

# DISEASES OF THE FETUS AND NEWBORN

*Pathology, radiology and genetics*

*Edited by*

G.B. REED, A.E. CLAIREAUX and A.D. BAIN

# DISEASES OF THE FETUS AND NEWBORN

*Pathology, radiology and genetics*

EDITED BY

G. B. REED

*Natividad Medical Center,  
Salinas, California*

A. E. CLAIREAUX

*Professor Emeritus in Histopathology,  
University of London,  
and Consulting Pathologist,  
Hospital for Sick Children,  
Great Ormond Street, London*

and

A. D. BAIN

*Late Honorary Senior Lecturer in Pathology,  
University of Edinburgh,  
and Consultant Paediatric Pathologist,  
Royal Hospital for Sick Children,  
Edinburgh*

THE C.V. MOSBY COMPANY

St Louis    Baltimore    Philadelphia    Toronto

First published in 1989 by  
Chapman and Hall Ltd  
11 New Fetter Lane, London EC4P 4EE

Distributed in the United States  
by The C.V. Mosby Company  
11830 Westline Industrial Drive  
St Louis, Missouri 63146, USA

Distributed in Canada by  
The C.V. Mosby Company, Ltd  
5240 Finch Avenue East  
Scarborough, Ontario,  
Canada M1S 5A2

© 1989, Chapman and Hall Ltd

Printed in Great Britain

ISBN 0 8016 5800 4

All rights reserved. No part of this book may be reprinted, or  
reproduced, or utilized in any form or by any electronic,  
mechanical or other means, now known or hereafter invented,  
including photocopying and recording, or in any information  
storage and retrieval system, without permission in writing from  
the publisher.

DISEASES OF THE  
FETUS AND NEWBORN

*Dr A. Douglas Bain, our co-editor, died in January 1987 just as the manuscript was being completed. His sudden death was greatly mourned by colleagues and friends all over the world. We wish to dedicate this book to his memory and his many contributions to pediatric genetic pathology*

# CONTRIBUTORS

CARLOS ABRAMOWSKY, MD

Institute of Pathology,  
Case Western Reserve University,  
Cleveland,  
OH,  
USA.

LINDSEY ALLAN, MD, FRCP

Department of Paediatrics,  
Guy's Hospital,  
London,  
UK.

ROBERT H. ANDERSON, BSc, MD,  
FRCPath

Department of Paediatrics,  
Cardiothoracic Institute,  
Brompton Hospital,  
London,  
UK.

DEREK A. APPEGARTH, PhD

Biochemical Diseases Laboratory,  
Vancouver Children's Hospital,  
Vancouver,  
BC,  
Canada.

A. DOUGLAS BAIN, MD, FRCPE,  
FRCPath

Department of Genetic Pathology,  
Royal Hospital for Sick Children,  
Edinburgh,  
Scotland,  
UK.

MURRAY D. BAIN, MD

St George's Medical School,  
Department of Child Health,  
London,  
UK.

GUY T. N. BESLEY, BSc, PhD

Biochemical Genetics Unit,  
Royal Hospital for Sick Children,  
Edinburgh,  
Scotland,  
UK.

GEORGE W. BEVERIDGE, MB, ChB,  
FRCPE

Department of Dermatology,  
The Royal Infirmary,  
Edinburgh,  
Scotland,  
UK.

FREDERICK R. BIEBER, PhD

Department of Pathology  
Brigham and Women's Hospital,  
Boston,  
MA,  
USA.

JOHN DOUGLAS BLAIR, MD

Department of Pathology,  
St Louis University Medical Center,  
St Louis,  
MO,  
USA.

ZVI BOROCHOWITZ, MD

Genetics Institute,  
Haifa Medical Center,  
Haifa,  
Israel.

KEVIN BOVE, MD

Cincinnati Children's Hospital,  
Cincinnati,  
OH,  
USA.

ROBERT J. BRADLEY, MD

Department of Obstetrics and  
Gynaecology,  
King's College Hospital,  
London,  
UK.

BRUNO BRAMBATI, MD

First Clinic of Obstetrics and  
Gynaecology,  
University of Milan,  
Milan,  
Italy.

DAVID J. H. BROCK, PhD

Human Genetics Unit,  
Western General Hospital,  
Edinburgh,  
Scotland,  
UK.

SEAMUS CAHALANE, MD, PhD

Department of Pathology,  
Temple Street Children's Hospital,  
Dublin,  
Ireland.

ANTONIO CAO, MD

Paediatric Clinic,  
University of Cagliari,  
Cagliari,  
Italy.

SARAH CHAMBERS, MD

Simpson Memorial Maternity Pavilion,  
Edinburgh,  
Scotland,  
UK.

ROMA S. CHANDRA, MD

National Medical Center  
Children's Hospital,  
111 Michigan Avenue NW,  
Washington DC,  
USA.

ALBERT E. CLAIREAUX, MD, FRCPE,  
FRCOG, FRCPath

Department of Histopathology,  
Great Ormond Street Hospital for Sick  
Children,  
London,  
UK.

SHIRLEY G. DRISCOLL, MD

Department of Pathology,  
Brigham and Women's Hospital,  
Boston,  
MA,  
USA.

PATRICIA M. ELLIS, MSc, Dip RCPATH

Department of Cytogenetics,  
Royal Hospital for Sick Children,  
Edinburgh,  
Scotland,  
UK.

JOHN R. ESTERLY, MD

Department of Pathology,  
University of Chicago,  
Chicago,  
IL,  
USA.

DANIEL A. GALVIS, BA  
Department of Pathology,  
Children's Hospital of Los Angeles,  
Los Angeles,  
CA,  
USA.

ENID F. GILBERT-BARNES, MD  
Department of Pathology,  
University of Wisconsin Medical  
School,  
Madison,  
WI,  
USA.

WILLIAM HAMILTON, MD  
Department of Child Health,  
Royal Hospital for Sick Children,  
Glasgow,  
Scotland,  
UK.

BRIAN N. HARDING, MA, DPhil, BM,  
BCh, MRCPath  
Department of Neuropathology,  
Great Ormond Street Hospital for Sick  
Children,  
London,  
UK.

BRIAN E. HARDY, MD  
Department of Surgery – Urology,  
Children's Hospital of Los Angeles,  
Los Angeles,  
CA,  
USA.

FRED HARUDA, MD  
Pediatric Neurology,  
Salinas,  
CA,  
USA.

G. MICHAEL A. HENDRY, MD  
Department of Radiology,  
Royal Hospital for Sick Children,  
Edinburgh,  
Scotland,  
UK.

KAREN A. HOLBROOK, PhD  
Department of Biological Structure and  
Medicine,  
University of Washington School of  
Medicine,  
Seattle, WA,  
USA.

HART ISAACS, Jr, MD  
Department of Surgical Pathology,  
Children's Hospital of Los Angeles,  
Los Angeles,  
CA,  
USA.

BENJAMIN H. LANDING, MD  
Department of Pathology,  
Children's Hospital of Los Angeles,  
Los Angeles,  
CA,  
USA.

GIAN BATTISTA LEONI, MD  
Paediatric Clinic,  
University of Cagliari,  
Cagliari,  
Italy.

VLADIMIR MAHNOVSKI, MD  
Department of Pathology,  
Children's Hospital of Los Angeles,  
Los Angeles,  
CA,  
USA.



SUE MALCOLM, PhD  
Institute of Child Health,  
London,  
UK.

ALAN M. MICHELSON, PhD, MD  
Department of Biochemistry and  
Molecular Biology,  
Harvard University,  
Cambridge,  
MA,  
USA.

MASSIMO MUSENGA, MD  
Villa Mafalda Clinic,  
Rome,  
Italy.

KYPROS H. NICOLAIDES, MD  
Department of Obstetrics and  
Gynaecology,  
King's College Hospital,  
London,  
UK.

STUART H. ORKIN, MD  
Division of Hematology – Oncology,  
Children's Hospital,  
Boston,  
MA,  
USA.

ZDENA PAVLOVA, MD  
Department of Pathology,  
University of Southern California  
Medical School,  
Los Angeles,  
CA,  
USA.

EUGENE V. D. K. B. PERRIN, MD, DD  
(hc)  
Department of Pathology,  
Wayne State University,  
Detroit,  
MI,  
USA.

MARTIN C. POWELL, FRCS  
Department of Obstetrics and  
Gynaecology,  
University Hospital,  
Nottingham,  
UK.

RAYMOND W. REDLINE, MD  
Department of Pathology,  
Brigham and Women's Hospital,  
Boston,  
MA,  
USA.

GEORGE B. REED, MD  
Formerly Department of Pathology,  
Cayuhoga County Hospital,  
Cleveland,  
OH,  
Presently Monterey,  
CA, USA.

DAVID L. RIMOIN, MD, PhD  
Department of Pediatrics,  
Cedars Sinai Medical Center,  
Los Angeles,  
CA,  
USA.

CHARLES H. RODECK, MD, FRCOG  
Institute of Obstetrics and Gynaecology,  
Queen Charlotte's Hospital,  
London,  
UK.

M. CRISTINA ROSATELLI, PhD  
Paediatric Clinic,  
University of Cagliari,  
Cagliari,  
Italy.

PHILIP ROSENTHAL, MD  
Department of Gastroenterology,  
Children's Hospital of Los Angeles,  
Los Angeles,  
CA,  
USA.

GIUSEPPE SIMONI  
First Clinic of Obstetrics and  
Gynaecology,  
University of Milan,  
Milan,  
Italy.

RICARDO U. SORENSEN, MD  
Department of Pediatrics,  
Case Western Reserve University,  
Cleveland,  
OH,  
USA.

J. THOMAS STOCKER, MD  
Department of Pediatric Pathology,  
Armed Forces Institute of Pathology,  
Washington DC,  
USA.

VIRGINIA P. SYBERT, MD  
Department of Pediatrics, (Medical  
Genetics) and Medicine (Dermatology),  
Children's Hospital and Medical Center  
and University of Washington,  
Seattle,  
WA,  
USA.

EDWIN M. SYMONDS, MD, MRCOG  
Department of Obstetrics and  
Gynaecology,  
University Hospital,  
Nottingham,  
UK.

ARON E. SZULMAN, MB, ChB, FRCPath  
Department of Pathology,  
Magee Hospital,  
Pittsburgh,  
PA,  
USA.

CARLO VALENTI, MD  
Villa Mafalda Clinic,  
Rome,  
Italy.

JOSEPH VOLAND, MD  
Department of Pathology,  
University of California at San Diego  
Medical School,  
La Jolla,  
CA,  
USA.

THEADIS R. WELLS HT (ASCP)  
Department of Pathology,  
Children's Hospital of Los Angeles,  
Los Angeles,  
CA,  
USA.

BRIAN S. WORTHINGTON, FRCR  
Department of Radiology,  
University Hospital,  
Nottingham,  
UK.

# PREFACE

Our understanding of the pathogenesis of diseases and disorders in the fetus and newborn infant has undergone considerable change during the past decade. Hitherto, most textbooks were concerned with the description of structural changes due to disease processes or developmental abnormalities occurring *in utero*.

In the present volume we attempt to expand our understanding and concepts beyond pure morphology by incorporating studies utilizing new diagnostic and screening techniques in examining the pregnant mother, fetus and newborn child. The opening chapters consider some of the more general aspects of disease, malformation and neoplasia.

This first section is followed by an up-to-date consideration of pathological changes in the more important organs and systems. In this portion of the book the authors do not confine their discussions to pure morphology but include some of the newer types of investigation, including immunology, enzyme histochemistry and molecular biology. The latter has recently made fundamental advances in our knowledge of the haemoglobin molecular defects in sickle cell disease and in thalassaemias.

It is important to remember that a number of abnormalities which are present at birth may not manifest themselves clinically until later infancy or childhood.

The third section is mainly concerned with prenatal screening and diagnostic investigations of the fetus and newborn using a variety of new techniques such as Imaging: ultrasonography, MRI and nuclear medicine.

In the final section on medical genetics, the impact of molecular biology and recombinant DNA are emphasized as also are cytogenetics, oncogenes, biochemical genetics and maternal blood markers. The interventional methods of chorionic villous sampling, amniocentesis and fetal tissue sampling are reviewed by experts in their fields.

Some suggestions are given by the authors as to the relative value, usefulness or accuracy of each diagnostic technique. The necessity of correlating findings and of communicating them between the team of experts is stressed.

Several themes recur throughout the book and will become evident to the reader. One is the assumption that biomedical and technical advances have revolutionized obstetrics and medical genetics, and the benefits of these advances enhance the likelihood of improved medical care. Another theme is the basic interdependence of many disciplines, such as enzymology, cytogenetics, ultrasonography, and *in utero* interventional methods and the proper use of pre and postnatal genetic counselling. Finally there is the common thread that ties the DNA molecule in the genome, which may untie or break during gametogenesis. This in turn may lead to such seemingly disparate disorders such as retinoblastoma, Down's syndrome or Huntington's

chorea. Therefore despite the genome and its importance we lack information about its relationship to development, maldevelopment or its reaction to the environment. Pathologists can play a pivotal role in such studies and improve the understanding of the pathogenesis of many diseases that remain unsolved. As Douglas Bain wrote:

'... Even in those disorders where the metabolic defect is not expressed in the cultured cells, advances in molecular biology ... [such as fetal DNA] suggest that prenatal diagnosis and carrier detection may prove feasible. These powerful techniques hold great hope for the future but the development of their potential will depend on a supply of appropriate samples.'<sup>\*</sup>

More recently in the Farber lecture<sup>†</sup> Opitz has drawn attention to the importance of chromosomal abnormalities in total mortality and stresses the need for diagnostic and genetic counselling, appropriate monitoring of the next pregnancy and the possibility of monitoring teratogenic activity or increases in mutation rates.

In a book of this nature, some overlap is inevitable. We have tried to keep this to a minimum and have cross-referenced information where it seemed appropriate.

We hope this book appeals to a wider audience than the pathologist or laboratory scientist. The care of the fetus and future well being of the infant and child can only be safeguarded by the concerted effort of a multidisciplinary team, including obstetricians, paediatricians, histopathologists and scientists devoted to that objective.

Increased knowledge increases responsibility. Some of the new techniques may reveal abnormalities in the fetus in early pregnancy. In some instances these abnormalities may be of such a nature that a termination of pregnancy is the only reasonable course to follow. In others the defect may be amenable to treatment either before or after delivery and termination of pregnancy is not the correct approach. The vigilance by a team of experts devoted to the study of all aspects of each individual case will ensure that in future correct decisions are made.

We would like to thank Mr G. W. Anderson, Mrs S. Chibett and Miss J. Barber and all the staff of the Department of Histopathology, Hospital for Sick Children, Great Ormond Street, London and the Department of Pathology, Royal Hospital for Sick Children, Edinburgh. In particular Sheila Bartholomew, Guy Besley and Patricia Ellis.

<sup>\*</sup>Editorial (1984) Perinatal pathology. *Lancet*, i, 431–2.

<sup>†</sup>Opitz, J. (1987) Prenatal and perinatal death. *Pediatr. Pathol.*, 7, 363–74.

# CONTENTS

CONTRIBUTORS	xi
PREFACE	xvii
<b>PART ONE INTRODUCTION AND GENERAL DISEASE PROCESS</b>	<b>1</b>
1 OVERVIEW OF ANTENATAL AND NEONATAL PERIOD <i>George B. Reed, Murray D. Bain and Joseph Voland</i>	3
2 THE PLACENTA AND ADNEXA <i>Raymond W. Redline and Shirley G. Driscoll</i>	41
3 EVALUATION OF SPONTANEOUS ABORTION AND OF THE MALFORMED FETUS <i>Frederick R. Bieber and Shirley G. Driscoll</i>	59
4 CONGENITAL ANOMALIES AND DYSMORPHOLOGY <i>Eugene V. D. K. B. Perrin and Enid F. Gilbert-Barness</i>	75
5 INFLAMMATION AND PERINATAL INFECTION <i>John R. Esterly and Fred Haruda</i>	89
6 BENIGN TUMOURS <i>Albert E. Claireaux</i>	99
7 CONGENITAL MALIGNANT TUMORS <i>Hart Isaacs, Jr.</i>	131
8 TROPHOBLASTIC DISEASE: PATHOLOGY OF COMPLETE AND PARTIAL MOLES <i>Aron E. Szulman</i>	153
<b>PART TWO SYSTEMIC PATHOLOGY</b>	<b>167</b>
9 THE BRAIN <i>Brian N. Harding</i>	169
10 THE HEART <i>Robert H. Anderson and Lindsey Allan</i>	217
11 NEONATAL PULMONARY PATHOLOGY <i>J. Thomas Stocker</i>	247

12	THE GASTROINTESTINAL SYSTEM <i>Vladimir Mahnovski and Philip Rosenthal</i>	275
13	THE PANCREAS <i>Albert E. Claireaux and George B. Reed</i>	291
14	THE LIVER AND BILIARY SYSTEM <i>Roma S. Chandra</i>	299
15	CLINICAL PATHOLOGY AND THE ENDOCRINE SYSTEM <i>William Hamilton</i>	317
16	THE REPRODUCTIVE SYSTEMS <i>John Douglas Blair</i>	333
17	DISORDERS OF THE KIDNEYS AND URINARY TRACT OF IMPORTANCE IN THE PERINATAL PERIOD <i>Benjamin H. Landing, Daniel A. Galvis, Theadis R. Wells and Brian E. Hardy</i>	373
18	THE IMMUNE SYSTEM <i>Carlos Abramowsky and Ricardo U. Sorensen</i>	393
19	BLOOD DISORDERS <i>Vladimir Mahnovski and Zdena Pavlova</i>	417
20	ANTENATAL PATHOLOGY OF THE SKIN <i>Virginia P. Sybert and Karen A. Holbrook</i>	441
21	SKIN ERUPTIONS IN THE NEWBORN <i>George W. Beveridge</i>	455
22	MUSCLE DISORDERS <i>Kevin Bove</i>	475
23	SKELETAL PATHOLOGY: THE CONGENITAL CHONDRODYSPLASIAS <i>Zvi Borochowitz and David L. Rimoin</i>	497
	<b>PART THREE RADIOLOGY</b>	<b>515</b>
24	IMAGING TECHNIQUES IN THE PERINATAL PERIOD <i>G. Michael A. Hendry</i>	517
25	MAGNETIC RESONANCE IMAGING (MRI) IN OBSTETRICS <i>Martin C. Powell, Brian S. Worthington and Edwin M. Symonds</i>	559
26	PRENATAL DIAGNOSIS BY ULTRASOUND <i>Sarah Chambers</i>	573

PART FOUR MEDICAL GENETICS AND PRENATAL DIAGNOSIS	597
27 SCREENING FOR GENETIC DISEASE <i>Seamus F. Cabalane</i>	599
28 MATERNAL BLOOD MARKERS (ALPHA-FETOPROTEIN) <i>David J. H. Brock</i>	615
29 FETAL KARYOTYPE DIAGNOSIS BY FIRST-TRIMESTER CHORIONIC VILLUS SAMPLING <i>Giuseppe Simoni and Bruno Brambati</i>	627
30 MID-TRIMESTER DIAGNOSTIC AMNIOCENTESIS <i>Carlo Valenti and Massimo Musenga</i>	641
31 FETAL TISSUE SAMPLING <i>Robert J. Bradley, Kypros H. Nicolaides and Charles H. Rodeck</i>	661
32 PRENATAL DIAGNOSIS BY ANALYSIS OF FETAL DNA <i>Alan M. Michelson and Stuart H. Orkin</i>	673
33 PRENATAL DIAGNOSIS OF INHERITED HAEMOGLOBINOPATHIES <i>Antonio Cao, Gian Battista Leoni and M. Cristina Rosatelli</i>	695
34 BIOCHEMICAL GENETICS <i>Derek A. Applegarth and Guy T. N. Besley</i>	707
35 ASPECTS OF CLINICAL CYTOGENETICS <i>Patricia M. Ellis and A. Douglas Bain</i>	749
36 ONCOGENES AND CANCER CYTOGENETICS <i>Sue Malcolm</i>	769
INDEX	782
APPENDICES	
Post-mortem removal of the brain and cord	202
Examination of the brain after fixation (including organ weights and body measurements)	205
Inherited metabolic disorders	733

PART ONE

# INTRODUCTION AND GENERAL DISEASE PROCESS



