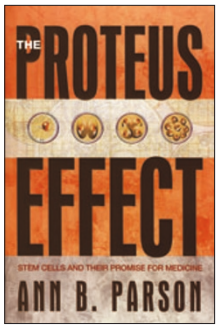
Stem cells: real or imaginary promise?



The Proteus Effect: Stem Cells and Their Promise for Medicine

Ann B Parson

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Reviewed by Alan Trounson

Stem cells are like the mythical Proteus, unpredictable and variable in their transformations. The stem cell defines the organism: primary embryonic stem cells give rise to every cell of the body and adult stem cells are maintained in a tissue niche to be released in a regulated manner to maintain and repair tissue function. Scientific interest in the stem cell has been rapidly growing in more recent times as its potential applications in medicine have begun to be appreciated.

Ann Parson begins her book in the mill ponds of the Dutch countryside in 1740. Abraham Trembley studied the regenerative ability of the hydra when dissected or damaged. "A tiny piece from an older hydra could grow into the entire animal just the way the embryo did": how was this feasible in an animal that normally reproduced sexually? Trembley's surgical experiments were the origins of cloning. His cousin, Charles Bonnet, studied regenerative processes in worms and salamanders, which can regenerate lost limbs as adults and even regenerate the eye, including the lens. The presence of embryonic-like cells in hydra and multipotent stem cells in the salamander and other amphibians and lizards is the foundation for the optimism that stem cells could be harnessed in the human for regenerative cell therapies.

The narrative comes alive with modern-day cell biology when Parson explores research by Roy Stevens at the Jackson Laboratory in the 1950s and 1960s. Stevens became "captivated" by the teratomas that formed in the testes of about 1% of Strain 129 mice, which had some resemblance to the developing embryo. Despite a lack of interest by others, he showed that these "bizarre tumors" were derived from pluripotential germ cells that renewed and differentiated into a wide variety of cell types. Hence, the seeds were sown for studying differentiation pathways in the laboratory from the very beginning of development. Elizabeth Russell and Seldon Bernstein at the Jackson Laboratory also showed in the late 1950s that stem cells extracted from the fetal liver could cure anemia in mice. This initiated the search for the hematopoietic stem cell that could repopulate bone marrow and regenerate the entire blood cell system. James Till and Ernest McCulloch were recognized for experiments which showed that bone marrow contained stem cells that, when injected into the blood of irradiated mice, developed as colonies in the spleen of the recipient. Later, Irv Weissman isolated mouse and human hematopoietic stem cells by immunophenotype. This procedure is now the basis for much of bone marrow transplantation medicine today.

Research in this area flourished dramatically with the findings by Martin Evans and Matt Kaufman at Cambridge University and Gail Martin at the University of California San Francisco that pluripotential embryonic stem cells could be isolated from the cultured inner cell mass cells of the early mouse embryo. These cells became the foundation for determining mammalian gene function through phenotypes of transgenic mice and targeted mutations and were the inspiration for Jamie Thomson at the University of Wisconsin at Madison, and my colleagues and me at Monash University and National University of Singapore to try to develop human embryonic stem cells.

Parson explores the state of contemporary stem cell science by interviews with scientists, primarily in eastern North America, and there is a strong flavor of the laboratory interests from this region. It is at times difficult to reconcile the narrative of developments with my own experiences and memories. However, I am sure the path linking Edwards' and Steptoe's breakthroughs with human *in vitro* fertilization, Jamie Thomson's success in developing nonhuman primate embryonic stem cells, John Gearhart's demonstration that human embryonic germ stem cells are pluripotential, our laboratory's independent success at developing human embryonic stem cells and directing their differentiation to neurons, as well as other advances will long be debated. What is certain is that a scientific revolution has happened and the front edge of science is stretching the social and political boundaries in almost all the countries of the world.

The present great debates are about the merit of using nuclear transfer to produce individual-specific human embryonic stem cells. Opinions have been made even more extreme by the bizarre behavior of the Korean researchers and their colleagues who apparently fabricated data concerning the production of the world's first, and only, nuclear transfer–derived human stem cell lines. Members of the US President's Ethics Advisory Board are busy trying to redefine embryos, or finding evidence for alternatives to nuclear transfer embryos for generating pluripotential cells. Carefully crafted and rigorous experiments quite quickly undid evidence for transdifferentiation of mature somatic cells and it is unlikely that ethicists will themselves derive any evidence that pluripotentiality can be reprogrammed in these cells.

Where the adult stem cell fails to be clinically useful or cannot be recovered and used for regenerative medicine, we could have the opportunity to apply cell therapies, tissue engineering and gene therapy based on embryonic stem cells for recovery of tissue and organ function. As described in the book, many laboratories around the world have a natural and informative juxtaposition of research on both adult and embryonic stem cells.

Ann Parson's book is a great read and an important contribution to scientific memory. Students of cell biology will be informed and those of us involved in research will be reminded that stem cells have a long and checkered history. There is now a large cast of highly motivated scientists opening Pandora's box and looking for the Proteus effect among stem cells, progenitor cells and reprogrammed somatic cells in an exciting new field of scientific inquiry.

Monash Immunology and Stem Cell Laboratories, Monash University, Clayton, Victoria 3800, Australia.
e-mail: jill.mcfadyean@med.monash.edu.au