

LE Magazine February 1998

INTERVIEW

'Turning on' Telomerase To Stop Cell Aging: The Quest for Immortality

Telomeres consist of special DNA regions at the ends of each chromosome. Each time a cell divides, it loses part of its telomeric DNA, causing telomere shortening. Apparently, when telomeres become too short, "cell aging" occurs. But there is an enzyme, telomerase, that can reset telomeres back to their youthful lengths, suggesting to Dr. Michael Fossel the possibility of radical extension of the healthy human lifespan in the near future.

Dr. Michael Fossel received his Ph.D in neurobiology and his M.D. at Stanford University, and is currently a professor of clinical medicine at Michigan State University. Dr. Fossel's 1996 book, *Reversing Human Aging* (William Morrow and Co. Inc.), considers that much or most of normal aging may be due to shortened telomeres. He also is the editor of the newly-launched *Journal of Anti-Aging Medicine*.

This interview-a far-ranging and often witty discussion of the nature of aging, and possible theories of how life span may be extended- originally appeared in *AGE News*, the newsletter of the American Aging Association. It is reprinted with permission.

What are telomeres?



Michael Fossel: The telomere is a set of repeated base pairs at the end of the chromosome (DNA is made up of base pairs lined up in a special sequence). For example, in a human at conception, telomeres are probably about 9,000 base pairs long.

Also on the chromosome are perhaps an additional 5,000 base pairs, and below that there are essentially normal genes that probably include, among others, some critically important regulatory genes that have effects on genes elsewhere. So you have the telomere and the sub-telomere, and then you have a set of telomere-like genes that may be regulatory in function.

Then there is telomerase, an enzyme which shows signs of resetting telomeres back to their original, youthful lengths. There are some data showing that you can have telomerase in the cell and not have it active, and there are some other indications that you can lack telomerase and still have telomerase activity. It makes you wonder if something else is going on that can lengthen telomeres, independent of telomerase.

I'd be shocked if there weren't going to be some vast surprises about how telomeres work, how telomerase functions-I can't imagine it being otherwise. For me to talk to you about the telomere hypothesis is premature and is going to be sketchy, but is also a lot of fun. It is a fascinating hypothesis.

How would you summarize the telomere hypothesis as it relates to aging?

Fossel: There are two main forms of the telomere hypothesis, the weak form and the strong form. The weak version is more acceptable and more supported by current data.

The weak version is that telomere shortening is associated with and times the onset of cellular senescence. Now, note that I didn't say that telomere shortening causes aging.

If you had to talk about causation, you'd also have to talk about gene function, control of gene function, sub-telomeric shortening, and how that affects gene expression. There's a lot more to cellular senescence than telomere shortening, per se.

But, in a nutshell, the weak hypothesis is that telomere shortening times the onset and progression of cellular aging. I would guess that if you polled the people involved in aging, you'd find that the majority of people accept the weak telomere hypothesis now. That is, people who are aware of aging and are aware of telomeres and what they do-probably the majority of them-say that cellular aging is timed by telomere shortening.

I think we have to make a distinction. When you're talking about cellular aging, you're talking about replicative senescence or in-vitro aging, and many biologists would not accept that as being cellular aging in a living creature.

Fossel: Absolutely, which brings up the strong hypothesis, much less supported and more controversial. The strong telomere hypothesis is that telomere shortening ultimately times the onset and progression of organismal [whole body] aging. Again, it doesn't cause aging, it times the onset and progression of aging.

Suppose you had two animals with the exact same telomere length, and one of them had very inefficient superoxide dismutase and the other had very efficient superoxide dismutase.

You'd expect that organismal aging would be faster in the one with the more inefficient superoxide dismutase. So it wouldn't be fair to say that telomere length determines biological age. Telomere length times the onset and progression of aging, but it does that in a genetic context.

The strong telomere hypothesis is, I think, very unaccepted. My guess is that you're probably looking at a very small percentage of telomere biologists or aging biologists in this country who honestly believe that a large percentage of organismal aging is accounted for by telomere shortening.

What are your estimates of the implications of this research on human life span?

Fossel: We should be able to extend the human life span indefinitely. Not infinitely, but indefinitely. It's really any number you want to pick. If I said we could extend the human life span to 1,000 years, people would laugh hysterically. If I said we could extend it one year, people would yawn. So when I say 200 years, it's because I need a number we can talk about that doesn't seem either silly or boring.

Are you saying that there need not be any clear-cut objective limits to the human life span?

Fossel: Let me put that differently. I would say there are at least two kinds of limit to the human life span. One is stochastic: sooner or later, you get hit by a meteor, fall off a ladder, get struck by a car, step on a land mine, or whatever-if you live long enough, whatever it is, one of those things will happen.

In your book, you give some numbers.

Fossel: If your risk remained equal to the risk of 30-year-olds in 1960 in the U.S., as I recall the median life span should be 1,776 years. That's assuming no cause of death other than trauma.

That's also assuming no reduction of trauma. For example, that we continue to drive cars, etc.

Fossel: Yes, but the end conclusion remains the same. We don't know how long we will live, but sooner or later, something's going to get us. Rabies doesn't care what your telomere length is or what your superoxide dismutase level is, either.

There are also likely to be secondary limits to aging. Let's say that lipofuscin [intracellular "trash"] is not currently a limiting factor, but let's say that it accumulates in cardiac muscle with age, as it does. And let's say, for the sake of argument, that it causes a deficit of function, or that there is a threshold above which it would cause injury.

While we may not reach that threshold for cardiac cells currently, if you reach 150 or 200. you've got to wonder if the probability of having a dysfunctional heart from lipofuscin accumulation is going to become limiting for your life span. Or, for that matter, DNA damage. If you live for 1,000 years, sooner or later-I don't know when it's going to happen- there's going to be sufficient uncorrected DNA damage that it may become a form of final aging.

There are two sorts of aging: wear-and-tear aging and active aging. My argument would be that telomere shortening is a form of active aging. But even if we got rid of that, there would still be weathering damage. Sooner or later, one neuron may die, for whatever reason. Sooner or later there may be sufficient loss of neurons to produce dementia, even without aging.

What is the history of the weak version of the telomere hypothesis?

Fossel: There are only three main points to that history. First is the observation in 1961 by Len Hayflick that somatic [normal body] cells have a replicative life span, a limit to their cell-division capacity, now called the Hayflick Limit. Before that, we had the feeling that if you could not culture somatic cells indefinitely, the reason was that you were technically inept.

Not surprisingly, Hayflick was accused of being technically inept, but he was actually much more careful than anyone who had gone before.

The second point occurred in 1971 and 1972 with Olovnikov and Watson's observation that linear chromosomes naturally show shortening, and that's built into DNA replication. Put facetiously, that left only two alternatives. Either there was something beyond normal DNA polymerase responsible for replication of telomeres, or none of us existed. And since the second option seemed unlikely, that only really left the first. Something else obviously had to be going on.

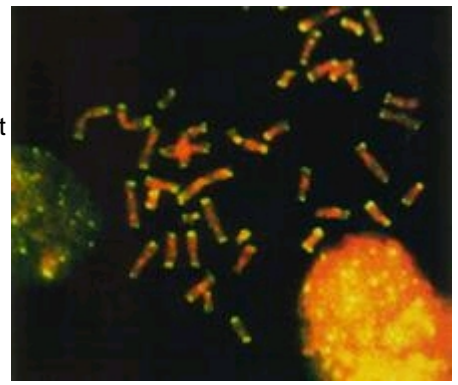
Olovnikov went one step beyond Watson, and suggested that maybe telomere shortening was linked with cellular senescence. That idea was first followed up by Cal Harley in 1975, but it wasn't until 1990 that he, Carol Greider and Bruce Fletcher put out a paper in Nature showing that telomere length correlates with cellular aging.

Notice that they didn't prove causation. What they proved was correlation. It was tempting and it was highly suggestive, but it wasn't proven. They showed that telomere length correlated with cellular senescence whether you were looking at cells you had cultured in the lab or you were looking at cells you had drawn from different age individuals.

The telomere length in the fibroblasts drawn from a given individual correlated with the remaining number of divisions from a Hayflick stand-point. So those were fascinating data.

Those are your three main historical high points in the telomere hypothesis so far. The point that cells age, the point that telomeres shorten, and the point that those two events go together.

A fourth point has been published by Jerry Shay and Woody Wright at the University of Texas. If telomere shortening times the onset and progression of cellular aging, then if you could reset the telomere length, you should be able to show that the cells have a longer replicative life span.



That would be excellent evidence that you were looking at causation. And that was what they achieved. They showed that when you increase telomere length, you increase replicative life span.

How did Shay and Wright increase telomere length so as to increase cell life span?

Fossel: They were actually trying to *shorten* telomere length and induce senescence in a HeLa-I cancer cell by giving what were essentially telomere fragments to the cancer cell. Curiously enough, what happened was that the HeLa cell took the telomere fragments and lengthened the telomere. Then they merged this cell with a cell that had replicative senescence and showed that you now had a non-cancerous cell with a longer life span.

Isn't there a virus that can induce telomerase activity?

Fossel: There's a question about that, whether you actually had telomere lengthening or something else going on.

You're not going to prove the telomere hypothesis without increasing telomere length.

Fossel: We need to find some way to induce telomerase. But the Stray and Wright result is a good start. At least it's very suggestive of causation. But yes, we need to do specific relengthening of telomeres and show that it has a direct effect on the Hayflick Limit.

What's the best way to do that?

Fossel: It's sort of an open question where you start. What we need to do is key in on telomerase expression—for example, find a drug that induces telomerase genes to express [make] telomerase. But it's probably more than that. We have to understand what makes telomerase active once it's expressed, what controls the binding of the components of telomerase, what controls whether telomerase binds to the telomere or not, what controls the rate at which it lengthens the telomere once it's bound... all of this is unknown. So the simple version would be, all we need to do is control telomerase gene expression, but there's certainly going to be a lot more to it than that.

We need to put more resources into understanding telomeres and telomerase.

What sort of experimental test could be done on whole animals in the near future that might provide evidence on the validity of the strong hypothesis?

Fossel: Currently, all we might be able to do is an ex vivo experiment: take cells out of the body, lengthen their telomeres, and put them back in. To my knowledge, this has not been done. Jerry Shay has talked about this.

How would this be done?

Fossel: Suppose we had a patient with an aging lymphocyte [Immune system cells] pathology. For example, Down syndrome kids have shorter telomeres in their lymphocytes, and they tend to die of infections.

What would happen if we increased the Hayflick Limit of their lymphocytes? Right now, Shay could take out lymphocytes, lengthen their telomeres using his model involving HeLa cells, and put them back in. It has to be a disease that's fatal, because nobody in his right mind wants to put hybridoma [former cancer] cells back into a human being unless you're really pushed into this. Still, that's what we'd like to do, and that's within the realm of technical possibility right now.

When are we going to see a clinical anti-cancer approach based on telomerase suppression?

Fossel: All I'm allowed to say is that I'd be very surprised if it takes as long as a decade. The first human trials should be starting soon. I think there will be side effects but they will be manageable; and they will be remarkably minimal compared to the side effects of current chemotherapy.

What about harming immune cells, which must divide to work?

Fossel: Circulating immune cells have longer telomeres than the average cancer cell. Most cancer cells are on the edge of a Hayflick cliff and will fall off very quickly once telomerase is inhibited.

Talk a bit about the human accelerated aging disease progeria, the condition whereby young children age prematurely and dramatically, and often die of "old age" before they are 10.

Fossel: Progeria provides moderate support for the telomere hypothesis. It's clear that progeric children (that is, Hutchinson-Guillford children) have, on the average, shorter telomeres. The mean telomere length in the fibroblasts of a 5-year-old progeric child is about the same as the mean length you would expect to find in the fibroblasts of an 80- or 90-year-old.

There is a suggestion that shortened telomeres in endothelial cells [cells that form the inside lining of blood vessels] correlate with atherosclerosis. If you look at progeric children, they die overwhelmingly of atherosclerotic disease, that is, strokes and heart attacks, for example.

And these children have none of the usual hallmark risk factors such as hypercholesterolemia, hypertension (although some of them do), diabetes- none of them to my knowledge has ever been a smoker. Yet they die overwhelmingly of things that you and I usually attribute to those "causes."

Is there a relationship between telomere shortening and atherosclerosis in normal people?

Fossel: This brings us right to the strong form of the telomere theory. And I want to emphasize that's what this is... theory. The data supporting this are weak and can be interpreted in a dozen ways. For me to interpret it as a strong version of the telomere theory is because I choose to do so, not because there aren't other options.

It's become clear in the last few years that, while the standard risk factors for atherosclerosis are important, it's not as simple as whether you have high cholesterol or whether you smoke or not. There's a lot more to it than that.

So the focus has begun to shift to endothelial cells and what they do that makes them help initiate this pathology. It must be that endothelial cells get lost more frequently when you have high risk factors for atherosclerosis.

The working hypothesis would go something like this: an endothelial cell dies, so the cell next to it has to divide to make up for the transient denudation of the vessel wall. When that happens, it marginally shortens its telomere.

As this progresses over the years, you get a slow onset of a senescent pattern of gene expression. The trophic [nutrition] factor production changes, and that allows the changes we see at a microscopic level-the early pathology of atherosclerosis.

The end result is the clinical one, an increased risk of heart attacks, strokes and death.

What is the evidence for this?

Fossel: We find there are shortened telomeres in endothelial cells very early in the onset of pathology. Anywhere you look where there's high shear stress, for example, in arteries versus veins or at specific spots in arteries, you find shortened telomeres. This is where you expect to see early onset of atherosclerotic lesions.

The other evidence is indirect and not tested. We know that progeric children have an enormously high rate of atherosclerosis and yet they lack most of the usual risk factors. They should have shortened telomeres in their endothelial cells, although we haven't directly measured it.

Now let me expand the argument. Again, this is speculation. The general argument or the general model would go something like this. You have a cell that divides. That cell, because it divides, alters its cellular behavior, and that has an impact on neighboring cells.

In the case of vascular disease, what you see is that endothelial cells, which divide, have an enormous impact on the smooth muscle cells underneath them, and that has a final impact on, for example, cardiac tissue down the road.

If I see someone who has died of a heart attack, very seldom do they have bad heart muscle. What they have is ischemic [blood-deprived] heart muscle. It wasn't the heart's fault; it just didn't have a vessel that was supplying it. Ultimately, we'd say that's the result of something that's happening at the endothelial cell level. The general model would be that in cells that divide and therefore shorten their telomeres, there's cellular aging. And that has an impact on cells that don't divide.

Here's an example: a lot of people would say that the reason the strong version of the telomere hypothesis doesn't work is that you get age-related diseases in tissues that don't show cellular division, like the heart, for example. What about the brain? You could certainly use this model to explain stroke, which I already did.

What about Alzheimer's? Well, people would say you can't use the telomere hypothesis because neurons [brain cells] don't divide, at which point I point out that the neurons are completely dependent upon glial cell function, and glial cells do divide-at least many of them do.

The classic example is microglia [the cells that form part of the supporting structure of the central nervous system]. We know that microglia are implicated early in the etiology of Alzheimer's. But we don't know how, whether it's primary or secondary. There's the tempting possibility, and it's no more than that, that the telomere shortening in microglia is responsible for changes in microglia that are ultimately responsible for something like Alzheimer's. It's no more than sheer speculation.

The point I'm making is that the model, that cellular aging is ultimately responsible for aging in non-dividing tissues, is coherent; it's tempting; it's elegant. But that doesn't mean it's true.

Why is it that certain cells don't age?

Fossel: In the case of non-dividing cells, from a telomere standpoint, we'd argue that it's because they don't divide. Why is it that certain cells that divide rapidly over your entire lifetime don't age? The argument would be that they have telomerase expression. Could it be that cells that divide but that don't have telomerase expression are ultimately responsible for the rest of organismal aging? My guess is that's possible, and we'll find that a lot of organismal aging can be laid at the foot of cellular aging.

What is the evidence, if any, that telomere shortening per se has an effect on gene expression?

Fossel: Telomere length correlates with senescent gene expression. Causation we don't know. And even if you accept causation, we do not understand the mechanism by which you get from telomere shortening to changes in gene expression. We know they go together, but the mechanism is uncertain.

If you had animals with identical genes and you could extend the telomere length in one sample of that population, then that sample population would have a longer life span. But if you added superoxide dismutase instead of extra telomere length, you would also extend life span. There are many ways of extending healthy functional life span.

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