

EDITED BY
JOHN PICKUP
AND GARETH
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TEXTBOOK OF DIABETES



VOLUME 1

BLACKWELL SCIENTIFIC PUBLICATIONS

TEXTBOOK OF DIABETES

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ROYAL LIVERPOOL HOSPITAL, LIVERPOOL

IN TWO VOLUMES

VOLUME ONE

OXFORD

BLACKWELL SCIENTIFIC PUBLICATIONS

LONDON EDINBURGH BOSTON

MELBOURNE PARIS BERLIN VIENNA

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Blackwell Scientific Publications
Editorial Offices:
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Other Editorial Offices:
Arnette SA
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Meinekestrasse 4
D-1000 Berlin 15
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Blackwell MZV
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First published 1991

Set in Palatino by Setrite Typesetters, Hong Kong
Printed and bound in Hong Kong by
China Translation & Printing Services

DISTRIBUTORS

Marston Book Services Ltd
PO Box 87
Oxford OX2 0DT
(Orders: Tel: 0865 791155
Fax: 0865 791927
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USA

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Blackwell Scientific Publications
(Australia) Pty Ltd
54 University Street
Carlton, Victoria 3053
(Orders: (03) 347-0300)

British Library

Cataloguing in Publication Data

Textbook of diabetes.

- I. Man. Diabetes
 - I. Pickup, John C. (John Christopher).
 - II. Williams, Gareth
- 616.462

ISBNs

Vol. 1 0-632-03056-9
Vol. 2 0-632-03058-5
The set 0-632-025948-1

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Foreword

The diabetic state commands more attention now than ever before. At a time when in all branches of medicine, indeed in all branches of science, the engagement generally with the problem becomes increasingly demanding and technologically complex, understanding diabetes occupies a continuingly prominent place. Diabetes has always stood out in the history of medicine and science. The graphic descriptions by ancient observers must put the severe, insulin-deficient diabetic state among the earliest of the readily recognized clinical conditions, the paradigm of the 'clinical syndrome'. Exploration of the nature of diabetes claimed the attention of the father of experimental medicine, the great Claude Bernard, so much of whose thought and perception remains with us today. He understood the importance of the balance between glucose production and glucose consumption in determining the level of glucose concentration though he had little conception of the factors which regulated them. He saw diabetes essentially as the outcome of a disturbance of relationships, a distortion of a homeostatic system, a disorder of adaptation.

Bernard shared the scientific stage with the other giant of 19th century biomedical science, Louis Pasteur, whose discoveries promoted a quite different model of disease, one that was more direct and simple. The disease process resulted from a single, well-defined causal agency — a germ. If the germ was not present, the disease could not occur, though having the germ did not guarantee the appearance of the disease. The Pasteurian notion of disease in the present day context can be extended to include the abnormal gene or a toxic substance as the causal agency of disease. Had Pasteur ever pronounced upon diabetes, he might well have wondered about some

specific enzymatic abnormality in the pathways of glucose metabolism, an area not unfamiliar to him.

In the contemporary world of diabetes, the Bernardian and the Pasteurian views contend. A pure Bernardian would regard the diabetic state as a disorder of adaptation, a breakdown in the interrelation and regulation of the balance of factors determining glucose production and disposal. It is perhaps best exemplified in the debates in the 1990s by the Reaven concept of glucose intolerance and non-insulin-dependent diabetes mellitus (NIDDM). His construct of the conditions resulting in the diabetic state introduces the interaction of regulatory mechanisms unknown in their nature to Bernard and Pasteur. This construct is compatible with the observed 'continuous distribution' of glucose tolerance/intolerance in most populations, showing no clear break between the normal and the abnormal.

The scientific advances of recent decades might seem to promote the Pasteurian view of the diabetic state. We have witnessed an explosive expansion of knowledge and understanding of the genetic control of cell structure and function, and its role in the causation of disease. The search for a diabetes (susceptibility) gene has excited much research interest and is best established in the insulin-dependent variety of diabetes. An environmental trigger which initiates a process culminating in the destruction of the pancreatic B cell is also sought and fulfils the Pasteurian expectation of a single causal factor of major effect operating in a genetically susceptible setting.

It becomes likely that these two major views of the causation of the diabetic state are not mutually incompatible and indeed both operate to explain the occurrence of diabetes in man. Thus, genetic

factors contribute to the adaptive disorder of NIDDM (though their nature remains far from clear) while the process affecting the B cell in the insulin-dependent variety of the disease may fall far short of complete destruction of insulin-producing cells in many of the people it affects and is itself presumably modulated by other genetic and environmental factors.

The diabetic state impacts upon mankind in many ways. At the 'macro' level, it throws up the question of the adequacy of provision of medical services, the question of prescriptive screening, and the social and emotional predicament of the diabetic individual. For the individual, it carries a variety of clinical and therapeutic problems, often complicated in the long course of the disease by damage to the eye, the kidney, the peripheral nerves, and the arterial wall. It is these delayed 'complications' which provide most of the burden of diabetes upon the individual and upon society. While the diabetic state appears to be the *sine qua non* of their appearance, other individual factors, some probably genetic, will also determine their time of onset, their rate of progression and their ultimate severity.

For clinical and basic scientists, diabetes is the

point of departure for research enquiries in many fields. The history of the discovery of insulin, its characterization, structure and synthesis have contributed much to broaden understanding of biochemistry and genetics. Research into the insulin receptor is telling us about the mechanisms of hormonal signals. Immunological mechanisms are bound up with some forms of the diabetic state; their understanding and control may well lead to the prevention of insulin-dependent diabetes in the foreseeable future.

These and many other aspects of the diabetic state are dealt with in the chapters that follow. Clear answers as to 'the cause' of diabetes and its complications are not yet available. However, the growing pace of research and its increasingly prompt application to the patient make the lot of the person with diabetes progressively easier to bear. The comprehensive account of our knowledge of the disease in this book will make a substantial contribution to improving both our understanding of the disease and the care of patients suffering from it.

HARRY KEEN
London, July 1990

Preface

Our main intention in producing this book was to disseminate information about diabetes mellitus amongst the many different people involved in tackling the scientific, medical and social problems of the disease. The ramifications of diabetes extend into so many areas that it demands a truly multidisciplinary approach. Its clinical management depends on an integrated team of specialists as diverse as physicians, chiropodists, nurses, psychiatrists and general practitioners, and research into the disease and its treatment requires the combined skills of immunologists, physiologists, pathologists, chemists and many others. The problems of diabetes will only be identified and solved if there is understanding and effective communication between these various groups.

We therefore set out to summarize the key clinical and scientific topics of diabetes in a form which would be useful to the specialist in a given area and yet readily accessible to the non-specialist who wishes to learn about the main principles and challenges of disciplines beyond his or her own. The 'clinical' chapters are intended to provide a clear and up-to-date guide to the features, diagnosis and treatment of diabetes and its complications, which will be of real practical value to those concerned with the everyday management of the disease. In the 'scientific' (non-clinical) sections, we have aimed to cover the major aspects of metabolism and what is known of the disease processes which result in diabetes; we hope that these are both comprehensive and, for the most part, interesting and intelligible to those who are not career scientists. Throughout the book, we have attempted to highlight recent clinical and scientific advances and their impact on the understanding and treatment of diabetes, as well as the questions which remain unanswered.

Overall, we have tried to cater for a wide range of interests and requirements. The book should also be useful for those preparing for postgraduate examinations.

Each chapter is constructed as a self-contained essay prepared by an expert in the field and, as such, should stand alone; we therefore make no apologies for the reiteration of important concepts in more than one chapter. At the same time, the book is designed as an integrated text and we have tried to avoid unnecessary repetition through extensive cross-referencing. We have edited each chapter according to a common format, beginning with a summary of its major points, and have made extensive use of figures, flow-charts and tables where these usefully illustrate important points in the text. If we have managed to produce an integrated book, we hope that this has been achieved without stifling the individuality of the contributors.

Every textbook runs the risk of various criticisms, some of which we have tried to anticipate. The first is that any book of this size will inevitably be out of date by the time it appears. We have tried to incorporate new and important material at all stages up to the final proofs, and can only hope that the great distress which this has caused our publishers has been justified. Secondly, every textbook is parochial to some extent. We have aimed to encompass a wider view of diabetes than that encountered in our own practice by including contributions from authors in a dozen or so countries, which cover topics such as diabetes in the Third World, malnutrition-related diabetes and diabetes in ethnic groups in the UK. Finally, the scope of a book such as this is sometimes questioned. We hope that our choice of chapters reflects both the breadth and the ex-

citement of diabetes and that, for example, those dealing with the historical background of diabetes and the short but thought-provoking personal view of the disease will not be neglected.

This book's gestation slightly exceeded that of the blue whale and, at times, the book seemed likely to join the whale on the list of endangered species. Fortunately, several groups of people have fought to ensure its survival. We are profoundly grateful for their contributions to the book, which range from the obvious to the invisible. The first, of course, is the 120 authors who have provided the substance of the book with skill and authority. We would like to thank them, not only for the quality of their contributions, but also for their stoical and (mostly) gallant tolerance of editorial interference with their work. We are particularly indebted to those who, through efficiency or intimidation, managed to meet or even beat our deadlines. The second group is the team at Blackwell Scientific Publications, who have distinguished themselves by their endless support, enthusiasm and ability to apply firm but generally painless pressure at crucial moments. Karen Anthony and Rachel Nalumosso deserve special mention for having served so nobly (and indeed survived) in the front-line skirmishes between publishers, authors and

editors. Peter Saugman initiated the project and provided constant support and encouragement throughout. Thirdly, many friends and colleagues have helped in various ways, particularly by providing clinical photographs and other material, hounding elusive references and making suggestions — sometimes kind but always constructive — about the content of the book. We have especially valued the help of Ian MacFarlane, Geoff Gill and Paul Drury in this respect, and also acknowledge the assistance of Charles Bodmer and Alan Patrick in struggling through the proofs, and of Jackie Williams and Adrian Brown in drawing up the tables for Chapter 79. The fourth group is our secretariat, namely Caroline Williams, Luine Weir and Denise Janson, whose skills in typing, organization and cryptography are fortunately underpinned by the rare virtues of patience and good humour.

Finally, we are indebted to our families for having tolerated the book's relentless invasion of evenings, weekends and holidays, and for having accepted so many times our increasingly flimsy assurances that it would be finished one day.

JOHN C. PICKUP

GARETH WILLIAMS

London and Liverpool, July 1990

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