Preface

The twentieth century saw the elucidation of many of the fundamental problems of the biological sciences. A major achievement was the development of metabolic biochemistry. However, within this general field, one of the most significant challenges was the endeavor to understand the mechanisms of bioenergetics. The complexity of this field became apparent when the links between the mechanisms of various processes in oxidative phosphorylation, photosynthesis, and cellular transport across membranes began to be appreciated. These areas had previously been studied independently, but in the middle of the century their relationships were increasingly understood and the term bioenergetics was often used to cover the emerging field.

Biologists have been concerned with mechanisms for several centuries, but with the development of modern methods, the significance of the term mechanism has been recognized. Philosophers, in a rather different way, have long had an interest in mechanism but this has been revitalized in recent times with the application of this concept to the philosophy of the biological sciences. So the idea of searching for a mechanism seems to be particularly appropriate to the consideration of the history of scientific studies about respiration. These developed through basic issues of metabolism to the crunch question of how cells acquire their energy from the oxidation of foodstuffs such as carbohydrates. Here I trace the history of the search for mechanisms in a group of key biological fields that progressively merged toward the end of the twentieth century. This study is not intended to add to the philosophical ideas on mechanism, but rather to see the way in which mechanisms in one specific area were elucidated over time, from the early seventeenth to the end of the twentieth century.

Few problems have taxed biologists as much as the fundamental mechanisms of bioenergetics. This book is designed partly to explore the often-heated debates particularly in the 1960s and 1970s, when theories and experimental interpretations in bioenergetics were fought over so passionately that the period was known by some as the Ox phos wars. It is also intended to place this important period in biological research in its historical setting. Thus the story of what is now known as bioenergetics is traced from the first experimental studies of respiration and photosynthesis in the enlightenment of the seventeenth and eighteenth centuries to the modern period. The climax of the account comes in the brilliant resolution of the mechanism of adenosine triphosphate (ATP) synthesis in animals, plants, and microorganisms by the proton-translocating ATP synthase at the end of the twentieth century. Such a history reflects the history of biology as a whole as it moved from a primarily observational study to the highly technical investigations of the second half of the twentieth century.

Like most history, writing a science history raises questions about defining the margins of the discussion both in time and in subject matter. A major issue has been where to start. In his history of respiration, David Keilin went back to the second-century Greek physician and philosopher Galen. I have chosen to start with a brief discussion of seventeenth-century ideas, when a truly experimental approach to the study of respiration was initiated. The photosynthesis story is best begun at the beginning of the eighteenth century with the work of Stephen Hales, whose ideas also contributed to the respiration story. I have concluded the story at the end of the twentieth century with a discussion of the enzyme-synthesizing ATP because of its innate interest and because it demonstrated an important result of the search for mechanism. The scope of the book has been slightly narrow, being confined to the discussion of respiration, oxidative, and related aspects of phosphorylation, photosynthesis, and cognate areas, such as facets of membrane transport and specific issues in microbial biochemistry. Fields such as muscular contraction, which might arguably have been included in a discussion of bioenergetics history, have been mostly omitted and similarly some areas of microbial energetics.

Of course, restrictions of space have entailed selecting issues to which particular attention should be given in order to maintain a comprehensible narrative, and this has necessitated some rather difficult choices. Thus judgments have had to be made about which particular scientific contributions should be included, which contributions should be seen as central to the history of bioenergetics, and which might be set aside in order to focus on the major lines of development. This is particularly so in the later part of the twentieth century in which there is a vast amount of material and a wide range of approaches to the subject. Inevitably many rather personal choices have been made. I apologize to those who feel that important aspects of the subject have been omitted or that the work of particular scientists who made valuable contributions has been ignored or should have been given more weight. Another issue that has emerged arises from the nature of the field of bioenergetics that has been noted for its lack of consensus. Although I have covered most of the most obvious disagreements in my discussion I have been advised that in some more recent research, I may not have been sufficiently sensitive to the varying viewpoints. I apologize to those who feel I have misrepresented particular aspects of their interests.

The history has been divided into several phases, each initiated by a major advance often outside the field of bioenergetics and affecting biochemistry more generally. These phases do not have broad applicability as the phases I have recognized for respiration and phosphorylation are not identical with those identified for photosynthesis. After having much in common at the beginning, the two areas of study have tended to proceed separately, partly because the events associated with the light reaction had no counterpart in animal cell respiration. However, in the second half of the twentieth century, the two fields have been more or less merged in the field of bioenergetics. Indeed it is not possible to consider the one without the other as each has made major contributions to the other.

In telling this story I have felt it right to make points through appropriate quotations of the leading workers in the field. This allows the historical figures to be heard. However, in the later period this becomes more difficult; frequently a wide variety of workers are jointly developing the field, and a somewhat random choice has been made. I have also attempted to minimize the technical aspects as much as possible, although it is not

possible to describe the development of ideas in a subject such as biochemistry without recourse to a certain amount of chemistry. Further, in the later stages, the use of highly complex techniques has been discussed without much explanation of what is actually involved.

What is the justification for a book on the history of cell bioenergetics? The history of science is a discipline in which it is important that both historians and scientists participate. This story is told by a scientist in the hope that his approach will provide some illumination on an area generally enlightened by contributions of historians and also philosophers. What I have sought to do here is to give a coherent though brief account of the history of those events associated with the energetics of cell respiration and photosynthesis over more than three centuries. There is already a widely acclaimed book by Joseph Fruton on the history of biochemistry as well as the extensive account by Marcel Florkin; both of these present aspects of bioenergetics within a broad discussion of biochemistry but do not give it the detailed attention it deserves. There have been a number of essays on specific events and short periods of biochemical history but there is clearly a need to put all of these within a broad historical perspective. That perspective also illustrates some of the effects of the major developments in the chemical aspects of biological science, the preparation of cell-free systems at the turn of the twentieth century, the ability to describe metabolic pathways, the development of techniques for handling membrane proteins, and so on. However, the justification for the book is in my view the need for a history of bioenergetics comparable to that of Michel Morange's *A History of Molecular Biology*. I hope I have come some way in achieving that goal.

But why single out bioenergetics? Metabolic biochemistry developed only slowly in the earlier part of the twentieth century, but its achievements were substantial—the glycolytic pathway, the citric acid cycle, and so on. The same period began to identify aerobic phosphorylation as a major source of ATP but the mechanism was not apparent. By the 1950s it was clear that there was a challenging problem to solve. The difficulties in finding a solution, the choice between different hypotheses, and the problem of successfully working with membranes provide interesting historical developments not as apparent in other areas of metabolic biochemistry. Such problems were solved by bringing together quite diverse researches, many drawn from cell biology. Thus the roots of this endeavor are to be found in several almost independent lines of research that come together to create the field in the 1950s. Such a story surely needs to be told.

I came into the study of bioenergetics in the 1960s, a most exciting period in the history of this field. I am grateful to those who encouraged me in this early period, particularly Dudley Cheesman, who taught me the value of the historical approach to biochemistry, to my colleagues Peter Zagalsky and particularly John Lagnado, who encouraged me to take up the teaching of bioenergetics in the single Honours biochemistry course at Bedford College, University of London. An abiding inspiration from that period was the occasional lectures of Peter Mitchell that sparked my enthusiasm for the subject. I should also record my appreciation of brief but sound advice on writing science history from my friend of student days, Bob Olby. I am grateful to colleagues who kindly read part or most of the manuscript and provided valuable comment, Bruce Weber and Peter Rich and also Ann Marshall. I also wish to record my appreciation of the detailed and constructive comments of two anonymous

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