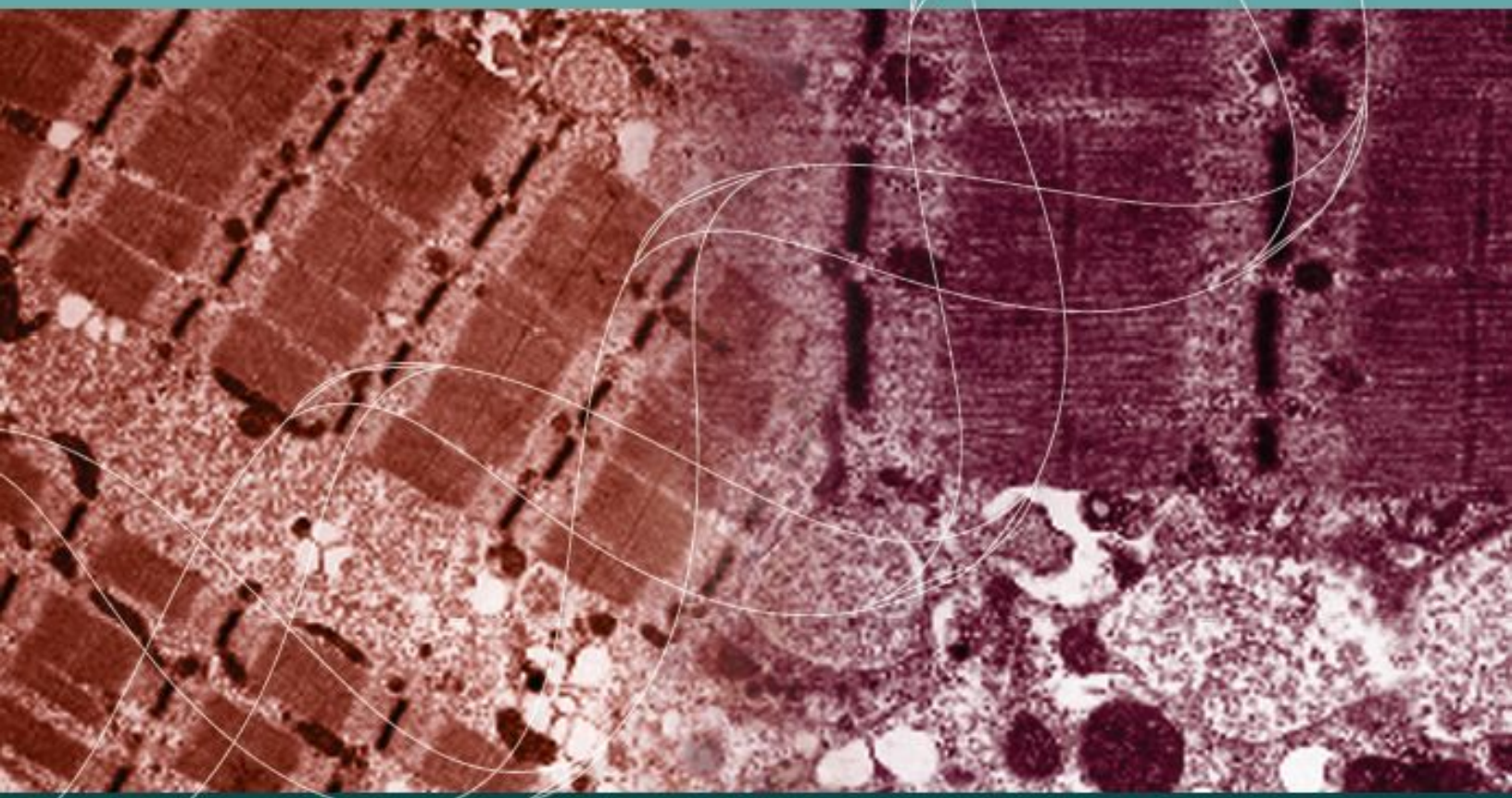
LYSOSOMAL STORAGE DISORDERS

A PRACTICAL GUIDE

Edited by Atul Mehta & Bryan Winchester



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Lysosomal Storage Disorders

A Practical Guide

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Preface

The concept of a lysosomal storage disorder is now almost 50 years old – an appropriate time, we feel, for a new review of the subject.

The term lysosome was coined by Christian de Duve [1], the discoverer of this organelle, to reflect its role as the major intracellular site for the enzymatic 'lysis' of macromolecules so that they may be recycled. The concept of a lysosomal storage disorder was first proposed by H G Hers [2], following the discovery that one of the glycogen storage diseases (Pompe disease, acid maltase deficiency) was due to deficiency of a lysosomal enzyme. The concept of 'cross-correction', formulated by Elizabeth Neufeld [3] and her group after the discovery that co-cultured fibroblasts derived from two patients with different lysosomal storage disorders mutually corrected each other, led to the notion of 'enzyme replacement therapy' (ERT). Roscoe Brady not only discovered the enzymatic basis for Gaucher disease and Fabry disease but also pioneered ERT for humans [4,5].

The last two decades, however, have seen a huge expansion in research in this area which has substantially extended our understanding of both the scientific and the clinical basis of lysosomal storage disorders [6]. Thus, at a scientific level it is now very well recognised that lysosomes are part of an endosomal/lysosomal network which plays a critical role in a whole range of cellular processes including the recycling of membrane and other organelles, the turnover of molecules and ingested matter through endocytosis and phagocytosis, and an emerging role in apoptosis and autophagy. At a clinical level successful treatments have been employed which reduce substrate

accumulation or promote substrate degradation but it is increasingly recognised that the protean multi-system manifestations of these conditions result from pathologic processes over and above simple lysosomal storage and damage.

This book is the fruit of an ambitious project which aims to review both the scientific and the clinical aspects of lysosomal storage disorders. We perceive a need for an accessible volume giving an up to date overview of the subject. Even when effective treatments are available, there remains an urgent need to highlight awareness of the diseases so that early and appropriate treatment may be sought [7]. Furthermore, in a rapidly changing world, there is a real need to improve access to expensive treatments. The first section of the book reviews current understanding of the physiology and pathophysiology of lysosomal storage disorders and we again to attempt to classify the conditions. The second part of the book reviews individual diseases, and gives perspectives from patients and experts looking towards future therapeutic directions. The book is aimed at a wide audience including scientists, clinicians, health care workers and administrators, those working in the pharmaceutical industry, patients and their organisations.

We are highly indebted to Christine Lavery, the Founder and Chief Executive of the Society for Mucopolysaccharidosis Diseases (MPS Society, UK). Christine has been an integral part of the project from the very beginning, a partner during its production and a driver towards its completion. The extremely high regard in which she is held internationally has allowed us to assemble a glittering array of distinguished contemporary scientists and clinicians working in this area. Furthermore, all contributors and the editors have donated their royalties to the MPS society, which is dedicated to promote research into these diseases and to the support of patients and families who

suffer from them. We are also grateful to Shire HGT which has made the project possible through an unrestricted educational grant given to the MPS Society. The Editors and contributors take full responsibility for the contents of the book and confirm that Shire HGT, the MPS Society and Wiley-Blackwell have not had any role in influencing the content of the work.

We would also like to thank Elisabeth Dodds, Production Manager, Nick Godwin and Rob Blundell at Wiley-Blackwell who have helped us at every stage of the project. Our distinguished contributors have made time in their busy schedules to prepare and revise their contributions and we thank them for their patience, timeliness, clarity and charity in delivering their chapters to us.

We would each like to acknowledge some, of our many, academic mentors. For Atul this has to be Lucio Luzzatto, a clinician and scientist who guided his early academic career, emphasising the need for meticulous and reflective observation and record. Atul would also like to thank Victor Hoffbrand, who has provided invaluable encouragement during his career as a clinician, academic – and as a writer. Bryan would like to thank Don Robinson for introducing him to lysosomal storage diseases and giving him his first job, and Bob Jolly, who taught him the importance of linking pathology and biochemistry through the study of animal models. Finally, we would both like to thank our respective wives and families for their continuing forbearance and support.

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