after about 50 fissions, over 99.9% of the cells will stop dividing altogether. The cessation of cell division by cells that can't maintain telomeres is gradual, occurring over a number of generations in the cell population. We hypothesize that the telomeres are switching into an uncapped state as they suffer gradual shortening. And, one by one, like tiny lights going out, these cells are ceasing to divide. Note that it is not like a major electrical blackout, in which all the lights go out at once. Rather, it is as though the lights slowly twinkle out. We think that underlying this very stochastic process is the two-state aspect of telomeres; they are capped or they are uncapped. If they are capped, the cells keep dividing. But as they shorten in the absence of telomerase, they stochastically switch into an uncapped state.

Now, what does this mean for humans? Most molecular mechanisms in very simple organisms are fundamentally conserved in our cells as well. There has been much interest in what happens to cells in our bodies, because some do and some don't have telomerase.

Germ line cells that make eggs and sperm have telomerase so our species can keep on going. Also, some self-renewing cells, such as skin cells in our bodies also normally have telomerase for perhaps most, if not all, of our lifespan. So do cancer cells, which I will return to later.

However, interestingly, many of the cells in our bodies don't have telomerase. Their telomerase switched off tightly. The genes are there, but the enzyme is shut down. In those cells, at least when grown outside the body in the laboratory in tissue-culture dishes, the telomeres gradually shorten as the cells continue to divide, and then they cease dividing.

Work done by Shay and Wright at the University of Texas, together with scientists in a biotech company in California, showed that in the laboratory you could put telomerase back into certain kinds of cells.[12] The experiment was very symmetrical to the one that we did with *Tetrahymena*. We turned off telomerase in *Tetrahymena*; it became mortal. They took cells that, growing in the laboratory, were mortal, put telomerase into them and made them apparently immortal. This has only been tested for a limited number of cell types, and for some cell types, it may not be enough to just add back telomerase. We are only beginning to understand the cell-type specificity of this phenomenon.

But these results are very intriguing to us, because we wonder if, since in the cells in our body that lack telomerase, the telomeres do gradually get somewhat shorter as we age, this has something to do with the aging process of human bodies. This is of great interest because perhaps one could do something about aging by adding telomerase back to cells. This speculation has attracted much interest and excitement, but we have to be aware that this has only been done in cells in the laboratory, and we don't know if this is going to be one of the things that's important for actual aging of our bodies. So there is much to find out still.

One kind of cell that we definitely do not want to keep on replicating is cancer cells. In fact, cancer cells very often have high levels of telomerase. This is a sort of two-edged sword (see[13]) which I will elaborate on in the lecture tomorrow. Here, I just want to say that the presence of telomerase does allow these unwanted cancer cells to keep on growing, which we don't want them to do. But the presence of telomerase also may have other kinds of effects which, paradoxically, may be actually protective against cancer.[13]

An important point I would like to emphasize is the great complexity of the situation in the human body. This means that making use of this information for human health is going to require more work and a better understanding of the status, meaning, and function of telomerase in cells. This is because telomerase is a two-edged sword. Nevertheless, telomeres and telomerase have created much interest as evidenced by growth in the number of papers published on telomeres worldwide in recent years.

We certainly weren't starting out to study aging or cancer when we originally began studying telomerase and telomeres in the lowly pond scum organism *Tetrahymena*. We were motivated by simple curiosity about how things work in cells. I think the important message is that we need to leave a lot of space in our planning for how scientific research will be done at universities and research institutes to allow study of things that might turn out to have unexpected potential applications. At the time, we certainly didn't think of what we were doing as attacking a medical problem. In fact, I would wager that it's probably true that many things that are now known to be true in biology were not dreamed of thirty, or ten, or even two years ago. So, things happen in unexpected ways. I think this is because of the very great complexity inherent to biological systems.

Finally, while on the one hand we have learned an enormous amount about telomeres and about many aspects of their biology, on the other hand, I am very humbled about how many mysteries of life still are remaining, how much we have to learn, and of course, how much thought we are going to have to put into applying these very complex pieces of knowledge we are obtaining to human health.

Thank you very much indeed.

COORDINATOR: Thank you very much for your excellent and very informative Memorial Lecture. We sincerely appreciate your kindness of giving us the opportunity to listen to your Memorial Lecture. We are deeply impressed.

Thank you so much.