Developmental Origins of Health and Disease

This landmark publication provides the first definitive account of how and why subtle influences on the fetus and during early life can have such profound consequences for adult health and diseases. Although the epidemiological evidence for this link has long proved compelling, it is only much more recently that the scientific basis for this has begun to be studied in depth and fully understood. This compilation, written by many of the world’s leading experts in this exciting field, summarises these basic and clinical advances. The link between early development and the onset of many chronic diseases such as coronary heart disease, diabetes and osteoporosis also raises important public health issues. Another fascinating theme in the book concerns evolutionary developmental biology and how the ‘evo-devo’ debate can cast light on these concepts. Clinicians and basic scientists alike will find this an authoritative book about this exciting and emerging field.

Peter D. Gluckman is Professor of Paediatric and Perinatal Biology, Director of the Liggins Institute (for Medical Research) and Director of the National Research Centre for Growth and Development, at the University of Auckland.

Mark A. Hanson is Director of the Developmental Origins of Health & Disease Research Division at the University of Southampton Medical School, and British Heart Foundation Professor of Cardiovascular Science.
Developmental Origins of Health and Disease

Edited by

Peter Gluckman
University of Auckland, New Zealand

Mark Hanson
University of Southampton, UK
Contents

List of contributors ix
Preface xv

1 The developmental origins of health and disease: an overview 1
   Peter D. Gluckman and Mark A. Hanson

2 The ‘developmental origins’ hypothesis: epidemiology 6
   Keith Godfrey

3 The conceptual basis for the developmental origins of health and disease 33
   Peter D. Gluckman and Mark A. Hanson

4 The periconceptional and embryonic period 51
   Tom P. Fleming

5 Epigenetic mechanisms 62
   Emma Whitelaw and David Garrick

6 A mitochondrial component of developmental programming 75
   Josie M. L. McConnell

7 Role of exposure to environmental chemicals in developmental origins of health and disease 82
   Jerrold J. Heindel and Cindy Lawler

8 Maternal nutrition and fetal growth and development 98
   Susan M. B. Morton
## Contents

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Placental mechanisms and developmental origins of health and disease</td>
<td>Leslie Myatt and Victoria Roberts</td>
</tr>
<tr>
<td>10</td>
<td>Control of fetal metabolism: relevance to developmental origins of health and disease</td>
<td>Abigail L. Fowden, Janelle W. Ward and Alison J. Forhead</td>
</tr>
<tr>
<td>11</td>
<td>Lipid metabolism: relevance to developmental origins of health and disease</td>
<td>Graham C. Burdge and Philip C. Calder</td>
</tr>
<tr>
<td>12</td>
<td>Prenatal hypoxia: relevance to developmental origins of health and disease</td>
<td>Dino A. Giussani</td>
</tr>
<tr>
<td>13</td>
<td>The fetal hypothalamic–pituitary–adrenal axis: relevance to developmental origins of health and disease</td>
<td>Deborah M. Sloboda, John P. Newnham, Timothy J. M. Moss and John R. G. Challis</td>
</tr>
<tr>
<td>14</td>
<td>Perinatal influences on the endocrine and metabolic axes during childhood</td>
<td>W. S. Cutfield, C. A. Jefferies and P. L. Hofman</td>
</tr>
<tr>
<td>15</td>
<td>Patterns of growth: relevance to developmental origins of health and disease</td>
<td>Johan G. Eriksson</td>
</tr>
<tr>
<td>16</td>
<td>The developmental environment and the endocrine pancreas</td>
<td>Brigitte Reusens, Luise Kalbe and Claude Remacle</td>
</tr>
<tr>
<td>17</td>
<td>The developmental environment and insulin resistance</td>
<td>Noel H. Smith and Susan E. Ozanne</td>
</tr>
<tr>
<td>18</td>
<td>The developmental environment and the development of obesity</td>
<td>Michael E. Symonds and David S. Gardner</td>
</tr>
<tr>
<td>19</td>
<td>The developmental environment and its role in the metabolic syndrome</td>
<td>Christopher D. Byrne and David J. W. Phillips</td>
</tr>
<tr>
<td>20</td>
<td>Programming the cardiovascular system</td>
<td>Kent L. Thornburg</td>
</tr>
<tr>
<td>21</td>
<td>The role of vascular dysfunction in developmental origins of health and disease</td>
<td>Lucilla Poston, Christopher Torrens, James A. Armitage and Mark A. Hanson</td>
</tr>
<tr>
<td>22</td>
<td>The developmental environment and atherogenesis</td>
<td>C. Napoli, O. Pignalosa, L. Rossi, C. Botti, C. Guarino, V. Sica and F. de Nigris</td>
</tr>
<tr>
<td>23</td>
<td>The developmental environment, renal function and disease</td>
<td>Karen M. Moritz, E. Maelynn Wintours and Miodrag Dodic</td>
</tr>
<tr>
<td>24</td>
<td>The developmental environment: effect on fluid and electrolyte homeostasis</td>
<td>Mostafa A. El-Haddad and Michael G. Ross</td>
</tr>
<tr>
<td>25</td>
<td>The developmental environment: effects on lung structure and function</td>
<td>Richard Harding, Megan L. Cock and Gert S. Maritz</td>
</tr>
<tr>
<td>26</td>
<td>Developmental origins of asthma and related allergic disorders</td>
<td>J. O. Warner</td>
</tr>
<tr>
<td>27</td>
<td>The developmental environment: influences on subsequent cognitive function and behaviour</td>
<td>Jason Landon, Michael Davson and Bernhard H. Breier</td>
</tr>
<tr>
<td>Chapter</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>28</td>
<td>The developmental environment and the origins of neurological disorders</td>
<td>Sandra Rees, Richard Harding and Terrie Inder</td>
</tr>
<tr>
<td>29</td>
<td>The developmental environment: clinical perspectives on effects on the musculoskeletal system</td>
<td>Cyrus Cooper, Avan Aihie Sayer and Elaine Margaret Dennison</td>
</tr>
<tr>
<td>30</td>
<td>The developmental environment: experimental perspectives on skeletal development</td>
<td>Richard O. C. Oreffo and Helmtrud I. Roach</td>
</tr>
<tr>
<td>31</td>
<td>The developmental environment and the early origins of cancer</td>
<td>Anders Ekbom</td>
</tr>
<tr>
<td>32</td>
<td>The developmental environment: implications for ageing and life span</td>
<td>Thomas B. L. Kirkwood</td>
</tr>
<tr>
<td>33</td>
<td>Developmental origins of health and disease: implications for primary intervention for cardiovascular and metabolic disease</td>
<td>Terrence Forrester</td>
</tr>
<tr>
<td>34</td>
<td>Developmental origins of health and disease: public-health perspectives</td>
<td>Catherine Law and Janis Bair</td>
</tr>
<tr>
<td>35</td>
<td>Developmental origins of health and disease: implications for developing countries</td>
<td>Caroline H. D. Fall and Harshpal Singh Sachdev</td>
</tr>
<tr>
<td>36</td>
<td>Developmental origins of health and disease: ethical and social considerations</td>
<td>Ray Noble</td>
</tr>
<tr>
<td>37</td>
<td>Past obstacles and future promise</td>
<td>D. J. P. Barker</td>
</tr>
<tr>
<td></td>
<td>Index</td>
<td></td>
</tr>
</tbody>
</table>
Contributors

Dr Avan Aihie Sayer, MSc, PhD, FRCP
MRC Clinical Scientist & Honorary Senior Lecturer in Geriatric Medicine
MRC Epidemiology Resource Centre
University of Southampton
Southampton General Hospital
Southampton S016 6YD, UK

Dr James A. Armitage, BOptom, MOptom, PhD
Postdoctoral Research Fellow
Maternal and Fetal Research Unit
Division of Reproductive Health
Endocrinology and Development
King’s College London
St Thomas’ Hospital
London SE1 7EH, UK

Dr Janis Baird, MBBS, PhD, MFPH
Research Fellow
MRC Epidemiology Resource Centre
University of Southampton
Southampton General Hospital
Southampton S016 6YD, UK

Professor David Barker, PhD, FRCP, FRS
Professor of Clinical Epidemiology
Developmental Origins of Health & Disease Centre
University of Southampton
Princess Anne Hospital
Southampton S016 5YA, UK
and Professor, Department of Medicine
Oregon Health and Science University
Portland, OR 97239, USA
List of contributors

Dr Chiara Botti, BiolD
Department of General Pathology
II University of Naples
80131 Naples, Italy

Associate Professor Berni Breier, MSc, PhD
Associate Director
Liggins Institute
University of Auckland
Private Bag 92019
Auckland, New Zealand

Dr Graham Burdge, BSc, PhD
Senior Research Fellow
Institute of Human Nutrition
University of Southampton
Bassett Crescent East
Southampton S016 7PX, UK

Professor Christopher D. Byrne, FRCP, FRCPath, PhD
Professor of Endocrinology & Metabolism
University of Southampton
Southampton General Hospital
Southampton S016 6TD, UK

Professor Philip C. Calder, BSc, PhD, DPhil
Professor of Nutritional Immunology
Institute of Human Nutrition
University of Southampton
Bassett Crescent East
Southampton S016 7PX, UK

Professor John R. G. Challis, PhD, DSc, FIBiol, FRCOG, FRSC
Vice-President, Research & Associate Provost
Professor of Physiology; Obstetrics, Gynaecology and Medicine
University of Toronto
27 King’s College Circle
Toronto M5S 1A8, Canada

Dr Megan L. Cock, PhD
Senior Research Officer
Department of Physiology
Monash University, Clayton
VIC 3880, Australia

Professor Cyrus Cooper, DM, FRCP, FMedSci
Professor of Rheumatology and Director
MRC Epidemiology Resource Centre
University of Southampton
Southampton General Hospital
Southampton S016 6YD, UK

Associate Professor Wayne Cutfield, MBChB, MD, FRACP
Director of Endocrinology
Starship Children’s Hospital
Director, Paykel Clinical Research Unit
Liggins Institute
Associate Director, Liggins Institute
University of Auckland
Private Bag 92019
Auckland, New Zealand

Professor Michael Davison, PhD, DSc, FRSNZ
Professor of Psychology
Director, Experimental Analysis of Behaviour Research Unit
University of Auckland
Private Bag 92019
Auckland, New Zealand

Professor Filomena de Nigris, BiolD, PhD
Assistant Professor
Department of General Pathology
II University of Naples, 80131 Naples, Italy
and Department of Pharmacological Sciences
University of Salerno, Italy

Dr Elaine Dennison, MA, MRCP, PhD
Senior Research Fellow/Honorary Consultant in Rheumatology
MRC Epidemiology Resource Centre
University of Southampton
Southampton General Hospital
Southampton S016 6YD, UK

Dr Miodrag Dodic, MD, PhD
Honorary Senior Research Fellow
Department of Physiology
Monash University
Clayton, VIC 3880, Australia

Professor Anders Ekblom, MD, PhD
Department of Medicine
Karolinska Institutet
171 76 Stockholm, Sweden
Professor Mostafa A. El-Haddad, MD, FRCOG
Assistant Professor in Perinatal Medicine
Harbor–UCLA Medical Center
University of California
Los Angeles, 1000 W. Carson Street
Torrance, CA 90502, USA

Adjunct Professor Johan G. Eriksson, MD, PhD
Head of Unit
National Public Health Institute
Department of Epidemiology and Health Promotion
Diabetes and Genetic Epidemiology Unit
Mannerheimintie 166, 00300 Helsinki, Finland

Dr Caroline H. D. Fall, MBChB, DM, FRCPCH
Reader in Epidemiology and Honorary Consultant in Child Health
MRC Epidemiology Resource Centre
University of Southampton
Southampton General Hospital
Southampton S016 6YD, UK

Professor Tom Fleming, BSc, PhD
Professor of Developmental Biology
School of Biological Sciences
University of Southampton
Bassett Crescent East
Southampton S016 7PX, UK

Dr Alison J. Forhead, BSc, PhD
University Lecturer
Department of Physiology
University of Cambridge
Downing Street
Cambridge CR1 3EG, UK

Professor Terrence Forrester, DM, FRCP, PhD
Director, Tropical Medicine Research Institute
Tropical Medicine Research Institute
University of the West Indies
Mona, Kingston 7, Jamaica

Professor Abigail L. Fowden, BA, PhD, ScD
Professor of Perinatal Physiology
Department of Physiology
University of Cambridge
Downing Street
Cambridge CB2 3EG, UK

Dr David Gardner, BSc, PhD, RNut
British Heart Foundation Lecturer
Centre for Reproductive and Early Life Health
School of Human Development
Academic Division of Child Health
Queen’s Medical Centre
Nottingham NG7 2UH, UK

Dr David Garrick, BSc, MA, PhD
MRC Molecular Haematology Unit
Weatherall Institute of Molecular Medicine
Oxford University
Oxford OX3 9DS, UK

Dr Dino A. Giussani, BSc, MA, PhD
Reader in Developmental Cardiovascular Physiology & Medicine
Department of Physiology
University of Cambridge
Downing Street, Cambridge CB2 3EG, UK

Professor Peter Gluckman, DSc, FRNZ, FRS
University Distinguished Professor
Director, Liggins Institute and National Research Centre for Growth and Development
University of Auckland
Private Bag 92019
Auckland, New Zealand

Professor Keith Godfrey, BM, PhD, FRCP
Reader in Epidemiology & Human Development
MRC Epidemiology Resource Centre
University of Southampton
Southampton General Hospital
Southampton S016 6YD, UK

Dr Carmen Guarino, MB
Department of General Pathology
II University of Naples
80131 Naples, Italy

Professor Mark Hanson, MA, DPhil, FRCOG
British Heart Foundation Professor of Cardiovascular Science
Director, Centre for Developmental Origins of Health and Disease
University of Southampton
Princess Anne Hospital
Southampton S016 5YA, UK
List of contributors

Professor Richard Harding, MSc, PhD, DSc
NH & MRC Senior Principal Research Fellow
Department of Physiology
Monash University
Clayton, VIC 3800, Australia

Dr Jerrold J. Heindel, PhD
Scientific Program Administrator
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
Research Triangle Park
NC 27709, USA

Dr Paul Hofman, FRACP
Senior Lecturer in Paediatric Endocrinology
University of Auckland
Private Bag 92019
Auckland, New Zealand

Associate Professor Terrie Inder, MBChB, MD, FRACP
Neonatal Neurologist
Royal Children's Hospital
Murdoch Children's Research Institute, Parkville
VIC 3052, Australia

Dr Craig A. Jefferies, MBChB, FRACP
University Honorary Senior Lecturer
Paediatric Endocrinologist
Paediatrician
University of Auckland
Private Bag 92019
Auckland, New Zealand

Dr Luise Kalbe, PhD
Institute of Life Science
Université catholique de Louvain
B1348 Louvain-la-Neuve, Belgium

Professor Tom Kirkwood, PhD, FMedSci
Professor of Medicine; Co-Director
Institute for Ageing and Health
Henry Wellcome Laboratory for Biogerontology Research
University of Newcastle
Newcastle upon Tyne NE4 6BE, UK

Dr Jason Landon, BSc, MSc, PhD
Research Fellow
Liggins Institute
University of Auckland
Private Bag 92019
Auckland, New Zealand

Dr Catherine Law, MD, FRCPCH, FFPH
Reader in Children's Health
Institute of Child Health
University College London
30 Guilford Street, London WC1N 1EH, UK

Dr Cindy P. Lawler, PhD
Scientific Program Administrator
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
Research Triangle Park
NC 27709, USA

Professor Gert S. Maritz, PhD, MBA
Department of Medical Biosciences
University of the Western Cape
7535 Bellville, South Africa

Dr Josie M. L. McConnell, BSc, PhD
Senior Research Fellow
Maternal and Fetal Research Unit
Division of Reproductive Health
Endocrinology & Development
King's College London
St Thomas' Hospital
London SE1 7EH, UK

Dr Karen Moritz, MSc, PhD
Research Fellow
Department of Anatomy and Cell Biology
Monash University
Clayton, VIC 3800, Australia

Dr Susan Morton, MBChB, PhD, FAFPHM
Senior Lecturer in Epidemiology
Liggins Institute and School of Population Health
University of Auckland
Private Bag 92019
Auckland, New Zealand

Dr Timothy J. M. Moss, PhD
Senior Research Fellow
School of Women's and Infants' Health
The University of Western Australia
M894, 35 Stirling Highway
Crawley, WA 6009, Australia
List of contributors

Professor Leslie Myatt, PhD
Professor of Obstetrics and Gynecology; Director
Physician Scientist Training Program; Director
Women’s Reproductive Health Research Scholars
Program
University of Cincinnati
College of Medicine, PO Box 670526
Cincinnati, OH 45267, USA

Professor Claudio Napoli, MD, PhD, MBE
Professor of Medicine and Clinical Pathology
Excellence Research Center on Cardiovascular Diseases and
Department of General Pathology
II University of Naples
Naples 80131, Italy
and Adjunct Professor of Medicine
Whitaker Cardiovascular Institute
Boston University, MA 02118, USA

Professor John P. Newnham, MD, FRANZCOG
Professor of Obstetrics and Gynaecology (Maternal Fetal
Medicine)
Head, School of Women’s and Infants’ Health
The University of Western Australia
King Edward Memorial Hospital
Bagot Road, Subiaco, WA 6008, Australia

Dr Ray Noble, BSc, PhD
Co-Director, Collaborative Centre for Reproductive Ethics
and Rights
Institute for Women’s Health
Department of Obstetrics and Gynaecology
University College London
London WC1E 6BT, UK

Professor Richard O. C. Oreffo, DPhil
Professor of Musculoskeletal Science
Bone and Joint Research Group
Developmental Origins of Health and Disease Division
University of Southampton
Southampton SO16 6YD, UK

Dr Susan Ozanne, BSc, PhD
British Heart Foundation Lecturer
Department of Clinical Biochemistry
University of Cambridge
Addenbrooke’s Hospital
Cambridge CR0 2QG, UK

Professor David I. W. Phillips, MA, PhD, FRCP
Professor of Metabolic and Endocrine Programming
MRC Epidemiology Resource Centre
University of Southampton
Southampton General Hospital
Southampton SO16 6YD, UK

Dr Orlando Pignalosa, MD
Department of General Pathology
II University of Naples
80131 Naples, Italy

Professor Lucilla Poston, BSc, PhD, FRCOG
Director of Research
Maternal and Fetal Research Unit
Division of Reproductive Health
Endocrinology & Development
King’s College London
St Thomas’ Hospital
London SE1 7EH, UK

Associate Professor Sandra Rees, MSc, MPhil, PhD
Associate Professor and Reader
Department of Anatomy and Cell Biology
University of Melbourne
Parkville, VIC 3010, Australia

Professor Claude Remacle, PhD
University Full Professor
Institute of Life Science
Université catholique de Louvain
B1348 Louvain-la-Neuve, Belgium

Dr Brigitte Reusens, PhD
Senior Scientist
Institute of Life Science
Université catholique de Louvain
B1348 Louvain-la-Neuve, Belgium

Dr H. I. (Trudy) Roach, PhD
University Orthopaedics
Southampton General Hospital
Southampton SO16 6YD, UK

Dr Victoria Roberts, BSc, PhD
Postdoctoral Fellow
Department of Obstetrics and Gynecology
University of Cincinnati College of Medicine
231 Albert Sabin Way
Cincinnati, OH 45267, USA
Professor Michael G. Ross, MD, MPH
Professor of Obstetrics/Gynecology and Public Health
UCLA School of Medicine and Public Health
Chair, Department of Obstetrics and Gynecology
Harbor-UCLA Medical Center
1000 W. Carson Street, Torrance
CA 90602, USA

Dr Loredana Rossi, MB
Department of General Pathology
II University of Naples
80131 Naples, Italy

Professor H. P. S. Sachdev, MD, FIAP, FAMS
Professor and In-charge
Division of Clinical Epidemiology
Department of Pediatrics
Maulana Azad Medical College
New Delhi 110 002, India

Professor Vincenzo Sica, MD
Professor of Clinical Pathology
Department of General Pathology
II University of Naples
80131 Naples, Italy

Dr Deborah M. Sloboda, PhD
Forrest Fetal Research Scientist
Postdoctoral Research Fellow
School of Women’s and Infants’ Health
The University of Western Australia
King Edward Memorial Hospital
Bagot Road, Subiaco
WA 6008, Australia

Noel Smith, BSc
Department of Clinical Biochemistry
University of Cambridge
Addenbrookes’ Hospital
Cambridge CB2 2QR, UK

Professor Michael E. Symonds, BSc, PhD
Professor of Developmental Physiology
Head of the Academic Division of Child Health
School of Human Development
Queen’s Medical Centre
Nottingham NG7 2UH, UK

Professor Kent L. Thornburg, PhD
M. Lowell Edwards Chair for Research in Clinical Cardiology
Professor of Medicine (Cardiology)
Director, Heart Research Center
Oregon Health and Science University
3181 S.W. Sam Jackson Park Road
Portland, OR 97239, USA

Dr Christopher Torrens, BSc, PhD
Postdoctoral Research Fellow
Maternal, Fetal & Neonatal Physiology
Centre for Developmental Origins of Health & Disease
University of Southampton
Princess Anne Hospital
Southampton SO16 5YA, UK

Dr Janelle Ward, PhD, BSc
Department of Physiology
University of Cambridge
Downing Street
Cambridge CB2 3EG, UK

Professor John O. Warner, MD, FRCP, FRCPCH
Professor of Child Health
Infection, Inflammation and Repair Division
School of Medicine
University of Southampton
Southampton General Hospital
Southampton SO16 6YD, UK

Professor Emma Whitelaw, DPhil
School of Molecular and Microbial Biosciences
University of Sydney
NSW 2006, Australia
current address: Queensland Institute of Medical Research
Brisbane, QLD 4029, Australia

Professor E. Marelyn Wintour, PhD, DSc, FAA
Department of Physiology
Monash University
Clayton, VIC 3800, Australia
Preface

This book could not have been written ten years ago. In the first instance, the field it covers, that of developmental origins of health and disease (DOHaD) was at that stage embryonic and highly controversial. While there was compelling epidemiological data, there was a lack of experimental and mechanistic data on which to create consensus. But over the last decade the science of DOHaD has advanced rapidly. The epidemiological evidence for the DOHaD paradigm is now strongly supported by prospective clinical data, experimental observations and a growing understanding of the underlying molecular and developmental mechanisms. Further, the scope of physiological systems that may be involved has expanded. The relevance of the phenomenon to the ecology of human disease in different populations is now much clearer.

So there is now a pressing need for a book such as this. By the time of its publication, three world congresses on DOHaD will have occurred; an international learned society has been formed; and there are a substantial number of reviews on many aspects of the field and its implications. Yet to date there is no definitive textbook. Students, clinicians and researchers need a volume that brings current knowledge together, whether to introduce them to the subject as a whole or to help them broaden their knowledge of an expanding field.

Moreover, the implications of the DOHaD concept are now becoming clear. The scientific implications now extend not only into epidemiology, developmental biology and physiology, but also into evolutionary biology and anthropology. DOHaD has very
important implications for public health policy, not only in developed but also in developing societies.

In this volume, we have assembled contributions from undisputed experts in the DOHaD field. Many are architects of the ideas that are reviewed throughout. We are enormously grateful to them for their timely and well-constructed contributions to the volume. Our thanks must also go to Peter Silver, who commissioned the volume from Cambridge University Press, and to Deborah Peach, Cathy Pinal and Karen Goldstone who worked so hard on the preparation of the manuscripts for publication.