Foreword

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The 5th Symposium on Lysosomal Storage Disorders was held April 10–12, 2008, in Paris, France. This year's symposium attracted more than 350 clinicians and scientists working in the field of lysosomal storage disorders (LSDs). These metabolic disorders, which as a group occur in ~1 in 5000 live births, share a common pathogenesis; namely, a genetic defect in one or more specific lysosomal enzymes, activator protein, or membrane protein that results in deficient enzymatic activity. The pathologic lysosomal storage of substrate leads to interference with normal cellular activity and clinical manifestations. These manifestations usually present at a young age and progressively affect multiple organ systems.

The emphasis of this year's symposium was on recent basic research findings, the importance of early diagnosis and timely intervention, and the evolving role of biomarkers in the clinical management of LSDs. The oral presentations delivered by key opinion leaders from around the world illustrate the significant progress that is being made in understanding the metabolic defects of LSDs and the clinical implications of treating these defects. Some of those oral presentations are abstracted here as short referenced papers; highlighted versions of the symposium's poster presentations are also provided.

Although awareness of LSDs among medical specialists has improved, our efforts to reduce diagnostic delays should be intensified, as timely intervention offers the best hope for an optimal clinical outcome, and genetic counseling, which is a critical element in the management of these disorders and in the provision of appropriate care for other family members, can then be offered. Screening among members of a patient's family, as well as implementation of carefully conducted screening initiatives for high-risk patient populations and newborns, were repeatedly discussed as effective methods for early identification.

The pioneering research conducted by Roscoe O. Brady, MD, and his colleagues at the National Institutes of Health defined much of what is currently known about the enzymology, biochemistry, and metabolic defects in LSDs. In 1966, Dr. Brady first suggested treating Gaucher disease by replacing the deficient enzyme, and his efforts ultimately led to approval by the US Food and Drug Administration of alglucerase (placentally derived glucocerebrosidase) in 1991. The concept of enzyme replacement therapy (ERT), involving regular IV administration of the deficient enzyme, has been proven safe and effective. Since then, several other effective ERTs for these rare disorders have become available.

The clinical experiences with ERT in Gaucher disease, Fabry disease, mucopolysaccharidosis I, and Pompe disease were reviewed during the symposium. These experiences, which overall have been positive, have shown that signs and symptoms usually ameliorate and that further disease progression can generally be stopped; irreversible damage, however, cannot be repaired. There is still room for improvement, and comprehensive guidelines that are used to assist physicians in making decisions regarding therapeutic intervention and monitoring could be further optimized. In particular, clearer direction is needed regarding when to start therapy in specific subpopulations (eg, pediatric patients, adult female patients with Fabry disease, patients with adult-onset LSD).

New insights into the lysosomal pathophysiology, which triggers a cascade of processes, may prove to be key in appreciating the implications of currently available and improved or new therapies, including ERT, active-site chaperone therapy, and substrate inhibition therapy. In this context, the bone metabolism, fundamentals of cardiovascular and blood–brain barrier biology, and muscle pathology (including the role of autophagy) were discussed by experts in their respective fields. In a separate session, the need was expressed for novel biomarkers that could provide better insight into the pathogenesis of LSDs, would be more precise in staging the disease, and be better predictors of response to therapy.

Since the discovery of the lysosome by Christian de Duve, MD, in 1955, and the proposed concept of inborn lysosomal disorders by Henri-Géry Hers, MD, in 1965, the field of LSDs has become increasingly complex, and a growing number of LSDs have been identified. The traditional classification system, which groups LSDs as metabolic diseases characterized by the type of stored undegraded macromolecules, may provide only partial

insights into the underlying cause of the pathologic storage. A proposed classification system—including the following classes: primary lysosomal hydrolase defects, enzyme modification defects, trafficking defects, enzyme protection defects, membrane protein defects, and coactivator defects—could prove to be more useful. Indeed, although most LSDs are caused by a primary hydrolase defect, others are not. Examples of various mechanisms were discussed at the meeting. For instance, a posttranslational modification defect occurs in multiple sulfatase deficiency (Austin disease) and results in a striking reduction of the catalytic activity of all known sulfatases. Functional deficiency of multiple lysosomal enzymes due to trafficking defects is seen in I-cell disease (mucolipidosis II) and pseudo-Hurler polydystrophy (mucolipidosis III). In these diseases, newly synthesized enzymes are excessively secreted by cells instead of being targeted to the lysosome, due to a deficiency in a Golgi-located enzyme normally involved in the synthesis of the mannose-6-phosphate recognition marker. In galactosialidosis, the catabolic enzymes are normally encoded, synthesized, and routed, but on entering the lysosomes, the enzymes are degraded due to the absence of a protein (protective protein/cathepsin A) normally protecting neuraminidase and β-galactosidase from intralysosomal degradation. The group of molecular defects involving lysosomal transmembrane proteins is rapidly growing; in most cases, such as Niemann-Pick type C disease and Danon disease, the precise function of these proteins is still poorly understood. In Salla disease and cystinosis, the defect is localized in one of many carrier-mediated transport mechanisms across the lysosomal membrane. In addition to numerous hydrolases, lysosomes also contain soluble nonenzymatic glycoproteins (the 4 saposins [A–D] and the GM2 activator) required for enzyme-catalyzing reactions. Defects in these coactivators have been found in variants of metachromatic leukodystrophy, GM2 gangliosidosis, and Gaucher disease.

In summary, we can look back at a very successful symposium that offered a great opportunity to review important new data and to exchange ideas between clinicians and scientists. We hope that, in the near future, more LSD patients and their families will benefit from the momentum gained over recent years.

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