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Scarred for life?

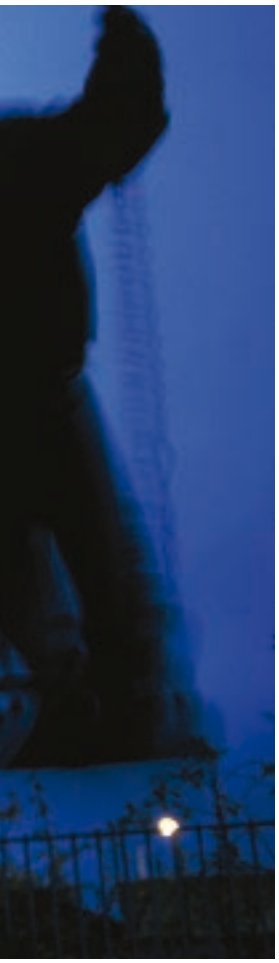
Bad experiences in childhood can have terrible effects mentally and physically – not only on us but also on our descendants. We are closing in on the biology behind the process, say **Marla B. Sokolowski**, **W. Thomas Boyce** and **Bruce S. McEwen**

CHILDHOOD as an idea may have its origins in the 18th century, when philosopher Jean-Jacques Rousseau described it as a brief period of sanctuary before the hardships of adult life. Before then, art had been in line with the spirit of the times, depicting children as little adults. Historically, too, we can track the change in attitudes. Enforced child labour, for example, gradually became unacceptable.

Even now, however, children are exposed early in life to disadvantage, distress, repeated neglect and abuse, leading to poorer health, learning and social functioning. Early adversity can put individuals on a lifelong trajectory of increasing risk. Fortunately, we know quite a lot about how this happens. Remarkably, we also know that some adversity is not linked to poverty or deprivation, and that there are resilient children who prosper and thrive despite the harsh and often damaging realities of their young lives.

To help those who will face such adverse conditions, and to find out why responses to these stresses are so different, we need to know much more about how experiences of childhood adversity affect cellular pathways and translate into the molecular and genetic changes that result in biological effects on development and health.

Large steps have been made in this field, as was demonstrated by the breadth and depth of papers emerging from a Sackler colloquium entitled Biological Embedding of Early Social Adversity: From Fruit Flies to Kindergartners. This was held in Irvine, California, just over a year ago, and was sponsored by the



PROFILE
Marla B. Sokolowski is professor of ecology and evolutionary biology, University of Toronto. W. Thomas Boyce is professor of child development, University of British Columbia, Vancouver. Bruce S. McEwen is Alfred E. Mirsky Professor of neuroendocrinology at Rockefeller University, New York. Most of the research in this article can be found in the special issue of *PNAS* (vol 109, supplement 2) that this article draws on

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It now seems clear that early adversity does cause biological changes. But how important to a child's development is this biological "embedding" in specific psychological or health consequences – and why do these changes persist through life?

Ever since the 1980s, when results from work by epidemiologist Michael Marmot at University College London on the relative health of civil servants started to be recognised, socioeconomic status has been understood to be the strongest predictor of human health. Before then, epidemiologists adjusted for it rather than studied it. This obscured a key reality: the relationship with health is graded and continuous, so at all social levels your health is on average slightly better than the person just below you, and slightly worse than the person just above you.

Even more compellingly, socioeconomic status is a predictor of most illness, not just a single disease, such as coronary heart disease, or a category, such as cancer. The effect holds across age groups, so children in disadvantaged or poor communities are, like their parents or caregivers, much more likely to be ill then and later as adults.

One explanation is that people in poorer communities experience more and greater adversity, which undermines their resistance and increases the risk of illness, injury and psychiatric disorders. Thus early adversity puts individuals on a lifelong trajectory of increasing risk: school failure, teen pregnancy, criminality, obesity, elevated blood pressure, depression, coronary heart disease, diabetes, premature ageing, and memory loss in old age.

Many studies on animals and humans, such as those by psychiatrist Michael Rutter of University College London, have pointed towards the importance of experience early in life for health and well-being later in life.

Elsewhere, research by one of us, Bruce McEwen, has closed in on how pre- and postnatal stress affects a complex set of interactions between the hypothalamus, the pituitary gland and the adrenal glands (the HPA axis). These are all part of the body's neuroendocrine system, which controls our reactions to stress and regulates many things, including digestion, the immune system, emotions, sexuality, and the storage and expenditure of energy. It is also involved in the inflammatory, metabolic and autonomic nervous systems.

Such systems help us cope with stress. But when people face stress in early life in the form of poor nutrition, neglect and abuse, the body increases the production of the stress hormone cortisol. Normally, cortisol washes over our organs, including the brain, increasing blood sugar and stopping the immune system from going into overdrive. But increased levels can suppress the immune system, and impair a part of the brain, the hippocampus, hampering learning and memory.

Programmed for stress

Poverty is not the only driver of poor environments. Children from middle or upper socioeconomic brackets also face adversity, as shown by decades of data from the Adverse Childhood Experience study, run by the Centers for Disease Control and Prevention in Atlanta, Georgia, and the Kaiser Permanente care consortium in San Diego, California. Such experiences are not just about dramatic events – chronic recurrent and often routine aspects of family chaos and neglect also affect development.

There are some interesting twists to these effects. If the early environment signals a lifetime of adversity and struggle, a baby may be "programmed" for physical and behavioural traits to help it cope with future challenges and stressors. This includes storing more fat to prepare for poor nutrition or hypervigilance to prepare for unpredictable environments.

Preparing the body for the worst is not always advantageous. If people with low birth weight go on to face overnutrition as adults, for example, they show high incidence of heart disease, diabetes and high blood pressure, according to work by David Barker of the University of Southampton, UK.

Another twist is that some children show a remarkable capacity to thrive despite being reared in very stressful, chaotic environments. The idea of "dandelion" children, who will grow and flourish under most circumstances, comes from research by one of us, Thomas Boyce, and Bruce Ellis, a developmental psychologist at the University of Arizona in Tucson.

"Early adversity can put individuals on a lifelong trajectory of increasing risk"

And then some alleles, or variations, on certain genes that make someone more vulnerable, say, to substance abuse or depression are actually genes that, in a nurturing environment, may lead to better-than-average traits. Such "orchid" children need an especially nurturing environment in order to flourish and shine. The key is that the consequences of such environments depend partly on individual susceptibilities.

Although research had provided evidence that early social environments are closely associated with individual differences in responses to stress, no fundamental biological processes had been convincingly linked to these differences until relatively recently. Research into gene-environment interplay is now providing decent candidates.

The first mechanism, gene-environment interaction, concerns how individuals with different alleles differ in their sensitivity to the environment. For example, many children born into adversity carry gene variants that predispose them to damage to the stress-handling system, while others carry genes that buffer them.

Many other genes are also important here, ›

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A bad environment shouldn't condemn a child to a poor future

including those involved in the HPA stress axis, in brain development and in communication within the brain. Even the immune system and gut microorganisms communicate with the brain and affect the way its genes express.

The second mechanism is epigenetics, by which, for example, stably inherited traits result from some genes being appended with a small chemical tag called a methyl group. This methylation can make a gene become less frequently expressed because it is no longer as accessible. Studies on rats by Michael Meaney and colleagues at McGill University in Montreal, Canada, show how this works.

Some rat mothers lick and groom their pups a lot, while others are far less demonstrative. When pups are licked and groomed infrequently, a gene involved in the stress axis that codes for glucocorticoid receptors – which mop up cortisol – is modified by methylation. This methylation means the pups end up with fewer of these receptors in their brains, which will, in turn, affect how well they cope with stress, learn, and act towards their own offspring. Cross-fostering the pups shows that adult females lick and groom according to how they were groomed by their mothers or foster mothers.

Evidence is emerging that major upsets early in human life are linked with differences in DNA methylation and the expression of genes that predispose individuals to cope with adversity. Meaney and others have shown that some suicide victims with an early history of abuse have methylation of the gene for the glucocorticoid receptor and a subsequent reduction in its expression in the brain.

Interesting patterns of methylation across whole genomes have been revealed by researchers including psychiatrist Marilyn Essex from the University of Wisconsin-Madison and epigeneticist Michael Kobor of the University of British Columbia in Vancouver, Canada. They found that patterns laid down early in life in those suffering early adversity still seem to be present in adolescence.

"Experiences in early life can affect many aspects of brain development"

Tantalising as these results are, we need to know a lot more before we can say exactly how the process programs what happens to an infant. For example, how long do epigenetic effects persist, and how stable or reversible are they in the face of interventions such as providing a more nurturing home environment or a school breakfast club?

If we want to make large claims about the molecular processes linking early adversity and what happens later, we are going to need a bigger picture of how genes and environment interact. This will have to show how differences in individuals and the risk of disease spring from the interplay of factors such as the variation of alleles, the many kinds of epigenetic modification and a host of social dimensions.

Early life is a period of high brain plasticity, where differences in cognitive, social and emotional development start to consolidate. Experiences then can affect many aspects of brain development, including the type (glia or neurons) and number of brain cells made, and the extent of branching and pruning. Luckily, this is not deterministic: critical development periods provide opportunities when the brain is especially open to new stimulation.

Opening the window

About three months before a child is born, for example, the key windows for establishing sensing pathways – including vision and hearing – open. These climb to a peak, and then decline when the baby is 3 months old. Research by Janet Werker at the University of British Columbia, for example, shows how babies learn sounds common to their native language in the womb. Critical periods for language learning peak between 6 and 9 months, then close at about 4 years old.

During critical periods, the neural circuits involved are sculpted and can be changed by experience. Neuroscientist Takao Hensch at Harvard University has identified molecules acting as "brakes" involved in the opening and closing of these critical periods. His team has shown that it is possible to manipulate these molecules to reopen or extend the critical development periods. This has exciting implications for restoring plasticity, increasing the potency of interventions of all kinds, and for treating neurological disorders.

The idea that early social adversity could be biologically embedded has come a long way, but has a long way still to go. We know, for example, that the brain plays a crucial role in embedding – but we still need to know how the interactions between genes and environment link up to social context and to the brain. Which brain circuits are involved? How do different genetic variants influence brain responses to social adversity? Which social conditions strongly affect growing brains? And what are the adaptive processes by which gene networks, epigenetic patterns and neural circuits work together to influence how we turn out?

Many economists agree that returns on investment in the early years – improved success at school, better health, less crime – far outstrip the costs of treating the problems arising from early inequities. Our goal should be to find the biological keys of optimal development. Then we can ensure that all children, especially those growing up in abusive or deprived environments, prosper. n