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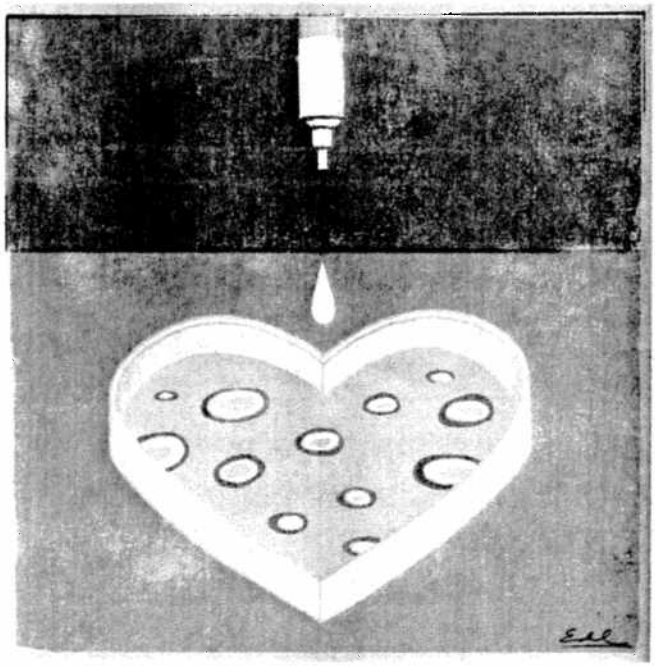
RESEARCH

Will Stem Cells Finally Deliver?

Major breakthroughs are propelling the field. Science becomes medicine.

MANY DISEASES INVOLVE THE DEATH OF CELLS THAT THE body cannot naturally replace. Sometimes cell death comes suddenly, as in a heart attack. Other times it is slow and inexorable, as in Alzheimer's disease. The great promise of stem cells—the body's equivalent of renewable energy—is that they could be coaxed into becoming and then replacing cells lost to disease.

But daunting scientific challenges, ethical concerns and even politics have slowed progress for more than a decade. In the past two years, however, a series of remarkable breakthroughs has advanced the field: suddenly, it appears possible to create cells with all the potential of embryonic stem cells without using embryos, eliminating most of the ethical concerns surrounding stem-cell research.



Embryonic stem cells have two extraordinary properties that make them, potentially, the most medically useful. First, they are "pluripotent," with the capacity to become any type of specialized cell in the body—a heart-muscle cell that pumps blood, an acid-producing cell in the stomach, a cell in the retina of your eye that sees light, or a brain cell that stores memories. Second, embryonic stem cells can keep dividing and making unlimited copies of themselves—an important property, since huge numbers of new cells may be needed to replace cells lost to disease.

Scientists have also been studying adult stem cells, work that doesn't raise the ethical questions posed by embryonic-stem-cell research because it doesn't involve the use of human embryos. Bone marrow and organs like the heart and liver all naturally contain adult stem cells. These cells have the potential to develop into most of the cells in their specific organ. Adult stem cells help replace specialized cells that have been killed, since most specialized cells cannot naturally reproduce themselves. However, adult stem cells in most organs cannot naturally repair the massive injury caused by many diseases, although scientists are working on ways to change that. Also, adult stem cells are not pluripotent: unlike embryonic stem cells, they cannot be turned into any cell in the body.

The remarkable properties of embryonic stem cells, however, are difficult to exploit. Ideally, a patient in need of stem cells would want his own genetically identical stem cells because they would not be attacked as foreign by his immune system. But embryonic stem cells exist only briefly, within the first two weeks after conception. And stem cells from embryos produced for in vitro fertilization programs would be genetically different from the patient, raising the risk that they would be rejected by the immune system and would therefore require potentially toxic treatments to suppress the immune response.

Such cells also raise ethical questions, since some people believe an embryo with the potential to be implanted and develop into a baby has the moral status of a person and should not be destroyed, no matter how great the human benefit. In 2001, President George W. Bush restricted federal funding to existing lines of embryonic stem cells; government money could not be used for research that involved the further destruction of embryos. (President-elect Obama has pledged to reverse that policy.)

A possible solution to these daunting obstacles came from a team of Japanese researchers who asked a simple, if fanciful, question: is it possible to turn a specialized cell back into an embryonic stem cell, or at least into a cell with the same remarkable properties as an embryonic stem cell? It's the genes within every cell that determine how that cell acts and looks. While all of our specialized cells and our embryonic stem cells share exactly the same set of genes, very different genes are "turned on" in each type of cell. In other words, an embryonic stem cell turns into a specialized cell because certain genes are turned on, and others turned off.

In 2006, researchers led by Shinya Yamanaka from Kyoto University used a powerful and relatively new technology that can determine, in a particular type of cell, which of that cell's genes are turned on and off. Using this technology to study embryonic stem cells and specialized cells, Yamanaka's team identified a handful of genes in mice that are uniquely turned on in embryonic stem cells but not in specialized cells. Then in late 2007, Yamanaka's group and American teams led by James Thomson at the University of Wisconsin and George

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Daley of Harvard showed that turning on four of these genes in human skin cells caused those cells to revert to cells like embryonic stem cells. They called these new cells induced pluripotent stem (iPS) cells. Just like embryonic stem cells, the iPS cells could be transformed into any type of specialized cell, and reproduce copies of themselves indefinitely.

Thus, it now was theoretically possible to create, for anyone, their own stem cells, genetically identical and with all the potential of their own long-lost embryonic stem cells. Moreover, the adult cells to be transformed into iPS cells could be easily obtained from a skin biopsy, or even from the cells at the end of a plucked strand of hair. Most remarkably, the iPS cells could be generated without ever having to create or destroy an embryo, overcoming the moral objections to the use of embryonic stem cells.

As important as we think it is, this breakthrough does not mean human iPS cell therapy is just around the corner. Important questions remain to be answered, and new technologies need to be developed. The ability of cells in a laboratory dish to be turned into any type of cell is no guarantee that such cells will successfully treat a disease in a living animal or human. Yet, Rudolf Jaenisch at the Whitehead Institute and MIT has shown that iPS cells can successfully treat sickle-cell anemia in mice and Parkinson's disease in rats. What works in rodents doesn't always work in humans, but it often does.

Also, two of the four genes used in the original "cocktail" to create iPS cells are oncogenes that have the potential to turn the iPS cells cancerous. (The genes were used because they were among those naturally turned on in embryonic stem cells.) Moreover, a retrovirus was used to carry those four genes into the specialized cell, but this also carries a risk of turning the iPS cells cancerous. However, in late 2008, scientists reported that iPS cells could be created without the use either of oncogenes or a retrovirus. In 2009, many laboratories will be working on finding modifications to the current techniques that make human iPS cells both safer and more effective.

Another potential problem: how can iPS cells created in a laboratory dish reliably find their way into a diseased organ deep inside the body? And once there, will they "hook up" with the healthy cells in that organ to work in harmony with them? These are important and unanswered questions. One thing scientists have learned from bone-marrow transplantation—a type of stem-cell therapy widely used for 30 years—is that cells injected into the bloodstream can "home" to their proper place in the body, and once in place can respond to signals from the cells around them to work harmoniously. Still, this could be a daunting problem for some organs. Take the heart, for example. Suppose, after a heart attack that killed millions of heart-muscle cells, that millions of new "personalized" replacement heart-muscle cells created from your iPS cells were infused into your bloodstream. Would they find their way to your heart? If so, would they line up in the right position, and would they beat at the same time the old healthy heart cells were beating? If not, might they cause chaotic heart rhythms? If they landed in another organ besides the heart, would they cause damage there? Trial and error, first in animals and then in humans, is the only way to find out.

Most remarkably, the new type of stem cells can be generated without ever having to create or destroy an embryo.

Besides treatment, iPS cells may also help in the search for the cause of disease. Several teams of scientists at Harvard have now created iPS cells from patients with different genetically based conditions, including Lou Gehrig's disease or ALS, Parkinson's, Huntington's and type 1 diabetes. Since iPS cells can reproduce indefinitely, large numbers of cells carrying the genetic flaws that lead to these illnesses are being produced and studied. In the case of ALS, for example, scientists created iPS cells and then transformed them into the nerve cells that are destroyed by that disease. They are using these cells to screen for drugs that might counter the effects of ALS.

Researchers also wonder if it might be possible someday to trick one type of specialized adult cell into becoming another type—without even having to create iPS cells. Such an advance seemed farfetched until August of this year, when a team led by Harvard's Douglas Melton transformed non-insulin-producing pancreatic cells into insulin-producing cells inside living mice, treating diabetes.

If there is any lesson to be learned from the breathtaking events of the past two years it is that discoveries are unpredictable. Transforming stem-cell science into stem-cell medicine is the kind of enterprise that requires creativity and patience, and partnerships between universities, government and industry. It is the kind of innovative work at which America excels. Indeed, stem-cell medicine may be one way that American enterprise makes its mark on the future of medical care.

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