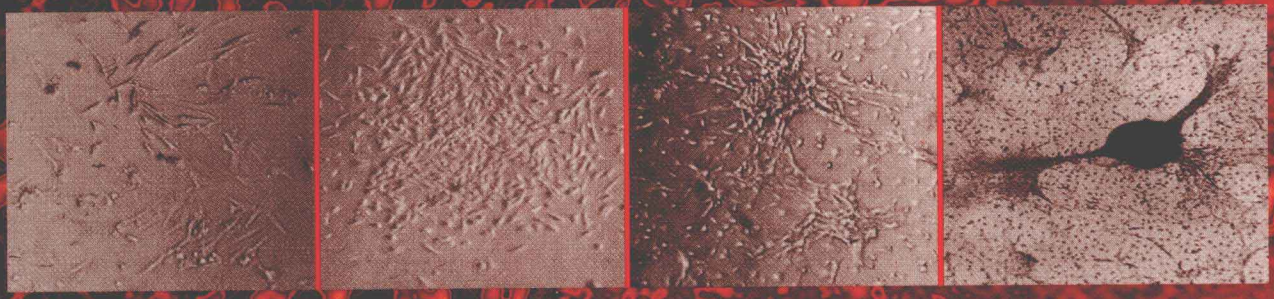
STEM CELLS

HANDBOOK

EDITED BY

STEWART SELL, MD



HUMANA PRESS

STEM CELLS HANDBOOK

EDITED BY

STEWART SELL, MD

WADSWORTH CENTER AND ORDWAY RESEARCH INSTITUTE
EMPIRE STATE PLAZA, ALBANY, NY

HUMANA PRESS
TOTOWA, NEW JERSEY

999 Riverview Drive, Suite 208
Totowa, New Jersey 07512
humanapress.com

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel.: 973-256-1699; Fax: 973-256-8341; E-mail:humana@humanapr.com; Website: humanapress.com

Cover illustrations: Fig. 3A from Chapter 37.

Cover design by Patricia F. Cleary.

This publication is printed on acid-free paper.∞
ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.

E-ISBN 1-59259-411-5

Printed in the United States of America. 10 9 8 7 6 5 4 3 2

Library of Congress Cataloging-in-Publication Data

Stem cells handbook / edited by Stewart Sell.
p. cm.
Includes bibliographical references and index.
ISBN 1-58829-113-8 (alk. paper)
1. Stem cells. I. Sell, Stewart, 1935-
QH587.S728 2003
616'.02775–dc21 2002191331

STEM CELLS HANDBOOK

Dedication

Professor Janis Klanis at the 7th Annual Meeting of IATMO in Kiev, Ukraine, 1990

Janis V. Klavins, MD, Professor Emeritus of Albert Einstein Medical College and former Chairman of Pathology at Catholic Medical Center, Queens, New York.

Professor Klavins was born in Riga, Latvia in 1921. His medical education was interrupted by both Nazi and Russia invasions during WWII and he had to flee Latvia to avoid deportation to Russia. He completed both medical and musical degrees in Germany. After WWII he and his young wife Ilga moved to Parkersburg, WV, where he worked as a physician's assistant. He completed pathology training and joined the pathology department of Tom Kinney at Western Reserve in Cleveland, OH. He moved with Dr. Kinney to Duke University and then to New York, first at Brookland-Cumberland Medical Center and then as Chairman of Pathology at Catholic Medical Center. He is known internationally for his vocal interpretations of Shubert's lieder.

Professor Klavins not only has been a long time champion of the stem cell concept, but also, along with Georg D. Birkmayer of Vienna, Austria, is the founder of the International Academy of Tumor Marker Oncology, an organization that encourages the application of the products of stem cells and their cancerous progeny to the clinical diagnosis and prognosis of human cancer.

Preface

The power of stem cells for tissue development, regeneration, and renewal has been well known by embryologists and developmental biologists for many years. Those presently active in research in the stem cell field owe much to previous work by embryologists and cancer researchers for their insights into what stem cells can do. In the last 4–5 years, the rapid expansion of the concept of adult tissue stem cells as pluripotent progenitors for various tissues has led to an even greater appreciation of the power of stem cells. The demonstration that both embryonic and adult tissue stem cells have the ability to produce progenitor cells for tissue renewal has opened vast possibilities for treatment of congenital deficiency diseases as well as for regeneration of damaged tissues. Older concepts of determination leading to loss of potential during differentiation of adult tissues are being replaced by newer ideas that cells with multiple potential exist in different forms in various adult organs and that cells thought to be restricted to differentiation to one cell type may be able to "transdifferentiate" into other tissue cell types. Thus, the concept of "embryonic rests" in adult tissues, hypothesized to be the cellular origin of cancer by Durante and Conheim in the 1870s, now can be expanded to include survival of pluripotential embryonic-like stem cells in adult tissues.

The goal of *Stem Cells Handbook* is to present in one resource both the background and the current understanding of what stem cells are and what they can do. The authors of the various chapters were selected for their significant contributions to and expertise in various aspects of stem cell biology. First, the function of embryonic stem cells in early development and organogenesis, and germinal stem cells in reproduction are presented, followed by how embryonic stem cells may be cloned and how they are programmed. The role of stem cells in amphibian regeneration and mammalian wound healing shows the potential of these cells for tissue renewal. The participation of stem cells in normal tissue renewal of various organ systems, including blood, nervous tissue, retina, blood vessels, heart, kidney, skin, glandular organs, gastrointestinal tract, liver, pancreas, mammary gland, prostate, and lung are then specifically adumbrated, including not only the role of stem cells in tissue renewal and carcinogenesis, but also the isolation and characterization of various stem cell types, the potential for their manipulation, and the possibilities for future therapeutic uses in experimental models and in human diseases. The remarkable properties of hematopoietic stem cells and the clinical results achieved by transplantation of bone marrow stem cells are documented in several chapters. The potential future promise for clinical applications for regeneration of the cardiovascular and nervous system as described in preclinical models is also emphasized. Of particular interest to the editor is the potential for stem cell therapy for liver, not only because the liver has special problems and importance as the major metabolic organ of the body, but also because of its potential as an objective for transplantation and gene therapy.

Finally, a codicil for a book such as this that tries to cover an active field of research is that by the time it is published there will almost certainly be advances in understanding that have already made some of the material out of date. For example, in the last few months, there have been a number of additional papers on the plasticity of adult tissue stem cells as well as the observation that some effects believed to result from stem cell plasticity may be explained by cell fusion. Only ongoing studies will resolve these questions and provide the approaches required for potential breakthroughs in application to human diseases. In the meantime, we hope that the expert chapters in *Stem Cells Handbook* will provide useful and authoritative information to aid those who seek the answers to the unanswered questions.

The editor is indebted to G. Barry Pierce for his encouragement and insights into teratocarcinoma as a stem cell tumor, to Gerri Abelev for discovering alphafetoprotein, to the late Hidematsu Hirai for his enthusiastic support of international research in oncodevelopmental biology, to Fred Becker and Emmanuel Farber for their models and

concepts of chemical hepatocarcinogenesis, to Benito Lombardi and Hishasi Shinozuka for their early work on models of oval cell proliferation, to Hyam Leffert for his encyclopedic knowledge of liver cell culture, to the many postdoctoral fellows, graduate students, and technicians who did all of the real work in my laboratory, to Thomas Lanigan and Humana Press for their encouragement and patience, and especially to the distinguished authors who contributed chapters to *Stem Cells Handbook*.

Stewart Sell, *MD*

Contributors

W. French Anderson, MD, *Gene Therapy Laboratories, USC Keck School of Medicine, Norris Cancer Center, Los Angeles, CA*

Takayuki Asahara, MD, PhD, *Cardiovascular Research and Medicine, St. Elizabeth's Medical Center, Tufts University School of Medicine, Medford, MA*

Kurtis I. Auguste, MD, *Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA*

Stephen M. Baird, MD, *Professor of Pathology, University of California San Diego, and Chief Laboratory Services, VA Medical Center, San Diego, CA*

Emma M. A. Ball, PhD, *Centre for Urological Research, Monash Institute of Reproduction and Development, Monash University, Melbourne, Victoria, Australia*

Helen M. Blau, PhD, *Donald E. and Delia B. Baxter Professor, Director, Baxter Laboratory in Genetic Pharmacology, Stanford University School of Medicine, Stanford, CA*

Helmut Bonkhoff, PhD, *Institute of Pathology, University of Saarland, Saar, Germany*

Mario A. Bourdon, PhD, *La Jolla Institute of Molecular Medicine, San Diego, CA*

Luc Bouwens, PhD, *Department of Experimental Pathology, Free University of Brussels (VUB) Brussels, Belgium*

Mairi Brittan, BS, *Histopathology Unit, Cancer Research UK, Lincoln's Inn Fields, London, UK*

Arnold I. Caplan, PhD, *Department of Biology, Skeletal Research Center, Case Western Reserve University, Cleveland, OH*

Pierre Charbord, MD, *DR Inserm, Laboratoire d'Hématopoïèse, Faculté de Médecine, Batiment Bretonneau, Tours, France*

Jae-Jin Cho, DVM, PhD, *Assistant Professor, Division of Craniomaxillofacial Reconstruction, School of Dentistry, Seoul National University, Seoul, South Korea*

Kyunghee Choi, PhD, *Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO*

Heather A. Crosby, PhD, *School of Biosciences, University of Birmingham, and Liver Research Laboratories, University Hospital Birmingham, Birmingham, UK*

Marcel M. Daadi, PhD, *Layton Bioscience, Sunnyvale, CA*

James E. Dennis, PhD, *Department of Biology, Skeletal Research Center, Case Western Reserve University, Cleveland, OH*

Regis Doyonnas, PhD, *Baxter Laboratory in Genetic Pharmacology, Stanford University School of Medicine, Stanford, CA*

Curt R. Freed, MD, *Division of Clinical Pharmacology and Toxicology, University of Colorado School of Medicine, Denver, CO*

Juri Gelovani (aka Tjuvajev)**, MD, PhD,** *Associate Professor, Departments of Neurology and Radiology, Memorial Sloan Kettering Cancer Center and Sloan Kettering Institute, New York, NY*

Margaret A. Goodell, PhD, *Center for Cell and Gene Therapy and Department of Pediatrics, Baylor College of Medicine, Houston, TX*

Lynn M. Gruman, HT, *Department of Anatomy and Cell Biology, The University of Iowa College of Medicine, Iowa City, IA*

Peter Gruss, PhD, *Max-Planck Institute of Biophysical Chemistry, Department of Molecular Cell Biology, Göttingen, Germany*

Sanjeev Gupta, MBBS, MD, *Professor of Medicine and Pathology, Marion Bessin Liver Research Center, Department of Medicine, and Department of Pathology, Albert Einstein College of Medicine, Bronx, NY*

Anna-Katerina Hadjantonakis, PhD, *Department of Genetics and Development, College of Physicians and Surgeons of Columbia University, New York, NY*

Simon W. Hayward, PhD, *Department of Urologic Surgery; Vanderbilt Prostate Cancer Center; Department of Cancer Biology; and Vanderbilt-Ingram Comprehensive Cancer Center, Vanderbilt University Medical Center, Nashville, TN*

Mary J. C. Hendrix, PhD, *Department of Anatomy and Cell Biology, The University of Iowa College of Medicine, Iowa City, IA*

Jürgen Hescheler, PhD, *Department of Neurophysiology, Center of Physiology and Pathophysiology, University of Cologne, Cologne, Germany*

Angela R. Hess, PhD, *Department of Anatomy and Cell Biology, The University of Iowa College of Medicine, Iowa City, IA*

DOUGLAS C. HIXSON, PhD, *Carcinogenesis Laboratory, Department of Medicine, Rhode Island Hospital, Providence, RI*

SUI HUANG, MD, PhD, *Departments of Surgery and Pathology, Children's Hospital and Harvard Medical School, Boston, MA*

DONALD E. INGBER, MD, PhD, *Departments of Surgery and Pathology, Children's Hospital and Harvard Medical School, Boston, MA*

JEFFREY M. ISNER, MD, PhD (DECEASED), *Cardiovascuolar Research and Medicine, St. Elizabeth's Medical Center, Tufts University School of Medicine, Medford, MA*

SILVIU ITESCU, MD, *Director, Transplantation Immunology, Departments of Medicine and Surgery, Columbia University, New York, NY*

KATHYJO A. JACKSON, PhD, *Center for Cell and Gene Therapy and Department of Pediatrics, Baylor College of Medicine, Houston, TX*

SHERIF M. KARAM, MD, PhD, *Department of Anatomy, Faculty of Medicine and Health Sciences, Al-Ain, UAE University, United Arab Emirates*

KATHERINE S. KOCH, PhD, *Department of Pharmacology, School of Medicine, University of California, San Diego, La Jolla, CA*

MAHESH LACHYANKAR, PhD, *Department of Neurology, Harvard Medical School Harvard Institutes of Medicine, Beth-Israel Deaconess Medical Center, Boston, MA*

ROBERT LANGER, ScD, *Department of Materials Science and Engineering, and Department of Chemical Engineering, Massachusetts Institute of Technology, Boston, MA*

ERIN B. LAVIK, PhD, *Department of Materials Science and Engineering, and Department of Chemical Engineering, Massachusetts Institute of Technology, Boston, MA*

HYAM L. LEFFERT, MD, *Department of Pharmacology and Center for Molecular Genetics, School of Medicine, University of California, San Diego, La Jolla, CA*

HAIFAN LIN, PhD, *Department of Cell Biology, Duke University Medical Center, Durham, NC*

WILLIAM J. LINDBLAD, PhD, *Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI*

JEFFREY R. MANN, PhD, *Division of Biology, Beckman Research Institute of the City of Hope, Duarte, CA*

FIONA C. MANSERGH, PhD, *Cardiff School of Biosciences, Cardiff University, Cardiff, Wales, UK*

ALEKSANDRA E. MARCINIAK, BS, *Department of Neurology, Harvard Medical School Harvard Institutes of Medicine, Beth-Israel Deaconess Medical Center, Boston, MA*

MICHAEL A. MARCONI, BS, *Department of Neurology, Harvard Medical School Harvard Institutes of Medicine, Beth-Israel Deaconess Medical Center, Boston, MA*

TILL MARQUARDT, PhD, *The Salk Institute for Biological Studies, La Jolla, CA*

ERNEST A. MCCULLOCH, MD, FRS, *Cell and Molecular Biology, The Ontario Cancer Institute, Toronto, Ontario, Canada*

PAUL S. MELTZER, MD, PhD, *Human Genome Research Institute, National Institutes of Health, Bethesda, MD*

LUCIO MIELE, MD, PhD, *Department of Pathology, Loyola University Medical Center, Chicago, IL*

BRIAN J. NICKOLOFF, MD, PhD, *Department of Pathology, Loyola University Medical Center, Chicago, IL*

SARBJIT S. NIJJAR, PhD, *School of Biosciences, University of Birmingham, and Liver Research Laboratories, University Hospital Birmingham, Birmingham, UK*

JITKA OUREDNIK, PhD, *Department of Biological Sciences, College of Veterinary Medicine, Iowa State University, Ames, IA*

VACLAV OUREDNIK, PhD, *Department of Biological Sciences, College of Veterinary Medicine, Iowa State University, Ames, IA*

VIRGINIA E. PAPAIOANNOU, PhD, *Department of Genetics and Development, College of Physicians and Surgeons of Columbia University, New York, NY*

KOOK I. PARK, MD, DMSc, *Department of Neurology, Harvard Medical School Harvard Institutes of Medicine, Beth-Israel Deaconess Medical Center, Boston, MA, and Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea*

LESLEY ANN PATERSON, PhD, *Roslin Institute, Roslin, Midlothian, UK*

AMMON B. PECK, PhD, *Department of Pathology, Immunology & Laboratory Medicine, University opf Florida College of Medicine, Gainesville, FL, and Ixion Biotechnology, Inc., Alachua, FL*

ALAN O. PERANTONI, PhD, *Laboratory of Comparative Carcinogenesis, National Cancer Institute, Frederick, MD*

IAN PONTING, PhD, *Gene Therapy Laboratories, USC Keck School of Medicine, Norris Cancer Center, Los Angeles, CA*

VIJAYAKUMAR K. RAMIYA, PhD, *Ixion Biotechnology, Inc., Alachua, FL*

DERRICK E. RANCOURT, PhD, *Departments of Oncology, Biochemistry, and Molecular Biology, The University of Calgary, Calgary, Alberta, Canada*

SCOTT H. RANDELL, PhD, *Cystic Fibrosis/Pulmonary Research and Treatment Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

JOY RATHJEN, PhD, *Department of Molecular Biosciences, The University of Adelaide, Adelaide, Australia*

PETER DAVID RATHJEN, PhD, *Department of Molecular Biosciences, and ARC SRC for Molecular Genetics of Development, The University of Adelaide, Adelaide, Australia*

D. EUGENE REDMOND, MD, *Department of Neuropsychopharmacology, Yale University, New Haven, CT, and Neural Transplantation and Regeneration Program, Axion Research Foundation, Hamden, CT*

GAIL P. RISBRIDGER, PhD, *Centre for Urological Research, Monash Institute of Reproduction and Development, Monash University, Melbourne, Victoria, Australia*

LORRAINE ROBB, MBBS, PhD, *The Walter and Eliza Hall Institute of Medical Research, Victoria, Australia*

HEATHER L. ROSE, MA, *Department of Neurology, Harvard Medical School Harvard Institutes of Medicine, Beth-Israel Deaconess Medical Center, Boston, MA*

AGAPIOS SACHINIDIS, PhD, *Department of Neurophysiology, Center of Physiology and Pathophysiology, University of Cologne, Cologne, Germany*

HEINRICH SAUER, PhD, *Department of Neurophysiology, Center of Physiology and Pathophysiology, University of Cologne, Cologne, Germany*

GINA C. SCHATTEMAN, PhD, *Department of Anatomy and Cell Biology, The University of Iowa College of Medicine, Iowa City, IA*

ELISABETH A. SEFTOR, BS, *Department of Anatomy and Cell Biology, The University of Iowa College of Medicine, Iowa City, IA*

RICHARD E. B. SEFTOR, PhD, *Department of Anatomy and Cell Biology, The University of Iowa College of Medicine, Iowa City, IA*

STEWART SELL, MD, *Wadsworth Center and Ordway Research Institute, Empire State Plaza, Albany, NY*

DON D. SHERIFF, PhD, *Department of Anatomy and Cell Biology, The University of Iowa College of Medicine, Iowa City, IA*

RICHARD L. SIDMAN, MD, *Department of Neurology, Harvard Medical School Harvard Institutes of Medicine, Beth-Israel Deaconess Medical Center, Boston, MA*

GILBERT H. SMITH, PhD, *Mammary Biology and Tumirogenesis Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

EVAN Y. SNYDER, MD, PhD, *Department of Neurology, Harvard Medical School Harvard Institutes of Medicine, Beth-Israel Deaconess Medical Center, Boston, MA; and Stem Cells and Regeneration, The Burnham Institute, La Jolla, CA*

DAVID L. STOCUM, PhD, *Department of Biology and Center for Regenerative Biology and Medicine, Indiana University–Purdue University Indianapolis, Indianapolis, IN*

ALASTAIR J. STRAIN, PhD, *School of Biosciences, University of Birmingham, and Liver Research Laboratories, University Hospital Birmingham, Birmingham, UK*

HÉLÈNE STRICK-MARCHAND, PhD, *Unité de Génétique de la Différenciation, URA 2578 du CNRS, Institut Pasteur, Paris, France*

BARRY R. STRIPP, PhD, *Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, PA*

PIROSKA E. SZABÓ, PhD, *Division of Biology, Beckman Research Institute of the City of Hope, Duarte, CA*

ROSANNE M. TAYLOR, DVM, PhD, *Department of Animal Science, Faculty of Veterinary Science, University of Sydney, New South Wales, Australia*

YANG D. TENG, MD, PhD, *Departments of Neurology, Pediatrics, and Neurosurgery, the Children's Hospital, and Brigham & Women's Hospital, Harvard Medical School, Boston, MA*

ANK A. W. TEN HAVE-OPBROEK, MD, PhD, *Department of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands*

MARIA WARTENBERG, PhD, *Department of Neurophysiology, Center of Physiology and Pathophysiology, University of Cologne, Cologne, Germany*

WENDY C. WEINBERG, PhD, *Laboratory of Immunobiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD*

MARY C. WEISS, PhD, *Unité de Génétique de la Différenciation, URA 2578 du CNRS, Institut Pasteur, Paris, France*

KARIN WILLIAMS, PhD, *Department of Urologic Surgery and Vanderbilt Prostate Cancer Center, Vanderbilt University Medical Center, Nashville, TN*

IAN WILMUT, *Roslin Institute, Roslin, Midlothian, UK*

MICHAEL A. WRIDE, PhD, *Department of Optometry and Vision Sciences, Cardiff University, Cardiff, Wales, UK*

NICHOLAS A. WRIGHT, MD, PhD, *Department of Histopathology, Barts and the London, Queen Mary's School of Medicine and Dentistry, London, UK*

HIDEYUKI YOSHITOMI, MD, PhD, *Cell and Developmental Biology Program, Fox Chase Cancer Center, Philadelphia, PA*

STUART H. YUSPA, MD, *Laboratory of Cellular Carcinogenesis and Tumor Promotion, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

KENNETH S. ZARET, PhD, *Cell and Developmental Biology Program, Fox Chase Cancer Center, Philadelphia, PA*

YI ZHAO, MD, *Gene Therapy Laboratories, USC Keck School of Medicine, Norris Cancer Center, Los Angeles, CA*

Contents

DEDICATION v

PREFACE vii

CONTRIBUTORS ix

1 Stem Cells: *What Are They? Where Do They Come From? Why Are They Here? When Do They Go Wrong? Where Are They Going?* **1**
Stewart Sell

2 Stem Cells from Early Mammalian Embryos: *Common Themes and Significant Differences* **19**
Virginia E. Papaioannou and Anna-Katerina Hadjantonakis

3 Embryonic Stem Cells: *Isolation and Application of Pluripotent Cells from the Pregastrulation Mammalian Embryo* **33**
Joy Rathjen and Peter David Rathjen

4 From Stem Cells to Functional Tissue Architecture: *What Are the Signals and How Are They Processed?* **45**
Sui Huang and Donald E. Ingber

5 Germline Stem Cells **57**
Haifan Lin

6 Stem Cells and Cloning **75**
Ian Wilmut and Lesley Ann Paterson

7 Genomic Imprinting in Mouse Embryonic Stem and Germ Cells **81**
Jeffrey R. Mann and Piroska E. Szabó

8 Stem Cells in Amphibian Regeneration **89**
David L. Stocum

9 Stem Cells in Dermal Wound Healing **101**
William J. Lindblad

10 Bone Marrow Mesenchymal Stem Cells **107**
James E. Dennis and Arnold I. Caplan

11 Normal and Leukemic Hematopoietic Stem Cells and Lineages **119**
Ernest A. McCulloch

12 Developmental Origin of Murine Hematopoietic Stem Cells **133**
Lorraine Robb and Kyunghee Choi

13 Stromal Support of Hematopoiesis **143**
Pierre Charbord

14 Hematopoietic Stem Cells: *Identification, Characterization, and Assays* **155**
Ian Ponting, Yi Zhao and W. French Anderson

15 Hematopoietic Stem Cells in Leukemia and Lymphoma **163**
Stephen M. Baird

16 Neurons, Stem Cells, and Potential Therapies **177**
Fiona C. Mansergh, Michael A. Wride, and Derrick E. Rancourt

17 Neural Stem Cells: *From In Vivo to In Vitro and Back Again—Practical Aspects* 191
Michael A. Marconi, Kook I. Park, Yang D. Teng, Jitka Ourednik, Vaclav Ourednik, Rosanne M. Taylor, Aleksandra E. Marciniak, Marcel M. Daadi, Heather L. Rose, Erin B. Lavik, Robert Langer, Kurtis I. Auguste, Mahesh Lachyankar, Curt R. Freed, D. Eugene Redmond, Richard L. Sidman, and Evan Y. Snyder

18 Molecular Genetic Approaches in the Study of Retinal Progenitor Cells and Stem Cells **209**
Till Marquardt and Peter Gruss

19 Endothelial Progenitor Cells **221**
Takayuki Asahara and Jeffrey M. Isner

20 Development of the Cardiovascular System in Embryoid Bodies Derived from Embryonic Stem Cells **229**
Heinrich Sauer, Maria Wartenberg, Agapios Sachinidis, and Jürgen Hescheler

21 Transcription Factors, Growth Factors, and Signal Cascades Capable of Priming Cardiogenesis **239**
Agapios Sachinidis, Heinrich Sauer, Maria Wartenberg, and Jürgen Hescheler

22 Strategies Using Cell Therapy to Induce Cardiomyocyte Regeneration in Adults with Heart Disease **251**
Silviu Itescu

23 Generation and Stem Cell Repair of Cardiac Tissues **259**
Kathyjo A. Jackson and Margaret A. Goodell

24 Stem Cells in Kidney Morphogenesis **267**
Emma M. A. Ball and Gail P. Risbridger

25 Nephroblastoma: *A Metanephric Caricature* **277**
Alan O. Perantoni

26 Stem Cells in Nonmelanoma Skin Cancer **289**
Wendy C. Weinberg and Stuart H. Yuspa

27 The Stem Cell Plasticity of Aggressive Melanoma Tumor Cells **297**
Mary J. C. Hendrix, Elisabeth A. Seftor, Paul S. Meltzer, Angela R. Hess, Lynn M. Gruman, Brian J. Nickoloff, Lucio Miele, Don D. Sheriff, Gina C. Schatteman, Mario A. Bourdon, and Richard E. B. Seftor

28 Stem Cells in Glandular Organs **307**
Karin Williams and Simon W. Hayward

29 Gastrointestinal Stem Cells: *Proliferation Kinetics and Differentiation Hierarchies* **317**
Sherif M. Karam

30 Stem Cell Origin of Cell Lineages, Proliferative Units, and Cancer in the Gastrointestinal Tract **329**
Mairi Brittan and Nicholas A. Wright

31 Specification of Liver from Embryonic Endoderm **345**
Hideyuki Yoshitomi and Kenneth S. Zaret

32 Animal Models for Assessing the Contribution of Stem Cells to Liver Development **353**
Douglas C. Hixson

33 Normal Liver Progenitor Cells in Culture **367**
Katherine S. Koch and Hyam L. Leffert

34 Permanent Lines of Stem Cells from the Liver **385**
Hélène Strick-Marchand and Mary C. Weiss

35 Biology of Human Liver Stem Cells **397**
Alastair J. Strain, Sarbjit S. Nijjar, and Heather A. Crosby

36 Transplantation of Hepatic Stem Cells and Potential Applications for Cell Therapy **409**
Sanjeev Gupta and Jae-Jin Cho

37 Plasticity of Adult-Derived Pancreatic Stem Cells **417**
Ammon B. Peck and Vijayakumar K. Ramiya

38 Islet Cells **429**
Luc Bouwens

39 Mammary Epithelial Stem Cells **437**
Gilbert H. Smith

40 Morphogenesis of Prostate Cancer **445**
Helmut Bonkhoff

41 Stem Cells in Lung Morphogenesis, Regeneration, and Carcinogenesis **455**
Ank A. W. ten Have-Opbroek, Scott H. Randell, and Barry R. Stripp

42 Noninvasive Imaging in Stem Cell Therapies: *Current State and Future Perspectives* **473**
Juri Gelovani

43 What Is the Future for Stem Cell Research?: *Whether Entity or Function?* **491**
Regis Doyonnas and Helen M. Blau

INDEX **501**

1 Stem Cells

What Are They? Where Do They Come From? Why Are They Here? When Do They Go Wrong? Where Are They Going?

STEWART SELL, MD

The stem cell is the origin of life. At stated first by the great pathologist Rudolph Virchow, "All cells come from cells." The ultimate stem cell, the fertilized egg, is formed from fusion of the haploid progeny of germinal stem cells. The fertilized egg is totipotent; from it forms all the tissues of the developing embryo. During development of the embryo, germinal stem cells are formed, which persist in the adult to allow the cycle of life to continue. In the adult, tissue is renewed by proliferation of specialized stem cells, which divide to form one cell that remains a stem cell and another cell that begins the process of differentiation to the specialized function of a mature cell type. Normal tissue renewal is accomplished by the differentiating progeny of the stem cells, the so-called transit-amplifying cells. For example, blood cells are mature cells derived from hematopoietic stem cells in the bone marrow; the lining cells of the gastrointestinal tract are formed from transit-amplifying cells, progeny of stem cells in the base of intestinal glands. Nineteenth-century pathologists first hypothesized the presence of stem cells in the adult as "embryonal rests" to explain the cellular origin of cancer and more recent studies indicate that most cancers arise from stem cells or their immediate progeny, the transit-amplifying cells. Cancer results from an imbalance between the rate at which cells are produced and the rate at which they terminally differentiate or die. Understanding how to control the proliferation and differentiation of stem cells and their progeny is not only the key to controlling and treating cancer, but also to cell replacement and gene therapy for many metabolic, degenerative, and immunological diseases.

1.1. WHAT ARE THEY?

In the beginning there is the stem cell; it the origin of an organism's life. It is a single cell that can give rise to progeny that differentiate into any of the specialized cells of embryonic or adult tissues; that is, it is totipotent. The ultimate stem cell, the fertilized egg, divides five or six times to give rise to branches (lines) of cells that form various differentiated organs (Fig. 1). During these early divisions, each daughter cell retains totipotency. Then, through a series of divisions and differentiations, the embryonic stem cells (ESCs) lose potential and gain differentiated function (a process known as determination; *see* below). During normal tissue renewal in adult organs, tissue stem cells give rise to progeny that differentiate into mature functioning cells of that tissue. Stem cells with less than totipotentiality are called "progenitor cells". Except for germinal cells, which retain totipotency, most stem cells in adult tissues have reduced potential to produce cells of different types (i.e., are determined). However, there is increasing evidence for retention of some toti/multi-potent cells in the tissues of adults, especially in the bone marrow.

From: *Stem Cells Handbook*
Edited by: S. Sell © Humana Press Inc., Totowa, NJ

1.2. WHERE DO THEY COME FROM?

According to Leslie Brainerd Arey, the father of modern embryology (Arey, 1974), the first recorded attempt to understand the origin of life and the early development of the human was most likely made by Aristotle (384–322 BC). He recognized the early stages of development in the uterus and apparently was the first to contemplate the basic conflict of whether or not a new individual was formed *de novo* or was pre-formed in the mother and only enlarged during development (Arey, 1974). Aristotle deduced that the embryo was derived from the mother's menstrual blood, a conclusion that was based on the concept that living animals arose from slime or decaying matter (a hypothesis known in the middle ages as "spontaneous generation"). This concept was generally accepted for more than 2000 yr, until its validity became the major biological controversy of the 19th century. The hypothesis that life did not arise spontaneously, but rather only from preexisting life (*omne vivum ex vivo*) was pronounced by Leydig in 1855. Virchow (1855) then extended this to postulate that all cells in an organism are derived from preexisting cells (*omnis cellula e cellula*) (*see also* Oberling, 1944); all the cells of the human body arise from a preexisting stem cell, the fertilized egg. The counterhypothesis of spontaneous generation was not formally disproved until 1864,

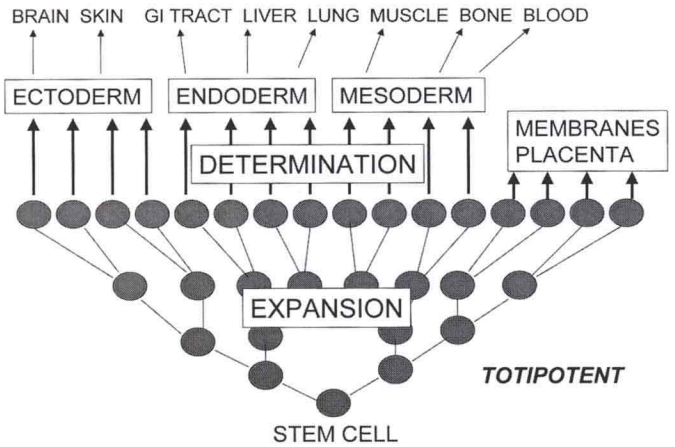


Fig. 1. Embryonic stem (ES) cell and progeny. During embryonic development, the ultimate stem cell, the fertilized egg, gives rise to progeny that retain totipotentiality as the population expands. Then determination occurs, and the cells begin to lose potential and to gain the specialized functions required to form mature organs. During blastulation the cells in the outer cells of the blastocyst (blasto- meaning embryo or germ; cyst - cavity) become determined for extraembryonic structures (placenta and membranes), whereas the ICM retains totipotentiality until the next stage of development, gastrulation (invagination of the blastula, *see* Fig. 4. During gastrulation the cells become determined to form the primary germinal layers: ectoderm, endoderm, and mesoderm. Ectoderm further differentiates to skin and brain; endoderm to gastrointestinal (GI) tract and internal organs; and mesoderm to connective tissue, bone, blood vessels, and blood-forming tissue. The relationship of cancers to the developing embryo is reflected in the use of the terms *carcinoma* for cancer arising from ectoderm-derived cells; *sarcoma* for cancer arising from mesoderm-derived cells.

when Louis Pasteur performed carefully controlled experiments that demonstrated the failure of microorganisms to grow (corruption) in sterilized broth in vessels having long necks that prevented ambient organisms from entering (Debre, 1998). At present, the question is posed in the context of the conflict over abortion: "When does life begin?" According to the principles derived from Leydig, Virchow, and Pasteur, life as we know it neither ends nor begins but is continuous (Fig. 2). The adult human, for example, is only one stage in the cycle of human life.

Until the 1800s, the dominant hypothesis was that pre-formed individuals resided in the egg or the sperm. This pre-formed individual was called a homunculus. The homunculus in the egg was activated to develop after stimulation with sperm, or, conversely, the homunculus in the male sperm was activated to develop when provided an appropriate environment in the uterus. By the early 1900s, this concept had been proven to be incorrect, the embryo was shown to be formed by the fertilization of an egg, which developed in the ovary of the female, by fusion with a sperm provided by the male (*see* Needham, 1959). The product of the union of a sperm with an egg is the primordial totipotent stem cell (*see* the terminology in Table 1). How the cycle of life originally began is a subject of controversy. The two major alternate hypotheses are that human life was either created by Divine intervention in 7 d or else it evolved from primordial chemical biosynthesis, followed by natural selection from preceding life forms, over millions of years.

Table 1.1
Terminology of Potential (Plasticity)

Prefix	*Meaning*	*Example*
Toti	All	Embryonal
Multi	Many/much	Hematopoietic
Pluri	Several/many	Hematopoietic
Oligo	Few/little	GI stem cell
Quadri	Four	GI stem cell
Tri	Three	Bronchial lining
Bi	Two	Bile duct
Uni	One	Prostate

Source: The Random House Dictionary of the English Language. Recent evidence indicates that some cells in the tissues used as examples of determined potential may have more potential than previously appreciated. For example, skin stem cells, believed to be uni- or bipotent, may contain multipotent progenitor cells (Liang and Bickenbach, 2002).

1.3. WHY ARE THEY HERE?

Until recently, most of what we understood about how the adult develops from the primordial stem cell was derived from classic studies in developmental anatomy (Arey, 1974). Following fertilization, the egg undergoes a process of cell divisions and cell migrations known as cleavage. In this early process, each daughter cell receives the full chromosome complement of the original cell, and each daughter cell appears to be the same. This is known as symmetric division, in contrast to the properties of somatic stem cells, which exhibit asymmetric division (Thrasher, 1966; Merok and Sherley, 2001) (Fig. 3).

The daughter cells, called blastomeres, stick together to form a cluster of cells known as a morula (from Morus, mulberry). At each division the blastomeres are reduced in size, but transplantation studies indicate that each embryonic blastomere is able to produce all differentiated cell types; that is, it is totipotent. Eventually, as the number of blastomeres approaches 32 or 64 cells, a cell-free center appears in the expanding cluster of blastomeres, and a hollow sphere of cells is formed (blastocyst). In mammals, the outer cells form the embryonic membranes and the placenta, whereas the mass of cells within the blastocyst, the inner cell mass (ICM), forms the embryo. At this stage not all the cells are still totipotent, as some of the outer cells become committed to membranes or the placenta. As ICM develops, the daughter cells begin to acquire properties different from one another, so that specific regions are formed that are destined to become different components of the developing embryo, a process known as gastrulation (Fig. 4). During gastrulation, the totipotency of the cells of the ICM is lost, and the blastula is rearranged by invagination of cells from the outer blastocyst to form layered "germ" zones known as ectoderm (outer skin), mesoderm (middle skin), and endoderm (inner skin), which are destined to form the adult organs. Skin, dermal appendages (including breast), and brain and neural tissue are derived from ectoderm; connective tissue, muscle, bone, and blood vessels from mesoderm; and the GI tract and internal glandular organs from endoderm (Arey, 1974).

The process of the loss of potential and the gain of specialized function is known as *determination*. In this process, the *totipotent* stem cells of the blastomere give rise to multi/pluripotent cells of the germ layers. These, in turn, give rise to progenitor cells of the developing organs. Tissue determination is accom-

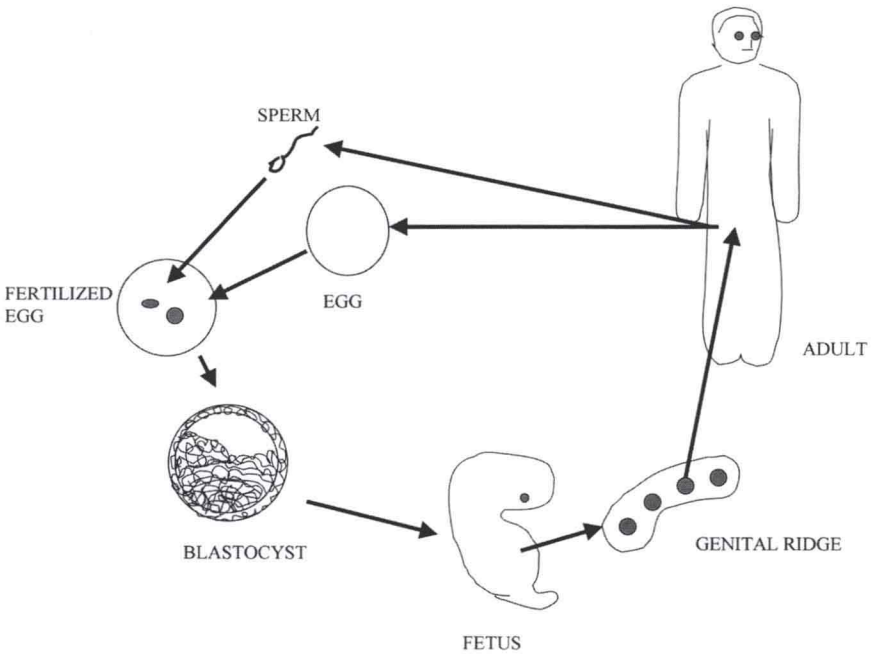


Fig. 2. Cycle of life. Human life is continuous. The life of an individual begins with fertilization of the egg and formation of a fetus. Totipotent cells in the developing fetus migrate to the genital ridge and in adults produce germinal stem cells in the gonads. Germinal cells give rise to gametes (egg and sperm) by reduction division (meiosis), resulting in cells containing half the chromosomes of an adult. Genetic reconstitution occurs when the sperm fertilizes the egg. In this process life is continuous; it is neither created nor destroyed.

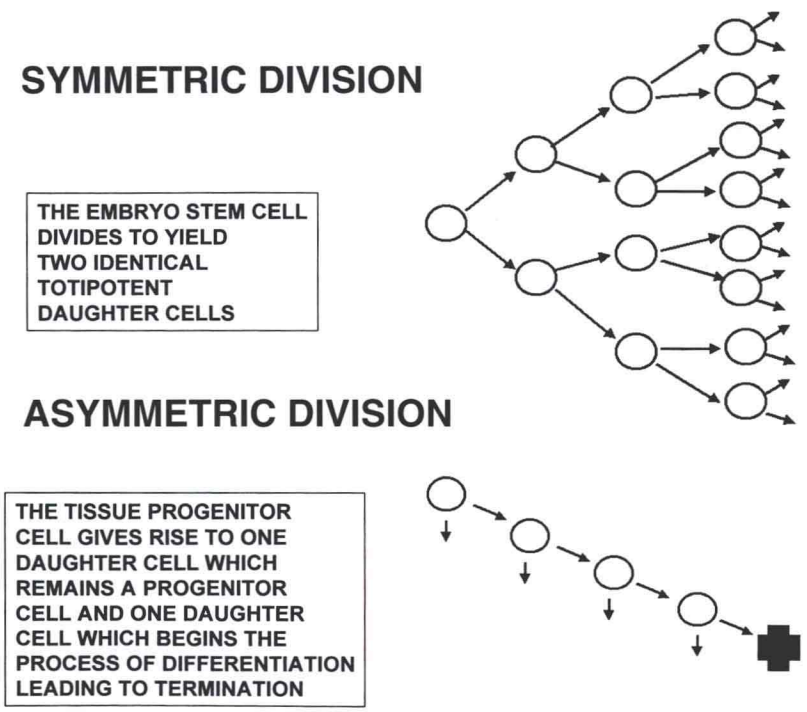


Fig. 3. Symmetric and asymmetric division. During early embryonic development, each cell divides and gives rise to two daughter cells with the same potential: symmetric division. During normal tissue renewal in the adult, each progenitor cell gives rise to one daughter cell that remains a progenitor cell, and one daughter cell that begins the process of determination to a terminally differentiated cell—asymmetric division. The number of cells increases exponentially during early embryogenesis, but the cell number remains constant during normal tissue renewal, as the number of new progenitor cells equals the number of cells destined to die.

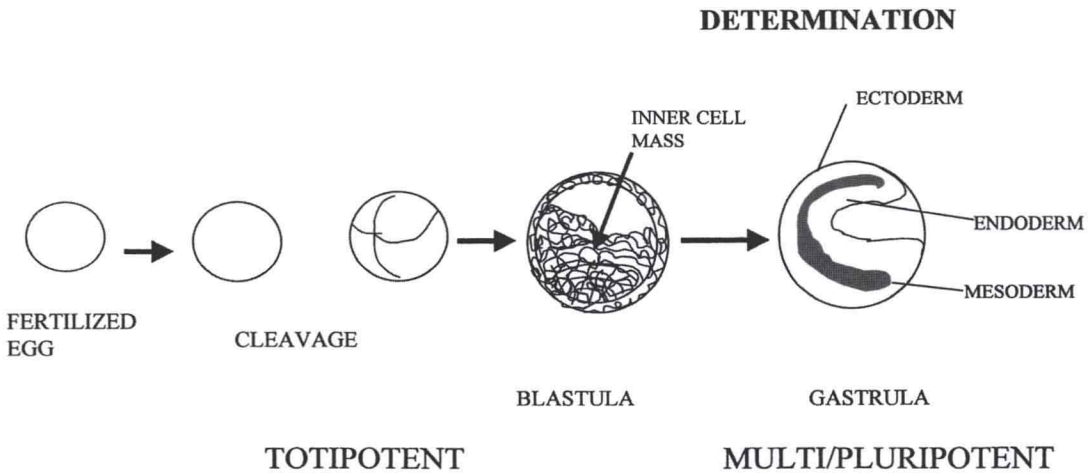


Fig. 4. Early development of embryo. Division of the fertilized egg results in the formation of a ball-like structure with a cavity on one end (the blastula). Until this stage, the cells divide by symmetric division, and all cells produced are totipotent. Invagination of one pole of the blastula leads to formation of the gastrula and establishment of the primitive germinal cell layers. During gastrulation and later formation of the fetus, the daughter cells lose potential as they gain specialized function.

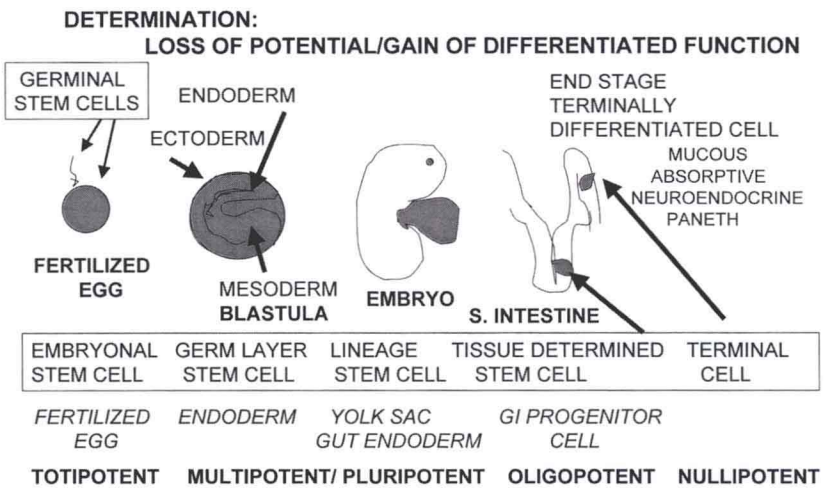


Fig. 5. Levels of progenitor cells during differentiation of small intestine. The small intestinal epithelium develops from a series of determinations from the embryonal stem cell (ESC), blastula, and endoderm. The intestinal progenitor is quadripotent; it can give rise to progeny that may become mucous, absorptive, neuroendocrine, or Paneth cells. Each of these becomes terminally differentiated in its fully mature form.

plished in progenitor cells through interaction with other cell types. For example, determination of primitive gut cells to liver (Matsumoto et al., 2001) or pancreas (Lammert et al., 2001) takes place in association with developing endothelium of blood vessels (Weinstein, 2002). As the cells become specialized into tissue, their potential becomes more limited, and they finally differentiate to terminally differentiated cells.

The terminology used regarding potential is listed in Table 1. The term *totipotent* should be reserved for those stem cells that can give rise to all of the differentiated tissues of the body as well as the placenta and membranes (ES cells, germinal stem cells). The terms *multipotential* and *pluripotential* are essentially synonymous: both refer to the ability of a given stem cell to form many different cell types. In an official National Institutes of Health primer released in 2000, pluripotent is defined as "capable of giving rise to most tissues of an organism," and totipotent as "having unlimited capacity" (www.nih.gov/news/stemcell/primer.htm). As depicted in Fig. 5, the potential decreases with the progressive development of the embryo.

The specialized cells in the adult that give rise to egg and sperm are called germinal cells. Germinal cells retain totipotentiality. Cancers derived from germinal cells may contain placental as well as adult tissues derived from more than one germ layer (teratocarcinomas; *see* below). Egg and sperm are derived from germinal cells by a special form of cell division called meiosis. As a result of meiosis, the egg and sperm each contain half of the

chromosomes of their respective parent cells. With the joining of a sperm and an egg, a newly formed animal inherits its characteristics from the genetic material provided by both parents.

In classic embryology, determination was understood as a one-way process: once a cell is fully differentiated in the adult, it is strikingly stable (Surani, 2001) and not able to "de-differentiate". On the other hand, under some circumstances, this differentiated state does appear to be reversible. Transfer of nuclei from differentiated adult organs into an oocyte can result in restoration of the totipotency of the nucleus in the oocyte (Wilmut et al., 1997; Surani, 2001). This appears to be true even for mature T- and B-cells, which have rearranged T-cell receptor and immunoglobulin genes, respectively (Hochedlinger and Jaenisch, 2002); every tissue in mice cloned from a B-cell has the same immunoglobulin sequence as the original donor nucleus. It has even been reported that fibroblasts may be *re-programmed* to express T-cell or neuronal markers using cell extracts (Hakelien et al., 2002). However, others have found more stringent restrictions for re-programming.

Nuclear transplantation was first carried out in *Amoeba* (Comandon et al., 1930), and was extended to the frog *Rana pipiens* in 1952 (Briggs and King, 1952). In 1962, it was demonstrated that the nucleus from the intestine of a feeding tadpole could provide all of the information required for an ovum to develop into an adult frog (Gurdon, 1962). Later, nuclei from a number of organs were used to reproduce this result, but the technique was successful only if the donor cells were cultured for a few days in vitro before the nuclei were obtained (Laskey and Gurdon, 1970). Thus, although the proportion of successful transplants is small, <1–2%, at least some of the cells of adult organs of vertebrates contain nuclei that carry an entire set of the normal genes also found in the normal fertilized ovum. The question then becomes: Which cells in adult organs can supply nuclei that provide all of the information needed to produce a complete individual when used for nuclear transplantation into an anucleate ovum?

It appears that this may be the capability of tissue stem cells in the adult. In experiments in which nuclei from the tadpole are used, totipotentiality was progressively lost during gastrulation (King and Briggs, 1955). It has been stated, "The first generalization is that nuclei from more advanced developmental stages and from more differentiated cells always promote less normal nuclear-transplant embryo development (quantitatively and qualitatively) than nuclei from early developmental stages or undifferentiated cells" (Gurdon, 1974, p. 28). In the case of the cloning of sheep, nuclei from a d-9 embryo, a 26-d fetus, and the mammary gland of a 6-yr-old ewe in the last trimester of pregnancy were used (Wilmut et al., 1997), the latter implies that nuclei from adult mammals retain all of the information of the germ cells. However, the exact nature of the cells in the mixture used for cloning that contributed the nuclei in the transplant from the pregnant ewe is not defined. It is difficult to imagine that the nucleus of a secretory glandular cell could be re-programmed in such a manner. On the other hand, the mammary epithelium during the third semester is actively proliferating, and the proliferating gland contains active progenitor cells. Thus, it seems likely that the nuclei from an adult tissue that are capable of re-programming in an oocyte could actually be the tissue progenitor cells, or even the putative circulating totipotent stem cells of adults (Van der Kooy and Weiss, 2000). In the latter case, re-programming may not even be necessary, as the nucleus of this cell would already be totipotent.

1.3.1. EMBRYONIC STEM CELLS Under optimal conditions, cells from the ICM of the preimplantation blastocyst are able to proliferate indefinitely (Evans and Kaufman, 1981). As well, under inducing conditions, they can undergo determination and differentiate into other tissue types. In contrast, after formation of germ layers, most somatic progenitor cells have limited life-spans, and they exhibit decreasing differentiation potential as mature organs are formed (Merok and Sherley, 2001). Cole and Edwards (1967) were able to isolate ESCs from pre-implantation blastocysts of rabbits using feeder layers, and outgrowths of these cells differentiated into blood islands, muscle, connective tissue, neurons, and macrophages. Gardner (1968) demonstrated that, after injection of ESCs into a normal blastocyst, the cells could cocolonize in the developing embryo and form a chimeric individual. Essentially, Gardner demonstrated, that prior to implantation, the cells of the ICM were pluripotent. Edwards and his colleagues were able to obtain human oocytes after gonadotropin stimulation, fertilize the eggs in vitro, and grow the fertilized eggs in vitro to the blastocyst stage (Edwards et al., 1980, Steptoe et al., 1980). Subsequent transfer of the in vitro–fertilized embryos to the uteri of infertile patients supplemented with luteal support, eventually led to the successful clinical application of in vitro fertilization.

The potential of the in vivo use of ESCs for therapy was demonstrated when it was shown that injection of ESCs into lethally irradiated mice could restore the lost bone marrow stem cells (Hollands, 1987). In 1998, the in vitro culture of human ESCs that could differentiate into gut epithelium, cartilage, bone, muscle, neurons, and other cell types was reported (Thompson et al., 1998, Shamblott et al., 1998). The potential for human ESCs to be cultured in vitro, the possibility of producing human embryonic cell lines (Schuldiner et al., 2001), and the likelihood that these cells can be directed to differentiate into different cell types (Pittenger et al., 1999), have sparked the tremendous contemporary interest in ESC research for replacement of lost or damaged tissue cells (Donovan and Gearhart, 2001). Because ESCs give rise to germ cells, germ cells to egg and sperm, egg and sperm to a fertilized egg, and a fertilized egg to embryonic cells (Fig. 2), it is expected that any of the diploid cells in this cycle can give rise to any of the cells of the adult individual.

A problem in using ESCs for replacement of adult tissues concerns the low efficiency and long time required for ESCs to differentiate into functional adult cells. These issues may be addressed either by using adult precursor cells (*see* below) or by directing ESCs to a specialized tissue pathway. ESCs require a series of signals in order to produce progeny of a more highly differentiated type. For example, specialized culture conditions, including exposure to and withdrawal from fibroblast growth factor (FGF) (Zhang et al., 2001a), or culture with FGF and other growth factors (Reubinoff et al., 2001) allow generation of neural precursor cells, which may subsequently be shown to incorporate into the developing brain, at least in the mouse. This requires identification of in vitro conditions for different potential uses of ESCs.

1.3.2. GERMINAL STEM CELLS Early in embryogenesis, a few cells are designated to become germinal cells (Meachem et al., 2001). These cells migrate into the primitive gonad (genital ridge) and differentiate into female or male germ cell precursors, depending on the presence of two X chromosomes (female) or one X and one Y chromosome (male). They can be recognized by expression of the transcription factor Oct4 and of alkaline