ments suggest that the RNA is helping telomerase perform its enzymatic reaction.[4–6] While we don't understand this, it's intriguing because it suggests that perhaps we are seeing in this RNA-protein collaboration a relic of a very ancient world in biology. This is a speculation, since one can only speculate about this kind of evolutionary idea, but it's intriguing that this enzyme has these curious properties.

What does telomerase accomplish for the cells? Telomerase action can make the DNA at the end of the chromosome longer. This matters because the normal DNA replication machinery has a problem replicating the very end of the chromosomes. The DNA replication machinery that replicates all the rest of the chromosomal DNA is a very elaborate machinery of protein enzymes. Each of the two DNA strands is copied to make its complementary strand. Thus, the single DNA molecule is replicated into two DNA molecules that become the two new chromosomes in two new cells once the cell divides. The salient point is that, while one of the DNA strands can be copied, in theory at least, to the very last nucleotide to make a full copy, because of the peculiarity of the replication machinery, the DNA has to be made in little pieces when copying the other strand. A very famous Japanese scientist, Dr. Okazaki, discovered that this DNA is made in little pieces, whose synthesis begins with small pieces of RNA that are used to get these molecules started.[7]

The very last act of finishing the end of the chromosome is that all these pieces have to be joined up, after all the bits of RNA have been removed. But the terminal bit of RNA, once removed, leaves a gap at the end of the chromosome.

The next time this happens, during the next round of DNA replication, the DNA will be shorter, and the next time, even shorter again. Well, we are not all extinct now, so something must have happened to allow that DNA make up for this deficiency.

That something is telomerase. Telomerase adds extra DNA to the chromosomal DNA end. Telomerase copies its own built-in RNA template into the complementary DNA. And now, when the DNA is replicated to two daughter chromosomes, the extended strand can be copied. The removal of the RNA again leaves a little gap, but since the DNA is longer, it has thus made up for the loss of the DNA that would have happened in the absence of this additional mechanism. Telomerase thus adds extra DNA to make up for the deficiency of the cellular DNA replication machinery.

The consequence of telomerase action at the end of the chromosome is that as a cell divides in the presence of telomerase, the telomeric DNA becomes a little longer as telomerase adds DNA and then, sometimes, a little shorter, as the DNA is incompletely replicated or chewed away by an nuclease enzyme that sometimes attacks the end of the DNA. Thus, telomeric DNA is not all the same length. Although the DNA can get a little bit longer or shorter, basically it stays replenished on average. It's replenishable because the telomeric DNA attracts telomerase to it.

We and others have learned a great deal about the balance between lengthening and shortening of telomeric DNA. When a balance is kept, on average the amount of DNA added is similar to the amount of DNA lost, preserving length overall. But I have described only a very simple part of what occurs. By studying not only the DNA and telomerase but also the proteins by the telomere, we are starting to get a picture of what the telomere does. It's very clever.

Built into telomeres is the ability for telomeres to maintain their own length (Fig. 5) which we call telomere length "homeostasis," a term familiar to those in the medical profession. "Homeostasis" implies keeping things in a certain, rather stable, form.

In Figure 5, at the top, the telomeric DNA repeats (rectangles) are represented on a rather short telomere with just a few repeats. At the bottom is shown a long telomere.

I haven't described much about the complicated set of proteins that clothe the telomeric DNA in a very elaborate and beautiful complex, like a "kimono." This protein complex can switch between two states. A short telomere is in a state which is welcoming to telomerase, which is able to get to the DNA end and act on the

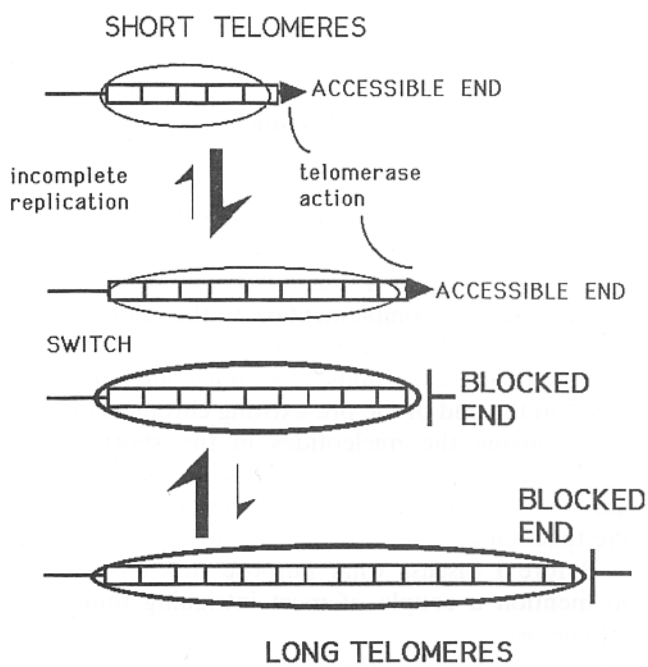

Fig. 5 Telomere length homeostasis: Regulation of telomerase access by switching states.