Mechanisms
of Disease
Mechanisms of Disease
An Introduction to Clinical Science
Second Edition

Stephen Tomlinson
Cardiff University, UK

Anthony M. Heagerty
University of Manchester, UK

Anthony P. Weetman
University of Sheffield, UK

Rayaz A. Malik
University of Manchester, UK
CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore, São Paulo, Delhi

Cambridge University Press
The Edinburgh Building, Cambridge CB2 8RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org

Information on this title: www.cambridge.org/9780521818582

© Cambridge University Press 2008

This publication is in copyright. Subject to statutory exception and to the provisions of relevant collective licensing agreements, no reproduction of any part may take place without the written permission of Cambridge University Press.

First published 2008

Printed in the United Kingdom at the University Press, Cambridge

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

Library of Congress Cataloguing-in-Publication Data
   p. ; cm.
   Includes bibliographical references and index.
RB113 M38 2008
613.07 – dc22


Cambridge University Press has no responsibility for the persistence or accuracy of URLs for external or third-party Internet websites referred to in this publication, and does not guarantee that any content on such websites is, or will remain, accurate or appropriate.

Every effort has been made in preparing this book to provide accurate and up-to-date information that is in accord with accepted standards and practice at the time of publication. Nevertheless, the authors, editors and publisher can make no warranties that the information contained herein is totally free from error, not least because clinical standards are constantly changing through research and regulation. The authors, editors and publisher therefore disclaim all liability for direct or consequential damages resulting from the use of material contained in this book. Readers are strongly advised to pay careful attention to information provided by the manufacturer of any drugs or equipment that they plan to use.
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of contributors</td>
<td>vii</td>
</tr>
<tr>
<td>Preface to the first edition</td>
<td>xi</td>
</tr>
<tr>
<td>Preface to the second edition</td>
<td>xiii</td>
</tr>
<tr>
<td>1  Molecular and cell biology</td>
<td>1</td>
</tr>
<tr>
<td>Julian R. E. Davis</td>
<td></td>
</tr>
<tr>
<td>2  Gaucher's disease: a model disorder for therapeutic exploration of the lysosome&lt;br&gt;Timothy M. Cox</td>
<td>42</td>
</tr>
<tr>
<td>3  Obesity</td>
<td>69</td>
</tr>
<tr>
<td>J. Shakher, P. G. McTernan and Sudhesh Kumar</td>
<td></td>
</tr>
<tr>
<td>4  Autoimmune mechanisms</td>
<td>85</td>
</tr>
<tr>
<td>Anthony P. Weetman</td>
<td></td>
</tr>
<tr>
<td>5  Mechanisms of disease – allergy and anaphylaxis</td>
<td>115</td>
</tr>
<tr>
<td>Richard S. H. Pumphrey</td>
<td></td>
</tr>
<tr>
<td>6  Infection – bacterial</td>
<td>136</td>
</tr>
<tr>
<td>Stephen D. Lawn and George E. Griffin</td>
<td></td>
</tr>
<tr>
<td>7  Infection – parasitic</td>
<td>160</td>
</tr>
<tr>
<td>Malcolm E. Molyneux</td>
<td></td>
</tr>
<tr>
<td>8  The acute coronary syndrome</td>
<td>169</td>
</tr>
<tr>
<td>Anthony M. Heagerty</td>
<td></td>
</tr>
<tr>
<td>9  Heart failure</td>
<td>178</td>
</tr>
<tr>
<td>Ludwig Neyses and Mamta H. Buch</td>
<td></td>
</tr>
<tr>
<td>10 Acute neurodegeneration: cerebral ischaemia and stroke</td>
<td>191</td>
</tr>
<tr>
<td>Craig J. Smith, Jerard Ross, Nancy J. Rothwell and Pippa J. Tyrrell</td>
<td></td>
</tr>
</tbody>
</table>
## Contents

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Diabetic neuropathy</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td>Adam Greenstein, Moaz Mojaddidi, Andrew J. M. Boulton and Rayaz A. Malik</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Renal cell carcinoma</td>
<td>226</td>
</tr>
<tr>
<td></td>
<td>Wasat Mansoor</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Alcoholic liver disease</td>
<td>242</td>
</tr>
<tr>
<td></td>
<td>James Neuberger</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Diet, health and disease</td>
<td>261</td>
</tr>
<tr>
<td></td>
<td>Michael E. J. Lean</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Trauma</td>
<td>275</td>
</tr>
<tr>
<td></td>
<td>Nick Payne and David W. Yates</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>The interaction between organic and psychiatric disease</td>
<td>286</td>
</tr>
<tr>
<td></td>
<td>Else Guthrie</td>
<td></td>
</tr>
</tbody>
</table>

Index

Colour plate section follows page 114.
Contributors

Andrew J. M. Boulton, MD FRCP
Faculty of Medical and Human Sciences
School of Medicine
Manchester Royal Infirmary
Manchester, UK

Mamta H. Buch
MRI Central Manchester and
Manchester Children's University Hospitals
Manchester Royal Infirmary
Manchester, UK

Timothy M. Cox, MA MSc MD FRCP FMedSci
University of Cambridge and
Department of Medicine,
University of Cambridge NHS Hospitals
Foundation Trust
Cambridge, UK

Julian R. E. Davis, MD PhD FRCP
Endocrine Sciences Research Group
School of Clinical & Laboratory Sciences
University of Manchester
Manchester, UK

Adam Greenstein, BSc (Hons) ChB MRCP
Faculty of Medical and Human Sciences
School of Medicine
Manchester Royal Infirmary
Manchester, UK

George E. Griffin, BSc PhD FRCP (Lon,E) FMedSci
St George's, University of London
London, UK
Else Guthrie, MSc MD MBChB FRCPsych
Manchester Royal Infirmary
Manchester, UK

Anthony M. Heagerty
Cardiovascular Research Group
Division of Cardiovascular and Endocrine Sciences
University of Manchester
Manchester, UK

Sudhesh Kumar, MD FRCP
Clinical Sciences Research Institute
Warwick Medical School
University of Warwick
Coventry, UK

Stephen D. Lawn, BMedSci MB BS MRCP MD DTM&H Dip HIV Med
The Desmond Tutu HIV Centre
Institute of Infectious Disease and Molecular Medicine
Faculty of Health Sciences
University of Cape Town
South Africa
and
Clinical Research Unit
Department of Infectious and Tropical Diseases
London School of Hygiene and Tropical Medicine
London, UK

Michael E. J. Lean, MA MD FRCP
University of Glasgow and
Glasgow Royal Infirmary
Glasgow, UK
and
University of Otago
Dunedin, New Zealand

P. G. McTernan
Division of Clinical Sciences
Warwick Medical School
University of Warwick
Coventry, UK

Rayaz A. Malik, MD ChB FRCP PhD
Division of Cardiovascular Medicine and Endocrine Sciences
University of Manchester
Manchester, UK

Wasat Mansoor, MBChB MRCP PhD
Christie Hospital
Manchester, UK

Moaz Mojaddidi, MB ChB
Faculty of Medical and Human Sciences
School of Medicine
Manchester Royal Infirmary
Manchester, UK

Malcolm E. Molyneux, MD
Malawi–Liverpool-Wellcome Trust Clinical Research Programme
College of Medicine
University of Malawi
Blantyre, Malawi

Ludwig Neyses, MD
University of Manchester
Manchester, UK

James Neuberger, DM FRCP
Queen Elizabeth Hospital and
University of Birmingham
Birmingham, UK

Nick Payne
Wythenshawe Hospital
Manchester, UK

Richard S. H. Pumphrey, MD
Honorary Consultant Immunologist
Manchester Royal Infirmary
Manchester, UK

Jerard Ross
The Department of Clinical Neurosciences
Western General Hospital
Edinburgh, UK
Nancy J. Rothwell, FRS FMedSci
Faculty of Life Sciences
University of Manchester
Manchester, UK

J. Shakher
Diabetes & Endocrine Centre
Birmingham Heartlands Hospital
and
University of Birmingham
Birmingham, UK

Craig J. Smith
Division of Medicine and Neuroscience–Hope
University of Manchester
Hope Hospital
Salford, UK

Pippa J. Tyrrell
Division of Medicine and Neuroscience – Hope
University of Manchester
Hope Hospital
Salford, UK

Anthony P. Weetman, MD DSc FMedSci
School of Medicine & Biomedical Sciences
University of Sheffield
Sheffield, UK

David W. Yates, MD MCh FRCP FRCS FCEM
University of Manchester
Manchester, UK
Preface to the first edition

This book reflects innovative approaches to the learning of core subjects and provides opportunities for in-depth study in undergraduate medicine, emphasising the understanding of principles rather than simply memorising facts. Our approach follows the direction of curricular development throughout the UK and the expressed educational aim of the General Medical Council. In addition, higher medical training at the postgraduate level will be increasingly based on the principles of clinical science; given the accelerating pace of advances in biomedical knowledge, requirements of continuing education are likely to have a strong scientific component.

The introductory section of the book sets out the essentials of molecular and cellular biology as they relate to mechanisms of disease. There is also a brief description of some established and more recently developed methodologies used in molecular and cell biology.

The book then outlines leading-edge scientific knowledge and demonstrates how this is fundamental to the practice of up-to-date clinical medicine. Each chapter focuses on one or more clinically important exemplar topics where science has helped to develop clinical practice or improved understanding of the basis of disease.

Each chapter falls broadly into two parts: the first is devoted to basic mechanisms and the second to the application of knowledge of these basic mechanisms to the understanding of the pathogenesis and diagnosis of an exemplar condition. Although the emphasis is on mechanisms of disease, aspects of treatment are also included.
where they have explanatory value in understanding disease processes. Authors have usually focused on one specific exemplar condition, but where appropriate, there is comment on other diseases relevant to the section ‘mechanism’. The overriding aim of the book is to meet the need for new approaches to learning medicine; it also provides information for students undertaking special study modules, encouraging self-directed learning by the study in depth of specific subjects chosen by the students themselves.

We are especially grateful to Professor David R. London, Registrar of the Royal College of Physicians of London, for the chapter on the historical development of concepts of disease, which we believe sets the scene for succeeding chapters.

S. Tomlinson, A. M. Heagerty and P. Weetman
Preface to the second edition

This second edition of *Mechanisms of Disease* builds on our original aims of providing a mechanistic, as opposed to traditional, list-based approach to medicine. This is in keeping with the huge transformation in both undergraduate and postgraduate teaching and learning and is in accord with the aims of the General Medical Council (GMC) described in *Tomorrow’s Doctors* (1993, 2003).

This book provides the essential knowledge required for the core curriculum and is delivered by leading clinicians and scientists. In keeping with one of the major remits of the GMC on delivering the core curriculum, *factual information* has been 'kept to the essential minimum that students need at this stage of medical education'. The use of principles of disease combined with an appropriate exemplar approach provides learning opportunities that help the student to explore knowledge and evaluate and integrate evidence critically, motivating them to develop the necessary skills for self-directed learning. The use of exemplars provides students with clinical information relevant to their special study modules and *student-selected components*, allowing them to study particular areas in depth. Again in keeping with the change from simply 'learning lists' to establishing principles of disease, each chapter provides knowledge of the sciences and scientific methods on which medicine is based.

Finally, to integrate theory with clinical practice, each chapter includes a series of clinical scenarios, followed by questions.