Logically enough, stopping this process involves reversing it: removing the phosphate groups on Jak2. SH-PTP1 does that job, reducing Jak2's capacity to attach phosphate groups and inhibiting the signal from passing into the stem cell's interior. Lodish and his collaborators knew they had found SH-PTP1's docking site when they discovered that in cell lines with receptors mutated or lacking in this site, Jak2 retains its phosphate groups, allowing cell growth and differentiation to keep chugging along.

And that's where the Finnish connection comes in. Since the 1960s, hematologists in Finland have puzzled over a large Finnish family in which many members inherit a rare disorder called autosomal dominant benign erythrocytosis. Far from being an affliction, however, the disorder's main symptom—highly elevated red blood cell levels—confers enhanced stamina on those who inherit it. Indeed, the family's most famous member, Eero Maentyranta, whose blood carries 25% to 50% more hemoglobin than the average male's, won three gold medals in cross-country skiing at the 1964 Winter Olympics in Innsbruck, Austria.

After reading a review article on the Lodish lab's EPO-R work several years ago, Albert de la Chapelle, a human geneticist at the University of Helsinki, realized that the answer to the familial erythrocytosis riddle might lie in a mutation in the EPO-R gene. Sure enough, de la Chapelle, hematologist Eeva Juvonen, and geneticist Ann-Liz Träskelin found that all 29 of the Maentyranta family's living erythrocytotic members harbored a mutation at position 6002 in the EPO-R gene (*Proceedings of the National Academy of Sciences U.S.A.* **90**, 4495–99, 1993). The mutation, a single altered nucleotide, cuts short one end of the EPO-R molecule by a full 70 amino acids.

De la Chapelle alerted Lodish to his findings, and the Whitehead researchers discovered that the segment of EPO-R deleted in the Finnish family includes the docking site for SH-PTP1. To put it another way, the affected members of the family lack a foothold for the system's brake. "As a result, cells expressing the mutant receptor are much more sensitive to erythropoietin," Lodish explains, adding that "this is the first fully characterized mutation that enhances athletic performance."

The discovery won't lead to the creation of world-class athletes, but it could lead to gene therapy for some hematologic disorders, says de la Chapelle. If introducing a truncated EPO receptor into the stem cells of anemic patients increased their red blood cell counts, for example, "that would really be fantastic," he says. The Whitehead group's next step, meanwhile, will be to try to produce a transgenic mouse that expresses the same nucleotide error as the hardy Finnish family. Its nickname, of course: "Mighty Mouse."

–Wade Roush

CLIMATE

Sun's Role in Warming Is Discounted

What is turning up Earth's thermostat? Climate researchers agree that average global temperatures have crept upward over the past century, but they are sharply divided about what is driving the rise. To most, the half-degree increase could be a first sign of a greenhouse warming, but a vocal handful have argued that the sun itself might be getting brighter. A paper in this issue of *Science*, however, could exonerate the sun—and pin the blame on greenhouse gases.

One reason that the sun has become a player in the debate over global warming is that the measured temperature rise isn't as large as some climate models predict it should be, if the increasing concentration of carbon dioxide is driving it. And at the same time, the sun has shown intriguing hints of variability that suggest that it could play a role in altering terrestrial temperatures.

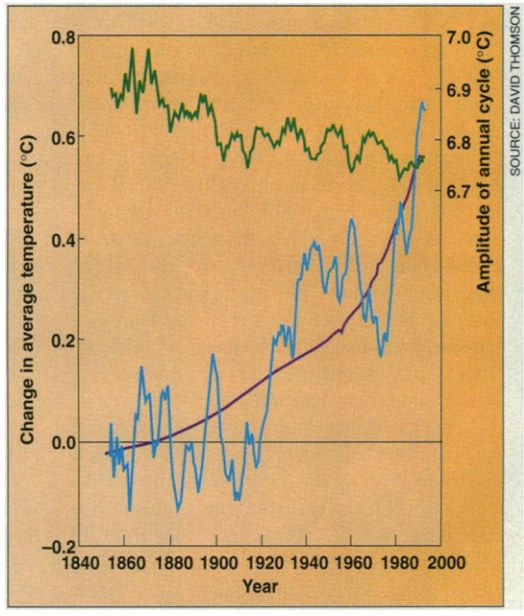
Although the brightness fluctuations measured in the 18 years since the first satellite-borne monitors were launched are far too small to explain the past century's warming, indirect clues to the sun's behavior (such as the number of sunspots) suggest to some researchers that solar brightness may have fluctuated more widely in the past. But on page 59 of this issue, David Thomson of AT&T Bell Laboratories in Murray Hill, New Jersey, tries to sweep away some of the uncertainty. Thomson tested the climate record for a specific signature of sun-driven warming and found little trace of it. He concludes that "solar variability ... is at most a minor factor in the increase in average temperature observed over the last century."

If Thomson is right, the rise in greenhouse gases would become the leading explanation for the warming, with some natural fluctuation within the climate system as a possible rival. "What Dave's doing is essential," says time-series analyst Jeffrey Park of Yale University, but it won't be the end of it. "If he's indeed got [the statistics] correct—and I think he does—that's going to focus people's attention on what kinds of modeling experiments should be tried" to confirm Thomson's assumptions about how the climate system works.

Thomson, a specialist in the analysis of all sorts of time series, was a stranger to the sun-climate debate until 1991, when a half-dozen colleagues sent him copies of a *Science* paper by Eigil Friis-Christensen and Knud Lassen of the Danish Meteorological Institute. That paper identified a stunningly tight correlation between the length of the sunspot cycle, which averages 11 years in length, and average temperatures in the Northern Hemisphere. The match-up implied that nearly all the warming was driven by the sun (*Science*, 1 November 1991, p. 652). Many climate specialists, however, were skeptical, and they hoped Thomson, with his sophisticated mathematical tools, could put the sun-climate connection to the test.

His solution was to look at the relation between the average annual temperature over the past century and the temperature contrast between winter and summer. If a brightening of the sun were warming Earth, he reasoned, both seasons would receive additional solar heating. But because summers capture a larger share of the year's total solar input than winters do, the added solar energy and therefore the warming would be greater in summer than in winter. In that case, the amplitude of the seasonal cycle should increase.

When Thomson analyzed a temperature record supplied by Philip Jones of the University of East Anglia, however, he found the opposite. While the Northern Hemisphere warmed by 0.6°C after 1900, the amplitude of the annual cycle slowly decreased rather



Traces of the greenhouse? While atmospheric carbon dioxide (*purple*) and Northern Hemisphere temperature (*blue*) were rising together, the amplitude of the seasonal cycle (*green*) declined, suggesting greenhouse gases rather than the sun as the cause.

than increasing, and the pattern in the Southern Hemisphere was much the same. That flatly contradicts the behavior expected if solar brightening were at work, says Thomson. If anything, he says, the decreasing seasonal amplitude implies the sun has been dimming in this century.

Other features of the temperature record suggest to Thomson that, instead of the sun, increases in atmospheric carbon dioxide and other greenhouse gases are driving the warming. For one, he shows, the rise of carbon dioxide and the rise of the temperature accelerate in step during this century, as expected if one were driving the other. Thomson is also persuaded by a striking shift he found in the timing of the seasons that began around the 1940s, just when the effect of greenhouse gases would have been mounting (*Science*, 6 January, p. 27). None of this proves an intensifying greenhouse is behind the last century's warming, says Thomson, but "you just have to take it more seriously."

Thomson says his results don't mean solar variations have played no role in climate. Another of his analyses suggests that until about 70 years ago, the sun could have shaped some shorter term climate fluctuations. When he compared seasonal amplitude and sunspot numbers, known to increase when the sun is brighter, he found that until about 1923 they tended to increase or decrease together, suggesting that the sun's variations were helping to warm and cool Earth. But more recently, the correlation between seasonal amplitude and sunspots fell apart when greenhouse warming overwhelmed the relatively weak sun-climate connection.

Researchers in the climate community say they trust Thomson's statistical analysis but that the climatic assumptions underlying his conclusions need to be examined more closely. Climate modeler Syukuro Manabe of the Geophysical Fluid Dynamics Laboratory in Princeton, New Jersey, for example, wonders how Thomson can be so sure that a brightening of the sun would increase the amplitude of the seasonal cycle. Climate is more complicated than Thomson allows, says Manabe. For example, anthropogenic aerosols, such as the fine sulfate particles formed from sulfur dioxide pollution, could help even out the warming between summer and winter. Such aerosols have increased in this century, and their sun-shading effect would be strongest in summer, masking the signal of a brightening sun, he says.

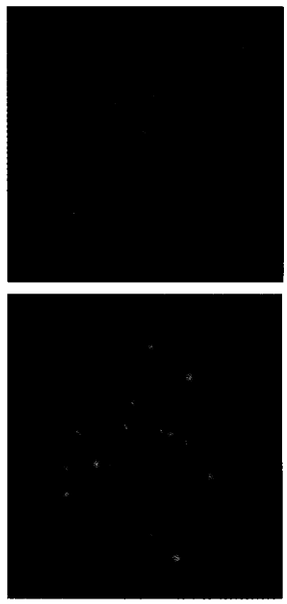
Thomson's assumption, and Manabe's critique of it, will be grist for climate modelers, who can test such proposals in their computer simulations. So far, modelers haven't been able to resolve the sun-climate debate. But by testing Thomson's provocative analysis, modelers may have a chance to settle the debate for good.

–Richard A. Kerr

CANCER RESEARCH

Telomeres Draw a Crowd at Toronto Cancer Meeting

For many years, researchers studying the telomeres—specialized structures found at the ends of chromosomes—labored in obscurity, concentrating on tiny one-celled organisms called ciliates. But no more. Recent research suggests that telomeres and telomerase (the enzyme that makes them) play key roles in controlling cell aging. What's more, when this control goes awry, abnormal telomerase activity may spur cancer development (*Science*, 16 September 1994, p. 1656). Interest in telomeres has become so intense that at this yeat's annual meeting of the American Association of Cancer Researchers (AACR), held from 18 to 22 March in Toronto, more than 1100 researchers packed a symposium entitled "Telomeres and Telomerase."



The long and short of it. The cell maintained in culture longer (*top*) has much shorter telomeres (*green stain*).

PHOTOS BY S. HENDERSON AND D. SPECTOR, COLD SPRING HARBOR LAB / S.-S. WANG AND R. ALLSOPP, GERON CORP.

What they heard will no doubt keep interest levels high. Researchers have further strengthened the case for telomerase's role in cancer. They also reported in Toronto that they have for the first time isolated both components of telomerase, an unusual enzyme requiring RNA and proteins for its activity. The telomerase discoveries reported at the meeting "represent a meteoric rise in our understanding," says Gregg Morin of the University of California, Davis, who found telomerase activity in human cells in 1989. One reason these advances are so exciting is that telomerase is an attractive target for cancer therapy. Having the enzyme may aid efforts to find drugs to inhibit telomerase and perhaps stop cancer cell growth.

While potential clinical applications are intriguing, most early telomere research was done on ciliates such as *Tetrahymena* because the nuclei of these organisms have many more telomeres and higher telomerase activity than those of mammalian cells. Early work on these simple organisms by Elizabeth Blackburn of the University of California, San Francisco (UCSF), and Carol Greider, now at Cold Spring Harbor Laboratory, showed that telomerase solves a major problem. Because of a quirk, the enzyme that duplicates the DNA before cells divide can't replicate the entire length of both strands of DNA. As a result, chromosomes ought to shorten with each round of cell division. Telomerase solves that problem by adding telomeric sequences, short repetitive DNA segments, onto chromosome ends.

Higher organisms, however, have a much different situation. After birth, their cells, except for those in the germ line and some blood-forming cells, shut off telomerase activity. Mounting evidence suggests the resulting telomere shortening serves as a "mitotic clock" that measures time until the telomeres reach a critically short length and cells go into senescence.

It may seem that activating telomerase could lead to cell "immortality." In fact, it does in ciliates, but in higher organisms immortality could do more harm than good. Beginning 4 years ago, researchers, including Calvin Harley of Geron Corp. in Menlo Park, California, Silvia Bacchetti of McMaster University in Hamilton, Ontario, and Greider, found first in cultured cells, and then in human ovarian tumors, that telomerase reactivation may lead to cancer.

At the AACR meeting, Jerry Shay of the University of Texas Southwestern University Medical Center in Dallas presented work from his group and others suggesting that telomerase reactivation occurs in many different cancers. They found that telomerase is active in nearly 85% of 454 primary tumors, including cancers of the breast, brain, and lung (*Science*, 23 December 1994, p. 2011). Indeed, studies of the childhood cancer neuroblastoma by the Shay team suggest the level of telomerase activity may indicate whether patients have a good or bad prognosis. The neuroblastoma results, says Shay, suggest that "you can have cancer or cell proliferation without telomerase activity; but for sustained growth of the cancer, telomerase must be turned on."

Such discoveries have researchers eager to know more about this enzyme, but they've been frustrated by the scarcity of telomerase in mammalian cells. Indeed, for many years, the only isolated telomerase component was RNA from ciliates. Then last year, two