PREFACE

The context for the first edition of this book, published in 1982, was that Mitchell's chemiosmotic theory of energy transduction had been widely accepted, as acknowledged by the award of the Nobel Prize in 1978, yet the underpinning principles of this theory were widely misunderstood and its full scope was not appreciated. The second edition in 1992 was written against the background that, on the one hand, many general textbooks still gave too superficial a treatment to chemiosmotic mechanisms, whereas on the other hand, the high-resolution structure of a bacterial reaction centre that operates according to Mitchell's ideas had recently been reported and recognised with the Nobel Prize in 1988. The third edition in 2002 followed the 1997 Nobel Prize to Paul Boyer and John Walker for their work on the ATP synthase enzyme and marked the beginning of the explosion in mitochondrial physiology and pathology, with the calculation that 34,000 publications in the previous decade could be retrieved from PubMed with the key word 'mitochondria.' A similar calculation for the decade from June 2002 to December 2012 raises this number to an extraordinary 95,000, the large majority of which deal with aspects of what might be termed 'mitochondrial physiology'—the study of healthy and dysfunctional mitochondria in the cellular, organ and whole body context. This explosion has necessitated a change in the organisation of this fourth edition, which we have divided into three interlocking sections: basic principles; structures and mechanisms; and physiology. This last is greatly expanded from the brief chapter in the third edition. Thus, Part 1 deals with the fundamentals of bioenergetics, ion transport pathways, thermodynamics and the basis of the proton circuit. Part 2 covers the current information on the structures and mechanisms of the protein complexes of the electron transport chains in mitochondria, bacteria and photosynthetic systems, the ATP synthase and transport proteins. Part 3 covers the application of these structures and principles to physiology and pathophysiology.

It is striking that many of the misunderstandings that surrounded the chemiosmotic idea in the 1960s reoccur in the 21st century. For example, it is still common in new textbooks to see the mitochondrion depicted as having no membrane potential but just a pH gradient, while we were recently alerted to a serious error in a national biology examination, where it was incorrectly asserted that a proton-impermeable outer

membrane was required for ATP synthesis. The mechanism of action of routine uncouplers such as FCCP is often erroneously described. Papers appear regularly in the most prestigious journals demonstrating a profound lack of understanding of bioenergetics—a criticism directed not only to the authors but also to deficiencies in reviewing and editing. The need to explain these fundamentals therefore continues.

Although we wish this book to continue to be considered the standard authority in the field, the present state of mitochondrial physiology poses some problems because few areas have established the same degree of precision or certainty characteristic of much of the structural and mechanistic studies. Rather than present uncritical reviews of the many physiological topics, we have imposed what we hope is a useful filter, namely that observations must be consistent with our understanding of bioenergetics at the isolated organelle and intact cellular level. There is undoubtedly a current tendency to propose an involvement of mitochondrial function and dysfunction in a large number of physiological and pathophysiological processes. Not all of these will be borne out by future experimentation. However, if only 10% prove to be verifiable in the future, this will mean that the mitochondrion will continue to play a central role in cell physiology.

The overall aim of the book is to allow readers with the standard basic knowledge of biochemistry to have an entry into the frontline research in bioenergetics, by providing a bridge to the primary research literature. To this end, we have employed a policy of focusing on the most recent authoritative reviews, with a very restricted number of key papers. Therefore, the choice of references tends to reflect the inverse of scientific priority. We trust our colleagues will recognise this limitation.

Since the last edition, there has been an explosion of crystal structures that in most cases are beginning to give mechanistic insight. The trouble with crystal structures is that they are too complex for the reader to see the woods for the trees. Consequently, we have continued our practice of using line drawings, but new for this edition is that these are usually superimposed on the actual structures. We hope this approach will be valuable. Of course, not all the mechanisms we discuss here will prove to be correct in every detail. There is a web site (http://booksite.elsevier.com/9780123884251) on which we shall post important corrections and updates in detail, and we suggest you bookmark this link.

We have been helped by generous advice and permissions to use original figures from numerous colleagues. A partial list includes Judy Armitage, Fraser Armstrong, Christopher Benz, Ben Berks, Egbert Boekema, Martin Brand, Michael Duchen, Terry Frey, Gyorgy Hajnoczky, Carola Hunte, Pankaj Kapahi, David Kelly, Edmund Kunji, John Lemasters, Zhenfeng Liu, Bernd Ludwig, Anthony Moore, Hindrik Mulder, Simon Newstead, Casey Quinlan, John Rubinstein, Guy Rutter, Leonid Sazanov, Orian Shirihai, Michael Stewart, Rolf Thauer, John Walker, Konstanze Winklhofer and Claes Wollheim. Doubtless we have overlooked some and to them we apologise whilst emphasising that we are entirely to blame for any misinterpretations and factual errors.

Writing a book such as this imposes large burdens on our families and colleagues. We thank them, in particular Solvig and Tina, very much for their forbearance.

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