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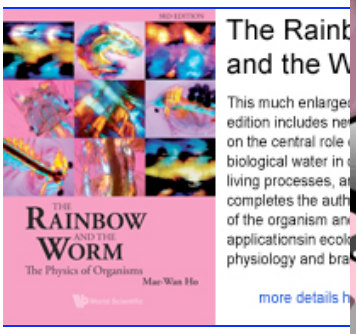
# Caring Mothers Strike Fatal Blow against Genetic Determinism

*New research on maternal care puts the environment and epigenetic potential at centre stage of how organisms shape their lives and the lives of their offspring* Dr. Mae-Wan Ho

## Neither genetic nor environmental determinism rules




Is it our genetic makeup or the environment that determines who we are? Startling new research results on how maternal care has lasting influence in the offspring's behaviour that perpetuates for generations [1] are saying that's not even the right question to ask.

Evidence has been emerging since the early 1990s that lack of parental care or childhood abuse can contribute to subsequent criminal behaviour [2]. A study sponsored by the US National Institute of Justice showed that a child who experienced neglect or physical abuse was 53 percent more likely to be arrested as a juvenile and 38 percent more as an adult compared with a child who was not neglected or abused. Another study found that 68.4 percent of male inmates from a New York State correctional institution reported childhood abuse or neglect: 71.2 percent for violent offenders and 61.8 percent for non-violent offenders.

It has been estimated that up to 70 percent of abusive parents were themselves abused [3, 4], and 20 to 30 percent of abused infants are likely to become abusers. These findings in humans are replicated in experiments on primates [1].

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

## Myth of genetic determinism perpetrated in academia

Mainstream genetics research during the decades since the discovery of the DNA double helix in 1953 has focussed on identifying 'genes' or 'genetic predisposition' for every 'trait', real or imaginary [5] (see Living with the Fluid Genome, ISIS publication). Imaginary traits are rife in the hybrid discipline of



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'evolutionary psychology', long dedicated to inventing stories on 'selective advantage' for each of the 'traits' so that the corresponding gene could become 'fixed' in the population by neo-Darwinian natural selection.

Another hybrid discipline 'behavioural genetics', formerly dedicated to studies based on identical twins, began identifying DNA (gene) markers for behaviour; and indeed claimed to have found one for increased tendency towards violent behaviour in boys who experienced maltreatment in childhood [6]. The gene encoding the enzyme monoamine oxidase A (MAOA) – involved in the metabolism of neurotransmitters - exists in two variants, one expressing high activity, the other, low activity. While all boys in the study showed increased "disposition towards violence" if they received maltreatment as children, those with low enzyme activity appeared to show a greater increase. The researchers claimed a weak residual effect due to the low activity MAOA, while conceding the large effect of the environment. But even this weak genetic predisposition soon faded away as more data became available [7].

Behavioural geneticists are not the only ones wasting time and resources chasing 'will o' the wisp' gene markers. The project to map genetic predisposition to diseases was the main rationale for the $3 billion Human Genome Project that decades later, delivered next to nothing; basically because it is not genomic DNA but epigenetic environmental influences that overwhelmingly affect our health and well-being [8] (see From Genomics to Epigenomics *SiS* 41).

## Epigenetic inheritance

.The term 'epigenetic' came from *epigenesis*, the process whereby an organism with differentiated organs, tissues and cells develop from a relatively featureless egg. Developmental geneticist and evolutionist Conrad Waddington [9] invented the concept of the 'epigenetic landscape' to represent the dynamical structure of the developmental system that defines the range of non-random changes for evolution, and that was the sense in which we had used 'epigenetic' in 1979 [10] (Beyond Neo-Darwinism: An Epigenetic Approach to Evolution, ISIS publication). Nowadays, 'epigenetic' usually refers to a heritable change that does not involve DNA sequence alteration [11], but that is becoming rapidly obsolete [6].

New research has abundantly confirmed the overriding importance of epigenetic environmental influences across the disciplines: from nutrition to toxicology, and most dramatically in brain development, where the boundaries between epigenetic and genetic is distinctly blurred (see other articles in this series, especially [12, 13] Epigenetic Inheritance through Sperm Cells, the Lamarckian Dimension in Evolution, and Rewriting the Genetic Text in Brain Development and Evolution, *SiS* 41).

Epigenetic inheritance is effectively the inheritance of acquired characters attributed to Jean-Baptiste de Lamarck (1744-1829) [14] (see Epigenetic Inheritance, "What Genes Remember", *SiS* 41), and has come into its own in maternal effects.

## Maternal effects galore

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

Prenatal stress [15] and malnutrition [16] experienced by the mother affects her neuroendocrine system and produced a shift in the development of the nervous system in her foetus. And, the care received (usually from the mother, but can be substituted by surrogates) during early infant life can produce changes in the development of the nervous system that regulates its response to novelty and social behaviour [17]. Thus, the maternal environment experienced by a developing organism can play a critical role in shaping its adult behaviour.

However, observations that certain effects can be transmitted across several generations, from mother to daughter and grand-daughters and beyond, have made researchers look more

carefully again.

## Caring mothers reduce stress for life

One of the best researched examples is maternal care in rats, which we first covered in 2004 [18] (Caring Mothers Reduce Response to Stress for Life, *SiS* 24), and the fascinating story continues.

To recapitulate, researchers at McGill University in Montreal, Canada, showed that mother rats that cared adequately for their pups and others who don't, shaped their offspring's response to stress accordingly for the rest of their lives that are correlated with different states of expression in relevant genes [19].

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

The adult offspring of high-LG mothers show increased glucocorticoid expression in the hippocampus, and enhanced sensitivity to glucocorticoid feedback. This enhanced sensitivity was due to increased expression of glucocorticoid receptor (GR) accompanied by the increased expression of a special transcription factor NGF-1-A, which binds to the promoter of the GR gene to increase its transcription. These differences in gene expression states are accompanied by significant differences in methylation of the GR promoter; with low methylation from offspring of high-LG mothers and high methylation from offspring of low-LG mothers. The researchers also found significantly higher acetylation of histone in chromatin protein around the GR gene (as consistent with active gene expression) in the offspring of high-LG than in the offspring of low-LG mothers.

Interestingly, cross-fostering the offspring of low-LG to high-LG mothers and *vice versa* at day 1 after birth induced changes in the offspring in line with the *foster* mother, with correlated changes in the gene expression states. (So, foster parents can influence their children biologically!)

The different gene expression states are acquired during the first week of life, and persist into adulthood. Pups of both high-LG and low-LG mothers start out practically the same. Just before birth, the entire region of the GR promoter was unmethylated in both groups. That is because most gene marks are erased in the germ cells. At day one after birth, methylation was also the same in both groups. But changes develop according to the behaviour of the mother within the critical period of the first week of life, and remain stable thereafter.

Nevertheless, these changes in DNA methylation and histone acetylation could be reversed, even in adults, as demonstrated by the rather drastic method of infusing chemical activators or inhibitors into the brain, with concomitant changes in the adult's response to stress.

Thus, infusing the histone deacetylase inhibitor Tichostatin A (TSA) into the brains of offspring from low-LG mothers increased histone acetylation, and decreased methylation of the GR promoter, thus boosting GR expression to levels indistinguishable from the brains of offspring from high-performing mothers. And when tested for anxiety levels, they performed like offspring from high-LG mothers [1].

On the other hand, injecting methionine, the precursor of S-adenosyl methionine (SAM) the co-factor of DNA methylase, into the brains of offspring from high-LG mothers increased methylation of the GR promoter to levels the same as those of offspring from low-performing mothers; thereby decreasing GR expression and caused them to switch their behaviour accordingly.to resemble that of offspring from low-LG mothers.

Thus, epigenetic states are stable yet dynamic and plastic, giving no support to any kind of determinism, genetic or environmental.

## Maternal care and sex hormones

What makes mothers caring or otherwise? The hippocampus is the 'emotion centre' of the brain. It is vulnerable to stress and richly supplied with receptors for the sex and reproductive hormones, and maternal care is regulated by those hormones.

In the rat, the McGill University team also found that oxytocin receptors are necessary for the expression of maternal behaviour [20]. Oxytocin (OT) is a hormone secreted by the posterior pituitary gland and stimulates the contraction of the uterus and ejection of milk. Variations in OT receptor levels in critical brain regions, such as the medial preoptic area (MPOA) of the hypothalamus (MPOS), are functionally linked to differences in maternal care. OT receptor binding in the MPOA is increased in high-LG compared with low-LG mothers. Furthermore, differences in OT receptor binding in the MPOA between high-LG and low-LG females are oestrogen-dependent; it is eliminated by ovariectomy, and reinstated with oestrogen replacement. However whereas ovariectomized high-LG females respond to oestrogen with an increase in OT receptor binding, low-LG females show no such effect. Studies with mice suggest that oestrogen regulation of OT receptor binding in the MPOA requires the a-subtype of the oestrogen receptor (ERa). Significantly increased expression of ERa, but not ERb (another oestrogen receptor subtype), was found in the MPOA of lactating high-LG and low-LG mothers as well as in their non-lactating, virgin female offspring.

ERa is a ligand-activated transcription factor that regulates gene transcription on binding oestrogen. The cellular response to oestrogen depends on the amount of ER present.

The researchers found that by day 6 after birth, ERa expression in the MPOA of female offspring from high-LG mothers is significantly increased compared with that of female offspring from low-LG mothers, and this state continues into adulthood, which explains why the female offspring of high-LG and low-LG mothers become high-LG and low-LG mothers accordingly, and this epigenetic state perpetuates itself via the female line until and unless disrupted by environmental intervention.

One effective environmental intervention is cross-fostering, in which the biological offspring of high- and low-LG mothers were reciprocally exchanged within 12 h of birth, reared to adulthood, and then examined for ERa expression in the MPOA. Sure enough, the ERa expression in the MPOA of the adult females born to low-LG mothers but cross-fostered to high-LG mothers, became indistinguishable from that of the normal biological offspring of high-LG mothers; and conversely, ERa expression in the MPOA of adult females born to high-LG mothers but reared by low-LG mothers resembled that of normal biological offspring of low-LG mothers. Cross-fostering as such had no effect, so exchanging offspring between two low-LG mothers or two high-LG mothers did not alter ERa expression in the MPOA of the offspring.

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

## Maternal care influences brain development and many gene functions

Obviously, maternal care does not just influence a few genes. The McGill University team has previously found that in the rat, increased anxiety in response to stress in the offspring from low-LG mothers is associated with decreased neuronal development and density of synpases in the hippocampus. The offspring of high-LG mothers, on the other hand show increased survival of neurons and synapses in the hippocampus, and improved cognitive performance under stressful conditions. These observations suggest a rather extensive influence of maternal care

on brain development and gene expression.

In order to examine the effect on gene expression of high- and low-LG mothers and TSA or methionine infusion, the four different treatment groups were compared with their respective control groups using microarrays to monitor changes in 31 099 unique mRNA transcripts [21]. A total of 303 transcripts (0.97 percent) were altered in the offspring of high-LG mothers compared to offspring of low-LG mothers: 253 transcripts (0.81 percent) up-regulated and 50 transcripts (0.15 percent) down-regulated. TSA treatment of offspring of low-LG mothers altered 543 transcripts (1.75 percent): 501 transcripts (1.61 percent) up-regulated and the rest, 42 transcripts (0.14 percent) down-regulated. Methionine treatment of offspring of high-LG mothers changed 337 transcripts (1.08 percent), with 120 (0.39 percent) up-regulated and 217 (0.7 percent) down-regulated.

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

The transcripts altered by maternal care, TSA and methionine treatment fall into several classes belonging to general cellular and energy metabolism; signal transduction (including membrane-bound receptors, intracellular messengers kinases, phosphatases and transcription factors); protein synthesis, turnover, folding and intracellular trafficking of proteins; and neuronal development, including extracellular matrix proteins and cytoskeletal proteins that define the architecture of synaptic connections. Although the transcripts affected by maternal care and TSA or methionine treatment fall into the same categories and overlap, they are not exactly the same. TSA treatment induced expression of a collection of unique transcripts. Similarly, methionine treatment down-regulates transcripts different from those in offspring of low-performing mothers.

## Implications for mental health

Although the epigenetic effects of maternal behaviour have been worked out in most detail in rodents, there is potential for similar effects in other species including primates and humans, as pointed out by Frances Champagne, a member of the McGill University team, now at Columbia University, New York, in the United States [1]. Abusive behaviour in rhesus and pigtail macaques has been demonstrated to be transmitted from mother to daughter with influences on multiple behavioural and neurobiological characteristics in the offspring. In humans, lack of parental care or childhood abuse can contribute to subsequent criminal behaviour (as mentioned earlier). Furthermore, lack of parental care and parental over-protection ("affectionless control") is a risk factor for depression, adult antisocial personality traits, anxiety disorders, drug use, obsessive-compulsive disorder and attention-deficit disorders. Conversely, people who reported high levels of maternal care were found to have high self-esteem, low trait anxiety and less salivary cortisol in response to stress. Longitudinal studies demonstrated that mother-child attachment is crucial in shaping the cognitive, emotional and social development of the child. Throughout childhood and adolescence, secure children are more self-reliant, self-confident and have more self-esteem. Secure infants also have better emotional regulation, express more positive emotion and respond better to stress. Infant disorganized attachment has been associated with the highest risk of developing later psychopathology, including dissociative disorders, aggressive behaviour, conduct disorder and self-abuse.

## Nutrition and mental health

The dramatic effects of TSA and methionine infusion in altering gene expression patterns in the rats also have obvious implications for drug intervention, or better yet, intervention/prevention through adequate nutrition, as stressed by the researchers in a review article [22].

In rats, dietary L-methionine has been shown to be crucial for normal brain development, and its deficiency implicated in brain

aging, and neurodegenerative disorders. Synthesis of SAM (cofactor for DNA methyl transferase) is dependent on the availability of dietary folates, vit B12, methionine, betaine, and choline. Developmental choline deficiency alters SAM levels and global and gene-specific methylation. And prenatal choline availability has been shown to impact neural cell proliferation and learning and memory in adulthood. Several studies have shown that additional dietary factors, including zinc and alcohol, can influence the availability of methyl groups for SAM formation and thereby influence CpG methylation. Maternal methyl supplements positively affect the health and longevity of the offspring.

Other studies have shown that certain dietary components may act as a histone deacetylase inhibitors (HDACis), including diallyl disulfide, sulforaphane and butyrate. For example, broccoli which contains high levels of sulforaphane, has been associated with H3 and H4 acetylation in peripheral blood mononuclear cells in mice 3-6h after consumption.

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

These experiments raise the possibility that diet can affect the phenotype through shaping the epigenotype. Thus, reversal of epigenetic damage may be triggered by stable variations in environmental conditions such as nutrition, and not just by pharmacologic agents.

All in all, these remarkable findings on the epigenetic effects of maternal care show how important it is for societies to look after the welfare of children and mothers to be, in order to ensure both mental and physical health of future generations.

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