Ichthyoses
Ichthyoses
Clinical, Biochemical, Pathogenic and Diagnostic Assessment
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Dedication

We would like to dedicate this volume to our ichthyosis patients and their families, from whom – by their courage and positive attitude as well as their generosity of time (and tissue!) – we have learned so much about how people meet the challenges of living continuously with an often debilitating and highly visible skin disease. As we look back over our careers, the advances in understanding these diseases, largely fueled by the molecular biological revolution and the work of many investigators, are truly astonishing. Yet, our ability to treat these disorders has experienced little change. It is our hope that integrating the insights gained from molecular genetics with the dynamics of the epidermal functional response to these disorders will point to new and effective forms of therapy for these disorders.
Preface

The initial impetus for this book, i.e. as an atlas of diagnostic ultrastructure, resulted from a clinical research project of Dr. Anna Bruckner’s (Stanford University). As a pediatric dermatology fellow at University of California, San Francisco, from 2004 to 2005 and without prior laboratory experience, Anna’s project was to assess whether clinicians, as novices in electron microscopy, could be trained to identify key ultrastructural abnormalities that assist in the diagnosis of different types of ichthyosis. Since Anna readily learned the ultrastructural features of the principal types of ichthyosis [chapter 1, this vol., table 4, pp. 25–26], we realized that by publication of representative images, we could make this structural information more widely available. Yet, because our interests ranged beyond descriptive morphology, this book subsequently evolved from its original scope as an ultrastructural atlas into a text of broader purpose, with substantial additional information on the clinical features, biochemical genetics and the cellular pathogenesis of the ( mendelian) monogenic inherited disorders of cornification (MeDOC).

Over the years, we have attempted to unravel the pathogenic mechanisms that lead to the clinical phenotype in many of the MeDOC. While most assessments of disease pathogenesis proceed from the gene to the phenotype (‘downstream’), our approach instead looks ‘upstream’ from the functional abnormalities, which ‘drive’ the phenotype, towards the responsible gene. Of course, this approach is most productive when the responsible gene is already known. But surprisingly, knowledge of the genetic abnormality often provides few insights into the pathogenesis of the skin phenotype, and instead can mislead the investigator (prominent examples include epidermolytic ichthyosis, loricrin keratoderma and transglutaminase-1-linked lamellar ichthyosis). The appropriateness of this backward-looking approach is evident when one considers the diversity of genetic defects that converge on quite similar phenotypes. These ichthyosiform phenotypes represent the ‘best attempt’ by the epidermis to sustain a barrier that suffices to allow survival in a xeric, terrestrial environment, i.e. the genetic abnormality partially thwarts this response and an ichthyotic phenotype is the result. Therefore, therapeutic interventions, which are not discussed in this volume, need to be consistent with and, if possible, support this attempt at barrier restoration. Accordingly, while gene replacement therapy still remains a distant dream, knowledge
of cellular pathogenic mechanisms could provide immediate opportunities for novel therapies aimed alternatively at disease pathogenesis.

Importantly, the application of ultrastructure to the diagnosis of the ichthyoses requires the utilization of both osmium tetroxide and ruthenium tetroxide (RuO$_4$) postfixation. Without the utilization of RuO$_4$, it is not possible to visualize either: (1) the amount of extracellular lipids; (2) the maturation of secreted lamellar body contents, and most importantly, (3) alterations in the structure and organization of the lamellar bilayers themselves. Because successful implementation of RuO$_4$ postfixation requires substantial training, Ms. Debra Crumrine provides a technical primer in Appendix 1, which we hope will assist laboratories that are attempting to add diagnostic ultrastructure to their morphological armamentarium. Yet, ultrastructural information, though potentially diagnostic, should always be considered provisional, until verified further by biochemical, immunohistochemical or molecular genetic studies. Moreover, this volume is not intended to be comprehensive. There are many disease entities that we have not examined, as well as several that we chose to exclude, most notably the palmar-plantar keratodermas, connexin-related disorders and trichothiodystrophy. Furthermore, we admit that in some instances, the literature cited is incomplete, and, as a result, it may fail to give sufficient credit to those who have made important contributions to the delineation of these entities. A final word of caution: we have no personal experience with the utility of cutaneous ultrastructure for the prenatal diagnosis of the ichthyoses. Because characteristic structural features of children and adults could differ during epidermal development in utero, it should not be assumed that the distinctive structural changes that we describe here for certain MeDOC will necessarily be present in fetal epidermis.

Our work on the pathogenesis and ultrastructural diagnosis of the ichthyoses has been dependent in large part upon the technical and interpretive skills of a master electron microscopy technician, Ms. Debra Crumrine. She has applied, and continues to apply, her highly developed skills to the biopsy material that we receive from all over the world. For Debbie, this project largely represented a labor of love, i.e. a way to help patients with ichthyosis by identifying potentially diagnostic, ultrastructural features of specific disease entities.

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