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FOREWORD

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Progress and promise

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The primary hyperoxalurias have long been recognized as the most devastating of the renal stone diseases. In these inherited conditions, deficiency in hepatic enzymes important in disposition of glyoxylate results in increased oxalate production. The resulting marked hyperoxaluria leads to progressive renal damage. Once renal failure ensues, the large oxalate load can no longer be eliminated by the kidney and accumulates in multiple organs causing debilitating disease and ultimately death. Dialysis and kidney transplantation each have limitations in addressing the consequences of the disease. The intensity of dialysis required to keep pace with daily oxalate production cannot be maintained for long periods by most patients. After kidney transplantation, oxalate deposition often leads to early graft failure. Liver transplantation can correct the metabolic defect, but necessitates removal of an otherwise healthy liver, and requires lifelong immune suppression.

A concerned community of physicians and scientists has been meeting every few years to share new findings and to work toward better solutions for the management of the disease. The first workshop in Brussels in 1990 was devoted to the then new approach of hepatorenal transplantation. Subsequent workshops were held in Cambridge, England 1992; Lyon, France 1994; Turin, Italy 1997; Zurich, Switzerland 1999; and Hanover, Germany 2002. During these years, our understanding of the enzymology and molecular genetics of primary hyperoxaluria, types 1 and 2 was advanced. The description of patients with clinical features of primary hyperoxaluria, but with normal AGT and GR/HPR enzyme activity, suggested new subtypes of the disease. Earlier diagnosis, more intensive dialysis, and earlier transplantation improved patient outcomes.

October 8–10, 2004 marked the Seventh International Workshop on Primary Hyperoxaluria, and the first in North America. Participants from 13 countries and more than 12 disciplines met at the Mayo Clinic in Rochester, Minnesota for scientific exchange. A new feature of the Seventh Workshop was a full day program for patients and their families, held in parallel with the scientific sessions. Inspired by the Oxalosis and Hyperoxaluria Foundation, the patient and family program was enthusiastically received by attendees from 21 US states and three Canadian provinces.

The session on genotype/phenotype correlations in primary hyperoxaluria (PH) chaired by Ernst Leumann illustrated the challenge of variability in disease expression and the importance of environmental influences. The increasing usefulness of molecular genetic testing was evident, though the complexity of a large number of mutations limits definitive molecular diagnosis to a minority of patients at present (Rumsby, this issue). The recognition that the most common mutation in PH type 1 is associated with responsiveness to pyridoxine raised important questions regarding prognosis and transplantation in patients known to be homozygous or heterozygous for this mutation. Exciting work in hepatocyte transplantation, discussion of efforts to insert functional AGT into hepatocytes, and a potential role for molecular chaperones marked the session on molecular approaches to treatment, chaired by Craig Langman.

There was agreement that the oxalate injury cascade involves both oxidative injury (Khan, this issue) and the renin angiotensin system (Toblli this issue). The question of whether oxalate ions can cause cell and tissue injury, or whether calcium oxalate crystal formation is a necessary prerequisite for injury was the focus of lively debate (Fred Coe, session chair, Verkoelen, Jonassen, Lieske this issue). Reports from disease registries (chair, Larry Greenbaum) confirmed a mean lag time of several years between first symptoms and diagnosis of PH. Despite advances in diagnosis, a significant proportion of patients are first recognized to have PH only after developing end stage renal disease or after recurrence of oxalosis in a

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transplanted kidney. New approaches to the management of hyperoxaluria (chair, Kay Latta) included discussion of transplantation strategies (Kemper, this issue), *Oxalobacter formigenes* as a potential therapeutic agent (Hoppe this issue) and preclinical work regarding oxalate metabolic pathways and pyridoxamine (Scheinman, this issue). Insights into pathogenesis of stone disease from new animal models (Worcester, this issue) and human histopathology (Evan, this issue), debate regarding stone disease in patients with PH (Pais, Hesse, this issue), as well as frontiers of imaging in stone disease (Vrtiska, this issue) characterized the session on management of urolithiasis in PH chaired by Martino Marangella.

Proceedings from the Seventh International Workshop are published in this issue of *Urological Research* (emphasis on oxalate injury, stone formation and management), and in the *American Journal of Nephrology* (emphasis on molecular genetics, enzyme pathways, and registry reports), electronic publication spring and summer 2005 with print publication fall 2005.

The Seventh International Workshop on Primary Hyperoxaluria and these proceedings are dedicated to Dr. Lynwood H. Smith and Dr. David M. Wilson, who provided invaluable research, laboratory, and clinical knowledge of the primary hyperoxalurias. The pioneering work of these valued colleagues helped to provide the groundwork for improved understanding of disease pathogenesis and thus for the current promising work.

It is with acknowledgment of the progress to date and optimism for the future that we publish these proceedings and look forward to the Eighth Workshop in London in 2007.

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Appendix

Dr. Smith sustained an interest in primary hyperoxaluria throughout his career, and cared for many patients with this diagnosis. A compassionate clinician, genuine concern for each of his patients was always in evidence. A keen observer, his translation of experience from the laboratory to patient care and back again enriched his research and illuminated otherwise obscure aspects of stone disease. His investigations of enteric hyperoxaluria and stones in patients with intestinal diseases, factors that influence crystal growth, citrate metabolism, contributions to EQUIL 2, and description of the stone clinic effect helped to define the landscape of urolithiasis research. He was a founder of the Research on Calculus Kinetics Society, an organizer of the 5th through the 7th International Symposia on Urolithiasis, and of the Gordon conferences on oxalate. With an enthusiasm founded in love of his work, he was a vigorous participant in scientific venues and a gentleman in all things. Lyn will long be remembered by the generations of students, fellows, and colleagues with whom he so freely shared his knowledge, offering encouragement and mentorship.

Lynwood H. Smith, M.D., 1929-2002.
M.D., University of Kansas 1960, Internal Medicine and Nephrology, Mayo Clinic 1961–1964;, Research Fellow, Johns Hopkins School of Medicine 1964–1965; Division of Nephrology, Mayo Clinic 1965–1994; Professor of Medicine, Mayo Medical School, University of Kansas 1994–2002

Dr. Wilson was an astute, compassionate nephrologist who was also a master of quantitative nephrology and clinical renal physiology. His expert measurement of urine and plasma oxalate, along with other laboratory techniques, provided essential tools for diagnosis and management of patients with primary hyperoxaluria. He was founder of a comprehensive clinical renal laboratory that has served countless patients for over three decades.

David M. Wilson, M.D., 1936-2003.
M.D., Washington University, St. Louis, MO 1959–1961; Residency, Lakeside Hospital Western Reserve, Cleveland, OH, 1962–1963; NIH Post Doctoral Fellow in Renal Disease, University of Illinois 1961–1962; USPHS Trainee in Renal Disease, University of Illinois 1966–1969; Division of Nephrology, Mayo Clinic 1969–1999 Professor of Medicine, Mayo Medical School

His contributions included development of a sensitive assay for plasma oxalate, application of quantitative ''wet chemistry'' for urine analyses, and development and refinements for the precise measurement of glomerular filtration rate, among others. He was a skilled analyst, who through his laboratory brought to his colleagues so many measurements necessary for their research and clinical work. He served as a consultative resource for laboratory assessment of patients with kidney stone disease and patients with fluid and electrolyte disorders. A patient and devoted teacher, Dave's Socratic sessions with students, residents, and fellows provided a foundation in renal physiology that has proved for many to be invaluable in their subsequent years.