Definitive answers to these questions have yet to emerge. However, the first major advance was provided a year ago with the finding that ectopic expression of hTERT in primary human cells could confer endless growth in culture (*4, 5*). Although the cells in question, human foreskin fibroblasts and retinal pigment epithelial cells (RPEs), normally ceased dividing after 40 to 80 population doublings, telomerase-positive derivatives able to maintain their telomeres progressed unimpeded beyond that usual life-span and have now been maintained in continuous growth for more than a year (*10, 11*). For practical purposes, these cells can be viewed as immortal—a characteristic illegitimately appropriated by many human cancers but normally preserved for the few cells that make up our germ line.

These studies received much attention as a potential cellular fountain of youth, with visions of an immediate impact on normal tissue and transplant repositories, while the popular press was distracted with speculations that telomerase could attenuate organismal aging and promote longevity in humans. A more guarded view (*12*) raised concerns that unscheduled telomerase expression in vivo may lead to an increase in cancer incidence by eliminating replicative senescence, hence obviating a potential tumor suppression mechanism.

The simple interpretation that hTERT expression alone can endow all cell types with unlimited growth potential has given way to a more complex story since the finding that immortalization of mammary epithelial cells and keratinocytes required not only hTERT expression, but also compromise in the RB pathway (*13*). Moreover, the observation that activated RAS and RAF signals can induce cellular senescence in pre-senescent primary fibroblast cultures well before telomeres have reached a critical length suggests that some physiological stimuli may be capable of acting dominantly to subvert the actions of hTERT (*14, 15*). Together, these findings raised concerns as to whether the life-extended hTERT-expressing fibroblasts and RPEs also had sustained additional genetic lesions. Two recent reports have gone a long way in addressing these important issues (*10, 11*). An extensive molecular and biological characterization of hTERT-immortalized fibroblasts and RPEs now indicates that they behave like their normal pre-senescent counterparts, harboring an intact RB pathway, functional DNA damage checkpoints, and normal karyotypes while lacking well-established hallmarks of neoplasia such as reduced serum requirements, anchorage-independent growth, and tumor formation in nude mice. The non-oncogenic nature of hTERT is in accord with the inability of this gene to substitute for the immortalizing oncoprotein Myc in the classical Myc/RAS cotransformation assay (*16*).

Why, then, are fibroblasts and RPEs different from mammary epithelial cells and keratinocytes? Part of the answer may lie in the simple fact that amounts of $p16^{INK4a}$ [a critical inhibitor of the RB pathway and key mortality gene (*17, 18*)] are low in fibroblasts, thus perhaps making it easier for telomerase alone to bypass senescence in those cells. A more likely explanation, however, could relate to cell type–specific differences in the signaling responses activated upon adaptation to culture and how those responses ultimately affect mortality pathways, particularly those governed by $p16^{INK4a}$ and its surrogate pRB. These cell culture–based studies underscore the need to frame these questions in a more physiological context, in which the long-term consequences of broad somatic TERT transgenic expression can be monitored.

It is nevertheless reassuring to know that the hTERT gene is not behaving as a conventional oncogene and that its effects are restricted to telomere metabolism. But do these findings exonerate telomerase as a culprit in cancer? Should we view it now as a "good" enzyme that can be used ad libitum to manipulate the life-span of human cells? Can we look forward to the repair of human tissues and rejuvenation of stem cell populations based on telomerase therapy? If

NOTA BENE: CLIMATE VARIABILITY

The North Atlantic Oscillation

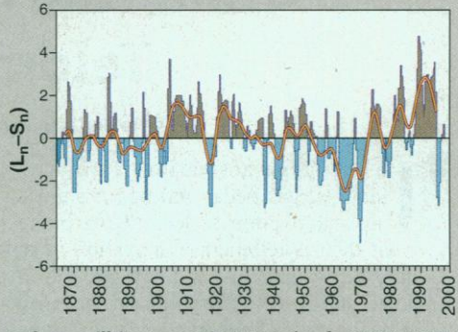
Ever since the 1997–98 El Niño dominated media attention because of its many, severe consequences around the globe (*1, 2*), the El Niño–Southern Oscillation (ENSO) has become quite familiar, even to nonscientists (see page 950). This oscillation has a variable period of around 3 to 7 years. Warm tropical waters in the eastern tropical Pacific in its El Niño phase alternate with cold tropical waters during its La Niña phase. However, another climate oscillation, the North Atlantic Oscillation (NAO) (*3, 4*), is also receiving increasing attention in the climate research community.

The NAO is characterized by a north-south difference in pressure. A low-pressure region is centered near Iceland and a high-pressure region in the subtropics near the Azores. This pressure contrast drives the surface winds and wintertime storms from west to east across the North Atlantic. When the pressure is lower than normal near Iceland, it tends to be higher than normal near the Azores and vice versa; this out-of-phase relation defines the NAO index (see the figure).

The NAO's impact is more restricted than ENSO's. In North America, Europe, and North Africa, precipitation patterns and wintertime temperatures can be attributed to its phases (*5*). The NAO may well be more influential than ENSO in regions surrounding the North Atlantic, where its climate shifts can affect food production, energy consumption, and other economic factors. Changes in marine and terrestrial ecosystems have also been attributed to the NAO (*6*).

Since the mid-1970s, the NAO index has generally been very high (see the figure). During this time, winters have been relatively warm in Europe and cold in the northwest Atlantic, and the Mediterranean has been particularly dry. This period may be about to end: The NAO index took a deep dive in 1996–97 (see the figure) (although it increased again in 1997–98, albeit to much lower values than in the early 1990s). Colder winters in Europe and wetter conditions in southern Europe may result, as in the 1940s and 1950s when the NAO index remained low.

These observations illustrate that decadal variability of the NAO is superimposed on interannual variability (see the figure) (*5*). The Atlantic climate patterns may hold clues for climate trends over long time periods and may help in identifying the human impact on climate change (*7*). Unfortunately, the NAO's periodicities are less regular than those of ENSO, making prediction particularly difficult. Thus, while much progress has been made in understanding ENSO's mechanisms—not least because of a large-scale integrated monitoring effort (*1, 2*)—the NAO remains comparatively poorly understood



Where will it go next? NAO index for 1864–1998 (Dec–Mar), updated from (*4*). See neit.cgd.ucar.edu/cas/climind/nao_winter.html.

telomerase does not conspire in the tortuous pathway of human tumorigenesis, why then is the enzyme activated in so many cancers? Although telomerase activity is associated with high proliferative rates in some cell types, such regulation fails to explain the appearance of hTERT in most cancers (*19*). After all, many normal human cell types do not express telomerase while they proliferate in vitro, but tumors derived from such cells do.

Could telomerase simply be a harmless by-product of one of the oncogenes causing malignant transformation? In this regard, it has recently emerged that the transcription of the hTERT gene is regulated directly by the immortalizing oncoprotein Myc (*16*, *20*), whose up-regulation is an obligate feature of virtually all human cancers. Is telomerase just an innocent passenger driven by c-Myc but not lending any growth advantage to tumor cells? This view is made unlikely by the finding that inhibition of telomerase or experimental interference with telomere function arrests and often kills cells even if they are transformed (*21–23*). Thus, telomerase activity would appear to make an important contribution to the viability of transformed cells, but its action does not fit the usual roles ascribed to oncogenes and tumor suppressors.

Instead of gas pedal or brake, telomerase and more specifically telomeres may be best viewed as the gasoline tank. Gasoline is not sufficient to drive or accelerate the car, nor does it affect the brakes, but when the gas is used up the car stops regardless of the status of its brakes or how hard one steps on the gas pedal. At times, other braking systems may operate early; such is the case with RAS-induced activation of the p16/Rb pathway or other oncogenic signals (*14*, *15*). In those cases, telomerase introduction alone does not immortalize the cells, because they also must overcome the cell cycle arrest. That is, telomerase is not sufficient for transformation, but cells will have indefinite replicative capacity upon telomerase activation if there is a drive for proliferation and if nothing else arrests the cells.

The major remaining challenges are to determine whether shortening of somatic telomeres really constitutes a tumor suppressor mechanism in vivo and to assess the actual contribution of telomerase to cancer. Answers to these questions could emerge from several mouse models: the telomerase knockout mice (*24*, *25*) and mice transgenic for telomerase in experimental settings where telomeres are limiting, in which it can be determined whether there is increased incidence of spontaneous or carcinogen-induced cancer. Ultimately, the definitive answer may have to come from the use of telomerase inhibitors in cancer patients. Although a complete understanding of the role of telomeres in cancer seems far off, the continued interest in telomerase should provide sufficient fuel to carry us to the end of this journey.

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(*4*). An international effort is now under way to improve the monitoring network for the NAO (*8*), with a view to forecasting its long-term evolution (*9*).

What drives these climate fluctuations in the North Atlantic? The atmosphere, the ocean, and the coupled atmosphere-ocean system have all been auditioned as its main driving forces. Atmospheric changes are much more rapid than those of the more sluggish ocean; thus, the atmosphere generally has a short memory, whereas signals in the ocean can be propagated over years or even decades. Which of the two is the more influential in determining climate oscillations then becomes a question of time scales. The fundamental dynamics of the NAO are likely to arise from atmospheric processes: Its position and spatial structure are determined by the basic features of the basin-scale atmospheric circulation. Scenarios with long-term atmospheric forcing invoke, for example, a stratospheric influence (*10*). However, on decadal time scales, the oceanic influence is likely to be important. Model studies have shown that wind-driven ocean gyres may play a large role in linking the atmospheric and oceanic components of the system (*11*). Significant changes in convective activity in the Arctic Seas have been shown to correlate with long-term NAO trends. Coordinated changes in the formation rate, salinity and location of oceanic water masses are thus likely to play a role in the long-term evolution of North Atlantic variability (*12*). Further studies will be required to establish the dominant mechanism.

In order to identify long-term trends in the NAO, researchers have extended the record back in time. Records using instrumental records (*5*, *13*) and tree rings (*14*) now go as far back as 1701. A proxy NAO index from ice accumulation records in Greenland for the past 350 years indicates that the NAO is an intermittent climate phenomenon that goes through active and passive phases (*15*). It is not yet known whether there are fundamental NAO frequencies during active phases that would enhance predictability.

No regional climate system exists in isolation. So-called teleconnections (*16*) linking the NAO to other climate systems—the tropical Atlantic as well as climate systems further afield such as ENSO (*17*)—are thus another focus of research, as world climate is increasingly seen as one integrated system. Especially with enhanced monitoring networks, predicting future climate on an interannual or even decadal time scale may move from fiction to fact in the foreseeable future, not only in the Pacific but also in the North Atlantic.

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