

# Regenerating the body



by Karen Burbach

Salamanders can do something humans can't. They can grow back legs, tails, part of their heart and the retinas and lenses in their eyes.

Now, scientists around the world are exploring ways humans can be more like salamanders. They are researching how to repair or restore diseased or damaged tissue using the body's own healthy cells.

That effort – led by stem cell applications – is the next step in the new world of regenerative medicine.

If it works in humans – as it has in some animal models – scientists may unlock the key to repairing tissue damage caused by trauma, disease or aging.

“Stem cell therapy has tremendous potential for treatment of diseases that we really can't treat at the present time,” said Stephen Rennard, M.D., Larson Professor of Medicine at UNMC.

Stem cells are the building blocks that form any organ. Scientists are amazed by their unique ability to “renew” themselves while also dividing to produce the more specialized cells that do the work of the body. When a stem cell divides or differentiates, each new cell has the potential to either remain a stem cell or become one of more than 200 specialized cells in the body, such as a muscle cell, red blood cell, or brain cell.

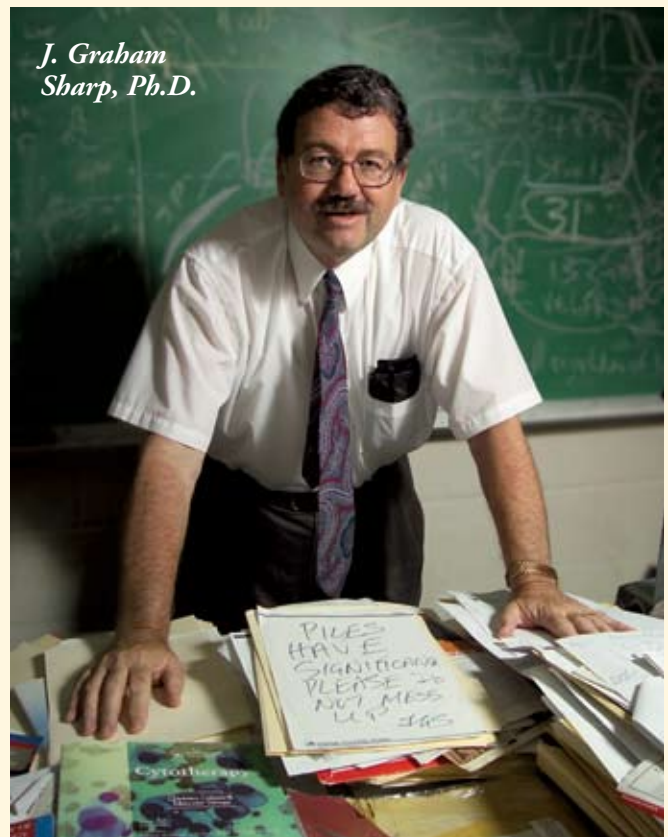
“Advances in biomedical research in the first 50 years of the 21st century will be based upon advances in stem cell technology,” said Tom Rosenquist, Ph.D., vice chancellor for research.

If that “magical” transformation can be better understood, stem cells – whether they are derived from adult tissues or the earliest cellular forms – could revolutionize how we treat a myriad of diseases, conditions and disabilities including emphysema, Parkinson's, spinal cord injuries, stroke, burns, heart disease, diabetes, liver and kidney disease, osteoarthritis and rheumatoid arthritis.

“Our goal is to understand stem cells from embryonic to tissue-specific, so that we can figure out how to make our own cells regenerate,” said Ira Fox, M.D., Charles W. McLaughlin Professor of Surgery, senior associate dean for research and development in the UNMC College of Medicine and one of two UNMC scientists working with the federally-approved embryonic stem cell lines. “To do that we have to understand the natural history of the disease we are studying, the cells responsible for causing the disease and the normal development of the diseased organ. Whether you pick diabetes, heart disease or neuroscience, somehow, understanding the role of stem cells will come up in the conversation.”

Scientists have worked with adult stem cells for the past 40 years. The medical center and Margaret Kessinger, M.D., are pioneers in the

J. Graham Sharp, Ph.D.



field of peripheral stem cell transplantation. In the 1980s, Dr. Kessinger postulated that immature bone marrow stem cells, which circulate in the bloodstream, could be harvested from the peripheral blood and used as a bone marrow rescue technique for patients who underwent high-dose chemotherapy or radiation capable of destroying bone marrow function.

Over time, her clinical studies proved the reinfused stem cells not only restored marrow function, but also restored it faster than in bone marrow transplants. The procedure for peripheral stem cell transplantation has now become standard practice worldwide.

Blood stem cells are routinely used for bone marrow transplants to successfully treat cancer

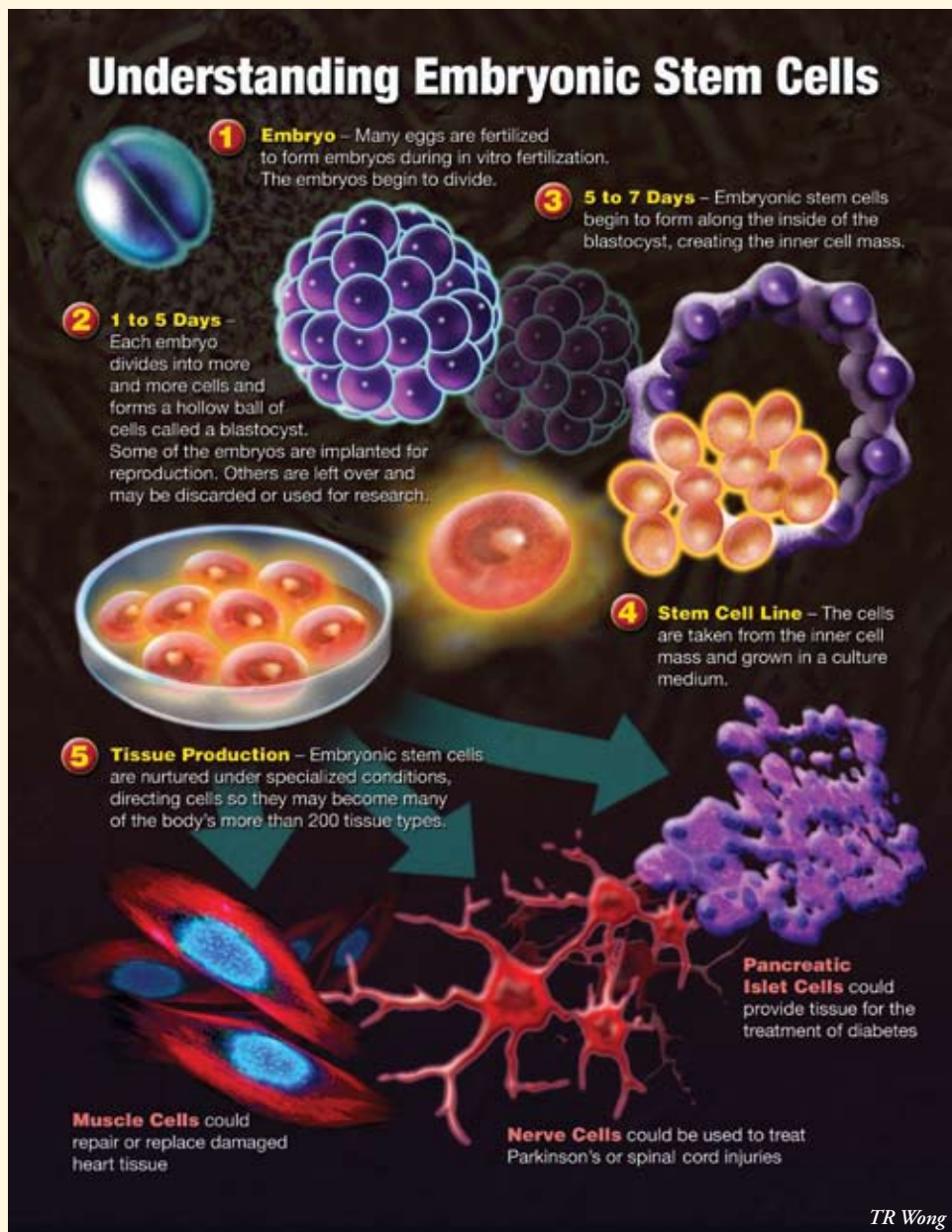
patients with such blood-related conditions as leukemia and lymphoma, as well as non-malignant diseases such as anemia.

Adult tissue-specific stem cells – which maintain and repair the body’s tissues – can be found in bone marrow, the blood stream, cornea and retina of the eye, placenta, umbilical cord, fat, the dental pulp of the tooth, liver, skin, gastrointestinal tract, lung and pancreas. These are multipotent cells because they give rise to a limited number of other cell types, generally within the same tissue or organ.

Investigators also are convinced that human embryonic stem cells, first generated in 1998, hold enormous potential for cell-based regenerative therapies. These cells are essentially a blank slate and can produce nearly all the cells of the body, making them pluripotent.

Early embryonic stem cells are found in the inner cell mass of the blastocyst about five days after fertilization of an egg. If the blastocyst – a microscopic group of cells much smaller than the period at the end of this sentence – is successfully implanted in the uterus, further reproductive development occurs. In research, the stem cells are removed from the blastocyst and placed in a culture dish where they grow and replicate over time. The great majority of human embryonic stem cell lines currently in use were obtained from embryos that were left over from in vitro fertilization procedures and would have been destroyed as medical waste.

“A stem cell can do some pretty remarkable things, but it’s unlikely that adult stem cells can do exactly what



embryonic stem cells can do. There just hasn't been any evidence of that in animal models," said David Crouse, Ph.D., associate vice chancellor for academic affairs. "Embryonic stem cells show greater promise."

Dr. Rennard has spent his career studying lung diseases, such as asthma, emphysema and chronic obstructive pulmonary disease (COPD). Now he is studying emphysema using human embryonic stem cell lines approved by President Bush. His research has determined that the cells responsible for healing appear to be abnormal in lungs with emphysema and COPD. He theorizes that the infusion of appropriately directed stem cells could help the healing cells in the lung to grow new tissue.

Dr. Rennard and his team previously have shown that mouse stem cells injected into mice go to the lung, differentiate or change, and form cells called fibroblasts which make up the connective tissue in the lungs and other parts of the body. Currently, it is unknown if mouse and human cells behave similarly in this process.

"Understanding how stem cells are directed to form new lung tissue offers great promise to treat lung diseases such as emphysema," Dr. Rennard said.

Meanwhile, Dr. Fox, a liver transplant surgeon, is trying to determine if embryonic stem cells can be turned into liver cells that can be infused into a diseased liver to correct liver failure. Over the past decade, Dr. Fox has devoted his research to looking at alternative ways – other than organ transplantation – to regenerate damaged liver cells.

"I've looked at developing ways of treating liver disease with cells rather than organs in every possible way," he said.

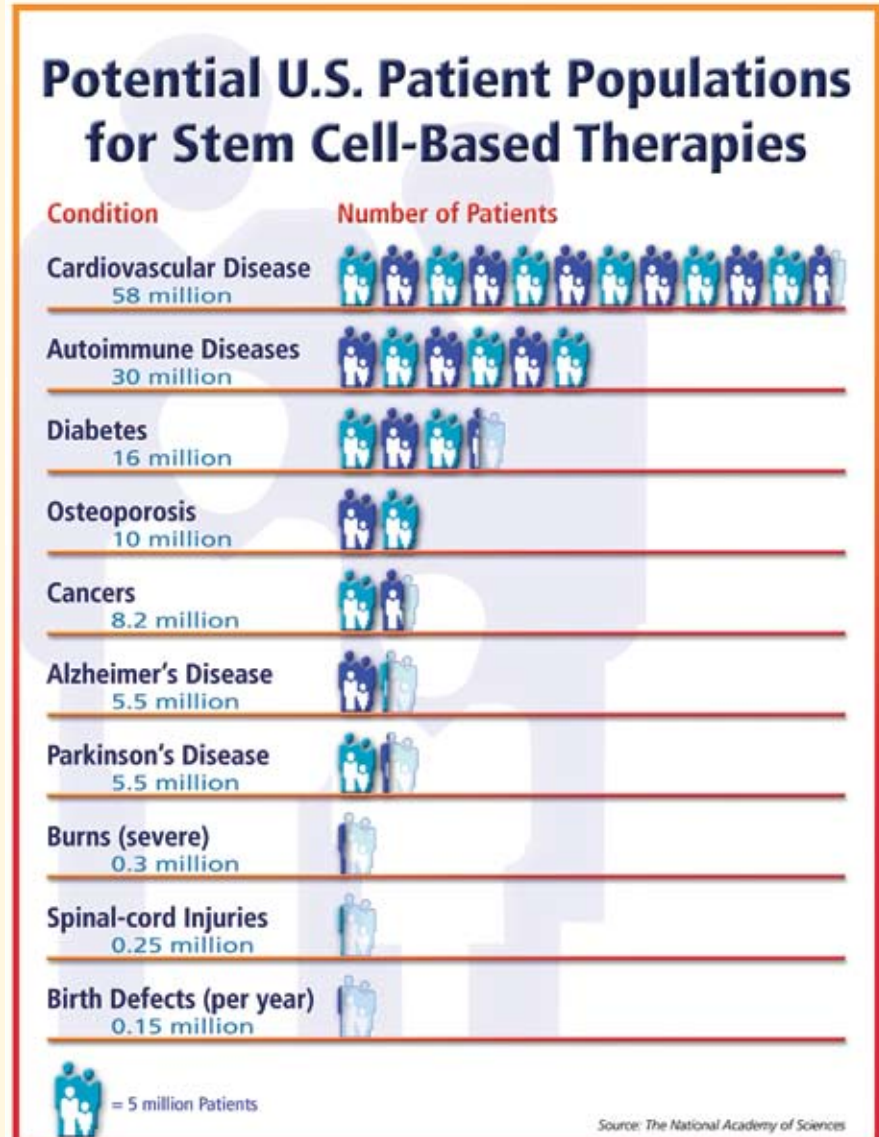
Infusing human liver cells into a diseased liver in 1997, Dr. Fox was the first to get the cells to function to partially correct

a patient's rare metabolic liver disease. In doing so, the patient was able to avoid undergoing a liver transplant for several years. The research was reported in the *New England Journal of Medicine* in May 1998.

Transplantation of the individual liver cells produced a clearing of the child's yellowish skin color, or jaundice, and dramatically reduced her risk of brain injury resulting from the metabolic abnormality. Unfortunately, the effect was not long-lasting.

The organ donor shortage is so great that scientists and clinicians are trying to use stem cells to regenerate diseased tissue as an alternative to organ transplantation to treat diseases.

Scientists have discovered distinct advantages and disadvantages associated with adult and



TR Wong

embryonic cells. Together, they say, the promise of regenerating or mobilizing one's own adult stem cells to repair tissue damage caused by trauma, disease or aging is great. Although the stem cells from the two sources are clearly different, there is much yet to be learned from both before they can be used most effectively.

"This is an era of scientific development and, like any other area of scientific development, will take many years to work out," Dr. Fox said. "What it really is giving us is a newer and altered view on how we think the body develops and regenerates."

For now, a better understanding of the science is of foremost importance. "Application of this work will take time," Dr. Fox said. "In general, attempts to bypass understanding basic biology in order to generate direct clinical therapies, more often than not, fail. Scientific process advances at its own pace."

J. Graham Sharp, Ph.D., professor of genetics, cell biology & anatomy, agrees. "On a theoretical basis, stem cells hold enormous promise," he said. "But, even if research progresses, it's going to take time to develop technologies for new therapies."

In the public arena, there is a great moral

and ethical divide on the use of stem cells, just as there was with the first heart transplants, blood transfusions and in vitro fertilization procedures. "Each suffered its own persecution because they were stretching the limits of what the public was willing to accept at the time," Dr. Crouse said.

"The idea that adult stem cells can do anything embryonic stem cells can do is false," Dr. Crouse said. "It also is true that there's no evidence anybody has been cured by embryonic stem cell therapy. But, you must recall that it took 30 years to develop adult stem cells for more routine therapies, so why should we expect embryonic stem cells, only discovered in 1998 and studied under very restrictive federal policies, to already produce significant discoveries. The results of studies conducted with animal models clearly show that the promise of embryonic stem cell therapy is real."

Said Dr. Crouse: "If we close the door to embryonic stem cell research, we'll never really know the full promise."

As editor of the science journal *Cytotherapy*, Dr. Sharp has seen a dramatic increase in the number of papers submitted on the use of embryonic stem cells in regenerative medicine. He and his colleagues hope to one day develop a regenerative medicine program at the medical center. Meanwhile, they are teaching stem cell biology and developing multi-investigator proposals to help fund their research projects.

Similar to pathology's role in disease detection, stem cells form the basis of human development. As a result, the study of embryonic stem cells will be fundamental to nearly every field of regenerative medicine. "This is a field that's as big as science itself," Dr. Fox said. "It is likely to be a critical component of every area of biologic science and health care. You may not necessarily have a stem cell center, but it's a critical issue if you're doing research in cardiology, liver disease, diabetes, muscular dystrophy, neuroscience or any aspect of disease."

"We recognize that some people oppose embryonic stem cell research on religious grounds, and we are sensitive to their concerns," Dr. Rosenquist said. "However, many others believe it is ethically compelling to use these cells for research rather than destroying them. If this country or the state of Nebraska bans this research, we will deny hope to millions and stop UNMC's research growth and progress in its tracks."



stem cell research has become a political firecracker.

In July, President Bush vetoed legislation to expand federally supported embryonic stem cell research on embryos slated for destruction by fertility clinics. The veto – his first in office – maintained the research restrictions he imposed on Aug. 9, 2001, which allowed research only on stem cell lines created before that date.

"I'm not aware of an executive order from the president that has so directly altered the path of what can be done in science," Dr. Crouse said.

Meanwhile, states such as California, Connecticut, Massachusetts, New Jersey, Maryland, Illinois and Ohio are funding stem cell research, in part, because of the potential for economic development. Seven states, including Arkansas and North and South Dakota, ban such research. Initiatives in the Nebraska legislature to ban embryonic stem cell research have not been successful.

