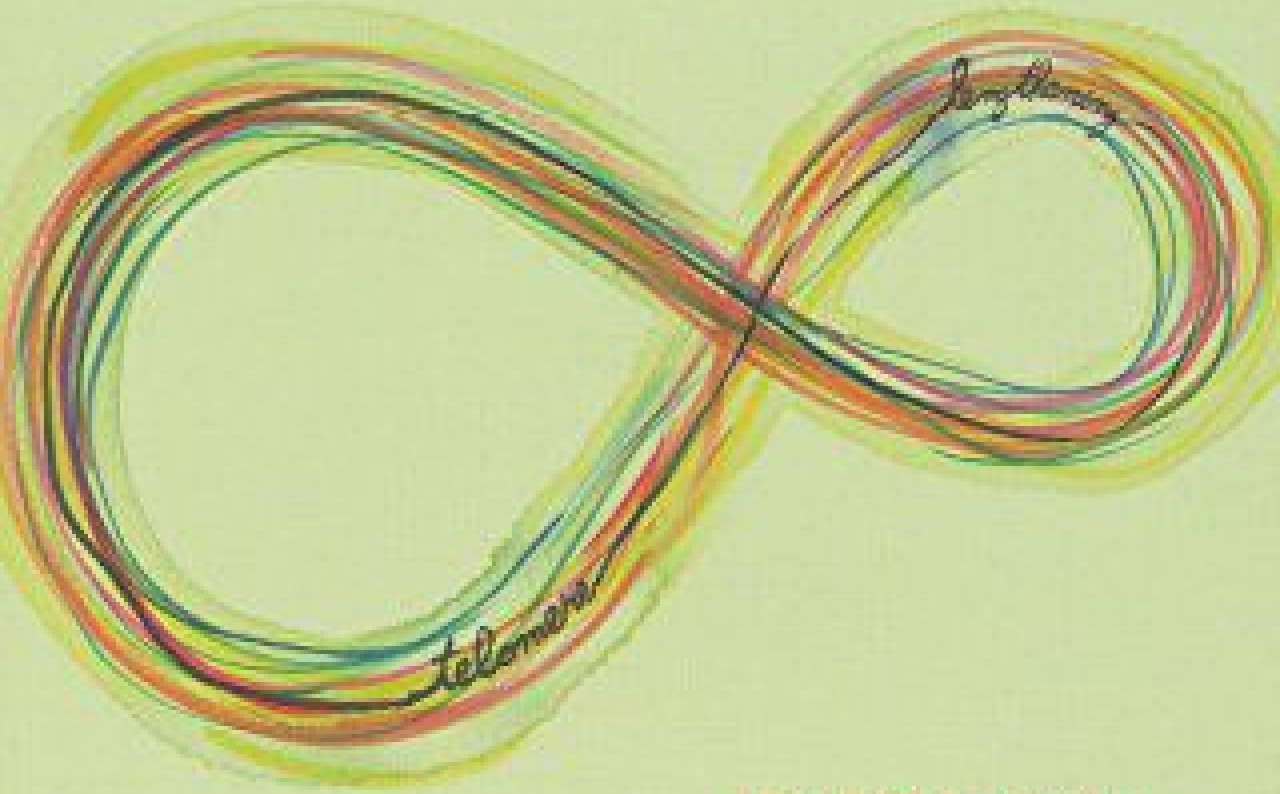
Telomere Lengthening

Curing all diseases including cancer and aging



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INTRODUCTION

I plan to live forever.

That was the first sentence of the book I wrote three years ago. It's just as true now as it was then, and the last three years have brought that plan a little bit closer to fruition. Anti-aging science is pushing forward at a remarkable rate, and it can be dizzying to be at the forefront of it all.

So then why take the time to sit down and write a second book? Well, whenever science or technology moves forward at this pace, it leaves a lot of misinformation in its wake. Some of that is well-meaning misinformation based on healthy skepticism. Some of it is dystopian fiction that starts sounding less fictional after being repeated a thousand times. The worst of it is intentional fear, uncertainty, and doubt being spread by those who have a vested interest in doing so.

It's important to set the record straight. Because, ultimately, it's public attitudes that will determine how fast a cure for aging becomes a reality. The science itself is clear and rather straightforward: it is completely possible to convince our bodies to stop aging. It is completely possible to live long, healthy lives

at our physical prime. And it is completely possible at a level of technology that is extremely close to what we already have today.

If we as a civilization want the cure, then we will have it. If we obstruct it, whether out of fear that it's too good to be true or disbelief that it's real, then we won't have it for a few more generations, and a billion people will age, decline, and die in ways they never had to.

It's public energy that drives technology forward. Science doesn't turn into technology without energy being behind it. energy to invest in prototypes, to promote adoption, to focus our attention on adopting a new way of thinking and a new way of living. Without that energy, all that's left is the potential to do something great when we eventually get around to doing it.

There are many examples of technology that just sat around without anyone adopting them for decades. To take one example, air conditioning was first invented in the early 1800s. Dr. John Gorrie, one of the more notable contributors to this invention, patented his "improved process for the artificial production of ice" in 1851, describing a close precursor to what we would see as the modern air conditioner.

But there were strong forces that opposed this technological

advance. It was huge business at the time to send ships to the Arctic, cut and harvest enormous chunks of ice, and ship them back south for use in iceboxes. Big dollars were on the line. So Gorrie was relentlessly mocked in the press, lobbied against in Congress, and ultimately died in poverty. Rumors were spread about imagined dangers of air conditioning, especially the rumor that an air conditioner would inevitably spew bacteria into the air. It became clear that anyone supporting or investing in the idea could suffer Gorrie's fate. Ultimately, no one would touch the idea with a ten-foot pole for decades.

It would be nearly a century later that air conditioning started to become a reality . and only because the United States Navy needed its ice-harvesting ships for military purposes during World War 2 and finally cleared the way for the population to adopt air conditioning, which then proceeded to spread rapidly throughout the world.

Studies have shown that the technology saves tens of thousands of lives worldwide every year: temperatures above 90 degrees are dangerous and can be fatal, especially to the elderly. And so, because there was insufficient public energy to drive that technology into mainstream use, because it was actively lobbied against by naysayers, tens of thousands of people died of heat

exhaustion and heatstroke every year for a century. Perhaps a million deaths were caused by misinformation and mockery.

That, in a nutshell, is why it's worthwhile to take time away from the lab bench to write this book. I always say "Every best product has the most critics". These kinds of critics.typically arguing on behalf of the product's competition.could be accused of being the cause of so many deaths. And compared to the number of people who used to die of heatstroke each year, the number who die of aging is astronomical. If we don't act, then most likely, you will one day be one of them.

Let's not let that happen. Let's correct the misconceptions about curing aging and ensure that the energy exists to make this technology a reality.

AGING ISN'T GRACEFUL; IT'S AWFUL

A lot of people claim that aging is something that we can do gracefully. It's not. Aging is one of the worst things that can happen to a person. Every single system in your body progressively fails. Your skin wrinkles; your hair whitens and falls out. Your internal organs shrink and stop functioning correctly. Your bones become porous. Your eyesight and hearing start to shut down. Your energy level plummets. Your muscles atrophy. Even your mind . your memories, your personality, the very core of your identity . falls into decline. You slowly waste away, and you die. There's no sugar-coating it; aging is horrible.

We often don't think about the level of suffering that aging brings because we don't see it. The people who are truly suffering are hidden away from the public view in hospices, assisted living homes, and nursing care facilities. I personally have a lot of experience visiting people in those places. They are miserable. And there are millions of people that are living in those assisted living homes and hospices that can no longer take care of themselves. At any given time, almost a million people in

the United States alone need assistance with their basic daily routine because they can no longer dress, bathe, or even feed themselves. They're depressed, hidden away from the world, and waiting to die.

We've tried to be at peace with this; after all, aging has always been a disease that everyone is guaranteed to get, assuming nothing else kills us first. So we've developed coping strategies. We talk about how, in our old age, we've gained wisdom. We can enjoy playing with our grandchildren. We have decades of experience. We can look back satisfied at a life of accomplishment. We can retire, relax, and enjoy what we've built.

And that's all true . but none of that is actually because of aging. It's because of experience and accomplishment, because of the things we've done and built and learned over the course of our lives. Aging doesn't refer to the amount of time that's passed since you were born. Aging is the process of your body breaking down and failing at the end of that time. A hypothetical person who is ninety years old and not actively dying from aging would be no less accomplished and no less wise than their aged neighbor, confined to a hospital bed, a financial burden on their loved ones.

Aging isn't just a problem for individuals, but for society itself . and that problem's going to get a lot worse. The Baby Boomers are one of the largest generations in human history, and now we're entering a period sometimes called the "silver tsunami." By about 2030, 30% of the world's population is going to be over 65. By 2050, this number is going to rise to 40%. There will be millions and millions of people over 65, many needing specialized care, and a terrible shortage of caretakers, because for every person over 65, there will only be one person in the workforce. There won't be enough people to take care of the elderly!

So the question is: how are we going to take care of them? And another question is: how are governments going to afford to cover all the medical costs of taking care of these old people? For all the bureaucratic ideas being thrown around, the ideal solution is simply to prevent them from getting old. To keep them young and healthy, able to take care of themselves, and able to participate in the workforce. And science is a lot closer to finding a cure for aging than a lot of people realize.

Some people protest that it makes no sense to talk of a "cure" because aging is a natural process. And of course it is. But so is cancer, and no one has ever disputed that cancer is a disease.

Osteoporosis is also completely natural, as is atherosclerosis, cataracts, diabetes, hypertension, and Alzheimer's.

We readily call all of these "diseases" and don't hesitate to attempt to treat and cure them. Yet when it comes to the disease of aging, we call its individual symptoms "diseases" and aggressively try to eliminate them, but we call the underlying disease itself "a natural process" and resign ourselves to letting it kill us in a slow, painful, and humiliating way.

That could hardly make less sense to me. What would make sense is to redirect some of the energy we spend treating the symptoms into addressing the fundamental cause of the systemic collapse we undergo late in life. The world calls this collapse "aging," but I sometimes think it would be better labeled "Short Telomere Disease." Because when it comes to curing aging, it really is all about the telomere.

Perhaps you've heard of telomeres by now.the region of repetitive DNA at the ends of every chromosome in our bodies. They were first discovered in 1938, but their clinical significance didn't become truly clear until the late 1990s, when my team at Geron Corporation was able to conclusively demonstrate the role of telomeres in cellular aging and cancer.

For the last ten years, whenever I haven't been directing

research on telomere lengthening at my company, Sierra Sciences, I've been writing books, giving speeches, doing interviews, and flying around the world spreading a simple and very important message: aging is not a graceful end to a long life. Aging is not an inevitable part of being alive. Aging is a disease, an ancient defect in every one of our cells.and it is a disease that can be cured, if we can simply summon the will and the attention to cure it.

THEORIES ABOUT AGING

If you read the news, there's little doubt you've heard stories implying that scientists have already conquered aging.that they've reversed aging in mice, that they've extended the lifespan of fruit flies, that they've isolated a compound from red wine that will have you youthful again in no time.

When it comes to reporting on science, the media really does have a habit of getting ahead of itself. Yes, the stories mentioned above were all based on important publications that represent steps forward, but none of them have actually reversed aging. When we see an 80-year-old walk out on stage looking twenty years old and being as athletic as if they were twenty, and they feel twenty, that's when we know we've cured aging.

Most of the "anti-aging" supplements available now are really just composed of ingredients that boost energy levels, since having more energy makes people feel younger. But increasing energy levels is not a reversal of aging; it's just scratching the surface of the symptoms that aging causes. We have to go a lot further than that.

We also need to be aware that not all animals on this planet

age by the same mechanisms (which will be discussed in more detail later in this book). Humans aren't mice! They are also not roundworms, fruit flies, or yeast.other organisms commonly used to study aging. Humans age by an entirely different mechanism than those other animals do. So, when you hear that someone found a cure for aging in these other animals, even if that's true, it doesn't necessarily mean that it will benefit humans. Though, science has certainly done a lot to help you extend the lifespan and healthspan of your pet mouse, roundworm, or fruit fly.

To fight aging, we have to understand aging. The most common understanding of aging fifty years ago, and one that's frustratingly prevalent today, is that we age the same way an old truck sitting in a field ages. We get exposed to the wind, the sun, and the rain, and we rust and fall apart for those kinds of reasons.

But even when I was in high school, that explanation never made any sense to me. If we're aging because of our environment, how is it that people in radically different environments age at essentially the same rate? It doesn't seem to matter much whether you live near the poles or right on the equator, whether you're by the sea in sunny San Diego or

landlocked in frigid Siberia: the human lifespan is roughly the same, and you can look at a person and place their age within a few years.

And how would the "truck in a field" theory account for the fact that animals age at such different rates? A pet dog lives in almost exactly the same environment as its human family, and yet the humans will live seven times longer. Obviously, environment isn't the only variable we're looking at here.

If our bodies were trying to stay alive as long as possible and just had to avoid environmental damage, it stands to reason that the healthiest possible lifestyle would be sitting on the couch in a room always kept at seventy degrees, watching TV to avoid exertion and injury and eating bland, processed food to avoid any digestive challenges. And yet we can easily observe that that is, in fact, a very unhealthy lifestyle.one that will dramatically shorten, not lengthen, your life expectancy.

Something wasn't adding up. The only thing that made sense to me was that there must be some kind of clock inside our bodies, telling us how old we were and how much longer we had left to live, and at the end, actively causing our declining health.

When I first got my Ph.D. and went into biotech, scientists hadn't really discovered anything that could be that clock of

aging. So I focused on cancer research, heart disease research, and inflammation research. But that clock has now been found, in part by my team at Geron Corporation, when I was awarded Second Place for United States Inventor of the Year for leading the research that led to the discovery of human telomerase. But more about that later.

In terms of aging, the biggest difference between humans and old trucks sitting in a field is that we renew ourselves. When we get a sunburn, and it kills cells on our skin, we have other cells that divide to replace that skin; parent cells divide to become daughter cells. Until 1961, it was thought that the daughter cells were identical to the parent cells in every way. Numerous experiments with cell culture showed that cells grew at a fairly consistent rate.a linear rate, even, if you're looking at a log scale.as long as they were provided with the proper nutrients and environment. No cell culture lasted forever, and eventually they'd reach a point where they'd stop dividing and level off, but scientists chalked this up to nutritional imperfections in the media they were feeding the cells, or to some other deficiency with the process of cell culture.

In 1961, Leonard Hayflick turned that conventional wisdom on its ear. He was able to show that when he took cells from a ten-

year-old, he could get them to divide about 90 times before they leveled off, but when he took cells from an 80 year old, they'd only divide about 20 times. So something was clearly going on: cells knew how old they were, and it had nothing to do with the media they were being fed. This limitation on cell division would eventually be named after him: the Hayflick Limit.

So the obvious question was: what could be causing something like that? How could a cell from a ten year old know how many times it's already divided and how many more times it has left? How could cells from the 90 year old know that they only had a few more divisions left to go? It was as though, when we were conceived, our cells had been given ride tickets like at an amusement park, and every time they went on the "ride" of cell division, a ticket was ripped off.

Figure 1-1: Amusment park anology, tickets equal a 'ride' for cell devision.

They had some kind of "memory" of how many tickets they had left, and when they'd used up all the tickets, it was tough luck for them if they wanted to go on the ride again.

When the "ride" is the cell division that we use to treat environmental injury, to replenish our immune system after an infection, and for routine maintenance of our organs, that's a serious problem. That's a disease.

In the late 1970s, while I was planning on what to do after I got my Ph.D., I applied to a lot of research labs interested in aging, saying that I wanted to find out what these ride tickets were that caused cells to reach this Hayflick limit. But, every lab that I interviewed had no interest in this. They all had their

own ideas.which were typically nonsense.and they wanted all my focus to be on pursuing those ideas. Temporarily discouraged, I went into biotech instead and worked on cancer, heart disease, and inflammation research. I was waiting for the big breakthrough when someone would discover something that could shed light on what the ride tickets were.

Then, in 1992, it happened! I listened to a scientist named Calvin Harley talk about the shortening of telomeres, the tips of our chromosomes, as our cells divide. This was it! Telomeres were the first sensible explanation for the "ride ticket" phenomenon that I had ever seen. And over the ensuing decades, it turned out to be an explanation that is undeniably part of (if not the whole) picture of human aging.

Let me repeat: we've now found these ride tickets; they're found at the very tips of our chromosomes.

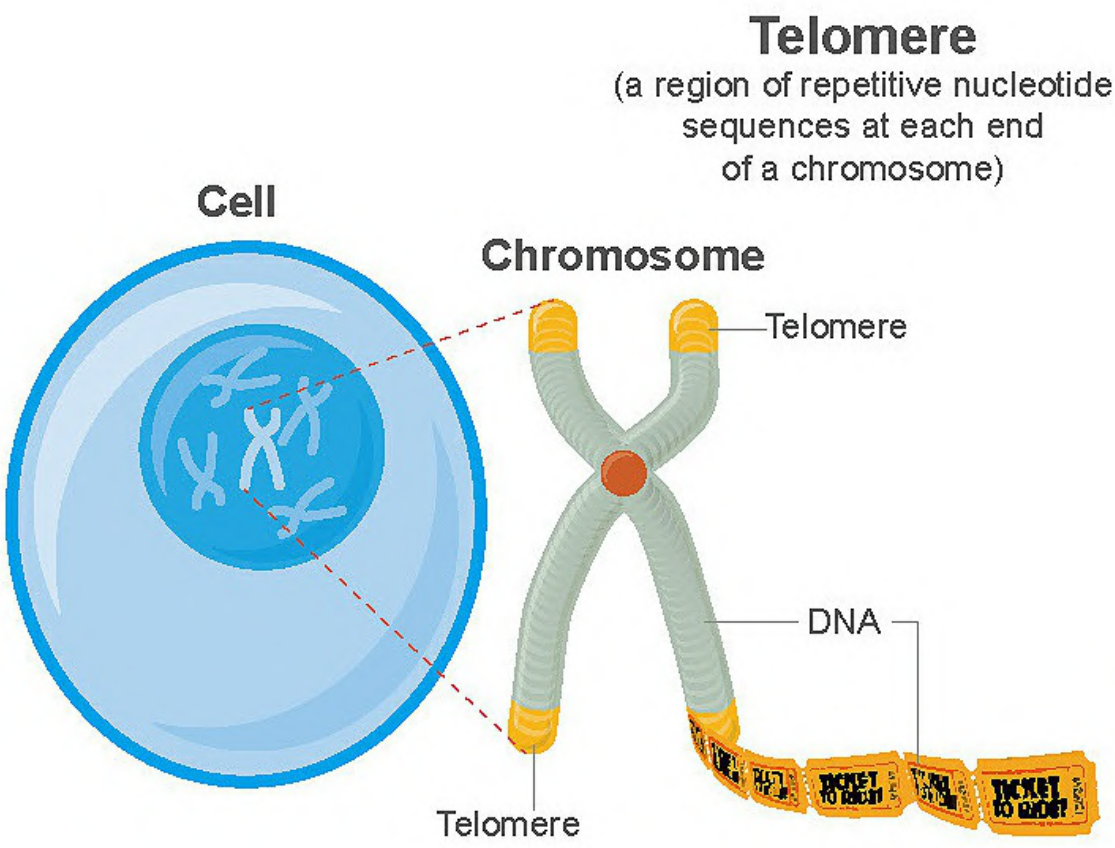


Figure 1-2: Telomere, A region of repetitive nucleotide sequences at each end of a chromosome.

They're a region of repetitive DNA called "telomeres." And we know that, just like a roll of ride tickets, they get shorter as people age, and our health declines as they get shorter. If we want the cells to keep dividing, we need to find a way to provide these chromosomes with more ride tickets.

And we now know that if we lengthen the telomeres by adding telomerase to these cells, they do not reach the Hayflick Limit. This isn't a hypothesis, but a repeatedly observed reality: when

my lab at Geron first put telomerase into cells, they gained the ability to divide indefinitely, and the experiment has since been repeated at many labs around the world.

There's only one method that's ever been developed that can actually do this, and that method is gene therapy. Gene therapy has been responsible for quite a few support-of-concept experiments in this field. It has extended the Hayflick Limit in cell culture; it has reversed aging in human tissues; it has reversed aging in mice.

Reversing aging in human tissue was something first accomplished at Geron. The scientists grew human skin on the backs of mice; some mice were given skin grown from cells from an elderly person, and some were given skin grown from cells from a young person. Then, from each those two groups of mice, some were treated with telomerase and some weren't.

What they saw is that human skin treated with telomerase looked visibly younger. The skin grown from old cells had all the characteristics of old skin: wrinkles and age spots and similar flaws. When they lengthened the telomeres, all those flaws disappeared. And it wasn't just a temporary cosmetic improvement; the skin actually became young skin. It behaved young; old skin blisters much more easily than young skin, and

when testing the old skin treated with telomerase, they saw no more blistering than they did on untreated young skin.

Geron also carefully examined the gene expression inside the formerly old skin, and found that of the 30 genetic biomarkers we looked at, every single one of them had returned to an expression level absolutely indistinguishable from young cells. So the telomerase-treated old skin had become indistinguishable from young skin on three levels: it was visibly the same; it behaved the same way; and it had the same gene expression. It was old skin made young again on every level.

Perhaps the most exciting support-of-concept experiment has been the reversal of aging in mice. My lab doesn't work with mice; we tend to focus on cell biology, molecular biology, and genetics. Also, as I said earlier, mice don't age by the same mechanisms that humans do. But at Harvard Medical School, a team led by Dr. Ron DePinho created a line of genetically engineered mice that expressed no telomerase, and so telomere shortening became a cause of aging in these mice, and he engineered these mice so that they would express telomerase when he added a certain hormone to their food.

Dr. DePinho bred these mice for several generations to get their telomeres to shorten to the length of human telomeres, and

he saw many of the hallmarks of human aging: graying hair, senility, arthritis, infertility, atrophy of the internal organs, etc. Then he added the telomerase-inducing substance into their food, and saw that this aging was reversed by every method of measurement available. The mice grew longer telomeres. They regained their ability to breed. Their organs grew back. Their sense of smell returned, which was exciting, because smell is largely a function of the brain. They began to remember how to navigate mazes that they were earlier becoming lost in.

Critically, they saw a greatly increased survival rate in these mice, and no sign that the treatment caused cancer. A decade ago, there was some concern that telomerase induction might cause cancer; this is only one of many studies to help lay that misconception to rest. I'll be discussing that at length later in this book.

The study was also instrumental in establishing telomere shortening as the most viable theory of aging in humans. When we discovered the role of telomere shortening in aging, scientists were initially skeptical that it could possibly be that simple. After all, gerontologists had already established that oxidative stress and mitochondrial dysfunction were two of the engines driving aging.at least, in mice.

Yet, attempts to mitigate those specific problems in a laboratory setting, through antioxidant therapy or any other combination of therapies, have never done a fraction of what lengthening telomeres has. In Dr. DePinho's experiment, telomeres were shown to actually also be in control of oxidative stress and mitochondrial dysfunction; when telomeres are kept long, those issues become less and less problematic in our cells. Papers are coming out at an increasing rate suggesting that there's a unified theory of aging and that, of all the culprits causing humans to age, telomere shortening is the kingpin.

I don't necessarily believe the idea of a true unified telomere theory is going to hold true for every possible cause of aging. As soon as we figure out a way to prevent the telomere shortening problem, there may be another problem forty years down the road that will cause our health to start declining all over again. But I'm hopeful that lengthening telomeres will give me another forty years to solve that problem. As I sometimes say, if our cells are full of sticks of dynamite that will kill us, the one we have to focus on is the one with the shortest fuse. Until that one is defused, the others are irrelevant. And I'm quite convinced the shortest fuse of aging in the human body is telomere shortening.

And the reason I'm convinced? Well, let's recap: by

maintaining telomere length, we've extended the Hayflick Limit. We've reversed aging in human tissues. We've reversed aging in mice. Maintaining telomere length has been shown to have control over other theorized causes of aging. No experiment based on a single other theory on aging has ever been able to do any of these things. So my money's on telomeres.

TELOMERES

If you've read my first book, "Curing Aging," these next two chapters will be review for you. If it's still relatively fresh in your mind, you may want to skip ahead. But we can't talk about the promise of telomere lengthening without discussing what a telomere is. Telomeres are at the heart of what causes us to age and causes our health to decline. Whether or not it's the only cause of aging, it's certainly a very key one, and the first and foremost one we need to solve.

Telomeres are found inside every one of our cells, so they're very, very small. If we were to zoom in on a human being, we would first see that the human is made up of cells . one hundred trillion of them, give or take. Most theories on aging hold that we age because these cells age. So we focus on studying the aging process in the cells before attempting to apply any techniques to animals or humans.

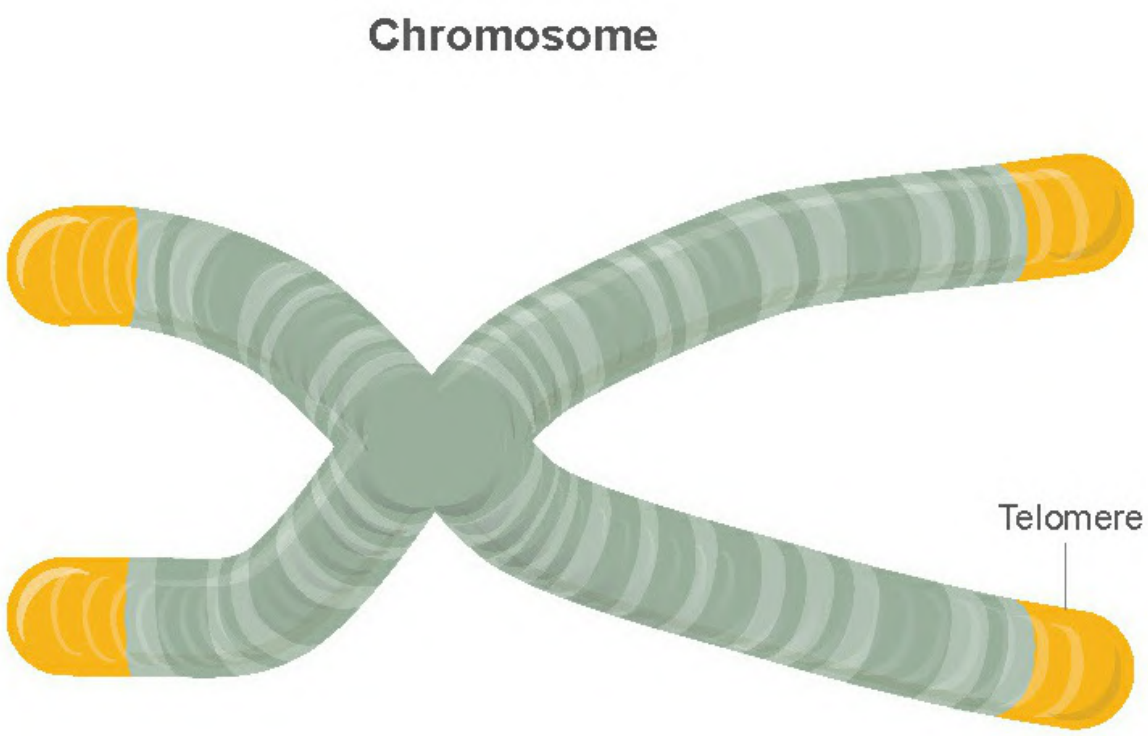


Figure 2-1: Diagram of a Chromosome, showing where the Telomere is present.

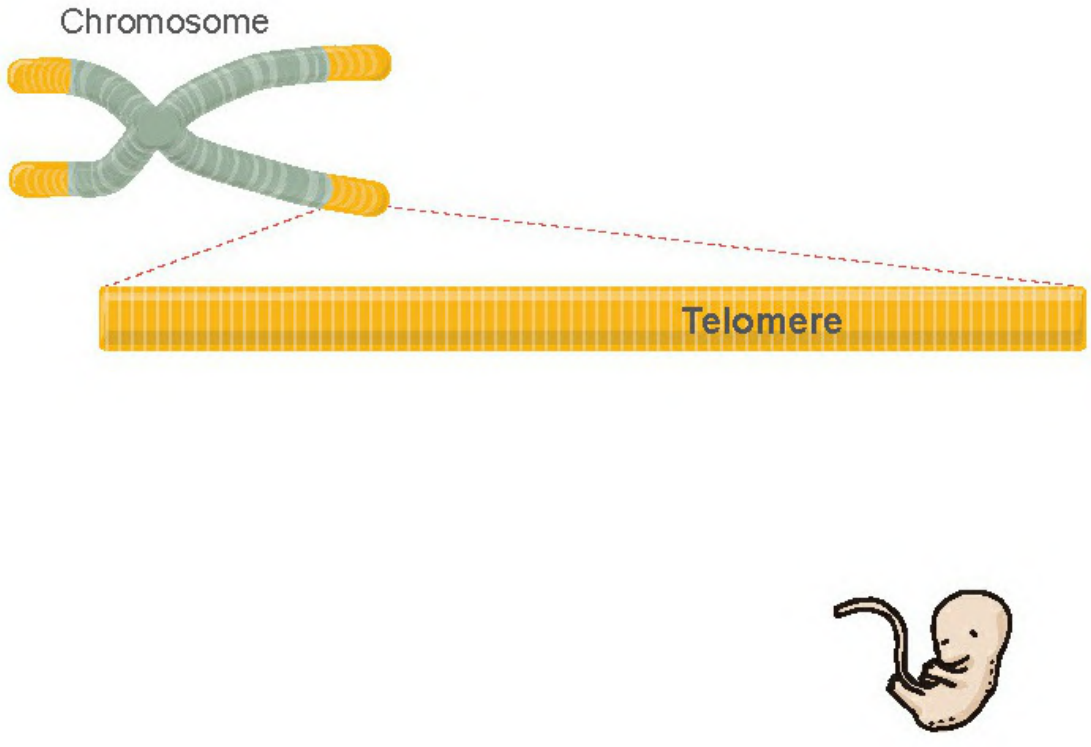
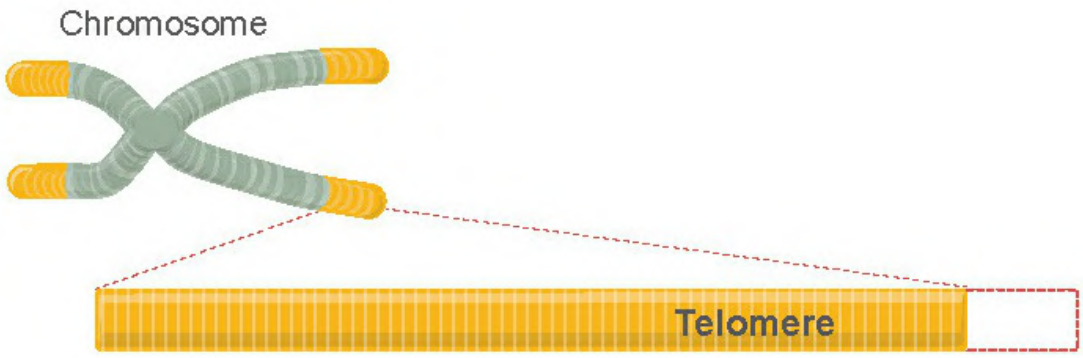


Figure 2-2: Telomere length of a fetus.



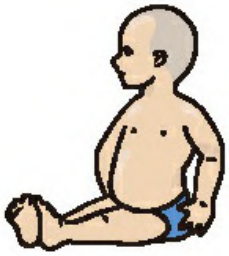


Figure 2-3: Telomere length of an infant.

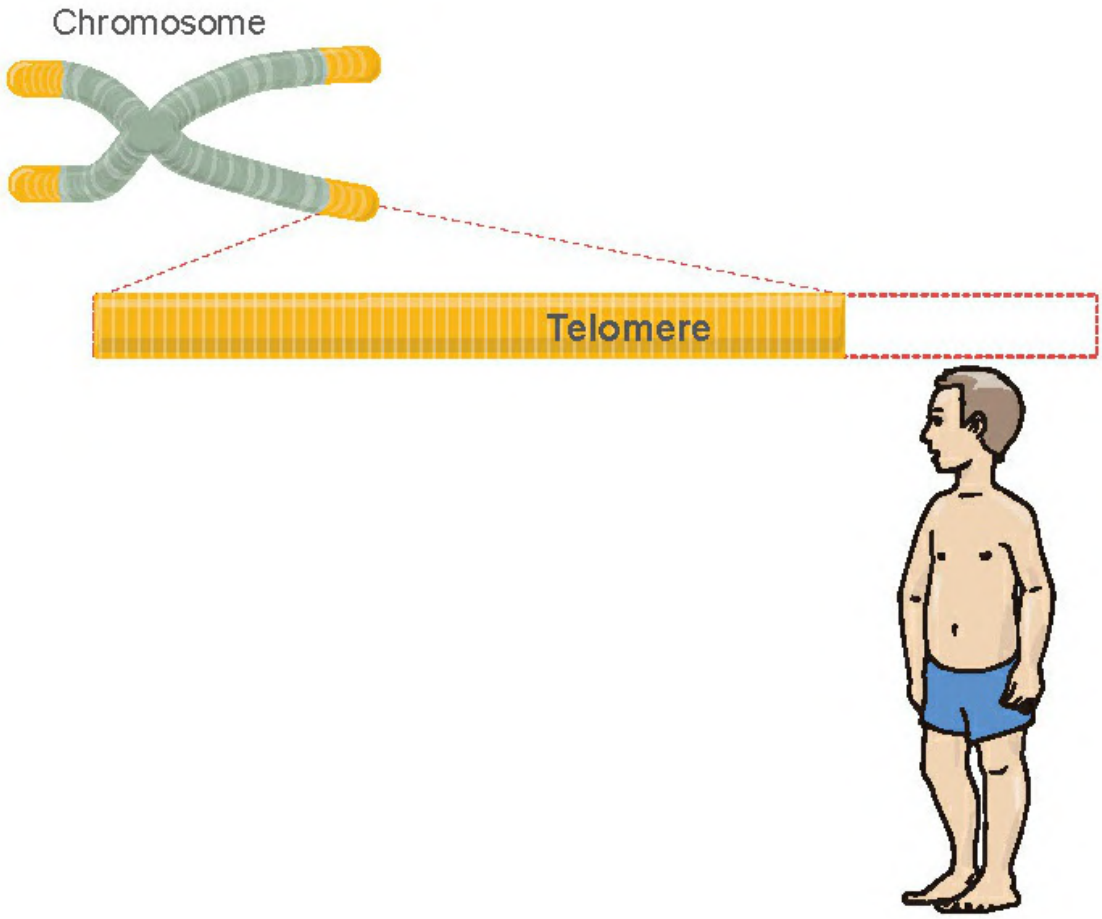


Figure 2-4: Telomere length of a child.

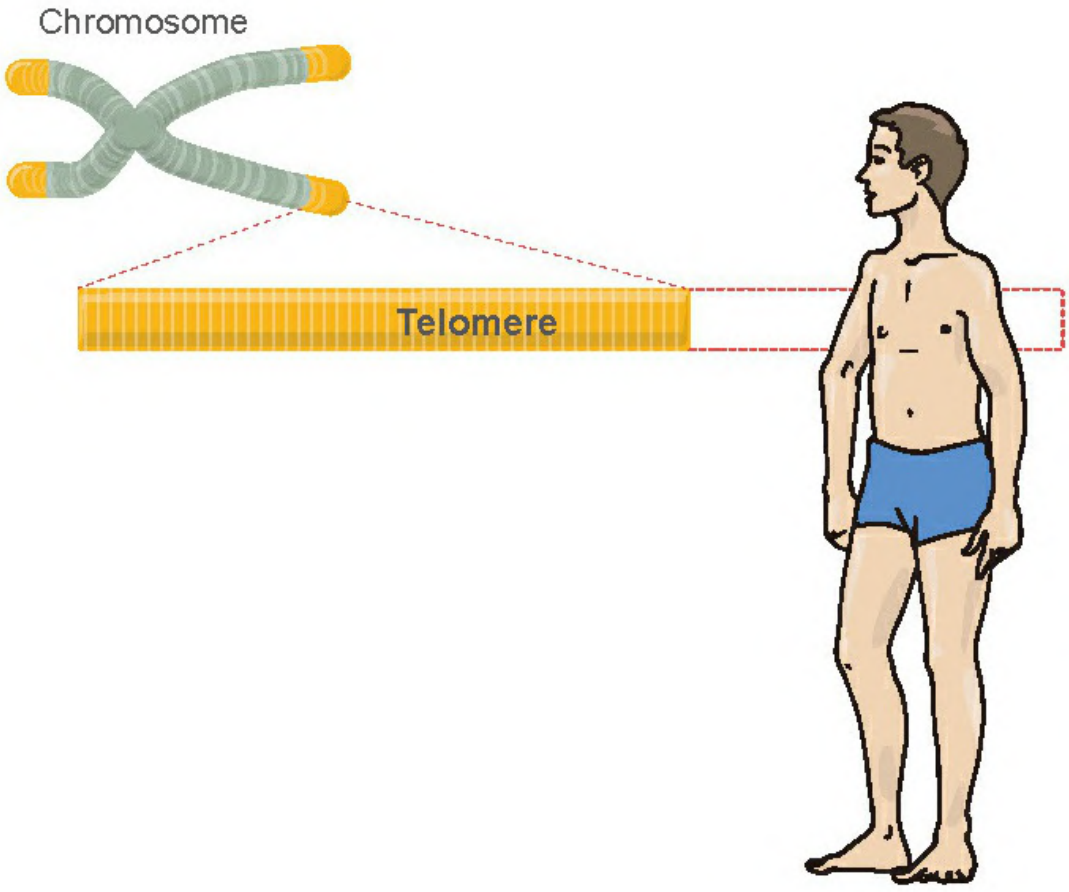


Figure 2-5: Telomere length of a teenager.

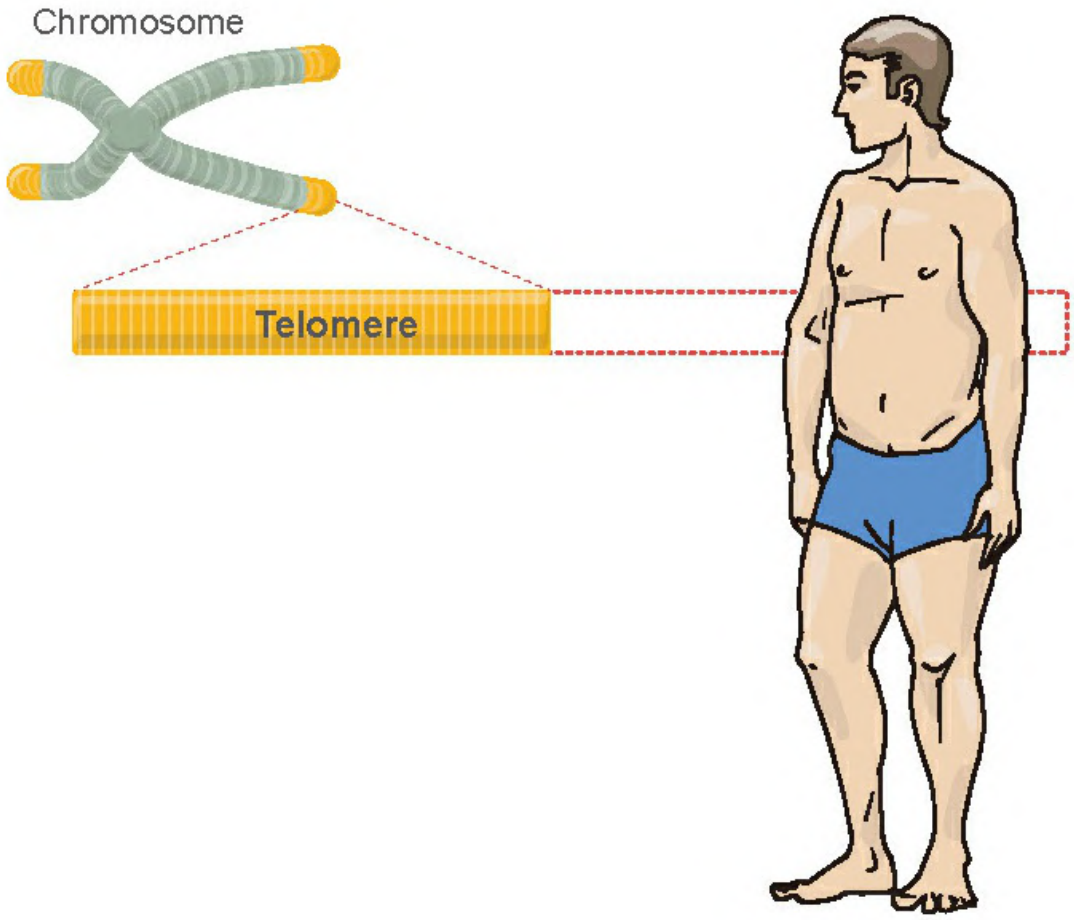


Figure 2-6: Telomere length of an adult.

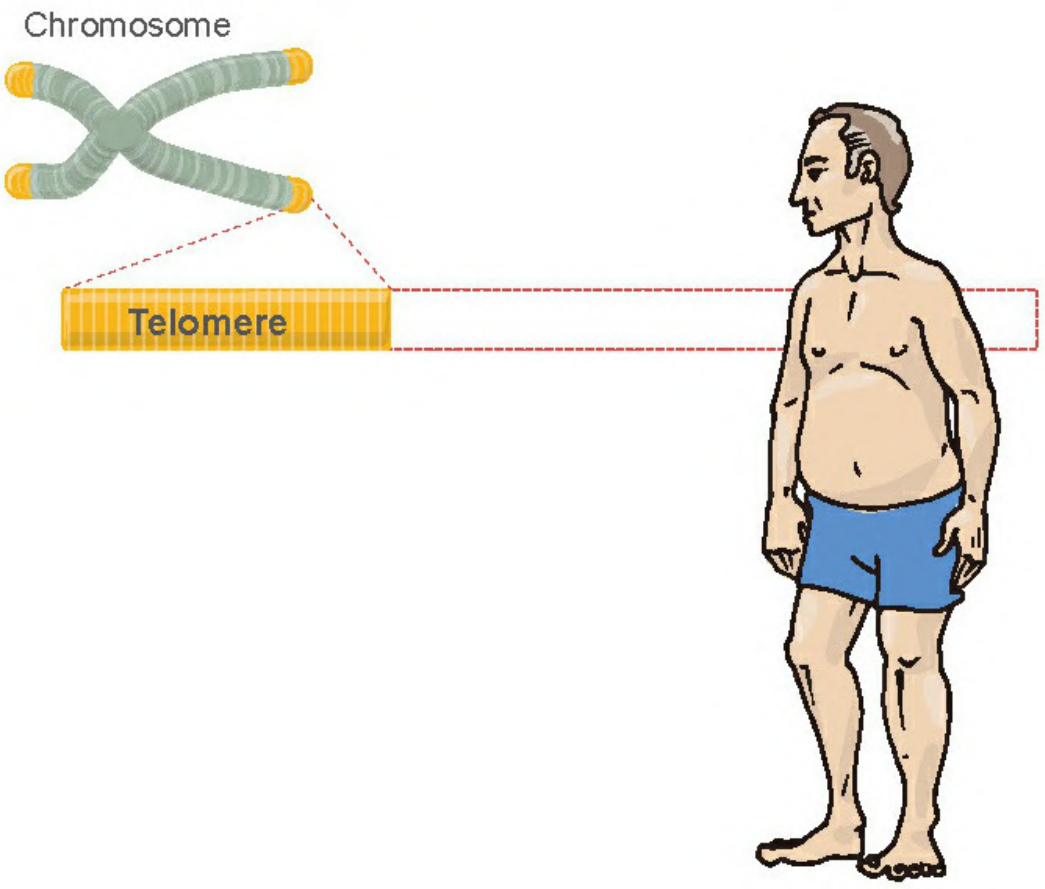


Figure 2-7: Telomere length of a middle-aged adult.

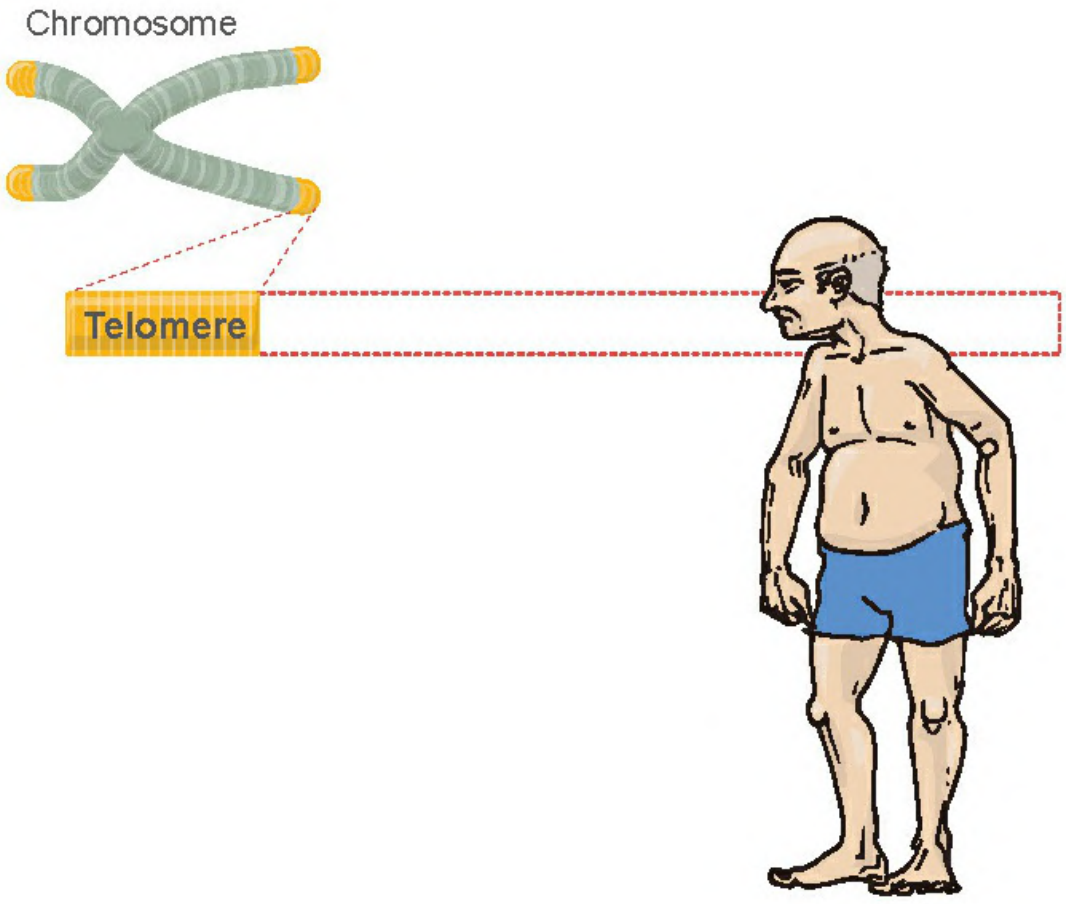


Figure 2-8: Telomere length of an elderly adult.

Every one of our cells contains a nucleus, and were we to zoom in even further to the nucleus, we'd see our chromosomes. Our chromosomes are the structures where our genes are stored . the information that makes us us, that gives us all of our individual characteristics. If we zoom in on one of those chromosomes even further, we'd see that the chromosome is made up of two arms, a top arm and a bottom arm. And inside each of these arms is our DNA, which resembles a long string of

beads all coiled up like a Slinky.

Were we to unwind this Slinky, we'd have all our genetic material laid out in a line on a long "string." Think of this string as a shoelace. The ends of your shoelaces have little plastic caps . they're technically called "aglets" . to ensure the shoelace doesn't unravel and fall apart. Should those aglets wear down and fray away, you're left with a mess of a shoelace that's difficult to lace and just gets worse with every use. Without the aglet, the shoelace falls apart.

Well, our chromosomes have aglets, too.and that's what the telomere is. It's the very end portion of the chromosome.the "cap" that holds the whole structure together. Early experiments in the 1930s with maize chromosomes showed that when the telomere breaks off, the chromosomes recombine in ways often completely incompatible with life.

When we're first conceived, our telomeres are about 15,000 bases in length. Our chromosomes average about 100 million base pairs in length, so the telomere region, at 15,000, is really a pretty small part of the chromosome.

The aging process begins immediately in the womb, during the very early blastocyst phase of our development or before. Our telomeres start shortening before our bodies are made of even a

hundred cells, and it takes a massive amount of cell division to develop from a tiny embryo to a newborn baby. So much, in fact, that by the time we're born, our telomeres have already shortened down to 10,000 bases . half the telomere shortening we'll undergo in the course of our entire lives.

But of course telomere shortening doesn't stop there; we continue to grow after birth, and our cells continue to divide, first as part of the process of development and later as simple maintenance. We undergo a great deal of cell division even as fully-matured adults, especially in our immune systems. And as the cells divide, our telomeres get shorter and shorter, and when they get down to about 5,000 bases, our cells lose the ability to function.

I am often asked where I get these numbers. There are reports saying that the numbers are very different. In many ways, the question is semantic; it all depends on the method used to measure the telomeres. I personally prefer a method called Terminal Restriction Fragment (TRF), while others use methods called PCR and FISH. These methods disagree to some extent on what would rightfully be called the beginning of the telomere. In many ways that's actually a very arbitrary decision, much like asking how long the tip of your finger is. Where do you start

your measurement from.from the second knuckle, the beginning of the fingernail, or elsewhere? The same is true when measuring the length of a telomere.

When our telomeres are too short and too many of our cells stop functioning, we die of old age. And there is absolutely nothing we can do about this yet. No matter how well we eat, no matter how well we exercise, no matter whether we do everything our doctors tell us to do, we cannot stop this shortening.

Our cells themselves age, and this is not a mere hypothesis: it's observable fact. Anybody who works with human cells in Petri dishes now knows this is happening. Once a cell's telomere shortens to about 5,000 base pairs, the cell won't divide any further. Too many of these cells, and the entire culture becomes non-viable. In research, it's an annoyance, because you can't work with a cell line indefinitely unless it's an immortal cell, like a cancer. In the human body, it's not just an annoyance; it's a catastrophe.

As mentioned above, I learned about this phenomenon in the early 1990s, when telomere biology was in its infancy, and I instantly recognized this as the clock of aging I'd always been looking for. Geron Corporation was just starting to connect all

the dots between telomeres and aging, and during a presentation by their CSO, Calvin Harley, he mentioned to the audience that he could measure the length of anyone's telomeres and tell how old they are. And more importantly, he could tell how long it would be before you died of old age. I could immediately see that telomeres were a better candidate for an accurate clock than anything I'd heard of before.

And so I stopped all the work I had been doing, all the work on heart disease and cancer and inflammation, and I immediately went to work for Geron on telomeres. And what I found was that, lo and behold, all my research was still related to cancer, heart disease, inflammation, and practically every other disease on the planet.

That's because telomere shortening doesn't only cause aging. There are hundreds and hundreds of scientifically peer-reviewed journal articles showing every disease under the sun to be correlated with telomere shortening. Some of the articles don't try to determine cause and effect, but in other cases, it's demonstrated that certain diseases are actually directly caused by telomere shortening, such as dyskeratosis congenital, idiopathic pulmonary fibrosis, aplastic anemia, idiopathic infertility, etc.

When our telomeres get short, it causes our bodies to decline in virtually every way possible. When we're in our prime, around age 24, most of us are in close-to-perfect health. So for any disease that we are more likely to get at age 80 than at age 24, there's going to be a telomere element to the disease.and most likely a peer-reviewed study correlating it to short telomere length.

This is true of diseases most people would never conceive of as diseases of aging. Take, for example, bedsores. Initially, bedsores aren't caused by aging; they're caused by the friction between skin and sheets in people who are lying in one position. But as we all know, human skin heals. The patient will be rolled over, and other cells in the skin will divide and replace the damaged cells. So at first, bedsores won't be a problem.

But the cycle goes on and on. The patient is wounded, heals, is wounded, heals. And every cycle of healing means cell division, and every cell division means telomere shortening. So the telomeres near the wounds will start to get down to 5,000 base pairs even if the patient is relatively young. And at that point, you have wounds that can't heal. You have bedsores that are persistently open, prone to infection, and life-threatening.

This is a major problem in hospitals, and if we could find a

way to keep telomeres long, it would prevent bedsores. There's a similar mechanism taking place in nearly every other disease you've ever heard of. For example, in muscular dystrophy, there are cells dying in the leg muscles and other cells replacing them; the symptoms only become severe with telomere shortening. Aging is not the initial cause of muscular dystrophy, but it does cause much of the pathology in that disease.

This is even true of colds and flus. We've all observed that healthy young adults get over these diseases much more quickly than the elderly. Fighting an infectious disease requires a great deal of cell division in the immune system. As that cell division causes the immune system to age, an infection that would have been a mere annoyance can become a life-threatening emergency.

A strong example of how short telomeres will cause age-related disease.even in the absence of chronologically old age.is that there are children born with their telomeres already short. This disease is called Hutchinson-Gilford progeria syndrome, or Progeria for short, and it's caused by a mutation leading to a misshapen Lamin A protein. This mutant protein accumulates on the surface of the nucleus, where the chromosomes attach, and actually prevents the telomeres from being protected, causing

them to shorten at an accelerated rate.

So, these kids are born with their telomeres already short, and they die of old age by the time they're 20 years old, of all the same age-related ailments that most people succumb to in their eighties and nineties. If we could find a way to prevent telomeres from shortening, we could cure this disease. Even though it's very rare, with only 250 afflicted children on the planet at any given time, it's a terrible disease and something I'd love to see cured.

It's almost as though, when telomeres really start to get short, your health falls of a cliff. You suddenly start having multiple age-related problems, all at the same time. Progeria, it seems, just moves that cliff closer, and causes us to fall off it decades earlier.

BRICKLAYING MODEL

I've explained that every time a cell divides, its telomeres get a little bit shorter. But why is that? How does that process work? If we're going to solve telomere shortening, we have to know why telomeres are shortening to begin with.

In cell division, the original cell is called a "parent cell," and the two new cells after the division are known as "daughter cells." When the parent cell divides, everything inside it has to first be duplicated so that when division is complete, the two daughter cells have everything the parent cell had. That includes the chromosome, and the DNA inside that chromosome.

The process of DNA replication is a bit complicated, and this book isn't meant to be an advanced molecular biology text, so for DNA replication, I'm going to use an analogy of bricks on a brick wall. Imagine that the top row of bricks on the wall is the DNA in your chromosome, and to replicate that row, you have to place a new row of bricks on top of that wall, which will be the new chromosome.

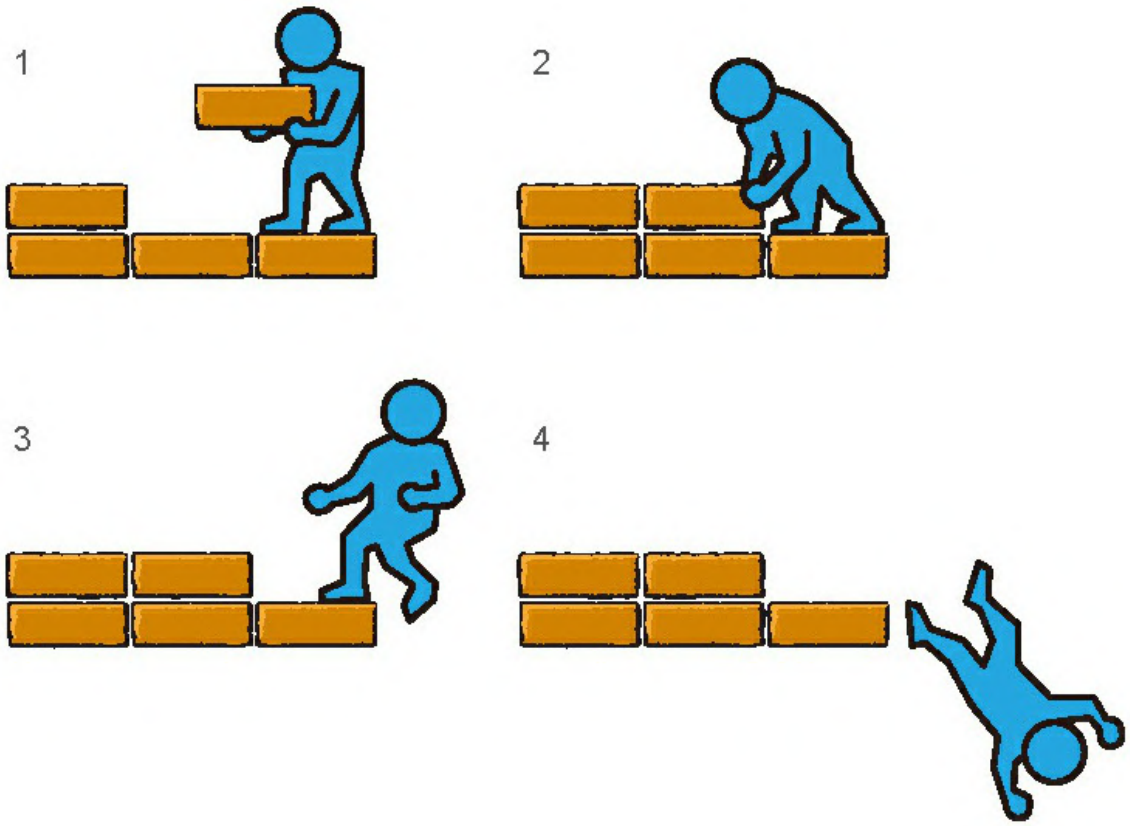


Figure 3-1: Bricklayer anology for DNA replication.

Now imagine a bricklayer standing on top of the wall, backing up as he lays a new row of bricks, one brick at a time. Believe it or not, this is very much like what is happening inside of our cells; the bricklayer represents an enzyme called DNA polymerase 1. Remember, DNA is a long molecule, so laying these bricks is a long, repetitive process, and it has to be done without errors.otherwise we'll end up with mutations that could have some pretty nasty effects.

But what we're focusing on right now is what happens at the

end of the “brick wall”.the telomere. Because the bricklayer is standing on the wall, there’s no room to lay that last brick. He’s essentially “painted himself into a corner.” The bricklayer’s going to fall right off the wall before being able to set it down. And as a result, the new chromosome is slightly shorter than the old chromosome.

This metaphor is actually remarkably close to the reason that DNA polymerase 1 doesn’t replicate chromosomes all the way to the end. And it’s the mechanism by which our telomeres inevitably shorten, no matter how well we live. The chromosome isn’t necessarily being “chewed away.” It’s not always fraying due to exposure from the environment. The cell simply lacks the ability to duplicate the very end of the chromosome.

So the new “row of bricks” is a little shorter, and when the cell divides again, the bricklayer’s going to go and make a new row of bricks on top of that row, and, again, is going to fall off just before he lays the last brick. And once again, the chromosome’s going to get shorter. Every time the cell divides, it gets shorter and shorter. I call this “basal level telomere shortening.” It’s an entirely passive process; nothing is happening at all except that the bricklayer can’t lay the last brick. Unfortunately, that means there’s absolutely nothing you can do about it. No matter how

well you eat, no matter how much you exercise, and no matter how much you do everything your doctors tell you to do, you can't stop basal level telomere shortening. When telomeres shrink down to 5,000 bases, you're dead. Nothing claiming to cure aging has really cured aging unless it can solve the telomere shortening problem, and so far, nothing has.

This basal level telomere shortening mathematically gives humans a theoretical maximum age of 125; several recent papers in peer-reviewed journals have used statistics on population studies to determine that that's the theoretical maximum. No matter how good your lifestyle is, you will never live past 125 without fixing the telomere shortening problem . and so far, no one's even made it to 125 in documented history. Only two human beings have even made it past 120, the oldest being Jeanne Calment, who died in 1997 at age 122.

Now, if for some reason you wished to age faster, there's a lot of good news for you: telomere shortening can certainly be accelerated. Essentially anything we associate with an unhealthy lifestyle has been shown to cause telomere shortening: obesity, smoking, a lack of exercise, psychological stress, etc.

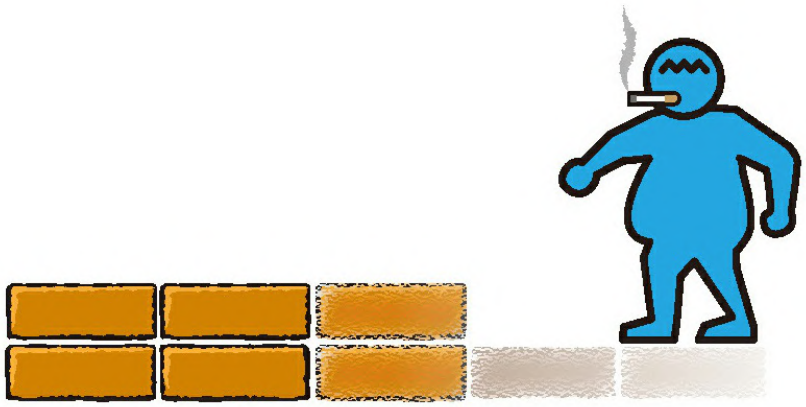


Figure 3-2: Brick anology, The result of an unhealthy lifestyle has been shown to cause telomere shortening.

These factors cause the production of free radicals and inflammation that cause your telomeres to shorten at an accelerated rate. It's been known for a long time that lifelong cigarette smokers look older than non-smokers; what we're now finding out is that it's because, biologically, they are older. I'm not aware of any laboratory that's studied the telomere lengths of methamphetamine addicts who appear alarmingly prematurely aged, but I'd be astonished if this weren't exactly the phenomenon causing that premature aging.

Basal level telomere shortening can't be affected by any conventional treatment, but accelerated telomere shortening can. You can lose weight; you can quit smoking; you can

meditate; you can exercise. All these things do affect your rate of telomere shortening. Certain dietary supplements can help as well, and I'll be going into more detail on that a little later.

TELOMERASE

At this point, I've explained the two reasons telomeres shorten: the basal level telomere shortening and the accelerated telomere shortening. And both of these things are happening at the same time inside all the cells of our bodies.

But there's an obvious unanswered question: if our telomeres inevitably shorten, and cannot lengthen, then how do we reproduce? I said earlier that when we are conceived, our telomeres are 15,000 base pairs in length, and when we're born, they're about 10,000 base pairs in length. So if you're a healthy adult with telomeres that average, say, 8,000 base pairs, and you conceive a child, where does your body even find a cell with telomeres 15,000 bases long to serve as a starting point for that child?

The answer is that our genes do carry instructions on how to lengthen telomeres. They can't prevent the shortening, but they can lengthen them every time shortening occurs. Our reproductive cells divide constantly, but they don't show any telomere shortening, because if they did, our children would be

born biologically older than us. Our species would be extinct in a matter of a few generations.

So our reproductive cells have a mechanism to re-lengthen their telomeres every time they shorten. This mechanism takes the form of an enzyme called telomerase.the enzyme my team researched and discovered in humans back in the mid 1990s.

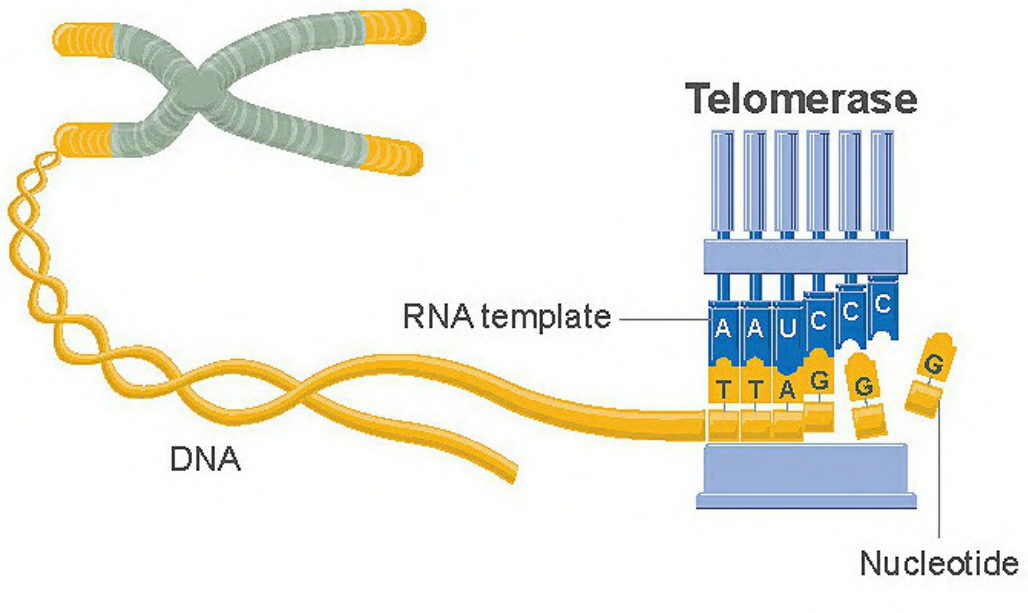


Figure 4-1: Telomerase enzyme, “presses” a new telomere sequence onto the chromosome.

The telomerase enzyme can be relatively simple because of the

repetitive nature of the telomere. Human telomeres are a repetitive sequence of six base pairs: T-T-A-G-G-G. That means that lengthening the telomere is as simple as adding those six bases to the end of the chromosome. We can conceptualize telomerase as a factory that contains a "template".a piece of RNA in the cell. that "presses" a new telomere sequence onto the chromosome.

If you go back to the metaphor of telomere shortening as a clock, telomerase doesn't actually stop the clock at all. The clock still ticks forward. What telomerase does is to push it back a tick. The shortening's still occurring, but now a re-lengthening force has been introduced.

Or, referencing our bricklaying model, telomerase doesn't prevent the bricklayer from falling off the end of the wall and leaving the new wall slightly incomplete. Rather, telomerase acts like an angel that flies in and adds a brick to the end so that the new wall is just as long as the old one. That's essentially what's happening in our reproductive cells.and what I'd like to make possible in all of our cells.

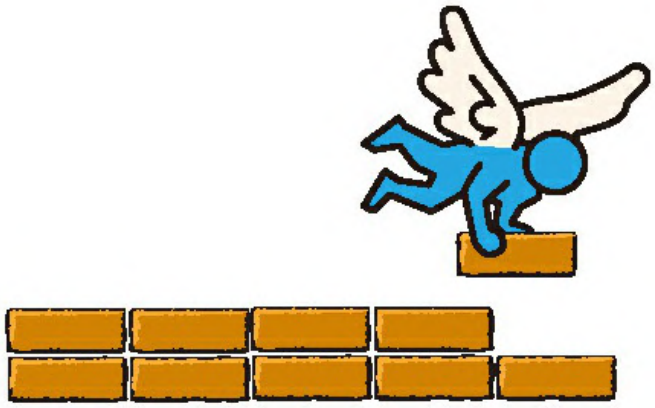


Figure 4-2: Bricklayer anology, telomerase acts like an angel that flies in and adds a brick to the end.

But, it gets even better. The amount of telomerase our cells produce is going to determine just how many more bricks get added to the wall. If you have just a little bit, the brick won't be replaced every time.just some of the time. But on the whole, even replacing it some of the time will cause the shortening to take place at a slower rate. So it would still be good to have a little bit of the telomerase enzyme around.

On the other hand, suppose that you have a lot of extra telomerase. What we find then is that we can be adding multiple bricks to the wall, so that the new row is actually longer than the old row. Which leads us to the question: if the telomere is the

clock of aging, and we're actually lengthening the telomere, does that mean aging is being reversed?

TUG OF WAR

So, as we've just shown, telomere shortening is caused by our body's inability to replicate chromosomes to the end, and telomere lengthening is caused when telomerase adds DNA directly to those chromosomes.

Those are two essentially unrelated processes. They are both going on at the same time. The rate at which shortening is happening has no bearing on the rate at which lengthening is happening, and vice-versa.

To make an observation, this is kind of like a tug of war.

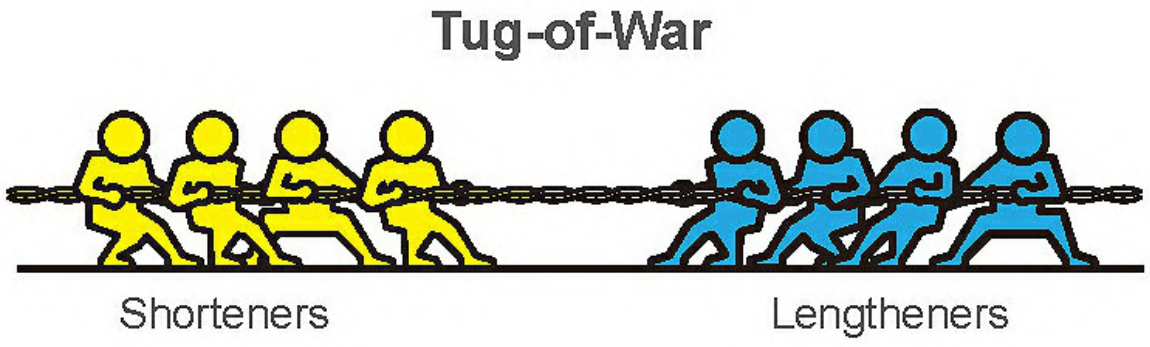


Figure 5-1: Tug-of-War.

Imagine people pulling on one side to shorten our telomeres,

and people pulling on the other side to lengthen them. In our reproductive cells, this tug of war is tightly regulated by our own biology. When the "shortening" side pulls a few inches to one side, the "lengthening" side pulls right back.

But in all the other cells of our body, there's nobody pulling on the lengthening side at all.

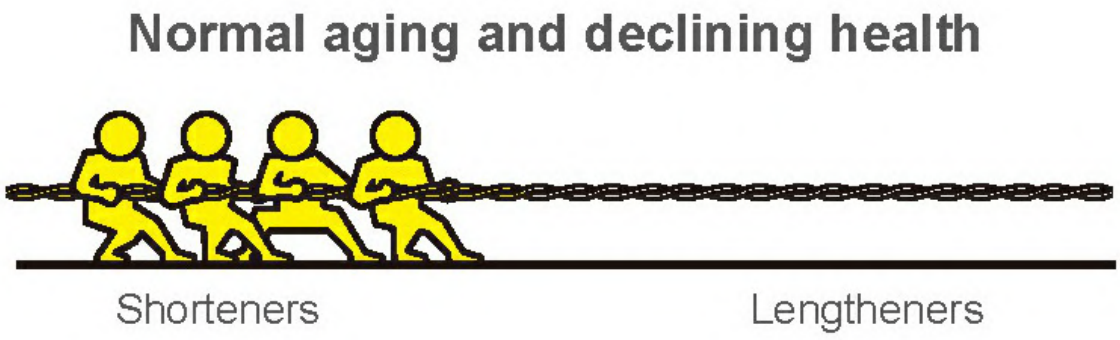


Figure 5-2: Normal aging and declining health.

The shortening side just drags the rope along the ground; every time our cells divide, they get a little bit shorter, and ultimately we die of old age.

I've mentioned that there are some things you can do to decrease accelerated telomere shortening, like reducing psychological stress or quitting smoking. This is the equivalent, perhaps, of sending one of the people pulling on the shortening team to the bench.

Figure 5-3: Protecting Telomeres (slow down aging?).

But if there's still nobody on the lengthening side, it's not hard to see that while you may have slowed the shortening, you haven't stopped it.that rope will still get dragged, if slightly more slowly, to the shortening side, with little resistance at all. And you can only send the "Accelerated Telomere Shorteners" to the bench (by leading a healthy lifestyle). There is no way to send the "Basal Level Telomere Shorteners". So improvements in lifestyle can never be used to completely stop telomere shortening; only slow it down.

Of course, slowing the shortening is still a very good thing to do!But we don't just want to slow telomere shortening; we want to see telomeres lengthened. And if we could induce telomerase in our cells, then we could finally start getting people pulling on the lengthening side. Outside the tightly regulated environment

of our reproductive cells, we can induce telomerase at a whole range of levels.

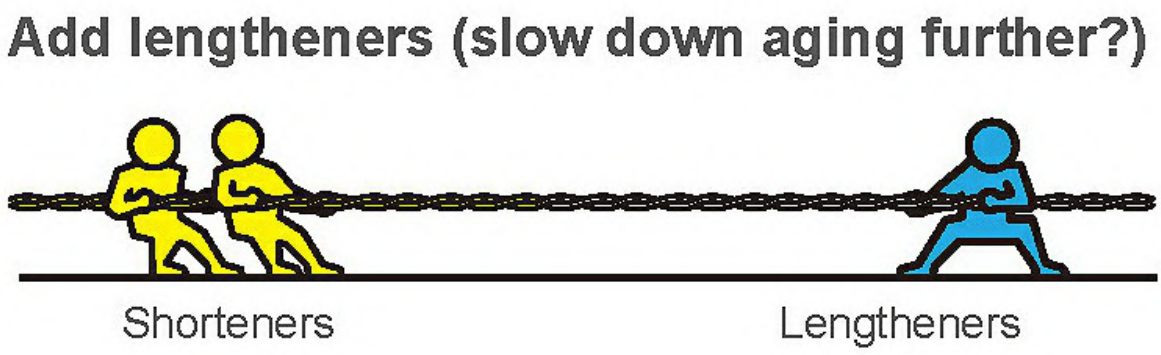


Figure 5-4: Add lengtheners (slow down aging further?).

At really low levels, the shorteners would still be winning the tug of war, but the lengtheners would be slowing them down. Which would mean you wouldn't be stopping the aging process, but you'd live longer and stay healthier longer.

Better yet, we could induce telomerase to a level where the lengtheners and shorteners are deadlocked, where neither of them were making any progress. This would represent stopping the aging process in its tracks, and allowing you to maintain your current age no matter how many years passed.

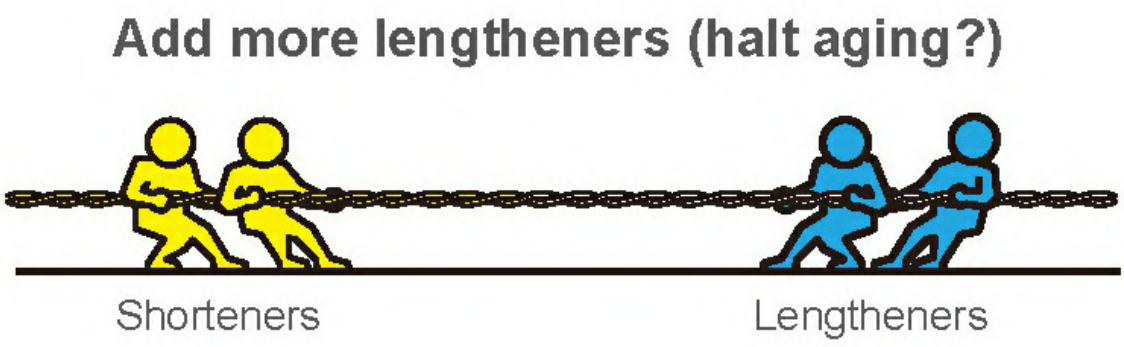


Figure 5-5: Add more lengtheners (halt aging?).

But ideally, what we'd like to have is more people pulling to lengthen than to shorten. Because that's when we can actually experience age reversal.seeing old people get young again, all the way to their prime, where they'd look and function like 24 year olds. Where they would be, biologically, 24 years old.

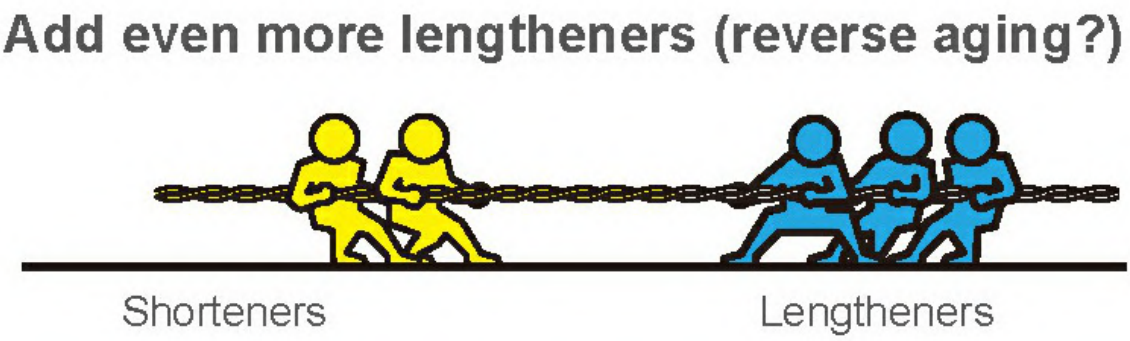


Figure 5-6: Add even more lengtheners (reverse aging?).

People often remind me that adult stem cells also produce telomerase. That's true! But, the amount of telomerase they

produce is far to low to prevent telomere shortening or even slow it down significantly. In every case where I have seen a published study showing telomerase expression in stem cells they have never measured the amount being produced. So, if telomerase expression is low in stem cells, why do stem cells express it at all? I believe it is just an artifact of leaky expression. Stem cells only express telomerase when they are dividing rapidly. When they stop dividing the telomerase gene gets shut off. I believe the reason we see telomerase expression in rapidly dividing stem cells is because every time a cell divides it has to first duplicate (or replicate) the DNA. And, the telomerase gene is located in the DNA. When the new DNA is produced there is a short period of time that the telomerase gene can express before the repressor finds the new gene to shut it off.

I believe that the only natural cell in humans that produces telomerase at levels sufficient to maintain telomere lengths are our reproductive cells; more specifically, I mean our embryonic stem cells and/or primordial germ cells. But, I would like to see all our cells produce sufficient telomerase to maintain and even lengthen our telomeres.

People sometimes ask me if it would be possible to go too far,

and to reverse their aging to where they looked and functioned like a 12 year old. The answer is no. Development and aging are two completely unrelated biological processes. Telomere shortening is the clock of aging, but it has nothing to do with development. Our development clock and aging clock may both be ticking at the same rate when we're children, but they are, in fact, two completely separate clocks.

When I first started researching telomeres, no one was sure whether age reversal was a real possibility; we had no evidence whether a therapy would work in a living organism. Now that age reversal has been demonstrated in human cells, human tissues, and mice, I'm a lot more confident that it's a very real possibility for humans. The only reason that aging hasn't been cured already is because of the attitudes of the public.

If more people took this field seriously enough to start securing funding sources for the research, the cure for aging would happen very quickly.

STRATEGIES FOR TELOMERASE INDUCTION

So, what can we actually do to cause production of telomerase inside of our cells to lengthen telomeres enough to at least reduce their rate of shortening? The strategies for lengthening telomeres fall into three basic categories:

1) the pharmaceutical approach;

2) the nutraceutical approach; and

3) gene therapy.

The Pharmaceutical Approach

My company, Sierra Sciences, has been working on a pharmaceutical approach to curing aging since 1999, and in that time we've made some remarkable progress.

The idea behind the pharmaceutical approach is simple: discover a chemical that will induce our bodies to do what they could already, theoretically, do naturally. Almost every cell in our bodies contains our complete genetic code, and therefore the gene for telomerase. The exceptions would be red blood cells that lack nuclei and some immune cells that have rearranged immune-related genes. Thus, any cell in our body containing

telomeres could lengthen its telomeres—if only the telomerase gene were not repressed. The idea behind the pharmaceutical approach, then, is to develop a chemical that will de-repress it.

Gene expression often uses a kind of lock-and-key approach for regulation, where a chemical "key" is released to fit a genetic "lock" to turn a gene on or off. For example, when our bodies receive signals indicating it's time to relieve pain (for example, during strenuous exercise), the pituitary gland produces a neuropeptide called endorphin, which is essentially a "key" that binds to the receptor "locks" on the body's other cells. This receptor then signals a gene or genes to turn on or off.

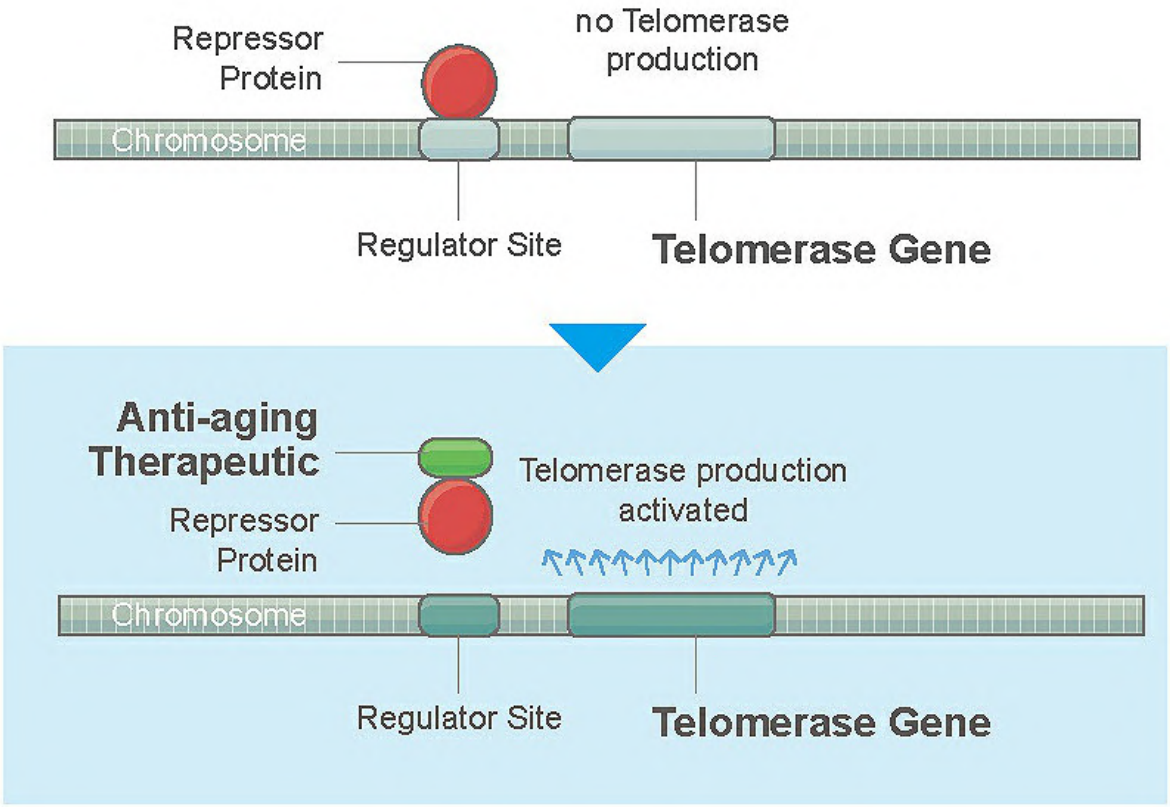


Figure 6-1: Diagram showing the idea behind the pharmaceutical approach to develop a chemical that will de-repress the Telomerase Gene.

Sierra Sciences has spent nearly a decade (and tens of millions of dollars) screening hundreds of thousands of chemicals to identify molecular keys that turn on the telomerase gene in our cells. We designed an automated method for screening the ability of chemicals to produce telomerase we call the "hTERT RT-PCR assay," which allowed us to test up to 4,000 different chemicals a day, and then spent years testing libraries of random molecules that had a high potential to be biologically active.

Then we took all of our positive hits and hired medicinal chemists to use the information we gathered from the screen to design molecules that were more effective still.

And based on our discoveries, we've designed several molecules that mostly definitely fit into the lock–if perhaps a little imperfectly–and cause some de-repression of telomerase. The most potent molecule we've created so far is called C0314818 (aka TAM818); it is beyond any doubt the strongest telomerase inducer ever discovered anywhere on the planet.

I believe the pharmaceutical approach likely holds the key to making age reversal available to everyone. One of the most widespread dystopian beliefs about the cure for human aging is that "it will only be available to the rich, while the rest of us have to age naturally." I could perhaps believe that if we were talking about some kind of complicated, involved therapy–but pharmaceuticals just don't work that way. They're easy to mass-produce and companies rarely find it profitable to try to sell them to only a select, elite few–they make money by putting them in every pharmacy in the world.

The Nutraceutical Approach

If you're wondering why you can't buy TAM818 at your local

pharmacy right now, it's because getting a pharmaceutical drug onto the market takes about twelve years and costs an average of $2 billion. All that regulation may keep us all safer—it's a hotly debated topic that I won't weigh in on here. But it does make it excruciatingly difficult to develop and sell a pharmaceutical drug in many countries, and especially the United States.

But there's an interesting loophole in this regulation: the FDA does not regulate any chemical purified directly from a plant that people have a long history of eating or using medicinally. The thought is that if something in gingko or guarana or cabbage were toxic or had terrible side effects, we would have known about it hundreds of years ago.

Is it possible that a chemical in one of these plants might hold a cure for aging? Many people are immediately skeptical of that idea, because if a commonly eaten plant held the cure for human aging, one would think we'd already know. People eating that plant for centuries would have been living at least slightly longer, and scientists would have taken notice.

But actually, it might be more likely than you think that the chemical "key" to turn on telomerase is lurking in a common plant. In any plant, there are thousands of chemical compounds known as "phytochemicals" that have the potential for being

active as drugs. Some of them are present in only very, very minute quantities. By separating them from each other by column chromatography and other separation protocols, purifying them, concentrating them, and screening them, it well may be possible to find one that fits into—or at least wiggles—the "lock" to allow telomerase expression in our cells.

So it's possible that very common plants hold the cure for aging, but in quantities so small we never noticed. It's also possible that there are plants that contain telomerase activators, but also telomerase inhibitors, so the net effect would be zero unless we separate one from the other.

In an attempt to find out, Sierra Sciences has screened thousands of natural ingredients, and we've indeed found several samples that test positive for telomerase induction. None of them have been as powerful as C0314818, but it's a promising avenue of research, and there are hundreds of thousands more species of plant for us to screen.

Gene Therapy

In reality, both the pharmaceutical approach and the natural product approach described above are forms of "gene therapy" because they are, literally, therapies that affect our genes. But in

this section, I'm using the phrase "gene therapy" to describe a technique that, instead of working on an existing gene, delivers a new gene to the cell.

This kind of gene therapy is where it starts really getting exciting. With gene therapy, we don't just convince the cells of the body to produce telomerase naturally; we actually provide the cells with an alternate way to produce it. To use the same lock and key analogy for gene expression, in gene therapy we first engineer a modified gene for telomerase that lacks any lock at all. So, it needs no key to turn it on; it is always turned on. And then we deliver this gene directly to our cells, which will dutifully do whatever the gene codes for—in this case, producing telomerase to lengthen telomeres.

Gene therapy would have taken scientists far longer to discover and perfect if millions of years of evolution hadn't already virtually perfected it for us in the form of viruses. Viruses are extremely adept at dropping a genetic payload into cells; after all, their very existence depends on it. So by altering a virus by leaving its delivery methods intact while carefully modifying the genes intended for delivery, we can engineer a means of providing our cells with whatever genes we want them to have.

Remember: the classic viruses that you hear about every day

are dangerous, not because they are viruses, but because of the payload that they are delivering. In the case of our gene therapy the only thing being delivered is the telomerase gene.

We've already done this in our lab in cells in a Petri dish, with unambiguously successful results. Going back to the tug-of-war analogy, with this gene delivery technique, we've been able to add so many "people" to the telomere lengthening side that the lengtheners exceed the shorteners thirty-fold, thus lengthening their telomeres and creating cells lines that are effectively much younger.

My team at Geron Corporation first performed these experiments back in the late 1990s. Not on living human beings–that would have been beyond reckless given the level of technology at the time–but on human cells in tissue cultures. Gene therapy was how we extended the Hayflick Limit and created lines of cells that were immortal but not cancerous. But, when we can get to the point of actually treating people with gene therapy I believe that we will actually see people get younger in every way imaginable. I can't wait for the day when we see the 95 year old actress and comedian, Betty White, walk out on stage and look, feel, and behave 24 years old again.

Gene therapy has already allowed scientists to achieve three of

the most fundamental milestones on the way to curing aging in human beings. First, we've broken the Hayflick Limit in human cell culture. Second, we've reversed aging in human tissues. And finally, as we talked about earlier, we've reversed aging in mice.

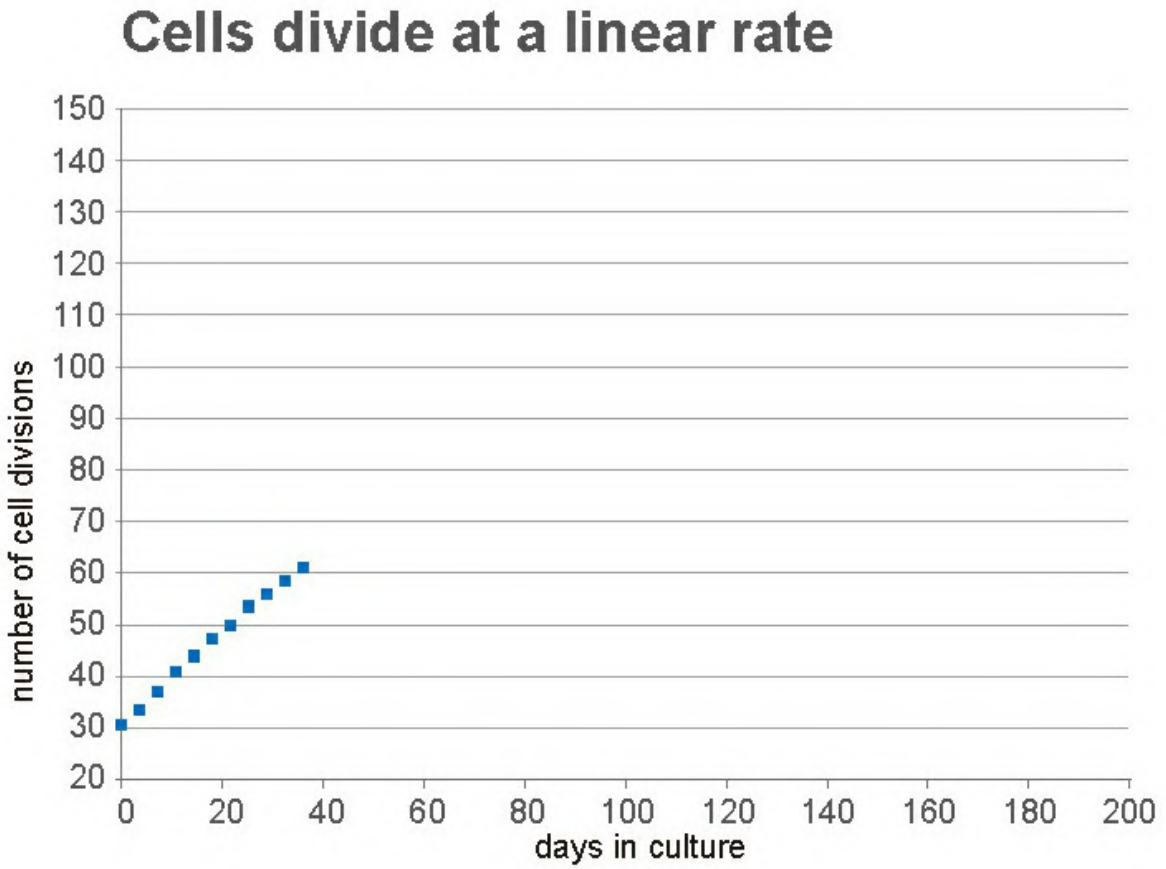


Figure 6-2: Diagram, Cells divide at a linear rate.

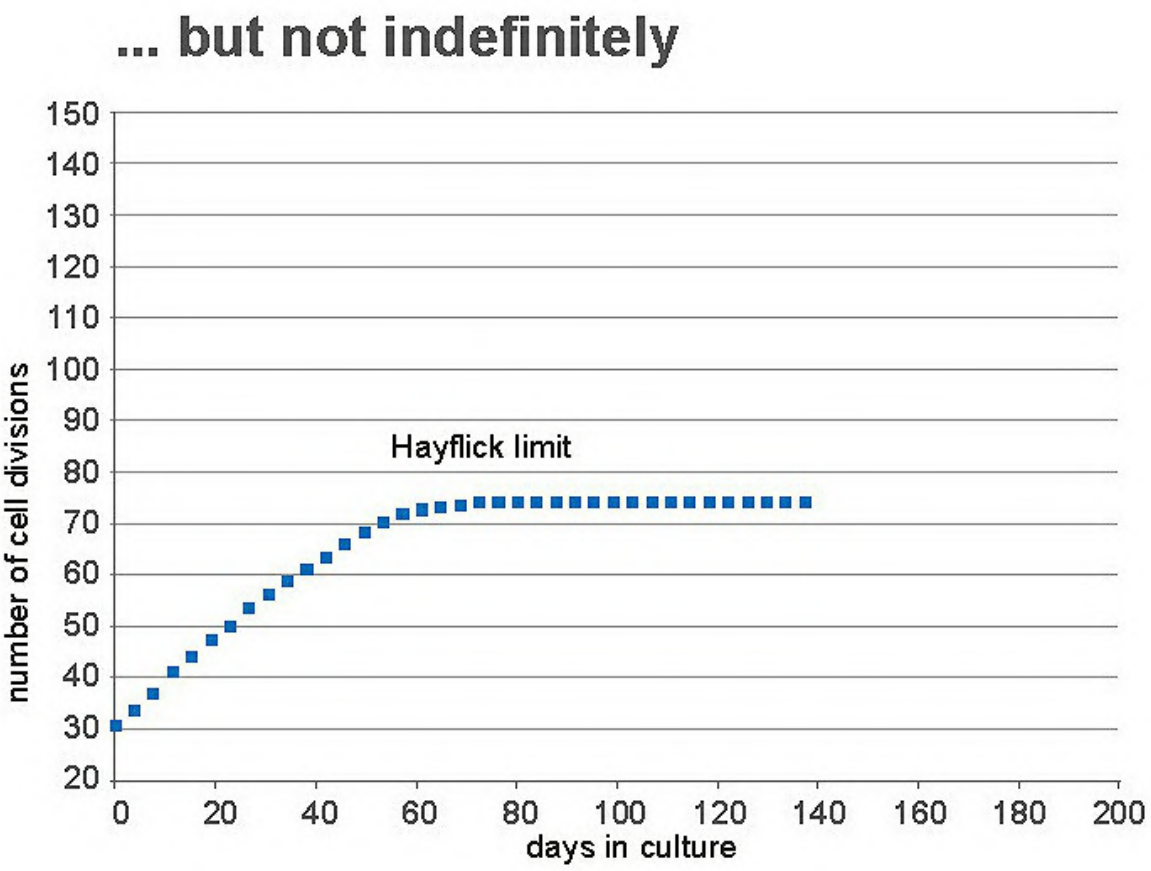


Figure 6-3: Diagram, Hayflick limit.

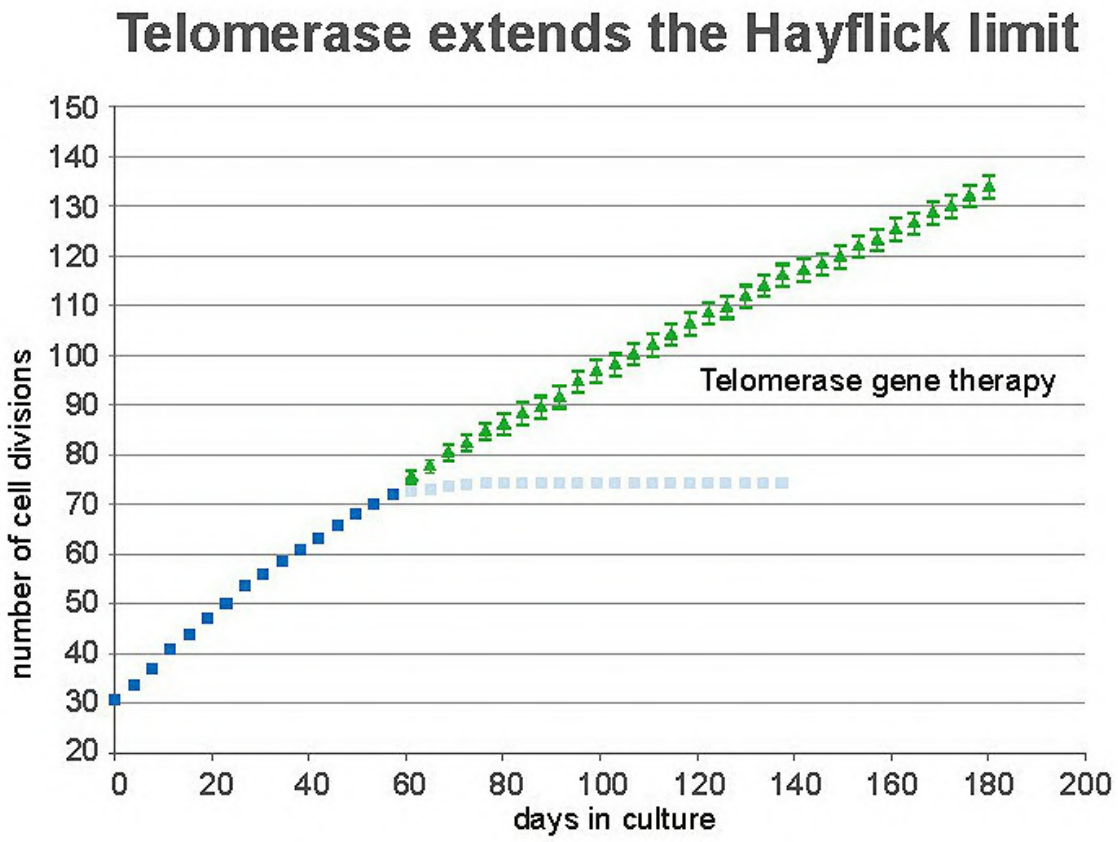


Figure 6-4: Diagram, Telomerase extends the Hayflick limit.

Earlier, I talked about how human cell cultures divide and level off on a graph–the visual representation of the Hayflick Limit. When we use gene therapy in human cells in a Petri Dish, we abolish that limit entirely.

The cells grow indefinitely at a linear rate, and they grow for as long as we care to nourish them. Given that all evidence points to telomere shortening as the primary, if not sole, cause of human aging, gene therapy cured those cells of aging.

From there, we moved to reversing aging in human tissues.

These experiments took place almost fifteen years ago. Scientists at Geron Corporation, led by Dr. Walter Funk, with whom I shared the 2nd place National Inventor of the Year award, took skin cells from elderly people and grew them into human skin on the backs of immunocompromised mice. Those cells gave rise to visibly old skin, full of wrinkles and blisters and age spots. Then they took those same cells and treated them with telomerase gene therapy, and when they grew that into skin, they saw that it looked visibly young. It behaved young, as well; by all benchmarks such as elasticity and resistance to blistering, it was young skin.

So they took it one step further and looked at thirty different genes associated with aging – the thirty genes whose expression levels change most noticeably with age. When they lengthened the telomeres in the old skin, every single one of those genetic markers reversed.

Geron Corporation reversed aging in cell cultures and in human tissues during my tenure there. Ron DePinho reversed aging in genetically engineered mice about a decade later. Every support-of-concept experiment performed so far has added weight to the proposition that gene therapy could reverse aging in a living human being. Hopefully, it won't be long before we

have an opportunity to test a gene therapy protocol on a small group of volunteers – and that could be truly world-changing stuff.

You may wonder why no one's taken the plunge yet and attempted gene therapy on themselves or some brave, informed volunteer. The main reason is that a lot of the gene therapy protocols in the past were inarguably dangerous and caused disease. They were based on viruses that dropped a piece of genetic code into the chromosome at random, and in doing so, they had a tendency to break the genes at the beginning and end of the regions where they integrated. If they picked a particular nasty genetic sequence to interrupt, the cell could almost immediately become cancerous. It wasn't the genes being carried into the cells that caused cancer; the gene therapy itself would do so.

We're working with protocols today that don't show signs of causing that kind of disease; the genes don't integrate into the chromosome, and all that's seen is a mild immunological response–the kind likely to cause a case of the sniffles, if that. We didn't invent these protocols ourselves; they've been used in 117 different clinical studies (at the time of this writing) using genes other than telomerase. And so far, no one has experienced

any severe side effects in those trials. Synthesizing our work on telomerase with all this work on modern gene therapy could bring about an effective anti-aging therapy very soon.

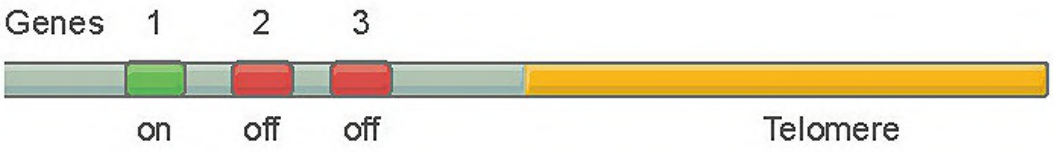
TELOMERASE PREFERENTIALLY LENGTHENS THE SHORTEST TELOMERES

Interestingly, when it comes to predicting health and longevity, measuring "average telomere length" may mean very little. That is, when it comes to telomeres, what probably causes most of the decline in health in our older years is how many cells in our body have telomeres that are critically short, not necessarily what the average telomere length is. In other words, a hypothetical person with both many long telomeres and many short telomeres might have the same average telomere length as someone with uniformly medium-length telomeres, but would probably have the health of a much older person. More research is needed in this area, but very few studies have ever come up with a good explanation why average telomere lengths have anything to do with overall health and aging. But, there are many great theories on why critically short telomeres would.

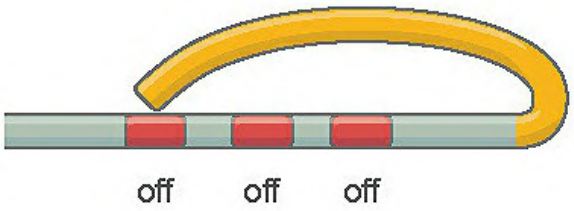
The best data suggesting that average telomere length might have some relevance is a recent study from the labs of Drs. Woodrow Wright and Jerry Shay showing that shortening and

lengthening of telomeres that are still long does have an effect on the expression of a gene called Dux4. This could be saying that telomeres have the ability to fold over and interact with genes along the chromosome as if they were magic wands reaching over and tapping on genes to turn them on or off.

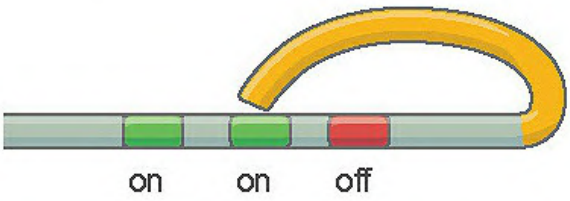
Fold-back Model



Fold back turns gene 1 off



Fold back turns gene 2 on



Short Telomere can’t reach genes

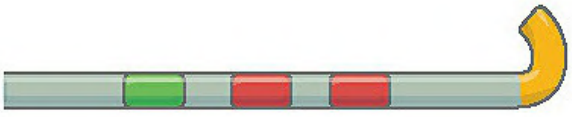


Figure 7-1-4: Fold back model of a Telomere.

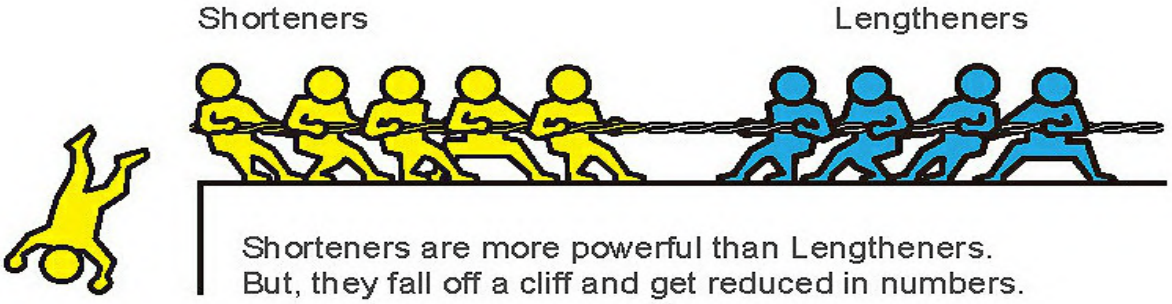
There is actually strong precedent for this type of mechanism, as it has been shown to be the explanation for why enhancer sequences can affect gene expression of genes greater than 100,000 bases away from the enhancer sequence. That is, enhancer sequences have been shown to come into contact with genes to regulate their expression by folding the chromosomes in such a way as to bring the enhancer and the gene promoter in contact with one another. Telomeres may be very much like enhancer sequences. And, the shorter the telomere gets, the shorter distance it can reach during chromosome folding.

Because “average telomere length” is so closely correlated with “percentage of cells with critically short telomeres,” the hypothesis that critically short telomeres were the true benchmark with actual relevance seemed purely academic at first; it could perhaps be applied in terms of designing telomere length measurement tests, but it was hard to see how it could inform any anti-aging therapies. But then evidence emerged suggesting that telomerase in yeast somehow finds the shortest telomeres in the cell and preferentially lengthens them. This

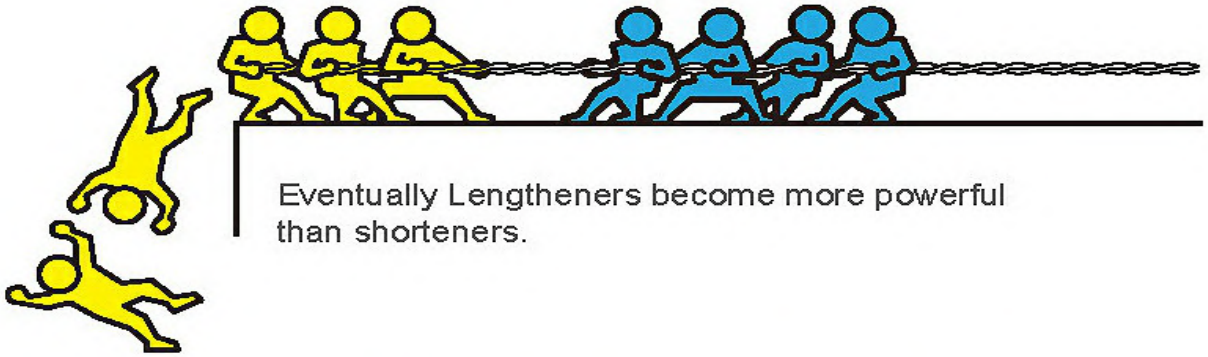
phenomenon was soon confirmed in mice cells, and then, in 2009, a team at Cardiff University confirmed that it's true for human cells as well.

So what does this mean? Well, it completely changes the way we think about inducing telomerase at low levels. Using the tug of war analogy, if we had four people pulling on the "shortening" side and we added two to the "lengthening" side, all we'd see is a subtle slowdown of the aging process . not a halt to it, and certainly not age reversal! But imagine that the shorteners fall off a cliff after they back up a bit. Eventually, there will be only one shortener pulling against two lengtheners. This would allow lengthening of the shortest telomeres even in the presence of low amounts of telomerase until more shorteners could be added back.

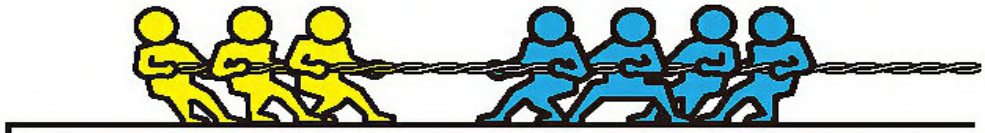
Low Levels of Telomerase



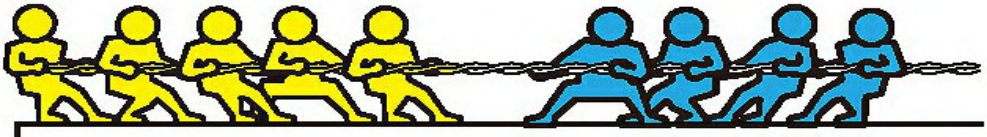
Shorteners are more powerful than Lengtheners.
But, they fall off a cliff and get reduced in numbers.



Eventually Lengtheners become more powerful
than shorteners.



So, Lengtheners begin to win for a while and
the shortest telomeres experience lengthening.



But this is temporary because Shorteners get added back
and telomere shortening resumes at the normal rate.

Figure 7-5: Low levels of Telomerase.

Because telomerase lengthens the shortest telomeres first, it's actually possible for someone's average telomere length to continue shortening while their telomeres with critically short telomeres lengthen! So, even a fairly weak telomerase inducer could cause age-reversal properties in the short term, though those improvements would be more temporary.

And I do believe we've seen this already. There are several products on the market that my lab has determined to have some effect on telomerase activation and/or induction, but not to the levels I'd expect to be necessary to represent age reversal. And yet, people are reporting improvements at levels well beyond what I believe could be explained by placebo.

Lengthening the shortest telomeres may induce some anti-aging effects, but it certainly doesn't mean that anti-aging science has crossed the finish line.though even temporary relief from the disease of aging is a pretty welcome accomplishment.

An interesting observation that I still remember from my time at Geron Corporation is that when we cloned different cells that

were expressing different amounts of telomerase, we saw that the telomere lengths of these clones correlated directly with the amount of telomerase being produced in each clone. This means that when you produce lots of telomerase in a cell, the telomeres don't just keep getting longer and longer. They reach some stabilization point that is correlated with the amount of telomerase being produced. So, even when the shortest telomeres are preferentially lengthened, they don't get lengthened very much by low levels of telomerase.

BALL OF YARN MODEL

Another way to explain the preferential lengthening of the shortest telomeres by relatively weak telomerase inducers is to imagine that telomeres are rolled up like a ball of yarn Telomeres, and other DNA, are often depicted as a long, straight double helix. But in our cells, the DNA isn't stored as a nice, straight continuous thread. There simply isn't room for that: if you took the human genome and laid it out perfectly straight, it would be over three feet long. Yes, every one of our one hundred trillion cells contains DNA that could stretch half our height.

So in order to fit inside our nuclei, that DNA is all wound up like a Slinky. But, think of a telomere as folded up like a ball of yarn. When a telomere is long the tip of the telomere could be buried in the center of that ball of yarn, where telomerase can't physically reach it to lengthen it. But as the telomere becomes short, the tip of the telomere becomes less and less buried and more and more accessible to telomerase to lengthen it.

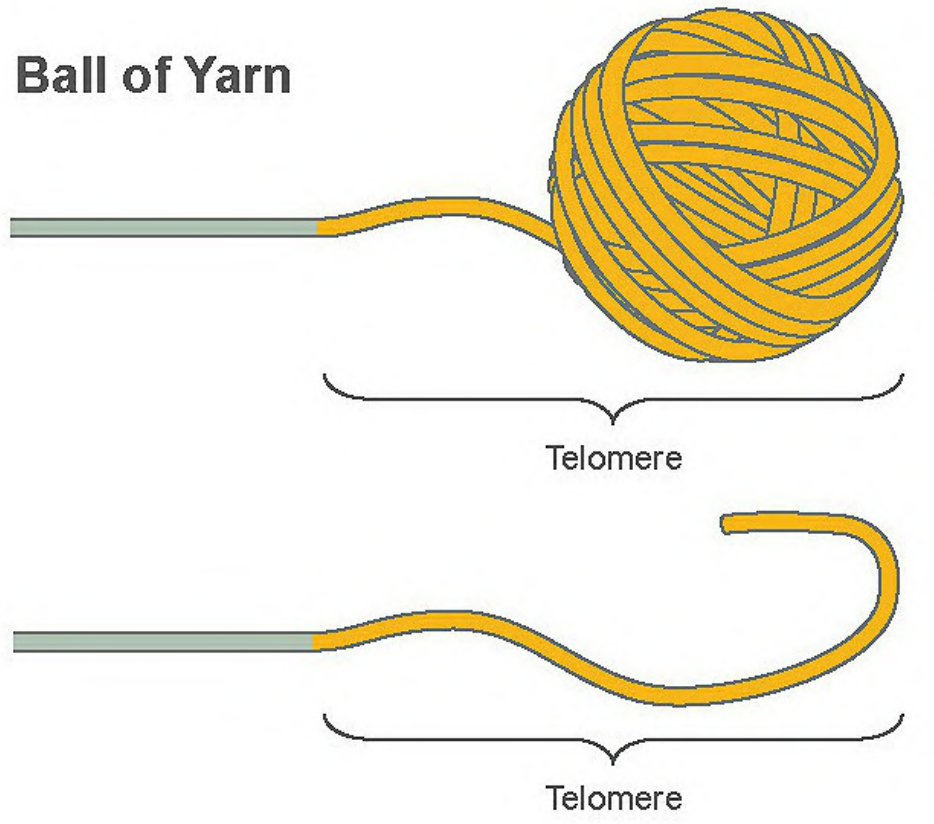


Figure 8-1: Telomere shown as a 'Ball of Yarn'.

This creates a simple, elegant regulatory mechanism to allow telomerase to target our shortest telomeres where it's most needed: because of the simple yarn-like structure of the telomere, the shortest telomeres are the ones exposed so that they can be lengthened. It's an entirely passive system for allowing telomerase to seek out the highest-priority targets; no complex machinery is required.

TUG OF WAR AGAIN

Think of that tug of war we talked about earlier between telomere shorteners and lengtheners. It appears, with natural products and even the early synthetics telomerase inducers, that the shortest telomeres are getting longer.but the longest telomeres are still getting shorter.

That's still better than nothing. Frankly, it's a lot better than nothing. If we can do anything to slow down that rate of telomere shortening, even a combination of antioxidants and anti-inflammatories, combined with a weak or medium-strength telomerase inducer, you can really do the best you can to keep your telomeres long for as long as possible.

What we'd like to do, eventually, is to get to the point where the shorteners and lengtheners are actually deadlocked in a tie. You're going to find people all over the world who are going to tell you that there are things on the market that can do this already. Those claims are all based on wishful thinking or weak data. With the exception of gene delivery forms of gene therapy, there is nothing that is actually strong enough to stop telomere shortening.at least, not yet.

What we'd like to do is develop a treatment to induce such a high level of telomerase that all the telomeres actually get longer, and the lengtheners win this tug of war. Again, you're going to be told there are products that do this. They do not. As of the publication date of this book, nothing exists that does this.

There have certainly been claims made that this exists. There's even been evidence produced in the form of telomere length measurements. A poorly-kept secret is that telomere length measurement technology is still in its infancy and is still extremely imprecise. When you do telomere length measurement on a thousand people, the imprecisions cancel each other out and you can see the clear correlations between telomere shortening, age, and declining health. But when you do telomere length measurement on one person, often the results are little better than throwing a dart at a dartboard, blindfolded. Though, I do believe that measuring the percent of your telomeres that are critically short is a lot more meaningful than measuring your average telomere length.

So, yes, telomere length measurement results have been produced that showed that a patient's telomeres got longer as a result of some treatment. That's not because the treatment

worked. It's because the test was so imprecise. Whenever you have a test that is imprecise, the results will show that roughly 50% of the people tested saw improved results and 50% of the people tested saw a decline in results. But, you will only hear the people with the improved results making their results public. The people with the decline in results will most likely hide their results so that no one knows. The result is a false belief that an imprecise test is a meaningful test.

No, a doctor can't prescribe a telomere-lengthening pill to their patients. Not just yet. But my lab has been making steady and occasionally remarkable progress for over a decade and a half, and so I'll just say: check back in a few years. Even sooner, if funding in this area of research improves.

WHAT DOCTORS NEED TO TELL THEIR PATIENTS

I'm aware that some of the people following my research, and therefore some of the readers of this book, are medical doctors. If you're one of them, this section is especially for you.

"Telomere" is the new buzzword in health and medicine, and it's an interesting one, because while you can't offer to lengthen your patients' telomeres, neither can you tell them it's a fad and a scam: it isn't. It's a major future sphere of medicine that's still in its infancy.

But because it's in its infancy, there are a lot of people out there that are trying to get their foot into the door even though they don't know what they're talking about. They're going to tell you all kinds of things about what you can do to lengthen your telomeres, and most of them don't even realize they're wrong.

So I want to tell you the actual facts. I'm going to talk about three different things that patients will likely ask questions about: telomeres as a biomarker, telomere protection, and telomere lengthening.

Telomere Length Measurement

Let's first talk about telomeres as a biomarker. What do you say when a patient walks in and says "I want to know how long my telomeres are"? Well, that's not as easy a question to answer as it may seem, despite what anybody else may be telling you. We always hear that when you look at a graph of person's age vs. their telomere length, you pretty much see a straight line: the older somebody is, the shorter their telomeres.

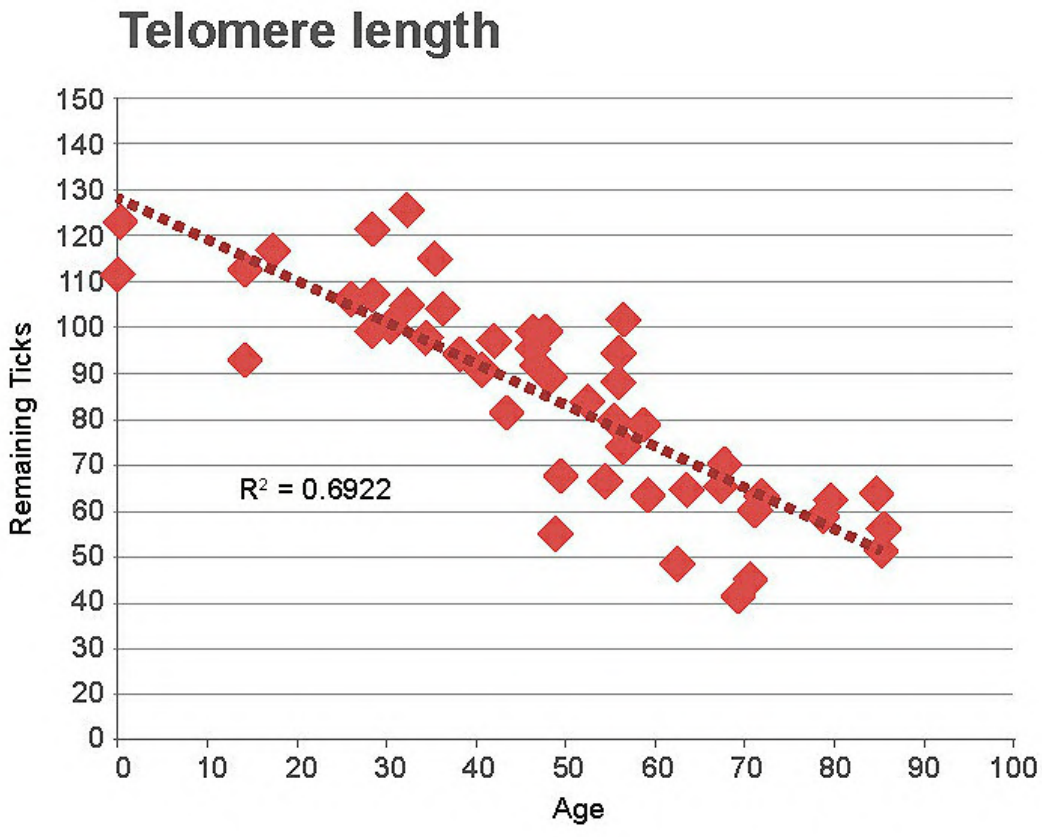


Figure 9-1: Diagram, Telomere length.

I wish that were true. When we actually measure a large number of people's telomeres and graph them against their age, we see a very chaotic mess of scattered data. It's not because people of the same age have wildly different telomere lengths; it's because the methods that exist to measure average telomere length, so far, are very imprecise.

Telomere length measurement is great for large population studies; if you look at 100,000 people, all that imprecision cancels itself out and you're left with a nice clear line of regression.

But, at least as of the time of this writing, it's not very good for drawing any conclusions about an individual. There's just too much scatter in the data. If you draw your own blood five different times, and you go get the telomere length measured in each, it's more likely than not that you're going to get five completely different answers. There are companies measuring telomeres that are insisting this isn't true, but despite what you might be hearing, tests with the necessary precision just haven't been developed yet.

If you're looking around to find a place to get your patients' telomeres measured, you're going to find that there are about six

different techniques currently in use. Many of them are based on measuring the length of the average telomere. But as I explained before, average telomere length may be correlated with age, but it isn't really the important biomarker when it comes to the question of health. Far more important is how many of those telomeres are critically short. It's when telomeres get critically short that they start wreaking havoc throughout the genome and the cells.

There are two protocols I've seen developed that do look at the shortest telomeres. Only one of them is actually commercially available right now. Measuring the proportion of telomeres that are critically short has proven both more precise and more relevant than trying to measure the average telomere length in a patient's blood. So when looking for a lab that measures telomere lengths, ask if they measure the percent of telomeres that are critically short. You will be saving your patients a lot of frustration or false optimism about their health.

Telomere Protection

The most crucial thing we can do, right now, to protect our telomeres is to simply adopt a healthier lifestyle. We talked earlier about how smoking, obesity, excessive stress, and similar

unhealthy practices that doctors have known to avoid for decades will cause accelerated telomere shortening. It's always been said that these lifestyle factors will make people "die young"; the truth is worse than that. They will make people "die old".only, sooner. I highly recommend that you read the book The Telomere Effect, recently published by Nobel Prize winner Dr. Elizabeth Blackburn and the world's foremost expert on lifestyle & psychological effects on telomere lengths, Dr. Elissa Epel. Though I don't agree on their claims about cancer and endurance exercise, I believe it to be the best book ever written on keeping telomeres long through lifestyle choices. These are things you can tell your patients to do now.

Exercise, in particular, is critical. There are at least ten papers now that conclude that the more endurance exercise you do, the longer your telomeres. None of the studies have been able to identify a "point of diminishing returns" in their samples. You may have heard claims that some exercise is good, while too much is bad, but the studies don't back those claims up. Endurance athletes (runners, bikers, swimmers, etc.) have longer telomeres than those who exercise several times a week at a gym, who in turn have longer telomeres than sedentary individuals. I think it's probable that people who exercise to the

point of physical collapse.those who cross the finish line and drop to their knees, vomiting.aren't doing themselves any favors with respect to telomere length, but in general, those that treat endurance exercise as a form of causal moving meditation, as I do, find great benefits to their telomere lengths. And in such cases, more exercise is better.

Stress reduction is also more important than some people might think. Doctors have known for a long time that stress can lead to cardiovascular problems, and there have always been jokes about rambunctious children turning their parents' hair grey, but only recently has it become clear that stress really does biologically age people. Elissa Epel has reported that caregivers of Alzheimer's patients have been shown to have shorter telomeres than the average person their chronological age; adults who were abused as children similarly have shorter telomeres than the general population. Not every stressful situation is avoidable, but if there is avoidable stress in your life, consider reducing it if you want to stay young longer.

Depression and even simple pessimism also cause accelerated telomere shortening; there are two studies showing that people who self-identify as pessimistic have shorter telomeres than those who self-identify as optimistic. Just like stress, sadness

causes hormonal changes in the body that are not conducive to ideal health, and which, over time, will lead to shorter telomeres and premature aging.

A healthy diet will help our bodies stave off accelerated telomere shortening caused by environmental factors, but most people don't eat the ideal human diet. In particular, there are three supplements that quite a few scientifically peer-reviewed studies have been shown to protect telomeres from accelerated shortening: Omega-3s, Vitamin D, and antioxidants. If you're taking these, your telomeres are probably longer than your friends' who aren't taking them. I've talked to some of the authors who have published papers on these supplements, and they've given me their recommendations.

For Omega-3s, assuming you're an adult of relatively average size, you want to take 1.4 grams of EPA and 1 gram of DHA per day. Simple enough.

With Vitamin D, it's helpful to have a doctor order regular blood draws. You should take five to ten thousand IU per day until your blood levels are between 60 and 100 nanograms per milliliter, and then reduce your intake to a maintenance level around 5,000 IU. It typically takes about a month to get Vitamin D levels to where they ought to be.


defytime
TAM
TAM Spray
With Telomerase Activating Molecule
20ml
Aqueous Propolis
PCT/NZ2016/050124
defytime
TAM
TAM Spray
With Telomerase Activating Molecule
20ml
Aqueous Propolis
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Figure 9-2: Defytime TAM Spray.

Antioxidants are the most complicated, and overdosing on antioxidants can lead to pro-oxidant activity in the body. Generally, it's best to take whatever dosage is indicated on the bottle.

None of this should be taken as medical advice for patients. I'm a Ph.D. biologist, not a medical doctor. This is advice I give to medical doctors, who then individualize their advice to their specific patients' needs. If you plan to start a telomere protection regimen, talk to your doctor. But, ask your doctor to talk to me.

Telomere Lengthening

There are a number of products on the market that claim to reverse aging, and even to lengthen telomeres. I'll put it bluntly: at the time of this book's publication, there are no products on the market that will reverse aging or lengthen telomeres more quickly than their natural rate of shortening, for a net lengthening effect.

But that doesn't mean these products aren't worthwhile. I take

several of them, myself. I believe in a concept that Dr. Terry Grossman eloquently expressed as: “Live long enough to live forever.” Science is on the very cusp of being able to control and reverse human aging. If a supplement gives me just six more weeks to live, that could allow me to be young and healthy enough to take a supplement that gives me six more years to live, which in turn could allow me to be young and healthy enough to take a supplement that gives me sixty.

And so I need to stress: while there are no products on the market that will cause a net telomere lengthening effect, that does not mean that everything on the market is snake oil. I’ve participated in both screening and peer-reviewed studies of some of these products and supplements, and I can confirm that, yes, some are having a positive effect on the telomere.

I won’t get into specific product endorsements in this book;

I’m writing this book as an educational tool, not as a brochure for pills. So I encourage you to do some research on your own. But as a general principle, when it comes to supplements on the market today that claim to slow the rate of telomere shortening in the body, try not to be too optimistic or pessimistic. None of them will make you young again, but they aren’t wastes of your time and money, either.

TELOMERASE DOES NOT CAUSE CANCER

One of the reasons I'm writing this book is to explain why public enthusiasm for pursuing telomere lengthening science and technology is very well-founded. That age reversal is not science fiction, but something we can really bring to fruition within our lifetimes. So it's important to address one of the biggest obstacles to that enthusiasm.the persistent rumor by some that telomerase induction, once achieved, would cause cancer.

In a way it's inevitable that such a rumor would come to exist, simply because of the relationship that modern culture has with science. For centuries, we've read literature that presents a cure for aging as far too good to be true, as some sort of "deal with the devil." From The Picture of Dorian Gray to Tuck Everlasting to lighter fare like movies like Death Becomes Her, age reversal in fiction always comes with strings attached.strings so pernicious that the "moral" of these stories is invariably that extending life is a disastrously bad idea, while those who choose to age and die will ultimately be happier.

The false idea that telomerase induction causes cancer fits that

ancient narrative pretty nicely, so when the faintest suggestion was discovered that telomerase and cancer are part of the same picture, it's the narrative people grasped for.

I was there when that suggestion first took hold. When I led the research at Geron Corporation that discovered human telomerase, we took telomerase and we put it into regular human skin cells, where telomerase is not naturally expressed. And we were able to show that they did not age and that their health did not decline. But at the same time, we took what's called the antisense of telomerase.a complementary DNA strand that prevents any telomerase production.and we put that into cancer cells. And what we discovered was that the cancer cells died, essentially from accelerated aging. Better yet, the same treatment had no effect on normal cells.

Initially, it looked like we had a cure for cancer on our hands, and although it hasn't turned out to be as straightforward as it initially seemed, telomerase inhibition is still a major target for fighting cancer, with telomerase inhibitors currently in clinical trials. And this is the reason I was awarded second place for National Inventor of the Year in 1997: it appeared my team had actually discovered a plausible cancer cure.

But those experiments also turned out to be the genesis of the

rumor that telomerase causes cancer: some people read about them and leapt to the conclusion that if telomerase inhibition cures cancer, telomerase induction must cause it. It's not good logic; it's completely unscientific; but to some people it just felt like something that somehow must be true.

Everything else set aside, when asking the question if telomerase causes cancer there is always one element of the issue that everyone seems to overlook. That is, we absolutely already know without a doubt that a lack of telomerase definitely causes cancer. For every study that suggests that telomerase might cause cancer, there are a hundred studies that show that the lack of telomerase does cause cancer.

Doesn't that almost make the question "does telomerase cause cancer?" irrelevant? Even if telomerase did cause cancer, you either have telomerase turned on or you don't; there is no third option. So now the pertinent question becomes not "does telomerase cause cancer?", but "does telomerase cause cancer more than the lack of telomerase does?"

And the answer is no, because telomerase doesn't cause cancer at all. Telomerase actually prevents cancer. Most cancers have telomerase turned on not because the cancers were caused by telomerase; in fact, it's the other way around. The cancers

caused the production of telomerase, and they did so by allowing their telomeres to get really short, dramatically increasing their mutation rates, and finding a mutation, such as a chromosome rearrangement, that turned the telomerase gene on.

But, I might be going too fast here. Let me explain in more detail: one of the biggest causes of mutations in human cells, including chromosomal rearrangements, is short telomeres. It's again very much like the shoelace. When the caps on our shoelaces get short, our shoelaces start to fall apart. Well, the same thing is true in our chromosomes. When our telomeres get really short, our chromosomes start falling apart. This is typically seen under a microscope as chromosome rearrangements. A typical cancer cell with short telomeres can often have hundreds of chromosome rearrangements, and tens of thousands of smaller mutations that cannot be visualized by light microscopes. A related phenomenon called chromothripsis is also common when telomeres get really short.that is, when tens to hundreds of clustered DNA rearrangements suddenly result from a single dramatic event. In fact, the word chromothripsis is derived from Greek affixes meaning "the shattering of the chromosome" because the genetic damage is so profound. This really wreaks havoc on the chromosomes. With this many mutations occurring

on a very frequent basis, the cancer cells can mutate to almost anything imaginable. This is why most cancers come back after chemotherapy. Sure, chemotherapy will kill 99.9% of the cancer cells. But, a few always mutate to survive the chemotherapy, and the cancer comes back. And, guess what: the mutations also lead to the expression of the telomerase gene, either by derepressing the telomerase promoter or rearranging the DNA so that the telomerase gene is expressed from an entirely different promoter. Or, the mutations lead to an alternative method for lengthening telomeres generally called the Alternative Lengthening of Telomeres (ALT) pathway. So much for killing cancer cells by letting their telomeres get short!

It is now well established in the scientific literature that treating cancer by inhibition of telomerase to force cancer cells' telomeres to get critically short is leading to cancers returning with mutations to maintain their telomere lengths using the ALT pathway. And things still get worse! The short telomeres induce even further mutations that cause metastasis to occur and the cancer spreads throughout the body.

Let's not forget that our best defense against cancer is our immune system. That, too, will suffer from short telomeres because for the immune system to fight the cancer, it needs to

undergo lots of cell division and cell division causes telomeres to shorten. Very quickly the telomeres in the immune cells become so short that they lose the ability to fight the cancer. This is called immune senescence.

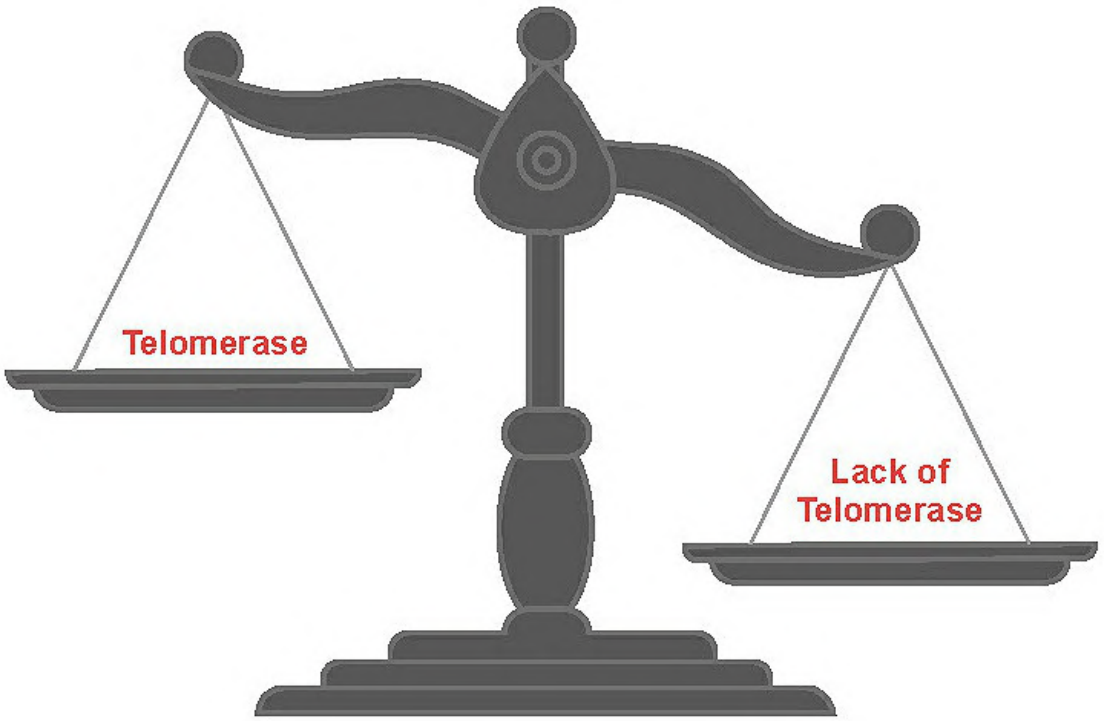
So, what do we have here? Short telomeres are bad. That's why I always say "Bad Things Happen When Telomeres Get Short!"

Now, let's return to the question "Does telomerase cause cancer." I can't imagine how telomerase could actually be the cause of cancer. However, I could imagine a scenario where telomerase causes a very small new cancer to become healthier. There are lots of things that do that including the food we eat. Should we starve ourselves to death to kill our cancer? No, of course not. But, something that is often overlooked when accusing telomerase of causing cancer or making cancers healthier is that telomerase will strengthen our immune system by lengthening the telomeres in our immune cells, increasing the ability of our immune system to destroy our cancers.

Yes, if our cancer cells were the only cells in our body that expressed telomerase, that would be a bad thing. But that is exactly the problem we already have. Every time a cancer gets big enough to even detect, it has already undergone enough cell

division to cause its telomeres to get so short that the cancer should have succumbed to senescence. But, it doesn't senesce because the cancer mutated to maintain its telomere lengths either by telomerase induction or ALT. This is like two armies fighting where only one has weapons. If we were to induce telomerase in the other cells of the body, it would give the immune system a fighting chance to defeat the cancer.

As I said before, for every study that suggests that telomerase might cause cancer, there are a hundred that show that the lack of telomerase does cause cancer.



There are now many studies, including meta-analyses, that show that cancers are caused by short telomeres, not long ones. But the latest attempts to implicate telomerase as a cause of cancer is recent studies looking at the presence of gene variants that are correlated with long telomeres. Some of these studies have shown that the presence of these gene variants increased a person's risk of cancer. But, the authors have never been able to show that the gene variants didn't cause cancer by other, non-telomere-related events in the cell. And, the authors never actually measured the telomere lengths. So, I am reluctant to give much weight to these studies until the gene variants are better understood.

I would like to conclude the discussion of cancer with the following. In my opinion, the best way to fight cancer is not to inhibit telomerase to cause the telomeres to get short, but to induce telomerase to lengthen telomeres to strengthen the immune system. If we could combine this treatment with a telomerase poison that kills telomerase-positive cells without allowing the telomeres to shorten, that would be even better. But, before we get cancer, the best way to prevent cancer is to induce telomerase to prevent the large number of mutations caused by short telomeres that cause cancer.

An Evolutionary Basis

So, why do our telomeres shorten? That sounds like an awful thing to have happen to us when we should have supposedly evolved ways to live healthier longer, not shorten our lifespans. A popular hypothesis among some scientists is that telomere shortening is actually an anti-cancer mechanism. The thought is that perhaps our telomeres shortened specifically so that cancers couldn't become particularly dangerous, and that aging itself might just be an unfortunate side effect of cancer prevention. But, hopefully, after reading everything I just said about telomeres and cancer you know this doesn't make any sense. Allowing telomeres to shorten is a very ineffective way to fight cancer.

To answer the question "why do telomeres shorten," we need to understand evolution more carefully. Evolution doesn't strive to make us live longer and healthier. It strives to increase the chances that we pass on our genes, while simultaneously shuffling our genes to ensure that we can always survive a rapidly-changing environment. Shuffling of our genes is much more efficient when offspring breed among each other instead of breeding with their elders. Evolution also strives to keep the

offspring alive and healthy so that they will be more likely to breed and produce more offspring.

But, after they have raised their offspring, the parents of those offspring are just in the way. Then they become competition with their offspring for food, mates, and in the case of modern humans, jobs. So, for a species to be successful in a rapidly changing environment it is always best to "knock off" the old. The bottom line is that there is no evolutionary advantage to living longer than it takes to raise your young. So, in the case of humans, other primates, dogs, cats, horses, sheep, pig, and deer, these animals all evolved a mechanism of knocking of the old called telomere shortening. Rodents, such as mice, evolved an entirely different mechanism. They actually have no telomere shortening. And, they have telomerase produced in all their cells. Rodents typically die from declining health due to oxidative stress and mitochondrial dysfunction. It's almost as if they are born with a person inside them blasting a machine gun in all different directions until they succumb to all the bullet holes.

And, then, there are animals on this planet that have no detectable aging. Somehow their species survived despite lacking a clear mechanism for knocking off the old. These animals include lobsters, tortoises, clams, and whales, to name a few. All

these animals have been shown to have telomerase produced in all their cells, and they have no telomere shortening. And, they rarely get cancer and other diseases.

So, how long do these animals live? We still don't know. Most animals don't have something like rings on a tree that we can count. The only way to tell, in most cases, is to be there when the animal is born, put it in a cage or aquarium, and then watch it. People never really thought of doing such a thing until the time of Darwin, but now people have been watching some of these animals for more than 150 years and they see no detectable aging.

It's not typically possible to determine these species' age, but there's one interesting exception: clams. Clams grow a little bit like trees, where they accumulate a new "stripe" like a tree's rings every year. Clams have been now found with over five hundred stripes, suggesting that Columbus may have sailed over claims that are still alive today.

It would seem, then, that it is not inevitable that we must decline and die. Some may claim that agelessness is unnatural, but as we can observe, it's perfectly natural, in that many animals already do not have an aging process. And soon, we will have the opportunity to join them.

IN CONCLUSION

A cure for aging exists. It can be done. Eventually, it will be done. There is enough proof of concept that we can confidently say it is definitely possible, just as those in the know could confidently predict the rise of the Internet by the early 1980s or even before. Many of the particulars are yet to be fully worked out, and there is a great deal of work ahead for scientists and engineers, but there is now no longer any serious debate on three points:

1) We age because our cells age;

2) Our cells age because they contain a clock of aging;

3) That clock can be altered in a number of ways, even in a living human being.

And in my expert opinion, there is no longer even a worthwhile counterargument to a fourth point:

4) The telomere is that clock. Telomere shortening causes aging as we know it. Lengthen the telomeres, and we can prevent or reverse aging.

After hundreds of years of searching for it, we now know exactly where the Fountain of Youth is. We can point to it on a

map (a map which turned out to be a diagram of the human cell). All that's left is the question: do we have the will to reach it? Will we travel there and drink from it? Or will we distract ourselves with arguments that maybe it won't work; that maybe those who advocate for it and invest in it will be embarrassed; that maybe it will cause side effects; that maybe some of our social institutions depend on aging and death; that maybe we should just stick to the natural condition of dying slow and painful deaths of old age for another few generations?

I can't answer that question. It isn't up to me. That's a question that we'll all have to answer together.