The Long and the Short of It

October 31, 2014

Think of your body like an automobile. Both require regular maintenance, periodic repairs, and safe handling. Both inevitably wear down — and much earlier when they're subject to excessive strain and lax care.

And like a rusted undercarriage or a dying battery, the physical signs of decay are often unseen, lurking at a microscopic level.

Over the last 2 decades, scientists have been uncovering startling findings about the cellular signs of premature aging and health risks. And psychology researchers have played a vital role in those investigations, linking this kind of cellular deterioration to chronic stress — the strain that accompanies long-standing unemployment, physical abuse, the death of a family member, and many other life adversities.

The focus of this work involves telomeres, the protective caps on the ends of chromosomes that protect our genetic data. Over time, as telomeres become shorter, cells age and die — a fate known as senescence. Studies have tied shorter telomeres to a wide range of aging-related diseases, including dementia, osteoporosis, diabetes, stroke, cardiovascular disease, and some cancers.

"This marker turns out to be one of the strongest predictors of early diseases of aging and in many studies of early mortality," APS Fellow Elissa S. Epel of the University of California, San Francisco (UCSF), a leader in this line of research, said during a presentation in May at the 2014 APS Annual Convention. "So it not only predicts the life of the cell, but it also predicts the health span of humans when they get diseases of aging."

Epel collaborates extensively with UCSF molecular biologist Elizabeth H. Blackburn, who with two other scientists discovered telomeres in the 1970s and later identified telomerase, the enzyme that rebuilds and maintains telomeres. The work earned Blackburn a Nobel Prize in 2009.

Over the last decade, these scientists and others have investigated how protracted psychological stress lowers telomerase activity, leading to shorter telomeres. This line of research represents the height of integrative science, incorporating disciplines that include psychology, immunology, epidemiology, genetics, and even nutrition.

Corrosion and Caregiving

With considerable evidence showing heightened rates of depression, health problems, and mortality among people caring for an ailing loved one, much of the research on telomeres and telomerase has focused on the stress associated with caregiving. In a ground-breaking 2004 study, Epel and Blackburn led a multidisciplinary team that examined telomere length in a group of physically healthy mothers, including some who were caring for a chronically ill child and control participants who had at least one healthy child living at home. Women in both groups filled out questionnaires rating their stress levels over the previous month.

In examining the participants' blood samples, the scientists found no difference in telomere length and telomerase activity between caregivers and controls, although questionnaire results showed that the caregivers had significantly higher levels of perceived stress.

But the research team also found significant differences *within* the group of caregivers. The first was a dosage effect in the form of time: The longer a mother had been caring for an ailing child, the shorter her telomeres and the lower her telomerase levels.

Secondly, those caregivers who did not consider themselves severely stressed did not show the same level of telomere shortening as did those who reported feeling highly stressed and unable to control events in life. In short, perception seemed to offset the cellular wear and tear that caregiving can inflict.

Researchers have also uncovered the extent to which the stress–telomere relationship affects the immune system. Immunologist Amanda K. Damjanovic, working with researchers like psychological scientist and APS Fellow Janice K. Kiecolt-Glaser of The Ohio State University, examined people who were caring for someone with Alzheimer's disease. The researchers found that caregivers had significantly more symptoms of depression than controls and also had shorter telomeres — including telomeres in the T-cells that protect the body from infection. This discovery signaled that the stress of caregiving seemed to hamper the immune system.

A recent study led by psychological scientist Idan Shalev (Pennsylvania State University) and APS Fellow Terrie E. Moffitt* (Duke University) explored the link between a history of depression and other internalizing disorders and shortened length of telomeres on white blood cells, the core of the immune system. The researchers, working with a team of researchers that included APS Fellow Avshalom Caspi of Duke University, examined data from people taking part in the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behavior among more than 1,000 people born between April 1972 and March 1973 in Dunedin, New Zealand. Using DNA from blood collected at ages 26 and again at 38, they found that leukocyte telomere erosion was accelerated among men — and only men — who had been diagnosed with depression, generalized anxiety disorder, or other internalizing disorders during those 12 years. Writing in the journal *Molecular Psychiatry*, the researchers offered a few possible reasons for the gender difference, including the fact that telomerase activity increases in the

presence of estrogen.

Socioeconomic Differences

Most of the studies on telomeres and telomerase have involved Caucasians, raising calls for expanded research with more diverse populations. But a couple of recent studies have found particularly high cellular-aging vulnerabilities among a different population — African American males.

Epel herself worked on a recently published study, led by University of Maryland social epidemiologist David Chae, involving more than 90 African American men ages 30–50. In addition to analyzing the participants' blood samples, Chae and his team measured internalized racial bias using implicit association tests to gauge unconscious negative attitudes about the men's own ethnicity. They also asked the men about their personal experiences with racial discrimination.

The researchers found that neither discrimination nor internalized racial bias alone had a clear association with shorter lengths in leukocyte telomeres. But among the men who scored high on both measures, the telomeres were significantly shorter.

Another study looked at cellular evidence of chronic stress among African American boys living in unstable environments. University of Michigan sociologist Colter Mitchell* , working with a team that included APS Fellow Jeanne Brooks-Gunn* of Columbia University, along with experts in pediatrics and molecular biology, tapped into the Fragile Families and Child Wellbeing Study (FFCWS). A joint project of Princeton and Columbia universities, the FFCWS tracked nearly 5,000 children born in US cities between 1998 and 2000. These children and their parents, who come from a wide range of social backgrounds, were interviewed at regular intervals between the child's birth and age 9.

The researchers wanted to focus on African American boys because past studies have shown that boys may be more sensitive to their environments than girls. They restricted their FFCWS sample to 40 boys whose mothers self-identified as black or African American. Of the sample, half of the boys were raised in disadvantaged environments, which the researchers characterized by such factors as a low household income, low maternal education, an unstable family structure, and harsh parenting.

To measure telomere length, the researchers analyzed DNA from saliva samples the boys provided at age 9. They found that the boys who grew up in disadvantaged environments had shorter telomeres than their advantaged peers.

Mitchell and his team went further, studying the role that genetic differences might play in telomere length among the boys.

They found the impact that the social environment had on telomere length was most pronounced in boys who possessed specific gene variants related to pathways for the neurotransmitters serotonin and dopamine. These variants are associated with high levels of environmental sensitivity. Socioeconomic status had only a small impact on telomere length among boys who did not possess these genotypes but was found to spur significant differences among those who did have them. That is, those in the genetically sensitive group had longer telomeres if they lived in advantaged environments and significantly shorter telomeres if they lived in troubled environments.

An Early Start

Indeed, research in recent years has shown that *early* childhood stress — in the form of abuse, neglect, or other adversities — can speed up cell aging late in life. Brown University medical researchers, for example, examined the DNA of healthy adults who had a history of childhood maltreatment and found they had shorter telomeres than those who did not experience child maltreatment.

Another study, led by Ohio State's Kiecolt-Glaser, involved yet another group of older adults caring for a family member with dementia, along with a demographically similar control group of noncaregivers. This study focused on proinflammatory cytokines, which play a central role in age-related diseases such as cardiovascular disease, osteoporosis, and Alzheimer's disease. Kiecolt-Glaser and her team collected blood samples and questioned the participants about depression, health, health behaviors, childhood abuse, and other early-life adversities — including the death of a parent, a family member abusing alcohol or suffering from mental illness, and lack of at least one close relationship with an adult.

Analysis showed that participants who reported at least one childhood adversity had significantly shorter telomeres than those who reported no childhood adversities. And caregivers — in addition to showing a comparatively higher level of depressive symptoms — had significantly shorter telomeres than did noncaregivers. Interestingly, childhood abuse had no impact on telomere length, but individuals who reported at least one type of abuse, or any other adversity, had greater levels of proinflammatory cytokines. That effect was magnified among caregivers.

Using telomere attrition rates as a measure, Kiecolt-Glaser and her team estimated that participants who reported multiple childhood adversities could die 7–15 years earlier than those reporting no adversities.

But how far back in childhood does the erosion begin?

Shalev, Moffitt, Caspi, and other collaborators found signs of it starting before puberty. In a longitudinal study published last year, the researchers recruited 236 children who were participants in the UK Environmental-Risk Longitudinal Twin Study, representing a cohort of individuals born in 1994 and 1995. Using buccal swab samples first collected from the children when they were 5 years old, they found that those who experienced two or more types of violence had shorter telomeres in a second buccal DNA sample collection at age 10. And this effect held even after the researchers adjusted for gender, socio-economic status, and body mass index.

A 2011 study showed that telomere attrition could actually start in utero. University of California, Irvine, investigators Sonja Entringer and Pathik Wadhwa led the research with Epel, measuring the leukocyte telomere length in 94 healthy young adults in Germany. Roughly half of the participants were known to have been born to mothers who had endured significant psychological stress (e.g., death of a family member, loss of their homes) during the pregnancy, while the other participants' mothers had experienced no major distress during pregnancy.

Adjusting for other factors ranging from birth weight to early-life adversity, the researchers found that the young adults who had experienced prenatal exposure to stress had shorter leukocyte telomeres compared to those in the control sample.

Taking this line of research a step further, Entringer and Epel investigated telomere length in newborns who had been exposed to prenatal stress. They measured psychological stress levels in 27 expecting mothers during early gestation, then collected samples of cord blood after birth. They found that telomere length in the cord blood was significantly lower for infants whose mothers had experienced significant anxiety during pregnancy.

The researchers say these findings provide evidence that maternal stress during pregnancy may, in essence, "program" the developing telomere system in the first weeks or months of life.

"This is shocking," Epel exclaimed during her APS Convention presentation last May. "To me this has tremendous indications for public health — about where we need to start our efforts when we think about aging and health."

Lifestyle Factors

But this evidence doesn't mean individuals' aging trajectories are fixed. Researchers have begun to discover behaviors and habits that seem to promote cellular longevity.

One of those protectors is mindfulness. Researchers led by psychological scientist Tonya Jacobs and neuroscientist Clifford Saron of the University of California, Davis, compared 30 participants at a meditation retreat held at the Shambhala Mountain Center in Colorado with matched controls on a waiting list for the retreat. Participants who took part in the retreat meditated 6 hours per day for 3 months.

At the end of the intervention period, meditators were found to have on average about 30% higher levels of the telomere-restoring enzyme telomerase than did controls.

In a multiyear study published a few years ago in *Lancet Oncology*, researchers compared 30 men before and after they adopted lifestyle changes following a diagnosis of low-risk prostate cancer. The patients started meditating; switched to a healthy, plant-rich, low-fat diet; exercised; and attended a support group. Subsequent testing showed higher telomerase activity and a 10% increase in telomere length among the participants. In fact, the more these men adhered to the lifestyle program, the greater their improvements in telomere length.

In contrast, a control group of 25 men who were not asked to make lifestyle changes showed decreases in average telomere length over the span of the study.

In another study, published this year, a team of researchers led by UCSF psychological scientist Eli Puterman showed the role that healthy living can play in offsetting cellular aging.

In the study, the research team examined three healthy behaviors — physical activity, dietary intake, and sleep quality — over the course of a year in 239 postmenopausal, nonsmoking women. The women provided blood samples at the beginning and end of the year for telomere measurement and reported on stressful events that occurred during those 12 months. Among women who engaged in lower levels of healthy behaviors, there was a significantly greater decline in telomere length in their immune cells for every major life stressor that occurred during the year. Yet women who maintained active lifestyles,

healthy diets, and good-quality sleep appeared to be protected when exposed to stress: Accumulated life stressors did not appear to accelerate their telomere shortening.

“This is the first study that supports the idea, at least observationally, that stressful events can accelerate immune cell aging in adults, even in the short period of 1 year,” Puterman said. “Exciting, though, is that these results further suggest that keeping active and eating and sleeping well during periods of high stress are particularly important to attenuate the accelerated aging of our immune cells.”

In other words, proper maintenance can offset the physical wear and tear that distress exacts as we age. œ

To watch Elissa Epel’s address at the 2014 APS Annual Convention, visit www.psychologicalscience.org/r/taking-it-easy.

** Terrie E. Moffitt will deliver a keynote address at the inaugural International Convention of Psychological Science, March 12–14, 2015, in Amsterdam, the Netherlands.*
** Jeanne Brooks-Gunn and Colter Mitchell will be speaking on fragile families as part of an invited symposium at the 2015 APS Convention, May 21–24 in New York City.*

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