Heart Development and Regeneration

Volume 2

Edited by
Nadia Rosenthal and
Richard P. Harvey

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Heart Plate 2 was inspired by the artistry of Franco Mari, a living master of Majolica ceramic decoration working from Deruta, Italy. Each design band represents a theme in the volume. Motifs from center outward: circuit, discovery, access, dynamic, progenitor, renewal. *Artwork by Nadia Rosenthal.*

"Come potreste descrivere a parole questo cuore,
senza riempire un libro intero?"
(How could you describe this heart in words,
without filling a whole book?)

Note written by Leonardo da Vinci beside an anatomical drawing of the heart, 1513.

List of Contributors

Number in parentheses indicates the chapter to which the author contributed.

Jeffrey D. Amack (4.1), Department of Cell and Developmental Biology, SUNY Upstate Medical University, Syracuse, NY 13210

Brad A. Amendt (4.3), Institute of Biosciences and Technology, Texas A&M System Health Science Center, 2121 Holcombe Blvd, Houston, TX 77030

Robert H. Anderson (3.2, 3.4), Cardiac Unit, Institute of Child Health, University College, London, UK

Piero Anversa (14.3), Cardiovascular Research Institute, Departments of Medicine, New York Medical College, Valhalla, NY 10595

Ana Paula Azambuja (1.1), Laboratório de Genética e Cardiologia Molecular, Instituto do Coração, Faculdade de Medicina, Universidade de São Paulo, São Paulo-SP, Brazil; and Departamento de Biologia Celular e do Desenvolvimento, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo-SP, Brazil

David Bader (1.5), Stahlman Cardiovascular Research Laboratories, Program for Developmental Biology, and Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232-2561

Shoumo Bhattacharya (11.3), Wellcome Trust Centre for Human Genetics, University of Oxford, UK

Brian L. Black (9.5), Cardiovascular Research Institute and Department of Biochemistry and Biophysics, University of California, San Francisco, CA 94158-2517

Daniel G. Blackmore (13.1), Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, 4072, Australia

Rolf Bodmer (1.2), Development and Aging Program, NASCR Center, Burnham Institute for Medical Research, 10901 North Torrey Pines Rd, La Jolla, CA 92037

Thomas Brand (5.1), Heart Science Centre, National Heart and Lung Institute, Imperial College London, UK

Marianne Bronner-Fraser (7.1), California Institute of Technology, Pasadena, CA 91125

Nigel A. Brown (3.4, 4.3), Division of Basic Medical Sciences, St George's University of London, Cranmer Terrace, London SW17 0RE, UK

Benoit G. Bruneau (10.1), Gladstone Institute of Cardiovascular Disease and Department of Pediatrics, University of California, San Francisco, CA 94158

Margaret E. Buckingham (3.1), Department of Developmental Biology, CNRS URA2578, Pasteur Institute, 25 rue du Dr Roux, Paris, France

Todd D. Camenisch (6.1), Departments of Pharmacology and Toxicology, Molecular and Cellular Biology, Steele Children's Research Center, Bio5 Institute, University of Arizona, Tucson, AZ

Hozana Andrade Castillo (1.1), Laboratório de Genética e Cardiologia Molecular, Instituto do Coração, Faculdade de Medicina, Universidade de São Paulo, São Paulo-SP, Brazil; and Departamento de Biologia Celular e do Desenvolvimento, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo-SP, Brazil

Rodrigo Abe Castro (1.1), Laboratório de Genética e Cardiologia Molecular, Instituto do Coração, Faculdade de Medicina, Universidade de São Paulo, São Paulo-SP, Brazil; and Departamento de Biologia Celular e do Desenvolvimento, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo-SP, Brazil

Bishwanath Chatterjee (11.2), Laboratory of Developmental Biology, National Heart Lung Blood Institute, National Institutes of Health, Bethesda, MD 20892

Vincent M. Christoffels (2.3, 3.2), Heart Failure Research Center, Academic Medical Center, Amsterdam, The Netherlands

Ondine Cleaver (8.2), Dept. of Molecular Biology NA8.300, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390

Frank L. Conlon (9.4), Department of Genetics, Fordham Hall, University of North Carolina-Chapel Hill, Chapel Hill, NC 27599

Kimberly R. Cordes (10.3), Gladstone Institute of Cardiovascular Disease and Departments of Pediatrics, Biochemistry and Biophysics, University of California,

San Francisco, 1650 Owens Street, San Francisco, CA 94158

David M. Cox (11.5), MDS Sciex 71 Four Valley Drive, Concord, Ontario, Canada L4K 4V8

Richard M. Cripps (9.5), Department of Biology, University of New Mexico, Albuquerque, NM 87131-0001

Brad Davidson (1.1), Department of Molecular and Cell Biology, Division of Genetics and Development, Center for Integrative Genomics, University of California, Berkeley, CA 94720

José Luis de la Pompa (6.2), Departamento de Biología del Desarrollo Cardiovascular, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Melchor Fernández Almagro 3, E-28029 Madrid, Spain

Stefanie Dimmeler (14.2) Professor of Medicine, Molecular Cardiology, Department of Internal Medicine III, University of Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany

Pascal Dollé (3.3), Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), BP 10142, Illkirch, F-67400 France; Inserm, U 964, Illkirch, F-67400 France; CNRS, UMR 7104, Illkirch, F-67400 France; Université de Strasbourg, Faculté de Médecine, Strasbourg, F-67000 France

Min Du (11.5), Department of Biology, York University, Toronto, Ontario, Canada, M3J 1P3

Victor J. Dzau (14.1), Molecular and Genomic Vascular Biology, Duke University Medical Center, DUMC 3701, Durham, NC 27710

David A. Elliott (9.1), Monash Immunology and Stem Cell Laboratories, Monash University, Clayton, Victoria, 3800, Australia

Sylvia M. Evans (2.2), Skaggs School of Pharmacy and Pharmaceutical Sciences, and Department of Medicine, University of San Diego, La Jolla, CA

Max Ezin (7.1), California Institute for Technology, Pasadena, CA 91125

Ann C. Foley (1.3), Divison of Cardiology, Weill Cornell Medical College, New York, NY 10065

Richard Francis (11.2), Laboratory of Developmental Biology, National Heart Lung Blood Institute, National Institutes of Health, Bethesda, MD 20892

Manfred Frasch (1.2), Department of Biology, Developmental Biology Unit, University of Erlangen-Nürnberg, Erlangen, Staudtstr. 5, 91058, Germany

Daniel J. Garry (11.1), Lillehei Heart Institute, and Department of Internal Medicine, University of Minnesota, Minneapolis, MN 55455

Lior Gepstein (13.2), The Sohnis Family Research Laboratory for the Regeneration of Functional Myocardium, Department of Biophysics and Physiology, the Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Massimiliano Gnecchi (14.1), Department of Cardiology, Fondazione I.R.C.C.S. Policlinico San Matteo, University of Pavia, Viale Golgi 19, 27100, Pavia, Italy

Joseph Gold (13.2), Geron Corporation, Menlo Park, CA 94025

Joaquim Grego-Bessa (6.2), Sloan-Kettering Institute, 1275 York Ave., New York, NY 10065

Thomas Gridley (8.3), The Jackson Laboratory, Bar Harbor, ME

Rosa M. Guzzo (1.3), Department of Orthopedic Surgery, University of Connecticut Health Center, Farmington, CT 06034

Hiroshi Hamada (4.2), Developmental Genetics Group, Graduate School for Frontier Biosciences, Osaka University; and CREST, Japan Science and Technology Corporation (JST), 1-3 Yamada-oka, Suita, Osaka 565-0871, Japan

Natasha L. Harvey (8.4), Division of Haematology, The Centre for Cancer Biology, SA Pathology, Adelaide, South Australia, Australia

Richard P. Harvey (9.1), Victor Chang Cardiac Research Institute, Sydney, NSW, 2010, Australia and Faculties of Science and Medicine, University of New South Wales, Kensington, 2053, Australia

Steve Hauschka (11.4), Department of Biochemistry, University of Washington, Seattle, Washington, 98195

Charis Himeda (11.4), Department of Biochemistry, University of Washington, Seattle, Washington, 98195

Willem M. H. Hoogaars (2.3), Heart Failure Research Center, Academic Medical Center, Amsterdam, The Netherlands

Guo-Ying Huang (11.2), Pediatric Heart Center, Children's Hospital of Fudan University, Shanghai, China

Mary R. Hutson (7.2), Department of Pediatrics (Neonatology), Neonatal-Perinatal Research Institute, Jones Building, Room 401, Box 103105, Duke University Medical Center, Durham, NC 27710

Kimberly E. Inman (7.1), Stowers Institute for Medical Research, 1000 E. 50th Street, Kansas City, MO 64110

Silviu Itescu (14.2), Director of Transplantation Immunology, Columbia University Medical Center, 630 West 168th Street, New York, NY 10032; Columbia University College of Physicians and Surgeons, and Professor of Medicine, University of Melbourne, Melbourne, Australia

Jan Kajstura (14.3), Cardiovascular Research Institute, Departments of Medicine, New York Medical College, Valhalla, NY 10595

Robert G. Kelly (2.2), Developmental Biology Institute of Marseilles-Luminy, UMR 6216 CNRS-Université de la Méditerranée, Campus de Luminy, Marseilles, France

Margaret L. Kirby (7.2), Department of Pediatrics (Neonatology), Neonatal-Perinatal Research Institute, Jones Building, Room 401, Box 103105, Duke University Medical Center, Durham, NC 27710

Edwin P. Kirk (9.1), Victor Chang Cardiac Research Institute, Sydney, NSW, 2010, Australia; Department of Medical Genetics, Sydney Children's Hospital and School of Women's and Children's Health, Faculty of Medicine, University of New South Wales, Australia

Paul A. Krieg (8.2), Dept. of Cell Biology and Anatomy, University of Arizona College of Medicine, Molecular Cardiovascular Research Program, Medical Research Building MRB 311, 1656 E. Mabel St, Tucson, AZ 85724

Enrique Lara-Pezzi (14.4), Heart Science Centre, Imperial College London, Harefield, UK; Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

Shuaib Latif (11.1), Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX 75390

Kory J. Lavine (5.2), Department of Developmental Biology, Washington University School of Medicine, St. Louis, MO

Linda Leatherbury (11.2), Laboratory of Developmental Biology, National Heart Lung Blood Institute, National Institutes of Health, Bethesda, MD 20892

Annarosa Leri (14.3), Cardiovascular Research Institute, Departments of Medicine, New York Medical College, Valhalla, NY 10595

Michael Levine (2.1), Department Molecular and Cell Biology, Division of Genetics, Genomics and Development, Center for Integrative Genomics, University of California, Berkeley, CA 94720

Cecilia W. Lo (11.2), Laboratory of Developmental Biology, National Heart Lung Blood Institute, National Institutes of Health, Bethesda, MD 20892

Roger R. Markwald (6.1), Department of Cell Biology and Anatomy & Developmental Cardiovascular Biology Center, Medical University of South Carolina, SC

James F. Martin (4.3), Institute of Biosciences and Technology, Texas A&M System Health Science Center, 2121 Holcombe Blvd, Houston, TX 77030

John C. McDermott (11.5), Department of Biology, York University, Toronto, Ontario, Canada, M3J 1P3

Sigolène M. Meilhac (3.1), Department of Developmental Biology, CNRS URA2578, Pasteur Institute, 25 rue du Dr Roux, Paris, France

Mark Mercola (1.3), Burnham Institute for Medical Research, 10901 N.Torrey Pines Road, La Jolla, CA 92037

Takashi Mikawa (5.1), Cardiovascular Research Institute, University of California, San Francisco, CA

Timothy Mohun (11.3), Division of Developmental Biology, MRC National Institute for Medical Research, London, UK

Antoon F.M. Moorman (2.3, 3.2, 3.4), Heart Failure Research Center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Katherine Moynihan (1.5), Stahlman Cardiovascular Research Laboratories, Program for Developmental Biology, and Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232-2561

Ramón Muñoz-Chápuli (8.1), Departamento de Biología Animal, Facultad de Ciencias, Universidad de Málaga, Campus de Teatinos s/n, E-29071 Málaga, Spain

Charles E. Murry (13.2), Department of Pathology, Center for Cardiovascular Biology, Institute for Stem Cell and Regenerative Medicine, University of Washington, Seattle, WA 98109

Georges Nemer (9.2), Research Unit in Cardiac Growth and Differentiation, Institut de recherches cliniques de Montréal (IRCM), Montréal, QC H2W 1R7; Canada and Department of Biochemistry, American University of Beirut, Lebanon

Mona Nemer (9.2), University of Ottawa, Laboratory of Cardiac Growth and Differentiation, Department of Biochemistry, Microbiology and Immunology, Ottawa, Ontario, K1N 6N5, Canada

Karen Niederreither (3.3), Departments of Medicine and Molecular and Cellular Biology, Center for Cardiovascular Development, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030

Eric N. Olson (10.2), Department of Molecular Biology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390

David M. Ornitz (5.2), Department of Developmental Biology, Washington University School of Medicine, St. Louis, MO

Lil Pabon (13.2), Department of Pathology, Center for Cardiovascular Biology, Institute for Stem Cell and Regenerative Medicine, University of Washington, Seattle, WA 98109

José M. Pérez-Pomares (6.2, 8.1), Departamento de Biología Animal, Facultad de Ciencias, Universidad de Málaga, Campus de Teatinos s/n, E-29071 Málaga, Spain

Kenneth Poss (12.2), Department of Cell Biology, Howard Hughes Medical Institute, Duke University Medical Center, Durham, NC 27710

Rodney L. Rietze (13.1), Pfizer Regenerative Medicine, Granta Park, Great Abington, Cambridge, UK; Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, 4072, Australia

Nadia Rosenthal (14.4), Heart Science Centre, Imperial College London, Harefield, UK, Mouse Biology Unit, European Molecular Biology Laboratory (EMBL), Monterotondo, Italy; and Australian Regenerative Medicine Institute, Monash University, Melbourne, Australia

Raymond B. Runyan (6.1), Department of Cell Biology and Anatomy, University of Arizona, Tucson, AZ

Allysson Coelho Sampaio (1.1), Laboratório de Genética e Cardiologia Molecular, Instituto do Coração, Faculdade de Medicina, Universidade de São Paulo, São Paulo-SP, Brazil; and Departamento de Biologia Celular e do Desenvolvimento, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo-SP, Brazil

Daniel Schaft (9.1), Victor Chang Cardiac Research Institute, Sydney, NSW 2010, Australia

Robert J. Schwartz (9.3), The Institute of Biosciences and Technology, The Texas A&M University System Health Science Center, Houston, TX 77030

Ian C. Scott (1.4), The Hospital for Sick Children, Program in Developmental and Stem Cell Biology, Department of Molecular Genetics, University of Toronto, 101 College Street, East Tower Rm 11-307, Toronto, ON M5G 1L7, Canada

Yuan Shen (11.2), Laboratory of Developmental Biology, National Heart Lung Blood Institute, National Institutes of Health, Bethesda, MD 20816

Marcos Sawada Simoes-Costa (1.1), Laboratório de Genética e Cardiologia Molecular, Instituto do Coração, Faculdade de Medicina, Universidade de São Paulo, São Paulo-SP, Brazil; and Departamento de Biologia Celular e do Desenvolvimento, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo-SP, Brazil

Jonathan M. W. Slack (12.1), Stem Cell Institute, University of Minnesota, McGuire Translational Research Facility, 2001 6th Street SE, Minneapolis, MN 55455

Deepak Srivastava (10.3), Gladstone Institute of Cardiovascular Disease and Departments of Pediatrics and Biochemistry & Biophysics, University of California, San Francisco, 1650 Owens Street, San Francisco, CA 94158

Frank Stockdale (1.5), Department of Medicine, Stanford University, School of Medicine, Stanford, CA 94305-5151

Paul A. Trainor (7.1), Stowers Institute for Medical Research, 1000 E. 50th Street, Kansas City, MO 64110; and Kansas University School of Medicine, 3901 Rainbow Boulevard, Kansas City, KS 66160

Gert van den Berg (3.2), Heart Failure Research Center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Sandra Webb (3.4), Department of Basic Sciences, Anatomy and Developmental Biology, St George's University of London, Cranmer Terrace, London, UK

Wolfgang Weninger (11.3), Integrative Morphology Group, Center for Anatomy & Cell Biology, Medical University Vienna, Austria

Andy Wessels (11.2), Department of Anatomy and Cell Biology, Medical University of South Carolina, Charleston, SC 29425

José Xavier-Neto (1.1), Laboratório de Genética e Cardiologia Molecular, Instituto do Coração, Faculdade de Medicina, Universidade de São Paulo, São Paulo-SP, Brazil

Deborah Yelon (1.4), Skirball Institute of Biomolecular Medicine, Developmental Genetics Program, New York University School of Medicine, Department of Cell Biology, 540 First Avenue, 4th Floor, Lab 15, New York, NY 10016

H. Joseph Yost (4.1), Department of Neurobiology and Anatomy, University of Utah School of Medicine, Salt Lake City, UT 84112

Bryan D. Young (10.2), Department of Molecular Biology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390

Qing Yu (11.2), Laboratory of Developmental Biology, National Heart Lung Blood Institute, National Institutes of Health, Bethesda, MD 20892

Katherine E. Yutzey (9.4), Division of Molecular Cardiovascular Biology, Cincinnati Children's Hospital Medical Center, 240 Albert Sabin Way, ML7020, Cincinnati, OH 45229

Zhen Zhang (11.2), Laboratory of Developmental Biology, National Heart Lung Blood Institute, National Institutes of Health, Bethesda, MD 20892

Xiao-Qing Zhao (11.2), Laboratory of Developmental Biology, National Heart Lung Blood Institute, National Institutes of Health, Bethesda, MD 20892

Foreword

Developmental biology is slowly but surely moving to center stage in cardiovascular science and practice as a result of the increasing realization of its potential for understanding the basic mechanisms of a wide variety of congenital and acquired heart diseases. This stems from the fact that many of the factors which are operational during morphogenesis of the heart during fetal life continue to influence growth and adaptation during postnatal life. In addition, the developmental origins and lineages of different cells influence their behavior in adult life. Defining these factors offers exciting possibilities for developing novel therapies.

The recent sustained progress in the field has been driven by a handful of enthusiastic individuals around the world who have had the foresight to see the potential of the subspecialty, coupled with the availability of sophisticated experimental approaches involving genetic, molecular, imaging and engineering tools, which are being used alone or in combination.

Heart Development and Regeneration represents a unique achievement in bringing together leaders in the field presenting current knowledge in a lucid form, making it accessible to a wide range of readers. The inclusion of several chapters on regenerative therapy, arguably the hottest topic in medicine today, represents a natural extension to the topics of developmental biology.

Surgery is often likened to plumbing. There is no self-respecting plumber who would tackle a complex plumbing system in a building without demanding to see the blueprint of how this was put together in the first place!

I am confident that this book will be of great value and offer unique opportunities to both clinicians and researchers in almost every realm of cardiovascular science, medicine and surgery.

Professor Sir Magdi Yacoub FRS
Harefield Heart Science Centre
Imperial College London

Preface

It has now been a decade since our book *Heart Development* was published, and the field has again exploded. A more integrated picture of development, physiology and disease is emerging from our deeper investigations of the genes, proteins and cells, and the functional interactions between them, which build the cardiovascular system. This picture has been immeasurably enhanced by our explorations across the evolutionary landscape. Ten years ago, only a handful of cardiovascular malformations, the most common type of birth defect, could be associated with causative factors, but recent studies have uncovered the genetic basis of many more, and with the advent of forward mutagenic screens in fish and mice, genome-wide association studies in humans, and next generation sequencing, these investigations are now set on an entirely new course, with implications for genetic testing, counseling, long-term patient follow up and choice of intervention.

Much of the progress has been technical: advances in genomics, proteomics, transgenesis and imaging have supplied more exacting tools to dissect and manipulate the embryo and the adult. Furthermore, the amount of biological data generated over the past decade has overwhelmed our ability to understand it without powerful computational approaches. It is logical, then, that these approaches have made it possible to explore cardiac functionality with quantitative models of cells, tissues and organs. By far the most important development over the last decade has been in stem cell biology, yielding access to early processes in the embryo determining cell lineage, as mimicked in the differentiation of embryonic stem cells into cardiomyocytes, as well as providing a new understanding of adult lineages heretofore unimagined, ushering in exciting prospects for their use in regenerative medicine.

Additional important advances have been more conceptual, reflecting the shifting emphasis of the field towards integrative systems biology and the important role that noncoding RNAs and epigenetics play in the cardiac gene regulatory network and cardiovascular disease. Ten years ago, issues of lineage potency, stemness, robustness and meta-stable chromatin states were the purview of a small group of purists. Now they are fast becoming our bread and butter. In the world of systems biology, individual regulatory genes are seen as part of an information machine encoded in the genome, rather than individual enzymes working in an isolated pathway. The search for logic in regulatory circuitry is now well and truly focused at this level. The dominance of genetic determination and reductionism has given way to an appreciation of whole cell integration of activity, informing our approach to the study of cardiac growth and morphogenesis, and causality in disease. Epigenetic regulatory mechanisms assume a more prominent position in our models and the relationship between genome and phenotype grows more intimate. In the developing heart, as in other biological systems, it is becoming increasingly difficult to separate genetic instructions from the process of carrying them out, to distinguish plan from execution.

Heart Development and Regeneration, published in two volumes, attempts to capture a collective snapshot of this fast moving field. Volume I covers the early stages of cardiovascular determination, growth and morphogenesis across the phylogenetic tree, whereas Volume II reviews recent advances in transcriptional and post-transcriptional regulation, epigenetic circuits, systems analysis, the theory and evolution of stem cells, and the molecular and cellular basis of cardiac repair. The chapters are written by the world's experts and provide up-to-date reports from their laboratories, while treating the newcomer to a rich grounding in classical developmental biology of the cardiovascular system.

These books together represent a comprehensive catalog of the individual parts of the whole as we currently know them. They relay current progress on compiling the instructions for putting the parts together in the context of how form and function are generated in the cardiovascular system to sustain life, and how these processes go awry in disease. The stories told in these chapters are full of models; how we study the biology of the developing and regenerating heart is model-dependent, and therefore our models must remain flexible and responsive to the influx of new data. Integrative models are nowhere more relevant than in the cardiovascular system, where function substantially instructs form. Among all the complex organs, the developing heart is exceptionally susceptible to malformation; human congenital heart defects affect an astonishing 0.7% of live births. Although many defects have genetic underpinnings, very few are attributable to a single gene

or protein malfunction. Their origins will in many cases be subtle, context-dependent and grounded in the architecture of the regulatory network, with the environment playing a major role. The results from modeling the feedback loops between physiological function and gene expression may in the beginning seem counterintuitive, yet as we understand these at a systems level, we will gain vital clues to the development of preventative therapeutic approaches or clinical interventions.

As researchers and editors, we have prepared these volumes as a celebration of the beauty and complexity of heart development, its evolution and recapitulation in the context of regeneration. Working closely with our colleagues has been a rewarding experience and we thank them all for their generous donations of time and expertise, for the care and pride in their work, and for their patience in helping us keep these books current through several updates and refinements over the past two years. We thank our editorial assistants Lars Bochmann, Catarina Catela, Sally Dunwoodie, Marianne Hede, Danielle de Jong, Jason Kovacic, Paschalis Kratsios, Enrique Lara-Pezzi, Tommaso Nastasi, Ekaterina Salimova, Maria Paola Santini, Katia Semenova, Duncan Sparrow, Lieve Temmerman, Pascal te Welscher and David Winlaw for their careful comments on the chapter drafts. We are immensely grateful to our artist Kathy Stern, who has once again surpassed herself in the preparation of beautiful and informative illustrations. This book would not be in your hands without the attention and diligence of our publishers at Elsevier, April Graham, Caroline Johnson and Janice Audet, who have worked with us closely to complete this daunting project.

Nadia Rosenthal
Richard Harvey
Sydney, August 2009

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