Congenital Urinary Tract Obstruction State-of-the-Art Strategic Planning Workshop

Meeting Summary

The State-of-the-Art Strategic Planning Workshop on congenital urinary tract obstruction was held at Lister Hill Auditorium at the National Institutes of Health on March 11-12, 2002. The workshop was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases in cooperation with the American Society of Pediatric Nephrology, the Society for Pediatric Urology, the National Kidney Foundation, and the Section on Urology of the American Academy of Pediatrics. Members of the Organizing Committee were Robert L. Chevalier and Craig Peters, co-chairs, Leroy Nyberg (NIH), Laurence S. Baskin, Dolph Chianchiano, Jack Elder, R. Ariel Gomez, Frederick J. Kaskel, Stephen A. Koff, and Barry A. Kogan.

Congenital obstructive nephropathy remains one of the major causes of renal insufficiency and renal failure in infants and children. The pathogenesis of these disorders remains poorly understood, and in addition to the intense controversy surrounding the prevention and short-term intervention in affected fetuses and infants, the long-term outcome of these patients is a great concern.

As a result of initiatives developed by the Research Committee of the American Society of Pediatric Nephrology in conjunction with Dr. Josephine Briggs and Dr. Leroy Nyberg, both of NIDDK, a workshop was planned by Drs. Robert Chevalier and Craig

Peters to define the major research questions and therapeutic needs in the coming decade. Twenty-nine speakers were convened, including six international speakers. In addition, the workshop had 30 participants, 11 of whom presented posters.

The workshop had nine sessions:

- Epidemiology and Etiology
- Prenatal Evaluation and Intervention
- Clinical Predictors
- Clinical Outcomes
- Pathophysiology
- Experimental Model Systems
- Responses of the Developing Hydronephrotic Kidney
- Long-Term Adaptive Responses
- Research Needs

After the one-and-a-half day series of presentations, a writing committee convened to draft a set of recommended research priorities for future NIH support. This committee included Robert Chevalier, Barry Kogan, Leroy Nyberg, Craig Peters, and H. William Schnaper. In addition to general comments, discussion focused on biomarkers, registry, clinical trials, education, basic science, and upper versus lower urinary tract hydronephrosis. A summary of the discussion is as follows:

General Comments: The consensus is that the natural history of congenital obstructive nephropathy is poorly understood. Measures for determining degrees of injury and functional impairment, as well as for longitudinally assessing changes, are imperfect. Radiography and other measures of function, markers of injury and flow measurement, need improvement. Pathological description of the changes induced by congenital obstructive nephropathy is neither well defined nor correlated with functional parameters. The NIDDK should be asked to invest in studies that would be difficult to support in other ways, such as identifying markers of renal maldevelopment and "significant" congenital obstruction to develop correlations that can then be examined. Animal models need to be characterized. It is not known, for example, whether the rat or mouse model of ureteral obstruction is more similar to human disease, although each species offers its own advantages. Large animal models of these conditions may be preferable because they can be tailored to produce variable degrees of obstruction and because they offer the ability to assess interventions. However, large animal models are expensive and complex.

Biomarkers: The ability to determine relevant biomarkers in both humans and animal models is a significant need. Functional as well as cellular and molecular metrics must be developed, including a measure of "renal reserve" and a measure of resistance to urine flow that incorporates the compliance and capacity of the renal pelvis. Biomarkers should be correlated with injury or altered development to permit the development of less invasive monitoring approaches for either investigational study or clinical care. The

NIH should fund an effort to find new biomarkers that ultimately must be usable in humans.

Registry: Most desperately needed is a comprehensive registry with well-characterized patients. This registry would include samples of urine, serum, and biopsy or surgical tissue samples. A DNA bank of patients with congenitally diagnosed nephropathy could include results of tests on blood, urine, and tissue, with clinical follow-up. Radiographic parameters (i.e., pelvicaliectasis, echogenicity, cortical thinning, and cysts) must be established and their significance determined (including reversibility). Developing imaging technologies such as MRI should be anticipated and included in these registries. To enhance optimal acquisition of imaging studies, standards need to be developed for equipment and user proficiency. Perinatologists as well as radiologists, urologists and nephrologists should be enlisted to develop the standards. A uniform registry with subcomponents of prenatal intervention and reflux might prove most useful.

Education: Both obstetrical and neonatal health providers detect congenital urinary tract obstruction, but enormous variability exists in the quality of equipment used and in user skills. This variability ultimately affects detection rate. An educational process is needed for ultrasonographers. Uniform timing intervals should be established for prenatal sonography.

Clinical Trials: Multi-center clinical trials are needed to determine optimal management of both unilateral congenital hydronephrosis and bilateral hydronephrosis resulting from

bladder outlet obstruction. Clinical studies to amass biomarkers should proceed concurrently with animal studies. To what extent postnatal, long-term outcome can be predicted is unknown. Also unknown is whether children with these congenital anomalies will progress to renal failure and in what time frame. For infants with lower tract disease, long-term bladder, sexual, and reproductive function must be determined. Currently, there is no clear way to segregate those persons who will go on to end-stage renal disease (ESRD). Studies should focus on health outcomes, related to intermediate outcomes (including grade of hydronephrosis, renal growth, scarring, differential function, and histologic changes).

Basic Science: A clear need exists for additional investigators and hypothesis-driven basic science proposals that address the cellular and molecular basis of renal development, specific genetic defects, and the link between functional and developmental pathophysiology. Areas of interest are

- Regulation of collecting duct branching
- Afferent sensing mechanism in the tubule leading to dilatation or cystic changes
- Biology of the nephrogenic blastema
- Regulation of interstitial fibrosis
- Determinants of patterning of mesenchyme, calyceal branching, tubular length and diameter
- Stem cells
- Stimuli that initiate renal cellular response to obstruction

- Determinants of the physiologic responses to obstruction
- Determinants of the number of nephrons in the obstructed kidney

Knockout models used for other diseases should be investigated, as should genes and site-specific expression, cellular functions that affect developmental processes (inflammatory cells, stromal cells), environmental effects such as vitamin A, and markers of reactive oxygen species. New methodologies, including microarrays, proteomics, and laser capture microscopy should be applied.

Upper Versus Lower Urinary Tract Hydronephrosis: Because of the role of the lower urinary tract in congenital hydronephrosis, research proposals could include investigation of the relationship of lower tract to upper tract changes, including the gender differential (male:female 2:1).

Conclusions

Future research in congenital urinary tract obstruction should accomplish the following goals, which should lead to clinical trials:

- Define the natural history and pathological description of obstructive nephropathy by developing biomarkers in humans and animal models to generate measures of injury and functional impairment
- Elucidate the cellular and molecular basis of renal maldevelopment, focusing on the link between functional and developmental pathophysiology

- Develop a clinical research infrastructure with the creation of comprehensive registries that include urine, plasma, and tissue samples of patients, as well as standardized images.

Publication of the workshop proceedings in *Pediatric Nephrology* and in the *Journal of Urology* is anticipated. Both the speakers and participants indicated that the workshop fulfilled a significant need that has not been met by basic science or clinical subspecialty meetings. The collaboration of urologists, nephrologists, perinatologists, radiologists and developmental biologists will be necessary to advance this important area of pediatric health.