Transgenerational Epigenetics

James P. Curley, Rahla Mashoodh, and Frances A. Champagne
Columbia University, Department of Psychology, New York NY 10027, USA

INTRODUCTION

The regulation of gene expression through epigenetic modifications provides a dynamic route through which environmental experiences can lead to persistent changes in cellular phenotype. This plasticity plays an important role in mediating cellular differentiation and the potential stability of these modifications can lead to persistent and heritable differences in gene expression. Though there are numerous types of epigenetic mechanisms, studies of environmentally-induced changes in the epigenome have focused primarily on DNA methylation and post-translational modification of histone proteins. The process of DNA methylation whereby cytosine is converted to 5-methylcytosine is mediated by DNA methyltransferases which either promote maintenance (i.e. DNMT1) or de novo DNA methylation (i.e. DNMT3) [1–3]. The process of methylation is dependent on the presence of methyl donors (provided by nutrients such as folic acid, methionine, and choline).

The transcriptional repression associated with DNA methylation is sustained through binding proteins such as MeCP2 [4]. Histone proteins, which form the core of the chromatin, also significantly alter gene expression through their interactions with DNA. Histones can undergo multiple post-translational modifications, including methylation, acetylation, and ubiquitination, which can alter the accessibility of DNA and the density of chromatin structure. In particular, histone acetylation is associated with increased transcriptional activity whereas histone deacetylation is associated with transcriptional repression [1,5].

Role of epigenetic mechanisms in mediating the long-term effects of environmental stresses is a rapidly expanding field of study, and it has become evident that experiences across the lifespan can induce modifications to the epigenome. Moreover, these epigenetic changes have implications for neurobiology, physiology, and behavior of an organism and its divergent developmental outcomes. Thus the molecular mechanisms that underlie epigenetic modifications can contribute to the "epigenesis" of phenotype as described by Waddington in the 1940s, in which the term "epigenetics" has its roots [6]. Within the study of human development, the quality of interactions between parents and offspring is an increasingly salient aspect of the early environment and there is converging evidence from various experimental paradigms for parental influences on the regulation of gene expression and behavior [7–10]. Though maternal effects have been well established in animal models, there is increasing evidence for paternal regulation of offspring development


which may provide important insights into the role of epigenetic mechanisms in mediating the transmission of environmental experiences across generations. In this review, we will discuss evidence of maternal and paternal epigenetic influence on offspring development, with particular focus on studies indicating an association between parental experiences/environmental exposures and epigenetic alterations in offspring. An emerging theme within these studies is the transgenerational implications of these environmentally-induced effects (i.e., effects observed in grand-offspring generations or later) and here we will explore the pathways through which parental influences may persist across multiple generations leading to the stable inheritance of an epigenetically-mediated phenotype.

EpiGenetic Consequences of Prenatal Maternal Exposures

The quality of the maternal nutritional environment during pregnancy can have a significant impact on the growth and development of the fetus, with long-term consequences for brain development and metabolism [11–13]. Epidemiological studies of cohorts exposed prenatally to conditions of famine, as in the Dutch Hunger Winter, suggest a heightened risk of schizophrenia and other neurodevelopmental abnormalities — with the specific consequences dependent on the timing of exposure to maternal undernutrition [14,15]. Analysis of blood samples from siblings gestated during periods with or without maternal famine indicates that there is decreased DNA methylation of the insulin-like growth factor (IGF2) gene as a consequence of maternal periconceptual exposure to famine [16]. Laboratory studies in rodents have subsequently identified specific nutritional deficits, such as prenatal protein restriction or folic acid/choline deficiency, as having similar epigenetic consequences. Offspring of female rats placed on a protein deficient diet throughout gestation were found to have elevated hepatic glucocorticoid receptor (GR) and peroxisomal proliferator-activated receptor (PPAR) gene expression associated with decreased DNA methylation of these genes [17,18]. Moreover, these epigenetic effects are not observed when gestational protein restriction is accompanied by folic acid supplementation [17]. Dietary effects on levels of DNMT1 may account for these observed modifications in global and gene-specific methylation, as DNMT1 expression is increased in hepatic [19] and brain [20] as a function of protein/choline restriction. The impact of dietary supplementation of methyl-donors during fetal development is also clearly demonstrated by the consequences for phenotype among mice with the A alleles of the Agouti gene or Axin  alleles of the Axin gene. The expression of these alleles is epigenetically regulated through levels of DNA methylation, with decreased methylation associated with yellow coat color and obesity among A  mice or a “kinky” tail phenotype among  mice [21,22]. Though there is typically an epigenetic inheritance of these phenotypes, gestational exposure to methyl donators through dietary supplementation of the mother can effectively silence the expression of these alleles with the consequence of inducing a pseudo wild-type phenotype [23,24]. Thus the maternal nutritional environment can have a sustained impact on development through alterations in gene expression that are maintained through DNA methylation. Though the focus of these nutritional studies (as well as the majority of studies to be described further in this chapter) has been on epigenetic modifications within candidate genes implicated in the outcome of interest, it is likely that the transcriptional activity of multiple genes is altered by these experiences with the role of DNA methylation in these experience-dependent genome-wide changes yet to be determined.

The rapid period of cellular proliferation and differentiation that occurs during fetal development provides a critical window during which maternal gestational exposure to toxins may lead to long-term disruptions in offspring and there is increasing evidence for the epigenetic basis of these effects. In utero methyl mercury exposure in mice has been shown to lead to DNA hypermethylation, increased histone tri-methylation and decreased histone acetylation within the IV promoter of the brain derived neurotrophic factor (BDNF) in the hippocampus of offspring and is associated with depressive-like behaviors [25].
of pregnant mice to inhaled diesel exhaust particles combined with an allergen results in altered offspring immunoglobulin (IgE) levels associated with hypermethylation of the interferon (IFN)-gamma promoter and hypomethylation of the interleukin (IL)-4 promoter [26]. Altered DNA methylation within these immune pathways may account for observed maternal effects of prenatal smoking on offspring asthma risk [27]. In rats, prenatal exposure to the anti-androgenic fungicide vinclozolin or the estrogenic pesticide methoxychlor results in increased rates of prostate disease, kidney disease, immune system abnormalities, testis abnormalities, and tumor development [28]. Though the molecular pathways through which these endocrine disrupting chemicals exert epigenetic modifications has yet to be determined, this exposure is associated with altered DNA methylation patterns in sperm and impairments in reproduction in male offspring [29]. In utero exposure to the endocrine disruptor bisphenol-A (BPA) has been demonstrated to induce widespread changes in promoter methylation in the fetal mouse brain, with consequences for neural development [30]. BPA-induced hypomethylation of the Areads allele in mice leads to metabolic abnormality and obesity in adulthood. Interestingly, these toxin induced effects can be reversed through foetal supplementation in the mother's diet [31], suggesting that abnormalities in DNA methylation can be ameliorated through exposure to increased levels of methyl-donors.

Evidence for the epigenetic influence of antenatal maternal mood has emerged from human cohort studies and animal models – providing further support for the role of epigenetic mechanisms in mediating developmental outcomes. Analysis of cord blood samples from infants born to mothers with elevated ratings of depression (using the Hamilton Depression Scale) during the 3rd trimester of pregnancy indicates elevated GR 18 promoter DNA methylation levels associated with maternal depressed mood [32]. Moreover, the level of methylation within the neonatal GR 18 promoter predicts increased salivary cortisol levels in infants at 3 months of age, and these effects are independent of exposure to selective serotonin reuptake inhibitors during pregnancy. This study provides preliminary evidence for the utility of using epigenetic markers within blood samples to predict developmental outcomes; however, the relationship between these markers and changes in the brain in human cohorts remains an issue of debate. In rodents, the long-term consequences of prenatal stress for brain and behavior have been explored with recent evidence of altered gene expression and DNA methylation within the placenta and hypothalamus as possible mediators of these maternal effects. In mice, chronic variable stress during the 1st trimester is associated with decreased DNA methylation of the corticotrophin-releasing-factor (CRF) gene promoter and increased methylation of the GR exon 17 promoter region in hypothalamic tissue of adult male offspring [33]. Gestational stress within these experiments was found to exert sex-specific effects on the expression of DNMT1 in the placenta which may induce disruption of the epigenetic status of genes within this critical interface between mother and fetus. Imprinted genes, such as IGF2, may be particularly sensitive to this situation, leading to impairments in placental growth and function with subsequent consequences for offspring growth and neurodevelopment [34].

**Postnatal Maternal Regulation of the Epigenome**

The dynamic epigenetic modifications were once thought to be limited to the very early stages of development, evidence for continued parental influence on DNA methylation throughout the prenatal period has challenged this view. Studies of the effects of natural pheromones in postnatal care in rodents have established the mediating role of epigenetic factors in shaping individual differences in brain and behavior [9,35]. Postnatal maternal infant grooming (LG) behavior, in particular, has been found to induce increased maternal GR expression leading to more efficient negative feedback of the stress response, fostering studies have confirmed that these effects are mediated by the level of care received during postnatal development [36,37]. Analysis of the GR 17 promoter region promoters that variations in GR expression associated with differential levels of maternal
care are maintained though altered DNA methylation [38]. Thus, offspring who receive high levels of maternal LG during the early postnatal period have decreased hippocampal GR 17 promoter methylation, increased GR expression, and decreased stress responsivity whereas low levels of LG are associated with increased GR 17 methylation, decreased GR expression, and an increased HPA response to stress. Time course analysis has indicated that these maternally-induced epigenetic profiles emerge during the postnatal period and are sustained into adulthood [38]. The pathways through which these effects are achieved are currently being elucidated and it appears likely that maternal LG mediated up-regulation of nerve growth factor inducible protein A (NGFI-A) in infancy may be critical to activating GR transcription and maintaining low levels of DNA methylation within the GR 17 promoter. Though the exploration of these brain region-specific maternal effects in humans is limited by the inaccessibility of brain tissue, recent studies have illustrated the long-term effects of childhood abuse on hippocampal DNA methylation patterns of suicide victims [39,40]. Analysis of hippocampal tissue from suicide victims with a history of childhood abuse indicates decreased GR expression and elevated GR 17 promoter methylation associated with disruptions of the early environment and confirms the potential role of NGFI-A as a mediator of differential GR promoter methylation. Early life effects on GR signaling pathways in humans are further illustrated by a recent genome-wide analysis of gene expression of peripheral blood mononuclear cells from healthy adults who had experienced conditions of low vs. high socioeconomic (SES) status during childhood, with low childhood SES associated with a down-regulation of genes containing GR response elements [41].

**Paternal Influence on Offspring Development**

Mammalian development is characterized by intense prenatal and postnatal mother–infant interactions and thus studies of parental influence have primarily focused on maternal rather than paternal effects. However, even among species in which biparental care is not typical, significant paternal modulation of offspring development has been observed. In rodents, pre-mating exposure of males to alcohol is associated with reduced offspring litter size, reduced birth weight, increased mortality, and numerous cognitive and behavioral abnormalities [42–47]. Likewise, offspring of cocaine-exposed males perform poorly on tasks of visuo-spatial attention, spatial working memory, and spontaneous alternation and have a reduced cerebral volume [48,49]. When pre-mating housing conditions of male mice lead to reduced oxygen and increased carbon dioxide, female offspring are found to have elevated blood hemoglobin [50]. Among isogenic Balb/c mice, offspring anxiety-like behavior can be predicted based on paternal levels of open-field exploration, even when offspring have had no interaction with their fathers [51]. Significantly, these effects persist when factors such as maternal care, litter characteristics, and duration of time the male was housed with the mother during the mating period are statistically controlled. Moreover, variation in the dietary environment of fathers appears to be transmissible to offspring. For instance, reduced serum glucose and altered levels of corticosterone and IGF1 are found among offspring of male mice that undergo a 24-hour complete fast two weeks before mating [52]. Finally, epidemiological studies in humans have demonstrated increased risk of autism and schizophrenia that emerge as a function of increased paternal age [53–55]. Laboratory studies of paternal age effects in genetically-identical rodents also indicate that offspring of “old” fathers have reduced longevity and perform more poorly on learning and memory tasks [56–58]. The transmission of these paternal effects to offspring in the absence of any postnatal contact with fathers suggests that these exposures may lead to alterations in the male germine with consequences for early embryonic development.

Investigation of the role of epigenetic mechanisms in mediating these paternal effects suggests that environmentally-induced changes in DNA methylation within sperm may be transmitted to offspring with implications for development. In the case of paternal hypermethylation of ribosomal DNA has been found in the sperm and liver cells of...
(21–28 months) compared to "young/adult" (6 months) male rats [59], and twin studies suggest that a drift in epigenetic patterns of various cell types occurs with age, such that "old" twins have relatively divergent DNA methylation patterns compared to "young" twins [60]. Though there are many genetic and morphological abnormalities in sperm associated with aging, these epigenetic modifications may contribute to the aberrant developmental outcomes associated with increasing paternal age. In males, chronic exposure to alcohol or cocaine can induce chromatin remodeling and changes in DNA methylation within numerous genes in both the brain and periphery [61–63]. In particular, alcohol exposure has been shown to decrease DNMT mRNA levels in the sperm cells of adult male rats [64] and chronic cocaine exposure in adult male mice has been shown to decrease DNMT1 while increasing DNMT3 mRNA expression in the germ cell-rich cells of the seminiferous tubules of the testes [49]. Altered DNMT levels may have particular implications for imprinted regions within the genome as analysis of sperm DNA methylation levels in heavy drinkers indicates reduced methylation in the normally hypermethylated H19 and IGF regulatory regions [62]. Thus, environmental exposures in males may lead to altered levels of enzymes involved in maintenance of epigenetic marks, with possible paternal transmission of the epigenetic abnormalities to offspring.

Transgenerational Effects of Parental Influence

The stability of epigenetic modifications within an individual’s own development and evidence supporting a transmission of parental epigenetic changes to offspring provide a new perspective on the stable inheritance of traits. Moreover, there is increasing evidence that this non-genomic inheritance can be maintained over multiple generations, such that in addition to the developmental effects of parental experiences on offspring, there may be observed influences of parental (F0) experiences on grand-offspring (F2) and possibly great-grand-offspring (F3). In general, there may be two distinct routes through which these types of epigenetic inheritance patterns can occur: germline-mediated vs. experience-dependent/non-germline-mediated (Fig. 24.1). Within germline-mediated transgenerational effects, prenatal environmental exposures are thought to induce epigenetic alterations within developing gametes that persist in the absence of continued exposure with consequences for F1, F2, and F3 generations. In contrast, experience-dependent/non-germline mediated epigenetic transmission requires that a particular experience or environmental exposure be repeated in each generation to re-establish the epigenetic modifications which permit the trait to persist in subsequent generations. The distinction between these two routes can be difficult to establish experimentally, particularly in the case of prenatal exposures in which the offspring and the F1 offspring’s germine, which will give rise to the F2 generation, are exposed to the inducing environmental factor. Though both of these processes can lead to the stable inheritance of phenotype, there is certainly divergence in the routes through which this is achieved.

Germline-mediated Transgenerational Inheritance

Evidence for the transgenerational impact of early life nutrition or prenatal exposure to environmental chemicals provides support for an inheritance pattern that is likely germline-mediated, though in many cases, the specific effect on the germline has yet to be elucidated and the experimental design may not conclusively identify the effect as being independent from experiences occurring during formation of the germline which persist through developmental stages. Analysis of archival records from Sweden in which crop success (used as a proxy for food intake) and longevity can be determined in multiple generations, suggests that in years of a high level of nutrition during the slow growth period that precedes puberty is associated with diabetes and cardiovascular disease mortality of grand-offspring [65,66]. Interestingly, these effects are sex-specific, with paternal grandfather nutrition predicting son mortality and paternal grandmother nutrition predicting grand-daughter
longevity [67]. Laboratory studies in rodents have confirmed the transgenerational impact of nutrition and indicate that prenatal protein restriction can exert effects on growth and metabolism of offspring and grand-offspring through changes in methylation status of GR [68]. When F0 female mice are exposed to caloric restriction during late gestation, F1 grand-offspring are found to have impaired glucose tolerance and this effect is maintained even when the F1 generation is provided with ad libitum food throughout their lifetime. In human cohort studies, paternal consumption of betel nuts (which contain nitrosamines) leads to dose-dependent increases in offspring risk of metabolic syndrome [69] and in transgenerational studies of mice, 2–6 days of betel nut consumption by F0 generation males was found associated with increased glucose intolerance amongst F1, F2, and F3 generation offspring [70]. Similar metabolic effects are observed when males are exposed \textit{in utero} to dexamethasone, with increased glucose intolerance observed among the offspring of these males when mated with non-exposed females [71]. However, in the case of prenatal dexamethasone exposure, these metabolic phenotypes do not persist beyond the F2 generation indicating that there is either compensation for the germline effects or that the effect is mediated by experience-dependent transmission.

The consequences of \textit{in utero} exposure to endocrine-disrupting compounds has also been explored within a transgenerational model and provides evidence for the pervasive effect on epigenetic profiles of these early life exposures. In humans, matrilineal transmission of the effects of diethylstilbestrol (DES)-induced hypomethylation and increased cancer risk has been observed in daughters and granddaughters [72]. \textit{In utero} exposure to vinclozolin in rats has been demonstrated to disrupt DNA methylation in sperm and increase the risk of infertility and risk of prostate and kidney disease in F1, F2, and F3 offspring with transmission through the patriline [29]. Vinclozolin-induced alterations in gene expression...
within the hippocampus and amygdala have also been observed for up to three generations post-exposure with sex-specific effects on anxiety-like behavior [73]. Interestingly, mate-choice studies suggest that females presented with F3 vinclozolin-exposed or non-exposed males show a significant partner preference for non-exposed males, indicating an additional measure of decreased reproductive success as a consequence of treatment with endocrine disruptors [74]. The persistence of these disruptions beyond the F2 generation suggests that the effects of these exposures have become incorporated into the germline and there is incomplete erasure of the associated epigenetic marks during the process of gametogenesis, fertilization, and embryogenesis [75]. The sensitivity of sperm and oocytes to epigenetic disruption is further illustrated in findings of increased incidence of imprinting disorders, such as Angelman Syndrome and Beckwith-Wiedemann Syndrome, occurring following in vitro conception using assisted reproductive technology (ART) [76]. Ovarian stimulation with gonadotropins and the quality of the embryo culture medium have been found to alter DNA methylation and gene expression [77–79], particularly within imprinted genes, and there is recent evidence that in vitro conception is associated with decreased DNA methylation within the placenta and increased methylation within cord blood samples [80]. Thus, understanding the mechanisms through which these environmental effects lead to alterations in the epigenome will have significant implications for offspring disease risk.

**Experience-dependent Transgenerational Inheritance**

Across species, there is evidence for the transmission of individual differences in maternal behavior from mother to offspring and grand-offspring. In humans, mother–infant attachment classifications (secure, anxious/resistant, avoidant, disorganized) are similar across generations of female offspring [81,82] as are levels of parental bonding [83]. In mice and pigtail macaques, the frequency of postpartum maternal behavior has been observed to be transmitted across matrilines as are rates of maternal rejection and infant abuse [84–86]. Cross-fostering studies conducted between abusive and non-abusive macaques females indicates that the transmission of abusive behavior from mother to mother is dependent on the experience of abuse during the postnatal period [87]. As such, females born to abusive mothers who are then fostered to a non-abusive mother do not show increased rates of infant abuse. This matrilineal transmission is also evident in laboratory rodents. Natural variations in maternal LG observed in the F0 generation are associated with similar levels of LG in F1 and F2 generation females [88,89]. As such, adverse environmental conditions, offspring and grand-offspring of Low LG females display low levels of LG whereas offspring and grand-offspring of High LG females display high levels of LG. Similar to the transgenerational effects of abuse in macaques, cross-fostering studies have demonstrated that the transmission of maternal LG from mother to male offspring is dependent on the level of maternal LG received in infancy [36,88]. Evidence for the experience-dependent nature of these effects comes from studies in which maternal LG is altered, through chronic exposure to stress [90] or manipulation of the ACE environment [89], leading to a disruption of the inheritance of the predicted adult phenotype.

There is evidence that epigenetic mechanisms may be critical in mediating the transmission of certain behaviors across generations. Female offspring of low LG mothers exhibit a lower sensitivity to estrogen and have reduced levels of estrogen receptor α (ERα) mRNA expression in the medial preoptic area (MPOA) of the hypothalamus [91,92]. Analysis of methylation of the ERα 1b promoter region indicates that the experience of low levels of LG in infancy associated with increased methylation whereas high levels of LG in infancy are associated with low levels of methylation at several sites within the promoter [93]. This differential methylation results in reduced binding of signal transducer and activator of transcription (Stat)3 to the ERα promoter with consequences for the transcriptional activity of this gene. Thus, epigenetic modifications to a gene that regulates several aspects
of reproduction, including postpartum maternal behavior, results in differential levels of expression of ERα in adulthood, which alters estrogen sensitivity and consequently leads to variations in the level of maternal care that these females provide to their own offspring. The transmission from mother to daughter of variations in maternal LG within this transgenerational framework is mediated by the stability of brain region-specific epigenetic modifications that occur in infancy and influence behavior in adulthood [94]. Similar experience-dependent effects of the postnatal environment in rats have been induced through exposure to abuse. Increase in methylation of exon IV of the BDNF promoter and consequent decrease in BDNF mRNA in the prefrontal cortex has been found in association with exposure to periods of abusive maternal care (dragging, burying etc.) [95]. Moreover, these effects on exon 1v methylation are perpetuated to the F1 offspring of abused females suggesting a role for epigenetic mechanisms in this transgenerational effect. Enrichment of the postnatal environment in mice through use of communal nursing (multiple mothers and litters housed together) has also been found to alter F1 and F2 offspring brain and behavior [96], though the role of epigenetic effects has not yet been explored within this model. Overall, these studies highlight the stable inheritance of traits that can be achieved through behavioral transmission of epigenetic modifications.

Epigenetics, Plasticity and Evolving Concepts of Inheritance

Though the study of mechanisms of inheritance and the origins of individual differences has traditionally been the domain of the field of genetics, there is increasing evidence for the role of epigenetic modifications in maintaining environmentally-induced variations in phenotype both within and across generations. The dynamic nature of these epigenetic effects provides a mechanism through which a single genotype can give rise to multiple phenotypic outcomes conferring a heightened level of developmental plasticity to an organism. In contrast to environmentally-induced genetic alterations/mutations, which are thought to be non-directed, there may be adaptive consequences associated with experience-dependent epigenetic modifications. For example, nutritional “programming” of fetal metabolism has been explored as an adaptive consequence of early life experience [97,98] and, as has been described in previous sections, there is clearly a role for epigenetic mechanisms in mediating the effects of variations in prenatal food intake. When the prenatal period is characterized by undernutrition, a “thrifty phenotype” may result which allows an individual to be conservative with regard to energy output and which promotes storage of glucose [99,100] - with adverse health consequences associated with a mismatch between the quality of the prenatal and postnatal nutritional environment [101,102]. Similar adaptive consequences may be relevant to the development of heightened HPA reactivity. Though elevated stress responses are typically considered to be a negative outcome and associated with increased susceptibility to physical and psychiatric disease, within an evolutionary perspective, the ability to respond rapidly to threat would be particularly advantageous in conditions of high predation/low resource availability [103]. Laboratory studies of maternal care in rodents suggest that chronic stress and social impoverishment can lead to reduced growth with consequences for the increased stress response of offspring via differential methylation of hippocampal GR [37,38,89,90]. Though this environmentally-induced phenotype is associated with impaired cognitive performance under standard testing conditions [104], recent evidence suggests that synaptic plasticity is enhanced in offspring of low LG animals when corticosterone levels are elevated [105]. Thus, the consequences of early life adversity can be considered as adaptive or maladaptive dependent on the consistency or mismatch between early and later environmental conditions, and epigenetic mechanisms play a role in shaping these phenotypic adaptations.

The concept that experience-induced characteristics can be transmitted across generations is reminiscent of Lamarckian theories of use/disuse and the inheritance of acquired characteristics [106]. Though the role of heritable epigenetic modifications in evolutionary
processes is still questionable [107], the plasticity that these modifications confer certainly has implications for our understanding of the developmental origins of health and disease. Importantly, there is growing support for transgenerational epigenetic consequences of environmental exposures, though our understanding of the molecular, cellular, and behavioral pathways through which these outcomes are achieved is still in its infancy. Though these epigenetic effects have often been explored from the perspective of pathology, recent evidence suggests that genetically-induced impairments in learning and memory can be overcome through exposure to environmental enrichment – with improvements in cognition persisting across generations [108]. Thus, broadening our concept of inheritance to include both genetic and epigenetic mechanisms may provide insights into effective therapeutic approaches and lead to a greater appreciation of the benefits that can be achieved through intervention in parental and grand-parental generations.

ACKNOWLEDGEMENTS

The authors wish to acknowledge funding received from Grant Number DP2OD001674 from the Office of the Director, National Institutes of Health.

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