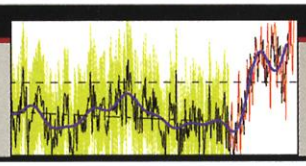

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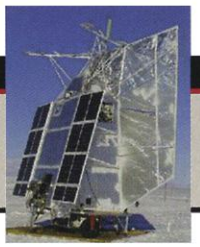
Global warming signal strengthens



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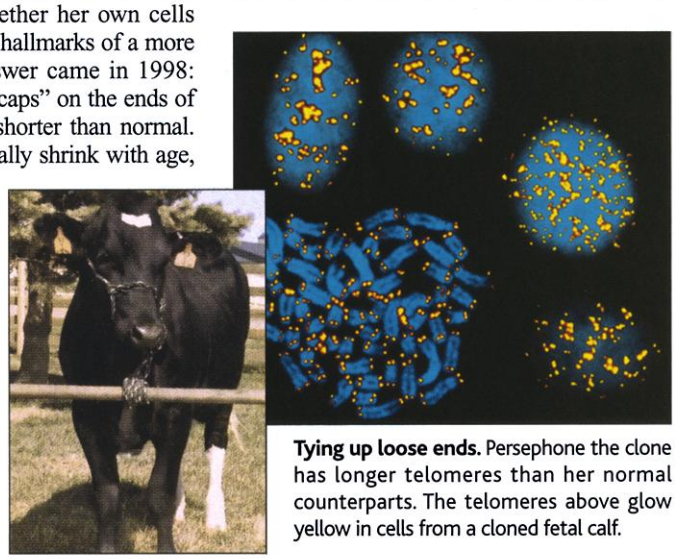
Boomerang returns a surprise

CELL BIOLOGY

In Contrast to Dolly, Cloning Resets Telomere Clock in Cattle

When researchers announced 3 years ago that they had cloned Dolly the sheep, many scientists asked a question that sounds almost metaphysical: Are her cells older than she is? Because Dolly had been cloned from an adult cell, they wondered whether her own cells would show some of the hallmarks of a more mature animal. The answer came in 1998: Dolly's telomeres—the "caps" on the ends of her chromosomes—are shorter than normal. Because telomeres normally shrink with age, this was a disturbing sign that her cellular clock hadn't been reset to zero. Not only did the finding imply that Dolly might age unusually quickly, but it also dampened hopes that the cloning technique might someday be used to produce replacement cells for patients suffering ills such as liver failure or Parkinson's disease, because such cells may be too "old" to use. Now, a surprising finding has diminished those concerns.



Tying up loose ends. Persephone the clone has longer telomeres than her normal counterparts. The telomeres above glow yellow in cells from a cloned fetal calf.

On page 665, physician Robert Lanza of Advanced Cell Technology (ACT) in Worcester, Massachusetts, and his colleagues report that cells from calves they cloned have telomeres that are *longer* than normal. Moreover, the cells show other signs of youth and can divide in culture many more times than normal cells do. Similar work in cattle and in mice, as yet unpublished, seems to support the ACT team's results.

Why these findings are so dramatically different from those on Dolly is not yet clear. But, as Lanza points out, it suggests that tissues produced by cloning might last at least as long as the original cells—and perhaps longer. Pathologist and gerontologist George M. Martin of the University of Washington, Seattle, agrees. A technique that can lengthen the life-span of cultured cells, he says, should be very useful for tissue engineering.

Ethical problems will remain, however. Cloning is accomplished by transplanting nuclei from somatic cells into eggs whose own nuclei have been removed. When the goal is to produce animal clones, embryos that develop from those cells are implanted in foster mothers in the hopes that they will produce live births. But for therapeutic cloning, the embryos would be allowed to develop just long enough to produce embryonic stem cells, which could then be used to generate replacement tissue. Using nuclei from a patient's own cells to produce the embryos should avoid rejection problems, because the resulting cells' nuclear DNA would be identical to that of the patient.

But such research cannot be done in many countries because the procedure requires creating and then destroying a human embryo, and many also worry that therapeutic cloning would open the door to human reproductive cloning. Earlier this month, however, the influential Nuffield Council on Bioethics in Britain said that the potential benefits of therapeutic cloning outweigh the ethical concerns, and a British government panel is expected to rule in favor of the research. Other countries, including the United States, seem further from allowing such research to be done with government funds.

When Lanza and his colleagues heard about Dolly's shortened telomeres, they decided to try a stringent test: Could they derive healthy animals from cells kept in culture until senescence, when they are no longer able to divide? To find out, the scientists obtained cells from a fetal calf and allowed them to replicate for several months, until near the end of their expected life-span. By then, Lanza says, the cells were showing characteristics of aging, including growing larger and accumulating cellular debris. They also had shortened telomeres.

The researchers then transferred nuclei from nearly 1900 of the cultured cells into enucleated egg cells and eventually produced six calves. At birth, the animals showed the now-expected characteristics of cloned animals—they were larger than normal newborns and had high blood pressure and difficulty breathing. But by 2 months of age, the animals seemed healthy and normal.

Indeed, when Peter Lansdorp and his colleagues at Terry Fox Laboratory in Vancouver examined blood cells from the young cattle 5 to 10 months after birth, they found that the animals' telomeres were significantly longer than the telomeres of normal cattle the same age, and in some cases were even longer than the telomeres of normal newborns. Another sign that the cloning process had somehow turned back the clock on the animals' cells came when the team cultured fibroblasts, a type of connective tissue cell, from the calves' ears. The cells expressed high levels of a gene called EPC-1, which is typically found at high levels in young cells and may be involved in cell division and proliferation.

In a related experiment, the team cloned five calf fetuses from adult cells kept in culture until senescence. They removed the fetuses at 6 weeks of gestation so they could compare their cells with those of normal fetal calves. The clones' cells divided an average of 93 times compared to only 61 for cells from normal calves. If this increased life-span extends to the whole animal, Lanza says, there is "a real possibility" that cloned animals might live as much as 50% longer than their normal counterparts—up to 180 to 200 years in the case of humans—an idea, he says, that "is going to raise an eyebrow or two."

Other scientists are more cautious, noting that aging is extremely complex and is controlled by more than just telomere length. But cell biologist Leonard Guarente of the Massachusetts Institute of Technology says the evidence does suggest that the oocyte was

CREDITS: (LEFT AND RIGHT) ROBERT P. LANZA

able to "restore a youthful state" to the donor cell's nucleus. But he cautions, "What you want to know is, will these cloned animals live longer?" The scientists will have to wait a while to answer that question, as sheep can live 12 years and cows about 20.

No one is yet able to explain the difference between Dolly and the cloned calves. It might be due to random variation, species differences, a difference in the cell type, or different methods of nuclear transfer. Telomere expert Jerry Shay of the University of Texas Southwestern Medical Center in Dallas hypothesizes that starting with relatively short telomeres in the senescent cells might prompt the early embryo to overcompensate and grow unusually long telomeres.

Whatever caused the difference, the Lanza team's results are consistent with preliminary findings of two other groups. In as yet unpublished work, Xiangzhong Yang of the University of Connecticut, Storrs, has found that the telomeres in calves cloned from adult cells were of at least normal length. And Teruhiko Wakayama of The Rockefeller University in New York City says that he, with colleagues in Hawaii and Japan, found a similar pattern in telomeres of cloned mice.

The researchers hope the findings will provide insights into the source of the egg cell's rejuvenating power. "Ultimately we want to understand how that reprogramming goes on in the oocyte so we could do it in vitro" and skip the embryo stage, Martin says. Several groups are working toward that goal, hoping to produce replacement tissues without the ethical baggage.

–GRETCHEN VOGEL

As you were. Prospective nominee Fischbach *(top)* and acting director Kirschstein.

CREDITS: NIH

BIOMEDICAL POLICY

NIH Nomination on Hold for This Year

Four months after Harold Varmus resigned as director of the National Institutes of Health (NIH), the agency has learned that it will have to go without a permanent chief for at least the rest of this year and probably for part of 2001. Deputy NIH director Ruth Kirschstein, a veteran research manager and former head of the National Institute of General Medical Sciences, who took charge of NIH in January, will continue as acting chief.

A federal official confirmed last week that Secretary of Health and Human Services Donna Shalala urged the Administration not to nominate a permanent replacement for Varmus at this time, and that White House officials agreed. In addition, sources say, Shalala consulted with the leading candidate for the NIH job, whose name has not been disclosed officially but privately is acknowledged to be Gerald Fischbach, director of NIH's National Institute of Neurological Disorders and Stroke. Varmus recruited Fischbach to NIH in 1998 from his position as chair of the departments of neurobiology at Harvard Medical School and Massachusetts General Hospital in Boston. Shalala and the candidate "mutually agreed" that it would be best not to send his name to the Senate for confirmation, the source said, primarily because time is running out for the Clinton Administration.

Fischbach and NIH officials aren't discussing the decision. But a Senate democratic aide who follows NIH affairs says that "NIH people were up here last week," explaining that they had shelved the nomination because of the "short time frame for moving a name through the Senate." In a nomination hearing, the aide said, "any nominee would have to expect tough questions regarding the use of fetal tissue and embryonic stem cells." Even if the review went smoothly, the new NIH director would have only a few months in office before the arrival of a new Administration—and possibly a move to change NIH's leadership. The decision to stick with the status quo, the Senate aide argued, is also a "vote of confidence" in NIH and "a recognition that Kirschstein is getting high marks for her handling of the job."

–ELIOT MARSHALL

NATIONAL ACADEMIES

Task Force Tinkers With Research Council

After several years of public turbulence, the U.S. national academies of science and engineering are about to embark on some private upheaval. The chiefs of the National Academy of Sciences (NAS) and its sister groups, the National Academy of Engineering (NAE) and the Institute of Medicine (IOM), have set their sights on restructuring the National Research Council (NRC), the huge think tank–like operation responsible for most of the reports, meetings, and workshops carried out each year by the academies.

A 15-member task force, chaired by retired Howard Hughes Medical Institute president Purnell Choppin and retired Honeywell vice president Gerald Dinneen, was formed in August 1998 and began meeting last spring. Its fourth and final session is scheduled for next month, with a report due in August. On the agenda are proposals that would streamline the Byzantine NRC structure, raise additional revenue from state governments and other nonfederal sources, and extend its influence beyond its bread-and-butter reports on topics ranging from defending the country against nuclear attacks to improving minority health care.

"It's not going to be simple to get members to recognize that changes will be good."

—Bruce Alberts

"It won't be wallpaper," predicts Mary Jane Osborn, a microbiologist at the University of Connecticut Health Center in Farmington and a member of the task force. But neither will it be as radical as the last review, instituted by then–NAS president Frank Press in 1981, that redrew the entire NRC map. "The layers of approval [for individual NRC reports] need streamlining, not removal," says NAS president Bruce Alberts, who also chairs the NRC.

There is widespread agreement that some sort of an overhaul is long overdue. The NRC, created in 1916, produces about 200 reports a year with help from a full-time staff of about 1000. However, its revenues—