telomere, making it longer.

Now, the chromosomal telomeric proteins will have a higher probability of switching into a state that is inaccessible to telomerase, blocking its action. This state probably has a higher order structure that we do not understand right now.

Some fraction of the telomeres is still accessible to telomerase, and could therefore get longer. If they do, they will have a very high probability of switching into the inaccessible state, and they will become blocked to telomerase. The consequence is that as these cells keep dividing, the blocked telomere, without telomerase action, will get progressively shorter, increasing the probability that it will switch into the accessible state.

So, you see, built into the telomeric structure and its interaction with telomerase is a very clever scheme. I have come greatly to admire this strategy of the telomere. At first, I thought it was very clumsy to have this type of repetitive DNA addition and loss. But now it is apparent that the telomere has built into itself the ability, when short, to become accessible to the action of telomerase, which will make it longer and more likely to switch into a state that will be more likely to become shortened, because telomerase won't act on it. This keeps the telomere at a favorable length. Much work by us and others has convinced us that maintaining this length within a well-defined range depends upon many different factors, including the states and amounts of the telomeric proteins and of telomerase. All these factors set the length of the telomere in a way that's probably very complicated.[8]

How does this play out in the cells in our bodies? I will describe one example of what happens in the blood cells in our bodies. This work was done by Bob Frenck and Kevin Shannon in the Pediatrics Department of the University of California, San Francisco.[9] They analyzed the average length of the telomeres in cells that have had telomerase active, and in which telomerase can be readily activated.

In these cells, the telomeres shorten very fast when humans are very young, with the average length dropping precipitously even before kindergarten age. Then, from that time to the time a person would have graduated from Keio University, they haven't changed much, despite similar amounts of cell divisions. Further into adulthood and old age, there is a general decline in telomere length, whose significance is unknown. Thus, telomere length changes in a complicated fashion over time. But telomerase is active in these cells for much, if not all, of the stages of life shown here.

These observations emphasize that in cells that have telomerase, there is a battle going on between lengthening and shortening activities, which is played out in a complicated way, such that it's very hard to predict telomere length from first principles.

As I mentioned, there are other types of cells in the adult human body that apparently have telomerase activity throughout much of life, and so their telomeres are likely to have complicated sets of rules determining their length.

Next, I will turn to cells without telomerase.

In the 1970's, predictions were made on theoretical grounds, based on the knowledge of DNA polymerase, the complicated machinery that copies cellular chromosomal DNA, that in the absence of some compensatory mechanism (not known then to be telomerase), that chromosomal DNA would get progressively shorter as cells divided, with eventual loss of genetic material. And the idea, suggested on these theoretical grounds by Alexei Olovnikov in the 1970's, was that perhaps cells would become senescent because they lost genetic information from their ends.[10]

In fact, it is not quite like that because the process of shortening, which does indeed occur in the absence of telomerase in cells that keep on dividing, actually stops well before any genes are lost, because the telomere becomes uncapped. Even when there is a lot of telomeric DNA still left, it can become uncapped and signal the cell to stop dividing.

We found evidence for this in a simple pond scum organism, *Tetrahymena*, as early as 1990.[3] We changed the RNA sequence in the telomerase RNA gene in *Tetrahymena* cells, producing a mutated telomerase RNA gene that was unable to do its job. It was like putting a stiletto into the heart of the enzyme, emphasizing the importance of the RNA. Then the telomeres gradually shortened because we had stopped the telomerase from working. After about twenty or so divisions, these cells stopped dividing. Thus we had stopped the cells from dividing by making a tiny change in their telomerase, so they sputtered out like a candle going out. This was remarkable because *Tetrahymena* cells normally have telomerase (in fact, we discovered the enzyme telomerase in *Tetrahymena*[11]) and normally can keep on dividing indefinitely, as long as they are provided with food.

Hence, by 1990, we knew that you need telomerase to keep these normally immortal cells dividing.

I will make one more point concerning this idea, using a different kind of cell: yeast. One can learn a great deal by studying simple organisms such as yeast, and then try to apply it to ourselves, the much more complicated human organism.

Normal yeast cells can form colonies on a plate of nutrient jelly, each colony consisting of millions of cells after about twenty or twenty-five cell divisions. However, yeast with their telomerase RNA gene removed by molecular genetic techniques, while at first growing apparently normally, soon exhibit some changes and growth problems. The colonies are much smaller, and