(nearly 30,000 in all) and yielded results that contradict conventional wisdom. Although the 24 countries span all levels of economic affluence, only modest differences were found in public awareness of environmental problems and support for environmental protection across their populations (*1*). In fact, Pearson product-moment correlation coefficients for the relationships between nations' per capita gross national product and 14 different measures of national-level environmental awareness and concern were more often negative than positive—that is, public concern over environmental problems was more likely to decline rather than increase with the level of national affluence (*2*).

Overall, the Gallup results contradict the view that "in the earlier stages of economic development, increased pollution is regarded as an acceptable side effect of economic growth [but] when a country has attained a sufficiently high standard of living, people give greater attention to environmental amenities." This assumption is also challenged by the widespread growth of grass-roots citizens' organizations devoted to environmental protection in poor nations around the world (*3*).

Environmental protection efforts are indeed typically stronger in wealthier nations than in poorer ones, as Arrow *et al.* state, and this likely stems from institutional and economic problems within the latter countries (limited government resources, high debt levels, limited scientific expertise, inadequate technological capacities, and so forth), rather than a lack of concern with environmental amenities by their residents. In sum, the idea that citizen support for environmental protection is strongly related to national affluence may be even more tenuous than the general proposition—so effectively questioned by Arrow *et al.*—that economic growth is inherently good for environmental quality.

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Telomeres, Telomerase, and Cancer

Telomerase is an enzyme (a ribonucleoprotein complex) that synthesizes telomeric DNA onto chromosome ends (*1*). Under certain conditions, it has been shown that lack of this enzyme will result in loss (shortening) of telomeres. Nam W. Kim *et al.* (Reports, 23 Dec. 1994, p. 2011) have developed a sensitive assay for detecting telomerase activity by means of which they show that

> [i]n cultured cells representing 18 different human tissues, 98 of 100 immortal and none of 22 mortal populations were positive for telomerase. Similarly, 90 of 101 biopsies representing 12 human tumor types and none of 50 normal somatic tissues were positive.

Their samples included seven colon tumor cell lines and eight samples of colon cancer tissues, all of which were positive for telomerase activity. The implication is that telomerase activity is required to maintain telomeres at the chromosome ends which, in turn, is necessary to maintain cell replication and tumor growth, and that is why cancer cells are positive for telomerase. The implication makes sense.

Hastie *et al.* (*2*), on the other hand, reported a significant *reduction* of telomere length in 20 human colorectal carcinomas (and in other conditions). Is it possible that cancers other than colorectal carcinoma will have shortened telomeres? If the conventional telomerase is responsible for the synthesis and maintenance of telomeres, then this data implies that there should be little or no telomerase activity in colorectal carcinoma. But this is not so if the results of Kim *et al.* and Hastie *et al.* are compared.

The findings by these two groups appear to be at odds, at least with respect to cancers of the colon (assuming that colon cancer and colorectal carcinoma are comparable). Kim *et al.* do not comment on this issue. It would be helpful to have a discussion of this apparent puzzle before embarking on "diagnostic and therapeutic applications" based on telomerase assay. Can there be an explanation to unify these apparently contradictory observations? Is telomere reduction independent of telomerase? Is there a telomere-degrading activity that is activated in "cancers of the colon" (to suggest any tumor involving the colon) and is the expression of telomerase (as assayed by Kim *et al.*) a measure to counter this activity? Are cancer cells an exception to the assumption that telomere loss represents a type of a biological clock with respect to the number of cell divisions in a given tissue? Or is it that sequential reduction of telomere length applies only to programmed cells, but not to cancer cells, because these cells may undergo an abrupt change in telomere size?

It is of interest to have a molecular marker that can be used to distinguish between benign and malignant tumors of bone and cartilage. To assay for telomerase activity, as suggested by Kim *et al.*, is a possibility. Our confidence in a diagnostic assay, however, will depend on the clear understanding of the underlying mechanism.

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Response: The simple hypothesis linking telomere dynamics to cancer (*1*) begins with the premise that cancer results from multiple genetic hits that drive the process of oncogenesis. Between hits, cell proliferation and selection occurs. Depending on the nature and number of hits, many cell doublings (more than 80) are likely required to generate an advanced cancer. Early hits leading to preneoplastic lesions (for example, adenomas) occur in cells that lack telomerase activity. These mutations typically result in loss of growth control or in genomic instability. Increased proliferation occurs in these cells, hence telomeres shorten more rapidly than in cognate normal tissue. Telomere loss per division does not change, only the rate of proliferation. More mutations, required for these cells to bypass the Hayflick limit, may involve functional inactivation of tumor suppressors such as p53 and Rb. Now in the phase termed "extended lifespan," these cells proliferate, and their telomeres continue to shorten. Cells then reach crisis, the second mortality checkpoint. To bypass

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.

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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.