaggerated stress responses in adult animals, and that subsequent drug treatment of the adults could eliminate these adverse DNA changes. In this case, reversing the chemical modification resulted in increased expression of genes that control the stress response, and when exposed to subsequent stress, the treated adult animals had a normal response (that is, the adverse effect of the early postnatal experience had, indeed, been reversed). We now know that the same types of epigenetic chemical modifications can occur in adult humans who endured extreme stress as children, such as from physical abuse.[19] This possibility of reversibility is generating a flurry of research activity, because it has direct implications for developing new interventions for physical and mental illnesses that we now know are due in part to epigenetic modification. As promising as this work appears to be, further research is needed to determine if and how the reversal of epigenetic modifications can be achieved in humans.

Correcting Popular Misrepresentations of Science

UNTIL RECENTLY, THE INFLUENCES OF GENES were thought to be set, and the effects of children's experiences and environments on brain architecture and long-term physical and mental health outcomes remained a mystery. That lack of understanding led to several misleading conclusions about the degree to which negative and positive environmental factors and experiences can affect the developing fetus and young child. The following misconceptions are particularly important to set straight.

Contrary to popular belief, the genes inherited from one's parents do not set a child's future development in stone. Variations in DNA sequences between individuals certainly influence the way in which genes are expressed and how the proteins encoded by those genes will function. But that is only part of the story—the environment in which one develops, before and soon after birth, provides powerful experiences that chemically modify certain genes which, in turn, define how much and when they are expressed. Thus, while genetic factors exert

potent influences, environmental factors have the ability to alter family inheritance.

Although frequently misunderstood, adverse fetal and early childhood experiences can—and do—lead to physical and chemical changes in the brain that can last a lifetime. Injurious experiences, such as malnutrition, exposure to chemical toxins or drugs, and toxic stress before birth or in early childhood are not "forgotten," but rather are built into the architecture of the developing brain through the epigenome. The "biological memories" associated with these epigenetic changes can affect multiple organ systems and increase the risk not only for poor physical and mental health outcomes but also for impairments in future learning capacity and behavior.

Despite some marketing claims to the contrary, the ability of so-called enrichment programs to enhance otherwise healthy brain development is not known. While parents and policymakers might hope that playing Mozart recordings to newborns will produce epigenetic changes that enhance cognitive development, there is absolutely no scientific evidence that such exposure will shape the epigenome or enhance brain function. What research *has* shown is that specific epigenetic modifications do occur in brain cells as cognitive skills like learning and memory develop and that repeated activation of brain circuits dedicated to learning and memory through interaction with the environment, such as reciprocal "serve and return" interaction with adults,[54] facilitates these positive epigenetic modifications. We also know that sound maternal and fetal nutrition, combined with positive social-emotional support of children through their family and community environments, will reduce the likelihood of negative epigenetic modifications that increase the risk of later physical and mental health impairments.

> **Adverse fetal and early childhood experiences can—and do—lead to physical and chemical changes in the brain that can last a lifetime.**

The Science-Policy Gap

THE FACT THAT THE GENOME IS VULNERABLE TO modification by toxic stress, nutritional problems, and other negative influences underscores the importance of providing supportive and nurturing experiences for young children in the earliest years, when brain development is most rapid. From a policy perspective, it is in society's interest to strengthen the foundations of healthy brain architecture in all young children to maximize the return on future investments in education, health, and workforce development. In this context, the epigenome is the chemical signature that explains how early life experiences become embedded in the circuitry of the developing brain and are associated with lifelong consequences. Research now shows that interaction between adverse environments and the genes we inherit—through the epigenome—can increase the risk for long-term negative mental and physical health outcomes. Nevertheless, many policy decisions do not yet reflect this growing knowledge, which logically calls for reducing the exposure of pregnant women and young children to environments and experiences that can have significant negative effects on the epigenome (and therefore powerful, indirect influences on genes). This gap between what we know and what we do is illustrated by the following four examples:

Child welfare. Because threatening or harmful environments can produce epigenetic modifications that affect a child adversely for a lifetime, the management of child abuse or neglect cases by child protective services is extremely time-sensitive. This sense of urgency is particularly important with respect to decisions about custody arrangements that involve non-family placements. The biology of adversity also tells us that assessment and planning for the mental health and broad developmental needs of vulnerable children—with the assurance of

nurturing, protective, and stable relationships as the highest priority—require attention in the child welfare system comparable to the conventional focus placed primarily on physical safety.

Mandated maternal employment and public assistance. Whether low-income mothers with very young children should be required to work in order to be eligible for public assistance is a political decision. Policies informed by scientific knowledge about early brain development and epigenetics, however, would link mandated maternal employment to a parallel investment in high-quality early care and education programs for affected children. When policies view child care simply as a custodial service whose primary purpose is to facilitate maternal work outside the home, they reflect a lack of understanding of extensive scientific evidence about how the developing architecture of the brain is shaped by epigenetic influences associated with the quality of adult-child interactions in the early childhood years. In contrast, policies that view high-quality child care and early education programs as strategic interventions to improve the life prospects of children whose parents have limited education and low income are more likely to increase the prosperity of communities across generations.

Prenatal and newborn health care. The fetal period is a highly active time for organ development and epigenetic modification, yet investment in prenatal services remains uneven. Policies that assure the availability, accessibility, and affordability of individualized support and monitoring of all pregnancies create a safety net that prevents harm and detects problems at a point when appropriate interventions can reduce the negative consequences of toxic stress and other adverse environmental exposures.

Support for new parents. The United States is one of very few developed nations that does not provide some amount of paid family leave for all parents after the birth or adoption of a baby. For parents of newborns who do not have the economic resources to make ends meet in the absence of paid employment, the supportive relationships that promote positive epigenetic changes and help very young children to manage stress can be compromised by a premature return to work and the inability to secure high-quality care for a young infant. Family leave is one way of helping parents build these critical relationships, but other policies that support parents during this important transition time can also have important, short-term effects on the quality of family life as well as long-term impacts that bring high returns to all of society.

Implications for Policy and Programs

BECAUSE EARLY EXPERIENCES CAN ALTER THE epigenome and influence developing brain architecture, policies affecting the life circumstances of pregnant women and young children can have enormous implications for all of society. The varied effects of environments on the epigenome are evident from the time of early embryonic development and extend into the early childhood years. Science tells us that children can be helped to reach their full potential through both appropriate experiences in the earliest years and the reduction of sources of toxic stress that can alter the epigenome and increase the risk of long-term problems in physical and mental health. Thus, public policies that harness the basic principles of neuroscience and epigenetics to address the needs of young children are likely to also generate long-term benefits, such as healthier communities and a more prosperous society.

The documented effects of toxic stress on negative epigenetic adaptations demonstrate the urgent need to alleviate sources of significant adversity as early as possible in the lives of children who live in threatening environments. In order to be maximally effective, programs and services targeting the precipitants of excessive stress—such as child abuse and neglect, violent neighborhoods and families, and caregiver mental illness—must have prompt access to specific expertise in the target areas in order to move quickly to protect young children from epigenetic changes that can lead to lifelong problems

in learning, behavior, and health. Because the clock is always ticking when the basic architecture of the brain is developing, informed policymakers understand that a delayed response to the needs of young children who are experiencing significant adversity jeopardizes their individual well-being as well as the broader human capital needs of society.

Epigenetic changes caused by the exposure of pregnant women, infants, and toddlers to environmental toxins, prescription drugs, alcohol, and illicit substances require an urgent look at what safeguards can be implemented to prevent such exposures. Lead paint laws are a good example of public policy that has been successful in reducing the harmful consequences of environmental toxins. Less aggressive policies with respect to mercury and organophosphate insecticides, on the other hand, are just two examples of many missed opportunities to mitigate the well-documented, adverse effects of environmental hazards on pregnant women and young children. The serious and continuing impact of prenatal exposure to alcohol and a wide variety of chemical substances (including prescription drugs) on child health and development calls for a more vigorous approach to environmental policies and public education. In view of the well-established scientific fact that embryonic, fetal, and early childhood brain development is considerably more susceptible to damage from neurotoxins than the mature brain of an adult, the establishment of safe levels of exposure to toxic substances should be based on scientific data that recognize the critical link between vulnerability and age, and that focus primarily on the best information available for the youngest children.[55]

Because prenatal and early postnatal experiences can affect long-term outcomes through epigenetic influences, the provision of high-quality health services and nutritional support for all pregnant women, infants, and toddlers would be likely to reduce preventable diseases across the lifespan—as well as the costly treatments for them. A range of currently available programs and systems has been established to meet these needs. Assuring access to appropriate, affordable, high-quality services that are well implemented, however, remains an elusive goal, particularly for many of the most disadvantaged families and those whose primary language is not English. Policies that succeed in connecting all pregnant women and young children to medical and nutrition services that match their individualized needs will produce measurable benefits in population health.

Certain epigenetic changes in humans can be transferred across generations, thereby underscoring important, long-term implications for policies that affect the circumstances in which young children are raised. Effective policies and programs that address conditions associated with economic hardship with or without other sources of adversity—especially those targeted to help families during pregnancy—can not only improve birth outcomes and short-term conditions for young children but should also be viewed as investments in building a stronger foundation for healthy communities and future prosperity across generations. When policymakers support positive environments for pregnant women and very young children, they reduce the risk of intergenerational transfer of negative epigenetic changes that can lead to impaired health, diminished learning capacity, and poor parenting of the next generation.

Because discoveries about the epigenome and its lifelong effects are so recent, a multi-faceted education campaign could bring important new information to a wide range of important audiences, including health professionals, judges and lawyers, educators, caregivers, families, and the general public. A broad-based understanding of cutting-edge, developmental science by people who influence the experiences and environments of young children could provide a framework for greater alignment and integration of the current patchwork of services and supports provided to families. In this vein, greater understanding of how toxic stress, poor nutrition, and toxic chemical and drug exposures can increase lifelong risks for physical and mental health impairments by changing the chemistry of our children's DNA would provide a powerful foundation for more effective public action to address the needs of young children—and all of society—for generations to come.

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