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Introduction

The approach to the diagnosis and management of patients with lysosomal storage disorders (LSD) can be viewed as a model of specialized care delivery in the current era of medical practice. In particular, the introduction of disease-specific therapies, directed at the underlying biochemical defect and putative downstream mechanisms of disease, stands out as a practical application of advances made in translational research.

This introductory chapter describes aspects relating to the LSDs that have allowed its distinction from the broader group of inborn errors of metabolism. Topics discussed include major historical milestones that have brought us to where we find ourselves today, in terms of understanding causation and the clinical manifestations and natural history of individual clinical entities within this class of disease. Recent progress in the development of therapy, including currently available options and those under investigation, is also briefly presented.

The Lysosome and Storage Defects

Essentially the group of diseases classified as an LSD represents metabolic defects associated primarily with a disruption in the catabolism and/or transport of by-products of cellular turnover, coupled with the secondary consequences of the accumulation of incompletely metabolized substrates within particular cell types (Table 1.1). The principal organelle involved in the disease process is the lysosome, wherein the acidified environment (pH 5.0–5.5; actively maintained by a proton pump V type H^+ ATPase) and action of various hydrolases normally facilitate the

Table 1.1. The lysosomal storage disorders classified according to the relevant substrate involved.

Stored Substrate	Disease	Enzyme/Protein Deficiency	Gene Locus
A. Sphingolipids			
GM ₂ -gangliosides, glycolipids, globoside oligosaccharides	Tay-Sachs	α -subunit β -hexosaminidase	15q23-4
	GM ₂ -gangliosidosis (three types)*		
	Sandhoff disease	β -subunit β -hexosaminidase	5q13
	GM ₂ -gangliosidosis		
GM ₁ -gangliosides, oligosaccharides, keratan sulfate, glycolipids	GM ₂ -gangliosidosis, AB variant	G _{M2} activator	5q32-33
	GM ₁ -gangliosidosis (three types)*	β -D-galactosidase	3p21.33
Sulphatides	Metachromatic leukodystrophy (MLD)	Arylsulphatase A (galactose-3-sulphatase)	22q13.31-qter
GM ₁ -gangliosides, sphingomyelin, glycolipids, sulphatide	MLD variant	Saposin B activator	10q21
Galactosylceramides	Krabbe disease	Galactocerebrosidase	14q31
α -galactosyl-sphingolipids, oligosaccharides	Anderson-Fabry disease	α -galactosidase A	Xq22
Glucosylceramide, globosides	Gaucher disease (GD) (three types)*	Glucocerebrosidase	1q21
Glucosylceramide, globosides	GD (variant)	Saposin C	10q21
Ceramide	Farber disease (seven types)	Acid ceramidase	8p22-21.2
Sphingomyelin	Niemann-Pick disease types A and B	Sphingomyelinase	11p15.1-15.4

(Continued)

Table 1.1. (Continued)

Stored Substrate	Disease	Enzyme/Protein Deficiency	Gene Locus
B. Mucopolysaccharidoses (Glycosaminoglycans)			
Dermatan sulphate (DS) and Heparan sulfate (HS)	MPS-I, Hurler, Scheie	α -L-iduronidase	4p16.3
	MPS-II, Hunter	Iduronate-2-sulphatase	Xq27.3-28
HS	MPS-IIIA, Sanfilippo A	Sulfamidase	17q25.3
	MPS-IIIB, Sanfilippo B	α -N-acetylglucosaminidase	17q21.1
	MPS-IIIC, Sanfilippo C	Acetyl CoA: α -glucosaminide-N-acetyltransferase	8p11
Keratan sulphate (KS)	MPS-IIID, Sanfilippo D	N-acetylglucosamine-6-sulfatase	12q14
	MPS-IVA, Morquio A	Galactosamine-6-sulphatase	16q24.3
	MPS-IVB, Morquio B	β -D-galactosidase	3p21.33
DS	MPS-VI, Maroteaux-Lamy	N-acetylgalactosamine-4-sulfatase	5q13-14
DS and HS	MPS-VII, Sly	β -D-glucuronidase	7q21.1-22
Hyaluronan	MPS-IX, Natowicz	Hyaluronidase	3p21.3
C. Glycogen			
Glycogen	Pompe, GSD II	α -D-glucosidase	17q25
Glycogen	Danon disease	Lysosomal associated membrane protein-2 (LAMP-2)	Xq24

(Continued)

Table 1.1. (Continued)

Stored Substrate	Disease	Enzyme/Protein Deficiency	Gene Locus
D. Oligosaccharides/ Glycopeptides			
α -mannoside	α -mannosidosis	α -mannosidase	19p13.2-q12
β -mannoside	β -mannosidosis	β -mannosidase	4q22-25
α -fucosides, glycolipids	α -fucosidosis	α -fucosidase	1p34.1-36.1
α -N-acetylgalactosaminide	Schindler/Kanzaki disease	α -N-acetylgalactosaminidase	22q13.1-13.2
Sialyloligosaccharides	Sialidosis	α -neuraminidase	6p21.3
Aspartylglucosamine	Aspartylglucosaminuria	Aspartylglucosaminidase	4q34-35
E. Multiple Enzyme Deficiencies			
Glycolipids, oligosaccharides	Mucopolipidosis II (I-cell disease); mucopolipidosis III (pseudo-Hurler polydystrophy) — three complementation groups	N-acetylglucosamine-1- phosphotransferase	4q21-q23; ML-III subtype C (a/b subunit 12q23.3; g subunit 16p)
Sulphatides, glycolipids, glycosaminoglycans	Galactosialidosis (protective protein/ cathepsin A)	Protective Protein/cathepsin A	20
	Multiple sulfatases (Austin disease)	SUMF-1	3p26

(Continued)

Table 1.1. (Continued)

Stored Substrate	Disease	Enzyme/Protein Deficiency	Gene Locus
F. Lipids			
Cholesterol esters	Wolman disease, CESD (cholesterol ester storage disease)	Acid lipase	10q23.2-q23.3
Cholesterol, sphingomyelin, GM ₂ -gangliosides	Niemann-Pick disease type C	NPC1; HE1	18q11-12; 14q24.3
G. Monosaccharides/Amino Acid Monomers			
Sialic acid, glucuronic acid	Salla, ISSD	Sialin	6q14-15
Cystine	Cystinosis	Cystinosin	17p13
H. Peptides			
Bone proteins	Pycnodysostosis	Cathepsin K	1q21
I. S-acylated Proteins			
Palmitoylated proteins	Infantile neuronal ceroid lipofuscinosis (NCL)	Palmitoyl-protein thioesterase	1p32
Pepstatin-insensitive lysosomal peptidase	Late-infantile NCL	Pepstatin-insensitive lysosomal peptides	11p15.5
Cathepsin D	Congenital NCL	Lysosomal cysteine protease	11p15.5

*Three types imply infantile, childhood and adulthood presentations.

processing of different macromolecules (substrates).¹ Lysosomal hydrolyses frequently act in a sequential way, which may partly explain the overlap in the nature of substrates stored and the associated clinical features (Figure 1.1).

Materials internalized by the cells rely on endocytosis and other mechanisms (e.g., phagocytosis) to expedite entry into common endosomal structures (Figure 1.2). Ultimately the ‘cargo’ reaches the lysosome,

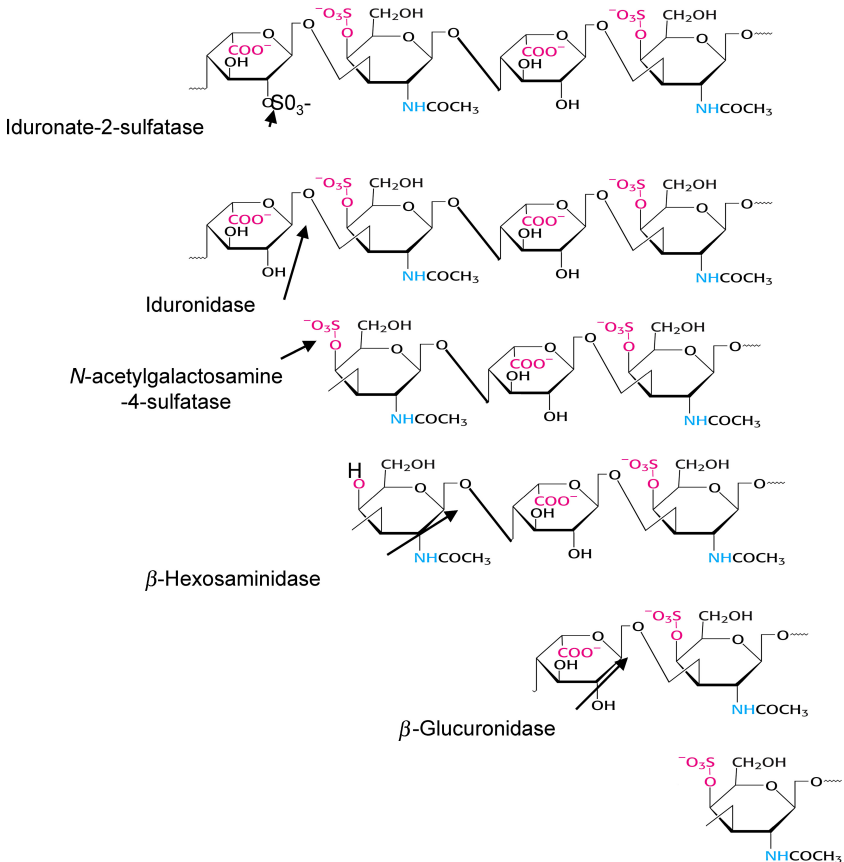


Figure 1.1. Schematic illustration of the sequential degradation of the glycosaminoglycan dermatan sulfate. Deficiency of distinct hydrolases gives rise to individual disorders, the overlap in clinical presentations among the conditions in this group is partly explained by the disruption of a common metabolic pathway.

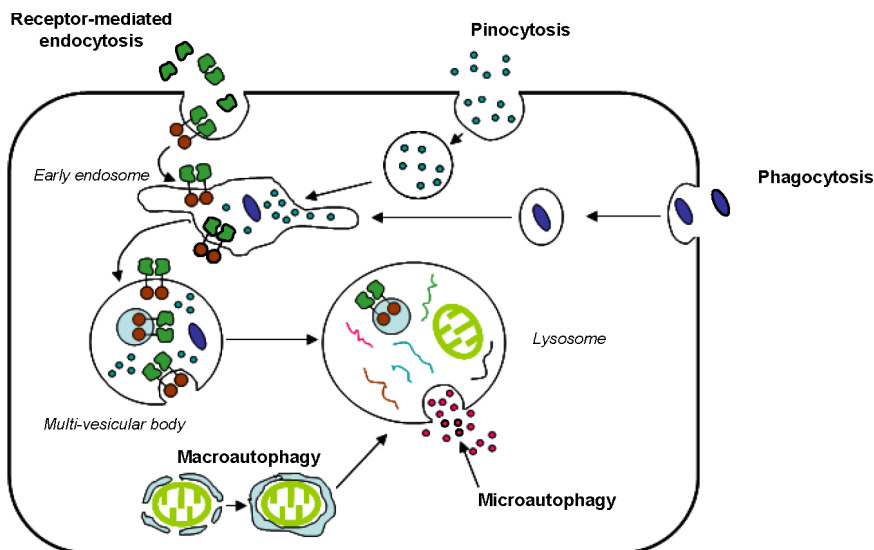


Figure 1.2. Schematic illustration of the endolysosomal system and the mechanisms involved in the delivery of exogenous and endogenous ‘cargo’ to the lysosome for processing.

which can be viewed as a central compartment in the cellular system for the breakdown and discharge or recycling of various substrates. The stability and integrity of the lysosomal limiting membrane is maintained with the assistance of highly glycosylated proteins, such as LAMP-1/2, that prevent lysosomal autodigestion.

Initial characterization of the lysosome was made by Christian DeDuve (circa 1955).² Coincidentally, it was another physician in the group at the *Universite Catholique de Louvain*, Henri-Géry Hers (c.1963), who described the enzyme (α -glucosidase) which is deficient in a glyco-gen storage disorder (*Pompe disease*), considered the first of the LSDs to be delineated as such. *Pompe disease* is named after the Dutch pathologist Johannes C. Pompe who in 1932 described a case of a 7-month-old infant with generalized muscle weakness and hypertrophic cardiomyopathy. Examination of the patient’s cardiac tissue revealed glycogen deposits that were membrane-enclosed. This observation supported the concept of disease associated with lysosomal membrane enclosed-deposits, as distinct

from conditions associated with organ infiltration by malignant cells or infectious agents. Eventually, it was recognized that the storage material represented incompletely degraded substrates that accumulated on account of an underlying enzyme deficiency or transport problem. These pivotal studies established the concept of lysosomal storage disorders, and provided a unifying framework for a diverse group of disorders discussed in greater detail in subsequent chapters.

Besides *Pompe disease (glycogen storage disorder type II)*, several LSDs have been given an eponym in recognition of the physician/scientist who played a role in their seminal description (Table 1.2). *Salla disease* is unique in being named after a locale rather than an individual; this disorder was first described by P. Aula and colleagues in 1979, and named after a district in the Finnish Lapland. *Salla disease* is one of nearly 40 diseases (including two other LSDs, *aspartylglucosaminuria* and *infantile neuronal ceroid lipofuscinosis*) that make up the Finnish ‘disease heritage’; a consequence of founder effect (i.e., shared identity by common descent).³ A similar phenomenon is observed among the Ashkenazi Jews, in whom there is a high frequency of carriers for four LSDs, specifically, *Tay-Sachs disease*, *Gaucher disease*, *Niemann-Pick type A* and *mucopolysaccharidosis type IV*.⁴

To date, the LSDs encompass at least 50 different clinical entities. Initially, the individual disorders were grouped according to the chemical composition of the storage material, e.g., *sphingolipidoses*, *mucopolysaccharidoses*, *oligosaccharidoses*. More recently, these disorders have been clustered according to their underlying biochemical or molecular basis. In most, disease arises because of a deficiency of an enzyme or its co-factor, or because of a defect in a transport protein or other protein involved in the post-translational modification of the hydrolytic enzyme which precludes its functional maturation (a subject covered in more detail in Chapter 5).

Clinical Presentations and Diagnosis

By and large, the characteristic signs and symptoms of the individual LSDs reflect the cell types that are the principal sites of substrate deposits. Besides mechanical tissue disruption, investigations have revealed other pathogenic mechanisms, such as the activation of the endoplasmic reticulum

Table 1.2. Brief biographical sketches.

Designation	Year	Description Date	Biographical Notes
ANDERSON, William	1842–1900	1898	Born in London, UK; he was surgical registrar and demonstrator in anatomy at St. Thomas' Hospital, London
AUSTIN, James H.	1925–	1973	Born in the USA; studied Medicine at Harvard Medical School, Boston; trained in Neurology at the Neurological Institute, Columbia University, New York; Chair of the Department of Neurology, sequentially, at the University of Oregon Medical School and then at the University of Colorado Medical School
BATTEN, Frederick E.	1866–1918	1903	Born in Plymouth, England; studied Medicine at St. Bartholomew's Hospital, London; pathologist at the Hospital for Sick Children and physician at the National Hospital, Queens Square; regarded as father of British pediatric neurology
FABRY, Johannes	1860–1930	1898	Born in Germany; studied Medicine at St. Bartholomew's Hospital, London; dermatologist in Dortmund, Germany, trained at the Royal Clinic for Skin and Venereal disease in Bonn
FARBER, Sidney	1903–1973	1952	Born in Buffalo, New York, USA; studied Medicine at Harvard Medical School, Boston; was a pathologist at the Children's Hospital in Boston; became president of the American Association of Pathologists
GAUCHER, Phillipe C.E.	1854–1918	1882	Born in Champfleury, Nièvre, France; dermatologist at the Hopital Saint-Antoine, Paris

(Continued)

Table 1.2. (Continued)

Designation	Year	Description Date	Biographical Notes
KRABBE, Knud	1885–1965	1913	Born in Denmark; Professor of Neurology and chief of service at the Community Hospital of Copenhagen; founded the <i>Acta Psychiatrica et Neurologica Scandinavia</i>
HUNTER, Charles	1873–1955	1917	Born in Auchterlass, Aberdeenshire, Scotland; studied Medicine at the University of Aberdeen; practiced as an internist in Winnipeg, Canada; taught at the Faculty of Medicine, University of Manitoba
HURLER, Gertrud (nee Zach)	1889–1965	1919	Born in Taberwiese, district of Rastenburg, Prussia; studied Medicine at the University of Munich; trained in Pediatrics at the Hauner Children's Hospital, and moved to private practice in Neuhausen
LAMY, Maurice	1895–1975	1963	Born in France; Professor of Pediatrics at the Hopital des Enfants Malades, Paris; co-organized the 4th International Congress of Human Genetics (ICHG) Paris
MAROTEAUX, Pierre	1926–	1963	Born in Versailles, France; studied Medicine at the University of Paris; director of the National Center of Scientific Research, Hopital des Enfants Malades, Paris; co-organized 4th ICHG
MORQUIO, Luis	1867–1935	1929	Born in Montevideo, Uruguay; studied Medicine at the University of Munich; Professor of Pediatrics at the University of Montevideo
NIEMANN, Albert	1880–1921	1920	Born in Berlin, Germany; Professor of Pediatrics at the University Children's Clinic, and Director of The Infant's Home at Berlin-Halensee
PICK, Ludwig	1868–1944	1914	Born in Landsberg, Germany; Professor of Pathology at the University of Berlin; died in the concentration camp at Theresienstadt

(Continued)

Table 1.2. (Continued)

Designation	Year	Description Date	Biographical Notes
POMPE, Johannes C.	1901–1945	1932	Born in Holland; Pathologist; executed by the Nazi's for his role in the resistance
SACHS, Bernard	1858–1944	1887	Born in Baltimore, Maryland (USA); Professor of Neurology at the Polyclinic, Mount Sinai & Bellevue, New York
SANDHOFF, Konrad	1939–	1965	Born in Berlin, Germany; degree in chemistry at the Ludwig Maximillian University; headed the Department of Neurochemistry, Max Planck Institute for Psychiatry, Munich; Professor of Biochemistry, University of Bonn
SCHEIE, Harold	1909–1990	1962	Born in North Dakota (USA); trained in Ophthalmology and was Professor at the Department of Ophthalmology in University of Pennsylvania
SLY, William	1932–	1973	Born in the USA; studied Medicine at St. Louis University, and trained at the NIH and CNRS Laboratory in France; Professor and Chair, Departments of Biochemistry and Molecular Biology, St. Louis University School of Medicine
TAY, Warren	1843–1927	1881	Born in Plymouth, England; studied Medicine at London Hospital; practiced as an ophthalmologist, pediatrician, and surgeon
WOLMAN, Moshe	1914–	1984	Born in Warsaw, Poland; Professor and Chairman of Pathology at the University of Tel-Aviv, Israel

stress response, inflammatory and/or apoptotic cascade. At this time, details of disease mechanisms that promote tissue damage and organ dysfunction are incompletely understood.

Several clinical manifestations, such as hepatosplenomegaly, coarse facial features and skeletal dysplasia, can serve as an important clue which should lead to consideration of the patient's problems as likely to be due to an LSD (see Chapter 2). Of note, on presentation, especially in a young child, the diagnosis can be missed, especially when the family history is uninformative. Broad heterogeneity in clinical presentation and the wide variability in age at onset and rate of disease progression are additional factors that can lead to significant delay in diagnosis. Diagnostic confirmation necessitates biochemical and/or molecular genetic testing (Chapter 3).

The molecular basis of a majority of the LSDs has been identified. Characterization of the gene defects in affected individual has revealed the occurrence of several distinct mutations. Although this phenomenon partly explains differences in disease severity, extensive studies to examine the relationship between genotype (gene defect) and phenotype (clinical expression) have often shown the lack of perfect concordance. However, in general, deleterious (null) mutations that give rise to a complete or severe enzyme deficiency tend to be associated with an earlier age of disease onset and a graver clinical course. Missense mutations associated with residual enzyme activity usually lead to attenuated clinical subtypes. Investigations of the factors that may influence disease expression are subjects of great interest and are further explored in Chapter 5.

In another group of inborn metabolic errors, the peroxisomal disorders, testing of plasma/serum levels of a single analyte (i.e., very long-chain fatty acids, VLCFA) can point to the diagnosis. Unfortunately, such is not the case with LSDs, in which the diagnosis when suspected often necessitates testing for the presence of excess substrates in body fluids or the activity of several different enzymes in blood or tissues. Thus, it is helpful to have some familiarity with the principal signs and symptoms of particular entities or subgroup of LSDs, so that appropriate testing can be undertaken. Population and newborn screening strategies for LSDs are currently under consideration. This topic and a discussion of methods used to confirm the diagnosis are reviewed in Chapter 3.

Disease Burden and Therapeutic Considerations

The LSDs are defined by regulatory agencies as ‘orphan’ disorders, that is, affecting individuals numbering < 200,000 in the United States (US), or no more than 5/10,000 in Europe. In the United States, therapeutic options for the LSDs have and are being developed, pursuant to two landmark legislation: the Bayh-Dole Act (BDA, 1980) and the Orphan Drug Act (ODA, 1983). Essentially, these acts of congress enabled universities to patent their discoveries and license them to private corporations (BDA); in turn, the biotech companies have received several incentives (including the potential of fast-track approval and marketing exclusivity) to stimulate the development of medical drugs and devices for rare disorders (ODA).⁵ Patient advocacy groups have played a major part in upholding the enactment of these and related legislation, including the more recent Genetic Information Non-discrimination Act (GINA) of 2007–2008.

With the introduction of therapy for LSDs (reviewed in Chapter 6), mainly consisting of the infusion of the relevant recombinant formulation of the deficient enzyme, several guidelines for measuring disease burden or stage and monitoring therapeutic outcomes have been developed (Chapter 4). In practice, the choice of clinical investigations to assess disease severity is usually driven by knowledge of the major organs that can be involved in particular conditions. With advances in disease management and the resultant increase in patient survival, there is a need to ensure continuity of care by physicians, especially when dealing with major life transitions. This can be a challenge, particularly for those trained in ‘adult medicine’ who may not fully appreciate the medical and psychological needs of affected individuals with an LSD, as historically these patients were managed primarily by pediatricians and metabolic specialists.⁶ The complex nature of the disease processes encountered in patients with an LSD necessitates care by a multidisciplinary team, ideally at designated ‘centers of excellence’.

As the number of study patients in the various clinical trials was small, the issue of optimal dose and frequency of exogenous enzyme administration and other management considerations remain open subjects for debate.^{7,8} Meanwhile, other therapeutic options, including the use of small molecules that either inhibit substrate synthesis or serve as a pharmacologic chaperone, have been developed or are under investigation.

Moreover, there are on-going pre-clinical investigations involving gene therapy and stem cell transplantation for the LSDs (covered in Chapter 6). These developments are anticipated to lead to significant improvement in patient survival and quality of life, for diseases that until recently could only be dealt by palliative measures.

Screening and Genetic Counseling Issues

Although individual disorders are rare, the LSDs collectively account for a significant proportion of the population that is chronically ill as a consequence of a genetic disease (Table 1.3). Unfortunately, the diagnosis and

Table 1.3. Disease incidence for selected LSDs.*

Disease	Incidence
• Aspartylglycosaminuria	1 in 3643 (Finland)
• Cystinosis	1 in 281,000
• Anderson-Fabry disease	1 in 117,000
• Gaucher disease	1 in 59,000 (non-Jewish population)
• Krabbe disease	1 in 201,000 [†]
• Metachromatic leukodystrophy	1 in 121,000 [‡]
• Mucopolysaccharidosis (MPS)	Collectively 1 in 25,000
• MPS-I Hurler syndrome	1 in 111,000
• MPS-II Hunter syndrome	1 in 136,000
• MPS-III Sanfilippo syndrome	Collectively 1 in 63,700 [§]
• MPS-VI Maroteaux-Lamy syndrome	1 in 300,000
• Multiple sulfatase deficiency	1 in 1.4 million
• Neuronal ceroid lipofuscinosis	Collectively 1 in 12,500
• Niemann-Pick A/B	1 in 249,000
• Niemann-Pick C	1 in 230,000
• Pompe disease	1 in 201,000

*Mainly drawn from Meikle PJ, Hopwood JJ, Claque AE, Carey WF. *JAMA* 1999 January 20;281(3): 249–254.

[†]1 in 25,000 for *early infantile form* in Sweden.

[‡]1/2,520 live births in Navajo Indians of the Southwestern United States, 1/75 live births in a small Jewish community in Habban, Yemen.

[§]MPS IIIA is the most common subtype in Northern Europe, whereas MPS IIIB is more prevalent in Southern Europe.

management of afflicted patients remains a major challenge, particularly for those with clinical variants associated with central nervous system involvement. Several advances, including methods for carrier detection and prenatal and pre-implantation genetic diagnosis, are providing individuals at risk with options in the course of family planning. However, in most cases the inability to accurately predict long-term prognosis is a confounding factor in the counseling of families.

Rapid scientific progress has enabled the development of an increasing number of therapeutic options. Symptomatic and directed therapies have resulted in increased survival, with significant improvement in quality of life in a significant proportion of treated patients. Keys to good outcome include early diagnosis and timely intervention. Meanwhile, intensive investigation of disease mechanisms is anticipated to provide additional targets for pharmacologic intervention to enable optimal health outcomes.

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Vignette

In 1919, while training in Pediatrics, Gertrude Hurler described two patients with corneal clouding, short stature (associated with skeletal dysplasia) and mental retardation. The patients' clinical features were noted to be similar to two brothers whose medical histories were presented by Charles Hunter at a meeting of the Royal Society of Medicine in London in 1917. Subsequently, these patients were found to have excessive mucopolysaccharides (glycosaminoglycans) in their urine; an observation that led to their categorization as having a biochemical disorder, designated *mucopolysaccharidosis (MPS)*.

The concept of disease as resulting from an inborn error of metabolism was developed by Archibald Garrod, and first introduced in a 1908 Croonian Lecture and at the Huxley Lecture given at Charing Cross Hospital in London in 1927. The notion encompasses defects of amino and organic acid metabolism, peroxisomal disorders and lysosomal storage disorders (LSD). In this scheme, the *MPS* disorders represent a subgroup of the LSDs.

With identification of distinct enzyme deficiencies as the basis for the *MPS* disorder, numerical designations were given to each entity based on the chronologic order of their description. *Hurler syndrome*, the prototypical *MPS* which is caused by a deficiency of α -L-iduronidase, became known as *MPS-I*, and *Hunter syndrome* (iduronate-2-sulfatase deficiency) was designated *MPS-II*. Several mutations have been identified in the relevant genes, responsible for *MPS-I* or *II*, which segregate as an autosomal recessive and X-linked trait, respectively.

Suggested Reading

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