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.

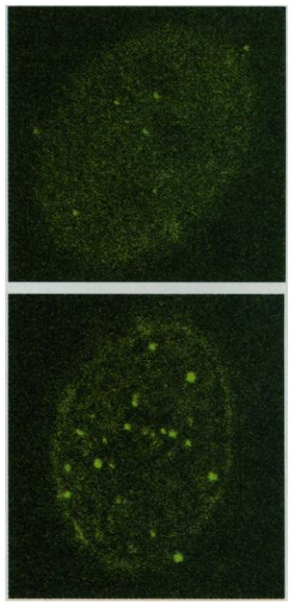
Thomson's assumption, and Manabe's critique of it, will be grist for climate modelers, who can test such proposals in their computer simulations. So far, modelers haven't been able to resolve the sun-climate debate. But by testing Thomson's provocative analysis, modelers may have a chance to settle the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

groups, one led by Dan Gottschling of the University of Chicago and the other by UCSF's Blackburn and Michael McEachen, isolated telomerase RNA from two different species of yeast (*Science*, 21 October 1994, p. 404).

In Toronto, several groups presented results indicating the pace in this field is accelerating. Harley announced that his group, led by Bryant Villeponteau, with Greider's, has cloned the gene for human telomerase RNA, making it the first mammalian telomerase component to be captured. The researchers are pretty sure they have the right gene because the RNA is found in the same fraction as telomerase activity when researchers attempt to purify telomerase activity from cells. But, Harley says, most important, mutating the RNA gene creates mutated telomerase activity.

Perhaps even more encouraging was Greider's announcement that her group has isolated telomerase proteins from the organism where the search began: *Tetrahymena*. Greider's team pulled out two proteins, one with a molecular weight of 80,000 and the other 95,000. Armed with partial amino acid sequences of these proteins, the team cloned the genes. Surprisingly, telomerase isn't closely related to any other enzyme that synthesizes DNA, although it is very slightly related to an ancient viral RNA synthesizing enzyme.

Telomere researchers welcomed the discovery with excitement. "We have been waiting for these proteins for 10 years," says Morin. Many researchers hope that having the *Tetrahymena* telomerase protein genes will help identify those from higher organisms.

But even without the protein, the RNA component of the human telomerase will "greatly speed research into the developmental regulation and tumorigenic activation of telomerase," according to Morin. Using this information, researchers hope to devise strategies to battle cancer by inhibiting telomerase activity—rendering cells "mortal" once more.

Several groups are on the trail of such inhibitors. "We are aggressively pursuing drugs to inhibit telomerase," says Harley. Southwestern's Shay says his group is looking for the cell's own telomerase inhibitor, the one that turns the enzyme off during development, in hopes of reactivating it in cancer cells. They have evidence that human chromosome 3 carries a gene for such an inhibitor.

No matter which method succeeds, progress reported in Toronto suggests researchers may soon begin to find ways to counteract the deadly immortality telomerase promotes—a development that would only help keep telomeres and telomerase in the limelight.

–Lisa Seachrist

Lisa Seachrist is a writer with United Press International.

MEETING BRIEFS

Physics Festival Brightens Rainy San Jose

A week after floodwaters surged through parts of San Jose's downtown, a flood tide of physicists—almost 6000 of them—appeared for the annual March meeting of the American Physical Society (APS). Gloom and drizzle continued for the first 4 days of the gathering, but there were plenty of bright spots inside the hall.

Pinpoint Chemistry

Its ability to explore and reshape atomic-scale hills and valleys with its microscopic tip has long made the atomic force microscope (AFM) a favorite tool among devotees of nanotechnology. Most of the fans have been physicists, but now chemists are getting in on the fun: A mixed group of chemists and physicists, all from the University of California, Berkeley, and Lawrence Berkeley National Laboratory, has developed an AFM that wields a catalytic tip to transform the chemical landscape of a surface, molecule by molecule. "By moving this 'pen' around we're able to localize the chemistry and 'draw' a chemical reaction," physicist David Klein told an audience at the APS meeting.

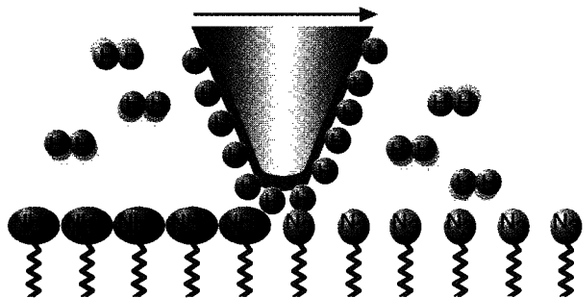
So far, the group has done no more than a proof-of-principle experiment. But the effort, led by chemist Peter Schultz, could eventually offer a new way to dissect catalytic reactions by precisely controlling how the reactants and the catalyst interact. A catalytic AFM could also build complex structures, such as electronic circuits or micromachines, on a scale of nanometers (billionths of a meter), says Klein. "I think it will be very important for making prototype devices," agrees University of Texas, Austin, physicist Alex De Lozanne, who chaired the APS session at which Klein spoke.

The work isn't the first venture into nanocatalysis. Berkeley chemist Gabor Somorjai last year led a team that performed a similar feat with the platinum-coated tip of a scanning probe microscope (STM), a device that utilizes an electrically charged probe that hovers a few atoms' widths above a surface (*Science*, 2 September 1994, p. 1415). Hoping to take a somewhat more direct approach, Schultz, Klein, and their colleagues instead mounted their platinum catalyst on the tip of an AFM, which actually touches the surface.

They staged their first test of the device by soaking the tip in a hydrogen-containing solvent, then applying it to a so-called self-assembled monolayer—an orderly array of molecules that Klein likens to a field of wheat. At the end of each stalklike molecule is a collection of three nitrogen atoms known as an azide group. The hydrogen-imbued platinum, the group hoped, would add hydrogen to the azides to transform them into amines, which contain one nitrogen atom and two hydrogen atoms each.

And so it did, the Berkeley researchers found when they scanned the catalytic tip over a square of the monolayer measuring 10 microns by 10 microns. A fluorescent tag that binds to amine groups but not to azides lit up a green, glowing square exactly where the tip had passed. "We see a nice clear signal where the AFM scan was done, indicating catalysis," says Klein.

This fine control could help researchers explore questions such as how long a catalyst must be in contact with a target to drive a reaction. "You could set up some nice chemical experiments, we hope," says Klein. But Klein and his colleagues also think that with the right choice of reactants and catalyst, they might be able to assemble complex nanostructures, such as transistors, by hooking on molecules other than fluorescent tags.



SOURCE: P. SCHULTZ *ET AL.*

A special touch. A platinum-coated AFM tip adds hydrogens to azide groups (N_3), transforming them to amines (NH_2).

If AFM or STM catalysis is to become more than a laboratory tool, however, Klein and his colleagues will have to improve the technique's speed and reliability. The tip