Nurturing Nature

How Parental Care Changes Genes

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Ruth Hubbard against Genetic Determinism

It has been thirty years since I first met Ruth Hubbard and her husband George Wald at the conference "Towards a Liberatory Biology" in Bressanone in the Italian Alps.[1] From a broad sociopolitical perspective, Hubbard was already a leading light in the radical critique of genetic determinism—the idea that organisms are hardwired in their genetic makeup. As a research scientist who had worked on visual pigments for many years, she was by no means unaware of the hormones and enzymes encoded by genes that enable an organism to transform energy, grow, and develop in a certain way, but she insisted that there are social determinants for what people are, or are perceived to be, that are much more powerful than biology and genes.

I suspect that she was getting rather impatient with the anodyne and frequently opaque rhetoric of sociologists who fail to come to grips with the real issues, not to mention the obfuscation by some "bioethicists" who were a contradiction in terms. The unsuspecting public was left at the mercy of slick propaganda from vested interests intent on profiting by blaming people's ills on their genes and selling them both the diagnosis and appropriate remedies: abortion for the unborn, gene drugs and gene therapies for adults scared witless after having tested positive for genes that would allegedly give them incurable diseases. Ruth Hubbard's book, coauthored with Elijah Wald, *Exploding the Gene Myth: How Genetic Information Is Produced and Manipulated by Scientists, Physicians, Employers, Insurance Companies, Educators and Law Enforcers,* is admirable

for delivering its important message clearly, succinctly, and with punch and panache, true to how she is in real life.[2]

How Scientific and Social Critiques Converge

My critique of genetic determinism is based more on science than on politics, which I take broadly to be reliable knowledge of nature that enables us to live sustainably with it.[3] That is certainly not to understate the large influences that society and politics have on science and, more to the point, what passes as science, which can be very much mistaken and unreliable, as is the case of genetic determinism. Science is what we live by and hence has large implications for how we live and choose to live.

My critique converges with Hubbard's because social and environmental influences are indeed powerful determinants on how we grow and develop, precisely as Hubbard has been saying, so much so that they can mark and change our genes for life. That is what the Human Genome Project to sequence the entire human and other genomes has ended up telling us, in spite of the fact that it was inspired and promoted by genetic determinism.

The new genetics of the "fluid genome" had already emerged by the early 1980s, long before the human genome project was conceived.[4] It belongs in the organic paradigm of spontaneity and freedom ("quantum jazz biology")"[5] that defies any kind of determinism, whether biological or environmental.

A Decade of the Human Genome Yields Next to Nothing

More than ten years ago, President Bill Clinton announced the first draft of the human genome sequence and said that it would "revolutionize the diagnosis, prevention and treatment of most, if not all human diseases." Francis Collins, then director of the genome agency at the U.S. National Institutes of Health, said that genetic diagnosis of diseases would be accomplished in ten years and that treatments would enter the market perhaps five years after that.[6]

The anticlimax came just eight months later when the complete map was announced.[7] Chief gene sequencer Craig Venter admitted, "We simply do not have enough genes for this idea of biological determinism to be right." The environment, he said, is critical.

More than ten years later, genomics research has yielded no cures, and the hope of identifying genes for common diseases is fast receding. Nina Paynter and her research team at Brigham and Women's Hospital

in Boston looked at 101 genetic variants (single-nucleotide polymorphisms) from whole genome scans that had been linked to heart disease. Together, these turned out to be of no value in predicting the disease among 19,000 women in a study that tracked their health for twelve years.[8] In contrast, family history was the most significant predictor, as it had been before genomics. As Harold Varmus, now director of the National Cancer Institute, said: "Genomics is a way to do science, not medicine."[9]

Demise of Genetic/Biological Determinism

The assumption that genes are stable and insulated from environmental influences is pivotal in neo-Darwinian theory, the root and stem of genetic/biological determinism.[10] It was inspired by Weismann's theory of the germplasm, which was flawed from the start. Plants do not have separate germ cells at all; every somatic cell is potentially capable of becoming a germ cell, which is why plants can be propagated from cuttings. Most animals also do not have germ cells that separate from the rest of the body early in development. Furthermore, there is no evidence that genes in germ cells are stable or immune from environmental influences. We now know that the environment can directly affect the germ cells in the developing fetus, giving rise to the grandparent effects. Toxic environmental substances such as bisphenol A and other endocrine disrupters specifically affect germ cells in the developing fetus.[11] Even more surprisingly, sperm cells are efficient vehicles for carrying foreign (altered) genes into egg cells at fertilization,[12] and these foreign genes can be expressed in embryos developed from the fertilized eggs.[13]

Evidence that genes are neither stable nor immune from direct environmental influence has been accumulating almost since the inception of genetic engineering—applied to unraveling the detailed molecular machinery of genetics—began in the mid-1970s. To their astonishment, molecular geneticists soon witnessed classical genetics being turned upside down on their lab benches. They found exceptions and violations to every tenet of classical genetics. In direct contradiction to the concept of a relatively static genome with linear causal chains emanating from genes to the organism and the environment, they discovered constant crosstalk between genome and environment. Feedback from the environment not only determines which genes are turned on where, when, by how much, and for how long, but also marks, moves, and changes the genes themselves. By the early 1980s molecular geneticists had already coined the

term "the fluid genome"[14] to capture what I later described as a molecular "dance of life" necessary for survival.[15]

Just when we finally got used to thinking that a gene in molecular genetics was a coding sequence (eventually "read out" as an amino-acid sequence forming proteins) equipped with various control regions for start and stop that would determine how actively the gene is expressed, when, where, and for how long, we had to think again. New research is revealing how such "genes" are in bits dispersed throughout the genome, interweaving with bits of other genes.[16] As genes are intertwined, so are their functions. Multiple DNA sequences may serve the same function, and conversely, the same DNA sequence can have different functions. It is futile to try to define a gene or a separable function for any piece of DNA. This is ultimately why genes for common diseases can never be found. Incidentally, this is also why genetic modification is both dangerous and futile: human genetic engineers do not know the steps of this incredibly complex molecular dance of life.[17] All they can do, even now, is to follow and marvel at some of the footprints of this dance, marks left on the DNA and the histone proteins bound to the DNA, a script that an individual will pass on to the next generation.

Perpetuation of the Myth of Genetic Determinism in Academia

Mainstream genetics research during the decades since the discovery of DNA's double helix in 1953 has focused on identifying "genes" or a "genetic predisposition" for every "trait," real or imaginary.[18] Imaginary traits are rife in the hybrid discipline of evolutionary psychology, long dedicated to inventing stories on "selective advantage" for each of the "traits" so that the corresponding gene could become "fixed" in the population by neo-Darwinian natural selection.

Another hybrid discipline, behavioral genetics, formerly dedicated to studies based on identical twins, began identifying DNA (gene) markers for behavior and indeed claimed to have found one for an increased tendency toward violent behavior in boys who experienced maltreatment in childhood.[19] The gene encoding the enzyme monoamine oxidase A (MAOA)—involved in the metabolism of neurotransmitters—exists in two variants: one expressing high activity, the other, low activity. Although all boys in the study showed increased "disposition towards violence" if they were maltreated as children, those with low enzyme activity were purported to show an increase in violence. The researchers claimed a weak residual effect due to the low-activity MAOA while

conceding the large effect of the environment. But even this alleged genetic predisposition soon faded away as more data became available.[20]

Behavioral geneticists are not the only scientists wasting time and resources chasing will-o'-the-wisp gene markers. The project to map genetic predisposition to diseases was the main rationale for the $3 billion Human Genome Project that, decades later, has delivered next to nothing, basically because it is not genomic DNA but epigenetic environmental influences that overwhelmingly affect our health and well-being.[21]

Epigenetic Inheritance

The term "epigenetic" came from epigenesis, the process whereby an organism with differentiated organs, tissues, and cells develops from a relatively featureless egg. Developmental geneticist and evolutionist Conrad Waddington invented the concept of the "epigenetic landscape" to represent the dynamic structure of the developmental system that defines the range of nonrandom changes for evolution.[22] This was the sense in which we Ho and Saunders used "epigenetic" in 1979.[23] Nowadays "epigenetic" usually refers to a heritable change that does not involve DNA sequence alteration,[24] but that use of the term is rapidly becoming obsolete because of epigenetic mechanisms that actually change DNA sequences directly or via an RNA intermediate that undergoes editing, alternative splicing, and other processes coupled with reverse transcription.[25]

Epigenetic inheritance is effectively the inheritance of acquired traits, usually attributed to Jean-Baptiste de Lamarck (1744–1829),[26] and it has come into its own in maternal effects.

New research has abundantly confirmed the overriding importance of environmental influences across disciplines from nutrition to toxicology, and most dramatically in brain development.[27]

Neither Genetic nor Environmental Determinism Rules

For as long as anyone can remember, people have been debating whether it is our genetic makeup or the environment that determines who we are. New research findings on how maternal care has a lasting influence on her offspring's behavior that persists for generations are telling us that this is definitely not the right question to ask. The epigenetic interplay between genes and the environment puts the ball right back into our court. The question we should be asking is perhaps this: how can we give everyone the best opportunity in life?

Maternal effects on development are well known and demonstrated across many species. In mammals the long period of gestation and postnatal mother-child relationship provides maternal influences that extend well into the adult life of the offspring.

Prenatal stress and malnutrition experienced by the mother affects her neuroendocrine system and, in turn, the development of the nervous system in the fetus.[28] The care received (usually from the mother, but possibly by surrogates) during early infancy can produce changes in the development of the nervous system that regulates its response to novelty and social behavior.[29] Thus the maternal environment experienced by a developing organism can play a critical role in shaping its adult behavior.

Infant rhesus macaques socially isolated for periods of three to twelve months play much less, are highly aggressive with peers, perform poorly in learning and cognitive discrimination tasks, and are inhibited and fearful of novelty.[30] These behavioral patterns continue into adulthood and affect reproductive success, particularly in artificially reared females, who display high rates of infant abuse, neglect, and infanticide. Maternally deprived macaques also have an elevated hypothalamic-pituitary-adrenal (HPA) response to stress, impairments in learning and social behavior, and altered serotonergic systems (which regulate anxiety), suggesting that it is the disruption of the mother-infant relationship rather than the general consequence of social isolation that contributes to these effects.

In humans, environmental adversity occurring early in life is associated with an increased risk of both physical and psychiatric disorders in adulthood. The experience of childhood abuse and neglect has been demonstrated to increase the rates of diabetes and cardiovascular disease, as well as susceptibility to drug abuse, depression, schizophrenia, and anxiety-related disorders.[31]

There is substantial evidence that lack of parental care or childhood abuse can contribute to subsequent criminal behavior.[32] A study sponsored by the U.S. National Institute of Justice showed that a child who experienced neglect or physical abuse was 53 percent more likely to be arrested as a juvenile and 38 percent more as an adult compared with a child who was not neglected or abused. Another study found that 68.4 percent of male inmates from a New York State correctional institution reported childhood abuse or neglect: 71.2 percent for violent offenders and 61.8 percent for nonviolent offenders.

It has been estimated that up to 70 percent of abusive parents were themselves abused,[33] and 20 to 30 percent of abused infants are likely to become abusers. These findings in humans have been replicated in experiments on primates.[34]

Clearly the environment plays a large role, but it does not determine whether children will grow up to be criminals, any more than their genetic makeup determines what they will become. More important, changing the environment can often undo the harm that individuals or their parents have experienced in early life.

Epigenetics of Maternal Behavior

Researchers at McGill University in Montreal, Canada, and Columbia University in New York have been studying maternal behavior in rats for many years. They have found that mother rats that care adequately for their pups and others that do not do so shape their offspring's response to stress accordingly for the rest of their lives, correlated with different states of expression in relevant genes.[35]

The mother rat licks and grooms (LG) her pups in the nest and while nursing them also arches her back. Some (high-LG) mothers do that more often than others (low-LG). The offspring of high-LG mothers grow up less fearful and more able to cope with stress than those of low-LG mothers, and involves the HPA pathway of response to stress. The magnitude of the HPA stress response is a function of the corticotrophin-releasing factor (CRF) secreted by the hypothalamus, which activates the pituitary-adrenal system. The pituitary-adrenal system is in turn modulated by glucocorticoid secreted in the hypothalamus, which feeds back to inhibit CRF synthesis and secretion, thus dampening the HPA response and restoring homeostasis.

The adult offspring of high-LG mothers show increased glucocorticoid expression in the hippocampus and enhanced sensitivity to glucocorticoid feedback. This enhanced sensitivity is due to the increased expression of glucocorticoid receptors (GRs), boosted in turn by the increased expression of the transcription factor NGF-1-A that binds to the promoter of the GR gene. These differences in gene expression are accompanied by significant differences in DNA methylation (addition of methyl groups) of the GR promoter, with low methylation from offspring of high-LG mothers correlating with high expression, and high methylation from offspring of low-LG mothers correlating with low expression. The researchers also found significantly higher acetylation of histone in chromatin protein around the GR gene (consistent with active gene expression) in the offspring of high-LG mothers than in the offspring of low-LG mothers.

Interestingly, cross-fostering the offspring of low-LG to high-LG mothers and vice versa at day one after birth induced changes in the offspring in line with the foster mother, with correlated changes in the gene expression states. Foster parents can influence their children biologically.

It turns out that the different gene expression states are acquired during the first week of life and persist into adulthood. Pups of both high-LG and low-LG mothers start out practically the same. Just before birth the entire region of the GR promoter is unmethylated in both groups because most gene marks are erased in the germ cells. Changes develop according to the behavior of the mother within the critical period of the first week of life and remain stable thereafter.

Nevertheless, these changes in DNA methylation and histone acetylation can be reversed, even in adults, as demonstrated by the rather drastic method of infusing chemical activators or inhibitors into the brain, with concomitant changes in the adult's response to stress.[36] Thus infusing the histone deacetylase inhibitor trichostatin A (TSA) into the brains of offspring from low-LG mothers increased histone acetylation and decreased methylation of the GR promoter, thus boosting GR expression to levels indistinguishable from those in the brains of offspring from high-performing mothers. When these offspring were tested for anxiety levels, they performed like offspring from high-LG mothers.

On the other hand, injecting methionine, the precursor of S-adenosyl methionine (SAM), the cofactor of DNA methylase, into the brains of offspring from high-LG mothers increased methylation of the GR promoter to levels the same as those of offspring from low-performing mothers, thereby decreasing GR expression and causing them to switch their behavior accordingly to resemble that of offspring from low-LG mothers. Thus epigenetic states are stable but dynamic. They are truly plastic and give no support to any kind of determinism, genetic or environmental.

Maternal Care and Sex Hormones

What predisposes mothers to be caring or otherwise? Apparently the female offspring inherit the characteristics of their mothers with regard to maternal care, not genetically but epigenetically. The hippocampus is the "emotion center" of the brain. It is vulnerable to stress and richly supplied with receptors for the sex and reproductive hormones, and maternal care is regulated by those hormones.

In rats, the researchers found oxytocin receptors linked to the expression of maternal behavior.[37] Oxytocin (OT) is a hormone secreted by the posterior pituitary gland and stimulates the contraction of the uterus and ejection of milk. Variations in OT receptor levels in critical brain regions, such as the medial preoptic area (MPOA) of the hypothalamus, are associated with differences in maternal care. OT receptor binding in the MPOA is increased in high-LG compared with low-LG mothers. Furthermore, differences in OT receptor binding in the MPOA between high-LG and

low-LG females are dependent on estrogen, which is eliminated by ovariectomy and reinstated with estrogen replacement. However, whereas ovariectomized high-LG females respond to estrogen with an increase in OT receptor binding, low-LG females show no such effect. Studies with mice suggest that estrogen regulation of OT receptor binding in the MPOA requires the α-subtype of the estrogen receptor (ERα). ERα is a transcription factor that regulates gene transcription on binding estrogen. The cellular response to estrogen depends on the amount of ERα present.

The researchers found that by day six after birth, ERα expression in the MPOA of female offspring from high-LG mothers is significantly increased compared with that of female offspring from low-LG mothers, and this state continues into adulthood and is correlated with the female offspring of high-LG and low-LG mothers becoming high-LG and low-LG mothers accordingly. This epigenetic state perpetuates itself via the female line until and unless it is disrupted by environmental intervention.

Cross-Fostering Reverses the Damage

One effective environmental intervention is cross-fostering. The biological offspring of high- and low-LG mothers were reciprocally exchanged within twelve hours of birth and reared to adulthood. When these offspring were examined, ERα expression in the MPOA of the adult females born to low-LG mothers but cross-fostered to high-LG mothers became indistinguishable from that of the normal biological offspring of high-LG mothers; conversely, ERα expression in the MPOA of adult females born to high-LG mothers but reared by low-LG mothers resembled that of normal biological offspring of low-LG mothers. Cross-fostering in itself had no effect; exchanging offspring between two low-LG mothers or two high-LG mothers did not alter the expression of ERα in the MPOA of the offspring.

Correlated with the high and low ERα expression in the MPOA were significant differences in the methylation of cytosine-guanine (CpG) sites across the entire ERα promoter. Overall, significantly elevated levels of methylation were found in the promoter of offspring with low ERα expression in the MPOA compared with high ERα expression in the MPOA.

Maternal Care Influences Brain Development and Many Gene Functions

Obviously, maternal care influences more than a few genes. Prior to the findings detailed in the preceding sections, the McGill University team found that in rats, increased anxiety in response to stress in the offspring of low-LG mothers is associated with decreased neuronal development

and density of synapses in the hippocampus. The offspring of high-LG mothers, on the other hand, show increased survival of neurons and synapses in the hippocampus and improved cognitive performance under stressful conditions.[38] Researchers at the University of Amsterdam and Leiden University in the Netherlands have also found that the pyramidal neurons in layers 2 and 3 of the brain cortex from high- and low-LG adult rats have different morphologies.[39] The high-LG rat neurons have more slender "dendritic trees"—the branching processes receiving inputs from other neurons—with fewer branches than those from low-LG rats. The density of dendritic spines (small projections from the surfaces of the dendritic trees) is also significantly lower in high-LG rats. These observations suggest a rather extensive influence of maternal care on brain development and gene expression.

In order to examine the effect of high- and low-LG mothers and TSA or methionine infusion on gene expression, the four different treatment groups were compared with their respective control groups using microarrays to monitor changes in 31,099 unique messenger RNA transcripts.[40] A total of 303 transcripts (0.97 percent) were altered in the offspring of high-LG mothers compared with offspring of low-LG mothers: 253 transcripts (0.81 percent) upregulated and 50 transcripts (0.15 percent) downregulated. TSA treatment of offspring of low-LG mothers altered 543 transcripts (1.75 percent): 501 transcripts (1.61 percent) upregulated and the remaining 42 transcripts (0.14 percent) downregulated. Methionine treatment of offspring of high-LG mothers changed 337 transcripts (1.08 percent), with 120 (0.39 percent) upregulated and 217 (0.7 percent) downregulated.

The results suggest that maternal care during the first week of life determines the expression of hundreds of genes in the adult offspring, but changes in gene expression are nevertheless reversible even into adulthood. Caring mothers tend to activate more genes in their offspring than mothers that do not provide adequate care. TSA treatment results predominantly in gene activation, and methionine treatment results predominantly in silencing genes.

Epigenetic Effects of Enriched Environment

Researchers at Tufts University School of Medicine, Boston, Massachusetts, and Rush University Medical Center, Chicago, Illinois, have demonstrated that exposure of 15-day-old mice to two weeks of an enriched environment that includes novel objects, increased social interactions, and voluntary exercise enhances long-term potentiation not just in the

mice but also in the future offspring of female mice through early adolescence, even if the offspring never experienced the enriched environment.[41] Long-term potentiation (LTP) is a persistent increase in strength of synapses between neurons following high-frequency stimulation and is a form of synaptic plasticity known to be important for learning and memory. The effect of the enriched environment lasts for about two months and is not canceled by cross-fostering, indicating that the transgenerational effect occurs before birth, during embryogenesis. The effect is age dependent because it cannot be induced in adult mice. In both generations of mice, LTP induction is accompanied by the new appearance of a whole new signalling pathway, the cAMP/p38 MAP (mitogen activated protein) kinase-dependent signalling cascade. If the effect occurs in humans, it means that an adolescent's memory can be influenced by environmental stimulation experienced by the mother when she was young.

Epigenetic Footprints of Childhood Trauma in Humans

Are the epigenetic footprints of maternal care identified in detailed animal studies relevant to the human species? Michael Meaney and his colleagues at McGill University have extended their findings in rats to humans. They examined epigenetic differences in a neuron-specific promoter of the glucocorticoid receptor in postmortem hippocampi (twelve in each group) obtained from suicide victims with a history of childhood abuse, suicide victims with no history of childhood abuse, and nonsuicide victims who died from other causes, none of whom had a history of childhood abuse.[42]

They found decreased expression of glucocorticoid receptor and increased DNA methylation of the specific promoter that binds the transcription factor NGF1-A in suicide victims with a history of childhood abuse compared with suicide victims without childhood abuse, who were indistinguishable from controls. These are the same epigenetic footprints that the team had previously discovered in rodents that did not provide adequate maternal care.

Psychiatric disorders such as major depression and posttraumatic stress disorder are commonly connected with disorders of the cardiovascular, metabolic, and immune systems. Recent studies suggest that accelerated aging of cells may be an explanation. Telomeres are DNA repeats that cap the ends of chromosomes and make them more stable, and they shorten with each cell division, making them a marker for biological age. Physiological stress such as radiation and toxins, oxidative stress, and cigarette smoke can shorten telomeres.

The body responds to stress by the coordinated activities of several systems, including the HPA axis, the sympathetic nervous system, and the immune system. They mobilize energy and prepare the individual to cope with the stress. Chronic stress, however, can damage the endocrine, immune, and metabolic systems and may result in shortening the telomeres.

Individuals giving care to patients with Alzheimer's disease experience chronic stress, and when their white blood cells were examined, the telomeres were found to be shortened. The same telomere shortening has been linked to pessimism in healthy postmenopausal women and in patients with unipolar and bipolar mood disorders.

Researchers at Butler Hospital and Brown University Medical School, Providence, Rhode Island, have now found that stress in childhood due to maltreatment also leads to telomere shortening.[43] Telomere shortening is a major risk factor for a range of adverse conditions, including major depression, anxiety disorders, and substance abuse.

The researchers tested thirty-one adults (twenty-two women and nine men) aged 18 to 64 years, recruited via advertisement in the community for a larger study of stress reactivity and psychiatric symptoms. Of these, twenty-one reported no history of childhood maltreatment, and ten reported a history of moderate or severe childhood maltreatment. None had acute or unstable medical illness, endocrine diseases, or ongoing treatment with drugs that might influence HPA axis functions.

The maltreatment group did not differ significantly from the control group with respect to age, sex, smoking status, body mass index (a measure of obesity), hormonal contraception use in female subjects, race, education, socioeconomic status, or perceived stress. The maltreatment group had significantly shorter telomeres than the control group and was associated with both physical neglect and emotional neglect. The sample size was small, so there was no association of telomere length with age in the sample, which made the association with childhood abuse or neglect all the more significant.

Implications for Health

Although the epigenetic effects of maternal (parental) care have been worked out in the most detail in rodents, there is a potential for similar effects in other species, including primates and humans, as recent evidence indicates.

In humans, a lack of parental care or childhood abuse can contribute to subsequent criminal behavior. Furthermore, lack of parental care and

parental overprotection ("affectionless control") are also risk factors for depression, adult antisocial personality traits, anxiety disorders, drug use, obsessive-compulsive disorders, and attention-deficit disorders.[44] Conversely, people who reported high levels of maternal care were found to have high self-esteem, low anxiety, and less salivary cortisol in response to stress. Longitudinal studies demonstrated that mother-child attachment is crucial in shaping the cognitive, emotional, and social development of the child. Throughout childhood and adolescence, secure children are more self-reliant and self-confident and have more self-esteem. Secure infants also have better emotional regulation, express more positive emotion, and respond better to stress. Infant disorganized attachment has been associated with the highest risk of developing later psychopathology, including dissociative disorders, aggressive behavior, conduct disorder, and self-abuse.

Nutrition, Environmental Enrichment, and Mental Health

The dramatic effects of TSA and methionine infusion in altering gene expression patterns in rats also have obvious implications for drug intervention or, better yet, intervention and prevention through adequate nutrition.[45] Epigenetic drugs such as inhibitors of DNA methylation or histone deacetylation lack specificity[46] and may have unintended and untoward side effects.

In rats, dietary L-methionine has been shown to be crucial for normal brain development, and its deficiency has been implicated in brain aging and neurodegenerative disorders. Synthesis of SAM (a cofactor for DNA methyl transferase) is dependent on the availability of dietary folates, vitamin B_{12}, methionine, betaine, and choline. Developmental choline deficiency alters SAM levels and global and gene-specific methylation, and prenatal choline availability has been shown to affect neural cell proliferation and learning and memory in adulthood.[47] Several studies have shown that additional dietary factors, including zinc and alcohol, can affect the availability of methyl groups for SAM formation and thereby influence CpG methylation. Maternal methyl supplements positively affect the health and longevity of the offspring.

Other studies have shown that certain dietary components may act as histone deacetylase inhibitors (HDACis), including diallyl disulfide, sulforaphane, and butyrate. For example, broccoli, which contains high levels of sulforaphane, has been associated with H3 and H4 acetylation in peripheral blood mononuclear cells in mice three to six hours after consumption.

HDACis are an active area of research as anti-inflammatory and neuroprotective agents in autoimmune diseases, such as lupus and multiple sclerosis. Sodium butyrate has been shown to have antidepressant effects in mice.

The new findings on environmental intervention, such as environmental enrichment to reverse the damages of social isolation and fostering to reverse the harm of parental neglect, are indicative of the huge potential for saving our children with the appropriate social policies. All in all, these remarkable findings on the epigenetic effects of maternal care show how important it is for societies to look after the welfare of children and mothers to be in order to ensure both the mental and the physical health of future generations.