Silke Rickert-Sperling · Robert G. Kelly
David J. Driscoll *Editors*

Congenital Heart Diseases: The Broken Heart

Clinical Features, Human Genetics and Molecular Pathways

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This book is dedicated to my mentors
Hanno D. Schmidt, Peter E. Lange, and Hans Lehrach.
Their training, support, and encouragement have
made this book possible.

Silke Rickert-Sperling

Foreword

As is indicated in its title, the book you are about to read is concerned with the congenitally malformed heart. Approximately eight neonates in every thousand born alive present with such a "broken heart". This number has changed little since Maude Abbott, when describing the first plate in her Atlas devoted to congenitally malformed hearts, commented that "An understanding of the elementary facts of human and comparative embryology is essential to an intelligent grasp of the ontogenetic problems of congenital cardiac disease". Paul Dudley White, when writing the foreword to her Atlas, commented that it had been left to Abbott to "make the subject one of such general and widespread interest that we no longer regard it with either disdain or awe as a mystery for the autopsy table alone to discover and to solve". It is perhaps surprising, therefore, to realise that it has taken nearly a century for us to achieve the necessary understanding of the "elementary facts" emphasised by Abbott. Indeed, it is not that long since, in company with my very good friend and collaborator Anton Becker, we suggested that interpretations based on embryology might prove to be a hindrance, rather than a help, in understanding the congenitally malformed heart. The contents of this book show how much has changed in the years that have passed since we made that comment, such that we now need to eat our words.

As is revealed by the multiple chapters of this book, the recent advances made in the fields of cardiac embryology and molecular genetics have been truly spectacular. It was these fields that were expertly summarised in the volumes edited by Rosenthal and Harvey. The details contained in the central part of this book, related to central molecular pathways, recapitulate and extend those reviews. Such extensive knowledge of the genetic and molecular background, however, is of limited value if these interpretations cannot properly be translated into the findings observed on a daily basis by those who diagnose and treat the individual cardiac lesions. The first part of this book, therefore, provides a necessarily brief overview of normal cardiac development, while the final chapters then incorporate the developmental and molecular findings into the clinical manifestations of the abnormal morphogenesis.

I know from my own experience how difficult it is to obtain such chapters from multiple authors, who nowadays are themselves under greater pressure to produce primarily in the peer-reviewed realm. The editors, therefore, are to be congratulated

on assembling such a panoply of authoritative texts. As might be expected, not all of the texts are of comparable length or content. The critical reader will note that several of the topics addressed remain contentious, and that opinions continue to vary between the chosen experts. This is no more than to be expected, since the topics remain very much moving targets. One hopes, therefore, that this is but the first edition of a work which itself, for the first time, seeks to provide in detail the scientific background to the specific lesions that continue to break the normal heart. As the pages of this book demonstrate, we still have much to do if we are fully to understand the mechanics of normal as opposed to abnormal cardiac development.

London, United Kingdom Robert H. Anderson
August 2015

Preface

Leonardo Da Vinci made the first drawing of partial anomalous pulmonary venous connection in the fifteenth century, and 300 years later Karl von Rokitansky described ventricular septal defects. Since then the history of clinical recognition, therapeutic opportunities, and understanding of the developmental and genetic origin of congenital heart diseases (CHDs) has evolved rapidly. The first wave of progress was dedicated to the improvement of clinical diagnosis and therapy based on anatomical, physiological, and surgical considerations. Thus, the mortality of patients with CHD declined below 1 in 100,000 cases and a new group of adult patients with corrected and palliated CHD was formed.

A second wave of progress focused on the developmental, genetic, and molecular aspects of CHDs. Here significant insights were gained by studying animal models along with human. A large collection of genes, signaling pathways, and other molecular or hemodynamic insults have been discovered, frequently considering the developmental perspective as a starting point.

After decades of basic research focusing on animal models, the human phenotype will be the central dogma in the following years. This shift is based on significant developments to overcome technological limitations now enabling studies addressing more and more complex biological questions and systems together with the recognition that improving human health is a central aim of life science research. This book brings together clinical, genetic and molecular knowledge starting from the perspective of the observed human phenotype during development and in the disease state. It aims to reach basic scientists as well as physicians and it might contribute to the current third wave of progression where basic science of cardiovascular development is translated into clinical diagnosis and therapy of CHDs.

To reach this goal, this book is structured in three main parts providing an introduction to the development of the heart and its vessels, an overview of molecular pathways affecting the development of multiple cardiovascular structures, and a textbook-like structure focused on the different types of congenital heart diseases with their clinical features, underlying genetic alterations and related animal models and pathways. We are grateful to all the contributors to this volume, who have provided state of the art accounts of their fields of expertise.

Berlin, Germany — Silke Rickert-Sperling
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Abbreviations

22q11DS	22q11 deletion syndrome
AAA	Aortic arch anomalies
ACTC1	Cardiac alpha-actin
ACVR	Activin A receptor
AD	Arterial duct
ADAM19	ADAM metallopeptidase domain 19
ADAR	Adenosine deaminase that acts on RNA
ADP	Adenosine diphosphate
AGS	Allagile syndrome
AICD	Automatic internal cardiac defibrillator
ALCAPA	Anomalous origin of the left coronary artery from the pulmonary artery
AKT	V-akt murine thymoma viral oncogene homolog
AngII	Angiotensin II
ANP	Atrial natriuretic peptide
ANK2	Ankyrin B
ANKRD1/CARP	Ankyrin repeat domain 1, cardiac muscle
Ao	Aorta
AP	Action potential
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ASD	Atrial septal defect
ATFB	Atrial fibrillation
ATP	Adenosin triphosphate
AV	Atrioventricular
AVB	Atrioventricular bundle
AVC	Atrioventricular canal
AVN	Atrioventricular node
AVSD	Atrioventricular septal defect
BAF	Brg1-associated factor
BAV	Bicuspid aortic valve
BBS	Bardet-Biedl syndrome
BET	Bromodomain and extra terminal
BMP	Bone morphogenetic protein

BNP	Brain natriuretic peptide
BRAF	v-Raf murine sarcoma viral oncogene homolog B
BRG1	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4 (also known as brahma-related gene 1)
BRGDA	Brugada syndrome
BWIS	Baltimore Washington Infant Study
CAA	Coronary artery anomalies
CACN	Calcium channel, voltage-dependent, L type
CAD	Coronary atherosclerotic disease
CaMK	Calmodulin dependent kinase
cAMP	Cyclic adenosine monophosphate
CALM	Calmodulin
CASQ	Calsequestrin
CAT	Common arterial trunk
CBP	CREB-binding protein
CC	Cardiac crescent
CCDC	Coiled-coil domain containing
CCS	Cardiac conduction system
CCVA	Congenital coronary vascular anomalies
CF	Cephalic folds
CFC1	Cripto, FRL-1, Cryptic family 1 (CRYPTIC)
CGH	Comparative genomic hybridization
CHARGE	*C*oloboma of the eye, *H*eart defects, *A*tresia of the nasal choanae, *R*etarded growth and/or development, *G*enital and/or urinal abnormalities, and *E*ar anomalies
CHD	Congenital heart disease
CHD7	Chromodomain helicase DNA binding protein 7
CHF	Congestive heart failure
ChIP	Chromatin immunoprecipitation
CITED2	Cbp/P300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain 2
CNCCs	Cardiac neural crest cells
CNV	Copy number variation
CoA	Coarctation of the aorta
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CRE	Cre recombinase
CRELD1	Cysteine-rich protein with EGF-like domains 1
CRISPR	Clustered regularly interspaced short palindromic repeats
CTD	Conotruncal defects
CTGF	Connective tissue growth factor
CTVM	Canine tricuspid valve malformation
CX	Connexin
DCM	Dilated cardiomyopathy
DGC	Dystrophin-glycoprotein complex