Biological Psychiatry: Celebrating 50 Years

Telomeres, Trauma, and Training

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There was no glamour in this. My first patient of the New Year was a 5-year-old found in a clothes dryer, face bloodied. She had been hit by her pregnant mother, hit over and over with a bludgeon of pantyhose stuffed with shards of broken glass. How could I survive?

—Samuel Shem, *The House of God*

Immortality. The idea has captured human attention for thousands of years: from Herodotus' writings in the 5th century BC to Ponce de Leon's quest for the Fountain of Youth (spoiler alert: it's not in Florida) to *Harry Potter and the Sorcerer's Stone*. At its core, though, immortality is not just an existential question, but a biological one. Our bodies are composed of 37.2 trillion cells. Each day about 2 trillion of them divide in order to replace dead or damaged cells. In our skin alone, 30,000 to 40,000 cells die and are replaced every minute. But how many times can cells divide before things go awry?

The dogma of the early 20th century was that cells could, in fact, divide indefinitely (1). This idea was propagated by French surgeon Alexis Carrel, who grew embryonic chicken cells that purportedly lived for 20 years—longer than the life span of an actual chicken! But Carrel's results were never replicated, and in the 1960s, anatomist Leonard Hayflick demonstrated that fetal cells in culture divided only 40 to 60 times before becoming senescent and ceasing to divide. This new idea—that there was a fundamental limit on the number of possible divisions—came to be known as the Hayflick limit.

Why can't cells divide forever? The problem stems from a basic aspect of DNA replication. Because of the mechanics of how RNA primers engage with linear DNA (always moving in the 5′ to 3′ direction), it is not possible to copy the tip of the lagging strand. Thus, every replication necessarily leads to some amount of shrinkage, and over time, the incremental impact can become significant. Solving this "end replication problem" became a central question in biology.

The answer emerged across generations of work by three female Nobel Laureates. Barbara McClintock was first, in the 1930s and 1940s—during her research on maize plants, she observed that the damaged ends of chromosomes would become "sticky" and behave differently from natural ends. This led her to conclude that the tips of chromosomes must normally be protected by some sort of cap to maintain stability and prevent them from fusing together. This confirmed earlier work that the ends of chromosomes were not susceptible to genetic alterations (deletions and insertions) and so must be sheltered (2).

Next came Elizabeth Blackburn. In 1978, working with an invertebrate model, she elucidated the actual form of a telomere: a tandemly repeated hexanucleotide sequence, $(TTGGGG)_n$, that occurred at the end of each chromosome. A similar guanine-rich pattern was then discovered across all eukaryotes (in humans a $[TTAGGG]_n$ repeat). While this work demonstrated the existence of a protective region at the end of each chromosome, it left open the bigger mystery: if every replication leads to shrinkage but organisms live longer than 40 to 60 cell divisions, how then do the telomeres re-expand?

Finally, in the 1980s, Blackburn's protégé, Carol Greider, discovered a mechanism: telomerase, an enzyme designed to expand the tandemly repeating sequence and thereby preserve the function of the region. In humans, this enzyme is (not surprisingly) expressed most robustly in germline cells and some types of cancer cells (which manage to hijack telomerase, thereby gaining the ability to proliferate indefinitely).

For most of our lives, this system remains in homeostatic balance—telomeres may shrink with replication but are restored by telomerases. Ultimately, with age and with oxidative stress, the telomeres become worn down and are no longer able to protect the chromosomes. At this point the cells may begin to have compromised function and ultimately apoptose.

While we tend to think about cellular division and replication as reductionistically distant from our day-to-day clinical work, it may actually lie at the heart of some of our most complex clinical phenomena. One striking example in psychiatry is the broad range of conditions now known to be associated with adverse childhood experiences (ACEs). For more than 30 years, ACEs (such as household violence, parental divorce/separation, abuse, and neglect) have been shown to confer a host of problems later in life (3). Seemingly inexplicably, these include increased cardiovascular morbidity and mortality, diabetes, stroke, emphysema, and cancer, to say nothing of psychiatric conditions, such as depression and substance use disorders (3–5). Estimates of the impact of ACEs on overall mortality indicate up to a 20-year loss of projected lifespan (6). Moreover, there seems to be a dose-response relationship in which more ACEs correlate with increased risk for these downstream consequences (6). These findings have been mystifying. How can early trauma get "under the skin" and cause such a diverse range of biological illnesses and dramatically foreshortened mortality?

Enter telomeres. It has long been known that telomeres are vulnerable to various forms of stress, including oxidative stress. What has only recently been demonstrated is that both subjective and objective measures of stress correlate with shorter telomere length and lower telomerase activity (7). This may prove to be the missing mechanistic link between the well-established hypothalamic-pituitary-adrenal axis dysfunction seen with ACEs and their multifarious associated downstream health consequences (5). It is not just that

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hypothalamic-pituitary-adrenal axis dysfunction causes a proinflammatory milieu but that the overload of oxidative stress on the system may also lead to early senescence of immune cells (7).

While these findings demonstrated that early, severe trauma may disrupt normal telomere regulation, only recently has it become clear that later life experiences may have a similar impact. And one of the most interesting results in this regard comes from a seemingly unlikely—and uncomfortably close to home—study.

Over the past 12 years, the Intern Health Study has been following young physicians as they progress through their medical training (8). The initial impetus for the research was to use medical training as a unique model system to explore, prospectively, the impact of a uniform and substantial stressor on a large and relatively healthy population. By engaging participants both before and throughout their training, researchers have been able to meticulously explore the impact of various risk and protective factors (both internal and external). Data include levels of depression at various time points, number of stressful life events, and average work hours. The findings, drawing from approximately 20,000 trainees, have been eye-opening: the point prevalence of depression in interns is around 25%, and the cumulative annual prevalence may be 40% to 50% (9).

In this issue of *Biological Psychiatry*, researchers from the Intern Health Study now report perhaps the most shocking and disturbing finding to date (10). Using salivary DNA, they found that in 247 physicians the average telomere length decreased over the course of internship by 143.5 base pairs—nearly 6 times what was reported in a reference meta-analysis. Furthermore, telomere attrition increased exponentially with increasing intern work hours: those working 75 or more hours per week lost more than 750 base pairs—30 times that of a normal year of life.

On one hand, these data offer a tantalizing glimpse into the future of psychiatry—the development of real, actionable biomarkers. Historically, we have had little ability to quantify the subjective experience of "stress." This study opens up the possibility that we could objectively measure the impact of stressful events, monitor individuals at highest risk, implement treatment for those in need, and track progress using clear metrics. It will be fascinating to see the extent to which this approach can generalize to other types of life stressors and with specific psychiatric populations.

At the same time, these data turn a dark mirror on the medical profession itself. When *The House of God* was first published in 1978, it scandalized the nation with its searing, satirical view of the inner workings of the medical establishment: the massive structural flaws; the rank abuse of physicians in training; and the shamefully poor, dehumanizing patient care that resulted. Yet despite the uproar that the book caused, substantive change has (at best) been slow.

Four decades later, the work of the Intern Health Study continues to call attention to critical issues in the field of medicine. The present data make it clear that the current protections in place for young physicians remain woefully inadequate. Perhaps learning that biological aging is accelerated as much by abusive work hours as by childhood abuse will propel key stakeholders to finally implement large-scale structural solutions. Assuming that the responsibility of a physician will always entail some degree of stress, our goal must be to support and protect trainees enough that the stress remains manageable. The future of our profession—and our telomeres—depends on it.

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