MATERNAL CARES

WHAT SCIENCE IS TEACHING US ABOUT THE NATURE OF NURTURING OUR YOUNG

by Peter Jon Mitchell

When Dr. Michael Meaney enters his research laboratory in Montreal, it's to mixed reviews. Some freeze and panic, others stand at attention but then resume eating their lunches, without a care, or even so much as a "hello." We're talking about rats, here. With people, the reviews are pretty much unanimously positive. Dr. Meaney, the McGill professor at the department of Psychiatry, Neurology and Neurosurgery, is commanding much attention these days – he has twice received invitations to confer with the Dalai Lama. But back in the lab, it's the rats he is concerned with; he's been working with them for almost two decades. And when he claps his hands, all the rats freeze at the sound as they should, but some, the better adjusted ones, are soon able to return to eating, or doing whatever it is rats do, realizing that the scientist poses no threat. Others – those poor vermin who are poorly adjusted – remain immobilized for upward of 10 minutes.[1] Why the different reactions?

The answer stems from a new twist on a very old debate. You might recall the nature-versus-nurture discourse from your high-school days. Teacher after teacher for years has posed the same question: Is who we are and how we behave a function of our biology determined by our genes, or a result of our environment and how we've been socialized? Forget what you thought you knew. The old terms, and the debate itself, are changing.

The reason for the change? The human genome project – started in 1990 and finally completed in 2003 – provided new insights into how the body develops and behaves by charting the sequence and function of particular genes. In so doing, science left the nature-versus-nurture squabble and shifted to an emphasis on nature *and* nurture; how environmental factors interact with our biology. It is a question of interplay, and the new discoveries are incredible. Emerging to the forefront is the study of epigenetics: How physical and social environments affect gene expression without altering the DNA structure. In short, how nurture can affect nature; how environment can change a person's biology. High-school students may soon be jotting down a whole new set of notes.

You are more than what you eat

Researchers like Moshe Szyf, pharmacology professor also at McGill University, have high hopes for what epigenetics might mean for curing or preventing fatal diseases. His research examines how environmental factors such as toxins or even the foods we eat may turn genes linked to diseases like cancer on or off. The potential is great: Scientists could one day be able to reverse the onset of disease by controlling the mechanism which activates particular genes.[2]

But it's not just what we eat or ingest that matters. Along with Szyf, researchers like Meaney and Toronto physiology professor Stephen Matthews, are discovering that our life experiences can influence our genes. Our quality of family life may influence our vulnerability to obesity, heart disease and other illnesses later in life.[2] In particular, researchers have been examining how a mother's care determines processes in the brains of an infant that affect outcomes in the child's life, and could even impact the physiology of the next generation. In short, the science is showing that the environments and life occurrences of our grandparents might very well have programmed aspects of our own development.

Canadians are leaders in the epigenetic field; critical epigenetic research and its influence on maternal care is being conducted in our own backyard. Canadians should be proud – and compelled to examine the implications for health and welfare and public policy, too. The physical and emotional health of women is critical to the healthy development of children. Likewise, the quality of care children receive in the very early stages of life establishes health outcomes later in life. The scientists doing the research, like Meaney, are saying that the mother-child relationship requires protection and promotion. Canadian policy makers need to tune in and consider the findings that these fine Canadian academics are bringing to light on the world stage, knowing precisely what the science does – and does not – say.

It all starts in the womb

How a mother reacts to stressors in her immediate environment impacts the physiological development of her child even before offspring leave the womb.[4] Enter University of Toronto physiology professor Stephen Matthews, his small army of graduate students and a legion of guinea pigs. Dr. Matthews' focus? Examining how the foetal environment programs aspects of the brain to secrete chemicals that influence gene expression

Specifically, Matthews and his team of researchers are interested in the region of the brain called the hypothalamus, pituitary gland and adrenal cortex – or HPA axis – which influences stress responses and affects the function of the digestive and immune systems.[5] Matthews monitors a series of reactions in the HPA axis that determine a guinea pig's reaction to stress, which is

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similar to the response a human would have. The hypothalamus sends messages to the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). This important hormone, in turn, stimulates the adrenal cortex to secrete the hormone cortisol. Often referred to as a stress hormone, cortisol assists the body in gathering energy to cope with stress.[6] Measuring levels of cortisol in people (or the rodent equivalent, called corticosterone) allows researchers to gauge the severity of the body's reaction to environmental stressors

Matthews' studies examine the manner in which maternal stress programs HPA function and the resulting behaviour of the guinea pig pups by observing post-natal outcomes. In one of his experiments, female guinea pigs in the late stages of pregnancy were exposed to moderate levels of stress induced by a strobe light – the strobe is proven to cause the animals stress. The stressed guinea pigs produced offspring who were significantly underweight, and had increased stress hormone levels. These results indicate that those young whose moms were moderately stressed during certain periods of their pregnancy demonstrated physiological differences, like being underweight, as compared with the young of mothers who were not exposed to stress.[7]

The study also suggests that raised hormone levels in pregnant animals influence the elevation of stress hormones in offspring. In humans, increased cortisol levels have been found in patients with bipolar disorder. Also, HPA axis disorders are present in up to 30 per cent of patients with depression.[8] It's plausible that prenatal maternal stress may affect these types of diseases.

Another Matthews study involved exposing pregnant rats to purely psychological stressors such as strobe lights, forced foraging for food and wet bedding. These stressors produced raised stress hormones in the mother rats, things like changes in maternal behaviour within the first eight days of lactation.[9] For example, the stressed-out mothers were less attentive to their young. The alteration in maternal behaviour was a significant result. Additional studies of rat populations have the same result, showing that the offspring's development is influenced by mothering behaviours.

Matthews' studies are fascinating for several reasons. Maternal stress not only causes physiological changes within mothers as stress hormones are released, but this response results in physiological expression in the offspring. Animals in stressful environments during the late stages of pregnancy breed anxious offspring. The implications of this are just beginning to be grasped – and advocates of very different stripes are putting the information to use. For example, in March 2007, a study advocating for non-parental, state-funded daycare cited epigenetic research in describing how institutional early learning is important before children get to kindergarten.[10] The scientists themselves cautiously avoid such prognostications in the public-policy arena.

Meaney and mother rats in Montreal

Back at McGill, Dr. Michael Meaney examines how maternal care affects stress responses and even the maternal behaviour of female offspring. Meaney, in addition to his distinguished position in the department of Psychiatry and Neurology and Neurosurgery at McGill, serves as the director of the Program for the Study of Behaviour, Genes and Environment. He is one of the recognizable faces of epigenetic research in Canada, particularly in the area of maternal care. A highly-sought speaker internationally, Meaney was among the very first researchers to connect impact of maternal care on the expression of genes that regulate how the body reacts to stress.[11]

Dr. Stephen Matthews at the University of Toronto knows guinea pigs, Meaney, however, has done much of his work with rat populations. He noted in a 2001 journal article that nearly 40 years earlier, researchers who studied rats had unveiled evidence suggesting environmental events could alter effects not only on offspring but on the subsequent generation as well.[12] Even though the evidence for the trans-generational transfer of environmental-influenced effects was published in the well-known journal *Nature*, the results garnered little additional interest.

Years later, Meaney and his team picked up on the research with studies identifying maternal behaviour as a mediator of trans-generational effects.[13] His new work hinged on two critical assumptions. First, that the body's chemical response to stress helps it to cope, but prolonged activation can actually cause harm, leading to greater susceptibility to disease;[14] the second that early environmental factors in a rat's life could influence how it reacts to stress throughout life.[15]

Lifelong chemistry

In the first assumption, the series of HPA axis reactions that produce cortisol is the natural and healthy way for the body to cope with stress. Meaney asserted that a problem arises when prolonged exposure to stress causes continued production of cortisol, much like Matthews showed with his guinea pigs. The chemical reaction directs energy away from the synthesis of proteins including those essential to the immune system. This weakens the ability of the immune system to fight disease, leaving the body more susceptible to poor health.[16] Long-term exposure to stress can lead to insulin resistance and heart disease as well as memory and learning problems.[17]

In the second assumption, that early environmental factors could have lifelong effects, his work focused on how particular aspects of maternal care can regulate the process of cortisol production in offspring.

With his rat pack, Meaney set out to study the effect of stress on maternal behaviour and how quality of mother care influences their little ones. Mother rats (called dams) engage baby rats (called pups) in nesting behaviours shortly after birth that involve an arched-backed nursing position and licking and grooming. Meaney and his team observed dam and pup interaction over the first week postpartum. He noted which dams favoured lots of licking and grooming and which did not.[18] Observing the pups through to adulthood, Meaney examined the adult offspring of high licking and grooming mothers and compared them with the low licked and groomed offspring. He discovered that high licked and groomed offspring had reduced ACTH and corticosterone (stress hormone) levels.[19] The difference in cortisol levels accounts for the varied reactions of the rats when Meaney approaches the cage clapping his hands.

But what is actually transpiring in the brains of rats that causes them to react so differently? The answer is known as "methylation" to scientists like Meaney. A quartet of atoms called methyl group attach to a gene at a certain point, controlling the way the gene is expressed. Methylation patterns are not present in some regions of the rat genome until after birth. The first week of a rat's life is critical as methylation patterns begin, and the licking and grooming stimulates the development of these patterns. This accounts for the different reactions between high and low licked offspring.[20] In a sense, genes are turning on and off because of the level of maternal care. The methylation patterns are responsible for "flipping the switch" on the genes that control cortisol production.

Meaney continued to observe the behaviour of the pups as they grew and reproduced. He and his team found that the fearful, low licked rats produced "stress-reactive offspring," in other words, stressed-out rats beget more stressed-out rats.[21] The high licked rats demonstrated high licking and grooming behaviour with their own offspring and the maternal behaviour is transmitted via gene expression from generation to generation.[22]

This observation sparked further inquiry: Meaney wondered how this inheritance could work. So he subjected the second and third generations to "cross-fostering." Meaney switched the pups to different mothers within the first twelve hours after birth. He put some of the pups who had low licking mothers with high licking and grooming mothers and vice versa. Meaney discovered that the methylation patterns in the pups reflected the adopted parents in both cases.[23] Meaney reported, "Individual differences in fearfulness or maternal behaviour mapped onto those of the rearing mother rather than the biological mother."[24]

The results of the experiment suggest that environmental events occurring early in life can be transmitted to the next generation, however good maternal care – even adoptive maternal care – can reverse the effects of poor maternal care.[25]

Separation anxiety

Pups separated from their mothers for substantial periods of time, even when given all the comforts the creatures need, showed similar results to those who received little licking and grooming. "Predictably," the researcher writes, "the maternal separation animals were highly fearful in behavioural tests of novelty."[26] Fortunately, as with the low licked pups, the research shows that these effects can be reversed as the cross-fostering demonstrates. When separated pups are stroked with a brush simulating maternal licking and grooming, the physiological process is reversed.[27] The studies suggest that some level of compensation occurs through environmental enrichment later in life which could offset the effects of earlier trauma.[28]

When Meaney's contributions are applied to previous rodent research, important conclusions can be drawn. Previous research demonstrates that maternal care in the rat world stimulates the release of growth hormones. The work of the McGill professor confirms that maternal care has an immediate impact on HPA activity in infant rats with particular care in regulating stress hormones. The outcomes from rodent studies suggest that maternal licking and grooming promote growth and development. Previous studies have shown that offspring of high licking and grooming mothers demonstrate superior cognitive development in spatial learning and object recognition.[29]

The research also suggests that environmental adversity plays an important role in increasing stress and anxiety in mother rats which dictates the quality of maternal care. Lower-quality maternal care leads to higher stress hormones in offspring who develop into high-anxiety, low-quality maternal care mothers.[30]

Maternal cares: from rats to humans

Meaney's rats may help researchers understand findings about maternal care among humans. Seemingly obvious studies have demonstrated that depressed mothers are less positive towards their babies. Another study found that highly anxious mothers were more likely to have shy and timid children. A study in 2000 linked results of parental bonding tests to HPA responses to stress.[31] Meaney's results lend an epigenetic understanding to these results.

The Montreal-based researcher also says that high levels of stress hormones, while unhealthy in the long run, might serve a positive short-term purpose in some cases. He argues that children often inherit the previous generation's environment. Higher stress hormones might be an adaptive approach needed for survival.[32] For example, behaviour studies have demonstrated that in high-crime neighbourhoods, timid boys are less likely to get in trouble.[33] In this case, higher stress hormones may be desirable for survival.

Dr. Meaney and Dr. Matthews have looked beyond the rodent community for their current research project. The two men are engaged in the Maternal Adversity Vulnerability and Neurodevelopment (MAVAN) study. The $4 million multi-year study follows mothers who are depressed from pre-birth through the first years of the child's life. Meaney, Matthews and their colleagues tested the infants for 22 genes that may affect behaviour and be linked to learning disabilities and attention deficit disorder. The researchers are hoping to observe how depression in mothers influences the expression of their children's genes. They will test the children's cortisol levels, conduct brain scans for physical development and observe cognitive and social development. The research team has offered the mothers treatment but previous studies suggest that one-third of participants will not accept it.[34] The MAVAN study is ongoing.

HELPING MOTHERS COPE IN STRESSFUL SITUATIONS IS EASIER SAID THAN DONE: HOW CAN PROGRAMS REACH THOSE WHO REALLY NEED IT? WHAT LEVEL OF SUPPORT IS REQUIRED? HOW INVOLVED DOES THE STATE NEED TO BE?

Implications for public policy

What does it all mean? For Meaney his tests show that good maternal care is really important. "Together, the results of these studies suggest that the behaviour of a mother toward her offspring can 'program' behavioural neuroendocrine responses to stress in adulthood."[35] In short, maternal care programs gene expression in the part of the brain that regulates reactions to stress. This influences the vulnerability or resistance to stress-induced illness in adulthood.[36] For advocates of early-learning and child-care programs, the results demonstrate a need for accessible, quality child-care programs in the highly contentious debate over national daycare in Canada. For those who favour parental care the results lend meaning to their work – time spent with infants in the days and weeks after birth may affect their whole lives.

Meaney maintains his focus, saying that it is important to make sure mothers are cared for themselves. "Keeping moms happy should be a priority," says Meaney.[37] While it might sound like an advertisement for a greeting card company, happy and healthy mothers are critical. Pregnant mothers and their children both benefit when moms are healthy. One practical implication is for families to consider ways to reduce maternal stress.

Meaney himself advocates for policies that support moms, children and families. Meaney says poverty and mental illness – grave stresses on moms – are bad for the healthy development of children. "Women's health is critical. The single most important factor determining the quality of mother-offspring interactions is the mental and physical health of the mother. This is equally true for rats, monkeys and humans."[38] Public policy that helps moms might include generous maternity leave or community resources – such as visits from the public-health nurse. One study published in 1998 followed the children of low-income mothers who were visited by a public-health nurse throughout pregnancy and the first two years of the child's life. As adolescents these children were less likely to run away, be arrested or engage in cigarette and alcohol use than their peers.[39]

Helping mothers cope in stressful situations is easier said than done: How can programs reach those who really need it? What level of support is required? How involved does the state need to be? But this type of research – epigenetics – already helps with the problem of providing an awareness of the importance of good maternal care, and the importance of mothers in general for healthy kids and for intergenerational connections.

Epigenetic research confirms we cannot divorce social nurturing from biological nature and that valuing motherhood and promoting women's health today will result in a healthier society tomorrow. Dr. Matthews and Dr. Meaney will continue to spook small animals in the name of research – and families will reap the benefits. But while the research is new, exciting and engages new frontiers in genetic research – sometimes it seems like the results are astounding only in their simplicity – reminding us of something we knew all along. Mothers matter. Their health matters. And how they interact with their babies matters. But if it takes a host of rats and guinea pigs to help us remember the point, then the more the merrier.

endnotes

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