This has also been found in the elderly (see 'Telomeres tell'). Even experiencing fewer years of school education in early life is associated with having shorter telomeres in middle and old age.

Delaying actions that mitigate diseases such as diabetes until adulthood will only exacerbate personal and societal costs. One example of a proactive step is the US health programme Medicaid's Strong Start initiative, which aims to enhance pregnancy-related care. Improving the education and health of women of childbearing age in general could be a highly effective way to prevent poor health filtering down through generations.

To suggest that people's quality of life matters or that societies and governments should be allocating more resources to mothers and children is hardly new or controversial. What is new is the wealth of evidence demonstrating that telomeres powerfully quantify life's insults. They are shorter in people who were exposed to adversity as children, and shorter still for each year a person spends depressed, caring for a sick child, being abused and so on.

Telomeres send one more signal — from the tips of our chromosomes — that unmanageable social and psychological stress, especially during early life, is as insidious as smoking or too much fast food. ■ SEE COMMENT P.171

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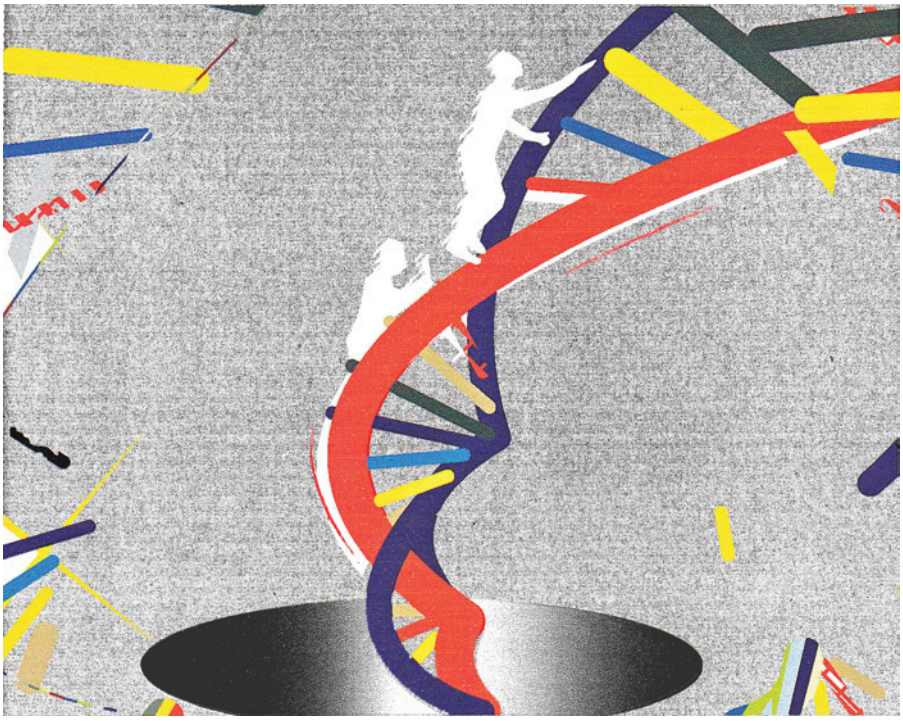


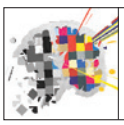
ILLUSTRATION BY PADDY MILLS

Stress makes its molecular mark

Trauma affects people differently. Epigenetics may be partly to blame, says **Eric J. Nestler**.

Some people exposed to severe stress, such as that caused by prolonged economic hardship or sexual or physical abuse, go on to develop devastating psychological or other health problems. Others are more resilient. If one identical twin shows symptoms of stress-related depression, for instance, the other will also be depressed in only around 40% of cases. I believe that epigenetic mechanisms help to explain why[1,2]. These are experience-dependent molecular alterations to DNA or to proteins that alter how genes behave without changing the information they contain.

Recent studies suggest that epigenetic mechanisms shape short-term (lasting hours) and long-term (lasting months, years or even a lifetime) responses to stress. Some studies even hint that epigenetic changes could affect the next generation. A serious effort to both map and substantiate associations between behavioural responses and epigenetic alterations — although costly and challenging — would almost certainly flag up possibilities for treatments that either reverse the effects of stress or enhance a person's ability to cope.



STRESS AND RESILIENCE
The links between adversity and mental illness. nature.com/stress

AGGRESSIVE MICE

When a person is stressed, gene expression in parts of the brain may be up- or down-regulated. This can occur through chemical modifications to DNA, to regulatory proteins in the nuclei of brain cells or to histones (proteins that package and order DNA). Many stress-induced changes are adaptive, but some seem to be damaging.

In my laboratory, we have stressed mice by repeatedly exposing them to more aggressive mice[1] (see 'A switch for resilience'). After ten days of this treatment, the stressed mice begin to avoid other mice, show less interest in things that normally excite them (such as sweets and sex), become less adventurous and even grow obese (they take less pleasure in eating but eat more). ▶

Many of these symptoms can persist for months and are treatable with standard antidepressant medications. We have also found that mice given cocaine the week before being exposed to an aggressive mouse have more extensive epigenetic modifications, which induce more stress-related symptoms[3].

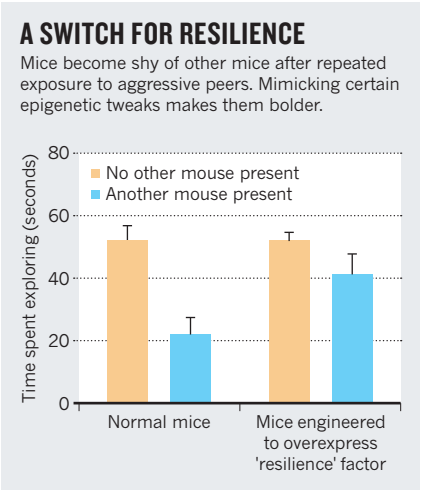
Of the hundreds of mice studied in my lab, roughly one-third become less adventurous when stressed but have no other symptoms. By looking at differences in gene expression and structural organization of DNA between these 'resilient' mice and more susceptible mice, we have linked distinct behavioural responses to specific molecular alterations — all in regions of the brain important in reward recognition[3–6]. These alterations include differences in DNA methylation, patterns of attachment of acetyl or methyl groups to histones and activity of various transcription factors. They last for days or, in some cases, for several weeks.

We can make susceptible mice resilient by blocking or inducing epigenetic modifications to certain genes or by altering the expression patterns of those genes to mimic the epigenetic tweaks. Likewise, epigenetic modifications and gene expression can be altered in resilient mice to make them more susceptible.

Other groups have found similar epigenetic alterations that last a lifetime. For instance, rat pups that are rarely licked and groomed by their mothers are more susceptible to stress later in life[7] than are pups with more diligent carers. They are less adventurous than better-cared-for offspring and put up less of a fight in unpleasant situations (such as being placed in a beaker of water). Moreover, the females are less nurturing towards their own offspring. Epigenetic modifications seem to occur at several genes in the hippocampus in response to how much grooming young rats receive, and these alterations persist into adulthood[7].

These findings are likely to hold up in humans. For example, researchers have found that the genes identified in the rat-grooming studies were more methylated in the hippocampi of suicide victims who had experienced trauma as children than in the those of people who had died from suicide or natural causes and whose childhoods were normal. Likewise, our findings in mice given cocaine mirror epidemiological studies from the past few decades that have linked drug abuse, obesity and conditions such as multiple sclerosis, diabetes and heart disease to increased susceptibility to stress in humans.

More controversial is whether animals inherit epigenetic vulnerability to stress. According to this notion, epigenetic modifications in sperm or eggs drive aberrant patterns of gene expression in the next generation[8]. Several groups have reported that male mice exposed to stress — by being removed from their mothers as pups or exposed to more aggressive mice as adults, for example — produce offspring that are more vulnerable to stress[9,10].



A mechanism is still elusive. Exposure to stress could somehow corrupt the male mouse's behaviour or affect some signalling molecule in his semen such that his partner alters her care for their young. Another possibility is that stress-linked epigenetic 'marks' in the sperm affect the development of offspring[9,10]. No causal evidence yet links epigenetic changes in sperm to altered behaviour in offspring.

MAPPING MARKS

Epigenetics is in vogue: over the past five years, researchers have proposed epigenetic explanations for all sorts of phenomena, from language acquisition to obesity, without clear proof. At a meeting I attended two years ago, people proposed that the spread of Christianity in the early centuries AD was partly due to epigenetic mechanisms. Furthermore, researchers too often identify correlations between behaviour and molecular alterations in cells without also establishing a causal link. Some biologists are, rightfully, wary.

Yet the results I have described show how important epigenetic mechanisms are likely to be in understanding the effects of stress and in discovering ways to manage it.

It is time for researchers to begin the difficult business of substantiating associations. Cost is one challenge to pinpointing the genes and biochemical pathways involved in epigenetically mediated responses to stress. Hundreds of known types of modifications probably act in complex combinations. Mapping each mark at specific points in development in a rat or mouse, and doing so in each brain region or peripheral tissue, would cost tens of thousands of dollars. Defining the alterations in the many cell types in a given brain region[2] pushes the cost several-fold higher. And the expense for doing so in humans is orders of magnitude higher still. Human genetic diversity means that researchers will probably need to study hundreds or thousands of people to obtain a meaningful picture. A related challenge is that of obtaining enough computational power to analyse the hundreds of terabytes of sequencing data that would be produced — although recent advances in bioinformatics are beginning to help.

At present, researchers study epigenetic alterations by up- or downregulating enzymes such as histone methyltransferases. But such enzymes can influence thousands of genes. Tools that allow researchers to target a specific type of epigenetic modification to a single gene in a particular cell type *in vivo* will usher in a far more compelling phase of research.

Work in simpler organisms, such as the roundworm *Caenorhabditis elegans,* is providing clues about the range of epigenetic modifications that can occur in sperm or egg cells. Of course, experiments in mammals will be needed to establish whether epigenetic transmission of information can occur across generations to a meaningful extent.

Thirty per cent of lost productivity worldwide is caused by psychiatric conditions such as depression, anxiety and schizophrenia — all of which are exacerbated by chronic stress. In the developed world, that proportion is 40%. The toxic levels of stress people are now exposed to — in part thanks to the increases in productivity, lifespan and competitiveness that come with a wealthier, healthier globalized economy — are here to stay. A serious endeavour to understand why people respond to stressful experiences so differently — challenging as it would be — is easily justified. ■ SEE COMMENT P.169

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