The new edition of this acclaimed text builds on the "many strengths" (New England Journal of Medicine) of the first edition. New content reflects our evolving understanding of cardiovascular disease in children and the very latest diagnostic tools, therapeutic agents and operative techniques. This important textbook:

• Maintains a focus on clinically relevant information while still explaining essential concepts in the pathophysiology and basic science of childhood cardiovascular disease in children and adults with congenital heart defects

• Presents a wealth of full color photographs and illustrations to underscore key information

• Includes a companion website with self-assessment questions for those preparing for board examination; video clips to help readers master challenging procedures; plus periodic updates on developments in the field

Designed to facilitate ease of use by clinicians, Pediatric Cardiovascular Medicine is the perfect reference for pediatricians, pediatric cardiologists, pediatric cardiac surgeons, trainees in the field, and also for general clinical cardiologists. All of these audiences require a solid foundation in the topics covered in this book in order to provide optimal care to the ever-growing number of adult patients with cardiovascular disease.

RELATED TITLES
Concise Guide to Pediatric Arrhythmias
Wren
ISBN: 978-0-470-65855-0

The Natural and Unnatural History of Congenital Heart Disease
Hoffman
ISBN: 978-1-4051-7927-0

Pediatric Cardiology: The Essential Pocket Guide
Johnson and Moller
ISBN: 978-1-4051-7818-1

COMPANION WEBSITE
This book is accompanied by a companion website:
www.mollerandhoffman.com
COMPANION WEBSITE

This book is accompanied by a companion website:

www.mollerandhoffmantext.com

The website includes:

- Interactive Multiple-Choice Questions
- Videoclips
Pediatric Cardiovascular Medicine

SECOND EDITION

SENIOR EDITORS:

James H. Moller, MD
Adjunct Professor of Medicine
Emeritus Professor and former Head of Pediatrics
University of Minnesota
Minneapolis, MN
USA

Julien I. E. Hoffman, MD, FRCP
Emeritus Professor of Pediatrics
University of California
San Francisco, CA
USA

ASSOCIATE EDITORS:

D. Woodrow Benson, MD, PhD
Professor of Pediatrics
Division of Cardiology
University of Cincinnati School of Medicine and
Cincinnati Children’s Hospital Medical Center
Cincinnati, OH
USA

George F. Van Hare, MD
Professor of Pediatrics
Washington University and
St. Louis Children’s Hospital
St. Louis, MO
USA

Christopher Wren, MBChB, PhD
Consultant Paediatric Cardiologist
Senior Lecturer in Paediatric Cardiology
Freeman Hospital
Newcastle upon Tyne
UK

WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication
This edition first published 2012, © 2012 by Blackwell Publishing Ltd

Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's publishing program has been merged with Wiley's global Scientific, Technical and Medical business to form Wiley-Blackwell.

Registered Office
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Offices
9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell

Previously published as Pediatric Cardiovascular Medicine, Published by Churchill Livingstone.

The right of the author to be identified as the author of this work has been asserted in accordance with the Copyright, Designs and Patents Act 1988.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by the UK Copyright, Designs and Patents Act 1988, without the prior permission of the publisher.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book. This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting a specific method, diagnosis, or treatment by physicians for any particular patient. The publisher and the author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device; for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. Readers should consult with a specialist where appropriate. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

Library of Congress Cataloging-in-Publication Data

p. ; cm.
Includes bibliographical references and index.
LC classification not assigned
618.92’1–dc23
2011030344

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Set in 10/12pt and Meridien by SPI Publisher Services, Pondicherry, India

1 2012
We dedicate this book to our families and those who supported us in developing our careers in pediatric cardiology.

The authors thank the staff of Wiley-Blackwell, particularly Cathryn Gates, Tom Hartman, Kate Newell, Phil Weston and Gill Whitley for their helpfulness at each stage of the publication of this book and supplemental material. Their editorial and production skills have made this an outstanding book.
Contents

List of Contributors, x
Preface, xvii

1 Normal and Abnormal Cardiac Development, 1
   Adriana C. Gittenberger-de Groot, Monique R. M. Jongbloed & Robert E. Poelmann

2 Genetics of Cardiovascular Disease in the Young, 23
   Lisa J. Martin, Robert B. Hinton & D. Woodrow Benson

3 Developmental Physiology of the Circulation, 33
   Abraham M. Rudolph

4 Basic Anatomy and Physiology of the Heart, and Coronary and Peripheral Circulations, 46
   Julien I. E. Hoffman

5 Pulmonary Vascular Pathophysiology, 71
   Marlene Rabinovitch

6 Clinical History and Physical Examination, 81
   James H. Moller

7 Electrocardiography, 102
   Anne M. Dubin

8 Echocardiography, 113
   Rajesh Punn, Mark K. Friedberg & Norman H. Silverman

9 Radiographic Techniques, 157
   Alison K. Meadows

10 Cardiac Catheterization and Angiography, 177
    John D. R. Thomson & Shakeel A. Qureshi

11 Exercise Testing, 200
    Per Morten Frederiksen

12 Thrombosis in Congenital and Acquired Disease, 206
    Lindsay M. Ryerson, M. Patricia Massicotte & Mary E. Bauman

13 Genetic Testing, 222
    Nitin Madan & Bruce D. Gelb

14 Practices in Congenital Cardiac Surgery: Pulmonary Artery Banding, Systemic to Pulmonary Artery Shunting, Cardiopulmonary Bypass, and Mechanical Ventricular Assist Devices, 231
    James D. St. Louis & Roosevelt Bryant III

15 Postoperative Problems, 239
    John M. Costello, Satish K. Rajagopal & Thomas J. Kulik

16 Fetal Treatment, 248
    Helena M. Gardiner

17 Newborn Diagnosis and Management, 254
    Kazuo Momma

18 Noncardiac Problems of the Neonatal Period, 261
    James M. Greenberg

19 The Epidemiology of Cardiovascular Malformations, 268
    Christopher Wren

20 Anatomy and Description of the Congenitally Malformed Heart, 276
    Robert H. Anderson, Anthony M. Hlavacek & Jeffrey Smallhorn

21 Atrial Level Shunts Including Partial Anomalous Pulmonary Venous Connection and Scimitar Syndrome, 289
    Carlos A. C. Pedra & Simone R. Fontes Pedra

22 Atrioventricular Septal Defects, 308
    Stuart Berger, Peter J. Bartz, David E. Saudek, John T. Hambrook & James S. Tweddell

23 Ventricular Septal Defect, 328
    Daniel J. Penny

24 Aortopulmonary Shunts: Patent Ductus Arteriosus, Aortopulmonary Window, Aortic Origin of a Pulmonary Artery, 343
    Jie Shen & D. Woodrow Benson

25 Sinus of Valsalva Fistula, 354
    Alpay Çeliker & Seden Erten Çelik

26 Systemic Arteriovenous Fistula, 358
    Ahmad I. Alomari

27 Left Ventricular Inflow Obstruction: Pulmonary Vein Stenosis, Cor Triatriatum, Supravalvar Mitral Ring, Mitral Valve Stenosis, 374
    Walter H. Johnson Jr & James K. Kirklin

28 Left Ventricular Inflow Regurgitation, 386
    Pierre-Emmanuel Séguela, Bertrand Léobon & Philippe Acar
<table>
<thead>
<tr>
<th>Contents</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>29 Right Ventricular Inflow Obstruction, 401</td>
<td></td>
</tr>
<tr>
<td>James H. Moller</td>
<td></td>
</tr>
<tr>
<td>30 Left Ventricular Outflow Obstruction: Aortic Valve</td>
<td></td>
</tr>
<tr>
<td>Stenosis, Subaortic Stenosis, Supravalvar Aortic Stenosis, and Bicuspid</td>
<td></td>
</tr>
<tr>
<td>Aortic Valve, 406</td>
<td></td>
</tr>
<tr>
<td>Colin McMahon</td>
<td></td>
</tr>
<tr>
<td>31 Left Ventricular Outflow Regurgitation and</td>
<td></td>
</tr>
<tr>
<td>Aortoventricular Tunnel, 426</td>
<td></td>
</tr>
<tr>
<td>Vijaya Joshi &amp; Roxane McKay</td>
<td></td>
</tr>
<tr>
<td>32 Coarctation of the Aorta and Interrupted</td>
<td></td>
</tr>
<tr>
<td>Aortic Arch, 436</td>
<td></td>
</tr>
<tr>
<td>Eric Rosenthal</td>
<td></td>
</tr>
<tr>
<td>33 Right Ventricular Outflow Tract Obstruction, 459</td>
<td></td>
</tr>
<tr>
<td>Philipp C. Lurz, Ingo Daehnert &amp; Philipp Bonhoeffer</td>
<td></td>
</tr>
<tr>
<td>34 Total Anomalous Pulmonary Venous Connection, 476</td>
<td></td>
</tr>
<tr>
<td>Shiv Kumar Choudhary, Sachin Talwar &amp; Sivasubramanian Ramakrishnan</td>
<td></td>
</tr>
<tr>
<td>35 Tricuspid Atresia, 487</td>
<td></td>
</tr>
<tr>
<td>P. Syamasundar Rao</td>
<td></td>
</tr>
<tr>
<td>36 Ebstein Anomaly of the Tricuspid Valve, 509</td>
<td></td>
</tr>
<tr>
<td>David J. Driscoll &amp; Joseph A. Dearani</td>
<td></td>
</tr>
<tr>
<td>37 Anomalies of the Coronary Sinus, 518</td>
<td></td>
</tr>
<tr>
<td>Shannon M. Choudhary, Sachin Talwar &amp; Sivasubramanian Ramakrishnan</td>
<td></td>
</tr>
<tr>
<td>38 Hypoplastic Left Heart Syndrome, 523</td>
<td></td>
</tr>
<tr>
<td>Robert B. Hinton &amp; D. Woodrow Benson</td>
<td></td>
</tr>
<tr>
<td>39 Univentricular Heart, 534</td>
<td></td>
</tr>
<tr>
<td>Jacqueline Kreutzer, César Vegas, Eduardo A. Kreutzer &amp; Guillermo O.</td>
<td></td>
</tr>
<tr>
<td>Kreutzer</td>
<td></td>
</tr>
<tr>
<td>40 Pulmonary Atresia with Intact Ventricular Septum, 572</td>
<td></td>
</tr>
<tr>
<td>Henry Chubb &amp; Piers E. F. Daubeney</td>
<td></td>
</tr>
<tr>
<td>41 Tetralogy of Fallot and Pulmonary Atresia with</td>
<td></td>
</tr>
<tr>
<td>Ventricular Septal Defect, 590</td>
<td></td>
</tr>
<tr>
<td>Andrew Redington</td>
<td></td>
</tr>
<tr>
<td>42 Complete Transposition of the Great Arteries, 609</td>
<td></td>
</tr>
<tr>
<td>Daniel Sidi, Pascal Vouhé &amp; Phalla Ou</td>
<td></td>
</tr>
<tr>
<td>43 Congenitally Corrected Transposition of the Great Arteries, 625</td>
<td></td>
</tr>
<tr>
<td>Tim S. Hornung &amp; A. Louise Calder</td>
<td></td>
</tr>
<tr>
<td>44 Transposition and Malposition of the Great Arteries with</td>
<td></td>
</tr>
<tr>
<td>Ventricular Septal Defects, 638</td>
<td></td>
</tr>
<tr>
<td>Daniel Sidi, Pascal Vouhé &amp; Phalla Ou</td>
<td></td>
</tr>
<tr>
<td>45 Common Arterial Trunk (Truncus Arteriosus), 651</td>
<td></td>
</tr>
<tr>
<td>Albert P. Rochini &amp; Bryan H. Goldstein</td>
<td></td>
</tr>
<tr>
<td>46 Pulmonary Arteriovenous Malformations, 660</td>
<td></td>
</tr>
<tr>
<td>Shivu Kaushik &amp; James Gossage</td>
<td></td>
</tr>
<tr>
<td>47 Vascular Rings, 667</td>
<td></td>
</tr>
<tr>
<td>Kevin K. Whitehead &amp; Paul M. Weinberg</td>
<td></td>
</tr>
<tr>
<td>48 Coronary Arterial Abnormalities and Diseases, 674</td>
<td></td>
</tr>
<tr>
<td>Julien I. E. Hoffman</td>
<td></td>
</tr>
<tr>
<td>49 Pulmonary Artery Sling, 696</td>
<td></td>
</tr>
<tr>
<td>Christian Apitz, Christoph Döhlemann &amp; Jürgen Apitz</td>
<td></td>
</tr>
<tr>
<td>50 Abnormalities of Situs, 702</td>
<td></td>
</tr>
<tr>
<td>Bruno Marino, Paolo Versacci, Paolo Guccione &amp; Adriano Caretti</td>
<td></td>
</tr>
<tr>
<td>51 Pediatric Pulmonary Hypertension, 730</td>
<td></td>
</tr>
<tr>
<td>Cécile Tissot &amp; Maurice Beghetti</td>
<td></td>
</tr>
<tr>
<td>52 Central Nervous System Complications, 753</td>
<td></td>
</tr>
<tr>
<td>Jane W. Newburger</td>
<td></td>
</tr>
<tr>
<td>53 Adults with Congenital Heart Disease, 762</td>
<td></td>
</tr>
<tr>
<td>Anji T. Yetman &amp; Gary D. Webb</td>
<td></td>
</tr>
<tr>
<td>54 Quality of Life and Psychosocial Functioning in Adults</td>
<td></td>
</tr>
<tr>
<td>with Congenital Heart Disease, 773</td>
<td></td>
</tr>
<tr>
<td>Elisabeth M. W. J. Utens, Elisabeth H. M. van Rijen, Petra Opic &amp;</td>
<td></td>
</tr>
<tr>
<td>Jolien W. Roos-Hesselink</td>
<td></td>
</tr>
<tr>
<td>55 Cardiac Arrhythmias: Diagnosis and Management, 784</td>
<td></td>
</tr>
<tr>
<td>George F. Van Hare &amp; Anne M. Dubin</td>
<td></td>
</tr>
<tr>
<td>56 Syncope, 806</td>
<td></td>
</tr>
<tr>
<td>John R. Phillips &amp; Larry A. Rhodes</td>
<td></td>
</tr>
<tr>
<td>57 Cardiovascular Disease, Sudden Cardiac Death, and</td>
<td></td>
</tr>
<tr>
<td>Preparticipation Screening in Young</td>
<td></td>
</tr>
<tr>
<td>Competitive Athletes, 814</td>
<td></td>
</tr>
<tr>
<td>Barry J. Maron</td>
<td></td>
</tr>
<tr>
<td>58 Cardiomyopathies, 826</td>
<td></td>
</tr>
<tr>
<td>Jeffrey A. Towbin</td>
<td></td>
</tr>
<tr>
<td>59 Pericardial Diseases, 855</td>
<td></td>
</tr>
<tr>
<td>Jonathan N. Johnson &amp; Frank Cetta</td>
<td></td>
</tr>
<tr>
<td>60 Infective Endocarditis, 871</td>
<td></td>
</tr>
<tr>
<td>Michael H. Gewitz &amp; Kathryn A. Taubert</td>
<td></td>
</tr>
<tr>
<td>61 Rheumatic Fever, 888</td>
<td></td>
</tr>
<tr>
<td>Shaji C. Menon &amp; Lloyd Y. Tani</td>
<td></td>
</tr>
<tr>
<td>62 Rheumatic Heart Disease, 905</td>
<td></td>
</tr>
<tr>
<td>Raman Krishna Kumar</td>
<td></td>
</tr>
<tr>
<td>63 Kawasaki Disease, 919</td>
<td></td>
</tr>
<tr>
<td>Hirohsa Kato &amp; Kenji Sada</td>
<td></td>
</tr>
<tr>
<td>64 Hypertension in Children and Adolescents, 938</td>
<td></td>
</tr>
<tr>
<td>Bonita Falkner</td>
<td></td>
</tr>
<tr>
<td>65 Cardiovascular Risk Factors: Obesity, Diabetes, and Lipids, 954</td>
<td></td>
</tr>
<tr>
<td>William A. Neal, Collin John &amp; Alia Rai</td>
<td></td>
</tr>
</tbody>
</table>
Contents

66 Cardiac Tumors, 963
   Saroja Bharati

67 Connective Tissue Disorders, 969
   Lut Van Laer & Bart Loey

68 Cardiac Involvement in the Mucopolysaccharide Disorders, 982
   Elizabeth A. Braunlin

69 Cardiovascular Manifestations of Pediatric Rheumatic Diseases, 992
   Bryce A. Binstadt

70 Pediatric Heart Transplantation, 1001
   Rebecca Ameduri & Charles E. Canter

71 Cardiac Failure, 1021

72 Pediatric Cardiology in the Tropics and Underdeveloped Countries, 1032
   Andrea Beaton, Stephanie Lace, Tom Mwambu, Charles Monde, Peter Lwabi & Craig Sable

Index, 1047

COMPANION WEBSITE

This book is accompanied by a companion website:

www.mollerandhoffmantext.com

The website includes:

- Interactive Multiple-Choice Questions
- Videoclips
Philippe Acar, MD, PhD
Pediatric Cardiology Unit
Children’s Hospital
Toulouse University Hospital
Toulouse
France

Ahmad I. Alomari, MD, MSc, FSIR
Program Director, PIR Fellowship
Co-Director, Vascular Anomalies Center
Assistant Professor
Division of Vascular and Interventional Radiology
and Vascular Anomalies Center
Children’s Hospital Boston
Harvard Medical School
Boston, MA
USA

Rebecca Ameduri, MD
Assistant Professor of Pediatrics
University of Minnesota School of Medicine
Minneapolis, MN
USA

Robert H. Anderson, BSc, MD, FRCPath
Visiting Professor of Pediatrics
Medical University of South Carolina
Charleston, SC
USA

Christian Apitz, MD
Staff Physician
Pediatric Cardiology
Pediatric Heart Centre
University Children’s Hospital
Giessen
Germany

Jürgen Apitz, MD
Emeritus Professor of Pediatrics
Division of Pediatric Cardiology
University Children’s Hospital
Tübingen
Germany

Peter J. Bartz, MD
Assistant Professor of Pediatrics
Medical College of Wisconsin
Milwaukee, WI
USA

Mary E. Bauman, RN, BA, MN, NP
Adjunct Professor, Department of Pediatrics
Program Manager, KIDClot Program
University of Alberta
Stollery Children's Hospital
Edmonton, AB
Canada

Andrea Beaton, MD
Professor of Pediatrics
Children’s National Medical Center
George Washington University Medical School
Washington, DC
USA

Maurice Beghetti, MD
Professor of Pediatric Cardiology
University of Geneva
Director of Pediatric Cardiology
The University Children’s Hospital of Geneva
Geneva
Switzerland

D. Woodrow Benson, MD, PhD
Professor of Pediatrics
Divisions of Cardiology
University of Cincinnati School of Medicine and
Cincinnati Children’s Hospital Medical Center
Cincinnati, OH
USA

Stuart Berger, MD
Professor of Pediatrics
Medical College of Wisconsin
Children’s Hospital of Wisconsin
Milwaukee, WI
USA

Saroja Bharati, MD
Director, The Maurice Lev Congenital Heart and
Conduction System Center
The Heart Institute for Children
Advocate Hope Children’s Hospital
Advocate Christ Medical Center
Oak Lawn, IL
Professor of Pathology
Rush University Medical Center
Clinical Professor of Pathology
Rosalind Franklin University of Medicine and Science
Chicago Medical School
Visiting Professor of Pathology
University of Illinois at Chicago
Chicago, IL
USA

Bryce A. Binstadt, MD, PhD
Assistant Professor of Pediatrics
Division of Rheumatology
Department of Pediatrics and Center for Immunology
University of Minnesota
Minneapolis, MN
USA

Philipp Bonhoeffer, MD
Former Professor of Cardiology
Great Ormond Street Hospital for Children
London
UK

Elizabeth A. Braunlin, MD, PhD
Professor of Pediatrics
University of Minnesota
Minneapolis, MN
USA

Roosevelt Bryant III, MD
Assistant Professor
Department of Surgery
University of Minnesota
Amplatz Children’s Hospital
Minneapolis, MN
USA
A. Louise Calder, MD
Paediatric Cardiologist
Green Lane Paediatric and Congenital Cardiac Service
Auckland City Hospital
Auckland
New Zealand

Charles E. Canter, MD
Professor of Pediatrics
Washington University School of Medicine
St. Louis, MO
USA

Adriano Carotti, MD
Associate in Pediatric Cardiac Surgery
Department of Pediatric Cardiology and Cardiac Surgery
Bambino Gesù Children’s Hospital
Rome
Italy

Seden Erten Çelik, MD
Associate Professor of Cardiology
Department of Cardiology
Acibadem University Medical Faculty
Acibadem Maslak Hospital
Maslak
Istanbul
Turkey

Alpay Çeliker, MD
Professor of Pediatrics and Pediatric Cardiologist
Department of Pediatrics
Acibadem University Medical Faculty
Acibadem Maslak Hospital
Maslak
Istanbul
Turkey

Frank Cetta, MD
Professor of Internal Medicine and Pediatrics
Chair, Division of Pediatric Cardiology
Department of Pediatrics
Mayo Clinic College of Medicine
Mayo Clinic
Rochester, MN
USA

Shiv Kumar Choudhary, MS, MCh
Additional Professor
Department of Cardiothoracic Surgery
All India Institute of Medical Sciences
New Delhi
India

Henry Chubb, MA, MBBS, MRCP, MRCPCH
Specialist Registrar in Paediatric Cardiology
Royal Brompton Hospital
London
UK

John M. Costello, MD, MPH
Associate Professor of Pediatrics
Feinberg School of Medicine
Northwestern University
Director, Regenstein Cardiac Care Unit
Division of Cardiology
Children’s Memorial Hospital
Chicago, IL
USA

Ingo Daehnert, MD
Clinical Head of Department of Paediatric Cardiology and Grown Up Congenital Heart Disease
University of Leipzig – Heart Center
Leipzig
Germany

Piers E. F. Daubeney, MA, DM, MRCP, FRCPC, DCH
Consultant Paediatric and Fetal Cardiologist
Royal Brompton Hospital
Reader in Paediatric Cardiology
Imperial College
London
UK

Joseph A. Dearani, MD
Professor of Surgery
Department of Pediatrics
Division of Pediatric Cardiology and Department of Surgery
Division of Cardiovascular Surgery
Mayo Clinic
Rochester, MN
USA

Christoph Döhlemann, MD
Emeritus Professor of Pediatrics
Division of Pediatric Cardiology
Dr. von Haunersches Kinderspital
University of Munich
Munich
Germany

David J. Driscoll, MD
Professor of Pediatrics
Department of Pediatrics
Division of Pediatric Cardiology and Department of Surgery
Division of Cardiovascular Surgery
Mayo Clinic
Rochester, MN
USA

Anne M. Dubin, MD
Director, Pediatric Arrhythmia Center
Lucile Packard Children’s Hospital
Stanford University
Palo Alto, CA
USA

Bonita Falkner, MD
Professor of Medicine and Pediatrics
Thomas Jefferson University
Philadelphia, PA
USA

Per Morten Frederiksen, PT, PhD
Head of Clinical Laboratory
Section for Pediatric Heart, Lung and Allergic Diseases
Division of Pediatrics
Women & Children’s Division
Oslo University Hospital
Nydalen
Oslo
Norway

Mark K. Friedberg, MD
Associate Professor of Paediatrics
The Labatt Family Heart Center
Department of Paediatrics
The Hospital for Sick Children
University of Toronto
Toronto, ON
Canada

Helena M. Gardiner, PhD, MD, FRCP, FRCPC, DCH
Reader and Director in Perinatal Cardiology
Department of Reproductive Biology
Division of Cancer
Imperial College London
Honorary Consultant
Queen Charlotte’s and Chelsea Hospital
Royal Brompton Hospital
London
UK

Bruce D. Gelb, MD
Professor of Pediatrics and Human Genetics
Departments of Pediatrics, Genetic and Genomic Sciences and Child Health and Development Institute
Mount Sinai School of Medicine
New York, NY
USA

Michael H. Gewitz, MD
Physician-in-Chief
Chief Pediatric Cardiology
Maria Fareri Children’s Hospital
Professor and Vice Chairman
Department of Pediatrics
New York Medical College
Valhalla, NY
USA
List of Contributors

**Adriana C. Gittenberger-de Groot, PhD**
Professor of Anatomy and Embryology
Department of Anatomy and Embryology
Leiden University Medical Center
Leiden
The Netherlands

**Bryan H. Goldstein, MD**
Instructor of Pediatrics
Division of Pediatric Cardiology
University of Michigan Health System
Ann Arbor, MI
USA

**James Gossage, MD, FCCP**
Professor of Medicine
Director of Pulmonary Vascular Diseases and HHT
Medical Director of HHT Foundation International
Department of Medicine
Section of Pulmonary and Critical Care Medicine
Medical College of Georgia
Augusta, GA
USA

**James M. Greenberg, MD**
Professor of Pediatrics
Director, Division of Neonatology
Cincinnati Children’s Hospital Research Foundation
Department of Pediatrics
University of Cincinnati College of Medicine
Cincinnati, OH
USA

**Paolo Guccione, MD**
Associate in Pediatric Cardiology
Department of Pediatric Cardiology and Cardiac Surgery
Bambino Gesù Children’s Hospital
Rome
Italy

**John T. Hambrook, MD**
Assistant Professor of Pediatrics
Medical College of Wisconsin
Milwaukee, WI
USA

**Robert B. Hinton, MD**
Assistant Professor
Division of Cardiology
Cincinnati Children’s Hospital Medical Center
University of Cincinnati School of Medicine
Cincinnati, OH
USA

**Anthony M. Hlavacek MD, MSCR**
Assistant Professor of Pediatrics
Cardiology
Attending Physician
Pediatrie Cardiology
Medical University of South Carolina
Charleston, SC
USA

**Julien I. E. Hoffman, MD**
Emeritus Professor of Pediatrics
University of California San Francisco
San Francisco, CA
USA

**Tim S. Hornung, MD**
Paediatric and Adult Congenital Cardiologist
Green Lane Paediatric and Congenital Cardiac Service
Auckland City Hospital
Auckland
New Zealand

**Collin John, MD, MPH**
Assistant Professor of Pediatrics
Department of Pediatrics
Robert C. Byrd Health Science Center
West Virginia University School of Medicine
Morgantown, WV
USA

**Jonathan N. Johnson, MD**
Assistant Professor of Pediatrics
Division of Pediatric Cardiology
Department of Pediatrics
Mayo Clinic College of Medicine
Rochester, MN
USA

**Walter H. Johnson Jr, MD**
Professor of Pediatrics
Division of Pediatric Cardiology
University of Alabama at Birmingham
Alabama Congenital Heart Disease Center
Women & Infants Center
Birmingham, AL
USA

**Monique R. M. Jongbloed, MD, PhD**
Assistant Professor of Cardiac Anatomy and Embryology/Cardiologist
Department of Anatomy and Embryology
Leiden University Medical Center
Leiden
The Netherlands

**Vijaya Joshi, MD**
Medical Director of Non Invasive Cardiology
Le Bonheur Children’s Medical Center
St Jude Children’s Medical Center
Mayo Clinic
Rochester, MN
USA

**Hirohisa Kato, MD, PhD, FACC**
Emeritus Professor of Pediatrics
Honorary President, The Cardiovascular Research Institute
Kurume University School of Medicine
Kurume
Japan

**Beth D. Kaufman, MD**
Director, Heart Failure/Cardiomyopathy Programs
Attending Physician, Division of Pediatric Cardiology
Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine
The Children’s Hospital of Philadelphia
Philadelphia, PA
USA

**Shivu Kaushik, MD**
Fellow, Department of Medicine
Section of Pulmonary and Critical Care Medicine
Medical College of Georgia
Augusta, GA
USA

**James K. Kirklin, MD**
Professor and Director
Division of Cardiothoracic Surgery
University of Alabama at Birmingham
Birmingham, AL
USA

**Eduardo A. Kreutzer, MD**
Chief Emeritus of Cardiology at Hospital de Niños Pedro Elizalde
Director, Centro Cardiovascular Infantil
Buenos Aires
Argentina

**Guillermo O. Kreutzer, MD**
Ex-Chief of Cardiovascular Division
Ricardo Gutierrez Buenos Aires Children’s Hospital
Ricardo Gutierrez Ex-Professor of Pediatrics
Head of Pediatric Cardiovascular Surgery
Department Clinica Baxtterica
University of Buenos Aires
Buenos Aires
Argentina
List of Contributors

Jacqueline Kreutzer, MD, FACC, FSCAI
Associate Professor of Pediatrics
University of Pittsburgh School of Medicine
Director Cardiac Catheterization Laboratory
Children’s Hospital of Pittsburgh of UPMC
Pittsburgh, PA
USA

Thomas J. Kulik, MD
Senior Associate in Cardiology
Department of Cardiology
Children’s Hospital Boston
Associate Professor of Pediatrics
Harvard Medical School
Boston, MA
USA

Raman Krishna Kumar, MD, DM, FACC, FAHA
Clinical Professor and Head of Department
Pediatric Cardiology
Amrita Vishwa Vidyapeetham
Amrita Institute of Medical Sciences and Research Center
Kerala
India

Stephanie Lacey, DO
Pediatric Cardiologist
Assistant Professor of Pediatrics
University of Florida College of Medicine
Jacksonville, FL
USA

Bertrand Léobon, MD, PhD
Pediatric Cardiology Unit
Children’s Hospital
Toulouse University Hospital
Toulouse
France

Kimberly Y. Lin, MD
Fellow, Division of Pediatric Cardiology
The Children’s Hospital of Philadelphia
Philadelphia, PA
USA

Bart Loeys, MD, PhD
Center for Medical Genetics
Antwerp University Hospital
University of Antwerp
Antwerp
Belgium

Philipp C. Lurz, MD
Senior Clinical Fellow
Department of Internal Medicine/Cardiology and Grown Up Congenital Heart Disease
University of Leipzig – Heart Center
Leipzig
Germany

Peter Lwabi, MD
Consultant Paediatrician (Cardiology)
Divisional Head
Department of Paediatric Cardiology
Deputy Director
Uganda Heart Institute
Mulago Hospital
Kampala
Uganda

Shannon M. Mackey-Bojack, MD
Anatomic and Clinical Pathologist
Jesse E. Edwards Registry of Cardiovascular Disease
United Hospital
St Paul, MN
USA

Nitin Madan MBBS, MD
Pediatric Cardiology Fellow
Department of Pediatrics
Mount Sinai School of Medicine
New York, NY
USA

Bruno Marino, MD
Professor of Pediatrics and Director of Pediatric Cardiology
Department of Pediatrics
“Sapienza” – University of Rome
Rome
Italy

Barry J. Maron, MD
Director, Hypertrophic Cardiomyopathy Center
Minneapolis Heart Institute Foundation
Minneapolis, MN
USA

Lisa J. Martin, PhD
Associate Professor
Divisions of Biostatistics and Epidemiology and Human Genetics
Cincinnati Children’s Hospital Medical Center
University of Cincinnati School of Medicine
Cincinnati, OH
USA

M. Patricia Massicotte, MSc, MD, MHSc, FRCP
Professor of Pediatrics
Peter Olley Chair, Pediatric Thrombosis
Director KIDClot Program
University of Alberta
Stollery Children’s Hospital
Edmonton, AB
Canada

Roxane McKay, MD, FRCS, FRSCC
600 Fourth Street SW
Rochester, MN
USA

Colin McMahon, FRCPI, FAAP
Consultant Paediatric Cardiologist
Our Lady’s Children’s Hospital
Crumlin, Dublin
Ireland

Alison K. Meadows, MD, PhD
Adjunct Professor of Pediatrics and Radiology
University of California San Francisco
Director, Adult Congenital Heart Program
Kaiser Permanente of Northern California
San Francisco, CA
USA

Shaji C. Menon, MD
Assistant Professor of Pediatrics
Adjunct Assistant Professor of Radiology
Division of Pediatric Cardiology
University of Utah
Salt Lake City, UT
USA

James H. Moller MD
Adjunct Professor of Medicine
Emeritus Professor and former Head of Pediatrics
University of Minnesota
Minneapolis, MN
USA

Kazuo Momma, MD, PhD
Emeritus Professor of Pediatrics Cardiology
Former Chairman of Department of Pediatric Cardiology
Tokyo Women’s Medical University
Shinjuku, Tokyo
Japan

Charles Mondo, MD
Consultant Physician (Cardiology)
Research and Fellowship Training
Division of Cardiology
Uganda Heart Institute
Mulago Hospital
Makerere University School of Medicine
Kampala
Uganda

Tom Mwambu, MD
Consultant Physician
Division of Cardiothoracic and Vascular Surgery
Uganda Heart Institute
Mulago Hospital
Makerere University School of Medicine
Kampala
Uganda
List of Contributors

Maryam Y. Naim, MD
Attending Physician, Pediatric Cardiac Intensive Care
Department of Anesthesiology and Critical Care Medicine
The Children’s Hospital of Philadelphia
Philadelphia, PA
USA

William A. Neal, MD
Professor and Walker Chair of Preventive Cardiology
Department of Pediatrics
Robert C. Byrd Health Science Center
West Virginia University School of Medicine
Morgantown, WV
USA

Jane W. Newburger, MD, MPH
Commonwealth Professor of Pediatrics
Harvard Medical School
Associate Chief for Academic Affairs
Department of Cardiology
Children’s Hospital
Boston, MA
USA

Petra Opic, MSc
Researcher
Thoraxcentre
Department of Cardiology
Erasmus Medical Centre
Rotterdam
The Netherlands

Phalla Ou, MD
Head of Cardiovascular Radiology
Hôpital Necker – Enfants Malades
Université Paris V
Paris
France

Akash R. Patel, MD
Fellow, Division of Pediatric Cardiology
The Children’s Hospital of Philadelphia
Philadelphia, PA
USA

Carlos A. C. Pedra, MD, PhD
Director, Catheterization Laboratory for Congenital Heart Disease
Instituto Dante Pazzanese de Cardiologia
São Paulo, SP
Brazil

Simone R. Fontes Pedra, MD, PhD
Director, Echocardiography Laboratory for Congenital Heart Disease
Instituto Dante Pazzanese de Cardiologia
São Paulo, SP
Brazil

Daniel J. Penny, MD, PhD
Chief of Cardiology
Texas Children’s Hospital
Professor of Pediatrics
Baylor College of Medicine
Houston, TX
USA

John R. Phillips, MD
Associate Professor of Pediatrics
Section of Pediatric Cardiology
Robert C. Byrd Health Sciences Center
West Virginia University College of Medicine
Morgantown, WV
USA

Robert E. Poelmann, PhD
Professor of Cardiovascular Developmental Biology
Department of Anatomy and Embryology
Leiden University Medical Center
Leiden
The Netherlands

Rajesh Punn, MD
Clinical Assistant Professor
Division of Pediatric Cardiology
Stanford University
Lucile Packard Children’s Hospital
Palo Alto, CA
USA

Shakeel A. Qureshi, FRCP, MD
Professor of Paediatric Cardiology
King’s College London
Consultant Paediatric Cardiologist
Department of Paediatric Cardiology
Evelina Children’s Hospital
Guy’s and St. Thomas’ Hospital
London
UK

Marlene Rabinovitch, MD
Dwight and Vera Dunlevie Professor of Pediatric Cardiology
Stanford University School of Medicine
Stanford, CA
USA

Alia Rai, MD
Research Assistant Professor of Pediatrics
Department of Pediatrics
Robert C. Byrd Health Science Center
West Virginia University School of Medicine
Morgantown, WV
USA

Satish K. Rajagopal, MD
Assistant in Cardiology
Department of Cardiology
Children’s Hospital Boston
Instructor of Pediatrics
Harvard Medical School
Boston, MA
USA

Sivasubramanian Ramakrishnan, MD, DM
Assistant Professor
Department of Cardiology
All India Institute of Medical Sciences
New Delhi
India

P. Syamasundar Rao, MD
Professor of Pediatrics and Medicine
University of Texas at Houston Medical School
Director, Division of Pediatric Cardiology
Children’s Memorial Hermann Hospital
Professor of Pediatrics
University of Texas MD Anderson Cancer Center
Houston, TX
USA

Andrew Redington, MD, FRCP
Professor of Paediatrics
University of Toronto
Head, Division of Cardiology
Hospital for Sick Children
Toronto, ON
Canada

Larry A. Rhodes, MD
Professor of Pediatrics
Chief, Section of Pediatric Cardiology
Robert C. Byrd Health Sciences Center
West Virginia University College of Medicine
Morgantown, WV
USA

Albert P. Rocchini, MD
Professor of Pediatrics
Division of Pediatric Cardiology
University of Michigan Health System
Ann Arbor, MI
USA

Jolien W. Roos-Hesselink, MD, PhD
Professor of Congenital Cardiology
Director of Adult Congenital Heart Disease Programme
Thoraxcentre
Department of Cardiology
Erasmus Medical Centre
Rotterdam
The Netherlands
Eric Rosenthal, MD, FRCP  
Consultant Paediatric and Adult Congenital Cardiologist  
Evelina Children's Hospital  
St Thomas’ Hospital  
London  
UK  

Abraham M. Rudolph, MD  
Emeritus Professor of Pediatrics  
University of California San Francisco  
San Francisco, CA  
USA  

Lindsay M. Ryerson, MD, FRCP  
Assistant Professor of Pediatrics  
University of Alberta  
Staff Physician Pediatric Cardiology and Pediatric Critical Care  
Stollery Children’s Hospital  
Edmonton, AB  
Canada  

Craig Sable, MD  
Director, Echocardiography and Cardiology Fellowship Training  
Medical Director, Telemedicine  
Children’s National Medical Center  
Professor of Pediatrics  
George Washington University  
Medical School  
Washington, DC  
USA  

David E. Saudek, MD  
Assistant Professor of Pediatrics  
Medical College of Wisconsin  
Milwaukee, WI  
USA  

Pierre-Emmanuel Séguela, MD  
Pediatric Cardiology Unit  
Children’s Hospital  
Toulouse University Hospital  
Toulouse  
France  

Robert E. Shaddy, MD  
Jennifer Terker Professor of Pediatrics  
University of Pennsylvania School of Medicine  
Medical Director  
Heart Transplant Program  
Division Chief  
Pediatric Cardiology  
The Children’s Hospital of Philadelphia  
Philadelphia, PA  
USA  

Mauly J. Shah, MBBS  
Director, Electrophysiology Section  
Division of Pediatric Cardiology  
Associate Professor of Pediatrics  
University of Pennsylvania School of Medicine  
The Children’s Hospital of Philadelphia  
Philadelphia, PA  
USA  

Jie Shen, MD  
Associate Professor  
Shanghai Jiaotong University  
Director of Cardiology  
Cardiology Department  
Children’s Hospital of Shanghai  
Shanghai  
China  

Daniel Sidi, MD  
Head of Pediatric Cardiology  
Hôpital Necker – Enfants Malades  
Université Paris V  
Paris  
France  

Norman H. Silverman, MD, DSc  
Professor of Pediatrics  
The Roma and Marvin Auerback Scholar in Pediatric Cardiology  
Division of Pediatric Cardiology  
Stanford University  
Lucile Packard Children’s Hospital  
Palo Alto, CA  
USA  

Jeffrey Smallhorn, MD, FRCP  
Professor of Pediatrics  
Staff Physician Pediatric Cardiology  
Program Director Pediatric Cardiology  
Stollery Children’s Hospital  
Edmonton, AB  
Canada  

James D. St. Louis, MD  
Aldo R. Castaneda Associate Professor  
Department of Surgery  
Director, Pediatric Cardiac Surgery  
University of Minnesota  
Amplatz Children’s Hospital  
Minneapolis, MN  
USA  

Kenji Suda, MD, PhD  
Associate Professor of Pediatrics  
Department of Pediatrics and Child Health  
Kurume University School of Medicine  
Kurume  
Japan  

Sachin Talwar, MS, MCh  
Associate Professor  
Department of Cardiothoracic Surgery  
Department of Cardiology  
All India Institute of Medical Sciences  
New Delhi  
India  

Lloyd Y. Tani, MD  
Professor of Pediatrics  
Division of Pediatric Cardiology  
University of Utah  
Salt Lake City, UT  
USA  

Kathryn A. Taubert, PhD, FAHA  
Professor of Physiology  
University of Texas Southwestern Medical School  
Dallas, TX  
USA  
Senior Science Officer  
World Heart Federation  
Geneva  
Switzerland  

John D. R. Thomson, FRCP, MD  
Consultant Paediatric Cardiologist  
Department of Congenital Heart Disease  
Leeds General Infirmary  
Leeds  
UK  

Cécile Tissot, MD  
Research Associate  
Pediatric Cardiology Unit  
The University Children’s Hospital of Geneva  
Geneva  
Switzerland  

Jeffrey A. Towbin, MD  
Executive Co-Director, The Heart Institute  
Kindervelt-Samuel Kaplan Professor and Chief  
Pediatric Cardiology  
Cincinnati Children’s Hospital  
Cincinnati, OH  
USA  

James S. Tweddell, MD  
The S. Bert Litwin Chair, Cardiothoracic Surgery  
Children’s Hospital of Wisconsin  
Professor of Surgery and Pediatrics  
Chair, Division of Cardiothoracic Surgery  
Medical College of Wisconsin  
Milwaukee, WI  
USA  

xv
List of Contributors

Elisabeth M. W. J. Utens, PhD
Clinical Psychologist
Associate Professor, Department of Child and Adolescent Psychiatry
Research Coordinator, Psychosocial Care
Erasmus Medical Centre
Sophia Children's Hospital
Rotterdam
The Netherlands

George F. Van Hare, MD
Director, Pediatric Cardiology
Professor of Pediatrics
Washington University
St. Louis Children's Hospital
St. Louis, MO
USA

Lut Van Laer, PhD
Center for Medical Genetics
Antwerp University Hospital
University of Antwerp
Antwerp
Belgium

Elisabeth H. M. van Rijen, PhD
Assistant Professor of Psychology
Institute of Psychology
Erasmus University Rotterdam
Rotterdam
The Netherlands

Paolo Versacci, MD
Staff Physician, Pediatric Cardiology
Department of Pediatrics
“Sapienza” – University of Rome
Rome
Italy

César Viegas, MD
Senior Associate in Cardiology
Ricardo Gutierrez Children’s Hospital Buenos Aires
Director, Postgraduate Pediatric Cardiology
Subspecialty Training Course
University of Buenos Aires Medical School
Buenos Aires
Argentina

Pascal Vouhé, MD
Head of Cardiac Surgery
Hôpital Necker – Enfants Malades
Université Paris V
Paris
France

Gary D. Webb, MD
Professor of Pediatrics and Internal Medicine
University of Cincinnati
Director, Adolescent and Adult Congenital Heart Disease Program
The Heart Institute
Cincinnati Children’s Hospital Medical Center
Cincinnati, OH
USA

Paul M. Weinberg, MD
Professor of Pediatrics and Pediatric Pathology and Laboratory Medicine
Associate Professor of Radiology
The Children's Hospital of Philadelphia
University of Pennsylvania
School of Medicine
Philadelphia, PA
USA

Kevin K. Whitehead, MD, PhD
Assistant Professor of Pediatrics
The Children's Hospital of Philadelphia
University of Pennsylvania
School of Medicine
Philadelphia, PA
USA

Christopher Wren, MBChB, PhD
Consultant Paediatric Cardiologist
Senior Lecturer in Paediatric Cardiology
Freeman Hospital
Newcastle upon Tyne
UK

Anji T. Yetman, MD
Associate Professor of Pediatrics
Director, Adult Congenital Cardiac Program
Primary Children’s Medical Center
University of Utah
Salt Lake City, UT
USA
Preface

With the expansion of knowledge and methods of diagnosis and treatment of cardiac abnormalities occurring in childhood, the major textbooks on the subject have also expanded, often beyond a single volume. In our book, *Pediatric Cardiovascular Medicine*, we have attempted to be concise and focused, and publish a single volume containing contemporary knowledge of pediatric cardiology. The book is available both as a text and online for the convenience of readers who may have different needs. For readers of the textbook there is supplemental material online, including videos of cardiac images. We have focused on the international aspects of pediatric cardiology, both in content and in the selection of authors from 16 countries to contribute chapters. In this edition we have included new chapters about pediatric cardiology in the tropics and developing countries, and about rheumatic heart disease in children (a major problem in many countries with limited health resources).

The chapters are grouped according to subject matter. The first five chapters present basic scientific information that underlies pediatric cardiology and includes cardiac development and developmental physiology, basic cardiopulmonary physiology, pulmonary vascular physiology and pathology and genetics. The subsequent eight chapters discuss the various diagnostic methods to evaluate cardiovascular problems in childhood, particularly echocardiography, advanced radiologic imaging techniques and genetic testing. Two chapters follow which discuss bypass techniques and postoperative care and three about the fetus and neonates, including fetal treatment, neonatal diagnosis and circulatory issues of small neonates.

A major portion of the book covers congenital heart disease. After chapters on epidemiology and cardiac anatomy, descriptions of individual malformations are presented primarily in the following order: left-to-right shunts, outflow and inflow tract obstruction and regurgitation, anomalies associated with a right-to-left shunt, and then vascular and situs anomalies. In most of the 25 chapters about congenital heart disease, the organization and structure of the chapters are similar, making it easier for the reader.

The final 22 chapters concern various acquired conditions affecting the cardiovascular system during childhood. The issues of adults with CHD and the quality of life after cardiac treatment are discussed in separate chapters and where relevant within individual chapters.

As editors, we sought to emphasize pathophysiologic principles or understanding to help the reader comprehend and retain the information. Each chapter contains pertinent references to enable the reader to explore the subjects further.

Since the previous edition, echocardiographic techniques have advanced significantly; interventional methods have been developed to include a wider range of abnormalities and imaging techniques, particularly with magnetic resonance which has allowed more detailed information about cardiovascular structure and function. These are being widely applied to children.

Finally, we added three Associate Editors to assist in the preparation of this expanded edition and we appreciate their careful review of chapters and editorial comments.

James H. Moller, MD
Julien I. E. Hoffman, MD, FRCP
Senior Editors
1

Normal and Abnormal Cardiac Development

Adriana C. Gittenberger-de Groot, Monique R. M. Jongbloed & Robert E. Poelmann
Leiden University Medical Center, Leiden, The Netherlands

Introduction

In this chapter, the main events of cardiac morphogenesis are discussed. We focus on morphologic descriptions and insights based on the molecular biologic approaches in animal models that have enhanced and modified our understanding of normal and abnormal cardiac development, including relevance for adult disease with a developmental background.

Advances and limitations in studying human development

The normal cardiovascular development of the human embryo in its crucial stages from 2 to 8 weeks’ gestation has to be deduced from postmortem morphologic studies of abortion material [1]. In this category we are mainly dealing with spontaneous abortions and do not know whether the material reflects normal morphogenesis. Descriptions in the literature referring to normal and abnormal human development do not emphasize this aspect. An addition to early detection of human embryonic malformations, mainly providing information on disturbed genes and chromosomes, is provided by amniocentesis, chorionic villus biopsies, and subsequent FISH (fluorescent in situ hybridization) analysis with genetic markers. However, these are not examined within the first crucial 8 weeks of development. Fetal diagnosis is a rapidly expanding area with increasing technical possibilities of ultrasound and echo-Doppler investigations in utero. The earliest observations indicating normal or abnormal heart development refer to 11–12 weeks’ gestation [2]. Consequently, our knowledge of detailed cardiac morphogenesis relies on describing processes in animal species, the main embryonic models being avians (chick and quail) and rodents (mouse and rat) and more recently the zebrafish. With the development of transgenic techniques, the mouse embryo has become important, and we will regularly refer to mouse embryo models when discussing certain abnormalities of cardiac development.

Knowledge about an embryonic lethal phenotype after a gene knockout and the absence of a phenotype might contribute little to the understanding of human congenital cardiac malformations [3]: 85% of the diagnosed human cardiac malformations are described as having a multifactorial origin. Epigenetic, environmental, biomechanical, and hemodynamic factors have been underestimated in research on cardiogenic programming. Their role in the development of cardiac malformations has previously been acknowledged, however, and has led to the so-called mechanistic classification [4]. There are a few recent publications linking hemodynamics to cardiovascular developmental abnormalities [5–8], but their relation to gene expression and cardiogenic patterning is unclear. A multidisciplinary approach combining clinical knowledge with basic science will lead to new insights into developmental processes.

Formation of the cardiogenic plates and the cardiac tube

The cardiac developmental program starts with the formation within the splanchnic mesoderm of the bilateral cardiogenic plates, which give rise to the myocardium and probably to parts of the endocardium (Figure 1.1). The splanchnic mesoderm at the endoderm/mesoderm interface differentiates into the vascular endothelium [9] and part of the endocardium [10,11]. The evidence for a cardiogenic plate origin of the endocardium supports a dual origin for this layer of the heart [12].
The bilateral asymmetric cardiogenic plates can be delineated early in embryonic life because several transcription factors and proteins are expressed. These expression patterns distinguish a first or primary heart field (PHF) laterally flanking the second heart field (SHF) component of the cardiogenic plate (Figure 1.2a). Whereas the first heart field differentiates, the secondary component remains part of the body wall mesoderm before its cells are recruited and incorporated into the poles of the cardiac tube. With formation of the cardiac tube, the pericardial coelomic cavity becomes continuous across the midline and the ventral mesocardium disappears. The cardiac tube is thereafter solely connected to the dorsal body wall or splanchnic mesoderm by the dorsal mesocardium that runs from the developing pharyngeal arches (arterial pole) to the sinus venosus (venous pole) (Figure 1.3). At this stage, the tube consists of an inner endocardial and an outer myocardial layer separated by cardiac jelly (Figures 1.2b and 1.3a).

Initially, the primitive cardiac endothelial network is remodeled into a single endocardial tube that connects the omphalomesenteric veins to the pharyngeal arch vasculature (Figure 1.1). The asymmetric cardiac jelly surrounding the endocardial tube suggests bilateral endocardial tubes, giving the wrong impression that two endocardial tubes have to fuse. From the onset, however, the endocardial tubes are connected by endocardial cells that cross the midline [13]. Real cardia bifida can occur spontaneously and can also be produced experimentally by retinoic acid overdose in the chicken embryo [14] or in a zebrafish mutational screen [15]. Therefore, each cardiogenic plate can potentially give rise to an independent cardiac tube, implying that fusion of the cardiogenic plates is unnecessary for the onset of cardiac formation. Nevertheless, cardia bifida is lethal to the embryo as further cardiac development is hampered and no connection with the endothelium of the pharyngeal vascular system is established.

**Looping of the cardiac tube**

The single cardiac tube is never completely straight as both cardiogenic plates have different dimensions [12]. Normally the cardiac tube loops to the right (D-loop) (Figure 1.2). Abnormalities in looping such as L-loop or anterior-loop formation are related to ventricular inversion, which differs from laterality problems as seen in abnormalities of the atrial situs.

The mechanisms underlying the looping direction are poorly understood, but several regulating genes have been described, such as sonic hedgehog, nodal and activin receptor I1a [16]. In mouse mutants iv/iv and inv, the laterality of the heart is also affected. The iv gene has been mapped to chromosome 12 in the mouse and is syntenic to chromosome 14q in the human. In the human, this abnormality is reflected in the heart by atrial isomerism and is discussed below when considering atrial development and septation.

During looping, the outflow tract becomes more ventrally positioned, moving in front of the atrioventricular (AV) canal. The arterial and venous poles remain fixed to the dorsal body wall (Figure 1.4 and Videoclip 1.1). Both remodeling of the inner curvature (site of the disruption of the dorsal mesocardium) and asymmetric addition of SHF-derived myocardium to the primary heart tube are essential for proper looping.

**Contribution of first and second heart fields**

Recent mouse studies, based on various transgenic mouse models with cell tracing [17–19], have shown that the primary heart tube does not contain all components necessary for the future mature heart [20]. The first heart field provides only for the AV canal and the future left ventricle (LV), implying that the primary heart tube already has additions of the second heart field (SHF) at both poles. The primary heart tube connects the omphalomesenteric veins at the venous pole via a small atrial component, the AV canal, and a primitive LV and small outflow tract component to the aortic sac and the first pair of pharyngeal arch arteries at the arterial pole (Figures 1.2 and 1.3).
Figure 1.2 Development of the heart from the first and second heart fields. (a) In the primitive plate, bilateral fields of cardiac mesoderm are present. Progenitor cells migrate from the primitive streak to the bilateral mesoderm (arrows). Cells depicted in yellow will contribute to the second heart field-derived parts of the heart, whereas cells depicted in brown depict the primary heart fields that will contribute the primary myocardial heart tube. (b) Schematic representation of the primary heart tube, consisting of endocardium and myocardium, with myocardial jelly between the two layers. Initially the primitive heart tube consists mainly of the AV canal and the LV. (c) After looping, several transitional zones can be distinguished in the tube, namely the sinoatrial transition (light blue, SAR) in between the sinus venosus and common atrium, the AV transition (dark blue, AVR) in between the common atrium and common ventricle, the primary fold (yellow, PF) in between the primitive right ventricle (RV) and LV, and a ventriculoarterial transitional (green, VAR) zone at the outflow tract (OT) of the heart. Second heart field-derived parts of the heart are depicted in yellow. (d) The heart after completion of atrial and ventricular septation. Due to outgrowth of the RV, a remodeling of the PF has occurred, and it has divided into a lateral septal part, the trabecula septomarginalis (TSM), that contains the right bundle branch [RBB, see (e)] and continues into the moderator band (MB). (e) Part of the transitional zones will contribute to definitive elements of the cardiac conduction system, depicted in red. Bright blue dots depict neural crest cells that contribute to the network of autonomic nerve fibers surrounding the sinoatrial node (SAN) and atrioventricular node (AVN). Shaded blue dots surrounding elements of the cardiac conduction system indicate neural crest cells with an inductive role in conduction system development. A, common atrium; AP, arterial pole; Ao, aorta; Ao sac, aortic sac; CV, cardinal vein; CS, coronary sinus; ICV, inferior caval vein; LA, left atrium; LAA, left atrial appendage; LBB, left bundle branch; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary veins; RA, right atrium; RAA, right atrial appendage; SCV, superior caval vein; VP, venous pole. (Copyright Leiden University Medical Center.)
The cardiac splanchnic mesoderm consists of so-called SHF. This precardiac mesoderm is added at both the arterial and venous poles of the heart, mainly contributing myocardium but also smooth muscle cells of connecting vessels.

The mesodermal cell population grows in a caudocranial direction [21]. Recruitment starts at the arterial pole and almost the complete myocardium of the right ventricle (RV) including the outflow tract and the larger part of the ventricular septum is derived from the SHF. The smooth muscle cells of the aortic sac are derived from this source, although probably asymmetric with respect of contribution to the pulmonary and aortic aspects. More restricted studies of the outflow tract have led to a confusing nomenclature with respect to anterior heart field [22] and secondary heart field [23], the latter often being confused with SHF that contributes to both arterial and venous poles.

At the venous pole, the myocardium lining the sinus venosus derives from SHF mesoderm referred to as posterior heart field (PHF) [24]. Incorporation of the sinus venosus implies that the myocardium of the sinoatrial node, the venous valves, the atrial septum, and the cardinal and pulmonary veins also come from this source. A further mesenchymal derivative of the SHF is the proepicardial organ (PEO), which is crucial for many aspects of differentiation of the heart (see below).

Several transcription factors and morphogenetic genes and cascades are important in the precardiac mesoderm of both first heart field and SHF [25]. Specification of the precardiac cells is accompanied by early expression of TGFβ family members, including BMP4 (bone morphogenetic protein), followed by the earliest known marker for the cardiogenic lineage – the homeobox (Hox)-containing gene Nkx2.5 (homolog to tinman in Drosophila) [26] and the zinc finger-containing GATA 4/5/6 cluster of transcription factors [27]. Mesp1 [28] and Mef2c [29] are also early cardiac mesoderm markers. Recently, the platelet-derived growth factor receptor (PDGFRα) was added to this list [30]. Patterning of the heart field from arterial to venous pole is accompanied by the expression of T-box gene family members Tbx1, 5 and 20, Fgf 8 and 10, and Isl1. Finally, differentiation during heart tube formation involves, for example, MLC and MHC, alpha cardiac actin and troponin I, and RhoA [31]. Mouse models in which these genes are used for cell tracing and complete or conditional knockout provide essential data on their relevance for normal and abnormal cardiac development. In some instances, such as Nkx2.5, [32] human mutations are known.
Segmentation of the heart tube

The primary heart tube consists of myocardium lined on the inside by cardiac jelly and endocardium. A number of genes are expressed along the anterior/posterior axis and there is from the onset a right–left designation. Chamber outgrowth or ballooning, intricately regulated by a balance of Tbx2 and Tbx3 transcription factor expression [33], brings out more clearly the segments (atrial and ventricular chambers) and the transitional zones. These areas stand out against the myocardial trabeculated atrial and ventricular walls. Figure 1.2b–e depicts the cardiac segments and transitional zones. Starting at the inflow at the venous pole, we can distinguish the sinus venosus, the atrium, the atrioventricular canal, the primitive LV, the primary fold, and the primitive RV that develops into a trabeculated part and a part lined by endocardial outflow tract cushions. In general, the endocardial cushion-lined transitional zones form the atrioventricular and semilunar valves and function initially as temporary valves accompanying peristaltic contractions of the cardiac tube. The myocardium of the sinus venosus (considered as a transitional zone), the AV canal, the primary fold, and the endocardial cushion-lined outflow tract are important for the formation of the future cardiac conduction system. Furthermore, these transitional zones are involved in septation.

Neural crest and epicardium contributions

For many years, the neural crest and epicardial cells were described as extracardiac contributors essential for proper differentiation of the developing heart. With new insights into the contribution of the SHF, we need to adjust their relevance.

Neural crest cells are an extracardiac source of cells that migrate from the neural crest through the mesoderm of the SHF to the cardiac tube. The main entrance site into the heart is at the arterial pole, but they also reach the venous pole of the heart [34,35] (Figures 1.3b and 1.5). These neural crest cells differentiate into smooth muscle cells of the great arteries and into the cells of the autonomic nervous system that are needed to innervate the great arteries and the coronary arteries, and for the nodes of the cardiac conduction system (Figures 1.2e and 1.5). The neural crest cells that migrate into the heart do not differentiate into a particular cardiac cell but go into apoptosis. Through release or activation of growth factors such as TGFβ they may induce myocardialization of the outflow tract septum and, at the venous pole, differentiation of the cardiac conduction system [36,37]. They are also important in the interaction with the SHF cells, mainly in the pharyngeal region, so that genetic mutations of both cell types can lead to congenital heart disease. This is best exemplified in the Tbx1-related 22q11 deletion syndrome [38].

The epicardium develops from the proepicardial organ, an epithelial derivative of the PHF at the venous pole (depicted in Figure 1.3b). These cells differentiate into smooth muscle cells and cardiac fibroblasts and migrate to many cardiac structures where their function is less known [39]. Suggestions, based on cell tracing in transgenic mouse
gene expression patterns, regard the pulmonary veins by Van Praagh and Corsini [45]. Other groups, focusing on mouse and the human embryo [43,44], and earlier postulated left atrium and pulmonary veins, as suggested for both the sinus venosus also contributes to the posterior wall of the sinus venosus incorporation and atrial septation.

The sinus venosus in the developing heart forms an intermediate transitional zone between the systemic cardiac veins and the developing atrium proper, and now receives much attention as the myocardium of the sinus venosus is derived from the PHF mesoderm, showing specific gene expression patterns. On the basis of endothelial vascular histochemistry, we demonstrated that the sinus venosus is derived from the PHF mesoderm, showing specific gene expression patterns that partly differ from the outflow tract. This refers to the transcription factors Tbx18, 20 [48], Shox2 [49], the functional marker HCN4 [50], and the growth factors RhoA [31] and PDGFRα [30,51]. The sinus venosus myocardium is Nkx2.5 negative before incorporation into the dorsal atrial wall and remains as such in the sinoatrial node. Transgenic mouse studies of these genes and some human mutations correlate with abnormalities in PHF-derived structures, including conduction system disturbances.

Figure 1.5 (a) Whole mount staining of a chicken heart (stage HH 35) that shows the neural crest-derived cells after a retroviral transporter gene marker containing lacZ. The neural crest cells are present at the arterial pole (AP) as smooth muscle cells in the vessel wall and over the heart as fine nerve fibers (N). The neural crest cells also reach the venous pole (VP) of the heart, where they enter the atrioventricular region through the dorsal mesocardium. (b) A section through the inflow and outflow tract of a chicken heart in which the neural crest cells are seen in the outflow tract septum (OTS) and also at the base of the atrial septum (AS) (arrows), where they have arrived through the dorsal mesocardium. The brown staining of the outflow tract septum (OTS) neural crest cells by the TUNEL [TdT-mediated dUTP (deoxyuridine triphosphate) nick end labeling] technique detected apoptosis of these cells. A, atrium; LA, left atrium; LVOT, left ventricular outflow tract; RA, right atrium; RVOT, right ventricular outflow tract; V, ventricle. (Copyright Leiden University Medical Center.)

Cardiac differentiation and development of cardiac malformations

Sinus venosus incorporation and atrial septation

The above data provide new insights into abnormal pulmonary venous connections and also atrial septal defects (ASDs). The primary atrial septum becomes perforated to form the ostium secundum that is never completely closed off by the septum secundum. The complex of the lower rim of the septum secundum and the ostium secundum is called the foramen ovale (Figure 1.6, arrow). The muscular secondary atrial septum is in its basal and dorsal part fused with the DMP. The major anterior and superior parts of the secondary atrial septum are merely a folding of the atrial wall forming the limbus fossa ovalis on the right side of the atrial septum.

Consequences for abnormal development

The above data provide new insights into abnormal pulmonary venous connections and also atrial septal defects (ASDs) and atrioventricular septal defects (AVSDs).

Abnormal pulmonary venous connection

As the plexus for forming the pulmonary veins has extensive connections to the cranial and caudal parts of the cardinal veins [52], persistent connections can lead to supracardiac and infracardiac pulmonary venous connection patterns. For cardiac abnormal pulmonary venous connection, the pulmonary veins do not grow out of the left atrial dorsal wall but...
are connected to the left atrial wall through incorporation of the sinus venosus. Disturbance of genes in the PHF can lead to abnormal formation of the wall of the pulmonary veins and the left atrium [53]. Familial total anomalous pulmonary venous connection (TAPVC) has been mapped to chromosome 4p13-q12 in the region near the PDGFRα gene. A knockout mouse of this gene shows TAPVC [51]. Interestingly, the DMP and mesenchymal cap are very hypoplastic in this model, leading to AVSD (see below). A recent review described the current clinical, genetic, and developmental data on pulmonary venous development and abnormalities [54]. Only pulmonary veins connected to the left atrium acquire a myocardial cuff [44]. This cuff is lacking in veins that connect to the right atrium or a spatium pulmonale.

**Atrial septal defects**

The most common defect is the septum secundum defect (ASD II), in which there is a discrepancy between the septum secundum (demarcated on the right side by the limbus) and the free edge of the fenestrated septum primum. In normal circumstances they overlap as two crescents (Figure 1.6) that fuse after birth. Defective development, including perforations, of the valve of the septum primum, the so-called valve of the foramen ovale, can also lead to an ASD. It is necessary to distinguish between retarded closure of the foramen ovale and a real secundum ASD.

Abnormalities in formation of the base of the atrial septum secundum can lead to so-called sinus venosus ASD, where both the inferior and superior caval veins are closely related to the defect and the pulmonary veins are often abnormally positioned [43].

Based on our new knowledge of addition of the PHF to both the atrial septal components and also the pulmonary veins, some genes are good candidates for study. We already know human mutations in Tbx5 (Holt–Oram syndrome) [55], Nkx2.5 [56], and the PDGFRα region [51] that explain the separate or combined abnormalities in atrial septation, pulmonary venous connection, and in...
some patients conduction system problems particularly related to pace-making.

**Atrioventricular septal defects**

AVSDs are intriguing malformations with many postulated causes, including deficient differentiation of the AV valves and the endocardium lining these valves. This has been extensively studied [57] for the trisomy 21 (Down syndrome) and the syntenic trisomy 16 mouse model without resolution. In the human embryo with AVSD, however, studies of the disposition of the conduction system demonstrated a deficiency of the spina vestibuli (now DMP) and the mesenchymal cap [58], now confirmed in mouse models [47,59]. The primary ASD resulting from non-fusion with the AV cushions can now be explained by the hypoplasia of the mesenchymal cap lining the lower rim of the primary atrial septum. The deficiency of the ventricular inlet septum in humans still needs clarification [60]. The fact that the AV valve tissue in AVSD seems structurally normal confirms that abnormal AV endocardial cushion differentiation is not the primary problem.

Although the heart has two left- and two right-sided chambers, asymmetry is a dominant feature in both form and function. The ventricular asymmetry is determined during looping, whereas the atrial differences are determined by genetic regulation, involving, for example, Pitx2 [61,62]. Pitx2 acts in breaking symmetry in early development, is present in the left-sided plate mesoderm only, and has subsequent roles in differentiation of the inflow and outflow segment of the heart. Pitx2 mutant mice present with right atrial isomerism, suggesting inhibition of the left program. Pitx2 mutants may present syndrome-like malformations also involving other organs, for instance the spleen, showing polysplenia in left isomerism and asplenia in right isomerism. Furthermore, DNA sequence variations close to Pitx2 have been described in patients with atrial fibrillation and atrial flutter [63]. Morphologists and clinicians are aware of the differences in the right and left atria, the most obvious being the appendage. Furthermore, the right posterior wall is trabeculated whereas the left is smooth. Usually, atrial situs correlates with bronchial anatomy (see Chapter 50). Lung lobulation, difficult to assess for the clinician, is less reliable.

**Ventricular inflow tract septation and the formation of the RV inlet**

The RV myocardium with all its components, including at least the right part of the ventricular septum, is derived from the anterior SHF [18]. At the border between the primitive LV and the developing RV, a myocardial ring called the primary ring or fold, previously referred to as bulboventricular fold, can be distinguished [64]. The primary fold is considered a transitional zone and attracts a great deal of attention because it forms the major part of the ventricular inlet and trabecular septum and contains precursors of the AV conduction system.

The primary fold borders on the inner curvature of the heart where it coalesces with the right side of the AV canal (Figure 1.2c). The lower part of the primary fold becomes a real septum by local condensation of the ventricular trabeculae combined with ballooning of the apices of both the LV and RV. Closure of the primary interventricular foramen between the RV and LV takes place by fusion of the inferior and superior atrioventricular cushions in combination with one of the outflow tract endocardial ridges that is connected to this superior cushion.

The role of the primary fold as progenitor of the main body of the ventricular septum deserves special attention. A proper septum is only established when a RV with the tricuspid valve and its orifice is formed. This has to be achieved during development and is important for forming the right ventricular inlet compartment. The right part of the AV canal with the adjoining part of the primary fold has to be transferred to the right side (for remodeling of the primary fold, see Figure 1.2c–e and Videoclip 1.2). Our opinion is that this is achieved by a widening in the dorsal wall of the ventricle adjacent to the primary fold. We have been able to support this developmental concept in a model for Mahaim conduction [65]. With growth of the initial minute inflow part of the RV, a new posterior wall of the right ventricle is formed. In this way, the RV consists eventually of three parts: the RV inlet, bordered by the remnants of the primary fold (trabecula septomarginalis and moderator band), the RV trabecular part (embryonic proximal ventricular outlet segment), and part of the distal ventricular outlet segment underneath the pulmonary orifice.

From an RV view, the ventricular septum is made up of three parts (Figure 1.7): 1 The inlet septum that is formed concurrently with expansion of the RV inflow. 2 This is separated from the trabecular part of the septum by the crista supraventricularis (composed of the continuum of the ventriculo-infundibular fold and the trabecula septomarginalis and also contains the outlet septum; see Figures 1.7 and 1.8), and the moderator band. 3 The muscular outflow tract “septum” or infundibulum derives its myocardium from the distal endocardial cushion-lined outflow tract or conotruncal region (see below).

**Consequences for abnormal development**

Isolated or multiple muscular VSDs can result from noncompaction of the myocardial trabeculae. Several mouse models present an extensive spongy myocardium that show both myocardial and epicardial differentiation problems as a basis (see below).

**Tricuspid valve and orifice abnormalities**

Abnormal looping of the heart tube can lead to the tricuspid valve not being optimally brought above the RV, causing a spectrum of tricuspid atresia and hypoplasia, to straddling
tricuspid valve, and complete double inlet left ventricle. Severe deficient looping can also lead to double outlet right ventricle (DORV). In knockout mouse models with disturbed epicardial differentiation, the abnormalities result in abnormal looping, for example, the mutant RxRα [66], Sp3 [67], Ets1/2 [68], and TGFβ2 [69] mice. It is also possible that primary myocardial problems can cause these abnormalities.

Most perimembranous VSDs and also the outflow tract malalignment defects are the result of abnormal outflow tract septation (see below).

**Figure 1.7** Schematic representation (a) and human specimen (b) demonstrating the elements of the ventricular septum after septation has been completed, as viewed from the right side. The ventricular inlet septum is below the tricuspid valve (TV) ostium, and separated from the primitive septum by the myocardial crista supraventricularis. The crista supraventricularis consists of the ventriculo-infundibular fold (VIF), the trabecula septomarginalis (TSM), and the outlet septum (asterisks) that in the normal heart cannot be distinguished as a separate structure. The TSM (that contains the right bundle branch) becomes continuous with the moderator band (MB). The membranous septum is part of the fibrous heart skeleton. Ao, aorta; PT, pulmonary trunk; RA, right atrium. (Copyright Leiden University Medical Center.)

**CHAPTER 1** Normal and Abnormal Cardiac Development

We consider the AVSD anomaly to result from abnormal fusion of the DMP, the mesenchymal cap, and the AV cushion mass [47,58].

**Ventricular outflow tract septation**

The myocardial contribution of the SHF, referred to as anterior [22] or secondary heart field [70], forms almost the complete RV. The relevance of neural crest cells [35] for outflow tract septation is still important but no longer unique, following studies of the 22q11 deletion syndrome in both patients and mouse models [38]. This complicated syndrome has a high incidence of outflow tract malformations, including aortic arch anomalies, persistent truncus arteriosus, and tetralogy of Fallot. Eventually, the transcription factor Tbx1 was found to be the crucial gene. This gene was not expressed in neural crest cells but in the mesoderm of the SHF. An intricate interaction between neural crest and SHF cells results in disturbances of genes that are essential for either cell group can lead to outflow tract malformations.

We refer to the septation of the ventricular outflow tract as “separation” as in the normal heart the subpulmonary infundibular or muscular septum is mainly a free-standing sleeve of muscle in front of the vessel wall of the ascending aorta (Figure 1.8). Outflow tract separation has been described for the human embryo [71] and proved similar in animal species such as chick and mouse [64].

Outflow tract separation starts in the embryonic distal outflow tract that is lined by endocardial cushion tissue. This tissue consists of two opposing spiraling ridges. One ridge runs in a laterodorsal direction where it borders the myocardium of the primary fold at the future site of the ventriculo-infundibular fold in the full-grown heart. The other ridge runs ventroanterior to the myocardium of the primary fold as well as the superior atrioventricular cushion. This merging takes place in the bend of the inner curvature of the embryonic heart tube. The endocardial outflow tract ridges are the source of extensive nomenclature confusion. Some authors consider these ridges to consist of proximal or conal ridges (leading after septation to the conal septum) and distal or truncal ridges (leading to a truncal septum). Pexieder [72] clarified this nomenclature confusion. We indicated in a scanning electron micrograph both boundaries and ridges in their full length (Figure 1.8). It is practical to distinguish proximal and distal ridges, which are clearly visible as separate structures in the chicken embryo but are more continuous in humans and rodents (mouse and rat). The proximal ridges mainly form the muscular outflow tract septum whereas the distal ridge area is important for semilunar valve formation and the septation of the arterial orifice level.

Understanding outflow tract separation starts with acknowledging that the arterial orifice level indicated by the mesenchymal (vessel wall) joining the myocardial (outflow tract heart) boundary is not an oval or a circle in one plane but has a three-dimensional saddle shape (Figure 1.9).
brings future aortic orifice more lateral and lower compared with the future pulmonary orifice. During normal looping, this orifice is brought even deeper into the heart, referred to as wedging of the aorta. We recently found (unpublished data) an asymmetric contribution of the SHF to the myocardium of the outflow tract. This Nkx2.5-expressing mesoderm differentiates into myocardium mainly confined to the subpulmonary region, explaining the relative growth of the subpulmonary outflow tract and the rotation to an anterior position with regard to the aortic orifice (see Videoclips 1.3 and 1.4). Molecular biologic experiments using retrospective clonal analysis [73] also showed a difference in subpulmonary and subaortic myocardium but did not link it to the asymmetric addition of SHF. This explains the known asymmetry in the outflow tract [74] for the human embryo. The final result is the well-known difference in position and plane of both arterial orifices.

The highest (most distal part) of the myocardium, always lined on the inside by endocardial cushion tissue, is positioned in the intersection between the sixth and fourth pharyngeal arch arteries. It is exactly at this site that the condensation of extracardiac mesenchyme takes place. The condensed mesenchyme extends two prongs that enter the endocardial cushions differentiating into the aortopulmonary septum [64] that undergoes myocardialization. Our own chicken chimera studies and also the neural crest indicator

Figure 1.8 (a) Scanning electron micrograph of a preseptation chicken heart showing the proximal (P) and distal (D) outflow tract ridges. The borderline between myocardium (lined on the inside by endocardial cushions) and arterial wall is indicated by arrows. The distal cushions remodel into semilunar valves. (b) Septation of the outflow tract is achieved by fusion of the outflow tract ridges and an ingrowth of condensed mesenchyme (CM), also called the aortopulmonary septum (APS). The APS extends two prongs into the ridges. (c) After septation of the outflow tract, a muscular subpulmonary infundibulum (inf) is formed, which separates the right ventricular outflow tract (RVOT) from the outside world and the aorta (Ao). In a normal heart, the actual outflow tract septum separating the left ventricular outflow tract (LVOT) and RVOT is minimal. (d) Depiction of the difference in length of the RVOT and the relative tilted position of the aortic and pulmonary orifice: LA, left atrium; LV, left ventricle; MB, moderator band; MV, mitral valve; PT, pulmonary trunk; P, prong of CM; RA, right atrium; RV, right ventricle; TSM, trabecula septomarginalis; TV, tricuspid valve; VIF, ventriculoinfundibular fold; IV, VI, pharyngeal arch arteries. (Copyright Leiden University Medical Center.)