Oxalosis & Hyperoxaluria Workshop
November 20-21, 2003
Annapolis, MD
Meeting Summary

DAY 1

NIDDK and the Oxalosis & Hyperoxaluria Foundation co-sponsored this meeting as part of an ongoing series designed to spur new and significant research on Primary Hyperoxaluria (PH). Dr. Josephine Briggs (NIDDK) opened the meeting by pointing out the importance of research to improve diagnosis and treatment of this disease. She noted that PH research can be seen as one part of the renewed dedication of NIH to translational research formalized in the new NIH Roadmap formulated by the NIH Director, Dr. Elias Zerhouni.

The introductory lecture was given by Dr. William Robertson (University College London) on the physiology of oxalate, in both normal individuals and in those with various diseases that alter oxalate metabolism. In addition, he discussed idiopathic and hereditary calcium oxalate kidney stone formation.

Enzyme Form and Function

Mutations in two different enzymes, alanine-glyoxylate aminotransferase (AGT) and glyoxylate reductase/hydroxypyruvate reductase (GR), are known to cause forms of Primary Hyperoxaluria (PH). In addition, there are PH patients without discernible defects in either AGT or GR. This session focused on the enzymes involved in oxalate metabolism. Dr. Chris Danpure (University College London) began by presenting data on the properties of mutant AGT proteins found in patients with PH type 1. Dr. Scott Cramer (Wake Forest University) followed with a lecture about mutations in the GR protein that cause type 2 PH. Dr. Emma Williams (University College London) discussed glycolate oxidase, a peroxisomal enzyme present in the peroxisome that produces glyoxylate from glycolate. Finally, to end the session, Dr. Ross Holmes (Wake Forest University) discussed other aspects of oxalate and glyoxylate metabolism, as a way of identifying candidate genes that might be defective in other forms of PH.

Oxalate and the Cell

Oxalate causes damage to the kidneys and other organs in PH by forming calcium oxalate crystals. The second session covered aspects of cellular metabolism of oxalate and factors that influence deposition of calcium oxalate crystals. Dr. Carl Verkoelen (Erasmus Medical Center) summarized some of his recent work looking at calcium oxalate crystal binding to cultured cells, proposing a model that inflammation enhances crystal binding. The theme of cellular damage was continued by Dr. Saeed Khan (University of Florida), who discussed the relationship between oxalate and calcium oxalate crystals and oxidative stress. Dr. Marguerite Hatch (University of Florida) shifted gears to talk about intestinal absorption of oxalate and the role *of Oxalobacter formigenes*. Dr. David Mount (Harvard Medical School) gave an overview of the many different cellular oxalate transporters. The final speaker, Dr. Michael Green (University of Florida), summarized his work on the ethylene glycol model used to induce calcium oxalate stone formation in animals.

Diagnosis of Primary Hyperoxaluria

There was a general consensus among participants that PH is often misdiagnosed initially. The purpose of the third session was to discuss the various diagnostic criteria that are available. Dr. Dawn Milliner (Mayo Clinic) gave an overview of the clinical criteria that can be used to identify the various types of PH. Dr. Gill Rumsby (University College London) summarized data about genetic diagnosis, which shows that there are numerous mutant alleles in both type 1 and type 2 PH, and nearly half of tested patients did not carry any of the common alleles. Dr. Jaap Groothof (Amsterdam Medical Center) discussed the use of enzyme assays in liver biopsy samples for diagnostics. The session concluded with a talk by Dr. Marion Coulter-Mackie (University of British Columbia) on the population genetics of polymorphisms in the AGT gene.

International Registry of Hhereditary Calcium Urolithiasis

Dr. John Lieske (Mayo Clinic) described and demonstrated this newly established patient registry, which is Web-based. The registry is being developed at the Mayo Clinic, with input from an international board of external advisors. The purposes of the registry include facilitating studies on epidemiology,

genotype-phenotype correlations, discovery of prognostic markers, evaluation of the efficacy of current treatments, developing consensus standard methods for evaluation, and allowing the establishment of patient cohorts for study and future clinical trials. Current plans call for the registry to open to non-Mayo patients in early 2004, and for the Web site (http://Mayoresearch.mayo.edu/mayo/research/nephrology/registry.cfm) to be fully functional by mid-2004.

DAY 2

Patient Presentations

The day began with presentations from the parents of two young children suffering from Primary Hyperoxaluria 1 and from a woman who also has Primary Hyperoxaluria 1. The presentations focused on issues related to diagnosis, prenatal diagnosis, and the course and treatment of the illness from a patient perspective.

Towards Rational Therapeutics

Given the depth of knowledge about the molecular events that lead to PH and its symptoms, there are increasing possibilities to apply that information to develop novel therapies. Dr. Jeff Kelly (Scripps Research Institute) gave a keynote talk about molecular chaperones and recent biochemical approaches to developing molecules that stabilize or redirect mutant proteins that are misfolded in diseases such as Gaucher Disease and transthyretin amyloidosis. Dr. Eduardo Salido (University La Laguna) followed by presenting data about the use of cell culture to explore the effect of chaperones on an aggregated mutant AGT protein found in patients in the Canary Islands. Dr. Xiaoxuan Zhang (University College London) discussed structural biology studies that use computerized "virtual drug screening" to identify potential chaperones for defective AGT proteins.

The balance of the session was devoted to a discussion of specific therapies. Dr. Craig Langman (Children's Memorial Hospital, Chicago) gave an overview of the existing therapies. Dr. Carla Monico (Mayo Clinic) summarized studies on the effectiveness of pyridoxine (vitamin B6) responsiveness, focusing on the relationship between genotype and response to the therapy. The next two talks focused on microbial therapies for PH that capitalize on the ability of bacteria to metabolize oxalate. Dr. Bernd Hoppe (University Children's Hospital, Cologne) described early clinical trials using *Oxalobacter*. Dr. John Lieske (Mayo Clinic) spoke about the use of "probiotics" (living microorganisms which, upon ingestion in certain numbers, exert health benefits beyond inherent nutritional status) in PH using a commercial mixture of bacteria with *in vitro* oxalate degrading activity known as Oxadrop (*Lactobacillus acidophilus, L. brevis, Streptococcus thermophilus, Bifidobacterium infantis*). The final speaker of the meeting, Dr. Jon Scheinman (University of Kansas Medical Center), presented data about kidney, kidney/liver and living donor liver transplants in PH patients.

The meeting concluded with a discussion led by Dr. Dawn Milliner (Mayo Clinic) about a consensus diagnostic algorithm among clinicians with extensive experience in treating PH. The group was able to develop and refine a flow chart, and a writing group was assembled to produce a manuscript for a peer-reviewed journal on this topic.