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Some Scientists See Shift in Stem Cell Hopes

By NICHOLAS WADE

In the five years since President Bush authorized and at the same time restricted research on human embryonic stem cells, a marked shift has taken place in some scientists' views of how the research is likely to benefit medicine. Many no longer see cell therapy as the first goal of the research, parting company with those whose near-term expectations for cell therapy remain high.

Instead, these researchers envisage a longer-term program in which human embryonic cells would be a research tool to study the mechanisms of disease. From this, they say, many therapeutic benefits may emerge, like new drugs, which would probably be available at least as soon as any cell therapy treatment.

Mr. Bush announced on Aug. 9, 2001, that government-financed researchers would be unable to work with human embryonic stem cells because the Dickey Amendment barred federal support for any research in which an embryo was destroyed. As a political compromise, Mr. Bush allowed research to proceed, but only with stem cell lines that were already established. Mr. Bush sustained his position last month by vetoing a bill that would allow research with new cell lines.

The approved cell lines, though regarded by many scientists as unusable for medical treatment and insufficient for many research purposes, have allowed a first round of experimentation. Work since 2001 has produced no significant advance, but has enabled a preliminary assessment of the field's possibilities. Many researchers now see human embryonic stem cells as part of a long-term research program, with any sort of cell therapy being at least 5 or 10 years off.

That projection shows a gap between scientists' views and those of the public and of people for whom the overriding purpose of research with human embryonic stem cells is to generate cells that can restore damaged tissues.

Thomas M. Jessell, a neurobiologist at Columbia University Medical Center in New York, said that he hoped to see the research generate new drugs for neurodegenerative diseases within the next five years but that it could be a long time before rational cell-based therapies are effective.

“Many of us feel that for the next few years the most rational way forward is not to try to push cell therapies,” Dr. Jessell said. Scientists have spent the last five years mostly in learning how to grow human embryonic stem cells in the laboratory and how to make them differentiate, meaning to turn into the body’s various types of mature cells.

Dr. Ron McKay, a stem cell researcher at the National Institutes of Health, said, “Progress has been mostly incremental, but it is clear that human embryonic stem cells can differentiate” to cells of the sort that might be useful in therapy.

Government policy has slowed research with human embryonic stem cells in many ways, scientists say. To work with unapproved lines, government-supported researchers must not only raise private money but also keep their government-financed work separate from their work on unapproved stem cell lines.

Christopher E. Henderson, a neurobiologist at Columbia University Medical Center, said his government-supported students were not allowed to visit the lab where he worked with unapproved cell lines, lest they opened the center to prosecution by contributing government-gained knowledge to the private work.

This segregation of effort makes it much harder to integrate research on human cells with other relevant research, much of which is done first in animals and then needs to be cross-checked in human cells, said Dr. Arnold R. Kriegstein, director of stem cell biology at the University of California, San Francisco. “Doing things in parallel would work much better,” Dr. Kriegstein said.

The hope of using human embryonic stem cells for cell therapy has been driven in part by the great success of bone marrow transplants, in which a patient’s blood supply is regenerated from his own blood-making stem cells. But these cells are different from embryonic cells; they already exist in the adult body. Bone marrow

transplants are “a special case, but the general applicability of that to any other disorder is a very big step,” Dr. Jessell said.

Dr. Henderson added, “We all thought cell therapy first, then many of us realized there were a lot of hurdles to be crossed before that.”

Making the embryonic stem cells convert in the laboratory into specialized types — like liver or heart cells — is not straightforward or predictable. Cells that look and behave like human muscle-activating neurons can be generated with just a couple of chemical signals. But some cells, like the insulin-making cells of the pancreas, have proved extremely hard to grow.

Besides the technical difficulty of growing the precise type of cell needed for cell therapy, researchers face the theoretical problem that new replacement cells are likely to be vulnerable to the same disease that killed the patient’s cells in the first place. Ideally, a disease process must be understood and arrested before new cells are introduced.

Many researchers have come to see the primary benefit of human embryonic stem cells as models for human disease. The idea is to take a cell from a patient, convert it to embryonic form, and then make the embryonic cell mature into the type that goes awry in the patient’s disease, whether it be a dopamine-producing cell for Parkinson’s disease or an insulin-making cell for diabetes.

Somewhere down this developmental path, the basic cause of the disease may emerge, and be available for study in a dish of cells. The diseased cells should also provide an excellent means of screening thousands of chemicals for new drugs.

“Stem cell biology is just a rubric that applies to many things going on in biology,” said John D. Gearhart, a Johns Hopkins University stem cell expert. “I personally feel that the beauty of these cells is that we’ll learn a lot about human biology and disease processes, and that that information will be more important than the cells themselves.”

Researchers have not, however, abandoned cell therapy, in which cells themselves would be used to regenerate tissue. In Parkinson’s disease, for example, dopamine-producing cells from aborted

fetuses, when injected into the brains of Parkinson's patients, do have an effect, suggesting that a better source of cell could have therapeutic value. "So it's the perfect place to go in," said Dr. Asa Abeliovich of Columbia University Medical Center. Dr. Abeliovich said that with Alzheimer's disease, in contrast, "We don't know how or what to replace."

Cell therapy requires making a stem cell from an embryo develop in the laboratory into a heart or liver cell or whatever tissue needs replacing. So far it seems that some cell types are easier to generate in the laboratory than others. "For some tissues we are doing extremely well, and for others we're really hurting because we don't know enough about the early stages of differentiation," Dr. Gearhart said.

Other uncertainties remain. In the developing embryo, cells are exposed to a succession of new signals as they progress down a long path from embryonic state to their mature fate. Researchers cannot recapitulate that exact journey in the laboratory because many of the signals are unknown. They hope that they can use shortcuts, and indeed by using just a few known signals, they can reproduce heart cells and some neuron cells that look and appear to act like their natural counterparts.

But it is not yet certain if mature cells grown in a laboratory will possess all the information they need to behave properly when introduced into a patient's body.

For the dopamine-producing cells of Parkinson's, "We cannot recapitulate the entire developmental program because the rest of the brain is already there," said Dr. Abeliovich. "It's more interesting to hypothesize that there are ways to get around this, and ask what they might be."

Dr. Evan Snyder, director of the stem cell program at the Burnham Institute in San Diego, added that with some diseases "we initially hoped we could leapfrog over certain developmental steps."

But that has changed.

"We are starting to learn that doesn't always work," Dr. Snyder said.