crisis, it appears that cells must reactivate telomerase to prevent further loss of telomeres and to confer some measure of chromosome stability. The result is an immortal cell that proliferates indefinitely and shows stabilized telomeres generally at the shorter length. Thus, it is predicted that tumor tissue should have shorter telomeres than the normal tissue from which it was derived, but if telomerase is now active, no further telomere loss should be observed as the tumor proliferates.

This hypothesis is best addressed by prospective studies of telomere length and telomerase activity over the course of the disease. Such studies have been published for cultured cells (*2*) and for human carcinomas (*3*), and the results support our model. The findings in our recent report and in the study by Hastie *et al.* (*4*) are consistent, support the model, and address the concerns of Sarkar and Bolander. In three patients, Hastie *et al.* were able to determine that telomeres in adenomas (benign precursors of carcinomas) showed a reduction similar in extent to that found in the corresponding carcinoma. Hence telomere loss occurred during the progression from normal to adenoma tissue, but then no further loss occurred between adenoma and carcinoma tissue. Correspondingly, we found no telomerase activity in normal colonic tissue, colonic polyp, or colonic adenoma, but all colonic carcinomas examined were positive.

Beyond this simple model, other factors must be considered. Although an important function of telomerase is to maintain telomeres, regulation of the intracellular activity of telomerase could result in telomere stabilization at virtually any length. Telomeres that were short when telomerase was activated could remain short, or could be elongated until feedback stabilized them. Conversely, telomeres that were long when telomerase was activated could continue to shorten if insufficient activity were present until length stabilization occurred. There is no a priori reason why telomerase activity must be associated with any particular telomere length, as confirmed by the lack of correlation between telomere length and activity that we reported.

High amounts of telomerase in cell extracts can be a result of multiple factors, including a high fraction of telomerase-expressing cells in a mixed population and transitory imbalances in telomerase regulation in cells where telomere length is actually increasing. Little is known about these possibilities, but such findings remind us that telomerase is but one piece of the complex mechanism responsible for telomere length regulation.

Nam W. Kim
Calvin B. Harley
Karen R. Prowse
Scott L. Weinrich
Geron Corporation,
200 Constitution Drive,
Menlo Park, CA 94025, USA
Mieczyslaw A. Piatyszek
Woodring E. Wright
Jerry W. Shay
University of Texas
Southwestern Medical Center,
Dallas, TX 75235–9039, USA

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Corrections and Clarifications

In the ScienceScope item "NIH to review gene therapy program" (5 May, p. 627). Arno Motulsky is incorrectly identified as "an ethicist." Dr. Motulsky is a medical geneticist.