meeting on genetic screening held in San Francisco last month, Northrup reported that his group had used a battery-powered, hand-held device to simultaneously amplify eight different gene segments containing the most common mutation sites for cystic fibrosis. This multiple copying, Northrup explains, requires very precise temperature control to insure that all of the sequences are copied at the same rate. His group achieved the needed control, he says, by building a tiny heating element directly into the reaction chamber.

When the copying was complete, the researchers could check each fragment for mutations that can cause cystic fibrosis by applying the amplified sequences to simple paper test strips. "For the first time we have a battery-powered, hand-held system that can be used to check for common genetic disorders," says Northrup. But he acknowledges that PCR-on-a-chip isn't ready for the doctor's office. One reason is that extracting DNA from blood or other samples still requires complex sample preparation procedures that have not yet been scaled down.

Getting it all together

Microscale HPLC and PCR are only two results of this rush toward miniaturization. Separation techniques known as free-flow electrophoresis and capillary electrophoresis have undergone the same downsizing. And researchers at biotech start-ups such as Affymetrix in Santa Clara, California, and Hyseq Inc. in Sunnyvale, California, are making chip-based devices that carry an array of immobilized nucleotide sequences, designed to identify disease-causing sequences in DNA (*Science*, 3 June 1994, p. 1400).

Because individual analytical components like these can be faster and cheaper than their current counterparts, instrument-makers are already linking them to their full-scale laboratory instruments, says Harrison. But analysis-on-a-chip won't realize its full potential, researchers agree, until all the functions needed to carry out a particular reaction—including batteries to drive the system, reaction chambers and filters to prepare the sample, and detectors to read the results—can be miniaturized as well. Says Harrison: "We're only beginning to put this whole series of elements together."

This integration may have come farthest for capillary electrophoresis (CE), which separates snippets of DNA or amino acids. Unlike HPLC, which sorts molecules in liquids based on their interactions with solid particles in the separation column, CE does so by using an electric field to draw them through a narrow channel. The molecules' different sizes and charges cause them to migrate through the channel at different rates, so they emerge separately at the far end. Over the last few years several groups have succeeded in putting the separation step onto a chip threaded with a tiny channel. And they've even begun adding sample preparation and detection steps to their chips.

At last month's Pittsburgh Conference, an analytical instruments meeting held in New Orleans, separate teams led by Alberta's Harrison, Ciba-Geigy's Manz, and J. Michael Ramsey of Oak Ridge National Laboratory reported some of the most extensive integration to date. Ramsey's group, for example, demonstrated the first lab-on-a-chip that applies CE to the common DNA analysis technique known as restriction fragment analysis. To perform the chip-based version of the technique, Ramsey and his colleagues started by putting DNA and specialized enzymes into different chambers on the chip. They then used the same electric fields that draw molecules through the CE channel to pump liquids carrying the DNA and enzymes into a reaction chamber, where the enzymes cut the DNA into "restriction fragments"—snippets of different lengths. Applying the electric field again caused the chopped DNA fragments to migrate to the separation channel, where they were sorted by size and tagged with fluorescent dyes for detection.

Those reports and others bring fully miniaturized analysis one step closer, but "much work still remains to be done," says Satyam Cherukuri of the David Sarnoff Research Center in Princeton, New Jersey, who is leading efforts there to integrate chip-based devices. One "jugular issue," says Cherukuri, is the size difference between the milliliter-sized samples doctors and chemists are used to working with and the millionfold smaller quantities that suffice for a lab on a chip. Finding a representative fraction of a sample to feed into a microlab could be a problem for a test designed to find, say, a rare viral sequence.

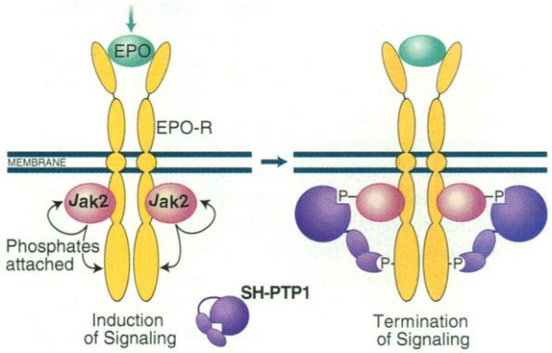
But with the example of computer scientists to inspire them, many researchers believe even that hurdle can be surmounted. "Miniaturization is inevitable in analytical techniques," says Ives. "There's nothing inherent in chemistry or engineering that prevents it." And that green light suggests the mantra of analytical chemistry will soon echo that of computing: Small is beautiful.

–Robert F. Service

CELL BIOLOGY

An "Off Switch" for Red Blood Cells

In biological systems, the brake is as important as the gas pedal. Take the production of red blood cells. In 1989, when the gene for the erythropoietin receptor (EPO-R) was cloned, biologists gained a much better understanding of the signaling mechanism that spurs production of red blood cells in human bone marrow. But the "off switch" that halts this process and thereby maintains the body's precise control over the number of red blood cells in the bloodstream remained unclear.



SOURCE: H. LODISH *ET AL.*, *CELL*

Stop sign. SH-PTP1 turns off the "develop" signal sent by phosphorylated Jak2.

Now scientists in the same Boston laboratory that cloned EPO-R have located the brake: the spot on the mouse version of the receptor where an important down-regulating enzyme docks. And, proving that basic research has serendipitous rewards, in the process they've solved a decades-old medical mystery from Finland that may have played a role in the awarding of three gold medals at the 1964 Winter Olympics.

In a recent issue of *Cell*, a team led by Harvey Lodish at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, including cell biologists Ursula Klingmüller, Ulrike Lorenz, Lewis Cantley, and Benjamin Neel, report that the binding of an enzyme called SH-PTP1 to a specific site on the mouse EPO-R slows the maturation of multipotential "stem cells" in the bone marrow into red blood cells. James Darnell, a molecular biologist at Rockefeller University in New York, says, "It's an important connection. ... The output of the receptor is being regulated somewhat surprisingly."

The surprise is that the switch that turns off hematopoiesis (production of red blood cells) isn't on the EPO-R molecule itself, but on an associated enzyme called Jak2. In both mice and humans, EPO-R is a 550-amino-acid-long protein that spans the stem cell's outer membrane. Lodish and his colleagues believe that when the hormone erythropoietin binds to the receptor's outer domain, it causes Jak2, which binds to the inner portion of the receptor, to attach phosphate groups to itself and to certain amino acids on the receptor. The addition of the phosphates creates docking sites for other proteins that pass the signal "develop into a red blood cell" on to the interior of the stem cell.

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.

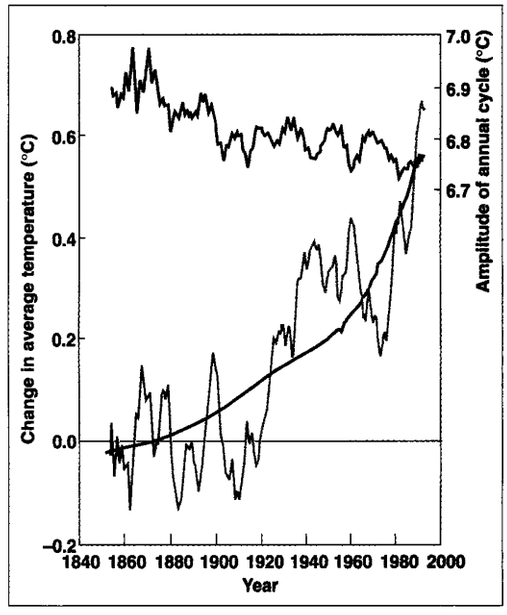
Although the brightness fluctuations measured in the 18 years since the first satellite-borne monitors were launched are far too small to explain the past century's warming, indirect clues to the sun's behavior (such as the number of sunspots) suggest to some researchers that solar brightness may have 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.