magnification. This is such a tiny creature that about a hundred of these would fit on the head of a pin. But this organism happens to have a very large number of telomeres. Thus, it was an excellent source of telomeres, and then later, of telomerase, simply because it has so many telomeres.

Figure 3 shows the molecular ends of the chromosomal DNA. I have represented a chromosome at the top. The rectangles represent the DNA repeats at the ends of chromosomes, the telomeres. This DNA is made of repeated units; a tiny DNA sequence is repeated at the ends of the chromosomes. In work done in Joe Gall's laboratory at Yale University, we found that in *Tetrahymena*, the repeat unit is TTGGGG, not very different from the repeat unit of our telomeres or the telomeres of other vertebrates, which is TTAGGG, or one base different. One also finds a few variations such as in some budding yeasts, including *Saccharomyces cerevisiae*, which brings us beer, among other good things. Thus, telomeres have the same general form in most eukaryotic organisms; that is: tandemly repeated sequences at the ends of chromosomes.

At the University of California, Berkeley, my then graduate student, Carol Greider, and I discovered the enzyme that not only makes the telomeric DNA sequence – specifically, the DNA strand whose sequence is shown here – but also decides what the sequence of that telomeric DNA will be. Figure 4 shows the action of telomerase schematically. On the left is the DNA at the very end of the chromosome, made of two strands with the bases as drawn. This DNA sequence is crucially important for the chromosome to be stably maintained. The bases on the top DNA strand stick out a little bit because that strand is a little bit longer than the bottom strand. The DNA sequence at the top is synthesized by a most unusual mechanism. This DNA binds to the enzyme telomerase, shown on the right, which has within it both protein and RNA (RNA is related to DNA, but it's chemically a little bit different). The telomerase RNA has a small segment within it whose bases are complementary to the telomeric DNA top strand, so they can base pair with that DNA. The enzyme telomerase adds, one nucleotide at a time, DNA to the end of the pre-existing chromosomal DNA end, copying the nucleotides in the short sequence that's part of the larger telomerase RNA, the telomerase ribonucleoprotein complex. Thus, telomerase has the function of elongating the end of the chromosome.

Before I discuss what purpose this serves, I want to mention a couple of most intriguing things about telomerase.

First of all, this enzyme copies RNA into DNA.[2,3] This was a surprise because the old idea had been that DNA was always copied into RNA, at least in normal cells. Now there were some errant creatures like retroviruses, of which the HIV virus which causes AIDS is the most notorious member; such viruses were known to copy RNA into DNA. But that wasn't thought to be a normal process in normal cells. And yet the enzyme telomerase is very much a part of normal cells. It was surprising to find a reverse transcriptase, that copies RNA to DNA, carrying out a normal process in not only our cells, but also the cells of most eukaryotes.

Second, telomerase is a very interesting enzyme, because it acts through a collaboration between RNA and the protein. Enzymes are catalysts that speed up chemical reactions. In the modern biological world of today, most enzymes are made just of protein. But it's thought that many many years ago RNA was the catalyst that carried out enzymatic reactions. Telomerases are peculiar enzymes because they have RNA, and the RNA is not just acting as the template. Rather, many experi-

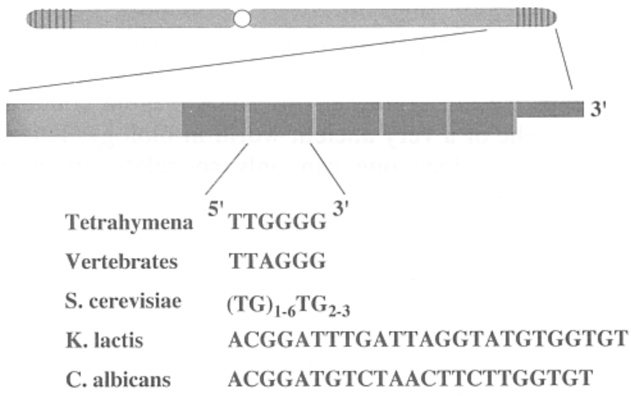

Fig. 3 Telomeric DNA contains simple tandem repeats.

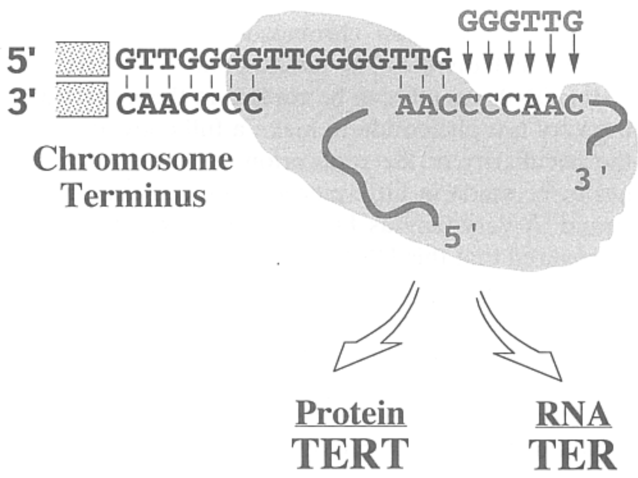

Fig. 4 Telomerase: a telomere-synthesizing reverse transcriptase.