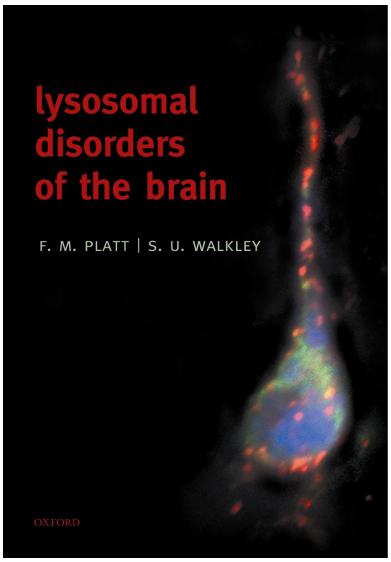
Lysosomal disorders of the brain: Recent advances in molecular and cellular pathogenesis and treatment.
Platt F.M. and Walkley S.U. eds., Oxford University Press, 2004.



The observations and historical perspective of Hers and colleagues on the recognition of lysosomal storage disorders (LSD) sets the scene for this first-rate book. The early half of the twentieth century heralded the beginnings of lysosomal biology and notables like DeDuve, Novikoff, Baudhuin, van Hoof, Hers and other colleagues who have their names associated with classic lysosomal storage disorders are introduced with the insight that only a forefather of the field can properly elucidate. This appropriately set the scene for the Prologue which presents the tragedy of LSD from the unique perspective of a professional who is also a parent of LSD patients. If one was soul searching for a reason or motivation to study and develop a cure for LSD, herein lays the essence. The agony of watching the "slow and methodical" progress of research towards some hope of a treatment is presented to the reader with the underlying courage that must be required to be a parent of an LSD patient.

Maxfield and Mukherjee, introduce a simplified view of the endosome-lysosome system, based mainly on the traffic of specific receptors and classical compartment markers. In reality this belies the extensive complexity and dynamics of the endocytic network of compartments. As highlighted by the authors, this is further complicated by specialisation in different cell types. The authors have done justice to this topic by discussing the clearly defined knowledge that they have developed in the area. The chapter covered some aspects of vesicular traffic in neurons, but mainly from an endocytic perspective.

The overview of LSD presented by Platt and Walkley provides the rationale for organising the book based on "underlying molecular mechanism" as opposed to the alternative, based on storage product. This makes inherent sense in that many LSD have secondary storage products, which can be in excess of the primary storage material. There was one minor omission in this section in that Chediak-Higashi and Hermansky Pudlak syndromes, despite reference later in the text, were not listed as trafficking defects.

An expert overview of clinical presentation of LSD completes the introductory section and sets the scene for the rest of the book. This chapter is by Wraith, whose attention to clinical detail and clarity has made a significant contribution to the LSD field. The major groups of LSD are introduced, giving the reader a feel for the important aspects of clinical presentation and how this varies between different LSD.

The chapter by Winchester is a detailed coverage of the nature of mutations in LSD patients, together with their impact on mutant protein and the role of different components of the processing network and the endosome-lysosome system on this mutant gene product. The chapter provides both an introduction for the novice but also a useful appreciation of the field for professionals. It gives the reader a good appreciation for the underlying molecular basis for LSD.

The chapter on defects in lysosomal modification is appropriately authored by von Figura and colleagues reflecting their work on the molecular mechanism for

sulphatase active site processing. This relates directly to the processing of a subset of LSD and specifically to multiple sulphatase deficiency.
Initially some of the diversity in the next chapter by Hasilik and Lemansky was distracting, but on completion of the chapter it linked well through out the text and was clearly used to support other parts of the book. This chapter effectively introduced mannose-6-phosphate targeting and raises important consequences of targeting defects and implications for LSD pathogenesis. The authors hint at the role of specific lysosomal enzymes in brain pathogenesis and the relative lack of knowledge on targeting mechanism in neurons.
The chapter on protection by d'Azzo introduces one of the few known lysosomal enzyme complexes and the role of cathepsin A as a protective protein for the other constituents of this complex. This has direct importance in relation to cathepsin A dysfunction, which leads to a neurodegenerative disorder through altered endothelial cell function and axonal damage.
Sphingolipid activator proteins have a critical role in glycosphingolipid metabolism and the latter are important storage products in the brain for many LSD, as discussed by Sandhoff and colleagues. The fact that defects in activator proteins lead to fatal LSD, indicates their importance to lysosomal function and lipid turnover, as further highlighted in the next chapter on defects in trans-membrane proteins. The critical role of membrane proteins in lysosomal enzyme targeting and traffic is introduced in chapter 9. It is clear that the field needs to develop a deeper understanding of lipid metabolism to fully appreciate LSD pathogenesis. Chapters 7 and 8 give a glimpse of the true internal complexity of the "lysosome" and thus our lack of knowledge on the internal structure of this set of organelles. This together with the function of constituents of the lysosomal membrane in chapter 9 (Ioannou), raise awareness of the links to other cellular function and the true impact of lysosomal dysfunction on cellular homeostasis.
The chapter by Pearce on non-mammalian systems highlights the importance of abstracting models of human disease to "simple systems". One of the take home messages from this chapter was that lysosomal biogenesis and traffic will be critically important in neuronal pathogenesis. In essence the "simpler systems" described in this chapter point to the value of animal models in the study of LSD, as discussed in chapter 11. Animal models, as reviewed by Hopwood and colleagues, have provided not only a means for the study of aspects of LSD pathology, which in many cases are not amenable to study in humans, but have also provided much of the evidence justifying the clinical trial of treatment strategies in human patients.
Walkley begins the chapter on brain dysfunction with the fundamental observation that the primary defect is not the cause of end stage pathology, as LSD patients often do not have obvious clinical signs at birth. He iterates the concept that this is rather due to a slow progressive cascade of events that inevitably results in pathology. For brain pathology this is particularly focused on lipid components of the endosome-lysosome system and in many cases relates to secondary accumulation as a result of the primary defects effect on endosome-lysosome function. He also discusses the cellular consequences of storage in the brain, together with the availability of methods for the functional assessment of the impact of these storage products.
The chapter by Neufeld is the first in a series of articles focused on treatment. A simple concept first suggested by De Duve and colleagues in the 1960s has taken decades before it has been established as a viable therapeutic option. The author made the critical observations linking cross correction and sucrosome correction pre-empting the studies on mannose 6-phosphate mediated uptake of lysosomal proteins.

However, it is becoming apparent that not all storage products are simply accessible by this mechanism and strategies like that employed for Gaucher disease (using alternative targeting mechanisms) are necessary to make ERT effective for all LSD. Equally important is the concept that selective targeting may be required to access certain sites of pathology.

Theoretically cross-correction should allow cell replacement therapy to be an effective therapeutic option. This is the basis of bone marrow transplantation and some gene replacement therapy strategies. Dobrenis suggests that progenitor cells provide an exciting prospect, but present very significant problems associated with directed differentiation. Much research is required to yield a viable treatment strategy using this technology, but the therapeutic potential warrants further investigation.

Substrate deprivation is a relatively new therapeutic option for LSD, based on small molecule inhibitors. This strategy may be a potential alternative or supplemental treatment strategy for LSD patients. Platt and Butters highlighted that there are side effect problems and downsides to this strategy and some of this relates to the non-specificity of current inhibitors. Despite these problems some therapeutic efficacy has been demonstrated in Gaucher patients.

The final chapter by Sands addresses gene replacement therapy. Again while conceptually simple, this is possibly the most technically difficult strategy that has been suggested for treating LSD patients. Gene delivery, integration and toxicity (due to over-expression) present as potential obstacles for successful gene therapy. Moreover this article highlights that different LSD may require different gene therapy strategies, reflecting the diverse biology of these disorders. It is likely that gene therapy provides the most hope in the long term of a solution for LSD patients with a single effective treatment. However, it is evident that much further developmental work is required and that like enzyme replacement therapy it will be even longer before this is then implemented in therapeutic practice.

Overall as a researcher in the LSD field, this book provided an excellent read and in many areas provided thought provoking ideas for further research activities. It certainly gives the reader a good perspective on historical advances in the field and the current status of knowledge on LSD with a specific focus on a major site of pathology, the brain.

Associate Professor Doug Brooks,
NH&MRC Senior Research Fellow,
Head of Immunochemistry-Cell Biology Section,
Lysosomal Diseases Research Unit,
Women's and Children's Hospital,
Adelaide SA, Australia.
douglas.brooks@adelaide.edu.au

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