Ewe Again? Cloning from Adult DNA

Udderly amazing. Scientists have for the first time used DNA from an adult mammal—specifically, genetic material from cells in the mammary glands of a 6-year-old ewe—to create a genetic duplicate. This clone, a healthy lamb named Dolly, was born last July, Ian Wilmut of the Roslin Institute in Edinburgh, Scotland, and his colleagues announce in the Feb. 27 NATURE.

The spectacular feat builds upon cloning research dating back to the early 1980s. At that time, scientists developed a procedure called nuclear transfer that enables them to replace the DNA-containing nucleus of an egg cell with a nucleus from another cell. Researchers soon found that the altered egg could develop into a clone of the animal that provided the nucleus—but only if the nucleus came from a cell of a barely developed embryo. Cloning attempts using nuclei from adult animals invariably failed.

Last year, Wilmut and his coworkers described a modified nuclear transfer method that allowed them to clone sheep from older embryonic cells (SN: 3/9/96, p. 148). By maintaining the intended donor cells in a nutrient-deprived medium, the scientists forced the cells out of their normal growth cycle and into a quiescent stage called G0. For reasons still under study, nuclei from these cells are more readily accepted by eggs.

With the birth of Dolly, Wilmut's group has now proved that at least some adult cells prepared in the same manner can generate a viable clone when their nuclei are transferred to eggs.

Many biologists had concluded that this was impossible, speculating that the DNA inside the nuclei of adult cells undergoes irreversible changes as the cells mature into the specialized roles they perform—secreting milk, for example. Yet Dolly's birth shows that the DNA in an adult nucleus either reprograms itself or is open to reprogramming by factors in the egg.

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Dolly the clone.

Exactly how the adult DNA changes once inside the egg is one of many fundamental biology questions raised by the birth of Dolly. The clone may also provide insight into whether a nucleus harbors a genetic clock that determines how old an organism is.

"Our 7-month-old lamb actually has a 6-year, 7-month-old nucleus in all her cells. It's going to be interesting to see what happens with the aging of this animal," notes Grahame Bulfield, director of the Roslin Institute.

More immediate research priorities, he says, are to determine whether other types of adult cells—liver, muscle, or brain cells, for example—can also generate clones, whether the same cloning process works in cattle and pigs, and whether researchers can add or delete genes from the donor cells before generating clones from them.

The latter issue will be key to the scientists' goals of using cloning to create animals that produce valuable pharmaceuticals in their milk or whose organs can be transplanted into people without being rejected.

Dolly's birth has also generated a predictable debate about the feasibility and morality of cloning humans. In response, President Bill Clinton has directed the new National Bioethics Advisory Commission to prepare a report examining the ramifications of the Scottish cloning technology.

"It's a pretty shocking change in the way we have to think about biology," observes Jeffrey Kahn, director of the Center for Bioethics at the University of Minnesota in Minneapolis. —*J. Travis*

Potent toxin complicates heart repair

Each year, heart surgeons in the United States plunge their gloved hands into 350,000 chests to fix faulty plumbing by replacing bad heart valves or bypassing blocked coronary arteries.

Although mortality from the surgery remains low, about 4 percent, complications are common. Yet many of these crises—infections, lung damage, and kidney collapse, among them—seem unrelated to the heart, and doctors have long wondered why they occur.

Now, a study done at Duke University Medical Center in Durham, N.C., indicates that people with low concentrations of an antibody called IgM EndoCAb are more likely to suffer these complications than people with higher amounts of this antibody.

"This is one of the first big studies that suggests that the immune system is important in how people do after surgery," says Elliott Bennett-Guerrero of Mount Sinai Medical Center in New York.

The research, published in the Feb. 26 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, stitches together an earlier observation that some patients suffer inflammation disproportionate to their surgical trauma and a theory that complications may be caused by a bacterial toxin.

Called endotoxin, the substance is made of pieces of the bacterial cell wall. Although the normal gut safely harbors 25 grams of endotoxin sloughed off by dead bacteria, the substance is so potent that even a tiny leak can cause blood poisoning. Doctors believe that such leaks may occur during surgery, when the gut loses blood, causing tiny holes to appear in the gut wall.

Bennett-Guerrero, formerly of Duke, and his colleagues decided to test whether a person's defenses against endotoxin influence the outcome of surgery. They recruited 301 volunteers scheduled to undergo heart surgery at Duke; 34 of the patients subsequently experienced major complications, and 10 died while in the hospital.

Before surgery, the doctors had removed samples of the patients' blood—which contains antibody-producing white blood cells—to test for total antibody concentrations and for two antibodies to the endotoxins of four species of bacteria: *Escherichia coli, Pseudomonas aeruginosa, Klebsiella aerogenes,* and *Salmonella typhimurium.*

The tests showed that just 3.7 percent of the patients with the greatest concentrations of the endotoxin antibody IgM EndoCAb had major complications, compared to 23 percent of those with the lowest amounts. Indeed, this antibody proved a better measure of risk than the amount of the second antibody to endotoxins, total antibody counts, or a profile of 19 standard surgical risks.

"What's so powerful about the study is that we showed IgM EndoCAb is an independent predictor of complications," Bennett-Guerrero says.

"I'm intrigued by this," says Robert G. Johnson of Harvard University. "It's a logical study and a nice step in a new direction." —*S. Sternberg*