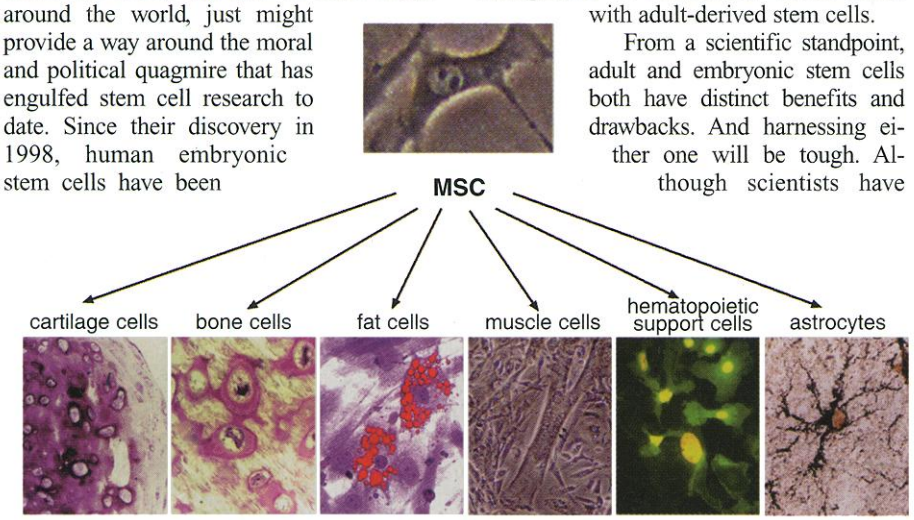
Can Old Cells Learn New Tricks?

Stem cells found in adults show surprising versatility. But it's not yet clear whether they can match the power of cells from embryos

Stem cell biologist Margaret Goodell has never seen her work on muscle and blood development as particularly political, so she was surprised when last month the Coalition of Americans for Research Ethics (CARE), a group that opposes the use of embryos in research, invited her to speak at a congressional briefing in Washington, D.C. She was even more astonished to find herself quoted by conservative columnist George Will a few weeks later.

Goodell gained this sudden notoriety because her work, and that of other teams around the world, just might provide a way around the moral and political quagmire that has engulfed stem cell research to date. Since their discovery in 1998, human embryonic stem cells have been one of the hottest scientific properties around. Because these cells can theoretically be coaxed to differentiate into any type of cell in the body, they open up tantalizing possibilities, such as lab-grown tissues or even replacement organs to treat a variety of human ills, from diabetes to Alzheimer's. Politically, however, human stem cells have been a much tougher sell, as they are derived from embryos or fetuses. Indeed, most research is on hold as policy-makers grapple with the ethics of human embryo research.



Multitalented. Mesenchymal stem cells (MSC) from adult bone marrow can become bone, cartilage, and even brain cells in lab culture.

Enter Goodell, whose work suggests that stem cells derived from *adults,* in this case, from mouse muscle biopsies, can perform many of the same tricks as embryonic stem (ES) cells can—but without the ethical baggage. Both CARE and George Will seized upon her work as an indication that research on ES cells could remain on hold with no appreciable loss to medicine. "There's a lot less moral ambiguity about the adult stem cells," says bioethicist and CARE member Kevin Fitzgerald of Loyola University Medical Center in Chicago.

But can adult stem cells really fulfill the same potential as embryonic stem cells can? At this stage, the answer is by no means clear. Indeed, scientists caution that it is too early to know if even ES cells will produce the cornucopia of new tissues and organs that some envision. "It is still early days in the human embryonic stem cell world," says stem cell biologist Daniel Marshak of Osiris Therapeutics in Baltimore, which works with adult-derived stem cells.

From a scientific standpoint, adult and embryonic stem cells both have distinct benefits and drawbacks. And harnessing either one will be tough. Although scientists have been working with mouse ES cells for 2 decades, most work has focused on creating transgenic mice rather than creating lab-grown tissues. Only a handful of groups around the world have discovered how to nudge the cells toward certain desired fates. But that work gained new prominence in late 1998, when two independent teams, led by James Thomson of the University of Wisconsin, Madison, and John Gearhart of The Johns Hopkins University, announced they could grow human stem cells in culture. Suddenly the work in mouse cells could be applied to human cells—in the hope of curing disease.

The beauty of embryonic stem cells lies in their malleability. One of their defining characteristics is their ability to differentiate into any cell type. Indeed, researchers have shown that they can get mouse ES cells to differentiate in lab culture into various tissues, including brain cells and pancreatic cells.

Studies with rodents also indicated that cells derived from ES cells could restore certain missing nerve functions, suggesting the possibility of treating neurological disorders. Last summer, Oliver Brüstle of the University of Bonn Medical Center and Ronald McKay of the U.S. National Institute of Neurological Disorders and Stroke and their colleagues reported that they could coax mouse ES cells to become glial cells, a type of neuronal support cell that produces the neuron-protecting myelin sheath. When the team then injected these cells into the brains of mice that lacked myelin, the transplants produced normal-looking myelin (*Science*, 30 July 1999, p. 754). And in December, a team led by Dennis Choi and John McDonald at Washington University School of Medicine in St. Louis showed that immature nerve cells that were generated from mouse ES cells and transplanted into the damaged spinal cords of rats partially restored the animals' spinal cord function (*Science*, 3 December 1999, p. 1826). Although no one has yet published evidence that human ES cells can achieve similar feats, Gearhart says he is working with several groups at Johns Hopkins to test the abilities of his cells in animal models of spinal cord injury and neurodegenerative diseases, including amyotrophic lateral sclerosis and Parkinson's disease.

While Gearhart and his colleagues were grappling with ES cells, Goodell and others were concentrating on adult stem cells. Conventional wisdom had assumed that once a cell had been programmed to produce a particular tissue, its fate was sealed, and it could not reprogram itself to make another tissue. But in the last year, a number of studies have surprised scientists by showing that stem cells from one tissue, such as brain, could change into another, such as blood (*Science*, 22 January 1999, p. 534). Evidence is mounting that the findings are not aberrations but may signal the unexpected power of adult stem cells. For example, Goodell and her colleagues, prompted by the discovery of blood-forming brain cells, found that cells from mouse muscle could repopulate the bloodstream and rescue mice that had received an otherwise lethal dose of radiation.

Bone marrow stem cells may be even more versatile. At the American Society of Hematology meeting in December, hematologist Catherine Verfaillie of the University of Minnesota, Minneapolis, reported that she has isolated cells from the bone marrow of children and adults that seem to have an amazing range of abilities. For instance, Verfaillie and graduate student Morayma

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Reyes have evidence that the cells can become brain cells and liver cell precursors, plus all three kinds of muscle—heart, skeletal, and smooth. "They are almost like ES cells," she says, in their ability to form different cell types.

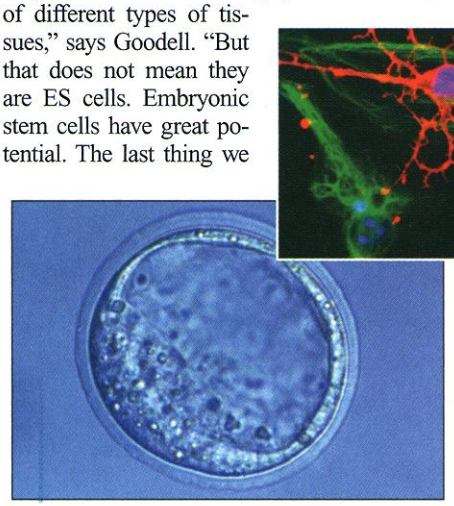
These malleable bone marrow cells are rare, Verfaillie admits. She estimates that perhaps 1 in 10 billion marrow cells has such versatility. And they are only recognizable by their abilities; the team has not yet found a molecular marker that distinguishes the unusually powerful cells from other bone marrow cells. Still, she says, her team has isolated "a handful" of such cells from 80% of the bone marrow samples they've taken. Although the versatile cells are more plentiful in children, Verfaillie's team has also found them in donors between 45 and 50 years old.

Verfaillie's work has not yet been published nor her observations replicated. Even so, many researchers are excited by the work. The cells "look extremely interesting," says hematologist and stem cell researcher Leonard Zon of Children's Hospital in Boston. Stem cell biologist Ihor Lemischka of Princeton University agrees. "I'm very intrigued," he says, although he cautions that data from one lab should not outweigh the decades of research on mouse ES cells.

Besides skirting the ethical dilemmas surrounding research on embryonic and fetal stem cells, adult cells like Verfaillie's might have another advantage: They may be easier to manage. ES cells tend to differentiate spontaneously into all kinds of tissue. When injected under the skin of immune-compromised mice, for example, they grow into teratomas—tumors consisting of numerous cell types, from gut to skin. Before applying the cells in human disease, researchers will have to learn how to get them to produce only the desired cell types. "You don't want teeth or bone in your brain. You don't want muscle in your liver," says stem cell researcher Evan Snyder of Children's Hospital in Boston. In contrast, Verfaillie says her cells are "better behaved." They do not spontaneously differentiate but can be induced to do so by applying appropriate growth factors or other external cues.

Adult stem cells have a drawback, however, in that some seem to lose their ability to divide and differentiate after a time in culture. This short life-span might make them unsuitable for some medical applications. By contrast, mouse ES cells have a long track record in the lab, says Goodell, and so far it seems that they "are truly infinite in their capacity to divide. There are [mouse] cell lines that have been around for 10 years, and there is no evidence that they have lost their 'stem cell–ness' or their potency," she says.

For these and other reasons, many researchers say, adult-derived stem cells are not going to be an exact substitute for embryonic or fetal cells. "There are adult cell types that may have the potential to repopulate a number of different types of tissues," says Goodell. "But that does not mean they are ES cells. Embryonic stem cells have great potential. The last thing we should do is restrict research." Right now, she says, stem cell specialists want to study both adult and embryonic stem cells to find out just what their capabilities might be.



Great expectations. Blastocysts, like this murine example, harbor embryonic stem (ES) cells that can become any tissue in the body. Inset shows oligodendrocytes (green) and astrocytes (red), derived from mouse ES cells.

That may be difficult. At the moment, human ES cells are unavailable to most researchers because of proprietary concerns (see next story) and the uncertain legal status of the cells. Internationally, most research on human ES cells is on hold while legislatures and funding agencies wrestle with the ethical issues. In the United States, the National Institutes of Health is the government agency that would fund the research, and currently, researchers are not allowed to use NIH funds for work with human ES cells. Many European countries, too, are still developing new policies on the use of the cells (see Viewpoint by Lenoir, p. 1425).

The final version of NIH's guidelines for use of embryonic and fetal stem cells will not appear before early summer, says Lana Skirboll, NIH associate director for science policy. The draft guidelines would allow use of NIH funds for ES cell research as long as the derivation of the cells, by private institutions, met certain ethical standards (*Science*, 10 December 1999, p. 2050). But several members of Congress are considering legislation that would overrule the guidelines and block federal funding of ES cell research. At least some of that debate is likely to focus on whether adult stem cells do in fact have the potential to do as much as their embryonic precursors.

–GRETCHEN VOGEL

NEWS

The Business of Stem Cells

Human stem cells have become one of the hottest areas in biotech as several companies have jumped in to try to exploit them commercially

When biologist James Thomson announced 15 months ago that he had grown human embryonic stem cells in a petri dish, scientists were excited about their potential uses in medicine. These cells, which are capable of developing into almost any other type of cell in the body, may one day provide an unlimited source of replacement tissues for treating human diseases. Some elected officials were less enthused, however; they were more concerned about the cells' source—human embryos. For now, at least, U.S. government rules that protect the embryo have put the cells off limits to most publicly funded researchers. But they aren't off limits for private companies. As a result, commercial enterprises now have the field almost exclusively to themselves.

One company, Geron Corp. of Menlo Park, California, has secured a commanding position. Geron not only bankrolled Thomson's work—gaining first rights to exploit the cells commercially—but it also funded the isolation of a second type of very early or "primordial" cell from human fetal tissue by John Gearhart of The Johns Hopkins University. Now, the company is gearing up an intensive research program aimed at turning both of these discoveries into therapeutic products. "We certainly have invested heavily" in the field, says Geron CEO and president Thomas Okarma, noting that exclusivity is the reward for "being smart and lucky."

While Geron has nabbed the early lead in exploiting embryonic and primordial fetal stem cells, almost a dozen other biotech firms are elbowing their way into a crowded field to develop therapies using so-called "adult" stem cells. Once thought to be less versatile than primordial stem cells because