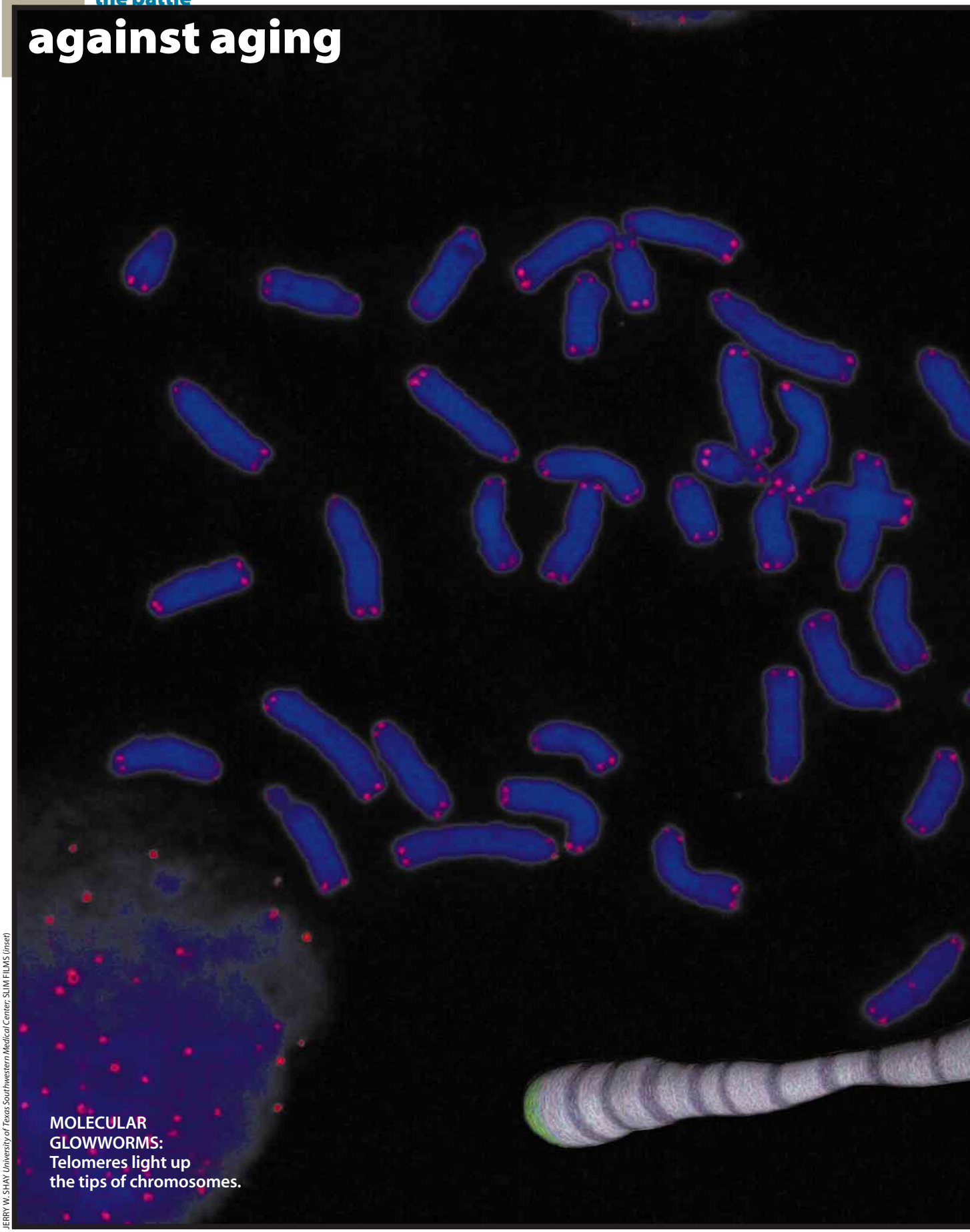
against aging



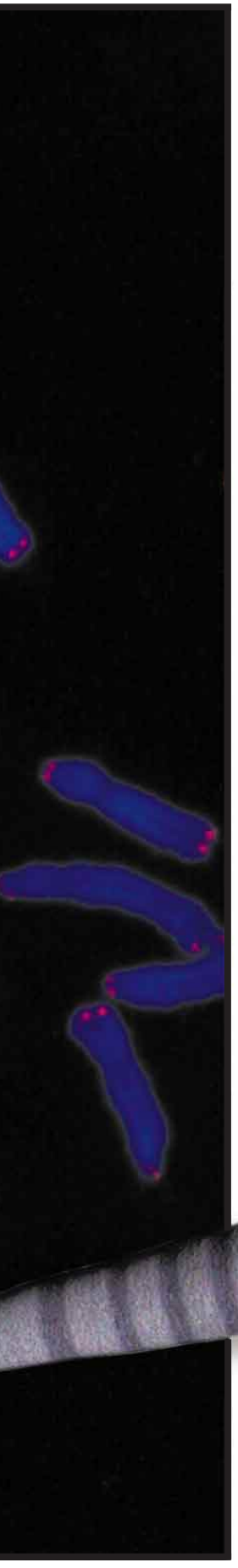
MOLECULAR GLOWWORMS: Telomeres light up the tips of chromosomes.

JERRY W. SHAY University of Texas Southwestern Medical Center; SLIM FILMS (inset)

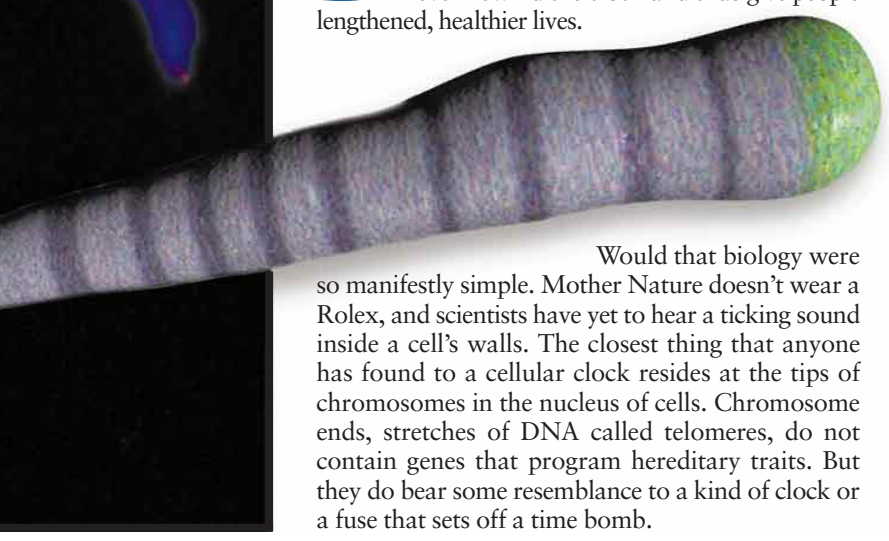
STUDIES OF CLOCKLIKE ELEMENTS IN THE NUCLEUS OF CELLS COULD LEAD TO A RANGE OF THERAPIES THAT MIGHT BOLSTER THE IMMUNE SYSTEM, REVERSE HEART DISEASE, EVEN COMBAT CANCER

counting the lives of a cell

BY EVELYN STRAUSS



Biologists have always warmed to the notion of a cellular alarm clock that would mark off the moments of a cell's life and ring when its time to die had arrived. The existence of such a molecular timepiece might suggest ways to slow the ticking or even rewind the clock and thus give people lengthened, healthier lives.



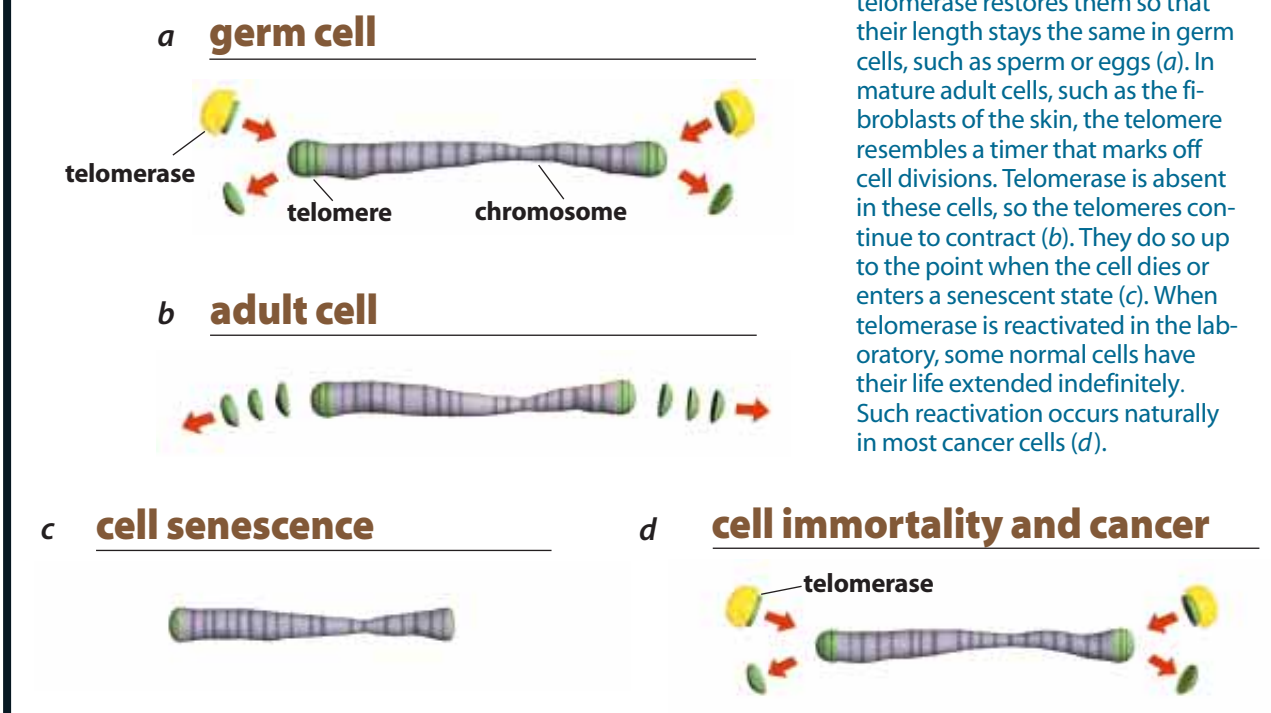
CAPPING CHROMOSOMES: Telomeres—stretches of DNA and the proteins that bind to them—protect the ends of chromosomes.

Would that biology were so manifestly simple. Mother Nature doesn't wear a Rolex, and scientists have yet to hear a ticking sound inside a cell's walls. The closest thing that anyone has found to a cellular clock resides at the tips of chromosomes in the nucleus of cells. Chromosome ends, stretches of DNA called telomeres, do not contain genes that program hereditary traits. But they do bear some resemblance to a kind of clock or a fuse that sets off a time bomb.

When some human cells are examined in the laboratory, their telomeres shorten each time a cell divides. As a cell divides more than a set number of times, its telomere fuses become too short. At that point, the cell may die, or else a kind of alarm may go off within it that causes the cell to go into a senescent state, in which it ceases multiplying.

Biologists have theorized that cell senescence might have a good side. It could be a defense against cancer, which is marked by uncontrolled cell division. Cells that are unable to regrow their telomeres should stop dividing before they can cause too much mischief. Yet telomere shrinkage could conceivably disrupt the repair and replenishment of tissues, making them age. "It's absolutely clear that the aging of many human cells in culture is a telomere-dependent process," states Titia de Lange of the Rockefeller University. "The question is how significant it is for aging of the whole organism." Does the behavior of cells that reside in the test tube have

the long and the short
of telomeres



LIKE A CLOCK: Telomeres, the tips of chromosomes, shorten every time a cell divides, but the enzyme telomerase restores them so that their length stays the same in germ cells, such as sperm or eggs (*a*). In mature adult cells, such as the fibroblasts of the skin, the telomere resembles a timer that marks off cell divisions. Telomerase is absent in these cells, so the telomeres continue to contract (*b*). They do so up to the point when the cell dies or enters a senescent state (*c*). When telomerase is reactivated in the laboratory, some normal cells have their life extended indefinitely. Such reactivation occurs naturally in most cancer cells (*d*).

SLIM FILMS

anything at all to do with how we age?

Scientists have now begun to explore de Lange's question. In animal studies, they are examining whether the wearing down of the telomere fuse can illuminate the process of growing old or at least explain why some organs start to deteriorate. "No one's ever proved that short telomeres cause aging," acknowledges Jerry W. Shay of the University of Texas Southwestern Medical Center. "The only way to do that is to prevent it from happening, and that's what needs to be done—but there's already some pretty suggestive evidence."

Some hallmarks of aging in humans, such as hair loss or skin wrinkling, are easy to understand as consequences of cells' inability to multiply, says de Lange, because the cells that replace hair and rejuvenate skin divide throughout a person's lifetime. Similarly, the immune system gradually loses its ability to bounce back. Even "nonrenewing" tissue might replenish itself. "We know now that even in brains, you can get new neurons," says Calvin B. Harley of the biotechnology firm Geron Corporation. "In every tissue except possibly the heart, cells divide. Some divide slowly, but we live a long time."

Age-related deterioration in these and other tissue types could result from cells running out of steam because of telomere loss, Harley asserts. At sharp turns in blood vessels, where turbulent blood flow wears out tissue and thus requires restoration, the telomeres are shorter than in long, straight stretches.

Walking the Telomere Plank

To explore methodically what telomeres mean to an intact animal, scientists genetically engineered mice so that they have unusually short telomeres. At first glance, you might think the animals in these experiments belong in a murine nursing home. They go gray, their hair thins, their skin turns papery, and they die young. Furthermore, they're infertile, presumably because the cells destined to become eggs or sperm can't reproduce or survive optimally. Some cells have "walked the telomere plank," says Ronald A. DePinho of Harvard Medical School. The mice have short telomeres, he says, and their stem cells can't multiply as many times as they usually do. Stem cells give rise to many cell types, such as the various components of skin.

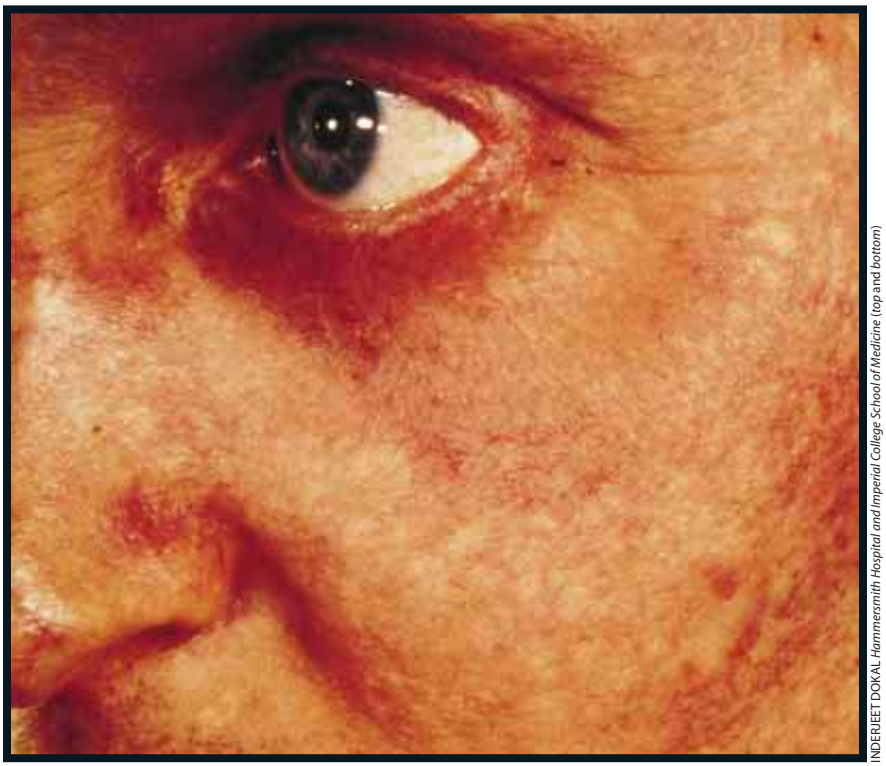
But the physiology of these mice doesn't mimic all aspects of aging, DePinho cautions. "We don't see an increase in cataracts or osteoporosis" or other pathology typical of old animals. "Telomere attrition does not precipitate a classical premature aging syndrome. But we do believe it influences an absolutely critical aspect of getting old—the ability of organisms to counteract acute and chronic stress."

As individuals age, their organs can still function adequately, but they re-

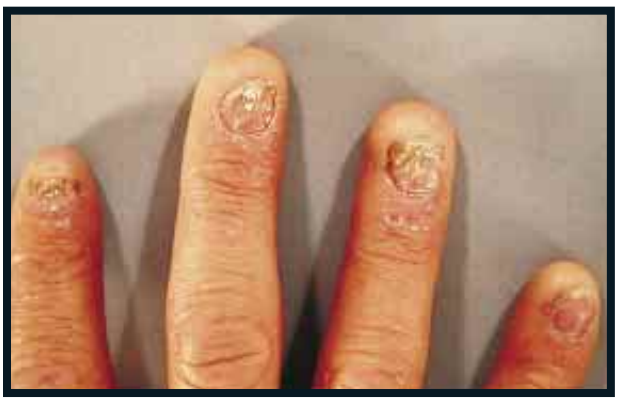
spond poorly when confronted by chemical or physical insults. "The difference between a young person and an old person is a diminished capacity to respond to major environmental stresses," DePinho notes. The mice in his experiments healed poorly after enduring various shocks—minor surgery and chemotherapy, for example. "Wound healing requires robust proliferative responses, and so does replenishing the blood supply after chemo wipes out white blood cells," he explains.

How relevant these results are to humans remains to be seen, however. "Mice are not little people," DePinho points out. Unlike human cells, for instance, mouse cells' telomeres do not grow shorter, so it is implausible that mice normally age as a result of the gradual shriveling of the ends of their chromosomes.

Although no one has directly tested the relation between telomeres and human aging or disease, nature may have inadvertently conducted a relevant experiment. Telomere defects might underlie a rare inherited disorder called dyskeratosis congenita (DKC). Patients with the disorder carry abnormally short telomeres. They have discolored-looking skin that doesn't renew itself well.They become anemic in their teens, and many die from infections. "We can see what happens in a telomere-deficient person," says Kathleen Collins of the University of California at Berkeley, warning that the results need to be confirmed in more than the two families studied so far.



INDERJEET DOKAL *Hammersmith Hospital and Imperial College School of Medicine (top and bottom)*



TELOMERE DEFECTS: A patient suffering from dyskeratosis congenita, which is characterized by aberrant telomeres, shows signs of premature aging.

The cell types that are most compromised in this disease, Collins says, are ones that in humans produce a telomere-restoring enzyme called telomerase. This enzyme resides in the stem cells that eventually become sperm and eggs (which need to multiply throughout a large part of a person's life). It is also present in certain other cells—those used to revitalize the blood and skin, for example—but not in most other types. "What the disease tells us," Collins says, "is that there are some cell types that need to turn on telomerase in a normal human life span."

Using telomerase to maintain the ends of chromosomes—and so heal damaged or tired organs in people of any age—has become a focus of research at Geron and a number of academic research laboratories. So far adding telomerase in the laboratory has increased the healthy life span of human cells from the skin, blood vessels, eyes, muscles and immune system, and Geron is currently targeting these and other cell types to develop new therapies.

Telomerase therapy might one day help generate a new supply of skin and blood cells to treat lesions that don't heal or to enhance the waning immunity of aging blood cells, both common problems of old age. Although some stem cells produce telomerase, there's not enough to maintain telomere length when demand for reproduction is particularly high, according to some researchers. Adding telomerase to stem cells that generate new blood and skin cells could permit them to survive longer and continue dividing to produce new cells virtually indefinitely.

Earlier this year researchers reported that a telomerase-based treatment allowed cells to stay alive in culture and that they functioned properly when transplanted back into a different animal. Someday a similar therapy that extracts cells from a patient, adds telomerase and then reimplants them into the donor's body might avert the risk of immune rejection. The telomerase could

also spur cells lining veins and arteries to make new blood vessels when plaque buildup blocks arteries, according to scientists at Geron.

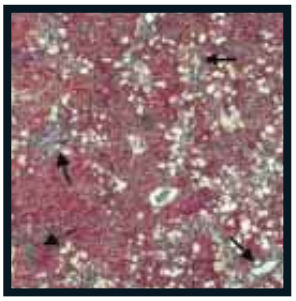
One approach may eventually involve gene therapy—in which the gene that gives rise to telomerase is delivered to the desired site in the body. Because telomeres are shorter in cirrhotic livers than in healthy ones—possibly a result of too many cycles of cell damage and subsequent regeneration—this method might increase the replicative capacity of surviving liver cells and thus could renew livers damaged by alcohol or disease. DePinho recently inserted the gene for telomerase into mice with artificially induced liver damage. Production of the enzyme reduced injury in the animals from cirrhosis of the liver.

Of course, gene therapy of any type confronts the same safety concerns that arose after the death last year of a patient receiving treatment for a rare metabolic disease unrelated to telomeres. As an alternative to gene therapy, researchers are seeking drugs that might control the gene when it is already present in cells so it can be turned on and off at will.

Human trials of telomerase therapy have yet to begin, and it's not clear what the first treatment will be. Telomere shortening, Harley posits, is probably "a fundamental underlying pathway that contributes to many diseases." And he adds: "The technology isn't decades away—it's on the horizon. We hope to be in clinical trials within a handful of years."

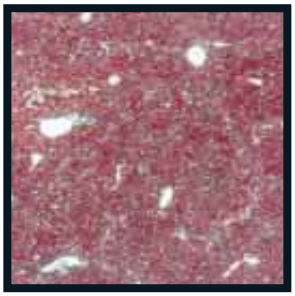
Harley's views have yet to achieve a consensus among molecular biologists and gerontologists. But even Harley derides the popular misconception that telomere research will increase longevity. "We're not saying that we have a maximum life span of 120 because of telomere loss and that if you were to activate telomerase in a controlled way, you'd live to be 200," Harley clarifies, adding that halting telomere loss may, however, alleviate age-related diseases.

Questions remain about whether telomere shortening actually makes cells deteriorate except in a laboratory dish. Even where scientists have established a causal link between telomere biology and cellular life span, they have done it in cells removed from the body. The strongest proof that telomerase reinvigorates tissues in an animal would be to produce the enzyme in cells that normally shut it off and then determine that it can extend life in those cells. Such experiments are under way in mice, but the results have yet to be reported.



SAFEGUARD: Damage to a mouse liver at the onset of cirrhosis (*arrows in top image*) was not as dire in another mouse liver that received the gene for telomerase (*bottom*).

Telomerase therapy may one day prevent liver cirrhosis.



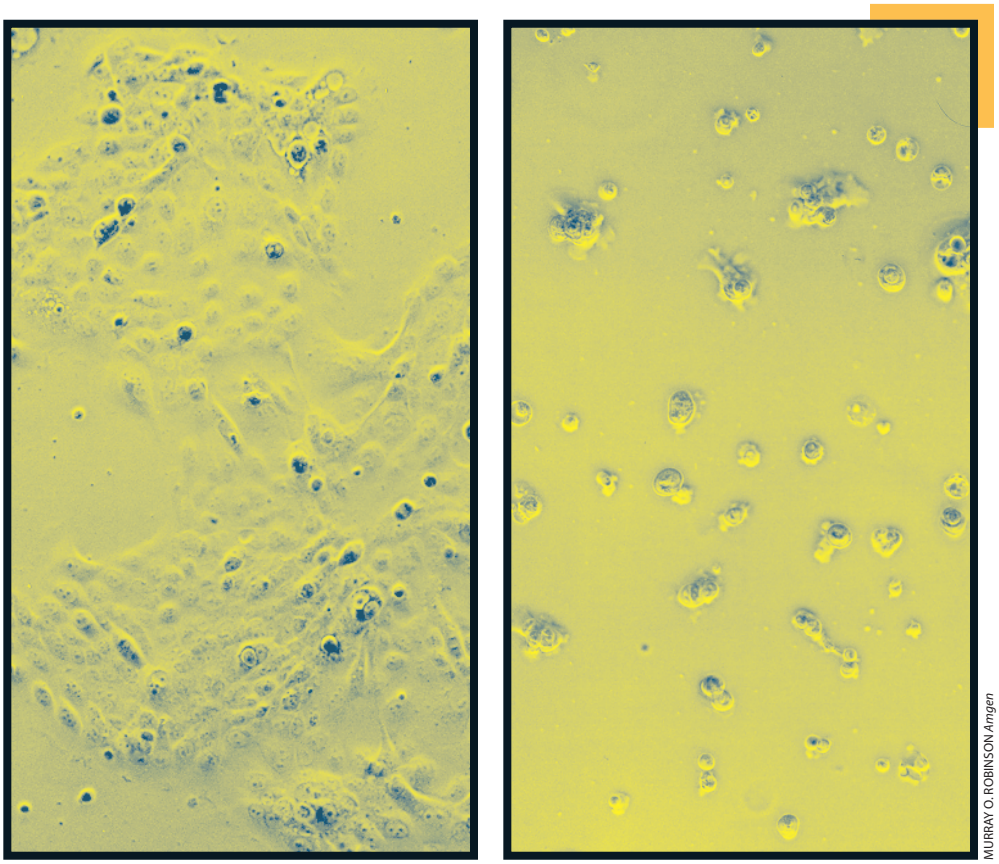
"To connect telomere shortening with aging may be a brilliant stroke of insight, or it may represent a distraction, having little to do with human aging," remarks Robert A. Weinberg of the Massachusetts Institute of Technology's Whitehead Institute. "To show a connection, you'd want to see that organs are giving out because they've lost telomeres. It would be wonderful if there was such a simple molecular explanation of the aging process, but biology doesn't necessarily oblige."

Even if it does help rejuvenate certain tissue, telomerase will not likely serve as an all-purpose antiaging preparation. The enzyme should not have an effect on cells that do not divide in the mature body, many of which are involved in processes of aging. "A lot of what we think of as aging takes place in nonreproducing cells," de Lange observes. "Alzheimer's is generally viewed as an important aspect of human aging. I don't think there's any reason to believe that those plaques [damage to the brain produced by the disease] have anything to do with loss of the proliferative abilities of nerve cells."

Not all human cells are likely to snap awake with the addition of telomerase; freeing some types from the chains of mortality (at least in the test tube) requires additional genetic alterations. Furthermore, some cell types senesce within a small number of generations—long before their telomeres have decayed significantly—indicating that other mechanisms can arrest growth. Even if you could make a cell immortal, you might not want to. Adding telomerase to a cell can have dire consequences. "You have to confront the reality that you're creating a cell that is one step closer to cancer," Weinberg says. "Cell mortality is an important impediment to cancer."

The Cancer Connection

Tumor cells, after all, can live forever. According to several studies, telomerase plays a critical role in maintaining, if not triggering, this disease that affects the elderly in disproportionate numbers. Telomerase by itself does not cause cancer: healthy cells err in multiple ways in their slide toward malignancy. But cancer cells do seem to have figured out how to use telomerase to sustain the abnormal cell division that is the hallmark of the malady. According to some researchers, they achieve this unchecked multiplication by activating telomerase or restoring telomere length by other mechanisms. In contrast to most normal cells, about 85 to 90



MURRAY O. ROBINSON *Amgen*

TUMOR INHIBITOR: Cancer cells thrive when the enzyme telomerase is present (*left*). When it is inhibited, the cells change shape and die (*right*).

percent of tumor cells produce telomerase. And treatments that inactivate telomerase kill cancer cells growing in the lab. "That is formal proof that the ongoing activities of telomerase are essential for proliferation in cancer cells," Weinberg concludes.

A drug or genetic therapy that blocked telomerase might quash the unbridled growth of malignant cells. "It's too early to tell, but based on the available evidence, we think the prospects look good for antitelomerase therapy," asserts Murray O. Robinson of Amgen, a biotechnology firm. "It's incredibly exciting that telomerase is a property that crosses virtually all tumor types, because such drugs might be universal chemotherapeutic agents." The idea of developing them is "not just a pie-in-the-sky hope," he continues. "We know if we inhibit this enzyme we can kill tumor cells, and we know we can make inhibitors against other enzymes of this type."

Some scientists expect that telomere-based anticancer strategies will trigger fewer severe side effects than other chemotherapies. Most healthy cells do not carry telomerase, and they would thus be expected to remain unaffected if a drug were to inhibit the enzyme. Normal cells that do produce telomerase—sperm, egg and stem cells—start out with much longer telomeres than about 50 percent of cancers, so cancer cells should stop dividing before they do. This aspect of telomere biology might provide a means to attack malignant cells without interfering with the normal renewing activities of other cells.

Still, some researchers worry that tumors might develop resistance to antitelomerase therapies. Mice that lack telomerase can still form tumors, and about 10 to 15 percent of human tumors apparently do not produce the enzyme, suggesting that not all cancer cells need it. "There's clearly some kind of bypass pathway in mammalian cells," warns Carol W. Greider of the Johns Hopkins University School of Medicine. Other researchers argue that resistance of this type is unlikely to pose a serious problem, because none of the investigations have discovered it in the types of cells from which most cancers arise.

Telomere research has created a paradox that must still be resolved: the enzyme telomerase might revive an aging liver. Alternatively, it might promote cancers. Only clinical trials will ultimately resolve the many lingering questions about which, if any, types of telomere therapies might succeed for aging or cancer. The original hope that we could trick Father Time into giving us immortality by manipulating telomeres will probably prove naive, however. We cannot simply rewind telomeres like an old-fashioned Swiss watch. But studying the tips of chromosomes as they fritter away may still yield insights into how the cell, the basic biological unit, grows old. That accomplishment alone would mark a fundamental contribution to the science of human aging.

Evelyn Strauss, *a molecular biologist turned science writer, freelances from Santa Cruz, Calif., and is a correspondent for* Science *magazine.*

Further Information

Endgames. John Travis in *Science News,* Vol. 148, No. 22, page 362; November 25, 1995.

Telomeres, Telomerase and Cancer. Carol W. Greider and Elizabeth H. Blackburn in *Scientific American,* Vol. 274, No. 2, pages 92–97; February 1996.

Descriptions of research at the biotechnology company Geron on telomerase for age-related disorders can be found at www.geron.com on the World Wide Web.