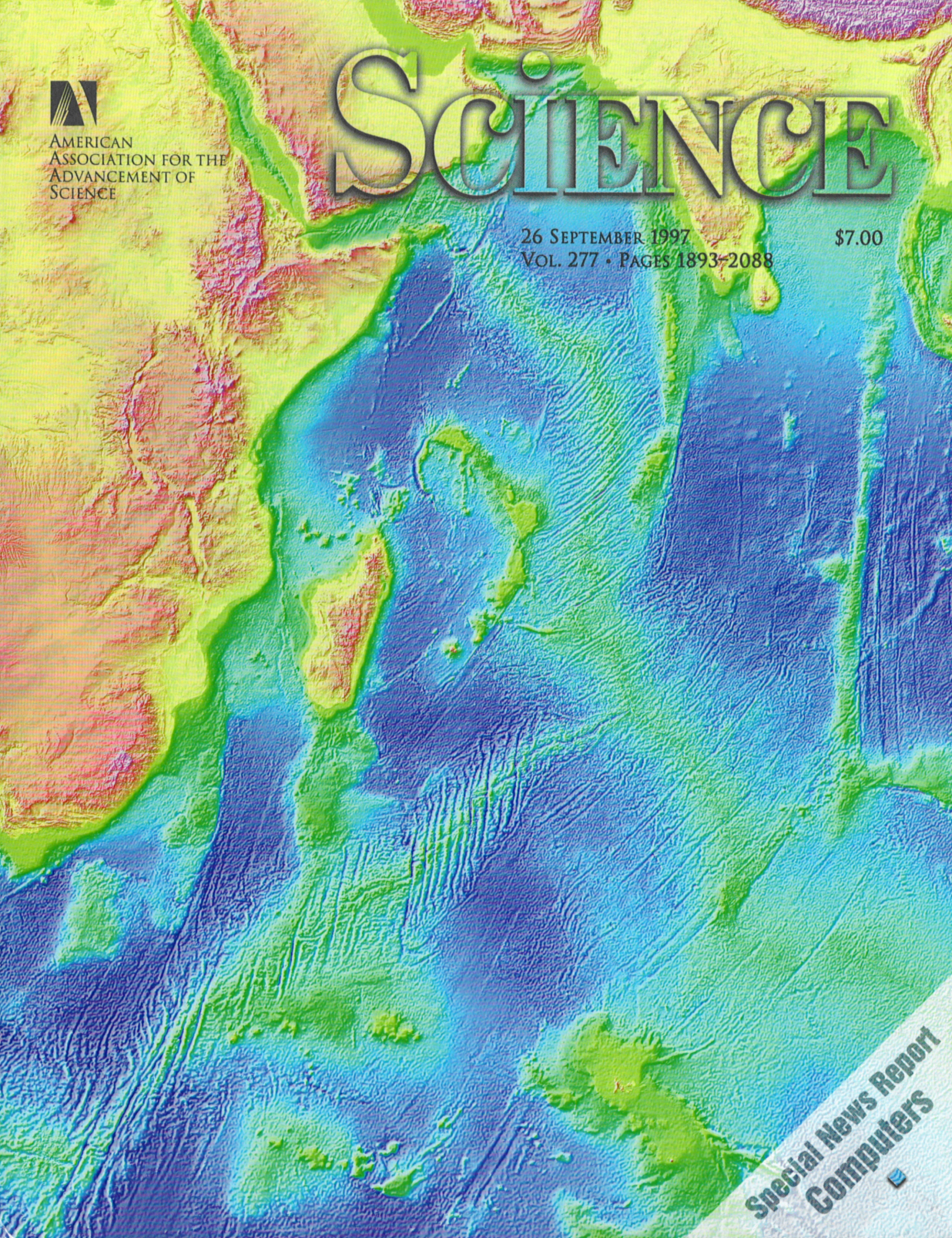


AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

SCIENCE

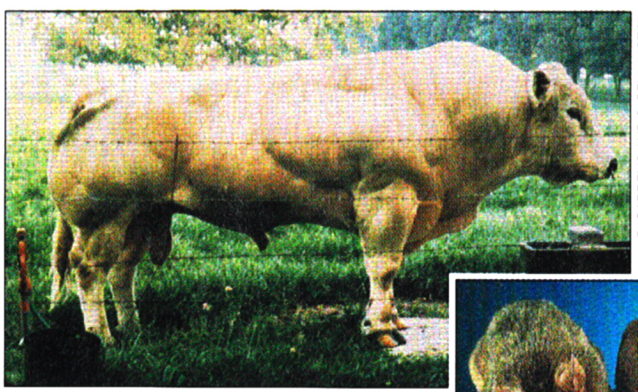
26 SEPTEMBER 1997
VOL. 277 • PAGES 1893–2088

$7.00

Special News Report
Computers

Gene Mutation Provides More Meat on the Hoof

Belgium is not exactly known for wide-open spaces and sprawling ranchlands. So farmers there had to learn to do more with less. Over the last 30 years, they have bred a strain of cattle—the mighty Belgian Blue—that gives 20% more meat per animal on roughly the same food intake as ordinary animals. Indeed, the cattle develop such bulging muscles that in extreme cases they have trouble walking and the calves are so big they have to be delivered by cesarean section. Now, three research groups have independently uncovered the genetic cause of this "double-muscling" trait, a discovery that may lead to meatier strains, not just of cattle, but of other agriculturally important animals as well.



D. GARRELIS AND C. PENNINGTON

K. WELLER/JHMI

Schwarzenegger gene? A mutated myostatin gene causes the heavy muscling of this Belgian Blue bull. The left-hand mouse of this pair also shows the effects of inactivating the gene.

In the September issue of *Nature Genetics*, a pan-European team led by Michel Georges of the University of Liège in Belgium reports that double muscling is caused by a mutation in the bovine version of a recently discovered gene that makes a protein called myostatin. The other two groups, one co-led by Tim Smith of the U.S. Department of Agriculture (USDA) lab in Clay Center, Nebraska, and the other by Sejin Lee of Johns Hopkins University, also found that the myostatin gene is mutated in Belgian Blues and have linked mutations in the gene to double muscling in a second breed of cattle, the Piedmontese, as well. [The Smith team's results are in the September issue of *Genome Research*, and Lee's are in press in the *Proceedings of the National Academy of Sciences* (*PNAS*).]

Discovered just 4 months ago in mice by Lee and his graduate student Alexandra McPherron, myostatin normally serves to limit skeletal muscle growth. Apparently, the mutations block its activity and the animal's muscles grow larger—but without harming meat quality. While some other cattle breeds are also abnormally well muscled, presumably because of as-yet-undiscovered mutations, the muscle fibers in those animals are thicker than normal, toughening the meat. In contrast, the muscles of animals with myostatin mutations have larger numbers of normal-size fibers. Indeed, says Smith, meat from the Belgian Blue is "so tender even round steaks fall apart on the grill." Nevertheless, the meat is lower in fat than that from ordinary breeds.

Given those effects of myostatin mutations, it's not surprising the gene is attracting attention from agricultural scientists. "This is the first gene identified in cattle that controls a combination of muscle size and tenderness," says molecular geneticist Mike Bishop of ABS Global, a biotech firm in Madison, Wisconsin. He notes that beef palatability, as well as yield, might be improved by introducing myostatin gene mutations into cattle or by finding drugs that turn down the gene's activity. Such strategies might also lead to meatier pigs, chickens, and turkeys, as the Lee team found that the myostatin gene has relatives in these and other farm animals.

The meandering cow path to this discovery started in Belgium in the 1950s, Georges says. Cow breeders there, who were under economic pressure from cheaper imports and high production costs, wanted to increase their yields and began to select for the double-muscling trait, which had been reported as early as 1807. Before long, nearly every beef cow in Belgium was a purebred double-muscled animal.

Beginning in the late 1980s, Georges's team spearheaded an effort to isolate the cause of double muscling. "We were so convinced that any gene ... that had such a spectacular effect on muscular development had to be a very important gene for animal agriculture," he recalls. By 1995, Georges and his colleagues mapped the gene to a region of cow chromosome 2, but then the effort stalled because they still had a lot of DNA to search through.

A break came in May of this year, however, when Lee and McPherron described the myostatin gene and showed that when it is missing in mice, the animals grow into muscle-bound hulks two to three times the size of normal animals. That publication launched a race to find the equivalent bovine gene, as the implications for cattle—if such a gene existed—were obvious.

The group led by Georges—which included researchers from Germany, Spain, and France—used a neat trick involving a third species, humans. The full human gene has not yet been published—it will be in Lee's *PNAS* paper—but the researchers found that a database of human ESTs (expressed sequence tags) contained sequences similar to those of the mouse gene. Although ESTs are short—100 or 200 bases long—Georges and his colleagues found enough overlapping ones to piece together most of the human gene. After cloning it and mapping its chromosomal location, they played a hunch and compared the site of the human gene with a map of bovine chromosome 2.

The effort paid off. "We then realized," says Georges, "that the position of the myostatin gene on the human map coincided exactly with the position of the double-muscling gene on our bovine genome map." From there, they cloned and sequenced the bovine myostatin genes from both double-muscled and normal cattle.

The sequences revealed that the gene from the double-muscled animals carries an inactivating mutation—an 11–base pair deletion—that results in "virtually complete truncation" of the active region of the protein, Georges says. That lifts the normal repression of muscle growth by myostatin and opens the way for extra brawn.

The Lee team used a similar approach to come up with the Belgian Blue gene. The researchers then guessed that double-muscled Piedmontese cattle would also have a mutated myostatin gene, and when they cloned it, that's what they found. Smith, working with John Baff's team at AgResearch in Ruakura, New Zealand, took a somewhat different tack, using the mouse gene to first find the gene in normal bovine DNA and then in Belgian Blues and Piedmontese, where they, too, found mutations. Similar mutations could also add bulk to other farm animals, for the Lee team has found the gene in all nine species they examined, including mammals, such as the pig, and birds, including chickens and turkeys.

The myostatin work may help to identify other genes that influence muscle growth. Piedmontese cattle don't develop the extreme double muscling of Belgian Blues, even though the mutation that the Smith and Lee teams found in their gene is probably suffi-

cient to inactivate the protein. That suggests that the lesser amount of double muscling in Piedmontese cattle is due to other genes that make up for the loss of myostatin.

Despite the interest in using the myostatin gene to improve beef production, researchers warn that it may be a difficult task. One possibility is to use either conventional breeding or genetic engineering to introduce the Belgian Blue mutation into other breeds. So far, however, U.S. breeders have only rarely attempted to do this, even by conventional breeding. This is partly for practical reasons. The need to deliver calves by cesarean section is a serious handicap in the United States, where cattle herds are larger and roam over much wider areas than they do in Belgium.

That problem might be overcome if researchers can find a less extreme myostatin mutation or identify another gene with a less drastic influence on muscle mass, allowing the calves to be delivered naturally. But there are also worries about whether the public would accept genetically engineered beef. The cattle industry has until now shied away from funding research into transgenic animals for human consumption. "They perceive it as too sensitive and risky an area," Smith says.

Another possibility would be to find some drug that can turn down myostatin activity in animals with the normal gene. And then there may be other genes that can be manipulated. Researchers in at least four countries are mapping the cattle genome, and reproductive physiologist Vernon Pursel of the USDA research labs in Beltsville, Maryland, says "we are getting to the point where there will be a number of genes" like myostatin identified in the near future. Extra helpings of tasty meat at essentially no cost could prove hard to resist.

–Steven Dickman

Steven Dickman is a writer in Cambridge, Massachusetts.

CLIMATE

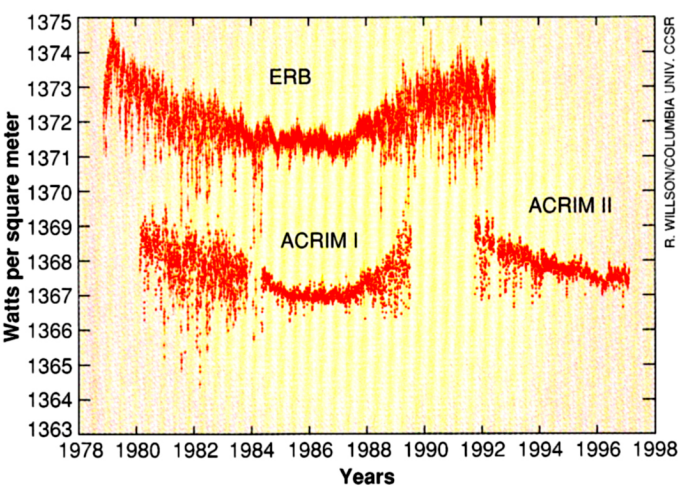
Did Satellites Spot a Brightening Sun?

In the debate over whether greenhouse warming has arrived and just how bad it will get, the sun has been a relatively minor player. But even a tiny dimming of the sun—the climate system's sole energy source—could greatly slow any warming due to greenhouse gases, while a slight brightening could worsen what might already be a bad situation. Unfortunately, the longest running direct observations of the sun have been too short to say whether its brightness actually varies over the decades needed to influence climate. But by splicing together separate satellite records, an atmospheric physicist has constructed a record long enough to suggest a striking trend: a strong recent brightening.

On page 1963 of this issue of *Science*, Richard Willson presents his analysis of observations by three satellite-borne sensors that together have monitored solar brightness since 1978. Willson, from the Altadena (California) branch of Columbia University's Center for Climate Systems Research, finds enough brightening to make the sun a major player in climate change, if the change signals a long-term trend. But his finding is controversial. While some analyses of the same data being prepared for publication support Willson's finding, others do not.

The central question is the reliability of one of the three records. Willson's analysis, which used a less sophisticated sensor to tie together an interrupted record, "seems quite reasonable," says Lee Kyle of NASA's Goddard Space Flight Center in Greenbelt, Maryland, whose instrument produced the linking data set. "I think Willson is correct in saying the best evidence shows an increase. How strong that evidence is, is another matter." Some say it is not strong at all. "I think we are not able to do it at this point," says Claus Frohlich of the World Radiation Center in Davos, Switzerland. "We just don't know."

To identify a long-term trend in solar brightness, or total solar irradiance (TSI), researchers need a record that spans at least one solar cycle—the 11-year cycle over which sunspots spread across the face of the sun and then vanish, with a corresponding rise and fall in the sun's brightness. The orbiting Active Cavity Radiometer Irradiance Monitor (ACRIM I) provided part of the necessary record from 1980 to 1989, showing that TSI fell 0.08% during the declining solar activity of an 11-year sunspot cycle. That's a sizable change, but too brief to overcome the climate system's inertia.



Solar ups and downs. The long-running ERB sensor on Nimbus 7 bridges the gap between the ACRIM sensors on UARS.

The space shuttle was supposed to launch a second instrument while the first was still operating, so that researchers could compare the readings from the two identical instruments and correct them to construct a seamless record. But the Challenger accident delayed the Upper Atmosphere Research Satellite launch by several years and opened a 2-year gap between ACRIM I, whose satellite failed in 1989, and the arrival of ACRIM II, which was finally launched in 1991.

Lacking such a comparison, Willson and other researchers have bridged the gap with a less capable instrument, the Earth Radiation Budget (ERB) experiment on the Nimbus 7 spacecraft. When Willson combined the records, he found a brightening of 0.036% per decade from 1986 to 1996. That brightening, if sustained for many decades, would lead to solar warming in a league with greenhouse warming in the next century. The current best estimate for greenhouse warming at the end of the next century is 2.0 degrees Celsius, while such a solar brightening sustained for 100 years might produce a warming of about 0.4°C, says Willson.

But the strategy of relying on ERB to bridge the two ACRIM records leaves room for doubt. ERB cannot monitor how much its collecting surface has been degraded by the harsh solar glare, as ACRIMs can. However, ERB made less frequent measurements, probably minimizing its degradation during the 2-year gap, say its operators, Kyle and Douglas Hoyt, who is now at Hughes STX in Greenbelt. They did correct the ERB record after finding a jump in measured TSI that they attributed to a one-time shift in the sensitivity of the instrument.

Yet the results conflict with some other studies. Solar physicist Judith Lean of the Naval Research Laboratory in Washington, D.C., has made indirect estimates of long-term brightness changes based on the shifting balance between dark sunspots and relatively bright areas on the sun, called faculae and network. That is the process that explains much of the brightness variation within a solar cycle. Based on past sunspot