HHS Public Access

Author manuscript

Prog Mol Biol Transl Sci. Author manuscript; available in PMC 2018 December 28.

Published in final edited form as:

Prog Mol Biol Transl Sci. 2014 ; 128: 177–198. doi:10.1016/B978-0-12-800977-2.00007-3.

The Intergenerational Effects of Early Adversity

Janina Galler and **Danielle Galler Rabinowitz**

Judge Baker Children's Center, Harvard Medical School (Boston, MA)

Abstract

Early insults during critical periods of brain development, both pre- and postnatal, can result in epigenetic changes that may impact health and behavioral outcomes over the lifespan and into future generations. There is ample evidence that these early stages of brain development are sensitive to various environmental insults, including malnutrition, childhood trauma and drug exposures. The notion that such changes, both physiological and behavioral, can also carry over into subsequent generations has long been recognized, especially in the context of experimental studies. However, epigenetic mechanisms capable of explaining such phenomena were not available until relatively recently, with most of this research published only within the last decade.

Keywords

Intergenerational; Malnutrition; Humans; Rats; Trauma; Epigenetics; Drug Abuse

Introduction

This chapter sets out to identify the significant findings of intergenerational studies of the impact of various environmental factors on brain and behavior. First, we examine the available literature relating to research conducted on the effects on multiple generations of malnutrition, early adversity and trauma, and chemical exposures in both human populations and rat models. Second, we provide detailed results from the Barbados Nutrition Stud and parallel rat studies in our laboratory. Third, we seek to highlight recent studies that have begun to look at underlying epigenetic mechanisms of such intergenerational transmission.

Intergenerational Studies of Malnutrition: Human.

Although the long-term effects of childhood malnutrition are now widely recognized [1, 2]studies documenting transgenerational effects of poor nutrition are less common. As early as 1949, Mussey considered: "It must be borne in mind that the diet of a given generation may effect several generations hence" [3]. The recent advances in epigenetic research associated with adversity during early development have resulted in an increasing number of pertinent studies that suggest intergenerational effects of poor nutrition and other environmental factors. These include both studies in human populations and pre-clinical investigations in animal models.

The earliest studies of the transgenerational effects of poor nutrition were almost exclusively based on work with low birth weight infants within Western populations. More recently, this work has expanded to include studies in developing regions of the world. Although not

always exclusively the result of poor nutrition, low birth weight is most prevalent in socioeconomically deprived populations and is thus closely associated with poverty. In the late 1950s, Sir Dugald Baird and his colleagues in Aberdeen, Scotland, followed a cohort of women who were short in stature and had an increased number of birth complications, likely associated with a history of inadequate nutrition during their own childhoods [4], [5], [6]. Follow up studies of this cohort revealed that the offspring of these women were more likely to have lower IQ scores than children of mothers of average height [7], [8]. One prevailing hypothesis was that maternal malnutrition resulted in aberrant pelvic shapes, ultimately translating to impaired reproductive competence. Although other possible mechanisms leading to transgenerational effects of poor nutrition were not recognized, this early study highlighted the important role of adequate maternal nutrition in preserving cognitive function from one generation to the next. Other studies, including those of Ounstead et al. [9], Hackman [10], and Emanuel et al. [11], similarly reported that women who were of low birth weight were more likely to have offspring who were of low birth weight, thus affirming the risk of poor intergenerational outcomes with respect to infant size [12].

The association between poor nutrition and birth weight has also been documented in epidemiologic studies of survivors of the Dutch Famine [13]. This series of studies showed that *in utero* exposure to malnutrition, especially during the 2nd and 3rd trimesters of pregnancy, was associated with decreased birth weights of infants even after correcting for maternal stature. Studies of transgenerational effects of birth weight have also been reported in developing countries, including Brazil, where maternal (but not paternal) birth weight and weight gain in early childhood was shown to be positively associated with birth weights in the next generation [14]. The persistence of low birth weight across generations was originally referred to as the Intergenerational Influences Hypothesis [15].

The Barker or the Developmental Origins of Health and Disease Hypothesis [12], as it is now referred to, states that low birth weight inevitably leads to a number of adult medical conditions including metabolic syndrome, cardiovascular disease [16], and other health-related phenotypes, which are all programmed prenatally and modified by a limited nutrient supply during within the early stages of development [17]. In their initial studies, Barker et al. [18, 19] found that small, normal-term babies had an increased risk of hypertension and other cardiovascular diseases later in life, a finding that has been successfully replicated in a number of epidemiologic studies [20], [21],[22]. The association between prenatal malnutrition, low birth weight and adult-onset diabetes and obesity have also been reported among survivors of the Dutch Famine [23]. Although glucose intolerance was not increased in the adult survivors of the siege of Leningrad, an increased prevalence of obesity and hypertension were identified [24]. In a Finnish cohort of adults born between 1933 and 1944, poor maternal nutrition and low birth weight were also correlated with an increased rate of obesity [25], cardiovascular disease and associated mortality [26, 27]. These medical conditions in adulthood may, in turn, compromise pregnancy and the in utero experience of the offspring, thereby contributing to the intergenerational transmission of malnutrition-related deficits. More recently, many of the low birth weight cohorts have been reassessed and have been found to have higher rates of mental health disorders and cognitive/behavioral impairments in adulthood [28–30]. These adverse mental health outcomes may directly

impact the health and well-being of the next generation, as they contribute to impaired parenting and compromised educational, occupational and socioeconomic opportunities.

Previous research in humans has documented transgenerational effects of poor maternal nutrition on growth and health outcomes. Kaati et al., who examined nutrition-related factors among 15,000 Swedish men and women born between 1915 and 1929 [31] reported that the limited food supply available to the paternal grandparents increased the risk of mortality (and diabetic deaths) of their grandchildren. These data also confirmed the sex-specific, male line transmission of nutritional deficiency across generations. The 50 year follow-up of the grandchildren of survivors of the Dutch Famine revealed higher rates of neonatal adiposity [32] and higher BMIs [33], both a result of maternal exposure to undernutrition. These findings corroborated earlier research findings by [34] who already identified that there may be long-term biological impacts into the next generation not directly corresponding to birth weight.

Complementing the studies on the implications of nutritional deficits, the effects of good nutrition during childhood have been shown to positively impact growth in the next generation. Protein supplementation of mothers and young children in a nutritionally and socioeconomically disadvantaged population in Guatemala, the INCAP study, improved the nutritional status of the supplemented women, their children and grandchildren [35], [36]. The protein-supplemented (atole) women gave birth to progeny, especially males, who were significantly taller than the children of mothers who received the no protein, low-energy (fresco) supplements. This study, therefore, clearly identified the potential reversibility of certain nutritional deficits over two generations.

Long-Term and Intergenerational Effects of Postnatal Malnutrition: The Barbados Nutrition Study

Although the vast majority of studies of the developmental origins of health and disease have focused on maternal malnutrition, there is ample evidence that poor nutrition in the postnatal period may also lead to long-term, adverse effects on health, behavior and cognition. Thus, studies that have followed stunted children or children with early childhood malnutrition have reported cognitive and behavioral deficits lasting to 22 years of age [1, 37, 38]. Similar mechanisms to those involved in perturbations associated with prenatal maternal undernutrition may be at play, including effects on programming, gene expression and environmentally-mediated epigenetic changes. [39] [40] and others [41] have long recognized the importance of the timing of insults during the prenatal and postnatal periods with respect to brain development in different species. Typically, adverse environmental exposures in the human, including nutritional deficits and other developmental insults, result in permanent changes to the brain if they occur during pregnancy through two years of age. Changes associated with insults occurring after this critical period of brain development are generally considered reversible.

Because of malnutrition’s profound effects on neuronal growth, nutritional insults during infancy and early childhood put individuals at risk for lifelong impairment. These deficits can result in poor health, lower educational attainment and diminished social status in

adulthood. If the affected individuals themselves become parents, the impact of their early nutritional insult may even extend into the next generation. Thus, while there are numerous direct effects of childhood insult on brain and behavior, there may also be indirect effects of a social nature. Socioeconomic status is a powerful predictor of intellectual functioning and academic achievement, and the decreased social status of the parents has the potential to translate to intellectual compromise in their children, despite adequate nourishment throughout their development.

We consequently opted to examine the direct and indirect effects of childhood malnutrition in the context of the Barbados Nutrition Study, a 47-year longitudinal and now intergenerational study based on an epidemiologic sample of children who had experienced an episode of moderate to severe protein-energy malnutrition in the first year of life. The development of these children was compared, using a case control design, with that of healthy children recruited from the same neighborhoods and classrooms. Following their hospitalizations, study participants were enrolled in a nutritional intervention program that monitored their growth and development and assured adequate nutrition and good health from infancy to 12 years of age. Thus, for individuals initially identified as malnourished, our intervention guaranteed that their malnutrition episodes were limited to the first year of life; healthy controls had no growth failure or malnutrition throughout their lives. All participants were followed, at regular intervals, from early childhood to middle adulthood as part of their enrollment in the Barbados Nutrition Study.

Although the previously malnourished children achieved complete catch-up in their physical growth by adolescence [42], we found that their cognitive and behavioral development remained adversely affected. A key finding from the Barbados Nutrition Study was the four-fold increase in attention deficits (from 15% to 60% of participants) throughout childhood, adolescence, and adulthood as compared to healthy controls [43–45]. In childhood and adolescence, the previously malnourished cohort also demonstrated lower IQ scores [46], poor academic performance [44] and increased mood and behavioral problems [47, 48] relative to the control group. Differences in academic performance between groups were largely assessed through analysis of grade reports and scores on the national eleven-plus examination, a test required for entrance into secondary schools on the island. [44]

When assessed at 40 years of age, the previously malnourished participants demonstrated continuing deficits in attention [49] and cognition [50]. In comparison with unaffected peers, the adults with histories of infant malnutrition had higher rates of attention deficits and lower IQ, approximately one standard deviation in magnitude, even after adjusting for the effects of childhood socioeconomic circumstances. In addition, approximately 25% of previously malnourished participants had IQs in the range of intellectual disability, and this prevalence rate was nine times higher than in the control group. Behavioral and neuropsychological tests conducted at this time also showed increased prevalence of maladaptive personality traits [49] and cognitive rigidity, slow processing and impaired cognitive control [51]. The long-lasting differences identified between the two study groups underscored outright the lack of brain plasticity and the irreversible nature of the nutritional insult despite comprehensive intervention.

In addition to the increased behavioral and cognitive impairments in the affected Barbados Nutrition Study cohort, there were also identifiable differences in social outcome between malnourished and control participants. Of note were the poorer socioeconomic outcomes observable among the previously malnourished individuals [52]. This was demonstrated through the substantially widening gap in weekly household income between the index and control groups over their life spans, likely mediated by differences in behavioral and cognitive functioning. We also speculated that the reduced socioeconomic circumstances of these individuals could very likely impact the cognitive development of their children, thereby perpetuating the effects of the original insult into the next generation.

In the most recent phase of the Barbados work, we have opted to assess functioning in the offspring of the previously malnourished individuals and of the healthy comparison group. Initial results indicated significant transgenerational effects on attention and cognitive performance. Importantly, differences on measures of attention, IQ and executive control were similar to those seen in the original cohort, even though this generation had never personally experienced any episodes of malnutrition. Parallel epigenetic studies of the G1 and G2 participants confirmed altered gene expression (Schahram Akbarian et al, unpublished data). In these preliminary epigenetic analyses, we found significant correlations between DNA methylation levels with metabolic indexes and various metrics for adverse cognitive and behavioral outcomes. These results are currently being validated.

Intergenerational Studies of Malnutrition: Animal Studies

Animal studies have provided the clearest evidence of intergenerational effects of malnutrition on brain and behavioral outcomes. Although these findings cannot be directly extrapolated to the human [53],[41], they provide a clear indication that long-term research on malnutrition in human populations is necessary. Early animal studies by Cowley and Greisel [54] over three generations, and by Chow [55] over two generations, demonstrated that the nutritional status of the rat mother had effects on the growth and development of subsequent generations of rats. Later, by Bresler and Zamenhof [56, 57] lengthened the time frame of their study and also expanded the research criteria to include behavioral parameters. In studies that extended to ten generations of both maternal and paternal malnutrition, these investigators demonstrated increasing growth and behavioral deficits over each subsequent generation. In a parallel series of studies, Stewart et al [58, 59] similarly reported a pattern of increasing growth deficits involving both body length and weight in rats with up to twelve generations of moderate protein malnutrition (8% protein diet versus 25% for controls). Subsequently, they also documented that, after exposure to 10–12 generations on the low protein diet, three generations of rehabilitation on an adequate protein diet were required for the rats to achieve the same growth rate as control rats, but performance on a Lashley jump stand did not improve [60]. When we were given the original Stewart colony in 1973, in the meantime transferring the rats from England to Cambridge, MA, the research focus was broadened to include comprehensive studies of behavioral and cognitive outcomes following intergenerational malnutrition[61–72].

In the ensuing series of reports, malnutrition exposure was extended to twenty generations, which was then followed by a period of nutritional rehabilitation that sought to reverse the

effects of the nutritional deficits within one to four generations [66], [64], [70]. The rats were divided into two groups and were provided with either a low protein diet (7.5% casein) or an adequate level of protein (25% casein), with supplementation of methionine added to both diets. A third group was derived through cross-fostering a select number of rats from the low protein, intergenerationally malnourished group to healthy control mothers; these rats were then provided with adequate nutrition after weaning (25% casein) and studied over the next few generations. We found that deficits in mother-pup interaction [68, 69, 71] persisted up to four generations after instituting dietary rehabilitation. In studies of the pups during their early development we identified significant deficits persisting to four generations of nutritional rehabilitation on a test of home-orienting behavior, which allows pups to find the maternal nest when displaced from it. [64, 67]. Further, we confirmed that, in adulthood, rats with histories of intergenerational malnutrition were significantly more impaired on learning tests than animals with a single generation of malnutrition[65, 70]. Following dietary rehabilitation for up to two generations, we documented recovery on the Lashley jump stand test among the females, but observed no such recovery in the males [70].

Studies of growth and development in this colony showed that rats given a low-protein diet for multiple generations were stunted in size, but physical growth relative to controls was quickly recovered after the administration of an adequate protein diet. In fact, after one generation on the adequate (25%) protein diet, we found that physical growth exceeded growth rates observed in the control rats [69]. Further, in the first-generation rehabilitated animals, we found that they exhibited increased reproductive incompetence in adulthood as compared to controls [73]. Thus, while physical size recovered quickly after dietary rehabilitation, reproductive competence and certain behavioral and cognitive functions were impaired, even after several generations. Similar to the Barker Hypothesis [12], our data suggested the presence of biological adaptations to the intergenerational history of malnutrition, changes which persisted long after an adequate diet was provided. Because these experimental studies were carried out many years ago, however, mechanisms underlying the transgenerational effects we observed, including possible epigenetic mechanisms, were not studied and remain unknown.

Finally, it is interesting to note that findings exhibited in a series of animal studies of intergenerational malnutrition on insulin production are parallel to our own findings on the long-term effects of malnutrition in both rats and humans. Reusens et al. and Pinheiro et al. looked at long-term and transgenerational effects of maternal malnutrition in the rat through analysis of the endocrine pancreas and associated transmission of altered glucose metabolism [74, 75]. Aets and Van Assche found that prenatal malnutrition was linked with diabetogenic effects in the adult offspring, which resultantly impacted their pregnancies and the next generation [76]. Another study examining the inheritance of an insulin-resistant phenotype also demonstrated the transgenerational presence of abnormal glucose metabolism, similarly supporting the conclusion of nutritionally induced heritable mechanisms [77]. Thus, pre- and postnatal malnutrition in the rat have been implicated in an increased risk of transgenerational diabetes.

Relatedly, in both US and Belgian studies, experimental diabetes, produced by injecting streptozotocin (a beta cell killer) in utero, has been associated with increased prevalence of

diabetes over several generations [78], [79]. These studies indicate that the offspring of treated females ultimately developed diabetes, in turn producing offspring with a greater likelihood of developing diabetes than the offspring of non-diabetic mothers. The offspring of the second-generation pregnancies also had abnormal glucose tolerance tests.

The relevance of the findings of these animal studies may also lie in their direct relationship to results previously procured in human populations, such as that of the Pima Indians, whose diabetes appears to be generationally transmitted [80], and other high-risk populations with prior exposure to malnutrition. These populations, including that of the Dutch Famine Study [81], the Chinese Famine [82] and the Barbados Nutrition Study and have at this point already demonstrated an increased rate of diabetes within a transgenerational context.

In summary, despite the paucity of published human and animal studies relating to intergenerational malnutrition, the consistency of the existing evidence strongly supports the intergenerational effects of malnutrition on brain and behavior. Likely mechanisms underlying these effects, which require further investigation, can include environmentally-induced epigenetic changes that often result in a compromised intrauterine environment and altered programming and gene expression. In addition, a history of malnutrition is also associated with aberrant patterns of child-rearing and fewer educational and professional opportunities, factors that may both impact future generations.

Intergenerational Studies of Early Adversity and Trauma: Human and Animal Studies

Environmental factors including early life adversity and trauma exposure may also play an important role in contributing to the risk of psychological disorders in adulthood and transgenerationally As is the case in studies of malnutrition, the impact of early childhood trauma is similarly thought to be mediated in large part by epigenetic mechanisms that can alter gene expression and perpetuate life-long effects into subsequent generations [83, 84]

To this end, a recent study by Yehuda et al. identified an increased risk of PTSD and mood disorders, including anxiety disorders and, to a less extent, substance abuse disorders, in the offspring of Holocaust survivors [85, 86]. These investigators found that maternal PTSD was specifically associated with increased reports of PTSD in the adult offspring. Moreover, relative to controls, these adult offspring reported having higher levels of childhood trauma through self-administered surveys, especially trauma categorized as emotional abuse and neglect. The extent of perceived childhood abuse was significantly correlated with the severity of PTSD reported by these subjects. In addition, the degree of childhood emotional abuse was found to be precisely associated with 24-hour urinary cortisol levels. This study suggested that the experience of childhood trauma may represent an important link in the transmission of PTSD from parent to child.

Although Yehuda et al. (2008) looked predominantly at environmental factors that may play a role in the transgenerational transmission of PTSD, other studies have confirmed the importance of maternal care relevant to such transmission. A recently conducted study involving a population of children whose parents were exposed to the Rwandan genocide

serves as one such example [87]. This study suggested that child rearing practices were most closely aligned with the resultant onset of a child's PTSD and that the increased familial risk could not be explained by genetics alone, or by other factors such as parenting constitutional factors, namely temperament. Thus, although constitutional factors may play an important role, the authors of this report highlighted the importance of the rearing environment for young children and their mental health. Interestingly, another recent study demonstrates explicitly that perceived maternal care in childhood can modify fetal growth of the next-generation offspring, of which brain development is major part. Neuwald et al.[88] reported that fetal growth interacts with perceived maternal care by the mother as a child and affects attentional skills of the offspring at 18 months of age. The findings of both of these studies further support the role of environment as a modifier of trauma transmission. Epigenetic changes may provide an explanation as to how such transmission occurs.

Relatedly, an epigenetics-centered follow-up of Yehuda et al.'s 2008 PTSD cohort found the previously identified transgenerational outcomes associated with trauma to be linked to changes in the glucocorticoid receptor [89]. Adult offspring of Holocaust survivor mothers with PTSD had higher levels of GR-1 methylation than controls. However, offspring with two parents with a history of PTSD demonstrated lower levels of GR-1 methylation, a finding which was also associated with greater post-steroid cortisol suppression. A study by McGowan et al. similarly implicated abuse in the early environment in the establishment of altered methylation patterns in the brain, especially that of the glucocorticoid receptor [90]. Methylation in the neuron-specific glucocorticoid receptor promoter in the brains of suicide victims who experienced childhood abuse was significantly higher than those measured in suicide victims who were not abused, or in controls. Increased methylation was correlated with decreased glucocorticoid receptor expression in these brains [90].

The demonstrated relationship in humans between mental health disorders and childhood maltreatment have led researchers to investigate the potential role of changes in DNA methylation using animal models. In the rat, variations in the amount of maternal care provided during the litter period has been shown to impact the pattern of DNA methylation in the pup's brain at adult ages. Based on naturally occurring individual differences in maternal care provided by female rats, [91–93] explored epigenetic mechanisms that may underlie such variations. Female rats were selected based on their nurturing ability and placed in two experimental groups, high archback nursing and licking/grooming (ABN-LG), and low ABN-LG. Studies of pups reared by high ABN-LG mothers showed that these pups, when adult, had higher glucocorticoid receptor (GR) expression in the hippocampus and stronger glucocorticoid feedback sensitivity than pups reared by low ABN-LG mothers [94]. The pups with high ABN-LG rearing showed lower levels of DNA methylation in the promoter region of the glucocorticoid receptor and an associated increase in binding of the nerve growth factor-inducible protein-A transcription factor to the promoter region of GR [94]. In a follow-up study, Weaver et al. reported that all effects of high ABN-LG rearing could be reversed in the adult offspring by intracerebroventricular infusion of L-methionine, which acts as a methyl group donor [95]. The results obtained from the later study suggest that certain epigenetic changes established during the early postnatal period of development of the rat can be reversed in adulthood, thus emphasizing the plasticity of the adult rat brain with regard to the epigenome.

In another study of early life maltreatment, rat pups received daily abusive maternal care from non-biological mothers in the first week of life (postnatal days 1 to 7), which included stepping, dropping, dragging, and active avoidance [96]. The maltreated pups in this study were reported as having reduced BDNF expression and increased BDNF methylation in the prefrontal cortex as adults. The maternal abuse during early development led to poor mothering in the exposed female offspring when they reared their own young; cross-fostering to healthy mothers did not fully reverse these changes in methylation levels [96]. Altered BDNF methylation in the brain of the offspring from the maltreated mothers may have resulted (1) from transmission of methylation via the gametes or (2) changes in methylation elicited by the transmission of poor maternal care across generations.

These findings are noteworthy because, in humans, increased methylation of the BDNF gene in the frontal cortex is associated with major psychoses, including schizophrenia and bipolar disorder [97]. Thus, maltreatment during early development may not only predispose individuals to adverse mental health outcomes but may also predispose their offspring to similar conditions via transmission of abnormal methylation patterns across generations.

Other Intergenerational Studies: Chemical Exposures

Recent evidence of intergenerational effects of pre-conception drug abuse has been summarized in a review by Vassoler et al. [98]. Parental abuse of drugs, even without direct fetal exposure, may impact the physiology and behavior of the offspring and later generations. Given the difficulty in separating out human abuse from other environmental and biological factors associated with addiction, including malnutrition, most available studies to date have made use of animal models, and epigenetic mechanisms are thought to underlie these effects [99].

Alcohol, the most common drug of abuse worldwide, has been reported as producing changes in basal activity levels in both humans [100] and in rodents[101]. Additionally, documented behavioral effects include impaired learning, memory and attention in both human studies [102] and rodent models [103, 104], and also increased anxiety and depression-like phenotypes in rodents [105, 106].

In the human, there is limited evidence of intergenerational transmission relating to both maternal and paternally-linked alcohol abuse [107]. A recent three generation study reported an increased risk of alcohol abuse in the G3 offspring [108]. Jamerson et al. identified that paternal alcohol exposure of rats that ended prior to fertilization resulted in neurobehavioral changes in the progeny [109]. Animal studies have also confirmed transgenerational effects of other drugs of abuse in non-exposed offspring, including those of parental [110] opioid [111] and cocaine [112] use.

Because most of the reported human and animal studies of drug abuse have only been conducted across two generations, further generations need to be studied to confirm epigenetic mechanisms impacted by such insults. Analyses of studies that have preliminarily looked beyond two generations seem to suggest that the behavioral and cognitive phenotypes persist. The specific mechanisms underlying the generational transmission of alcohol and

drug abuse remain unknown, however, and may be associated with underlying epigenetic phenomena, a likely possibility given the evidence of patrilineal inheritance patterns accompanying most of these exposures.

Intergenerational Transmission: Epigenetic Mechanisms

Recent advances in science and technology have underscored the plausibility of attaining precise biological mechanisms to explain the transgenerational transmission of the effects of various early environmental insults, and there is already evidence that points to the ability of environmental factors, especially those of nutrition and trauma, to alter chromatin state. For example, a current report directly links nutritional intake and epigenetic transmission to the next generation in a group of 18–45 year old Gambian women [113]. In this study, analysis of 12 plasma biomarkers confirmed that seasonal variations modified the intake of specific methyl-donor groups, especially those associated with Vitamin B6 and folate. The level of these biomarkers predicted increased or decreased methylation at metastable epialleles in DNA extracted postnatally from lymphocytes and hair follicles of their infants. The findings from this study demonstrated that maternal nutritional status in the periconception period resulted in persistent and systemic epigenetic changes in human metastable epialleles that are passed on to the next generation. The functional consequences of these changes, however, remain unknown. As such, transgenerational epigenetic inheritance is the best candidate mechanism to explain such transgenerational effects, especially those associated with male-line transmission, which have now been reported in a number of studies relating to both malnutrition [31] and drug abuse [114].

The potential role of epigenetic mechanisms has also been noted in a number of papers documenting evidence of changes in DNA methylation many years after exposure to malnutrition, including the 60-year follow-up study of the prenatally malnourished offspring of women exposed to the Dutch Famine [115]. When compared with same-sex siblings who had no exposure to prenatal malnutrition, the exposed study participants demonstrated a reduction in DNA methylation of the imprinted IGF2 gene, a gene with an important role in determining growth and development. This association was specific for periconceptional exposure, reinforcing the conclusion that early stages of development are critical for establishing and maintaining epigenetic marks. In another study by the same group, lower methylation levels of the INSIGF gene and higher levels of methylation in *IL-10, LEP, ABCA1, GNASAS* and *MEG3* genes were also reported in adulthood [116]. These genes are known to play a role in inflammatory and metabolic processes, as well as cardiovascular disease.

In animal studies of maternal malnutrition, there is already confirmed evidence that methylation changes may occur in the context of reduced maternal dietary intake at levels that do not necessarily impact birth weight. For example, a 30% reduction in maternal intake altered gene expression and methylation levels in monkey kidneys in the absence of any demonstrable reduction in birth weight [117, 118]. Functional consequences of such “hidden forms” of malnutrition in the rat have previously been reported as capable of producing brain and behavioral deficits without impacting size at birth or postnatal growth rates [119].

Hence, use of birth and postnatal size as a proxy for perinatal health status is inadequate and should be supplemented by more comprehensive nutritional measurements.

Although numerous human and animal studies have identified changes in gene expression, the mechanisms underlying transgenerational transmission are not yet well understood. The intergenerational reappearance of acquired epigenetic marks, which was once deemed impossible, has now been documented in both plants and animals [114]. It was previously thought that the process of epigenome erasure and resetting during fertilization excluded any possibility of intergenerational transmission of acquired epigenetic marks. This conclusion evolved from early studies showing that global DNA-methylation levels were much lower after fertilization when compared with methylation levels present in mature gametes and after implantation. While it is true that most of the acquired marks are, in fact, likely erased early after conception, the emphasis of current research is now on how and why certain acquired marks survive classical intergenerational reprogramming.

In fact, it has been suggested that demethylation of the genome following fertilization may in fact be nonexistent. This conclusion is attributed largely to the work of Li et al., who observed instead that such demethylation in mice appears to be the result of antigenic masking. Through the employment of a variety of different testing methods, these researchers demonstrated that methylation was maintained after fertilization and throughout early embryo development [120]. Franklin and Mansuy similarly demonstrated epigenetic modifications of the genome in a mouse model, successfully tracing such changes through several generations [121].

Relevantly, alterations in DNA-methylation of several genes have now been observed in sperm of both F2 and F3 males of early stressed mice [122]. Radford et al. recently published a high profile transgenerational study in a mouse model of malnutrition that was the first to report explicit alterations of the germline DNA methylome [123]. In this model, malnutrition was induced through restriction of the maternal diet in the last week of pregnancy [124]. While decreased methylation in the Radford study was not maintained in adult males in the next generation, locus-specific gene expression was nevertheless perturbed. Hence, these studies strongly suggest that acquired modifications in behavior and brain function due to malnutrition and other environmental stressors are transmitted to later generations through the germline.

Finally, because environmental influences can alter the epigenetic profile not only of the child-bearing female but also of her developing fetus, it has been proposed that changes in the second generation are not truly transgenerational. Graff and Mansuy [125] have therefore suggested that even in animal models, only effects documented in the third generation should truly be considered as intergenerational effects[125] [126]. Further epidemiologic and basic research is consequently needed to document intergenerational changes in pre-clinical and human populations, in order to identify specific patterns of epigenetic change and their explicit relationship to brain and behavioral functions. Future studies of this nature are also necessary to foster the development of realistic approaches to reversing environmental effects on programming.

Conclusion

Early insults during critical periods of brain development, both pre- and postnatal, can result in epigenetic changes that may impact health and behavioral outcomes over the lifespan and into future generations. There is ample evidence that these early stages of brain development are sensitive to various environmental insults, including malnutrition, childhood trauma and drug exposures. The notion that such changes, both physiological and behavioral, can also carry over into subsequent generations has long been recognized, especially in the context of experimental studies. However, epigenetic mechanisms capable of explaining such phenomena were not available until relatively recently, with most of this research published only within the last decade.

Although researchers have clearly demonstrated chromatin modifications in animal studies involving early environmental stressors and their long-term effects on behavior and brain function, there are relatively few intergenerational studies involving human populations. As such, future long-term research is needed in order to more precisely document the impact of chromatin remolding on changes in the brain and the intergenerational transmission of these effects.

Acknowledgments

This research was supported by grants (to JRG) from the National Institute of Health (HD060986 and MH 074811). We also acknowledge the contributions of the late Dr. Peter Morgane and the late Sir Dr. Frank C. Ramsey, who were integral to our research program on the long-term effects of childhood malnutrition.

References

1. Grantham-McGregor S, et al., Developmental potential in the first 5 years for children in developing countries. Lancet, 2007 369(9555): p. 60–70. [PubMed: 17208643]
2. Prado EL and Dewey KG, Nutrition and brain development in early life. Nutr Rev, 2014 72(4): p. 267–84. [PubMed: 24684384]
3. Mussey RD, Nutrition and human reproduction; an historical review. Am J Obstet Gynecol, 1949 57(6): p. 1037–48. [PubMed: 18127594]
4. Baird D, The contribution of obstetrical factors to serious physical and mental handicap in children. The Journal of Obstetrics and Gynaecology of the British Empire, 1959 66: p. 743–7. [PubMed: 13795907]
5. Thomson A, Maternal stature and reproductive efficiency. The eugenics review, 1959 51(3): p. 157. [PubMed: 21260778]
6. Thomson AM and Billewicz WZ, Nutritional status, maternal physique and reproductive efficiency. The Proceedings of the Nutrition Society, 1963 22: p. 55–60. [PubMed: 13981226]
7. Birch HG, et al., Mental Subnormality in the Community: A Clinical and Epidemiological Study. 1970, Baltimore, MD: Williams and Wikens.
8. Birch HG and Gussow JD, Disadvantaged Children: Health, Nutrition and School Failure. 1970, New York, NY: Harcourt, Brace & World.
9. Ounstead M, Scott A, and Ounstead C, Transmissions through the female line of a mechanism constraining human fetal growth. Annals of Human Biology, 1986 13: p. 143–151. [PubMed: 3707043]
10. Hackman E, et al., Maternal birth weight and subsequent pregnancy outcome. JAMA: the journal of the American Medical Association, 1983 250(15): p. 2016–9. [PubMed: 6620503]

11. Emanuel I, et al., Intergenerational studies of human birthweight from the 1958 birth cohort. 1. Evidence for a multigenerational effect. British Journal of Obstetrics and Gynaecology, 1992 99(1): p. 67–74. [PubMed: 1547177]
12. Barker DJP, Mothers, Babies and Health in Later Life. 1998, Edinburgh: Churchill Livingstone: A Division of Harcourt, Brace and Company Limited.
13. Lumey LH, Decreased birthweights in infants after maternal in utero exposure to the Dutch famine of 1944–1945. Paediatr Perinat Epidemiol, 1992 6(2): p. 240–53. [PubMed: 1584725]
14. Horta BL, et al., Intergenerational effect of weight gain in childhood on offspring birthweight. Int J Epidemiol, 2009 38(3): p. 724–32. [PubMed: 19376883]
15. Emanuel I, Maternal health during childhood and later reproductive performance. Ann N Y Acad Sci, 1986 477: p. 27–39. [PubMed: 3545017]
16. Barker DJ, et al., Fetal nutrition and cardiovascular disease in adult life. The Lancet, 1993 341(8850): p. 938–941.
17. Nathanielsz PW and Nathanielsz P, Life in the Womb: The Origin of Health and Disease. 1999: Promethean Press Ithaca, NY.
18. Barker DJ, et al., Fetal and placental size and risk of hypertension in adult life. Bmj, 1990 301(6746): p. 259–62. [PubMed: 2390618]
19. Barker DJ, Coronary heart disease: a disorder of growth. Horm Res, 2003 59 Suppl 1: p. 35–41.
20. Forsen T, et al., Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow up study. British Medical Journal, 1997 315(7112): p. 837–40. [PubMed: 9353502]
21. Leon DA, et al., Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. Bmj, 1996 312(7028): p. 401–6. [PubMed: 8601110]
22. Rich-Edwards JW, et al., Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. Bmj, 1997 315(7105): p. 396–400. [PubMed: 9277603]
23. Ravelli AC, et al., Glucose tolerance in adults after prenatal exposure to famine. Lancet, 1998 351(9097): p. 173–7. [PubMed: 9449872]
24. Stanner SA, et al., Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study. Bmj, 1997 315(7119): p. 1342–8. [PubMed: 9402775]
25. Salonen MK, et al., Role of childhood growth on the risk of metabolic syndrome in obese men and women. Diabetes Metab, 2009 35(2): p. 94–100. [PubMed: 19246228]
26. Barker DJ, et al., Size at birth and resilience to effects of poor living conditions in adult life: longitudinal study. Bmj, 2001 323(7324): p. 1273–6. [PubMed: 11731388]
27. Kajantie E, et al., Size at birth as a predictor of mortality in adulthood: a follow-up of 350 000 person-years. Int J Epidemiol, 2005 34(3): p. 655–63. [PubMed: 15764690]
28. Lahti M, et al., Growth in infancy and childhood and hospitalization for personality disorders in adulthood: the Helsinki Birth Cohort Study. Journal of Personality Disorders, 2011 25(5): p. 620–33. [PubMed: 22023299]
29. Lahti M, et al., Trajectories of physical growth and personality dimensions of the Five-Factor Model. J Pers Soc Psychol, 2013 105(1): p. 154–69. [PubMed: 23713700]
30. Raikkonen K, et al., Growth trajectories and intellectual abilities in young adulthood: The Helsinki Birth Cohort study. Am J Epidemiol, 2009 170(4): p. 447–55. [PubMed: 19528290]
31. Kaati G, et al., Transgenerational response to nutrition, early life circumstances and longevity. Eur J Hum Genet, 2007 15(7): p. 784–90. [PubMed: 17457370]
32. Painter RC, et al., Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. Bjog, 2008 115(10): p. 1243–9. [PubMed: 18715409]
33. Veenendaal MV, et al., Transgenerational effects of prenatal exposure to the 1944–45 Dutch famine. Bjog, 2013 120(5): p. 548–53. [PubMed: 23346894]
34. Lumey LH and Stein AD, Offspring birth weights after maternal intrauterine undernutrition: a comparison within sibships. Am J Epidemiol, 1997 146(10): p. 810–9. [PubMed: 9384201]
35. Stein AD, et al., Prospective study of protein-energy supplementation early in life and of growth in the subsequent generation in Guatemala. Am J Clin Nutr, 2003 78(1): p. 162–7. [PubMed: 12816786]

36. Behrman JR, et al., Nutritional supplementation in girls influences the growth of their children: prospective study in Guatemala. Am J Clin Nutr, 2009 90(5): p. 1372–9. [PubMed: 19793851]
37. Walker SP, et al., Child development: risk factors for adverse outcomes in developing countries. Lancet, 2007 369(9556): p. 145–57. [PubMed: 17223478]
38. Venables PH and Raine A, Poor nutrition at age 3 and schizotypal personality at age 23: the mediating role of age 11 cognitive functioning. American Journal of Psychiatry, 2012 169(8): p. 822–30. [PubMed: 22772085]
39. Dobbing J, Vulnerable periods of brain development. In: Lipids, Malnutrition & theDdeveloping Brain. Ciba Foundation Symposium, 1971: p. 9–29.
40. Morgane PJ, et al., Prenatal malnutrition and development of the brain. Neurosci Biobehav Rev, 1993 17(1): p. 91–128. [PubMed: 8455820]
41. Galler JR, Shumsky JS, and Morgane PJ, Malnutrition and brain development, in Nutrition In Pediatrics: Basic Science and Clinical Application, Walker WA and Watkins JB, Editors. 1996, J. B. Decker Europe, Inc: Neuilly-sur-Seine, France p. 196–212.
42. Galler JR, et al., Long-term effects of early kwashiorkor compared with marasmus. I. Physical growth and sexual maturation. Journal of Pediatric Gastroenterology and Nutrition, 1987c 6(6): p. 841–6. [PubMed: 3119811]
43. Galler JR, et al., The influence of early malnutrition on subsequent behavioral development. II. Classroom behavior. Journal of the American Academy of Child & Adolescent Psychiatry, 1983 22(1): p. 16–22.
44. Galler JR, et al., The long-term effects of early kwashiorkor compared with marasmus. IV. Performance on the national high school entrance examination. Pediatric Research, 1990 28(3): p. 235–9. [PubMed: 2122403]
45. Galler JR, et al., Infant malnutrition is associated with persisting attention deficits in middle adulthood. Journal of Nutrition, 2012b 142(4): p. 788–94. [PubMed: 22378333]
46. Galler JR, et al., Long-term effects of early kwashiorkor compared with marasmus. II. Intellectual performance. Journal of Pediatric Gastroenterology and Nutrition, 1987a 6(6): p. 847–54. [PubMed: 3119812]
47. Waber DP, et al., Cognitive impairment as a mediator in the developmental pathway from infant malnutrition to adolescent depressive symptoms in Barbadian youth. Journal of Developmental and Behavioral Pediatrics, 2011 32(3): p. 225–232. [PubMed: 21285893]
48. Galler JR, et al., Early childhood malnutrition predicts depressive symptoms at ages 11–17. Journal of Child Psychology & Psychiatry, 2010 51(7): p. 789–98. [PubMed: 20331492]
49. Galler JR, et al., Malnutrition in the first year of life and personality at age 40. Journal of Child Psychology & Psychiatry, 2013 54(8): p. 911–919. [PubMed: 23488644]
50. Waber DP, et al., Impaired IQ and academic skills in adults who experienced moderate to severe infantile malnutrition: a 40-year study. Nutr Neurosci, 2014b 17(2): p. 58–64. [PubMed: 23484464]
51. Waber DP, et al., Neuropsychological outcomes at midlife following moderate to severe malnutrition in infancy. Neuropsychology, 2014a 28(4): p. 530–40. [PubMed: 24635710]
52. Galler JR, et al., Socioeconomic outcomes in adults malnourished in the first year of life: A 40-year study. Pediatrics, 2012a 130(1): p. e1–7. [PubMed: 22732170]
53. Galler J and Kanis K, Animal models of malnutrition applied to brain research, in Basic and Clinical Aspects of Nutrition and Brain Development, Rassin D, Harber B, Drujan B, Editor. 1987, Alan R Liss: New York, NY p. 57–73.
54. Cowley JJ and Griesel RD, The effect on growth and behaviour of rehabilitating first and second generation low protein rats. Animal Behaviour, 1966 14(4): p. 506–17. [PubMed: 6008473]
55. Chow BF, Effect of maternal dietary protein on anthropometric and behavioral development of the offspring. Advances in Experimental Medicine and Biology, 1974 49(0): p. 183–219. [PubMed: 4429044]
56. Bresler DE, Ellison G, and Zamenhof S, Learning deficits in rats with malnourished grandmothers. Developmental Psychobiology, 1975 8: p. 315–323. [PubMed: 1225698]
57. Zamenhof S and van Marthens E, Effects of prenatal and chronic undernutrition on aging and survival in rats. The Journal of Nutrition, 1982 112(5): p. 972–7. [PubMed: 7077427]

58. Stewart RJ, Preece RF, and Sheppard HG, Twelve generations of marginal protein deficiency. The British Journal of Nutrition, 1975 33(2): p. 233–53. [PubMed: 1115762]
59. Stewart RJ, Preece RF, and Sheppard HG, Recovery from long-term protein-energy deficiency. Proc Nutr Soc, 1973 32(3): p. 103a.
60. Stewart RJ, et al., The effect of rehabilitation at different stages of development of rats marginally malnourished for ten to twelve generations. Br J Nutr, 1980 43(3): p. 403–12. [PubMed: 6774742]
61. Galler JR, Home orientation in nursling rats: the effects of rehabilitation following intergenerational malnutrition. Developmental Psychobiology, 1979a 12(5): p. 499–508. [PubMed: 114442]
62. Galler JR and Rosenthal M, The effects of intergenerational malnutrition on the mother—pup relationship in rats. Infant Behavior and Development, 1979 2(0): p. 1–12.
63. Galler JR, The effects of intergenerational and postnatal malnutrition on the behavioral development of rats, in Behavioral Effects of Energy and Protein Defecits, J. Brozek, Editor. 1979b p. 22–38.
64. Galler JR, Home-orienting behavior in rat pups surviving postnatal or intergenerational malnutrition. Developmental Psychobiology, 1980 13(6): p. 563–72. [PubMed: 7429017]
65. Galler JR and Manes M, Gender differences in visual discrimination by rats in response to malnutrition of varying durations. Developmental Psychobiology, 1980 13(4): p. 409–16. [PubMed: 7390021]
66. Galler JR, et al., Varying deficits in visual discrimination performance associated with different forms of malnutrition in rats. The Journal of Nutrition, 1980 110(2): p. 231–40. [PubMed: 7354393]
67. Galler JR and Seelig C, Home-orienting behavior in rat pups: the effect of 2 and 3 generations of rehabilitation following intergenerational malnutrition. Developmental Psychobiology, 1981 14(6): p. 541–8. [PubMed: 7297765]
68. Galler JR and Propert KJ, Maternal behavior following rehabilitation of rats with intergenerational malnutrition. 2. Contribution of mothers and pups to deficits in lactation-related behaviors. The Journal of Nutrition, 1981a 111(8): p. 1337–42. [PubMed: 7264769]
69. Galler JR and Propert KJ, Maternal behavior following rehabilitation of rats with intergenerational malnutrition. 1. Persistent changes in lactation-related behaviors. The Journal of Nutrition, 1981b 111(8): p. 1330–6. [PubMed: 7264768]
70. Galler JR, Visual discrimination in rats: the effects of rehabilitation following intergenerational malnutrition. Developmental Psychobiology, 1981 14(3): p. 229–36. [PubMed: 7196357]
71. Galler JR and Propert KJ, Early maternal behaviors predictive of the survival of suckling rats with intergenerational malnutrition. The Journal of Nutrition, 1982 112(2): p. 332–7. [PubMed: 7057270]
72. Galler JR, Intergenerational effects of undernutrition, in Understanding Mental Retardation: Research Accomplishments and New Frontiers Kavanagh JF, Editor. 1988, Paul H. Brooks Publishing Company: Baltimore, MD p. 35–40.
73. Galler JR and Zartarian G, Reproductive performance in rats with different histories of malnutrition. The British Journal of Nutrition, 1981 45(2): p. 251–5. [PubMed: 7213580]
74. Reusens B and Remacle C, Programming of the endocrine pancreas by the early nutritional environment. The International Journal of Biochemistry & Cell Biology, 2006 38(5–6): p. 913–22. [PubMed: 16337425]
75. Pinheiro AR, et al., Protein restriction during gestation and/or lactation causes adverse transgenerational effects on biometry and glucose metabolism in F1 and F2 progenies of rats. Clinical Science (London, England: 1979), 2008 114(5): p. 381–92.
76. Aets L and Van Assche FA, Animal evidence for the transgenerational development of diabetes mellitus. The International Journal of Biochemistry and Cell Biology, 2006 38: p. 894–903. [PubMed: 16118061]
77. Thamotharan M, et al., Transgenerational inheritance of the insulin-resistant phenotype in embryo-transferred intrauterine growth-restricted adult female rat offspring. Am J Physiol Endocrinol Metab, 2007 292(5): p. E1270–9. [PubMed: 17213472]

78. Van Assche F and Aerts L, Long-term effect of diabetes and pregnancy in the rat. Diabetes, 1985 34(Supplement 2): p. 116–118. [PubMed: 3888737]
79. Oh W, Gelardi NL, and Cha CJ, The cross-generation effect of neonatal macrosomia in rat pups of streptozotocin-induced diabetes. Pediatr Res, 1991 29(6): p. 606–10. [PubMed: 1866217]
80. Knowler WC, et al., Diabetes incidence and prevalence in Pima Indians: a 19-fold greater incidence than in Rochester, Minnesota. Am J Epidemiol, 1978 108(6): p. 497–505. [PubMed: 736028]
81. van Abeelen AF, et al., Famine exposure in the young and the risk of type 2 diabetes in adulthood. Diabetes, 2012 61(9): p. 2255–60. [PubMed: 22648386]
82. Zheng X, et al., Risk of metabolic syndrome in adults exposed to the great Chinese famine during the fetal life and early childhood. Eur J Clin Nutr, 2012 66(2): p. 231–6. [PubMed: 21970943]
83. Kundakovic M and Champagne FA, Early-Life Experience, Epigenetics, and the Developing Brain. Neuropsychopharmacology, 2014.
84. Gudsnuk K and Champagne FA, Epigenetic influence of stress and the social environment. Ilar j, 2012 53(3–4): p. 279–88. [PubMed: 23744967]
85. Yehuda R, Halligan SL, and Grossman R, Childhood trauma and risk for PTSD: relationship to intergenerational effects of trauma, parental PTSD, and cortisol excretion. Dev Psychopathol, 2001 13(3): p. 733–53. [PubMed: 11523857]
86. Yehuda R, et al., Maternal, not paternal, PTSD is related to increased risk for PTSD in offspring of Holocaust survivors. Journal of Psychiatric Research, 2008 42(13): p. 1104–1111. [PubMed: 18281061]
87. Roth M, Neuner F, and Elbert T, Transgenerational consequences of PTSD: risk factors for the mental health of children whose mothers have been exposed to the Rwandan genocide. Int J Ment Health Syst, 2014 8(1): p. 12. [PubMed: 24690436]
88. Neuwald MF, et al., Transgenerational effects of maternal care interact with fetal growth and influence attention skills at 18 months of age. Early Hum Dev, 2014 90(5): p. 241–6. [PubMed: 24602473]
89. Yehuda R, et al., Influences of Maternal and Paternal PTSD on Epigenetic Regulation of the Glucocorticoid Receptor Gene in Holocaust Survivor Offspring. Am J Psychiatry, 2014.
90. McGowan PO, Meaney MJ, and Szyf M, Diet and the epigenetic (re)programming of phenotypic differences in behavior. Brain Research, 2008 1237: p. 12–24. [PubMed: 18694740]
91. McGowan PO, et al., Broad epigenetic signature of maternal care in the brain of adult rats. PLoS One, 2011 6(2): p. e14739. [PubMed: 21386994]
92. Zhang TY, et al., Epigenetic mechanisms for the early environmental regulation of hippocampal glucocorticoid receptor gene expression in rodents and humans. Neuropsychopharmacology, 2013 38(1): p. 111–23. [PubMed: 22968814]
93. Meaney MJ and Szyf M, Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. Dialogues Clin Neurosci, 2005 7(2): p. 103–23. [PubMed: 16262207]
94. Weaver IC, et al., Epigenetic programming by maternal behavior. Nature Neuroscience, 2004 7(8): p. 847–54. [PubMed: 15220929]
95. Weaver IC, et al., Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. J Neurosci, 2005 25(47): p. 11045–54. [PubMed: 16306417]
96. Roth TL, et al., Lasting epigenetic influence of early-life adversity on the BDNF gene. Biological Psychiatry, 2009 65(9): p. 760–9. [PubMed: 19150054]
97. Mill J, et al., Epigenomic profiling reveals DNA-methylation changes associated with major psychosis. Americal Journal of Human Genetics, 2008 82(3): p. 696–711.
98. Vassoler FM, Byrnes EM, and Pierce RC, The impact of exposure to addictive drugs on future generations: Physiological and behavioral effects. Neuropharmacology, 2014 76 Pt B: p. 269–75. [PubMed: 23810828]
99. Vassoler FM, et al., Epigenetic inheritance of a cocaine-resistance phenotype. Nat Neurosci, 2013 16(1): p. 42–7. [PubMed: 23242310]

100. Goodwin DW, et al., Alcoholism and the hyperactive child syndrome. J Nerv Ment Dis, 1975 160(5): p. 349–53. [PubMed: 1151353]
101. Abel EL, Paternal alcohol exposure and hyperactivity in rat offspring: effects of amphetamine. Neurotoxicology and teratology, 1993 15(6): p. 445–449. [PubMed: 8302247]
102. Tarter RE, Jacob T, and Bremer DL, Specific cognitive impairment in sons of early onset alcoholics. Alcohol Clin Exp Res, 1989 13(6): p. 786–9. [PubMed: 2690663]
103. Abel EL, Effects of physostigmine on male offspring sired by alcohol-treated fathers. Alcohol Clin Exp Res, 1994 18(3): p. 648–52. [PubMed: 7943670]
104. Abel EL and Lee JA, Paternal alcohol exposure affects offspring behavior but not body or organ weights in mice. Alcohol Clin Exp Res, 1988 12(3): p. 349–55. [PubMed: 3044161]
105. Abel EL, Alcohol consumption does not affect fathers but does affect their offspring in the forced swimming test. Pharmacology & toxicology, 1991a 68(1): p. 68–69. [PubMed: 2008415]
106. Abel EL, Paternal alcohol consumption affects grooming response in rat offspring. Alcohol, 1991b 8(1): p. 21–3. [PubMed: 2006980]
107. Schmidt CM and Tauchmann H, Heterogeneity in the intergenerational transmission of alcohol consumption: a quantile regression approach. J Health Econ, 2011 30(1): p. 33–42. [PubMed: 21035217]
108. Handley ED and Chassin L, Alcohol-specific parenting as a mechanism of parental drinking and alcohol use disorder risk on adolescent alcohol use onset. J Stud Alcohol Drugs, 2013 74(5): p. 684–93. [PubMed: 23948527]
109. Jamerson PA, Wulser MJ, and Kimler BF, Neurobehavioral effects in rat pups whose sires were exposed to alcohol. Brain Res Dev Brain Res, 2004 149(2): p. 103–11. [PubMed: 15063090]
110. Byrnes JJ, et al., Cannabinoid exposure in adolescent female rats induces transgenerational effects on morphine conditioned place preference in male offspring. J Psychopharmacol, 2012 26(10): p. 1348–54. [PubMed: 22516667]
111. Byrnes JJ, et al., Adolescent opioid exposure in female rats: transgenerational effects on morphine analgesia and anxiety-like behavior in adult offspring. Behav Brain Res, 2011 218(1): p. 200–5. [PubMed: 21138744]
112. He F, Lidow IA, and Lidow MS, Consequences of paternal cocaine exposure in mice. Neurotoxicol Teratol, 2006 28(2): p. 198–209. [PubMed: 16458479]
113. Dominguez-Salas P, et al., Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. Nat Commun, 2014 5: p. 3746. [PubMed: 24781383]
114. Grossniklaus U, et al., Transgenerational epigenetic inheritance: how important is it? Nature Reviews Genetics, 2013 14(3): p. 228–235.
115. Heijmans BT, et al., Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proceedings of the National Academy of Sciences of the United States of America, 2008 105(44): p. 17046–9. [PubMed: 18955703]
116. Tobi EW, et al., DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. Human Molecular Genetics, 2009 18(21): p. 4046–53. [PubMed: 19656776]
117. Unterberger A, et al., Organ and gestational age effects of maternal nutrient restriction on global methylation in fetal baboons. J Med Primatol, 2009 38(4): p. 219–27. [PubMed: 19602098]
118. Nijland MJ, et al., Epigenetic modification of fetal baboon hepatic phosphoenolpyruvate carboxykinase following exposure to moderately reduced nutrient availability. J Physiol, 2010 588(Pt 8): p. 1349–59. [PubMed: 20176628]
119. Resnick O, et al., Overt and hidden forms of chronic malnutrition in the rat and their relevance to man. Neurosci Biobehav Rev, 1982 6(1): p. 55–75. [PubMed: 6803197]
120. Li Y and O'Neill C, Persistence of cytosine methylation of DNA following fertilisation in the mouse. PLoS One, 2012 7(1): p. e30687. [PubMed: 22292019]
121. Franklin TB and Mansuy IM, Epigenetic inheritance in mammals: evidence for the impact of adverse environmental effects. Neurobiol Dis, 2010 39(1): p. 61–5. [PubMed: 19931614]
122. Franklin TB, et al., Epigenetic transmission of the impact of early stress across generations. Biol Psychiatry, 2010 68(5): p. 408–15. [PubMed: 20673872]

123. Radford EJ, et al., In utero undernourishment perturbs the adult sperm methylome and intergenerational metabolism. Science, 2014.

124. Jimenez-Chillaron JC, et al., Beta-cell secretory dysfunction in the pathogenesis of low birth weight-associated diabetes: a murine model. Diabetes, 2005 54(3): p. 702–11. [PubMed: 15734846]

125. Graff J and Mansuy IM, Epigenetic codes in cognition and behaviour. Behav Brain Res, 2008 192(1): p. 70–87. [PubMed: 18353453]

126. Jablonka E and Raz G, Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. The Quarterly review of biology, 2009 84(2): p. 131–176. [PubMed: 19606595]