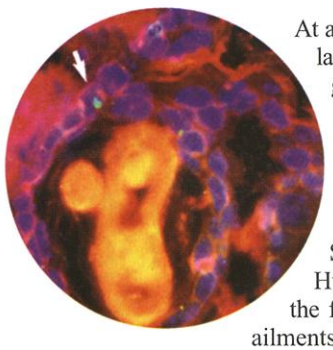
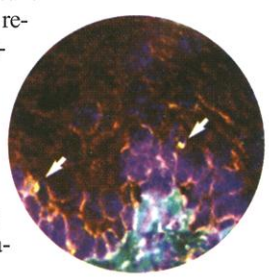
In the political debate over the use of embryonic stem cells, some opponents claim that malleable adult cells can take the place of their embryonic cousins. Many scientists aren't so sure

Can Adult Stem Cells Suffice?



At a U.S. Senate hearing last month, a lobbying group passed out a flyer to reporters and congressional staff members entitled "Current Clinical Use of Adult Stem Cells to Help Human Patients." On the front it lists a dozen ailments, including autoimmune diseases, anemia, and cancer, all of which have been treated with stem cells derived from bone marrow or other tissues. At the bottom, the flyer reads: "Other side of page: complete list of conditions for which embryonic stem cells are in clinical use to help human patients." The other side, of course, is blank. The flyer is correct—but misleading. Adult bone marrow cells, at least, have been in use for more than a decade, whereas human embryonic stem (ES) cells were isolated for the first time just 3 years ago.

The group behind the flyer, called the Coalition of Americans for Research Ethics, believes research using embryos is immoral and unnecessary. To bolster their case, they cite recent papers that demonstrate the often surprising flexibility of stem cells found in a variety of adult tissues, from human fat, placenta, and even dead brains.



But most scientists in the field—including those who work with adult-derived cells—caution that recent advances, although promising, do not mean that adult cells can replace the need for those derived from embryos or fetal tissue. For some diseases, they say, adult cells may indeed turn out to be the better choice. But for other applications, embryo-derived cells have some distinct advantages. Scientists working mostly with ES cells derived from mice have found that they multiply more readily in the lab than do their adult counterparts, providing as many cells as needed, and they seem far more proficient in producing certain specialized cell types, such as dopamine-producing neurons and insulin-producing cells. "It's incorrect to say that these published papers show that the adult cells are equivalent to embryonic stem cells for treating diabetes and Parkinson's," says Ron McKay of the National Institute of Neurological Disorders and Stroke (NINDS) in Bethesda, Maryland.

This scientific dispute over the relative merits of embryonic versus adult stem cells might seem arcane, but it is at the heart of raging political debates in several countries, including Germany (see p. 1811) and the United States. In Washington, the Bush Administration is weighing whether to let the National Institutes of Health go forward with its plan to fund studies of human embryonic and fetal stem cells. Both sides are lobbying hard.

Fat and Frankenstein

Both types of cells could prove to be a tremendous boon to medicine. Eventually, scientists would like to use stem cells to replace damaged or worn-out tissues—for instance, to treat paralyzing spinal cord injuries. This might work if scientists can figure out how to guide the growth of stem cells—immature cells that can replicate themselves and give rise to mature daughter cells. The stem cells themselves are found in many tissues in the body and also in developing embryos and fetuses. Those isolated from embryos are pluripotent—meaning that, with the correct cues, they can give rise to any kind of cell in the body. Stem cells in adult tissue are often multipotent—they can produce many, but not all, cell types.

For many years scientists assumed that development was a one-way street: Once committed, cells lost the ability to turn back. Only embryonic cells, they believed, had the power to develop into any desired cell type. But over the past several years, that assumption has been debunked as dozens of studies have shown that cells from the brain could become blood cells, for example, and vice versa.

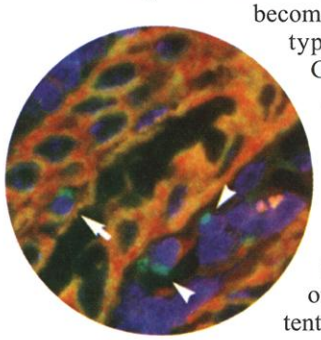
One recent paper captured the public's imagination as few others have. In the April issue of *Tissue Engineering*, surgeon Marc Hedrick of the University of California, Los Angeles, and his colleagues reported that fat cells isolated after liposuction could become cells resembling cartilage, bone, and muscle. The paper has prompted numerous sound bites, with several politicians volunteering to give up some of their fat to further research. But although the image of liposuction as an altruistic operation might be attractive, developmental biologist Douglas Melton of Harvard University says the study leaves several key questions unanswered. He speculates, for instance, that the team may have cultured a circulating hematopoietic stem cell, rather than a fat cell. That may be so, says co-author Adam Katz of the University of Pittsburgh, but he suspects people will prefer liposuction to bone marrow donation any day.

Cell biologist Bruce Spiegelman of the Dana-Farber Cancer Institute in Boston is

CREDITS: (ILLUSTRATION) TERRY SMITH; (MICROGRAPHS) KRAUSE *ET AL.*, *CELL* **105**, 369 (4 MAY 2001)

similarly circumspect. He points out that the four cell types the team described—fat, cartilage, muscle, and bone—are all part of the mesenchymal cell family and have already been derived from several stem cell sources. The paper reports no sign that the cells could become nerve cells or the much-sought-after pancreatic cells. Fat cells might be abundant, Spiegelman says, but "they are a far cry from being the answer to everything we need."

The next paper to make a major splash described isolating stem cells from cadavers. "Frankenstein cells," several headlines proclaimed. As described in the 3 May issue of *Nature*, neuroscientist Fred Gage of the Salk Institute for Biological Studies in La Jolla, California, and his colleagues cultured neural progenitor cells from brain tissue taken from cadavers shortly after death. Gage notes that the team members were careful to call their cells neural "progenitors" instead of neural "stem cells." The cells could divide and differentiate in culture, but the team didn't show that they could both replicate themselves and produce mature daughter cells—the true test of a bona fide stem cell. The cells also had a limited lifetime in culture—a major disadvantage for scientists trying to coax cells to become a particular tissue type. In short, says Gage, the technique is a long way from clinical application.



At least two companies have announced—but not published—that they have identified or produced pluripotent cells without using embryos or fetal tissue. Although the claims got plenty of play in the press, most stem cell scientists are dubious. In April, a company called Anthrogenesis, located in Cedar Knolls, New Jersey, announced via a telephone press conference that it had isolated stem cells from human placentas that might be the equivalent of human pluripotent stem cells. These placental cells can differentiate into nerves and blood vessels, the company says, although chief scientific officer Robert Hariri says they are still characterizing the cells. "These claims ... were just absolutely absurd," says John Gearhart of Johns Hopkins University, who isolated pluripotent stem cells from fetal tissue in late 1998. "If you don't have published research reports, how are [colleagues] supposed to judge a claim?" Hariri says the company has submitted several papers describing the cells, although none have been published yet.

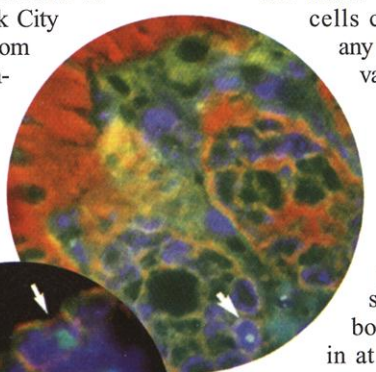
And PPL Therapeutics, based in Edinburgh, U.K., and Blacksburg, Virginia, says that its scientists have generated "pluripotent" cells from bovine skin cells. Company managing director Ron James announced the claim at a meeting in February but said researchers will not present their work in detail until they have secured a patent—a process that could take nearly a year, according to PPL scientist David Ayares.

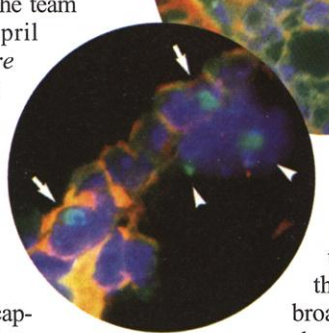
Strong signs from bones

In one tissue, at least, scientists agree that the results are encouraging. In the past few months, a series of papers has strengthened the idea that cells in the bone marrow can respond to cues from damaged tissue and help repair it. Until recently, doctors had only attempted to use bone marrow stem cells to reconstitute the blood or immune system.

But late last year, two teams reported that mouse cells derived from bone marrow could become neuronlike cells (*Science*, 1 December 2000, pp. 1775 and 1779). In April, another two groups reported that bone marrow–derived cells could help repair damaged heart muscle. In one study, Piero Anversa of New York Medical College in Valhalla and Donald Orlic of the National Human Genome Research Institute in Bethesda, Maryland, induced heart attack–like damage in 30 mice. They then injected the bone marrow cells into surviving heart tissue. Nine days after the injection, the transplanted cells were forming new heart tissue—muscle cells as well as blood vessels—in 12 of the 30 mice, the team reported in the 5 April issue of *Nature*.

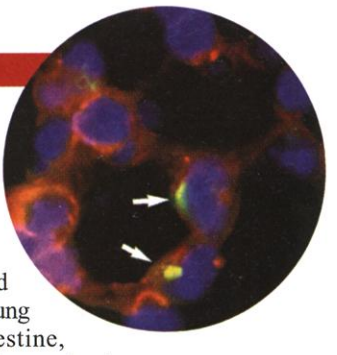
In the other study, Silviu Itescu of Columbia University in New York City and his colleagues isolated cells from the bone marrow of human volunteers, then injected the cells into the bloodstream of rats in which the team had induced heart attacks. Signals from the damaged heart evidently attracted the transplanted cells, the team reported in the April issue of *Nature Medicine*; 2 weeks after the injection, capillaries made of human cells accounted for up to a quarter of the capillaries in the heart. Four months after the operation, rats that received the blood vessel precursors had significantly less scar tissue—and better heart function—than control rats.





Multiple destinations. Bone marrow–derived cells are indicated by arrows in these false-color images of tissues. Left to right: skin, esophagus, stomach, bile duct, colon, and lung.

Perhaps most impressive, in the 4 May issue of *Cell*, scientists reported that a single cell from the bone marrow of an adult mouse can multiply and contribute to the lung tissue, liver, intestine, and skin of experimental mice.



Researchers knew that a tiny subset of cells purified from bone marrow had the potential to multiply and give rise to all the blood cell types, but isolating those cells has been very difficult. To increase their chances of capturing the elusive cells, Diane Krause of Yale University School of Medicine and Neil Theise of New York University Medical School and their colleagues performed a double bone marrow transplant. They first injected bone marrow cells from a male mouse, tagged with green fluorescent protein, into the bloodstream of female mice that had received a lethal dose of radiation. Two days later, they killed the recipient mice and isolated a handful of green-tagged cells that had taken up residence in the bone marrow. (Previous studies had suggested that the most primitive transplanted cells lodge in bone marrow.) They then injected irradiated mice with just one of the green-tagged cells accompanied by untagged, female-derived bone marrow cells that survive about a month. When the scientists killed the surviving mice 11 months after the second transplant, they found progeny from the cells in lung, skin, intestine, and liver as well as bone and blood. "Bone marrow stem cells can probably form any cell type," says Harvard's Melton.

Even so, Krause says her work highlights the need for more work on ES cells rather than suggesting a replacement: "We basically have a black box. We put the cells in at the beginning and look at the mice" several months later. Because only six of the 30 mice that received a single-cell transplant survived, Krause estimates that one-fifth of cells harvested from the first transplant recipients have such broad potential. The scientists don't know why the most versatile cells go to the bone marrow in the first transplant, nor can they predict which ones might have the potential to multiply and differentiate.

Melton also notes that cells from bone marrow have one major drawback: Although they are fairly easy to collect from donors,

CREDITS: KRAUSE *ET AL.*, *CELL* **105**, 369 (4 MAY 2001)

the cells do not grow well outside the body—and not for lack of trying. "Biotech companies have spent tens of millions of dollars on that problem," Melton says. "I don't think it's going to happen very easily."

Elusive islets

One of the most sought-after commodities is pancreatic islet cells—potentially the key to treating type I diabetes. Researchers are trying both embryonic and adult cells and arguing over which is most likely to pay off. The fragile pancreatic islets respond to changes in blood sugar and produce insulin, one of the key hormones that regulate metabolism. In type I diabetes, the immune system attacks and destroys the cells, leaving patients dependent on frequent injections of insulin and vulnerable to serious side effects.

A few teams have reported success in growing insulin-producing cells in the laboratory from precursor cells present in the pancreas of both adult mice and humans. Last year, Ammon Peck and his colleagues at the University of Florida, Gainesville, and Ixion Biotechnology in Alachua, Florida, did so with cells from adult mice. When they transplanted some of these lab-derived cells into three diabetic mice, two survived without insulin injections for 3 months. Last July, Susan Bonner-Weir and her colleagues reported in the *Proceedings of the National Academy of Sciences* that they had succeeded in growing insulin-producing cells from adult human pancreas cells. But NINDS's McKay cautions that the numbers in both papers are small. "There are interesting cells that you can get out of the adult pancreas. They may indeed generate [useful cells], ... but right now, the evidence for that is really very thin." Peck says he is confident his technique works. He and his colleagues are working to repeat the experiments in dogs and in pigs.

Washington whispers. Supporters and opponents of research on embryonic stem cells are lobbying the White House.

McKay and his colleagues also recently described a method for turning mouse ES cells into pancreas-like cells that produced insulin in response to glucose, albeit just a fraction of the amount that mature cells produce (*Science*, 18 May, p. 1389).

Two are better than one

Most researchers say they need access to both embryonic and adult stem cells. McKay points out that embryonic cells have one huge advantage over adult-derived cells: their ability to divide in culture. "The ES cell will be the basis for how you will get large numbers of cells," he says. Gearhart of Johns Hopkins adds that the ability of embryonic and fetal cells to divide in the lab makes them a vital tool for learning how differentiating cells behave. "Answers to the problems of how you would do things with adult stem cells will probably come from the embryonic and fetal cells," he says. "There's no other way you're going to get that information."

But ES cells have plenty of limitations, too. For one, murine ES cells have a disturbing ability to form tumors, and researchers aren't yet sure how to counteract that. And so far reports of pure cell populations derived from either human or mouse ES cells are few and far between—fewer than those from adult cells.

Even if adult-derived cells do become the favorite for some treatments, such applications are years away, says McKay. The long-term consequences of stem cell therapies are completely unknown, as few animal studies have looked at results longer than a year after transplants. And scientists need to know more about the process of cell differentiation before anyone will be able to tell which cells hold the most hope for curing disease, McKay notes. "All of these cells," he says, "are partial solutions for the moment."

–GRETCHEN VOGEL

ILLUSTRATION: TERRY SMITH

An Embryonic Alternative

The rallying cry of those who oppose work with embryonic stem cells is that cells from adults are sufficient (see main text). But if scientists must study embryonic stem cells, they should focus on those from rhesus monkeys. That's the argument of Kevin Fitzgerald, a bioethicist at Loyola University Medical Center outside Chicago. Fitzgerald, a Jesuit priest who holds a Ph.D. in molecular genetics, is a founding member of the Coalition of Americans for Research Ethics, a group that lobbies against the use of human embryonic stem cells. Biologists can't draw a line somewhere after fertilization that marks the start of "human life," says Fitzgerald. "It's a spectrum all the way along. That's why the end- and beginning-of-life issues are so difficult." For that reason, he thinks that embryos deserve the same protection and respect as infants and so shouldn't be destroyed to obtain embryonic stem cells.

To determine the potential of stem cells, Fitzgerald suggests pushing ahead with work on adult stem cells and, for any embryonic studies, using primate cells. "We've skipped the somewhat obvious middle step: primate research," he says. Such cell lines already exist: Reproductive biologist James Thomson of the University of Wisconsin, Madison, derived embryonic stem cells from rhesus monkeys before he succeeded with human cells. Not only can monkey cells enable scientists to answer most fundamental questions without treading on shaky ethical ground, says Fitzgerald, but preclinical trials will have to be conducted, likely in monkeys, before any human trials begin.

Thomson agrees that primate studies will be critical before attempting stem cell therapies in humans. But he says that for basic studies it is far more efficient to use human cells. Mouse and human reagents are readily available, but "every time you want to work with the rhesus cells, you really have to reinvent the wheel." And with data from the human genome project now available, identifying key regulatory genes is much simpler in human cells than monkey cells, he says.

John Gearhart of Johns Hopkins University in Baltimore, who works with stem cells derived from fetal tissue, also doubts that primate cells will suffice. "One of Alexander Pope's maxims was, 'The proper study of mankind is man,' " he says. Rhesus cell lines "would be far preferable to mouse [lines]. ... Would they be sufficient? I don't have an answer to that." Research over the past 2 decades has turned up surprising differences in how various mouse stem cell lines behave. If such differences exist in human embryonic and fetal cell lines, scientists need to understand them as well, Gearhart says. So although there is clearly a place for primate cells, Gearhart, for one, will concentrate on human cells.

–G.V.