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Too toxic to ignore

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COMMENT

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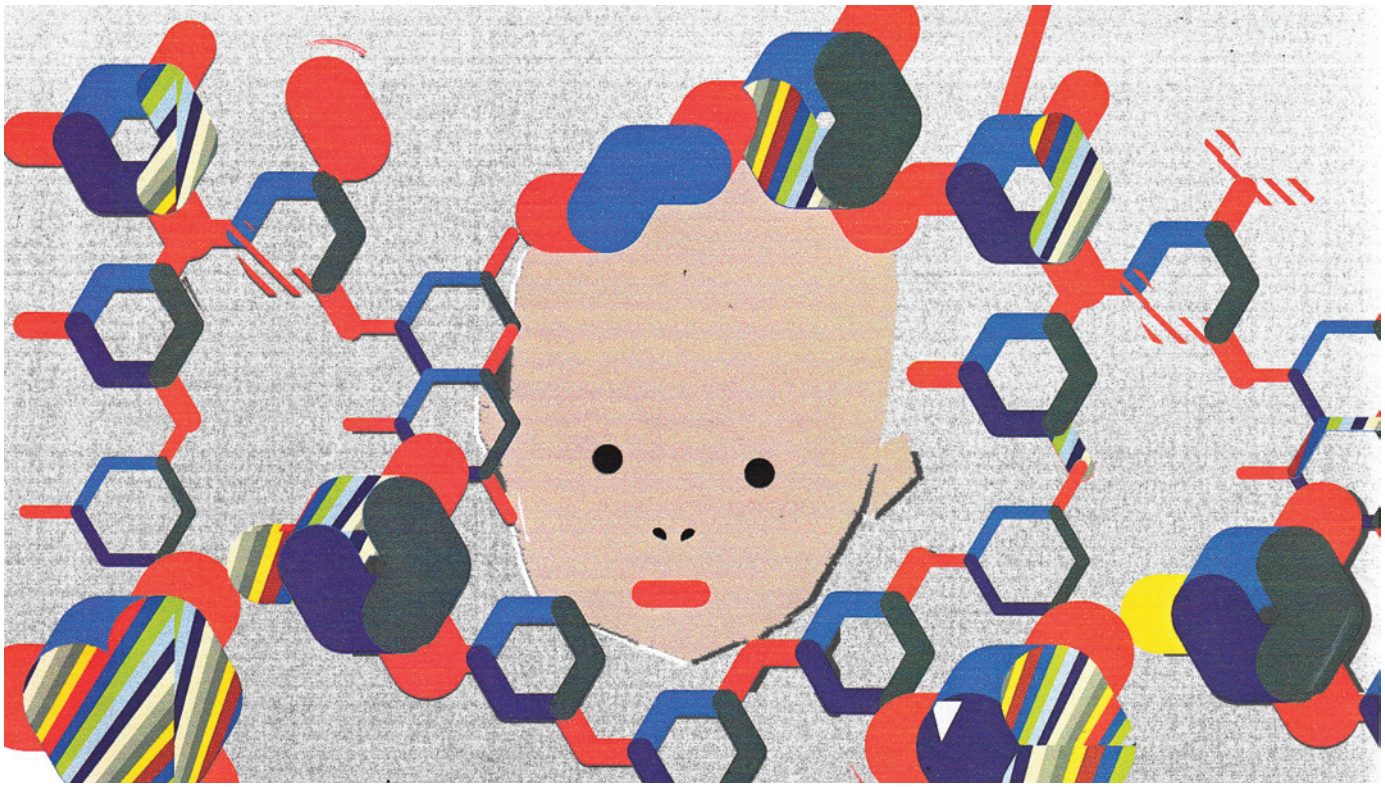


Too toxic to ignore

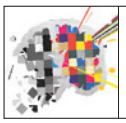
A stark warning about the societal costs of stress comes from links between shortened telomeres, chronic stress and disease, say **Elizabeth H. Blackburn** and **Elissa S. Epel**.

In the 2006 film *The Holiday*, the actress Cameron Diaz, playing a woman whose life is spinning out of control, exclaims: "Severe stress … causes the DNA in our cells to shrink until they can no longer replicate. So when we're stressed we look haggard."

Hollywood got that science right. The DNA to which Diaz's character alludes is the segment that makes up telomeres, structures that cap and protect the ends of chromosomes. She was referring to our 2004 publication[1] — the first to link chronic psychological stress to compromised telomere maintenance.

Since that paper, researchers have consistently found that various types of chronic stress are linked to — and probably cause — shorter telomeres. Meanwhile, both telomere shortness and stress have independently been associated with several common conditions, such as cardiovascular disease and diabetes.

These associations are so widespread and consistent that even without a detailed understanding of the biochemical pathways involved, the message is clear. Failure to alleviate severe stress caused by prolonged threats such as war, financial hardship, abuse and emotional neglect, particularly in children, will result in exponentially higher costs further down the line — personal, economic and otherwise.



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

SHORT ODDS

Human telomeres are several kilobases of repeated sequences of DNA bound by specialized protective proteins. A peculiarity of the DNA-replication mechanism causes telomeres to shorten as cells divide. Sometimes the enzyme telomerase can replenish the lost DNA, but as we age, our telomeres dwindle. If they get too short, through ageing or because telomere maintenance goes awry, cells can stop dividing. Such cells also become malfunctional. For instance, they can start secreting factors that cause inflammation or trigger the development of tumours.

In 2004, we compared telomere lengths in the white blood cells of mothers of chronically ill children to those in mothers of healthy children[1]. The longer a woman had spent being the main carer of her ill child (the children's conditions ranged from gut disorders to autism), the shorter were her telomeres. Moreover, in both groups, the more severe her psychological stress — as judged by her answers to standardized questions about, for instance, how in control she felt over her life — the shorter were her telomeres. The extra telomere shortening in the 'most stressed' mothers (compared with that in the 'least stressed' mothers) was equivalent to that caused by at least a decade of ageing.

"Telomeres powerfully quantify life's insults."

This relationship between stress and telomere length keeps showing up: from studies of kindergarten-aged children to adults as old as 80; from small clinical samples of less than 100 people to large population-based samples of thousands[2,3].

Under stress, the body ramps up its production of certain hormones, such as cortisol, and other biochemical factors. These compounds help to mediate an appropriate response to short-term stress. But when overproduced for months or years, they can alter gene expression, probably with deleterious effects (see page 171). In the laboratory, the same factors can shorten telomeres — in the case of cortisol, by reducing the activity of telomerase. It is likely that the pathways that mediate alterations to gene expression interact with those affecting telomere maintenance, although this has yet to be explored.

Although many studies have unearthed (and continue to uncover) associations between stress and eroded telomeres, others have forged links between telomere shortness and common disorders. Rare mutations of genes encoding components of telomerase cause telomeres to be too short. This results in immune-system disorders such as aplastic anaemia, and other conditions including pulmonary fibrosis, diabetes, some cardiovascular diseases and certain cancers. Remarkably, many of these inherited diseases, recently named 'telomere syndromes'[4], are those that are commonly associated with ageing.

Telomere shortness can even predict people's statistical risk of developing certain conditions. For instance, for 10 years after their telomeres had been measured, men and women with shorter telomeres were three times more likely than those with longer ones to develop certain types of cancers such as pancreatic cancer[5]. If elderly, people with shorter telomeres were also 50% more likely than those with longer telomeres to develop dementia and 50% more likely to die from any particular cause[6].

Evidence that lifestyle, well being and other environmental factors can contribute significantly to disease has been accumulating for decades. But we now have three pairwise links involving three factors: stress with telomere shortness; stress with disease risks; and telomere shortness with risks for these diseases. It is hard to avoid the inference that at least one of the ways stress causes chronic diseases is by shortening telomeres.

TIME TO ACT

How can policy-makers act now on the wealth of evidence that is accumulating from studies of telomeres?

Dissecting the cellular and physiological pathways linking unusually short telomeres to stress and disease could prove important for finding possible targets for treatments. But policy-makers don't need to wait for all the mechanistic details to be filled in (which could take decades) — especially given that what happens in the laboratory often fails to reflect what is going on in the body as a whole.

A striking message from the telomere story is the importance of considering environmental as well as genetic effects in addressing disease. From 2008 to 2011, the US National Institutes of Health (NIH) allocated a total of US$29 million to genetic research. By comparison, over the same period, it gave only $14 million to all behavioural- and social-sciences research. This is despite several analyses attributing roughly 50% of the variance in early mortality in the United States to largely modifiable behaviours such as overeating, alcohol abuse and smoking (which are also stress-related in part)[7].

Using current technologies, people's gene variations are easier to track down than the plethora of influences coming from outside the body, let alone how people behave, think and feel. Yet capturing a person's vulnerability to disease will require understanding all these inputs. Telomere length provides an especially good window into global physiological status and is a bellwether of disease. (Interestingly, it is often more affected by a person's life experience than by which variants of telomere-maintenance genes they carry.)

Telomere research also points to some practical ways to improve health. Mice that are genetically deprived of telomerase quickly become wizened and grey but such changes, normally associated with ageing, can be at least partly reversed by restoring telomerase activity[8]. Designing drugs to boost telomerase in humans without inducing unwanted side effects is a formidable challenge. More feasible approaches to alleviating telomere shortening could involve mitigating the conditions that lead to chronic stress and helping people to change certain behaviours.

Encouragingly for this latter approach, some pilot studies suggest that just three months of stress-reduction interventions, often along with increased physical activity and dietary changes, may slow or even reverse telomere attrition by increasing telomerase activity. An intriguing challenge is to see whether the idea of telomeres eroding (which many have told us conjures up a striking image of declining health) could motivate people to change their behaviour.

START YOUNG

Individual efforts apart, perhaps the strongest message to come from the work on telomeres is that to pre-empt many common diseases, especially those that are becoming increasingly prevalent in the world's ageing population, governments and other policy-makers need to prioritize what we call 'societal stress reduction'. Meditation retreats or yoga classes may help those who can afford the time and expense. But we are talking about broad socioeconomic policies to buffer the chronic stressors faced by so many.

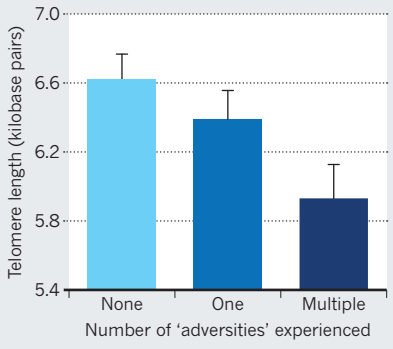
Together, the results from studies of telomeres, stress and disease reinforce a 2008 recommendation from the World Health Organization (WHO) for reducing health inequities. The WHO proposes that governments and global health organizations focus on improving education and the conditions surrounding early child development[9].

Several studies indicate that stress begins eroding telomeres in infancy, and maybe even before children are born. For example, studies have found that the more violence children had experienced, or the longer they had spent in an orphanage, the shorter were their telomeres[2]. Even young healthy adults whose mothers had experienced severe stress while pregnant (for instance, because of a close family member dying) had shorter telomeres than people whose mothers had relatively stress-free pregnancies[10].

What is more, the effects of stress early in life reverberate into adulthood. In more than 4,000 middle-aged UK women, for example, the more categories of adversity each woman had experienced as a child (such as physical abuse or parental divorce, unemployment or drug use), the shorter were her telomeres[3].

TELOMERES TELL

They are shorter in adults who experienced more trauma as children.



SOURCE: J. K. KIELCOLT-GLASER *ET AL. PSYCHOSOM. MED.* **73**, 16–22 (2011).

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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Competing financial interests declared; see go.nature.com/izngby for details.

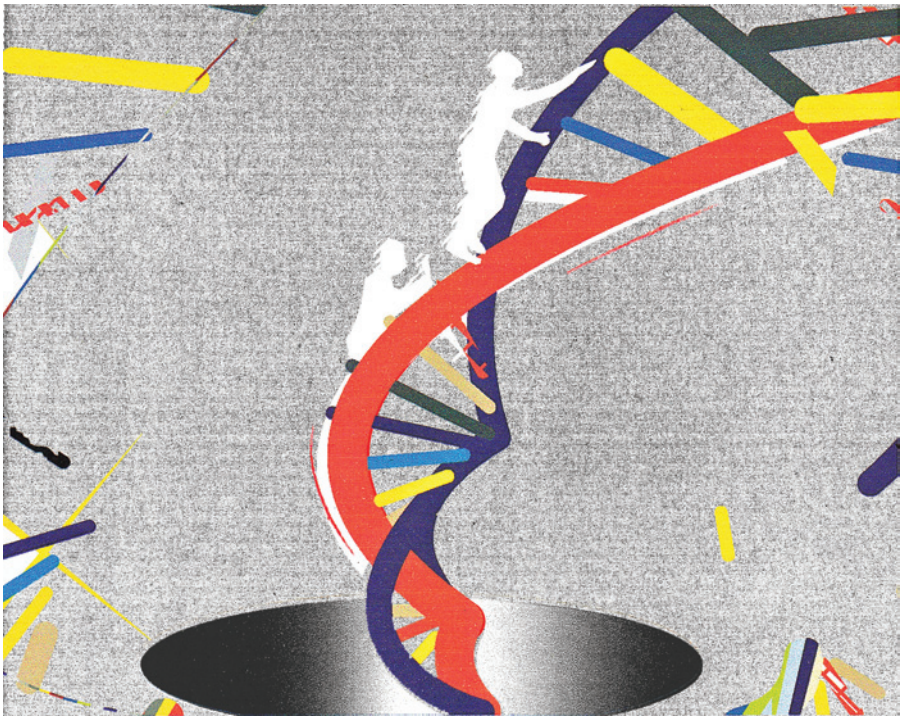


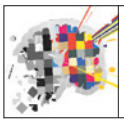
ILLUSTRATION BY PADDY MILLS

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.



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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). ▶