tion. Indeed, a simple calculation shows that the Coulomb repulsion and the phonon-mediated attraction roughly cancel each other. How do the electrons evade Coulomb repulsion in this mechanism? It turns out that the Coulomb repulsion gets screened (that is, the range of the interaction is decreased), and thus its effect on the electrons is much reduced, on a time scale far shorter than the time scale on which phonon-mediated attraction operates.

Consider magnetism as an example of why it is so difficult to infer mechanism from macroscopic measurements. We now know that the dominant mechanism of magnetism in solids is electrostatic interaction combined with the Pauli exclusion principle, known as the exchange interaction. We also know that this mechanism is rotationally symmetric. It only depends on the relative orientation of the electronic spin angular momenta and not on their orientation with respect to the crystal lattice. A complex set of weaker interactions that are due to the magnetic dipolar interaction, spin-orbit coupling, and crystalline electric fields break the symmetry (as opposed to the spontaneously broken symmetry discussed above) with respect to rotations of the spin coordinates. Although magnets with extremely high magnetic transition temperatures, such as iron, were known to the Phoenician sailors, or even earlier, the understanding of the mechanism is a 20th-century post–quantum-mechanical achievement. In other words, a major revolution in physics was necessary in order to understand the mechanism of magnetism. Do we need at least a minor revolution before we can understand the mechanism of superconductivity in high-temperature superconductors? I think the answer is yes.

Imagine that we knew nothing about the origin of magnetism but could perform very sophisticated measurements involving the excitation spectrum and the magnetic transition temperatures; for simplicity, it is enough to consider insulating magnets. First, we would quickly discover that there are magnets with a wide range of transition temperatures, from 1 mK to 1000 K. We may even discover that low-dimensional magnets have transition temperatures that are considerably lower than those of three-dimensional magnets, and we could understand this difference in terms of large fluctuation effects destroying order in low-dimensional systems. We could consider this to be a victory, and if we were to design a magnet with a high transition temperature, we would choose one that is three-dimensional.

With hindsight, does this bring us closer to the mechanism of magnetism in solids? I think not. Consider this magnet analogy further. Suppose that sophisticated experiments revealed that the elementary excitations in one class of magnets exhibit an energy gap in the spectrum. Let us define them to be the "Ising magnets." Suppose, also, that the same measurements revealed that there is another class of magnets, defined to be the "Heisenberg magnets," whose elementary excitation spectrum is a continuum without a gap or spin waves. Does this imply that the mechanism is fundamentally different for these classes of materials? The answer is no. With hindsight, we know why these two materials are so different. In both cases, the dominant mechanism is the exchange interaction, but the smaller anisotropic interactions are different. In the disordered phase, the small difference in anisotropies is difficult to discover, but in the ordered phase, the small difference is amplified because of long-ranged macroscopic correlations, a cooperative effect. To summarize this argument, the distinctly different elementary excitation spectrum is not necessarily simply related to the mechanism; in this case, the exchange interaction.

This leaves us little choice but to adopt a reductionist approach and begin with the chemistry of these materials. My feeling is that we may not have to go back too far. There are already some interesting clues. These materials have nearly universal but unusual normal state properties, whereas their superconducting properties are unusually varied (*5*). Could this be due to small microscopic differences, like the anisotropy energies in a magnet, that are magnified in the ordered phase? If we are to take the magnet analogy seriously, we must conclude that the fundamental mechanism is most likely unique but that smaller microscopic differences are in the way.

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Chromosome End Games

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The linear chromosomes typical of higher organisms have an obvious feature not found in circular bacterial chromosomes: They have ends. The DNA double helix in the chromosome interior is replicated by DNA polymerase. The polymerase does not start DNA chains de novo, but always reaches to one side and extends the end of a preexisting primer strand bound to the template. Such an enzyme is frustrated at the chromosomal end, or telomere. If you are already at the end of a line and reach outward, there is nothing there to extend. The solution to this problem is telomerase, a telomere-extending enzyme that until recently had been subject to molecular analysis only in ciliated protozoa. This situation has now changed with discoveries of telomerase enzymes in yeast cells, one of which is reported in this issue of *Science* (*1*).

Telomerase was first described a decade ago by Carol Greider and Elizabeth Blackburn in *Tetrahymena*, a single-celled pond organism with an unusually large number of nuclear DNA molecules and therefore many telomeres (*2*). Telomerase is not the usual protein enzyme but is instead a ribonucleoprotein. Its RNA subunit includes a 5'-CAACCC-3' sequence that serves as template for the addition of 5'-GGGTTG-3' repeats to chromosome ends (*3*) (see figure).

As in *Tetrahymena*, most other eukaryotic chromosomes terminate in repeats of a short DNA sequence with one strand rich in G (guanine) bases, so it seemed likely that telomerase would be key to telomere replication in general. Indeed, the *Tetrahymena* telomerase served as the springboard for cloning and sequencing the telomerase RNA subunits from a number of other ciliated protozoa (*4*). But the RNA turned out to have a fast evolutionary clock: Outside the template region its sequence diverged rapidly from species to species. Thus, although the activity of the enzyme could be detected in diverse cells, including human cells (*5*), isolation of any molecular component of telomerase remained restricted to the ciliated protozoa.

The announcement by Singer and Gottschling of the finding of the gene for telomerase RNA in the yeast *Saccharomyces cerevisiae* (*1*), a tractable system for genetic manipulation, has therefore been enthusi-

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astically received. The isolation of the telomerase RNA gene from another yeast, *Kluveromyces lactis*, has recently been reported (6), so there should soon be two new telomerases to study and compare.

There is little doubt that Singer and Gottschling have now found the yeast telomerase and cloned its RNA component. Knocking out the gene caused progressive shortening of yeast telomeres by about 3 base pairs per generation. This shrinking telomere phenotype is that expected for inactivation of telomerase, which compensates for the inability of DNA polymerase to complete replication at chromosome ends. Furthermore, the putative telomerase RNA contained a sequence perfectly complementary to the 13-nucleotide sequence frequently found at newly created telomeres in yeast cells (7). When Singer and Gottschling altered two bases in the proposed template sequence of their telomerase RNA gene and reintroduced it into yeast, the altered DNA sequence was incorporated at a telomere. Thus, their isolated gene encodes the RNA responsible for templating telomere synthesis in yeast cells.

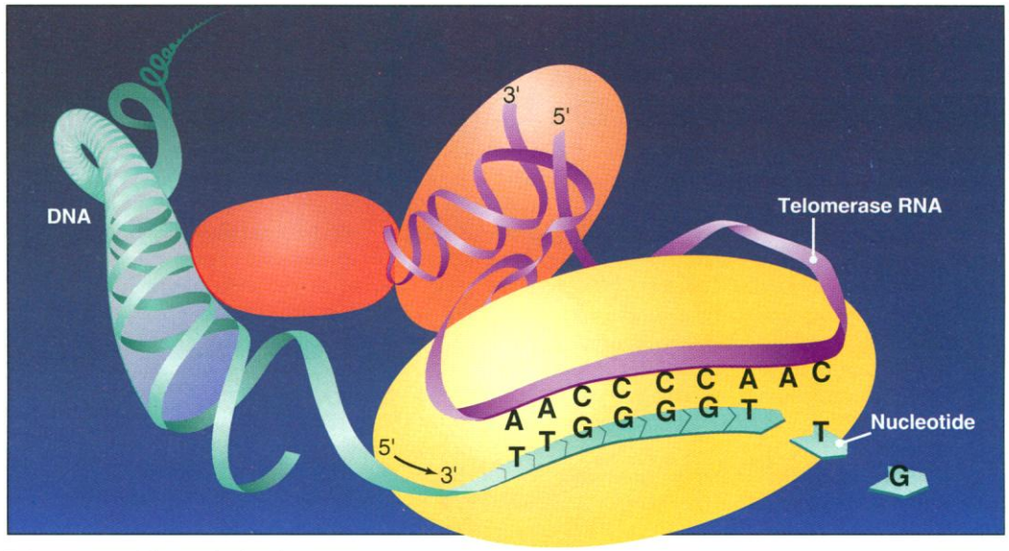

ILLUSTRATION: K. SUTLIFF

Telomerase at the end of a chromosome.

The strategy by which Singer and Gottschling unearthed the yeast telomerase RNA already provides some new insights into telomerase function. They engineered a system in which two reporter genes were placed near telomeres. Gene expression is repressed near yeast telomeres, presumably because the genes are buried in a higher order structure involving specific chromosomal proteins (8). Thus, the test genes were initially in the "off" state. These cells were transformed with a yeast complementary DNA expression library: a vast array of plasmids containing unidentified yeast genes, a different one in each cell. The hypothesis was that the production of an abnormal abundance of one component of the multicomponent telomeric complex could titrate another component and disrupt normal telomeric chromatin assembly. A cell containing such a plasmid would be relieved of telomere-proximal gene repression. So why should the telomerase enzyme turn up in such a screen? An intriguing possibility: One of the molecules binding to telomerase RNA may also serve as a component of the telomeric chromatin complex. It is even conceivable that the entire telomerase ribonucleoprotein is a component of the complex. This would not be tenable for all the telomeres in certain ciliated protozoa, because telomeres outnumber telomerase 100 to 1, but it may be possible in yeast cells, where telomerase seems moderately abundant and needs to serve only 16 chromosomes. An alternative hypothesis to explain the relief of gene repression by overexpression of telomerase RNA requires an indirect chain of events. Because the telomeric DNA shrinks when telomerase RNA is oversupplied, binding sites for telomeric proteins may be depleted and the inhibitory telomeric complex may thereby be disrupted.

Particularly exciting are the nine plasmids isolated by Singer and Gottschling that do not encode telomerase RNA, but also pass their screen and are therefore implicated in telomere function. Of course, these could be general chromatin proteins or other DNA binders, including molecules that do not even interact with telomeres unless overexpressed. A major breakthrough would result if this collection included another telomerase subunit—a protein subunit. Although there is evidence for such protein components and even some plausible candidates (9), no protein component of telomerase has been unequivocally identified in any organism.

Will protein components of telomerase really be very important? After all, we have the ribonuclease P paradigm: A ribonucleoprotein enzyme can have a catalytic RNA subunit and an accessory protein (10). However, I think it unlikely that telomerase is a ribozyme. Compared to RNAs known or thought to participate directly in catalysis (such as group I and II introns, ribonuclease P, U6 small nuclear RNA, and ribosomal RNA), telomerase RNA appears to be less structured and to have few conserved nucleotides. Thus, catalysis of DNA extension is likely to occur in a protein active site. Yet the RNA may serve more than just a template function. For example, it may organize a number of proteins into an active complex.

These new discoveries (1, 6) provide great optimism that telomerase RNA can now be identified in larger eukaryotes, including humans. Because activation of telomerase correlates with oncogenic transformation, both in cell culture and in human tumors, telomerase inhibitors might have anticancer activity (11). Having the human telomerase in hand would facilitate development of such pharmaceutical agents. Given telomerase RNA's fast evolutionary clock, the leap from yeast to human cells may be difficult. Meanwhile, the awesome power of yeast genetics, which has been so successful in unraveling secrets of another ribonucleoprotein machine, the spliceosome (12), will be unleashed on telomerase. Yeast genetics seems ideally suited to reveal additional functions of telomerase RNA and to identify protein components of this essential enzyme.

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