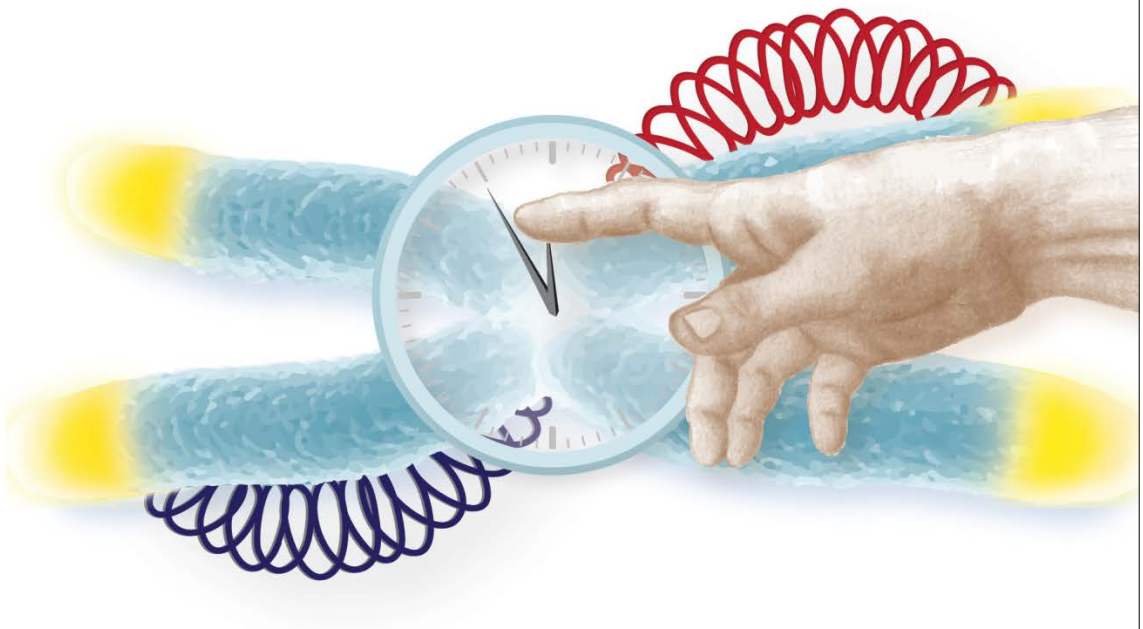
TELOMERE TIMEBOMBS

Defusing the Terror of Aging



ED PARK, MD

This is a free sample chapter from the book “Telomere Timebombs - Defusing the Terror of Aging.” The complete book is available from booksellers, in Kindle format, and as an audiobook on Audible.com

Praise for Telomere Timebombs:

"Dr. Ed Park is on to something. A new way to age by turning back the clock!"

- Suzanne Somers, Best-selling author and wellness expert

"Dr. Ed Park is one of America's leading physicians in personalized and preventative medicine – and one of the first to understand the clinical and critical importance of the biology of telomeres and telomere measurement as a biomarker for aging and health."

- Stephen J. Matlin, CEO, Life Length

"In my view, Dr. Park has chosen the correct attitude for us to think about the process of aging…For example, he first asks, not if aging will be slowed, but "When will aging become a thing of the past?" He then answers "Aging will soon become a choice rather than a curse… His writing style and persuasive logic are a pleasure to read.

- L. Stephen Coles, M.D., Ph.D., UCLA's Gerontology Research Group

"If you know Ed Park the way I do you know that Ed Park has no trouble thinking outside the box. The result is Ed's explanations, logic, and organizational style in this work are spot on, entertaining and 100% unique- like Ed himself! If you are looking for a comforting rehash of what has been said and written before you won't find it here. Ed digs deep and pulls no punches. He basically says out loud what many of us think but are afraid to say. 'Telomere Timebombs' is like no other book out there! Get it, read it and learn it, then use it to enlighten the world!"

- Dave Woynarowski MD, Author-The Immortality Edge

"If you want to know about living longer and healthier, Dr. Park is your man. If you want to know more about the origins of cancer and its treatment then Dr. Park is your man. His anecdotal studies are most impressive and speak to the effects of TA-65 on the action of telomeres and it seems that telomeres have been studied extensively allowing him to make statements about how long we can expect to live so if you care about a long life Dr. Park is your man"

- Dr. Arthur Janov, Director, Primal Center, Santa Monica, CA

Telomere Timebombs – Defusing the Terror of Aging by Ed Park, MD

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Chapter 3: What is a telomere?

> *"The curse of mortality. You spend the first portion of your life learning, growing stronger, more capable. And then, through no fault of your own, your body begins to fail. You regress. Strong limbs become feeble, keen senses grow dull, hardy constitutions deteriorate. Beauty withers. Organs quit. You remember yourself in your prime, and wonder where that person went. As your wisdom and experience are peaking, your traitorous body becomes a prison."*
>
> - Brandon Mull, *Fablehaven* (Aladdin, 2007)

Telomeres are timebombs on the end of every chromosome; hence the title of this book! Perhaps a better way to visualize would be to consider them burning fuses at both ends of a firecracker.

Telomeres are like burning fuses at the tips of chromosomes

We know that when the fuse reaches the firecracker, bad things happen. Likewise, when the telomeres in your stem cells burn too low, your genetic library becomes fragmented and recombined in unnatural ways.

The idea of billions of your chromosomes exploding daily might fill you with fear. Don't let it! As we will learn, it is an essential part of how our systems function properly.

The Central Dogma of Molecular Biology

Think of a chromosome as two very long text messages running in opposite directions. When I say long, I'm talking 50-200 million letters. Each of our 23 chromosomes has over 1,000 genes, or smaller segments, that encode for proteins, but these actual genes that encode "information" account for only 2% of the DNA and there are other many other poorly understood areas for controlling the expression of those genes and the form and function of the cell.

The "text" of the message consists of one of four distinct DNA molecules that we will call A,G,C and T. So a DNA chain, or chromosome, can be read as GATTACA, or whatever, 100 million times. It is a rule that the A type always pairs with the T type on the opposite, or complimentary, strand side. So let's say that in the diagram above, A is the red and T is the green. Do you see how they pair up? Likewise, a G always pairs with a C, and those would be the yellow and blue DNA molecules. Each rung of the chromosome's double helical ladder is what is known as a "base pair" and the base pair is the unit of length measurement to which we will refer when we discuss telomere lengths later. One entire chromosome might be 100 million base pairs but the telomere tips or burning fuses, are a maximum of about 15,000 base pairs in length in humans.

So unless there is a typographical error, one side precisely dictates how the other side, or its complimentary strand, must be assembled. Together, they are like a zipper. One strand consists of "the sense" and the other is just the other half of the zipper and is known as the "anti-sense" strand.

Without the unzipping and the precise assembly of complimentary strands, a process known as DNA replication, one mother cell could never divide into two daughters.

All life, I repeat, ALL life on this planet uses this exact same genetic coding language of DNA. Each gene is a discrete short sequence that can be transcribed into what is called messenger RNA. Messenger RNA, like the paper in a fortune cookie, emerges from the nucleus of a cell and is fed into micro-machines called ribosomes, which translate each three "letter" RNA message into the appropriate next amino acid in that protein, which is just a chain of amino acids.

If it takes three letters to encode an amino acid, then a gene encoding a protein with 100 amino acids would need to be at least 300 base pairs long. Get it?

Let's say the DNA message is "GTT." The messenger RNA would have to read "CAA." That CAA tells the ribosome that the next amino acid will be glutamine. The assembly of a chain of amino acids makes what we know as a protein and depending on the amino acid sequences, they predictably fold into shapes that will dictate their form and function in the body. Scientists call the process of transcription and subsequent translation from

the gene's DNA, into the messenger RNA, and finally into the gene's specific protein, the "central dogma of molecular biology."

By some inexplicable miracle, this same process takes place IN ALL LIFE ON THIS PLANET. Somehow, this process dictates cellular development and cooperation and results in amazing things from dragonflies to concert cellists when it occurs in stepwise and orchestrated fashion (pun intended).

So now that you understand the basics, let's ask a question: "Why do we have telomeres?" The answer is because our chromosomes are long and linear, not short and circular. I will explain by describing "less evolved" life forms that we call bacteria.

The Eukaryotic Revolution

Although bacteria use the same genetic machinery, they are each loners, or single cell organisms that possess only a miniscule circular chromosome. Bacterial chromosomes easily reproduce like one soap bubble becoming two soap bubbles and they don't have telomeres. There aren't any tips to protect with telomeres because a circle has no ends. That is also why bacteria (also known as "prokaryotes" or "before the kernel") don't need a cell nucleus that protects their precious genetic library like our eukaryotic cells do. Eukaryotes comes from the Greek for "good kernel" or "good nut" meaning those cells have a nucleus.

About 1.5 billion years ago on this planet, it is thought that some bacteria became incorporated into protozoan cells in a process known as symbiogenesis. "Genesis" means the creation of new life and "symbio" is short for symbiosis, or the interdependence of two distinct species for their mutual survival. This eukaryotic revolution was pivotal for the evolution of more complicated life forms on earth.

In plants, those bacterial helpers contain chlorophyll and are known as chloroplasts. They convert sunlight into energy by photosynthesis. In animal cells, the bacteria that were incorporated are now known as mitochondria and they use chemical reactions to power our cells.

Having a nucleus, like a protected bubble inside the bubble of the cell itself, allowed for the development of extremely long and elaborate genetic libraries that we know as discrete chromosomes. In humans, we have 22 pairs (one set from mom and one set from dad) and the 23rd pair is known as the "sex chromosomes." If you have two "X" chromosomes as your 23rd pair, you are female. If mom gave you an "X" but dad gave you a "Y" type 23rd chromosome, you are genetically, male.

As crazy as it sounds, the system of AGCT is the same one in all living things on this planet. There is no other way. Does a tree look like a fruit fly or an Olympic sprinter? In terms of molecular biology, they are indistinguishable. Believe it or not, Hussein Bolt and a Bristlecone Pine both use the same universal code for their 22 amino acids.

When condensed prior to a cell's division into two daughters, chromosomes look like furry bowties, like two silk worms twisted together near the middle. The number of chromosomes in a eukaryotic nucleus can vary from just one in a jack jumper ant to over a thousand per nucleus in the adder's-tongue fern. Chickens and dogs possess 78 chromosomes in each nucleus whereas cabbage has only 18 chromosomes in the nucleus of each of its cells.

You might ask yourself, "How the heck does a cell keep track of which chromosomes go to which daughter?" Using humans as the example, each daughter cell needs 46 chromosomes. Each one gets one copy of chromosomes number 1 through 23, both the maternal and paternal versions. A daughter cell has no use for an extra 21st chromosome, endowing her with 47 but leaving her sister cell with only 45 chromosomes.

When the chromosomes are distributed unevenly in the egg (or in less than 10% of cases, the sperm) we can get a problem that is like having 53, not 52 cards in a deck. The most common viable form of this trisomy (or three sets of chromosome copies) is called Down's syndrome and it occurs usually because mom's egg had an extra copy of the 21st chromosome before joining with dad's 23, giving a grand total of 47 chromosomes per cell, not 46.

The answer to my earlier question of how dividing cells keep track of which chromosomes go to which daughter is currently "we don't know." What we do know is that before cell division, chromosomes line up like dancing partners at a Virginia Reel or a Soul Train if you will. Forty-six chromosomes, or chromosomes #1-23 from your mother and #1-23 from your father will go to daughter A on one side and a matching set of 46 will go to daughter B. Chromosomes destined for A and chromosomes destined for B line up opposite each other right before the cell divides.

The chromosomes are tethered to spider webs called microtubules at their midsection (the centromere) and also at the their ends (the telomeres) so when the cell splits right down the middle, half the dancers are pulled one way and the other half are pulled the other way. In this way, both daughters end up with perfect copies of 46 chromosomes: 23 from mom and 23 from dad.

This process happens billions of times a day in your body just as the same cell division dance is taking place in all cells of all plants and animals. As inefficient as it may seem, every eukaryotic cell carries with it the entire library of its genetic information. For

humans, the sum total of our 46 chromosomes, listed as one long message, would roughly be the equivalent of 6 GB of information if you consider one A-T base pair to be a byte.

Stay with me because we're almost done with the bare necessities of genetic knowledge. Remember that one side of the zipper has the sense and the other has the anti-sense? Reading the DNA code in the sense direction would be like listening to The Beatles' song, "Revolution 9" normally. Anti-sense is like playing it backwards on a turntable with the hopes of making out some hidden message.

Each single strand of DNA has polarity like the positive and negative ends of a battery. One end of the DNA strand is known as the 5'end (read as "five prime") and the other is always the 3' end ("three prime"). It turns out that a DNA chain can only be assembled in one direction. I repeat: a DNA chain can only be assembled in one direction.

The sense strand that is assembled to match the anti-sense strand is called the leading strand because it is continuously and easily assembled in the 5' to 3' direction.

In contrast, assembling the anti-sense single strand that sits across from the sense single strand requires Okazaki fragments, which are discrete segments of 5' to 3' matching DNA that are 'backfilled' and connected like splicing a cassette tape hundreds of times as needed.

This unidirectional assembly is critical to understanding why telomeres must shorten every time one mother divides into two daughters. It is known as the "end replication problem" although I totally disagree with the pejorative term "problem." The "end replication problem," simply stated, is that you cannot assemble the anti-sense strand to the tip because the molecules doing the copying are not able to start exactly at the end. Therefore, every cell division results in the loss of 50 to 100 base pairs.

This failure to copy to the end results in what we call "replicative senescence" or aging from repeated copying of the DNA. It is as true as saying a ball can only bounce a percentage of the height that it is dropped from and has nothing to do with anything other than simple mechanics.

"Every dogma has its day"

- Anthony Burgess

Here's an interesting question:

Q: Are cells immortal or do they a have limited number of divisions in them?

A: Yes!

Confused? Well the answer is both. Or rather, it depends on how ‘stem-like’ they are and how much telomerase activity they possess. I am not a big fan of dichotomy: good versus evil, Democrat versus Republican, etc. But in the case of whether cells are immortal or not, two opposing scientists embody this debate nicely: Alexis Carrel and Leonard Hayflick.

Alexis Carrel, representing cellular immortality, claimed to keep cells from a chicken heart alive for over 20 years from 1912 to 1932. Sound incredible? Well, there is a cell line from a woman named Henrietta Lacks called HeLA that represents her cervical cancer cells and they are still used for standardized lab testing today because they are still alive and reproducing. Read more in Rebecca Skloot’s bestseller, *The Immortal Life of Henrietta Lacks* (Broadway Books, 2011). Incidentally, TA-65, a telomerase-activator mentioned later in this book, was validated as being a telomerase activator on Henrietta’s immortal cervical cells.

In the “cells are not immortal” camp is Leonard Hayflick who put differentiated skin cells into a dish and found they became non-viable and dysfunctional within 40-50 cellular divisions or doublings. This beloved “Hayflick Limit” is in keeping with many people’s limiting beliefs about our own potential immortality.

We will discuss it further in Chapter 5: “Stem Cells,” but trust me when I tell you that there are two generally recognized traits of “stemness.” First, is the ability to self-immortalize (which is directly correlated to telomerase activity, described in the next chapter). The second trait of stemness is the ability to divide asymmetrically. Asymmetric division means that a mother stem cell is capable of dividing into two distinct types of daughter cells: an identical mother stem cell copy and a more committed and differentiated daughter cell.

Carrel’s embryonic cells were sufficiently undifferentiated enough “mother stem cells” types so they were self-immortalizing. In contrast, Hayflick’s cells were telomerase-inactive daughter cells, destined to “burn out” like all non-stem/non-telomerase-active cell types.

So now we see that both Alexis Carrell and Leonard Hayflick were right. It’s just that they were constrained by a false dichotomy!

So, What is a Telomere?

We can now understand why telomeres exist, or at least what “purpose” they appear to serve. This is related to what happens to the cells’ chromosomes when their telomeres get too short, or the fuses burn down to the firecracker. This understanding was elucidated by

Hermann Muller, a research scientist in Woods' Hole in the 1930s, twenty years before Watson and Crick described the DNA's double helical structure.

Muller's experiments involved irradiating fruit flies to produce mutants with deletions and inversions involving the ends of chromosomes. High energy rays produce DNA breaks, which is why UV exposure promotes skin cancer. Although Muller's DNA damage was artificially generated, the same uncapping is inevitable in telomeres as they erode from the replicative senescence that we just learned about.

> *"Of note, he never found mutants with deletions or inversions involving the natural ends of the chromosomes and concluded that: 'the terminal gene must have a special function, that of* ***sealing the end of the chromosome****, so to speak, and that for some reason a chromosome cannot persist indefinitely without having its ends thus sealed.'*
>
> *Muller coined the term telomere for this terminal gene from the Greek, meaning simply ''end part,'' but the fact that this region of the chromosome deserved a specific name was a recognition that something unusual was going on there."*
>
> - excerpted from: McKnights article "Plant Telomere Biology", *The Plant Cel, April 2004*

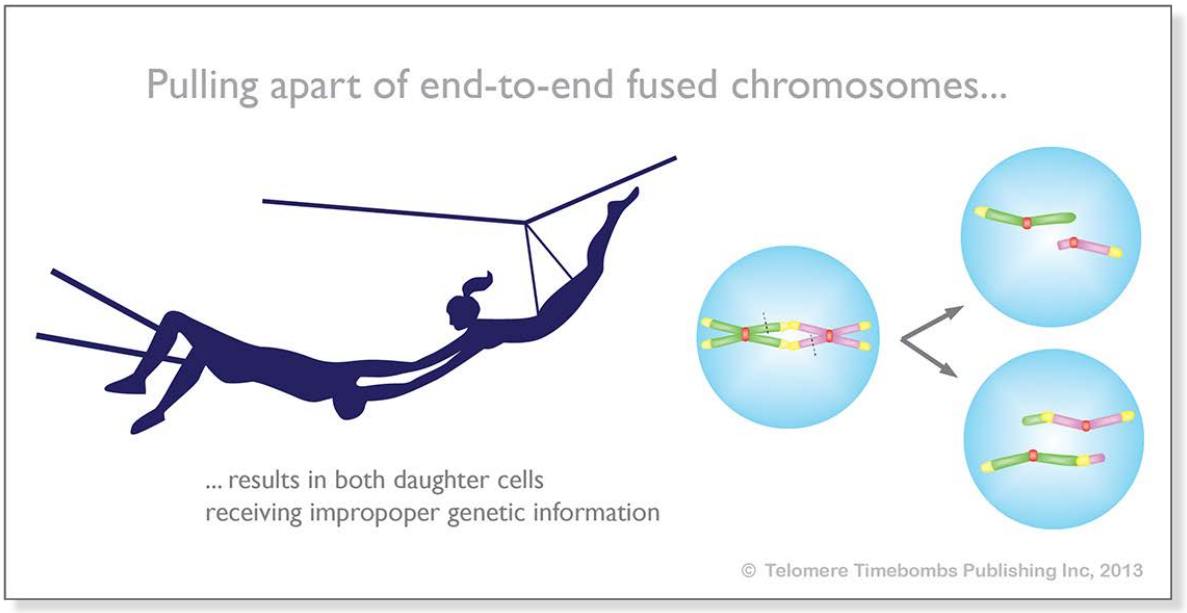
Muller used experiment and observation to correctly deduce the function of telomeres long before we even knew the structure of DNA. In short, telomeres cap and protect the ends of the DNA like the plastic tips of shoelaces.

Teleologically (no pun intended), the reason DNA can't exist uncapped is due to a critical process, always on, known as "double-strand breakage repair." When the enzymes responsible for genetic surveillance "see" an uncapped chromosome end, it "thinks" that the cut end needs to be rejoined to another cut end. To the double-strand breakage repair "team" inside the nucleus, it's as if Hermann Muller made one clean ultraviolet zap to slice a chromosome and the team needs to tape those ends back together again.

Now we can view the system with a clear understanding based in function, biochemistry, and that is sound from an evolutionary standpoint. Uncapped ends of DNA (or ones with critically-short telomeres from replicative senescence) are recognized by the double-strand breakage repair mechanisms and then inappropriately attached or spliced to existing, capped chromosomes.

When one chromosome is attached to another, we get a double chromosomes, like two trapeze artists Krazy Glued at the hands. The next time the mutant double chromosome or

double trapeze artist is pulled apart they will tear not at the hands, but at the shoulders or somewhere else, leading to endless possibilities of mutation.



Fused chromosomes will result in uneven distribution to daughter cells

Because of double-strand breakage repair, telomere shortening leads to double chromosomes, which leads to uneven segregation and that process cannot be corrected but rather worsens with each cell division. This is not a “bad” thing. It is a part of the system that is expected and dealt with by many mechanisms. It is only when the master copy stem cells acquire errors and fail to self-destruct that we encounter problems.

“This Tape Will Self-destruct in Five Seconds…”

The final tool we need for complete understanding of my stem cell theory of aging is called "apoptosis" or the unfortunately named “programmed cell death.” Since DNA erosion at the telomeres is inevitable, the splicing and mutation of the genome (a term describing the sum total of a cell's chromosomes) is also inevitable. When the chromosomes line up to divide, if there is an asymmetry detected by what’s called the “spindle assembly checkpoint,” the cell’s division can be prevented, effectively preventing mutation to propagate to the next generation of daughters.

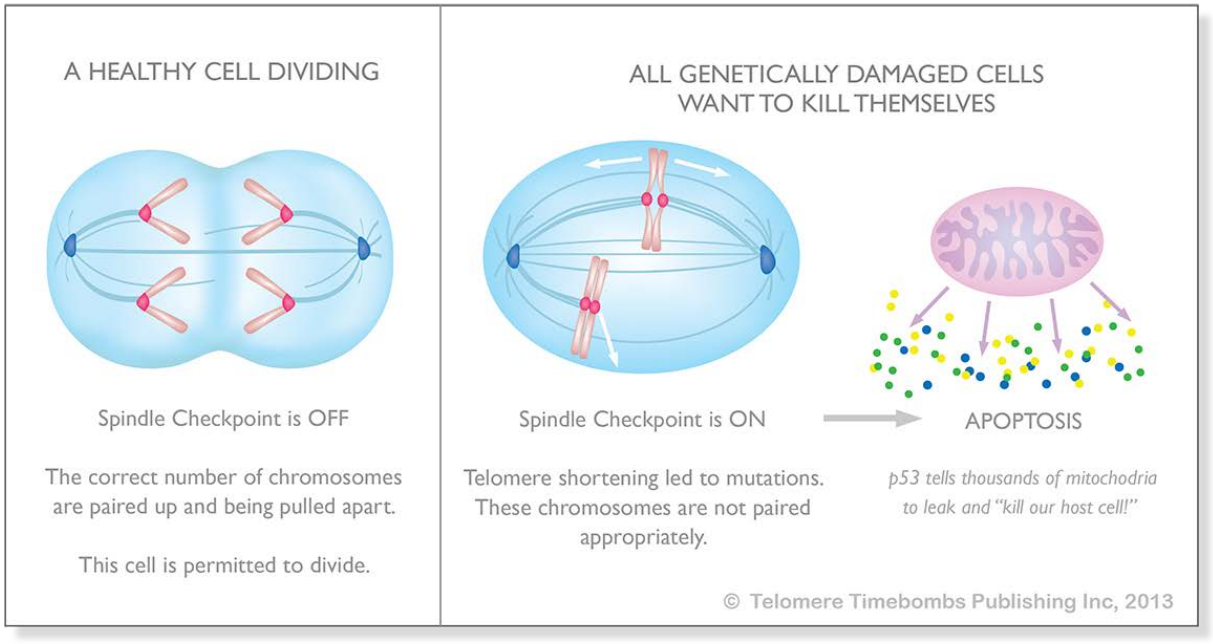
Spindle assembly checkpoint activation is like a fire alarm. It indicates the chromosomal pairing is not symmetric, or that one player will get 51 cards and the other will be getting

53. The activated checkpoint signals the enzyme p53, which is known as the "watchman of the genome" because of its central role in recognizing and responding to genetic damage.

When p53 decides it is time to activate the apoptosis or death program, it signals that cell's battery acid-containing mitochondria to melt the host cell like the Wicked Witch of the East taking a shower. This is accomplished by essentially poking holes in the cell's thousands of mitochondria, which are filled with a sort of battery acid.

This purposeful melting from within explains the red herring of mitochondrial damage and oxidation seen in older cells. I believe those features are not the cause of aging as most people currently believe, but rather the result of the damaged cell's attempt to self-destruct.

This "oxidation as a red herring" hypothesis will not sit well with many people who are deeply invested in their theories of aging and pushing anti-oxidants, but in my opinion, it is hard-to-vary and therefore a better explanation.



Damaged cells want to kill themselves by apoptosis

We must understand that apoptosis is a key function of every cell. In a variety of ways, cells are constantly checking for their own defects and willing and able to kill themselves if and when their own genetic damage is severe enough.

In the case of differentiated cells, like those that Leonard Hayflick studied, this is a good thing. As a thought experiment, if all cells were immortal and dividing, then within hours we would all become giant unsustainable blobs because two immortal cells would become 4, 8, 16, 32, etc., geometrically expanding into infinity and beyond, to borrow a phrase.

In the case of less differentiated, more stem-like cells like the ones that Carrel kept alive for 20 years, apoptosis was not widespread because the telomere fuses were maintained in length by telomerase. This prevents the inevitable telomere shortening, inappropriate splicing, mutation by uneven segregation at cell division, p53 activation, and mitochondrially-mediated self-destruction from ever taking place.

Did you know that chemotherapy works by the same mechanism? The goal of chemotherapy is to cause a lot of genetic damage in rapidly-reproducing cells so that the innate error detection mechanisms will kick in and apoptosis can occur. However, DNA mutation will eventually lead to more cancers down the road so a more precisely directed solution is desirable.

Causing DNA damage with chemotherapy to cure cancer is kind of like trying to solve inner city gang violence by sending in more guns and removing teachers and police officers.

In conclusion, chromosomes are simply long, paired DNA strands that contain instructions for RNA messages that are subsequently translated into proteins. Erosion is inevitable because of mechanical reasons and that is a good thing except in stem cells.

When the telomeres erode too much, stem the cell’s repair mechanisms initiate new splices that will spell the doom for future descendants because chromosomal mutation from uneven separation at cell division will trigger p53 to cause apoptosis or cell suicide.

Twenty years in a dish? Just how did those chicken heart stem cells manage that? That is the subject of our next chapter describing a magical, mystical enzyme called telomerase.

I hope you enjoyed this sample chapter of
Telomere Timebombs: Defusing the Terror of Aging.

To get a copy of the book, visit http://telomeretimebombs.com

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