Lister Hill Auditorium
National Institutes of Health
Bethesda, Maryland

Congenital Urinary Tract Obstruction

State of the Art Strategic Planning Workshop

March 11-12, 2002

Sponsored by:
National Institute of Diabetes and Digestive and Kidney Diseases
in cooperation with ASPN, SPU, NKF, and AAP Urology Section

SPONSORS

National Institute of Diabetes and Digestive and Kidney Diseases

American Society of Pediatric Nephrology

The Society for Pediatric Urology

National Kidney Foundation

AAP Section on Urology

ORGANIZERS

Robert L. Chevalier
University of Virginia

Dolph Chianchiano
National Kidney Foundation

Frederick Kaskel
Children's Hospital at Montefiore

Barry A. Kogan
Albany Medical College

Leroy Nyberg
National Institute of Diabetes and Digestive and Kidney Diseases

Craig Peters
Children's Hospital

CONTENTS

CONTENTS

CONTENTS

CONTENTS

AGENDA

March 11, 2002

7:30 am	Registration
8:00 am	Introduction *Robert Chevalier, Craig Peters, Leroy Nyberg*
SESSION 1:	**Epidemiology and Etiology**
8:15 am	Epidemiology: Incidence and Prevalence *Patricia McKenna*
8:35 am	Genetic Factors in Congenital Hydronephrosis *John Pope*
8:55 am	Lower Tract Factors - Developmental *Laurence Baskin*
9:15 am	Lower Tract Factors - Clinical *C.K Yeung*
9:35 am	Discussion
9:50 am	BREAK
SESSION 2:	**Prenatal Evaluation and Intervention**
10:10 am	Prenatal Diagnosis - Imaging *Carol Barnewolt*
10:30 am	Prenatal Evaluation and Treatment *Mark Johnson*

AGENDA

SESSION 3:	**Clinical Predictors**
10:50 am	Postnatal Imaging *Michael Carr*
11:10 am	Biochemical Markers *Michael Carr*
11:30 am	Upper Tract Urodynamic Studies *Antoine Khoury*
11:50 am	Discussion
12:15 pm	Poster Session #1 Presentations *Cachat, Dean, Donohoe #1, Donohoe #2, Kiley, Kirsch, Lange-Sperandio*
12:45 pm	LUNCH
SESSION 4:	**Clinical Outcomes**
1:30 pm	Delayed Postnatal Intervention *Stephen Koff*
	Prenatally Diagnosed Hydronephrosis – Selective Postnatal Intervention *H.K. Dhillon*
	Early Postnatal Intervention *Jack Elder*
	Early Postnatal Intervention *Craig Peters*
	Discussion

AGENDA

SESSION 5:	**Pathophysiology**
2:30 pm	Morphology of the Kidney *Seymour Rosen*
2:45 pm	Renal Tubular Development *Christopher Burrow*
3:00 pm	Pathology of Obstruction – Molecular Changes *Helen Liapis*
3:15 pm	Physiology of the Hydronephrotic Kidney: Fetus *Barry Kogan*
3:30 pm	Physiology of the Hydronephrotic Kidney: Neonate *Robert Chevalier*
3:45 pm	Discussion
3:55 pm	BREAK

AGENDA

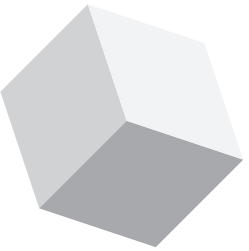
SESSION 6:	**Experimental Model Systems**
4:15 pm	Surgical Fetal Obstruction: Marsupial *George Steinhardt*
4:30 pm	Surgical Fetal Obstruction: Ovine *Craig Peters*
4:45 pm	Surgical Fetal Obstruction: Primate *Douglas Matsell*
5:00 pm	Congenital Obstruction: Rodent *Linda Shortliffe*
5:15 pm	Surgical Postnatal Obstruction: Murine *Robert Chevalier*
5:30 pm	Surgical Postnatal Obstruction: Porcine *Jorgen Frokiaer*
5:45 pm	Discussion

March 12, 2002

SESSION 7:	**Responses of the Developing Hydronephrotic Kidney**
8:00 am	Stromal – Epithelial Interactions in Development *Dori Herzlinger*
8:20 am	Tubulointerstitial Response: Proliferation and Apoptosis *Hiep Nguyen*
8:35 am	Vitamin A Controls Ureter Maturation via the Ret Proto-Oncogene *Cathy Mendelsohn*
8:50 am	Soluble Factors in Ureteric Bud Development *Hiroyuki Sakurai*
9:05 am	Low Obstructive Uropathies and Nephrogenesis *Bernard Gasser*
9:20 am	Discussion
9:30 am	Poster Session #2 Presentations *McLellan, Mesrobian, Rasoulpour, Tractman*
9:55 am	BREAK

AGENDA

SESSION 8:	**Long-Term Adaptive Responses**
10:15 am	Nephron Heterogeneity *Robert Chevalier*
10:30 am	Regulation of Interstitial Fibrosis *Diane Felsen*
10:45 am	Compensatory Fetal Renal Growth *Craig Peters*
11:00 am	Discussion
SESSION 9:	**Research Needs**
11:15 am	Gene Expression in Congenital Hydronephrosis *Jordan Kreidberg*
11:30 am	Pathophysiology of Congenital Hydronephrosis *Robert Chevalier*
11:40 am	Diagnostic Approach in Congenital Hydronephrosis *Craig Peters*
11:50 am	Long-term Outcomes of Congenital Hydronephrosis *Jack Elder*
12:00 pm	Clinical Trials *James Chan*
12:15 pm	Discussion
12:30 pm	LUNCH
1:00 pm	Breakout writing session – Natcher Building, Balcony B



SPEAKER ABSTRACTS

Epidemiology: Incidence and Prevalence

Patrick H. McKenna
SIU School of Medicine

The incidence and prevalence of antenatally detected urologic abnormalities are well documented in multiple large retrospective and prospective studies. Since no screening study exists to determine obstruction in the antenatal period, obstruction can only be inferred antenatally. The majority of studies have either incomplete postnatal evaluation of all patients identified in the antenatal period or incomplete antenatal information. The incidence of antenatally detected urinary abnormalities range from .2% to .9%. The overall percentage of obstructive abnormalities (including posterior urethral valves, ureteral pelvic junction obstruction, ureteral vesicle junction obstruction, and other obstructive lesions) is approximately .04% to .3%. Studies from different ethnic populations report similar overall incidences of disease. Posterior urethral valves, urethral atresia and vesicoureteral reflux occur more commonly in males while females have a greater likelihood of duplication a! bnormalities and ureteroceles. Hydronephrosis is more likely to occur on the left side of male patients. African-Americans have a significantly lower rate of vesicoureteral reflux. Other race and gender differences have yet to be conclusively determined. The routine use of ultrasound as a fetal screening tool has been hotly debated. The RADIUS study of 1993 reported no improvement in perinatal outcome with the selective use of ultrasonography in low risk pregnancies. These pregnancies represent approximately one fourth of the deliveries in the United States. Multiple studies in the United States and several countries have failed to conclusively overturn the findings of the initial study. Many issues come into play when an obstetrician decides to order a screening study. Even in the original RADIUS study, the group on average had .6 sonograms. The indications to do a screening study are broad and there is significant parental pressure to obtain at least one ultrasound in the a! ntenatal period. Other studies have shown cost benefits from screening in tertiary centers. These studies suggest improving equipment and education may improve the cost benefit in nontertiary centers. European centers routinely do screening studies and recent reviews have not proven a benefit to perinatal outcome but identify clear parental desire to continue the practice of screening. Significant research funding will be required to improve the techniques used in screening for antenatal urinary abnormalities. Understanding the true incidence of obstructive lesions, coordinating the antenatal identification with the appropriate postnatal evaluation and treatment, as well as the development of long-term follow up data, will be necessary to correctly advise parents in the antenatal period. Development of a national registry is a cost effective method to determine incidence, improve education, and provide a mechanism to understand the long-term consequences of these abnormalities.

Genetic Factors in Congenital Hydronephrosis

John C. Pope IV

Congenital anomalies of the kidney and urinary tract, CAKUT, are a family of diseases with a diverse anatomical spectrum, including kidney anomalies (e.g. renal aplasia and/or hypoplasia, multicystic dysplastic kidney), ureteropelvic anomalies (e.g. obstruction), ureterovesical anomalies, (e.g., vesicoureteral reflux or obstruction), ectopic placement of the ureteral orifice, duplicated collecting system, and anomalies of the bladder and urethra.

These abnormalities are often concurrently present, e.g., hypoplastic kidney and dysplastic kidney are frequently accompanied by vesicoureteral reflux or ureteropelvic junction obstruction involving the ipsilateral or contralateral kidney. Note that oligonephronia in embryos and newborns can be compensated by the hypertrophy of remaining nephrons without altering the gross anatomical appearance of the whole kidney or clinically appreciable changes in the overall renal function. These anomalies can also take a familial pattern, showing incomplete and variable penetrance. It has been speculated therefore that these assorted structural anomalies share a common pathogenetic mechanism and genetic cause.

Much has been learned over the past several decades about both the normal and abnormal development of the excretory system. What is still not understood, however, is the overall developmental process and how certain errors in that process lead to CAKUT. Also, it is not known whether these anomalies lead to progressive renal deterioration because of persistent anatomical defects (i.e. obstruction) or because of intrinsic, developmentally pre-programmed alterations in renal function. These unknowns make the clinical management of patients with these abnormalities very difficult.

From an anatomical standpoint, it is known that aberrant ureteral budding from the Wolffian duct leads to abnormal interaction of the bud with the metanephric blastema and ectopic location of the ureteral orifice. (Mackie, Stephens, 1975). Many animal studies have also shown that fetal/neonatal ureteral obstruction lead to anomalous development of the kidney. On a more biochemical level, many other studies have identified important genetic control over many aspects of kidney and urinary tract development. For example, it is known that intricate signaling pathways are involved in induction of proper ureteral budding, branching of the collecting system, and differentiation of the metanephros. Defects in certain points of these pathways can be brought about by genetic manipulation ultimately causing experimental anomalies. We know GDNF, c-ret, WT-1, PAX2, BMP4, and Agtr2 are but a few of the players in this intricate process and some of these will be specifically discussed. It is also known that apoptosis of certain cell types is required for normal development and disruption of programmed cell removal can lead to abnormal development.

Continued from Previous Page

Over 30 specific genes have been identified that are involved in the development of the mammalian kidney and urinary tract. Single genes have multiple functions in this development while at the same time, single developmental events are controlled by multiple genes. It is doubtful that there is a single inducer (ie. single gene mutation) that is responsible for CAKUT however it is important to understand the role of individual genes in the overall developmental pathway. Only by gaining a better understanding of the many small facets of development that lead to the ultimate formation of a very precise and efficient excretory system can we hope to impact, either through advances in prevention or treatment, patients in the clinical setting.

References:

1. Pope, JC IV, Brock JW III, Adams MC, Stephens FD, Ichikawa I: How The Begin And How They End: Classic And New Theories For The Development And Deterioration Of Congenital Anomalies Of The Kidney And Urinary Tract. J Am Soc Nephrol 10:2018-2028, 1999.

2. Mackie GG, Stephens FD: Duplex Kidneys: A Correlation of Renal Dysplasia with Position of the Ureteral Orifice. J Urol 114:274-280, 1975

3. Peters CA, Carr MC, Lais A, Retik AB, Mandell J: The Response of the Fetal Kidney to Obstruction. J Urol 148:503-509, 1992.

4. a. Chevalier RL, Thornhill BA, Chang AY: Unilateral Ureteral Obstruction in Neonatal Rats Leads to Renal Insufficiency in Adulthood. Kid Int 58:1987-1995, 2000. b. Chung KH, Chevalier RL: Arrested Development of the Neonatal Kidney Following Chronic Ureteral Obstruction. J Urol 155:1139-1144, 1996.

5. Pohl M, Stuart RO, Sakurai H, Nigam S: Branching Morphogenesis During Kidney Development. Annu Rev Physiol 62: 595-620, 2000.

6. Sutherland RW, Hicks MJ, Chevalier RL, Pope JC IV: The Role of Apoptosis in the Developing Genitourinary System. Dial Ped Urol 23:1-8, 2000.

7. Burrow CR: Regulatory Molecules in Kidney Development. Pediatr Nephrol: 240-253, 2000.

8. Ichikawa I, Kuwayama F, Pope JC IV, Stephens FD, Miyazaki Y: Embryogenesis of CAKUT: Paradigm Shift from Classic Anatomic Theories to Contemporary Cell Biological View of Congenital Anomalies of the Kidney and Urinary Tract. Kid Int (in press), 2002.

9. Durbec P, Marcos-Gutierrez CV, Kilkeny C., Grigorou M, Wartiowaara K, Suvanto P, Smith D, Ponder B, Constantini F, Saarma M, Sariola H, Pachnis V: GDNF Signaling Through the Ret Receptor Tyrosine Kinase. Nature 381:789-793, 1996.

10.a. Miyazaki Y, Oshima K, Fogo A, et. al.: Bone Morphogenetic Protein 4 Regulates the Budding Site and Elongation of the Mouse Ureter. J Clin Invest 105:863-873, 2000. b. Oshima K, Miyazaki Y, Pope JC IV, et. al.: Angiotensin Type-2 Receptor (AT2) Expression and Ureteral Budding. J Urol 166: 1848-1852, 2001.

Lower Urinary Tract Factors:
Mesenchymal Epithelial Cellular Signaling Bladder Development

Laurence S. Baskin
University of California at San Francisco

The urinary bladder is formed from endodermally derived epithelial cells and mesenchymal cells from the urogenital sinus and allantois (Baskin, Hayward et al. 1996). Bladder mesenchyme differentiates into bladder smooth muscle via an unknown signaling mechanism that originates from the urothelium (Baskin, Hayward et al. 1996). It is hypothesized that this signaling between the epithelium and mesenchyme, occurs via diffusable growth factors (Liu, li et al. 2000). Evidence supporting this hypothesis is that a number of known growth factors, such as TGF beta 2 and 3, KGF and TGF alpha, as well as their receptors are regulated as a function of bladder development and are also modulated during experimental bladder outlet obstruction (Baskin, Sutherland et al. 1996). Furthermore, growth factors most likely affect extracellular matrix degradative proteins which play a role in bladder remodeling during development, as well as in partial outlet obstruction (Sutherland, Baskin et al. 1997). Cellular signaling also occurs postnatally; such as during bladder injury. For example, KGF is directly responsible for the proliferation of urothelium during bladder injury (Baskin, Sutherland et al. 1997).

Urothelium exhibits the plasticity to transdifferentiate into an intestinal like epithelium as a result of mesenchymal/stromal stimulation from the gastro-intestinal tract (Li, Liu et al. 2000). Urothelial plasticity is germane to heterotypic stromal-epithelial interactions that are created in patients with urinary tract reconstruction's (intestinal augmentations, demucosalized urothelial lined bladder patches and internal urinary diversion such as ureterosigmoidostomies).

We propose that heterotypic stromal-epithelial interactions may play a role in determining histodifferentiation of urothelial cells at the anastomotic site between bowel and bladder tissue in patients with gastro-intestinal urothelial reconstructions.

References:

1. Baskin, L., R. Sutherland, et al. (1997). "Growth Factors in Bladder Wound Healing." J. Urol 157(6): 2388-2395.

2. Baskin, L. S., S. Hayward, et al. (1996). "Role of mesenchymal-epithelial interactions in bladder development." J. Urol 156: 1820-1827.

3. Baskin, L. S., S. W. Hayward, et al. (1996). "Ontogeny of the rat bladder: Smooth muscle and epithelial differentiation." Acta Anatomica 155: 163-171.

4. Baskin, L. S., R. S. Sutherland, et al. (1996). "Growth Factors and Receptors in Bladder Development and Obstruction." Lab Investigation 75: 157-166.

5. Li, Y. W., W. H. Liu, et al. (2000). "Plasticity of the urothelial phenotype: effects of gastro-intestinal mesenchyme/stroma and implications for urinary tract reconstruction." Differentiation 66: 126-135.

6. Liu, W., Y. li, et al. (2000). "Diffusable growth factors induce smooth muscle differentiation." In vitro cellular and developmental biology 36: 476-484.

7. Sutherland, R. S., L. B. Baskin, et al. (1997). "The role of type IV collagenases in rat bladder development and obstruction." Pediatric Research 41(3): 430-434.

8. Sutherland, R. S., L. B. Baskin, et al. (1996). "Regeneration of Bladder Urothelium, Smooth Muscle, Blood Vessels and Nerves Into an Acellular Tissue Matrix." Journal Urology 156(2): 571-577.

9. Wu, Y. H., L. S. Baskin, et al. (1999). "Understanding bladder regeneration: smooth muscle ontogeny." J. Urol 12: 1101-1105.

Prenatal Evaluation and Treatment of Fetal Obstructive Uropathy

Mark Paul Johnson
University of Pennsylvania School of Medicine

Prenatal evaluation of fetal lower urinary tract obstruction including high resolution sonography, karyotype analysis, and serial multi-component urinalysis has dramatically improved our ability to select fetuses who might benefit from in utero therapy. Successful placement of vesicoamniotic shunts has improved pulmonary survivals, but renal outcomes remain highly variable, in part due to the high incidence of shunt displacement. Little is known about long term medical and functional outcomes in children who have undergone successful shunt placement, although growth and weight gain appear to be significant issues in early infancy. Sexual and reproductive function in these children remains unknown as the oldest survivors are just reaching adolescence. Postnatal renal and bladder function appears to correlate with the underlying etiology of obstruction, with urethral atresia having the poorest survival and outcome. Also, fetal urinary electrolyte and protein elevations are strongly correlated with the degree of underlying damage to the renal parenchyma based on autopsy and postnatal renal function studies. Because of the high incidence of shunt displacement and failure, other in utero treatment approaches are being investigated. One promising area is in utero fetal cystourethroscopy for the identification of the source of obstruction and possible laser ablation for posterior urethral valves. Restoration of fetal bladder cycling may result in significant functional benefits for the bladder.

References:

1. Johnson MP. Fetal Obstructive Uropathy. In: Harrison MR, Evans MI, Adzick NS, and Holzgreve W (Eds), The Unborn Patient, The Art and Science of Fetal Therapy, 3rd Edition, W. B.Saunders Co, Philadelphia, PA, 2001. Chapter 18, pp 259-86.

2. Coplen DE, Hare JY, Zderic SA, et al. 10-Year experience with prenatal intervention for hydronephrosis. J Urology 1996; 156:1142.

3. Johnson MP, Bukowski TP, Reitleman C, et al. In utero surgical treatment of fetal obstructive uropathy: A new comprehensive approach to identify appropriate candidates for vesicoamniotic shunt therapy. Am J Obstet Gynecol 1994; 170:177.

4. Johnson MP, Corsi P, Bradfield W, et al. Sequential urinalysis improves evaluation of fetal renal function in obstructive uropathy. Am J Obstet Gynecol 1995; 173:59.

5. Qureshi F, Jacques SM, Seifman B, et al. In utero fetal urine analysis and renal histology do correlate with outcome in fetal obstructive uropathies. Fetal Diag Ther 1996; 11:306.

6. Freedman AL, Johnson MP, Smith CA, et al. Long-term outcomes in children after antenatal intervention for obstructive uropathies. Lancet 1999; 345:374.

Postnatal Imaging for Congenital Hydronephrosis: Clinical Utility and Challenges

Michael C. Carr
Children's Hospital of Philadelphia

Congenital hydronephrosis denotes the presence of dilation of the renal collecting system in utero. Serial ultrasonography will demonstrate whether this is a transient finding, one that is stable or one that progresses in utero. Measurements of the fetal renal pelvic diameter provide a quantifiable measurement that is easily compared both prenatally and postnatally. The size of the renal pelvis (anteroposterior diameter) can correlate with the likelihood of obstruction, but this does not diagnose obstruction, nor can it answer whether the hydronephrosis will improve or worsen. The Society for Fetal Urology devised a grading scale based upon the ultrasound appearance1. This becomes important when clinical studies are being devised, whether prospectively or retrospectively. As the severity of the hydronephrosis increases, there is found to be an increase in the relative pelvicaliectasis along with a decrease in cortical thickness. The ratio of renal parenchymal/pelvicaliceal area has been compared with the results of diuretic renography to further enhance the diagnostic accuracy of ultrasonography2.

Renal duplex Doppler ultrasonography and calculation of the resistive index has been shown to discriminate obstructive vs. nonobstructive hydronephrosis. When these Doppler studies were further modified with the addition of furosemide, the differences between obstructed and nonobstructed kidneys were further accentuated3. A number of sonographic variables had been identified which correlate with the presence of obstruction. These included increased echogenecity, parenchymal rim 5 mm or less, contralateral hypertrophy, resistive index ratio of 1.10 or greater, resistive index difference with diuresis of 70% or greater, ureteral diameter of 10 mm or greater and presence of aperistaltic ureter4.

Radionuclide renography has supplanted intravenous urography as the method used to diagnosis obstruction based on the differential renal function and an assessment of diuretic-induced washout from the individual kidney. The standardization of this methodology has proven crucial to providing reproducible results due to the number of variable that exist with the administration and interpretation of the study5,6. Despite such attempts at standardization, recent reports of infants who are found to have stable renal function and dilation despite impaired drainage on diuretic renography exist7. Further modifications are being made, including the use of captopril renography as a means of assessing hydronephrosis due to apparent ureteropelvic ureterovesical junction obstruction.

New, ultra fast magnetic resonance imaging (MRI) offers unique advantages for evaluating renal blood flow, anatomy and urinary excretion. Following experimental studies which showed that noncontrast MRI was able to precisely show dilation of the hydronephrotic pelvis and cortical medullary junction, gadolinium-enhanced and diuretic MR urography has gained acceptance in diagnosing ureteric obstruction9. Reports of its application in a pediatric population for the evaluation of hydronephrosis and renal scarring holds forth the promise that a single study can provide functional and anatomic information without ionizing radiation10. MRI appears to be

Continued from Previous Page

as good as existing modalities in the evaluation of renal scarring and cortical thinning. Further work will be needed to define the role of MR urography in the evaluation of antenatally detected hydronephrosis. Ultra fast HASTE sequence MRI is being used in the evaluation of congenital anomalies. As experience is gained, further insights into the MRI appearance of developing kidneys, both normal and obstructed, will be forthcoming.

References:

1. Maizels M, Reisman ME, Flom LS, Nelson J, Fernbach S, Firlit CF, Conway JJ. Grading nephroureteral dilatation detected in the first year of life: correlation with obstruction. J Urol 1992 Aug;148(2 Pt 2):609-614; discussion 615-616.

2. Cost GA, Merguerian PA, Cheerasarn SP, Shortliffe LM. Sonographic renal parenchymal and pelvicaliceal areas: new quantitative parameters for renal sonographic follow-up. J Urol 1996:145:725-729.

3. Palmer JM, DiSandro M. Diuretic enhanced duplex Doppler sonography in 33 children presenting with hydronephrosis: a study of test sensitivity, specificity and precision. J Urol 1995 Nov;154(5):1885-1888.

4. Garcia-Pena BM, Keller MS, Schwartz DS, Korsvik HE, Weiss RM. The ultrasonographic differentiation of obstructive versus nonobstructive hydronephrosis in children: a multivariate scoring system. J Urol 1997 Aug;158(2):560-565.

5. Conway JJ, Maizels M. The "well tempered" diuretic renogram: a standard method to examine the asymptomatic neonate with hydronephrosis or hydrouretero-nephrosis. A report from combined meetings of The Society for Fetal Urology and members of The Pediatric Nuclear Medicine Council—The Society of Nuclear Medicine. J Nucl Med 1992 Nov;33(11):2047-2051.

6. O'Reilly P, Aurell M, Britton K, Kletter K, Rosenthal L, Testa T. Consensus on diuresis renography for investigating the dilated upper urinary tract. Radionuclides in Nephrourology Group. Consensus Committee on Diuresis Renography. J Nucl Med 1996 Nov;37(11):1872-1876.

7. Gordon I. Diuretic renography in infants with prenatal unilateral hydronephrosis: an explanation for the controversy about poor drainage. BJU Int 2001 Apr;87(6):551-555.

8. Homsy YL, Tripp BM, Lambert R, Campos A, Capolicchio G, Dinh L, Chheda H. The captopril renogram: a new tool for diagnosing and predicting obstruction in childhood hydronephrosis. J Urol 1998 Oct;160(4):1446-1449.

9. Jung P, Brauers A, Nolte-Ernsting CA, Jakse G, Gunther RW. Magnetic resonance urography enhanced by gadolinium and diuretics: a comparison with conventional urography in diagnosing the cause of ureteric obstruction. BJU Int 2000 Dec;86(9):960-965.

10. Rodriguez LV, Spielman D, Herfkens RJ, Shortliffe LD. Magnetic resonance imaging for the evaluation of hydronephrosis, reflux and renal scarring in children. J Urol 2001 Sep;166(3):1023-1027.

Biochemical Markers of Congenital Obstruction

Michael C. Carr
Children's Hospital of Philadelphia

The evaluation of congenital hydronephrosis is undertaken to discern whether the dilation that is detected is due to an obstructive process that will irreversibly damage the kidney. Progression of the antenatal hydronephrosis may provide some indication that obstruction is present. Radiographic evaluation provides one means of determining the significance of hydronephrosis. Intravenous urography can define anatomy, whereas nuclear renography is able to quantitate the relative function of each kidney in addition to assessing diuretic induced washout. These studies assess the kidney at that moment in time and may prove that obstruction is present. An alternative (complimentary) approach is to use biochemical markers as indicators of renal tubular injury in the setting of obstructive uropathy. Such markers could be assessed to determine the need for intervention, based upon a detrimental change. N-acetyl-,-D-glucosaminidase (NAG), a proximal tubular lysosomal enzyme, has been shown to have a biphasic response to obstruction1. Following the onset of obstruction, there is a rise in urinary NAG which correlates with the early destructive phase followed by a later steady-state phase. Experimentally, intervention to relieve obstruction during the early phase will allow for recovery of function, whereas relief of obstruction during the steady-state phase preserves the function but does not allow for complete recovery. Clinically, NAG was found to be consistently elevated in urine obtained from the kidney in patients with a ureteropelvic junction obstruction2. Urine obtained from the bladder of these patients was not consistently elevated when compared to controlled patients. Urinary transforming growth factor-beta 1 (TGF-, 1) concentration was found to be elevated in children with upper urinary tract obstruction3. Mean bladder urine TGF-, 1 was four fold higher in patients with upper tract obstruction than in controls. In the obstructive group, mean TGF-, 1 in the renal pelvic urine was twice that of the bladder urine. Thus measurement of TGF-, 1 in a voided urine sample may provide an objective and noninvasive test which facilitates in the diagnosis of upper urinary tract obstruction.

The use of biochemical markers is predicated on an understanding of the response of the kidney to obstruction. Animal models of partial ureteral obstruction have demonstrated that mRNA levels for epidermal growth factor decrease, TGF-, 1 increases while insulin-like growth factor-II remains unchanged during the first 48 hours following ureteral obstruction4. The degree of obstruction that is seen clinically is variable, with severe obstruction ultimately leading to interstitial fibrosis. This process of fibrosis may be dependant on infiltration of the renal cortex with macrophages, leading to a rise in TGF-, 1. This induces a profibrogenic state and initiates a cascade of dysregulatory events including an upregulation of tissue inhibitor metalloproteinase one (TIMP-1)5,6. The issue concerning this experimental work is whether this reflects the response of the kidney that is subjected to congenital obstruction, since experimentally these obstructions were performed post-natally in weanling rats. The difficulty of performing partial ureteral obstruction in a fetus is obvious, but a small series of fetal sheep were subjected to partial ureteral obstruction7. Semi-quantitative reverse transcriptase PCR was used to quantify

Continued from Previous Page

several molecular changes. An increase in the level of renin, angiotensinogen AT1 receptor, TGF-, 1 and TIMP-1 mRNA was significant in the group subjected to partial ureteral obstruction. These findings agree with those seen in rats subjected to post-natal obstruction. The cascade of events that are triggered by partial obstruction has a temporal expression that must be understood. Thus a urinary marker such as TGF-, 1 or a panel of biochemical markers may provide very clear understanding of the health of the kidney, the need to intervene surgically to alleviate obstruction and the expected response and recoverability of the kidney following successful surgery.

References:

1. Huland H, Gannerman D, Werner B, Possin U. A new test to predict reversibility of hydronephrotic atrophy after stable partial unilateral ureteral obstruction. J Urol 1988;140: 1591-1594.

2. Carr MC, Peters CA, Retik AB, Mandell J. Urinary levels of the renal tubular enzyme N-acetyl-,-glucosaminidase in unilateral obstructive uropathy. J Urol 1994 Feb;151:442-445.

3. Furness PD 3rd, Maizels M, Han SW, Cohn RA, Cheng EY. Elevated bladder urine concentration of transforming growth factor-beta1 correlates with upper urinary tract obstruction in children. J Urol 1999 Sep;162(3 Pt 2):1033-1036.

4. Walton G, Buttyan R, Garcia-Montes E, Olsson CA, Hensle TW, Sawczuk IS. Renal growth factor expression during the early phase of experimental hydronephrosis. J Urol 1992 Aug;148(2 Pt 2):510-514.

5. Diamond JR, Kees-Folts D, Ding G, Frye JE, Restrepo NC. Macrophages, monocyte chemoattractant peptide-1, and TGF-beta 1 in experimental hydronephrosis. Am J Physiol 1994 Jun;266(6 Pt 2):F926-F933.

6. Engelmyer E, van Goor H, Edwards DR, Diamond JR. Differential mRNA expression of renal cortical tissue inhibitor of metalloproteinase-1, -2, and -3 in experimental hydronephrosis. J Am Soc Nephrol 1995 Mar;5(9):1675-1683.

7. Ayan S, Roth JA, Freeman MR, Bride SH, Peters CA. Partial ureteral obstruction dysregulates the renal renin-angiotensin system in the fetal ship kidney. Urology 2001 Aug;58(2):301-306.

Upper Tract Urodynamic Studies

Tony Khoury
University of Toronto

Physiologically significant obstruction can be defined as an impediment in urine transport which leads to compensatory changes in physiological renal parameters, including but not limited to renal pelvic pressure, renal blood flow, and glomerular filtration rate. However, a kidney identified to have physiologically significant obstruction may not necessarily suffer from functionally significant sequelae. Thus functionally significant obstruction can be separately defined as an impediment in urine transport which if untreated will ultimately result in the kidney having less than the full functional potential that it would otherwise possess Hydronephrosis , which results from an impediment in antegrade urinary flow, is a highly complex process at the physiological as well as molecular level.
However, it is fundamentally still a physical problem where the collecting system has excessively high resistance to urine flow. Diagnostic tools used in the evaluation of hydronephrosis can rely on one of two general principles: (1) the direct assessment of resistance to flow in the collecting system by measuring physical parameters including pressure and flow, and (2) the assessment of effects which occur secondary to the increased resistance to urine flow in the collecting system, including morphological, physiological, and functional alterations. The majority of the currently available diagnostic tools belong to the second category, demonstrating effects secondary to the increased resistance to urine flow (dilatation by US, decreased function or delayed excretion by nuclear renography).
Upper tract urodynamics encompasses the study of urinary transport efficiency and pressure-flow characteristics of the collecting system.
Unlike acute renal obstruction, congenital hydronephrosis is consistently found to have normal renal pelvic pressure at baseline hydration levels. This may be at the expense of compensatory changes in renal blood flow and GFR. This postulate is supported by the significant rise in renal pelvic pressure observed in congenitally hydronephrotic kidneys in response to diuresis, when compared to normal kidneys.
The pressure changes noted with antegrade pressure perfusion studies are dependent on the capacity and compliance of the renal pelvis, the rate of infusion and the outflow resistance.
In an attempt to standardize the studies and gather the maximum amount of data per study, the following modifications have been adopted:

1. All studies performed under GA with a bladder catheter
2. Baseline renal pelvic pressure measured
3. Diuresis induced challenge
4. Individualized infusion pressure-flow study
5. Pressure decay curve
6. Correlation with other functional and anatomical studies.

Continued from Previous Page

We have used this modified study in equivocal cases especially where there has been discrepancy between the investigations as in patients who demonstrate progressive increase in the degree of dilatation by US despite stable function and drainage by nuclear renography. We have reported on 54 patients (55 renal units) who have completed these detailed studies. Obstruction was "confirmed" in 43 patients who underwent surgical correction. Eleven patients were not considered obstructed of these seven deteriorated within 5 years and underwent pyeloplasty.

Conclusion:

The APPS is a powerful diagnostic tool in the evaluation of HN. It provides important information distinguishing innocuous dilatation from functionally significant obstruction. Because of the dynamic nature of HN in the pediatric patient, the APPS is unable to predict future improvement or deterioration in the functional or morphological status of a hydronephrotic kidney.

Bibliography:

1. Djurhuus, J. C., J. B. Nielsen, et al. (1987). "The relationship between pressure flow studies and furosemide urography in hydronephrosis." Scand J Urol Nephrol 21(2): 89-92.

2. Fung, L. C., B. M. Churchill, et al. (1998). "Ureteral opening pressure: a novel parameter for the evaluation of pediatric hydronephrosis." J Urol 159(4): 1326-30.

3. Fung, L. C. and A. E. Khoury (2001). Urodynamic Studies of the Upper Urinary Tract. Pediatric Urology. J. P. Gearhart, R. C. Rink and P. D. Mouriquand. Philadelphia, W.B. Saunders: 198-224.

4. Fung, L. C., A. E. Khoury, et al. (1995). "Evaluation of pediatric hydronephrosis using individualized pressure flow criteria." J Urol 154(2 Pt 2): 671-6.

5. Fung, L. C., A. E. Khoury, et al. (1996). "Pressure decay half-life: a method for characterizing upper urinary tract urine transport." J Urol 155(3): 1045-9.

6. Koff, S. A. (1983). "Determinants of progression and equilibrium in hydronephrosis." Urology 21(5): 496-500.

7. Lindahl, O. A., T. Backlund, et al. (1995). "Monitoring of renal pelvic pressure in patients with hydronephrosis." Physiol Meas 16(3): 169-79.

8. Lupton, E. W., D. Richards, et al. (1985). "A comparison of diuresis renography, the Whitaker test and renal pelvic morphology in idiopathic hydronephrosis." Br J Urol 57(2): 119-23.

9. Ryan, P. C., K. Maher, et al. (1989). "The Whitaker test: experimental analysis in a canine model of partial ureteric obstruction." J Urol 141(2): 387-90.

10. Vela-Navarrete, R. (1982). "Constant pressure flow-controlled antegrade pyelography." Eur Urol 8(5): 265-8.

11. Wahlin, N., A. Magnusson, et al. (2001). "Pressure flow measurement of hydronephrosis in children: a new approach to definition and quantification of obstruction." J Urol 166(5): 1842-7.

12. Woodbury, P. W., M. E. Mitchell, et al. (1989). "Constant pressure perfusion: a method to determine obstruction in the upper urinary tract." J Urol 142(2 Pt 2): 632-5; discussion 667-8.

Delayed Postnatal Intervention

Stephen A. Koff
The Children's Hospital

About 15 years ago when pediatric urologists were rather suddenly faced with a large number of infants with antenatally detected hydronephrosis they assumed (erroneously) that hydronephrosis was a harmful process that indicates the presence of obstruction and that most hydronephrotic newborn kidneys would progressively lose renal function unless surgery was performed. An alternative approach, which delayed postnatal surgical intervention until the diagnosis of obstruction was proven was not an experiment aimed at unadvisedly postponing needed surgical relief of obstruction. Rather it was based on the hypothesis that many of dilated kidneys were not obstructed and on facts extant at that time that that the definition of obstruction in infant hydronephrosis was inexact, its clinical diagnosis was difficult and the natural history of non-operated hydronephrosis was unknown.

Long term delayed postnatal intervention studies have established the natural history of this condition and demonstrated that about a quarter of severely dilated kidneys are or become obstructed and need surgery. Unfortunately, these studies have also demonstrated that partial upper urinary tract (as opposed to complete) obstruction (PUUTO), which is responsible for nearly all clinically significant post-natal obstruction, is unable to be accurately defined by conventional physiological parameters (pressure, flow, pressure-flow etc.) or accurately diagnosed by existing diagnostic testing protocols (ultrasonography, renography, etc.).

This humiliating clinical inability to define and diagnose PUUTO is compounded by a paucity of experimental data dealing with partial obstruction as it occurs in humans. There is currently no animal model which replicates the clinical entity. Experimental observations using complete upper urinary tract obstruction translate poorly or not at all to the perinatal process and those using external compression (partial obstruction models) produce pelvic volume expansion that generally reaches an equilibrium but does not progress. As a result even the most basic features of PUUTO remain obscure. It is not known for example whether human partial obstruction actually represents recurrent episodes of acute total obstruction or whether partial obstruction is chronic or perhaps both, and how these very different mechanical events translate into renal injury.

Delayed Postnatal Intervention

Continued from Previous Page

It would appear that the greatest potential for improving the care of children with obstructive uropathy exists by concentrating research efforts on clarifying the nature, definition, diagnosis and management of its most common and clinically significant form, namely PUUTO, and by focusing on the fetus and infant, where the potential for development, preservation and recovery of renal function is maximal.

References:

The following 3 articles describe the delayed postnatal intervention management approach to antenatally detected severe unilateral hydronephrosis:

1. Dhillon, H.K. Prenatally diagnosed hydronephrosis: The Great Ormand Street experience. Br J Urol, suppl., 81:39, 1998

2. Ransley, P.G., Dhillon, H.K., Gordon, I. Et al: The postnatal management of hydronephrosis diagnosed by prenatal ultrasound. J Urol, part 2, 144:584, 1990

3. Ulman, I., Jayanthi, R.J., Koff, S.A.: The long-term followup of newborns with severe unilateral hydronephrosis initially treated nonoperatively. J Urol, 164:1101, 2000.

The following article exemplifies the use of the Ulm and Miller model for partial obstruction. Equilibrated hydronephrosis occurs and this is assumed to represent continued partial obstruction.

1. Josephson, S., Lannergren, K., Eklof, A-C.: Partial ureteric obstruction in weanling rats. II. Long term effects on renal function and arterial blood pressure. Urol Int 48: 384, 1992.

Prenatally Diagnosed Hydronephrosis – Selective Postnatal Intervention

H. K. Dhillon
Great Ormond Street Hospital For Children, London, United Kingdom

Pre and postnatal ultrasound is the imaging modality which has helped us to identify the low risk population with a hydronephrosis of no consequence from a true pelviureteric junction obstruction which benefits from pyleoplasty.

We reviewed 920 children with a prenatally diagnosed unilateral hydronephrosis followed from 5-18 years (normal contralateral kidney with reflux excluded) in order to correlate outcome to pre and postnatal antero-posterior diameters of the renal pelvis.

Neonates with a high risk of requiring surgery had a pre and postnatal hydronephrosis of more than 20mm with dilated calyces. The risk of requiring surgery increased exponentially with each 10mm increase of the renal pelvis. A hydronephrosis of 20-30mm with dilated calyces and good function had a 30% risk of eventually requiring surgery. A dilatation of more than 50mm has a 100% chance of requiring surgery whether this be nephrectomy or pyleoplasty.

Only 7% of neonates with a postnatal hydronephrosis of less than 20mm warranted pyleoplasty. Surgery was only indicated where there was an intrarenal hydronephrosis or where there was a severe prenatal dilatation which appeared to improve postnatally. The dilatation always returned to the in utero dimensions.

Ultrasound has minimized the “grey” area in prenatally diagnosed hydronephrosis to the group of children with a severe hydronephrosis of between 20-30mm with calyceal involvement. A third of this population have needed surgery, a third have improved spontaneously, and a third remain stable in terms of dilatation and function.

Early Postinatal Intervention for Congenital Hydronephrosis

Jack S. Elder
Case Western Reserve University School of Medicine

Congenital hydronephrosis results from a variety of causes, and each has its own risks of UTI and renal functional deterioration without surgical therapy, as well as potential for functional recovery or renal functional stabilization following surgical treatment. A controversy regarding early versus delayed operative (or non-operative) therapy relates primarily to the anomalous ureteropelvic junction (UPJ) and non-refluxing megaureter. The reported outcomes are usually differential renal function, efficiency of diuretic-induced renal pelvic drainage, and severity of hydronephrosis. Attempts to standardize hydronephrosis grading and diuretic renography have not been very successful. In addition, whether abnormal parameters in the diuretic renogram can predict progressive renal injury has not been established.

An anomalous UPJ is the most common cause of congenital hydronephrosis. Lesser degrees of hydronephrosis often are secondary to fetal ureteral folds, whereas moderate and severe hydronephrosis typically results from a fixed intrinsic or extrinsic stenosis of the UPJ. At pyeloplasty, approximately 60% of kidneys have a normal or nearly normal histologic appearance, and 40% show changes of obstructive uropathy including cortical and medullary thinning, interstitial fibrosis, and glomerular hyalinization. The correlation between differential function of the involved kidney and its histologic appearance is not high. Approximately 1/4 with differential renal function > 40% have significant glomerulosclerosis, suggesting that either these kidneys have unilateral renal hyperfiltration or the differential renal function is erroneous. Long-term studies from our center have demonstrated that renal functional improvement is likely if the renal histology is nearly normal, whereas it is unlikely if there is glomerulosclerosis. With short-term follow-up, the SFU prospective randomized trial demonstrated that 25% of infants with grades 3 or 4 hydronephrosis showed renal functional deterioration. Furthermore, mean differential renal function of neonates with hydronephrosis diagnosed prenatally is higher than in those diagnosed postnatally or in those lost to follow-up. These observations support early surgical intervention over a non-operative approach for UPJ obstruction.

The non-refluxing megaureter usually is secondary to an aperistaltic distal ureteral segment. In children with this condition, deterioration in renal function is much less likely if the differential function of the involved kidney is normal. Approximately 17% ultimately need operative repair for deteriorating renal function, UTI, or symptomatic discomfort.

Continued from Previous Page

References:

1. Capolicchio G, et al: Prenatal diagnosis of hydronephrosis: imptact on renal function and its recovery after pyeloplasty. J Urol 162: 1029-1032, 1999.

2. Chertin B, et al: Does early detection of ureteropelvic junction obstruction improve surgical outcome in terms of renal function? J Urol 162: 1037-1040, 1999.

3. Elder JS, et al: Renal histologic changes secondary to ureteropelvic junction obstruction. J Urol 154: 719-722, 1995.

4. Gordon I: Diuretic renography in infants with prenatal unilateral hydronephrosis: an explanation for the controversy about poor drainage. BJU International 87: 551-555, 2001.

5. Gordon I, et al: Guidelines for standard and diuretic renography in children. Eur J Nucl Med 28: BP21, 2001.

6. Liu HYA, et al: Clinical outcome and management of prenatally diagnosed primary megaureters. J Urol 152: 614, 1994.

7. Lythgoe MF, et al: Assessment of various parameters in the estimation of differential renal function using technetium-99m mercaptoacetyltriglycine. Eur J Nucl Med 26: 155, 1999.

8. Maizels M, et al: Grading nephroureteral dilatation detected in the first year of life: correlation with obstruction. J Urol 148: 609, 1992.

9. Piepsz A, et al: Relative Tc-99m MAG3 renal uptake: reproducibility and accuracy. J Nucl Med 40: 972, 1999.

10. Society for Fetal Urology and Pediatric Nuclear Medicine Council: The 'well tempered' diuretic renogram: a standard method to examine the asymptomatic neonate with hydronephrosis or hydroureteronephrosis. J Nucl Med 33: 2047, 1992.

11. Wong DC, et al: Diuresis renography. The need for an additional view after gravity-assisted drainage in infants and children. J Nucl Med 41: 1030, 2000.

Early Intervention for Congenital Obstruction

Craig A. Peters
Harvard Medical School

The controversy surrounding the appropriate management of perinatally detected significant hydronephrosis due to upper urinary tract processes (UPJO and UVJO) has persisted in the face of much effort, more argument, and unfortunately little hard data. There seem to be several issues that have hindered the development of a consistently adhered to approach to this condition. Recognizing these issues and attempting to analyze them may help make some progress in this frustrating area.

Definition of "obstruction": Obstruction is a spectrum; hydronephrosis does not mean there is obstruction, but in the absence of reflux or prior surgery, obstruction should be assumed to exist until proven otherwise. Obstruction does not automatically mean that surgery is needed. Some mild degrees of obstruction clearly will resolve spontaneously with no negative effects on the kidney. Trying to define a line between obstructed and non-obstructed is doomed to failure. Choosing which patient may need surgery to protect renal function and health does require an arbitrary dividing line, but this should not be confused with the line between obstructed and non-obstructed. Attempts to create a dichotomy have lead to convoluted algorithms of treatment and testing.

Risk tolerance/avoidance: Much of prenatal diagnosis is directed toward risk avoidance; the risk of having a child with Trisomy-13, the risk of having reflux or an obstructive urinary tract lesion. These risks cannot always be defined with precision, and even when they are, the real-life health implications of that probability are often very difficult to interpret and act upon. Some individuals may be willing to tolerate higher levels of risk in their daily lives -

Outcomes measures: The definition of "success" in caring for a patient with unilateral severe hydronephrosis must be examined carefully. The hydronephrosis is of little consequence to the patient or family unless there is some health change associated with it such as pain, symptomatic infection, or hypertension requiring therapy. Preservation of "function", is an oft-stated goal, yet this may have little direct impact on the patient's perceived health. There is the risk that "function" as measured on a radionuclide scan may not reflect all aspects of renal function that may have clinical impact in some cases. Concentrating capacity and acid-base balance, for example are not measured on scans, yet may be impaired with obstructive processes and have significant clinical impact if impaired.

Continued from Previous Page

Cultural differences: It is clear that health care preferences are different in different countries, and even within one country. These differences are the products of issues such as risk tolerance, as well as long-established practices in certain countries that may be the result of differing health care systems. These systems, of course, reflect individual cultures.

Even with these potential areas of confusion being avoided, there is still going to be some disagreement as to the best means of dealing with these patients. It may ultimately relate to the family's preferences for dealing with risk and their willingness to put up with the risks/costs of surgical therapy as opposed to put up with the uncertainty of risk in an observational approach. Should a 25% risk of needing surgical intervention in five years motivate all families to follow an observational approach, or should it induce early surgical correction? There is clearly no "correct" answer to this question, no more than there is to saying someone should have a specific amount of insurance coverage – it depends on the individual.

Families will seek advice from us, however, and the currently available data support the safety of a defined period of observation between 1 and 2 years for infants with unilateral severe UPJO with relative functional uptake above 40%. This anticipates spontaneous rapid resolution in a small fraction of patients. If this has not occurred, there seems little risk of functional loss, and surgical correction can be undertaken. IN patients with more reduced functional uptake or with massive renal pelvic dilation (>30 mm and caliectasis), early surgical repair seems the most reasonable approach to limit unnecessary testing and protect renal function.

The Morphology of the Kidney in Ureteropelvic Obstruction

Seymour Rosen, Dawn McClellan, Weei-Yuarn Huang, Joseph Borer and Craig Peters
Harvard Medical School

Our previous studies (1) involved 21 biopsies obtained at the time of pyeloplasty from kidneys with ureteropelvic obstruction utilizing a classification dependent on the grade of severity: 1. No abnormality, 2. Occasional glomerulosclerosis; otherwise unremarkable; minimal tubular atrophy, 3. Great variation but with generally limited glomerulosclerosis; mild interstitial fibrosis and tubular atrophy, 4. Severe alterations including over 20% glomerulosclerosis, extensive interstitial-tubular atrophy/ drop out/fibrosis, extravasation of Tamm Horsfall like protein, and dysplastic changes. The present study includes 68 patients (58, single biopsies; 2, bilateral biopsies; 6, double biopsies; 2, nephrectomies; two cases were excluded from the data base, one with an obstructing papilloma, the other with overt dysplastic change). This report focuses on individual histological parameters.

A total of 5035 glomeruli were evaluated; averaging 71.9 + 64.3,S.D. per biopsy. The most common abnormality was glomerular and included global glomerulosclerosis, urinary space eosinophilic material (? Tamm Horsfall protein) and epithelial proliferation averaging 11.2 % + 17.6, S.D. per biopsy. The tubulo-interstitial change was usually not marked and consisted of tubular simplification/drop out with or without a component of fibrosis. Such changes were seen in 25% of biopsies, but were only marked (2+ of a 4+ grading scale) in 11%. Analysis of glomerular density/mm2 was done in an attempt to evaluate tubular mass. In patients over one year of age, values of <9 were most common and gradually decreased as the density reached levels >21. Under one year, a bimodal curve was seen with peaks at 13-15/mm2 and >21/mm2. Tamm Horsfall protein extravasation was seen in 8.8% of cases.

Six patients had two biopsies from the affected side and had similar histological findings of a low-level injury in both biopsies. On the other hand, when histologic changes were severe there was great heterogeneity of damage and such heterogeneity was most evident in nephrectomy specimens. In a few (9) biopsies, there was sufficient depth/orientation to assess the numbers of nephron generations, which were clearly reduced. However, remarkable reduction of nephron number could occur with relatively limited glomerular/tubulo-interstitial alteration.

Thus the changes in these biopsies were mostly those in the glomerulosclerosis spectrum and associated with limited tubulo-interstitial injury. In such material, there was homogeneity of change. At higher levels of injury, tubular mass diminished,glomerular density increased, and heterogeneity of damage was apparent.

(1) Zhang PL, Peters CA, Rosen S. Ureteropelvic junction obstruction: Morphological and clinical studies. In: Pediatr Nephrol 2000;14:820-826.

Renal Tubular Development

Christopher R. Burrow
Mount Sinai School of Medicine

The development of the nephron depends on a genetic program which regulates cellular proliferation and differentiation as well as morphogenesis to generate the complex array of segmentally organized cell types that provide the basis for the excretory function of the adult kidney. In this presentation, some of the most important molecular regulatory mechanisms which govern these processes will be presented with a focus on highlighting recent genetic insights that are most relevant to understanding human genitourinary malformations. A new frontier in the study of tubular development is the identification of the molecular processes which establish and maintain the precise ratio of lumen to tubule diameter that characterizes each nephron segment. Aberrant functioning of these processes result in cystic enlargement of tubular segments as seen in polycystic kidney diseases. In studies recently completed, we have shown that PRKX, a developmentally regulated cAMP-dependent serine-threonine kinase is aberrantly expressed in cyst epithelia in Autosomal Dominant Polycystic Disease (ADPKD). PRKX activates epithelial cell migration and morphogenesis and disrupts normal branching morphogenesis in cell culture experiments. These results suggest that aberrant expression of PRKX in ADPKD may contribute to the development and expansion of tubular cysts, and that further characterization of the downstream phosphorylation targets of this kinase may elucidate important components of the genetic program controlling normal tubulogenesis.

Pathology of obstruction: Molecular changes

Helen Liapis
Washington University School of Medicine

Congenital urinary obstruction interferes with branching of collecting ducts and tubular and glomerular formation. As a result, tubular cysts surrounded by undifferentiated mesenchyme, glomerular cysts and dysplastic features develop. Human dysplastic kidneys and or obstructed fetal opossum pup kidneys reveal multiple protein and gene alterations compared to kidney obstructed at maturity. Dysplastic epithelia and mesenchymal interstitial cells express increased proliferating cell nuclear antigen, decreased Bcl-2 (an inhibitor of apoptosis),and increased Bax (pro-apoptotic), suggesting that obstruction induces a profound imbalance between cell proliferation and physiologic apoptosis. Both in human and obstructed opossum pup kidneys, multiple genes and their proteins are altered, including PDGF, Pax-2, bone morphogenetic protein 1, osteopontin and WT1. Gene chip array analysis in a limited number of human dysplastic kidneys confirms previously reported results, e.g., decreased renin expression. Additionally, new concomitant genetic alterations are revealed, not previously known. Among extracellular matrix genes, transcripts consistently increased more than 5 fold, include: chondroitin sulfate proteoglycan versican, tenascin, fibronectin, collagen, elastin, matrilysin (MMP7) and thrombospondin. Consistently decreased are: retinol binding protein 4, cartilage GP-39 protein, tissue inhibitor metalloproteinase 4 (TIMP-4), collagen type 1/ thrombospondin receptor, collagenase 4 and macrophage elastase. Consistently increased (5 fold or more) signaling molecules are: TGF 3 and latent TGF binding protein, PDGF receptor , insulin-like growth factor binding protein 5, fibroblast activation protein and connective tissue growth factor, among others. We believe that significant (>5fold) changes in transcript profile expression are likely important in the pathogenesis of congenital urinary obstruction, but it is not currently known whether small quantitative differences (< five -fold) in gene expression are biologically important. Genechip arrays are a powerful technology, but the generated data will be more useful if combined with protein expression profile analysis to evaluate gene functionality and potential interactions among various gene products.

Physiology of the Hydronephrotic Kidney: Fetus

Barry A. Kogan
Albany Medical College

There are many reasons to believe that fetal urinary tract obstruction will have different consequences than obstruction post-natally. These include the presence of the placenta that modulates fluid, electrolyte and hormonal balances, the relatively low renal blood flow and generalized endocrine and vascular immaturity. Moreover, obstruction is likely to affect nephron development directly.

These changes have been studied in several different animal preparations, most commonly using fetal sheep. Models of both complete and partial obstruction have been used.

In complete obstruction, some of the important findings include:

1. early complete obstruction may create renal dysplasia in some (but not all) kidneys affected.
2. after complete obstruction, renal function is reduced, but this affect may be ameliorated by urinary diversion in-utero.

In partial obstruction, the most important findings include:

1. renal size is increased!
2. renal blood flow and function are increased!
3. renal fibrosis occurs, due in part to reduced degradation of extracellular matrix.
4. alterations in the development of the renin-angiotensin system are seen.

In general it is clear that obstruction alters the normal physiology of the fetus. What is most prominent in these studies however is that normal fetal physiology may be strikingly different than that seen post-natally. Studies have shown that this is particularly true for the renin-angiotensin system and for endothelin.

Further studies of normal and abnormal physiology in the fetal kidney are urgently needed. In addition, studies of the physiology of the in-utero release of obstruction are critical to developing new treatment paradigms.

References:

1. Peters CA. Animal models of fetal renal disease. Prenat Diagn. 2001; 21:917-23.

2. Ayan S, et al. Partial ureteral obstruction dysregulates the renal renin-angiotensin system in the fetal sheep kidney. Urology. 2001; 58:301-6.

3. Edouga D, et al. Recovery after relief of fetal urinary obstruction: morphological, functional and molecular aspects. Am J Physiol Renal Physiol. 2001 281:F26-37.

4. Gobet R, et al. Renal renin-angiotensin system dysregulation caused by partial bladder outlet obstruction in fetal sheep. Kidney Int. 1999; 56:1654-61.

5. Gobet R, et al. Fetal partial urethral obstruction causes renal fibrosis and is associated with proteolytic imbalance. J Urol. 1999; 162:854-60.

6. Attar R, et al. Short-term urinary flow impairment deregulates PAX2 and PCNA expression and cell survival in fetal sheep kidneys. Am J Pathol. 1998 ;152:1225-35.

7. Nguyen HT, Kogan BA. Renal hemodynamic changes after complete and partial unilateral Ureteral obstruction in the fetal lamb. J Urol. 1998; 160:1063-9.

8. Medjebeur AA, et al. Experimental bilateral urinary obstruction in fetal sheep: transforming growth factor-beta 1 expression. Am J Physiol. 1997; 273:F372-9.

9. Bogaert GA, et al. Exogenous endothelin-1 causes renal vasodilation in the fetal lamb. J Urol. 1996; 156:847-53.

10. Bogaert GA, et al. Renal preservation despite 35 days of partial bladder obstruction in the fetal lamb. J Urol. 1995; 154:694-9.

11. Bussieres L, et al. Creation of experimental urethral obstruction in utero: evaluation of fetal renal function. Eur J Pediatr Surg. 1993; 3:161-5.

Physiology of the hydronephrotic kidney in the neonate

R. L. Chevalier
University of Virginia

Severe partial unilateral ureteral obstruction (UUO) in the neonatal guinea pig prevents the normal maturational increase in renal blood flow. This is largely attributable to the enhanced production of angiotensin II by the obstructed kidney. Ischemia is likely to play a significant role in the marked stimulation of renal tubular apoptosis by UUO in the neonatal kidney, which is significantly greater than that in the adult. Following relief of UUO in the neonatal rat, tubular apoptosis decreases, and epithelial cell proliferation increases. It is likely that a reduction of intrarenal angiotensin II production following relief of obstruction contributes to these changes, as angiotensin inhibits tubular proliferation and promotes apoptosis in the obstructed kidney of the neonatal rat. In addition, angiotensin contributes to at least 50% of the interstitial fibrosis in the neonatal kidney subjected to UUO. The administration of exogenous epidermal growth factor or insulin-like growth factor-1 to neonatal rats with UUO suppresses tubular apoptosis, and attenuates tubular atrophy and interstitial fibrosis. Both of these growth factors preserve BAD phosphorylation, thereby enhancing tubular cell survival by preventing mitochondrial injury, which leads to apoptosis. Chronic partial UUO in the neonatal guinea pig increases intratubular pressure, both in the distal and proximal tubule. In the neonatal mouse, tubular apoptosis is directly related to tubular dilatation. Since graded mechanical stretching of rodent tubular cells in vitro results in a corresponding stimulation of apoptosis, axial strain secondary to increased intratubular pressure likely plays a significant role in tubular injury resulting from UUO. In addition, interstitial infiltration by macrophages contributes significantly to tubular apoptosis in the obstructed neonatal kidney. Localization of macrophages to the injured kidney is mediated by the expression of selectins. In addition, the metabolic milieu of the developing kidney also plays a role in the its enhanced susceptibility to UUO. The renal production of the sphingolipid ceramide is far greater in the neonatal than the adult kidney. Chronic UUO in the neonatal rat further stimulates the renal production of this pro-apoptotic compound, while UUO in the adult has no effect on renal ceramide content. Improved understanding of the unique physiologic and cellular responses of the neonatal kidney to UUO should lead the way to preserving renal mass and function in infants with congenital obstructive nephropathy.

Continued from Previous Page

References:

1. Chevalier, R. L., K. H. Chung, C. D. Smith, M. Ficenec, and R. A. Gomez. Renal apoptosis and clusterin following ureteral obstruction: the role of maturation. J.Urol. 156: 1474-1479, 1996.

2. Chevalier, R. L., S. Goyal, A. Kim, A. Y. Chang, D. Landau, and D. LeRoith. Renal tubulointerstitial injury from ureteral obstruction in the neonatal rat is attenuated by IGF-1. Kidney Int. 57: 882-890, 2000.

3. Chevalier, R. L., S. Goyal, J. T. Wolstenholme, and B. A. Thornhill. Obstructive nephropathy in the neonate is attenuated by epidermal growth factor. Kidney Int. 54: 38-47, 1998.

4. Chevalier, R. L. and M. J. Peach. Hemodynamic effects of enalapril on neonatal chronic partial ureteral obstruction. Kidney Int 28: 891-898, 1985.

5. Chevalier, R. L., B. A. Thornhill, and J. T. Wolstenholme. Renal cellular response to ureteral obstruction: role of maturation and angiotensin II. Am.J.Physiol. 277: F41-F47, 1999.

6. Fern, R. J., C. M. Yesko, B. A. Thornhill, H.-S. Kim, O. Smithies, and R. L. Chevalier. Reduced angioteninogen expression attenuates renal interstitial fibrosis in obstructive nephropathy in mice. J.Clin.Invest. 103: 39-46, 1999.

7. Kiley, S. C., Tang, S.-S., Ingelfinger, J. R., and Chevalier, R. L. Growth factor-mediated phosphorylation of BAD reduces mechanical strain-induced tubule cell death in vitro. J.Am.Soc.Nephol. 12, 681A. 2001.

8. Lange-Sperandio, B., F. Cachat, B. A. Thornhill, and R. L. Chevalier. Selectins mediate macrophage infiltration in obstructive nephropathy in newborn mice. Kidney Int. 61: 516-524, 2002.

9. Malik, R. K., B. A. Thornhill, A. Y. Chang, S. C. Kiley, and R. L. Chevalier. Renal apoptosis parallels ceramide content following chronic ureteral obstruction in the neonatal rat. Am.J.Physiol. (in press): 2001.

10. Norwood, V. F., R. M. Carey, K. M. Geary, P. A. Jose, R. A. Gomez, and R. L. Chevalier. Neonatal ureteral obstruction stimulates recruitment of renin- secreting renal cortical cells. Kidney Int. 45: 1333-1339, 1994.

The marsupial model of fetal ureteral obstruction Didelphis virginiana

George F. Steinhardt
St. Louis University School of Medicine

The North American opossum, Didelphis virginiana is a marsupial whose young are born at a very immature stage (approximately 8 week human equivalent). Lacking a placenta, the pups complete somatic development in the mothers pouch on the teat. At birth the pups weigh 130mg and demonstrate a well-developed mesonephros which does not completely involute until approximately 17 days of age. At 20 days of age the pups measure 4.5 cm and possess an immature but typically mammalian metanephric kidney with 2 glomerular generations. We have utilized the unique properties of this marsupial species to create a model of complete unilateral ureteral obstruction in a fetal kidney equivalent. When obstructed at this stage, the kidney develops unequivocal renal dysplasia with fibromuscular whorls of mesenchymal tissue surrounding primitive tubules. Following obstruction, the time course of development of glomerular cystic change, tubular cystic change, interstitial fibrosis, and inflammation has been closely studied. We have additionally characterized the events deriving from obstruction in terms of both the expansion of the extracellular matrix and differential cellular proliferation and apoptosis throughout the obstructed kidney. In addition to characterizing the sequence of histologic and molecular events subsequent to obstruction, we have utilized this model to investigate the possibility of therapeutic intervention. By administering IGF-I to pups with complete ureteral obstruction, we have in the short term, improved the histologic architecture of the affected kidney. We continue to investigate the effects of complete obstruction upon the developing kidney, hoping to describe the proximate molecular causes of fetal renal damage with the hope of discovering novel models of molecular therapy.

The model of experimental unilateral ureteral obstruction in the opossum has been useful, but there are disadvantages. Opossum are wild trapped and, in Missouri, they breed only in the early spring thereby prohibiting year around experimentation. Sophisticated animal care facilities are needed to maintain these animals in the laboratory. The experimental interventions themselves are both technically demanding and labor intensive. The advantage is that this model may mimic the human equivalent of obstruction better than other models.

Continued from Previous Page

References:

1. Cutts JH. Krause. and Lesson CR. General observations on the growth and development of the young pouch opossum, Didelphis virginiana. Biol Neonate. 33: 264, 1978.

2. Krause WJ. Cutts JH. and Leeson CR. Morphological observations on the mesonephros in the postnatal opossum, Didelphis virginiana. J Anat. 129(2):377, 1978

3. Krause WJ. Cutts JH, and Leeson CR. Morphologic observations on the metanephros in the postnatal opossum, Didelphis virginiana. J Anat. 129(3): 469-477, 1979.

4. Steinhardt GF. Vogler G. Salinas-Madrigal L. and LaRegina M. Induced renal dysplasia in the young pouch opossum. J Ped Surg 23(12): 1127-1130, 1988. December.

5. Steinhardt GF. Salinas-Madrigal L. Farber R. Lynch R. and Vogler. Experimental ureteral obstruction in the fetal opossum. I. Renal functional assessment. J Urol. 144(2): 564-566. 1990. August.

6. Steinhardt GF. Salinas-Madrigal L. deMello, D Farber R. Phillips R. and Vogler G. Experimental ureteral obstruction in the fetal opossum histologic assessment. J Urol. 152(6): 2133-2138, 1994. December.

7. Steinhardt GF. Liapis H. Phillips R. Vogler G. Nag M. and Yoon KW. Insulin-like growth factor improves renal architecture of fetal kidneys with complete unilateral ureteral obstruction. J Urol. 154(2): 690-693, 1995. August.

8. Liapis H. Nag M. and Steinhardt GF. Effects of experimental ureteral obstruction on platelet-derived growth factorA and type I pro collagen expression in fetal metanephric kidneys. Pediatr. Nephrol. 8: 548-554, 1994.

9. Liapis H. Yu H. and Steinhardt GF. Cell Proliferation, apoptosis, BCL-2 and BAX expression in obstructed opossum early metanephroi. J Urol. 164(2): 511-517, 2000, August.

10. Liapis H. Barent B. and Steinhardt GF. Extracellular matrix in fetal kidney after experimental obstruction J Urol. 166(4): 1433-1438, 2001. October.

Surgical Models of Congenital Obstruction: Ovine

Craig A. Peters
Harvard Medical School

Models of congenital obstruction in fetal sheep have provided great insight into the mechanisms of prenatal obstructive nephropathy and uropathy. The principle advantages of the fetal sheep model have been: 1. large size of the animals permitting complex and precise models of various congenital abnormalities, 2. the long gestation permitting early interventions and a more gradual progression of conditions more reflective of the human condition, 3. a hardy pregnancy that allows for high survival rates and the opportunity for multiple interventions, 4. manageable animals in the post-natal period that permit detailed physiological evaluation of the conditions produced. Some of these advantages are also concomitant disadvantages, particularly size and long gestation. The major disadvantages of the ovine model include: 1. expense, 2. less availability of molecular probes, 3. lack of strict renal homology with the human kidney, 4. limited study of the physiology of the postnatal renal and urinary tract.

The sheep has been the principle animal in which the fetal relationships of the lung and kidneys have been explored. From these studies the role of timing of gestation on the patterns of pulmonary maldevelopment have been demonstrated, as well as the potential reversibility of renal-pulmonary defects and the role of lung fluid in the renal-pulmonary axis.[1-3] This work has been tied directly with further study into the pathophysiology of diaphragmatic hernias and introduced novel therapies.[4] A continuing question remains regarding the possibility of a two-way feedback system regulating growth of the lung and kidneys.[5]

The renal effects of fetal obstruction have been studied extensively in the fetal sheep with the early demonstration of dysplastic development induced by early obstruction in Beck's seminal work.[6] This is completely unique to fetal preparations and permits study of the mechanisms of dysplastic development that cannot be approached with postnatal models. Several key determinants of renal development in the face of obstruction have been identified from fetal sheep preparations.[7-9] These include: 1. time of onset of the obstructive effect, severity of the obstructive effect, 3. cumulative duration of obstruction, 4. interaction of two kidneys. The over-arching conclusion that may be seen from this work is that obstruction in the fetus alters patterns of growth and differentiation of the kidney. While these activities do continue postnatally to some extent in some animals, the effects that produce significant obstructive nephropathy in human are prenatal and therefore need to be studied in the fetus. Specific mechanisms of congenital obstructive nephropathy have been elucidated using the fetal sheep, including the role of the renin angiotensin system,[10, 11] activity of particular growth factors such as TGFß,[12] IGF-1,[13] and the influence of apoptosis.[14] Renal vascular physiology in response to obstruction has been studied in the ovine fetus as well.[15, 16] Each of these observations has developed novel lines of investigation into pathophysiological mechanisms and therapies.

Continued from Previous Page

The fetal sheep model also permits a detailed study of the urinary tract in congenital obstructive nephro-uropathy. It is clear that the response of the urinary tract from the renal pelvis to the urethra is critical to the renal outcome, as well as having specific clinical consequences such as infection and incontinence when dysfunctional. The large size of the sheep permits assessment of the ureters,[17] ureterovesical junction, bladder, trigone and bladder neck, all of which contribute to the impact of an obstructive lesion and have both direct and indirect effects on renal function. Finally, fetal sheep have been used to develop novel technologies for fetal surgical techniques, several of which have been transitioned successfully to human application.[18, 19]

With the advent of a broad array of molecular probes for the sheep, the utility of this model remains strong in the investigation of COU. As basic mechanisms of renal maldevelopment are identified in small animals or in vitro systems, transfer into the larger animal with precise and reproducible models of human conditions will permit focused identification of relevant mechanisms. This will also set the stage for the identification and testing of therapeutic strategies in fetal sheep models, based upon specific mechanisms. Without testing in large animal systems that integrate the complex physiological interactions of the developing organism, conclusions based upon post-natal or short gestation, small animals are unlikely to be fruitful.

References:

1. Docimo, S.G., et al., Pulmonary development in the fetal lamb: morphometric study of the alveolar phase. Anat Rec, 1991. 229(4): p. 495-8.

2. Peters, C.A., et al., Effect of in utero vesicostomy on pulmonary hypoplasia in the fetal lamb with bladder outlet obstruction and oligohydramnios: a morphometric analysis. J. Urol., 1991. 146(4): p. 1178-83.

3. Peters, C.A., et al., The role of the kidney in lung growth and maturation in the setting of obstructive uropathy and oligohydramnios. J Urol, 1991. 146(2 (Pt 2)): p. 597-600.

4. DiFiore, J.W., et al., Experimental fetal tracheal ligation and congenital diaphragmatic hernia: a pulmonary vascular morphometric analysis [see comments]. J Pediatr Surg, 1995. 30(7): p. 917-23; discussion 923-4.

5. Glick, P.L., J.R. Siebert, and D.R. Benjamin, Possible trophic relationship between the growth of the lungs and kidneys in congenital diaphragmatic hernia (CDH) [letter; comment]. J Pediatr Surg, 1991. 26(5): p. 643-4.

6. Beck, A.D., The effect of intra-uterine urinary obstruction upon the development of the fetal kidney. J Urol, 1971. 105: p. 784-789.

7. Glick, P.L., et al., Correction of congenital hydronephrosis in utero III. Early mid-trimester ureteral obstruction produces renal dysplasia. J Pediatr Surg, 1983. 18(6): p. 681-7.

8. Peters, C.A., et al., The response of the fetal kidney to obstruction. J. Urol., 1992. 148: p. 503.

9. Matsell, D.G., T. Bennett, and A.D. Bocking, Characterization of fetal ovine renal dysplasia after mid-gestation ureteral obstruction. Clin Invest Med, 1996. 19(6): p. 444-52.

10. Gobet, R., et al., Renal renin-angiotensin system dysregulation caused by partial bladder outlet obstruction in fetal sheep. Kidney Int, 1999. 56(5): p. 1654-61.

11. Ayan, S., et al., Partial ureteral obstruction dysregulates the renal renin-angiotensin system in the fetal sheep kidney. Urology (in press), 2001. 58(2): p. 301-6.

12. Medjebeur, A.A., et al., Experimental bilateral urinary obstruction in fetal sheep: transforming growth factor-ß1 expression. Am J Physiol, 1997. 273(3 pt 2): p. F372-9.

13. Bussieres, L., et al., Fetal urinary insulin-like growth factor I and binding protein 3 in bilateral obstructive uropathies. Prenatal Diagnosis, 1995. 15(11): p. 1047-55.

14. Attar, R., et al., Short-term urinary flow impairment deregulates PAX2 and PCNA expression and cell survival in fetal sheep kidneys. Am J Pathol, 1998. 152(5): p. 1225-35.

15. Kim, K.M., B.A. Kogan, and C.A. Massad, Acute hemodynamic and endocrinological effects of partial fetal bladder obstruction. J Urol, 1992. 148(2 Pt 2): p. 497-502.

16. Bogaert, G.A., B.A. Kogan, and R.A. Mevorach, Effects of endothelium-derived nitric oxide on renal hemodynamics and function in the sheep fetus. Pediatric Research, 1993. 34(6): p. 755-61.

17. Santis, W.F., et al., Characterization of ureteral dysfunction in an experimental model of congenital bladder outlet obstruction [In Process Citation]. J Urol, 2000. 163(3): p. 980-4.

18. Luks, F.I., et al., Fetoscopy-guided fetal endoscopy in a sheep model. Journal of the American College of Surgeons, 1994. 178(6): p. 609-12.

19. Meuli-Simmen, C., et al., Fetal reconstructive surgery: experimental use of the latissimus dorsi flap to correct myelomeningocele in utero. Plastic & Reconstructive Surgery, 1995. 96(5): p. 1007-11.

Surgical Fetal Obstruction: Primate

Douglas G. Matsell, Alice F. Tarantal
University of Western Ontario, University of Californian

In order to further our understanding of the prenatal pathogenesis of obstructive renal dysplasia, a fetal monkey model was developed using ultrasound-guided techniques. Unilateral ureteral obstruction was induced during the early or late second trimester by the injection of purified guluronic alginate spheres. Obstructed kidneys displayed most features of renal dysplasia including numerous cortical cysts of various sizes derived predominantly from collecting ducts and glomeruli. Mesenchymal changes included expansion of both the cortical and medullary interstitium, as well as mesenchymal-myocyte transformation, expressed as pericystic and peritubular fibromuscular collar formation.

A striking feature of this model was the disruption of normal glomerular development and architecture, associated with significant podocyte apoptosis, evident as early as the prevascularized s-shape nephron, deficient cortical ureteric duct development and branching, reduced glomerular number, and altered glomerular basement membrane formation. As in other models, collecting duct cell apoptosis was apparent, particularly in areas of cyst formation and cellular atrophy. This nonhuman primate model will be an important tool for exploring the pathophysiology of congenital obstructive uropathy.

Experimental Model Systems Congenital Obstruction: Rodent

Linda M. Dairiki Shortliffe
Stanford University

We investigated an inbred Wistar rat with unilateral congenital hydronephrosis as a model for a) ureteropelvic junction obstruction, b) urinary tract infection in partial obstruction, and c) pharmacologic manipulation of renal pelvic pressure. This rat colony was first described by Friedman et al. in 1979 and was originally derived from matings of 3 female rats that had given birth to pups with unilateral hydronephrosis and their affected offspring. Selective breeding over the last 2 decades has led to a stable colony of rats with an incidence of unilateral congenital hydronephrosis in males of approximately 80-90% and in females of approximately 60% with an assumed polygenic inheritance pattern. Previous investigations have shown that the hydronephrotic kidney has physiological changes associated with obstruction including reduced single nephron glomerular filtration rates.

In a series of experiments simultaneous bladder and renal pelvic pressures were measured during different urinary flows, and during bladder filling and voiding in a) congenitally hydronephrotic rats (approx. 45 days old) and normal non-hydronephrotic rats b) a second group of rats treated with oxybutynin, and c) a third group that had pyelonephritis. Differential pressures between renal pelvis and bladder were determined. Hydronephrotic and nonhydronephrotic rats were also characterized using ultrafast MRI and then examined pathologically.

Hydronephrotic rats had higher renal pelvic pressures throughout bladder filling at all urinary flow rates than normal rats. Oxybutynin decreased pressures in the hydronephrotic rats to levels at or below nonhydronephrotic rats. In hydronephrotic infected kidneys, renal pelvic pressures exceeded those in nonhydronephrotic infected kidneys. Anatomic analysis using ultrafast MRI noncontrast studies showed precise delineation of the hydronephrotic pelvis and corticomedullary junction; contrast (Gd-DTPA) showed decreased blood flow, less medullary decrease, and delayed contrast excretion, allowing differentiation between obstructed and nonobstructed kidneys on physiologic in addition to anatomic basis.

This Wistar rat appears to model a congenital ureteropelvic junction obstruction characterized by elevated renal pelvic pressures. Manipulation of this model suggests that urinary tract infection further elevates these pressures and that oxybutynin may reverse some of these pressure changes. This model may be useful for understanding the pathophysiology of obstructive hydronephrosis.

Continued from Previous Page

References:

1. Friedman, J., Hoyer, J.R., McCormick, B., Lewy, J.E.: Congenital hydronephrosis in the rat. Kidney Int.15:567-571, 1979.

2. Boineau, F.G., Vari, R.C., Lewy, J.E.: Reversible vasoconstriction in rats with congenital hydronephrosis. Pediatr.Nephrol.1:498-501,1987.

3. Smyth TB, Shortliffe LM, Constantinou CE:. The effect of urinary flow and bladder fullness on renal pelvic pressure in a rat model. Journal of Urology. 146:592-6, 1991.

4. Issa, M.I., Shortliffe, LD., and Constantinou, C.E.: The effect of bacteriuria on renal and bladder pressures in the Sprague-Dawley rat. J. Urol. 148(2): 559-563, 1992.

5. Fichtner J, Spielman D, Herfkens R, Boineau FG, Lewy JE, Shortliffe LMD: Ultrafast contrast enhanced magnetic resonance imaging of congenital hydronephrosis in a rat model. Journal of Urology. 152:682-7, 1994.

6. Fichtner, J., Boineau, FG, Lewy, J.E., Vari, R.C., Shortliffe, L.D, Continuous renal pelvic and bladder pressures in congenital unilateral hydronephrosis in the rat. J. Urol. 152:652-657, 1994.

7. Hsia, T-Y, Shortliffe, L.D., The effect of pregnancy on the rat urinary tract. J. Urol. 154: 684-689, 1995.

8. Fichtner, J, Boineau, F, Lewy, J. , Shortliffe, LD: Oxybutynin lowers elevated renal pelvic pressures in congenital hydronephrosis of the rat. Journal of Urology. 3:887-891. 1998.

9. Cowan, BE and Shortliffe, LD: The effect of oxybutynin on normal and infected rat renal pelvic pressures. U. Urol. 3:882-886, 1998.

10.Angell, SK, Pruthi, RS, and Shortliffe, LD.: The urodynamic relationship between renal pelvic and bladder pressure with varying urinary flow rates in rats with congenital vesicoureteral reflux. Journal of Urology. 160:150-156, 1998.

Surgical postnatal ureteral obstruction: Murine

R. L. Chevalier
University of Virginia

Because most nephrogenesis in the neonatal rat and mouse takes place in the first two postnatal weeks, unilateral ureteral obstruction (UUO) on the first day of life roughly approximates UUO developing in the midtrimester human fetus. In contrast, nephrogenesis in the guinea pig is complete before birth, such that postnatal renal development more closely parallels that of the human. Complete UUO at birth in the rat impairs growth of the ipsilateral kidney, and this impairment is directly related to the duration of obstruction. Compensatory growth of the opposite kidney is directly related to the reduction in growth of the obstructed kidney. If 5 days of UUO in the neonatal rat is postponed to the second week of life (immediately following completion of nephrogenesis, and comparable to the human neonate), impairment of renal growth is even more severe than that resulting from UUO in the first 5 days of life. In the guinea pig, UUO in the immediate postnatal period results in severe renal growth impairment, whereas UUO in adulthood does not alter renal mass. In the neonatal rat, 5 days UUO reduces the number of nephrons by nearly 50%, whether the obstruction is during or immediately following the completion of nephrogenesis. In contrast, following relief of 5 days UUO in the adult rat, there is no reduction in the number of nephrons. In addition to its effects on renal growth and nephron number, UUO in early development significantly retards renal development. This is evidenced by a delay in the maturation of the preglomerular vasculature, of the glomeruli themselves, of the tubules, and of the interstitium. These results underscore the susceptibility of the developing kidney to even transient ureteral obstruction, and suggest that the reduction in the duration of obstruction has a salutary effect on the long-term structure and function of the kidney.

References:

1. Chevalier, R. L. Pathophysiology of obstructive nephropathy in the newborn. Seminars in Nephrology 18: 585-593, 1998.

2. Chevalier, R. L., R. A. Gomez, and C. A. Jones. Developmental determinants of recovery after relief of partial ureteral obstruction. Kidney Int 33: 775-781, 1988.

3. Chevalier, R. L., A. Kim, B. A. Thornhill, and J. T. Wolstenholme. Recovery following relief of unilateral ureteral obstruction in the neonatal rat. Kidney Int. 55: 793-807, 1999.

4. Chevalier, R. L., B. C. Sturgill, C. E. Jones, and D. L. Kaiser. Morphologic correlates of renal growth arrest in neonatal partial ureteral obstruction. Pediat Res 21: 338-346, 1987.

5. Chevalier, R. L., B. A. Thornhill, A. Y. Chang, F. Cachat, and A. Lackey. Recovery from release of ureteral obstruction in the rat: Relationship to neprhogenesis. Kidney Int. (in press): 2002.

6. Chevalier, R. L., B. A. Thornhill, J. T. Wolstenholme, and A. Kim. Unilateral ureteral obstruction in early development alters renal growth: Dependence on the duration of obstruction. J.Urol. 161: 309-313, 1999.

7. Chung, K. H. and R. L. Chevalier. Arrested development of the neonatal kidney following chronic ureteral obstruction. J.Urol. 155: 1139-1144, 1996.

8. Claesson, G., S. Josephson, and B. Robertson. Experimental partial ureteric obstruction in newborn rats. VII. Are the long term effects on renal morphology avoided by release of the obstruction? J.Urol. 136: 1330-1334, 1986.

9. Fern, R. J., C. M. Yesko, B. A. Thornhill, H.-S. Kim, O. Smithies, and R. L. Chevalier. Reduced angioteninogen expression attenuates renal interstitial fibrosis in obstructive nephropathy in mice. J.Clin.Invest. 103: 39-46, 1999.

10. Josephson, S., B. Robertson, G. Claesson, and I. Wikstad. Experimental obstructive hydronephrosis in newborn rats. I. Surgical technique and long-term morphologic effects. Invest.Urol. 17: 478-483, 1980.

Surgical postnatal obstruction: porcine

Jorgen Frokiaer, Anni Eskild-Jensen, Thomas Dissing,
Troels Munch Jørgensen, Jens Christian Djurhuus
University of Aarhus, Aarhus, Denmark

The pig has multicalyceal kidneys and a urinary tract, which anatomically and physiologically resemble those of man. The kidneys and the urine transport system combine a high pressure compartment with a low pressure compartment subjected to a large fluid volume and volume reduction. Thus, the system is challenged when pressure in both compartments are changed. Consequently, both pressure compartments have been the focus of intense research in order to achieve key pathophysiological predictors of obstructive nephropathy. The fundamental question in cases with dilated kidney is to determine whether kidney function will deteriorate. We have developed a variety of postnatal pig models with partial and complete ureteral obstruction, which allow insights in the acute and chronic responses to obstruction. The consequence of late fetal obstruction has been examined in neonatal pigs where unilateral partial obstruction was created by implanting the ureter into the psoas muscle and followed for up to 24 weeks. The major results from these study were that neonatally induced unilateral partial ureteropelvic obstruction causes impaired nephrogenesis with a significant reduction in the number of nephrons. However, renal function was not significantly impaired at adulthood. Renal counterbalance was examined using a variety of techniques. Initially kidneys contralateral to obstructed kidneys with decreased function had no increased growth or function. Furthermore, function and volume of the contralateral kidneys were not associated at the early age. Thus, the results of our study imply that determining the size (growth) or function of the contralateral kidney at an early age does not predict function decrease in a partially obstructed kidney in this pig model. When delayed obstruction was induced at age 2 weeks the variability and course of renal function in kidneys was similar to findings obtained in pigs obstructed at age 2 days. But in contrast these pigs developed a compensatory increase in function and size of the contralateral kidney, suggesting that contralateral compensation is an ability gained late in the nephrogenesis period. In conclusion, we believe that early evaluation of kidney function or volume, or contralateral kidney length do not predict the outcome of neonatally induced unilateral hydronephrosis in pigs.

That the pig model with partial unilateral ureteral obstruction is associated with high degree of hydronephrosis. The functional impact of the dilatation is variable, thus resembling the clinical cases with neonatal dilatation. Renal function is uniformely reduced .. is nduces .....Detailed
By detailed stereological techniques studies on renal hemodynamic changes in response to
An additional advantage using pig models.

Role of Stroma in Patterning Renal Tubules

K. Borodo, C. Cebrian, R. Guillaume, D. Herzlinger
Weill Medical College of Cornell University

During the past 15 years, remarkable progress has been made in elucidating the tissue interactions and molecules regulating kidney morphogenesis. From this work, it is now clear that nephron, collecting system and ureteral architecture is dependent on interactions between cells that give rise to these epithelial tubules and cells that differentiate into peritubular stroma. In vivo fate mapping studies performed in the developing chick indicate that tubular epithelial of the urogenital system and peritubular stroma cells derive from two distinct progenitor cell populations. Molecular marker analyses of the developing murine urogenital system demonstrate that peritubular stromal progenitors are incorporated into the kidney at the initiation of organ morphogenesis (E11.5) but do not undergo overt differentiation until substantial development has occurred (E16). Furthermore, we show that this normal temporal delay in stromal differentiation is perturbed in one animal model exhibiting stromal-dependent ureter and kidney defects. Finally, we have identified several factors secreted by peritubular stroma that regulate both the diameter and length of urinary tubules. These data suggest that further analyses focused on the regulation of tubule patterning will provide insight into the cellular and molecular defects leading to obstructive disorders.

Tubulointerstitial Response: Proliferation and Apoptosis

Hiep T. Nguyen
University of California at San Francisco

Though they are two dynamically opposing processes, both renal cellular proliferation and apoptosis are observed following urinary obstruction. Experiments using animal models have indicated that shortly after ureteral ligation, renal tubular and interstitial cell proliferation increases significantly and is followed by the onset of tubular cell apoptosis. Subsequent experiments using animal models and cell culture systems have begun to elucidate the molecular mechanisms of these processes. Extracellular factors (angiotensin II, reactive oxygen species, cytokines and growth factors) and physical forces such as those induced by hydrostatic distension can induce proliferation and/ or apoptosis through activating specific receptors on the cell membrane. Stimuli for proliferation may be signaled through the EGF, IGF and PGDF receptors, while those for apoptosis may be directed through Fas, TNF receptor-1, TRAIL receptor and AT2 receptor. These receptors in turn can activate intracellular signaling pathways (ERK-MAPK for proliferation and JNK for apoptosis). Through these signaling pathways, extracellular stimuli can induce renal tubular cells and interstitial fibroblasts to express / activate intracellular factors that regulate proliferation and/ or apoptosis (caspases, p53, TGF-b, p21, p27, Bcl-2, Bax, HB-EGF). With further understanding of the molecular mechanisms of proliferation and apoptosis, it is becoming evident that these two processes are closely inter-related. Many of the receptors and signaling pathways are used by both, and the activated intracellular factors can either induce cell proliferation or apoptosis depending on numerous factors including the cell type and the duration of the obstruction.

Vitamin A controls ureter maturation via the ret proto-oncogene

Ekatherina Batourina[1], Christopher Choi[1], Terry Hensle[1], Frank Costantini[1], Shankar Srinivas[1,2] & Robert L. Bacallao[3] & Cathy Mendelsohn[1]

[1]Columbia University, [2]National Institute for Medical Research, [3]Indiana University

Urogenital tract malformations are among the most common birth defects in humans, often affecting multiple aspects of kidney and ureter formation, however the underlying cause of these complex abnormalities is not well understood. More than 60 years ago studies in rodents demonstrated that maternal vitamin A was required for formation of most fetal organs and tissues, including the urogenital tract, where vitamin A deficiency induced a spectrum of abnormalities similar to those seen in humans including renal hypoplasia and mal-positioned distal ureters, that instead of joining the bladder joined the urethra or sex ducts (Wilson, 1948). We have generated mouse models of vitamin A deficiency by inactivating retinoic acid receptors (Rars); transcription factors that mediate vitamin A signaling. Deletion of two *Rar* family members, *Rara* and *Rarb2* resulted in vitamin A deficiency-like malformations with nearly 100% penetrance, including renal hypoplasia, mal-positioned distal ureters, hydronephrosis and mega-ureter, (Mendelsohn et al., 1994) providing a model system to study normal and abnormal ureter morphogenesis.

Our previous studies showed that renal hypoplasia in *Rarab2-* mice could be rescued by forced expression of *ret* (Batourina et al., 2001) a receptor tyrosine kinase required for formation of the ureter and for it's subsequent growth and branching in the embryonic kidney (Schuchardt et al., 1996). Here we show that expression of *ret* in the Wolffian ducts of *Rarab2-* mutants can genetically rescue ureter abnormalities, restoring distal ureters to their normal integration site in the bladder, also eliminating mega-ureter and hydronephrosis. *ret* function is required for epithelial remodeling at several stages of urogenital tract development, during primary ureter formation and during branching morphogenesis of the intra-renal ureter (Schuchardt et al., 1996). Here we show that ureter morphogenesis also depends on *ret*, and that vitamin A is important for *ret* expression in epithelial cells at the base of the Wolffian ducts that undergo remodeling as distal ureters establish mature connections with the bladder. The pleiotropic nature of urogenital tract malformations in humans has puzzled scientists for many years. Our studies suggest that such complex urogenital tract syndromes can be caused by disruption of genetic pathways such as vitamin A and *ret*, that control multiple events during kidney and ureter morphogenesis.

References:

1. Batourina, E. et al. (2001). Vitamin A controls epithelial/ mesenchymal interactions through Ret expression. Nat Genet 27, 74-8.

2. Frazer, J.E. (1935). The terminal part of the Wolffian duct. Journal of Anatomy 69, 455-468.

3. Mackie, G. G., and Stephens, F. D. (1975). Duplex kidneys: a correlation of renal dysplasia with position of the ureteral orifice, J Urol 114, 274-80.

4. Mendelsohn, C., Lohnes, D., Decimo, D., Lufkin, T., LeMeur, M., Chambon, P., and Mark, M. (1994). Function of the retinoic acid receptors (RARs) during development (II). Multiple abnormalities at various stages of organogenesis in RAR double mutants, Development 120, 2749-71.

5. Pope, J.C.t., Brock, J.W., 3rd, Adams, M.C., Stephens, F.D. & Ichikawa, I. (1999). How they begin and how they end: classic and new theories for the development and deterioration of congenital anomalies of the kidney and urinary tract, CAKUT. J Am Soc Nephrol 10, 2018-28.

6. Schuchardt, A., D'Agati, V., Pachnis, V. & Costantini, F. (1996). Renal agenesis and hypodysplasia in ret-k- mutant mice result from defects in ureteric bud development. Development 122, 1919-29.

7. Srinivas, S., Wu, Z., Chen, C.M., D'Agati, V. & Costantini, F. (1999). Dominant effects of RET receptor misexpression and ligand-independent RET signaling on ureteric bud development. Development 126, 1375-86.

8. Wilson, J. G. a. W., J. (1948). Malformations in the genito-urinary tract induced by maternal vitamin A deficiency in the rat. Am J Anat 83, 357-407.

9. Wilson, J.G., Roth, C.V. and Warkany, J. (1953). An analysis of the syndrome of malformations induced by maternal vitamin A deficiency. Effects of restoration of vitamin A at various times during gestation. Am J. Anat. 92, 189-217.

Soluble factors in ureteric bud development

Hiroyuki Sakurai, Kevin T. Bush, and Sanjay K. Nigam
University of California at San Diego

Mammalian kidneys are formed through interaction of two components: the epithelial ureteric bud (UB) and the metanephric mesenchyme (MM). The MM directs the UB to undergo multiple branching events to form collecting system. However, the nature of this MM derived signal has been elusive. When cells derived from the mouse UB are cultured in the extracellular matrix gels in the presence of conditioned medium elaborated by MM-derived cells (BSN-CM), the UB cells form branching tubules (1), suggesting that soluble factors are critical in this process. Furthermore, using an isolated UB culture system, we have shown that a combination of soluble factors including glial cell derived neurotrophic factor (GDNF) and BSN-CM is capable of inducing branching morphogenesis of the UB (2). Recently we have successfully isolated a morphogenetic molecule, pleiotrophin (PTN) from BSN-CM (3). Purified PTN has been shown to induce isolated UB branching morphogenesis in the presence of GDNF. Fibroblast growth factors play facilitory role in this in vitro process (4). Taken together, we hypothesize that interplay of multiple soluble factors regulates UB branching morphogenesis.

References:

1. Sakurai H, Barros EJ, Tsukamoto T, Barasch J, Nigam SK. (1997) An in vitro tubulogenesis system using cell lines derived from embryonic kidney shows dependence on multiple soluble growth factors. Proc. Natl. Acad. Sci. USA 94:6279-6284.

2. Qiao J, Sakurai H, Nigam SK (1999) Branching morphogenesis independent of mesenchymal-epithelial contact in the developing kidney. Proc. Natl. Acad. Sci. USA 96:7330-7335.

3. Sakurai H, Bush KT, Nigam SK. (2001) Identification of pleiotrophin as a mesenchymal factor involved in ureteric bud branching morphogenesis. Development, 128:3283-3293.

4. Qiao J, Bush KT, Steer DL, Stuart RO, Sakurai H, Nigam SK. (2001) Multiple fibroblast growth factors support growth of the ureteric bud but have different effects on branching morphogenesis. Mech. Dev. 109:123-135.

Low obstructive uropathies and nephrogenesis: quantitative evaluation in human and lamb fetus

B. Gasser, V. Lindner, L. Bussières, Mauss Y, K Laborde , JM Vetter
Institut de Pathologie, France

The state of the nephrogenic blastema (NB) and the number of glomeruli (GN) were quan-tified on frontal renal section in 99 control fetuses (9 - 40 weeks), in 42 aborted human fetuses with low urinary tract obstruction (14 - 36 weeks), in 52control fetal lambs (50 - 140 days), in two groups of 12 fetal lambs studied at 120 days (term:140 days) respectively obstructed at 60 and 80 days (urachal and urethral ligation). In controls, GN increase ended by the 32nd week (110 days in lamb) as a consequence of NB disappearance. About 16 lamb kidneys (50 - 140 days), the loga-rithms of GN on frontal sections and GN determined in the whole renal volume (dissector method and Cavalieri principle) were found to be linearly related (r = 0.99)

In human uropathy group, the renal changes showed a wide range of severity accounted for by the impairment of both NB and GN. From GN used as a time-dependent marker, the most severe kidney changes likely resulted from the earliest obstruction. These data were consistent with previous experimental studies and confirmed in our model. Obstructions created at 60 and 80 days respectively led to a significantly decreased GN and a normal GN at 120 days. The total or partial untimely disappearance of NB was the most striking feature observed in the human uropathy group.

To study the initial steps in obstructive nephropathies, cell proliferation rate was evaluated in two study groups: 7 human fetuses showing hydronephrosis and persistent blastema (14 -30 weeks), 13 fetal lambs obstructed at 60 days and studied after a 2 to 30 days duration of obstruc-tion. Cell proliferation rates in blastema were significantly decreased in human group and in lamb group when the obstruction duration reaches 30 days.

Those data led us to the followings: the initial step of obstructive nephropathies responds to a disease of the nephrogenic blastema on which renal development depends entirely. The time of the obstruction onset is undoubtedly the most important determinant of severity: the earlier obstruction occurs, the more disturbed the development of the fetal kidney.

Nephron Heterogeneity and Progression of Obstructive Nephropathy

R. L. Chevalier
University of Virginia

As a result of even temporary urinary tract obstruction during renal development, renal mass is lost. One month following relief of complete unilateral ureteral obstruction (UUO) in the neonatal rat, the renal interstitium is abnormal, with collagen deposition and expression of a-smooth muscle actin by fibroblasts. Despite this, GFR is normal. However, a year following relief of obstruction, GFR has decreased by 80%, and there is focal glomerular sclerosis, with scattered tubular atrophy. Partial UUO in the neonatal rat results in similar, but less severe changes. Severe partial UUO in the neonatal guinea pig leads to the formation of two nephron populations: one with normal nephron GFR and tubular fluid flow rates, and another comprising dilated tubules with markedly prolonged flow rates and reduced GFR. In addition to this internephron heterogeneity, there is marked tubular segmental heterogeneity that varies with species and impacts on the natural history of the lesion. Tubular expression of osteopontin (which is enhanced by UUO) is localized to the descending limb of Henle in the rat, but to the ascending limb in the mouse and human. Interstitial macrophage infiltration in the obstructed neonatal kidney is attenuated in mice with deficient expression of selectins, which in turn reduces tubular atrophy and interstitial fibrosis. Following chronic UUO in the neonatal mouse, there is severe dilatation of the collecting duct and distal tubule, but minimal dilatation of the proximal tubule. Such segmental heterogeneity can be demonstrated even after obstruction of single nephrons, with interstitial fibrosis being localized around the most dilated segments. Chronic UUO in the neonatal rat leads to marked heterogeneity of renin expression by afferent arterioles: the increased renin production, in turn, leads to preglomerular vasoconstriction. Proximal tubular cells in some nephrons of the obstructed kidney undergo necrosis, while cells of dilated collecting ducts undergo apoptosis. The patchy distribution of apoptotic tubular cells may result at least in part from the heterogeneous distribution of antiapoptotic factors, such as bcl-2 and clusterin. An improved knowledge of the factors regulating tubular and interstitial damage in the obstructed developing kidney may lead to new approaches to protect a greater proportion of the nephrons, thereby limiting the long-term progression of congenital obstructive nephropathy.

Continued from Previous Page

References:

1. Cachat, F., Chang, A. Y., Thornhill, B. A., and Chevalier, R. L. Renal tubular apoptosis and proliferation are regulated by tubular dilation resulting from neonatal ureteral obstruction. J.Am.Soc.Nephol. 12, 673A. 2001.

2. Chevalier, R. L. Chronic partial ureteral obstruction in the neonatal guinea pig II: pressure gradients affecting glomerular filtration rate. Pediat Res 18: 1271-1277, 1984.

3. Chevalier, R. L., K. H. Chung, C. D. Smith, M. Ficenec, and R. A. Gomez. Renal apoptosis and clusterin following ureteral obstruction: the role of maturation. J.Urol. 156: 1474-1479, 1996.

4. Chevalier, R. L., A. Kim, B. A. Thornhill, and J. T. Wolstenholme. Recovery following relief of unilateral ureteral obstruction in the neonatal rat. Kidney Int. 55: 793-807, 1999.

5. Chevalier, R. L., C. D. Smith, J. T. Wolstenholme, S. Krajewski, and J. C. Reed. Chronic ureteral obstruction in the rat suppresses renal tubular bcl-2 and stimulates apoptosis. Exp.Nephrol. 8: 115-122, 1999.

6. Chevalier, R. L., B. A. Thornhill, and A. Y. Chang. Unilateral ureteral obstruction in neonatal rats leads to renal insufficiency in adulthood. Kidney Int. 58: 1987-1995, 2000.

7. Chevalier, R. L., B. A. Thornhill, A. Y. Chang, F. Cachat, and A. Lackey. Recovery from release of ureteral obstruction in the rat: Relationship to neprhogenesis. Kidney Int. (in press): 2002.

8. Claesson, G., L. Svensson, B. Robertson, S. Josephson, and T. Cederlund. Experimental obstructive hydronephrosis in newborn rats. XI. A one-year follow-up study of renal function and morphology. J.Urol. 142: 1602-1607, 1989.

9. Lange-Sperandio, B., F. Cachat, B. A. Thornhill, and R. L. Chevalier. Selectins mediate macrophage infiltration in obstructive nephropathy in newborn mice. Kidney Int. 61: 516-524, 2002.

10. Stenberg, A., E. Jacobsson, E. Larsson, and A. E. G. Persson. Long-term partial ureteral obstruction and its effects on kidney function. Scand.J.Urol.Nephrol. 26: 35-41, 1992.

Regulation of Interstitial Fibrosis

Diane Felsen
Weill Medical College of Cornell University

Interstitial fibrosis is a hallmark of ureteral obstruction. This phenomenon has been studied extensively in experimental models of obstruction in mature animals. Much less is known about interstitial fibrosis in congenital or postnatal obstruction. Interstitial fibrosis is the result of an increased deposition of, and decreased degradation of, extracellular matrix [ECM]. Resident renal fibroblasts synthesize ECM; however, there is increasing evidence that activated fibroblasts [those displaying - smooth muscle actin expression] or fibroblasts resulting from renal epithelial-mesenchymal transformation may also contribute to increased ECM production. The role of infiltrating macrophages in fibrosis is controversial. The synthesis of ECM is under the control of various cytokines. A major pro-fibrotic cytokine is transforming growth factor- [TGF-], which has also been implicated in epithelial-mesenchymal transformation. Expression of TGF- is increased in ureteral obstruction. Decreasing expression of TGF- using antisense oligonucleotides, or blockade of TGF- with a monoclonal antibody, has been shown to decrease interstitial fibrosis in ureteral obstruction. Pharmacological interference with the angiotensin II pathway decreases fibrosis in obstruction. Decreased TGF- expression accompanies angiotensin II blockade , suggesting the importance of TGF- in multiple pathways of fibrosis. Conversely, nitric oxide [NO] has been shown to be anti-fibrotic in ureteral obstruction, as demonstrated both by pharmacological or by targeted gene deletion studies. Over the past several years there has been an increase in the number of reports on decreasing fibrosis in ureteral obstruction. The investigators have used a variety of techniques to implicate a number of substances including ICAM-1, osteopontin, tumor necrosis factor, cyclin kinase inhibitors, fas receptor, platelet derived growth factor, and epidermal growth factor in fibrosis. The challenges to investigators include understanding the processes which govern cell transformation in the obstructed kidney, the role of these cells in fibrosis and the importance and interaction of the multiple factors so far implicated in the fibrosis of ureteral obstruction. Finally, the contribution of interstitial fibrosis to the decreased function of the obstructed kidney remains to be elucidated.

Compensatory Fetal Renal Growth

Craig A. Peters
Harvard Medical School

Evidence:

It has long been an established "truth" that compensatory renal growth (CRG) did not occur in utero. The most definitive report was that of Griscom, et al., using neonatal IVP evidence that solitary kidneys were not larger than paired kidneys, but subsequently demonstrated rapid accelerated growth. With prenatal ultrasound imaging, the solitary fetal kidney has been closely followed and several reports have shown these kidneys to have greater growth than normal paired kidneys.[1-3] This has been indexed to somatic growth as well. Early studies in the fetal rat examined this question.[4] Early fetal sheep studies hinted at the possibility with acute changes in DNA and RNA.[5] Recent work in the ovine fetus has confirmed CRG after fetal nephrectomy and demonstrated increased nephron number (45% increase).[6] Fetal rabbit uninephrectomy has been reported to induce increased renal growth.[7] In the context of obstruction, this has been demonstrated with contralateral compensatory growth when the obstructed kidney was severely growth impaired.[8] The pattern of growth suggested one of predominantly hyperplasia with increased total renal DNA. The total renal mass of the obstructed and contralateral kidney equaled that of two normal kidneys. Glomerular number (by morphometry) was not increased in the contralateral kidney, despite reduction in glomerular number in the obstructed kidney. Unilateral fetal nephrectomy at 60 days gestation (0.45 total) demonstrated similar rapid compensatory growth of the remnant kidney, again with the total remaining renal mass being equal to two paired kidneys. Attempts at identifying specific growth factors responsible for these alterations have not been fruitful to date. It is clear that fetal compensatory renal growth occurs in the setting of solitary functional kidney or when one kidney is poorly functioning or dysplastic.

There is some evidence of compensatory fetal renal growth as part of a feedback loop with lung growth. These observations have been made in animal and human studies with diaphragmatic hernia in which small lungs are associated with larger kidneys. The specific nature of this growth regulatory system remains undefined.[9-11]

Significance:

The fascination with compensatory renal growth is very old and there is an enormous body of literature regarding postnatal CRG.[12] However, there is very little data regarding fetal CRG. Growth regulation of organs such as the kidney is extremely important in terms of both enhancing understanding of the means by which growth of all organs is regulated, as well as potentially offering means by which growth may be therapeutically controlled, either to enhance inadequate growth, or to inhibit abnormal growth, as in neoplasia.[13] In the kidney, if certain processes can induce an increase in the rate of glomerulogenesis, perhaps this may be turned to enhance development of kidneys with impaired nephrogenesis. The occurrence of CRG indicates that the development of one kidney is dependent upon the presence of the other and that there are mechanisms of communication between the two. This "cross-talk" should be able to be interpreted, thereby providing potentially valuable information regarding the condi-

Continued from Previous Page

tion of the abnormal and the remnant kidney. This may facilitate diagnosis of the "ailing" kidney before irreversible damage has occurred.

Research Directions:

The descriptive work of fetal CRG has been well established, and the mechanisms need to be worked out. This can be difficult in large animal systems, although there is potential. Initially description of the specific patterns of change of growth regulating factors should be undertaken, with particular emphasis on mapping the location of these changes within the nephron. The use of knockout technology to test the functional relevance of putative CRG-inducers is a logical further step. The complex regulatory system of renal vascularity, the renin-angiotensin system, as well as renal innervation are likely candidates as determinants of CRG in utero. The intuitive appeal of CRG as a biological phenomenon remains as a renal "call for help" in the obstructed kidney, and as a key process, by which kidneys and tissue sin general respond to growth stimuli in specific conditions.

References:

1. Glazebrook, K.N., F.P. McGrath, and B.T. Steele, Prenatal compensatory renal growth: documentation with US. Radiology, 1993. 189(3): p. 733-5.

2. Hartshorne, N., T. Shepard, and M. Barr, Jr., Compensatory renal growth in human fetuses with unilateral renal agenesis. Teratology, 1991. 44(1): p. 7-10.

3. Mandell, J., et al., Human fetal compensatory renal growth. J Urol, 1993. 150(2 Pt 2): p. 790-2.

4. Goss, R.J. and M.J. Walker, Compensatory renal hypertrophy in fetal rats. J Urol, 1971. 106(3): p. 360-2.

5. Moore, E.S., et al., Compensatory renal hypertrophy in fetal lambs. Pediatr Res, 1979. 13(10): p. 1125-8.

6. Douglas-Denton, R., et al., Compensatory renal growth after unilateral nephrectomy in the ovine fetus. J Am Soc Nephrol, 2002. 13(2): p. 406-10.

7. Abellan, M.C., et al., Compensatory renal growth post fetal nephrectomy in the rabbit. Eur J Pediatr Surg, 1997. 7(5): p. 282-5.

8. Peters, C.A., et al., Fetal compensatory renal growth due to unilateral ureteral obstruction. J Urol, 1993. 150(2 Pt 2): p. 597-600.

9. Glick, P.L., J.R. Siebert, and D.R. Benjamin, Pathophysiology of congenital diaphragmatic hernia: I. Renal enlargement suggests feedback modulation by pulmonary derived renotropins--a unifying hypothesis to explain pulmonary hypoplasia, polyhydramnios, and renal enlargement in the fetus/newborn with congenital diaphragmatic hernia. J Pediatr Surg, 1990. 25(5): p. 492-5.

10. Glick, P.L., J.R. Siebert, and D.R. Benjamin, Possible trophic relationship between the growth of the lungs and kidneys in congenital diaphragmatic hernia (CDH) [letter; comment]. J Pediatr Surg, 1991. 26(5): p. 643-4.

11. Hosoda, Y., J.E. Rossman, and P.L. Glick, Pathophysiology of congenital diaphragmatic hernia. IV: Renal hyperplasia is associated with pulmonary hypoplasia. J Pediatr Surg, 1993. 28(3): p. 464-9; discussion 469-70.

12. Fine, L., The biology of renal hypertrophy. Kidney Int, 1986. 29: p. 619-634.

13. Kushner, L., et al., Expression of a Wilms tumor gene in porcine kidney during compensatory renal growth. J Urol, 1992. 148(2 Pt 2): p. 555-8.

Research Needs: Pathophysiology of Congenital Hydronephrosis

R. L. Chevalier
University of Virginia

Advances in our understanding of the pathophysiology of congenital hydronephrosis will depend on progress on a number of important fronts. On the most basic level, we need to better understand the genetics, cellular, and molecular mechanisms of regulation of normal and adaptive renal growth and development. More specifically, we need to identify the determinants of the obstructive lesions in the upper and lower tract: genes and signals. The impact of obstruction on the development of the renal pelvis, ureters, and bladder must also be clarified.

We need to define the stimuli that initiate the renal cellular responses to obstruction (pressure, stretch), and the physiologic responses (changes in blood flow, GFR, and tubular fluid flow). Some studies suggest that developing glomeruli are particularly susceptible to injury from chronic obstruction. The tubules appear to play a major role in the response: an improved understanding is needed of the epithelial cell signal transduction of obstructed nephrons, and factors mediating cell survival and cell death. Attention must be focused on the unique characteristics of each tubular segment, its differentiation, and its response to obstruction. The tubular response is intertwined with the interstitial response that involves an inflammatory infiltrate and increased deposition of extracellular matrix. The response of the microcirculation (peritubular capillaries) also needs to be investigated.

What factors regulate the number of surviving nephrons: events taking place during or after nephrogenesis? The renal metabolic environment (which is compartmentalized) also needs to be addressed: ischemia, hypoxia, generation of reactive oxygen species, all play a role. While much attention has been paid to activation of the renin-angiotensin system, major gaps remain in sphingolipid, nitric oxide, and prostanoid signaling.

More information is needed regarding the impact of the fetal environment on the renal response to urinary tract obstruction, and of the relationship of the timing of obstruction in the sequence of renal development and maturation. The long-term outcome of congenital urinary tract obstruction depends on the number of remaining functional nephrons, and anatomic integrity of the vasculature, glomeruli, tubules, and interstitium. Animal models must be selected to answer specific questions that relate to clinical congenital obstructive nephropathy. Fetal models can be helpful in defining the role of the intrauterine environment; rodent models are useful in defining the role of specific genes; porcine and primate models may best approximate human renal development. These approaches will need to be coordinated with clinical studies as well as *in vitro* studies, with the goal of prevention of urinary tract maldevelopment, as well as improving the outcome of affected infants and children.

Research Needs: Diagnostic Approach in Congenital Hydronephrosis

Craig A. Peters
Harvard Medical School

In order to develop an appropriate methodology to evaluate children with variations of congenital obstructive nephron-uropathy, three key criteria need to be satisfied, and future research into this area should be guided in these directions. Any diagnostic evaluation must be first correlated with clinically relevant outcomes; second, it would reflect the affected kidney(s) in terms of its functional development; third it must be clinically practical.

Correlation with outcomes:
While this may seem self-evident, it is often either over-looked or assumed. This sort of correlation may require long-term studies, but may be linked to shorter-term indicators of the progression of renal development. They will need to be relevant to the patient as well, in that a measure of some element of kidney function that has not been associated with an actual or potential clinically deleterious outcome, cannot be a very useful parameter. There will also need to be some assessment of risk involved to permit realistic decision-making. The impact of testing will need to be incorporated into this assessment, including both medical and psychological factors.

Assess the affected kidney in terms of its functional development:
The best way to evaluate the effect of COU on the patient is to assess its effect on the obstructed kidney(s). This is in contrast to simply measuring the rate of washout of a tracer. This evaluation will be dependent upon a more detailed and mechanistic understanding of the pathophysiology of COU, from which appropriate mediators of this process can be examined. This may be possible in several ways. Direct evaluation of the renal tissue through biopsy may be possible with minimal risk and assessment of histology, patterns of protein and gene expression or levels of particular structural constituent of the kidney may be performed. The urine from the affected kidney may be assessed, either directly or mixed in the bladder, to seek markers of the pathological response to obstruction, including growth factors, inflammatory mediators, elements of the renin-angiotensin system, or aspects of renal fibrosis. Humoral factors involved in inter-renal cross-talk, or elements of the RAS may be measured in the serum. While measurement of clearances of one kidney (in unilateral disease) is not usually useful due to contralateral compensation, measuring signaling factors may have specific predictive potential. Pharmacological modulation of readily measurable aspects of renal function may be able to elicit different responses in the kidney at risk for functional impairment, such as seen with captopril renography.

Continued from Previous Page

Clinically practical:
Any diagnostic test must be practical from a clinical standpoint, and potentially permit multiple repeat testings to assess the change over time. This latter element may be very important as an element of any parameter used in diagnosis since the alteration over time may be of great significance. The testing must not be so onerous to induce fear of further testing.

As our understanding of the pathophysiological mechanisms of congenital obstructive nephropathy improves, so should out ability to identify kidneys and thereby patients at risk of renal functional impairment who might benefit from some form of intervention. If these potential diagnostic strategies can be correlated with outcomes, made to reflect the responses of the affected kidney(s), and be clinically practical, more specific assessments of this challenging group of patients will be possible.

Research Needs: Long-Term Outcomes of Congenital Hydronephrosis

Jack S. Elder
Case Western Reserve University School of Medicine

Critical to any treatment approach is the outcome assessment. Outcomes may be analyzed according to intermediate outcomes, health outcomes, harms of medical therapy, and risks of surgical therapy, taking into consideration patient (family) preferences. Each disorder that causes congenital hydronephrosis has its unique set of potential health consequences. It is imperative that the reliability of diuretic renography in neonates and infants with hydronephrosis be verified. It is important that unfavorable as well as favorable outcomes are reported. Factors that predict favorable or unfavorable renal outcome should be identified. The efficacy of fetal therapy as well as postnatal therapy must be analyzed. Consideration should be given to technological changes in patient assessment (e.g., newer radiologic studies), newer medications, and the development of minimally invasive surgical techniques.

Intermediate outcomes are those that are not perceived by the patient or family but that are associated with or precede health outcomes. These outcomes would include hydronephrosis grade, renal growth, renal scarring, differential renal function, half-time of clearance of radiopharmaceutical, overall renal function, renal hyperfiltration and histopathologic changes in the kidney.

Health outcomes are effects directly perceived in some way by the patient or family. Some can be measured objectively, whereas others require subjective assessment. Health outcomes would include need for a single or multiple operative procedures, pyelonephritis, cystitis, abdominal/flank pain, necessity for taking prophylactic medication, stone disease, hypertension, uremia, incontinence, reduced somatic growth, risk of renal injury from trauma, need for continued surveillance testing, anxiety of unresolved condition, cost of medical care and death.

Harms of medical therapy include adverse drug reactions of prophylactic antimicrobials and medications that affect bladder or renal function, need for hospitalization and adverse effects of surveillance testing (radiologic, serum and urine studies).

Risks of surgical therapy include iatrogenic obstructive uropathy; bleeding/necessity for blood transfusion; infection; pain; hospitalization; renal, ureteral, bladder, or urethral injury; anesthesia risk; injury to adjacent organs; urinary leak; need for secondary surgical procedure; and adverse effects of follow-up surveillance testing (radiologic, serum and urine studies).

Continued from Previous Page

References:

1. Cooper CS et al: Long-term followup of endoscopic incision of ureteroceles: intravesical versus extravesical. J Urol 164: 1097-1100, 2000.

2. Elder JS, et al: Pediatric vesicoureteral reflux guidelines panel summary report on the management of primary vesicoureteral reflux in children. J Urol 157: 1846-1851, 1997.

3. Farhat W, et al: The natural history of neonatal vesicoureteral reflux associated with antenatal hydronephrosis. J Urol 164: 1057-1060, 2000.

4. Horowitz M, et al: Laparoscopic partial upper pole nephrectomy in infants and children. BJU International 87: 514-516, 2001.

5. Husmann DA, et al: Is endoscopic decompression of the neonatal extravesical upper pole ureterocele necessary for prevention of urinary tract infections or bladder neck obstruction? J Urol 167: 1440-1442, 2002.

6. Husmann D, et al: Management of ectopic ureterocele associated with renal duplication: a comparison of partial nephrectomy and endoscopic decompression. J Urol 162: 1406-1409, 1999.

7. Palmer LS, et al: Surgery versus observation managing obstructive grade 3 to 4 unilateral hydronephrosis: a report from the Society for Fetal Urology. J Urol 159: 222-228, 1998.

8. Takla NV, et al: Apparent unilateral ureteropelvic junction obstruction in the newborn: expectations for resolution. J Urol 160: 2175-2178, 1998.

9. Ulman I, et al: The long-term followup of newborns with severe unilateral hydronephrosis initially treated nonoperatively. J Urol 164: 1101-1105, 2000.

10. Yeung CK, et al: Retroperitoneoscopic dismembered pyeloplasty for pelvi-ureteric obstruction in infants and children. BJU International 87: 509-513, 2001.

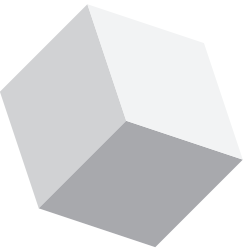
11. Woolf SH: The logic and limits of shared decision making. J Urol 166: 244-245. 2001.

Research Needs in Congenital Urinary Tract Obstruction: Clinical Trials

James C M Chan
Virginia Commonwealth University

In a complex, multi-centered, randomized clinical trial (RO1 DK 31370) to study growth failure in children with chronic kidney insufficiency: 71% of the children had obstructive uropathy as the primary diagnosis and 20% had kidney dysphasia/hypoplasia. Prevention and reversal of unrelenting progression to end-stage kidney disease following release of urinary tract obstruction need to be the focus of our research efforts.

Clinical trials to delineate the best strategy in ameliorating the post-obstructive proliferation, apoptosis and tubulointerstitial fibrosis, the glomerular hyperfiltration, oxidative stress and other pathways of injury and progression are needed. The child's rapid growth and changing kidney functions compound clinical trials in pediatrics. These considerations unique to pediatric studies will need to be explored.



POSTER ABSTRACTS

Renal Tubular Apoptosis and Proliferation are Regulated by Tubular Dilatation Resulting from Neonatal Ureteral Obstruction

F. Cachat, B.A. Thornhill, R.L. Chevalier
University of Virginia

Unilateral ureteral obstruction (UUO) markedly stimulates renal tubular apoptosis, leading to tubular atrophy. Because of the heterogeneous tubular response to injury, we wished to determine the cellular response of each tubular segment following UUO. Neonatal mice were subjected to UUO or sham-operation, and kidneys were harvested 5, 12 or 19 days after surgery. Proximal tubules (PT), distal tubules (DT) and collecting ducts (CD) were identified with specific lectins. Cellular necrosis, apoptosis, proliferation, tubular basement membrane (TBM) thickening, tubular dilatation, and interstitial collagen were quantitated by histomorphometry.

Following 12 days, UUO induced tubular necrosis in the PT, and apoptosis in the DT and CD. Tubular dilatation in the obstructed kidney was most severe in CD and least severe in PT. There was a significant correlation between tubular cell apoptosis and tubular dilatation ($r = 0.9$, $P < 0.05$). UUO stimulated tubular proliferation, which was most abundant in the PT, and almost absent in the DT and the CD. Following 19 days of UUO, the number of tubules was decreased by 60% ($p<0.05$). Fibrosis was restricted to the medullary area, and CD dilatation correlated with surrounding fibrosis ($r = 0.7$, $P < 0.001$). The percentage of tubules with an abnormal thickened TBM was greatest in the PT and peaked after 12 days of obstruction (62.30±6.37%), when compared with DT (41.79±6.28%) or CD (19.29±4.76%) ($p<0.05$).

In summary, following UUO, necrosis predominates in the PT, while apoptosis predominates in the dilated DT and CD, and is correlated with the severity of tubular dilatation. Interstitial fibrosis is restricted to the medulla. We speculate that the interplay of hemodynamics and the phenotypic characteristics of each tubular segment account for the predominance of necrosis in the PT, and of apoptosis in the CD: ischemic injury predominates in the PT, and stretch-induced apoptosis in the CD. As a result of stretching, a loss of cell-cell or cell-matrix interaction in DT and CD may provide a stimulus for apoptosis.

Stretch Activated Contraction in the Bladder:
A Path For Treating Congenital Outlet Obstruction Induced Hydronephrosis

Gregory E. Dean, John Rodgers, Stacy Heimburger,
Mark R. Zaontz, and Michael G. Packer

Introduction:

Congenital bladder outlet obstruction, most notably posterior urethral valves, has the potential for resulting in life threatening renal impairment with associated hydronephrosis. Renal damage occurs not only from the initial outlet obstruction but also from the elevated storage pressures which arise as the result of impaired compliance in the hypertrophied bladder. The normal fetal bladder has been noted to exhibit impaired compliance. Initial evidence supported the hypothesis that elevated Type III/ Type I collagen ratios were responsible. However, it was subsequently demonstrated that it is the response of bladder smooth muscle to stretch, rather than changes in the extracellular matrix, which are responsible for this impaired compliance. [1] We have subsequently focused on potential treatment strategies employing pharmacologic agents which modulate stretch-activated contraction. A spinal cord injured rat model was employed with the resultant sphincteric dysynergia providing a functional bladder outlet obstruction. The potassium channel opener Pinacidil was used to treat these animals. In vitro experiments were also performed examining the role of the calcium channel blocker Diltiazem

Materials and Methods:

Six month old male Sprague-Dawley rats underwent spinal cord transaction at T8-T10. At the time of spinal cord transection an Alzet model 2ML4 osmotic pump (Alza Corp., Palo Alto, CA.) was inserted subcutaneously to deliver medication over a thirty-day period. After spinal cord injury, the rats underwent twice daily bladder massage. Rats were placed into two groups, those getting Pinacidil 0.2 mg/day, and sham rats receiving only the vehicle (50% DMSO in sterile water). The animals were sacrificed at 4 weeks, at which time their bladders were harvested, weighed, and subjected to length-tension studies. For the length-tension study the strips were suspended in Krebs solution and attached by silk suture to a force transducer model FT 03 (Grass Instruments, Quincy, MA). Ninety five percent oxygen with 5% carbon dioxide bubbled through the baths. Using a low level DC amplifier, a model 7D polygraph (Grass Instruments, Quincy, MA), and CyberSense CyQ 508 A to D converter (CyberSense Inc., Nicholasville, KY) length-tension curves were obtained after equilibration and 75% prestretch. In vitro experiments using Diltiazem were also performed. SCI rats underwent transection of the spinal cord at T11/T12. Strips were incubated in Diltiazem at 0.25_g/ml, 2.5_g/ml, and 25_g/ml, at 37° C for 15 minutes and length tension studies were performed as above.

Stretch Activated Contraction in the Bladder:
A Path For Treating Congenital Outlet Obstruction Induced Hydronephrosis

Continued from Previous Page

Results:

The bladders of the rats receiving Pinacidil were significantly less hypertrophied than those of the sham rats (P = 0.024). The average masses of the bladders of the SCI rats without Pinacidil, SCI rats with Pinacidil, and normal rats were 0.973 g, 0.288 g, and 0.124 g respectively. The difference in masses between the rats receiving Pinacidil and normal rats did not reach statistical significance (P = 0.116). In regard to the length-tension studies, the difference between the bladders treated with Pinacidil and the sham bladders neared significance (P = 0.085). At a relative length of two, the average tensions for the Pinacidil and sham groups respectively were 1337.1 g/cm2 and 1830.4 g/cm2. These same length-tension studies demonstrated a significant difference between the non-treated SCI bladders compared to normals (P=0.002)
The diltiazem studies were performed with direct incubation of SCI bladder strips rather than through the osmotic pump delivery system. We noted a dose dependent improvement in compliance ($p<0.05$) in SCI bladder following exposure to all concentrations and all stretch ratios. The average decrease in force at a stretch ratio of 1.6 was 40% at 0.25 _g/ml, 60% at 2.5 _g/ml and 80% at 25 _g/ml. An opposite effect was noted in normal bladder with a dose dependent decrease in compliance that approached statistical significance (p=0.09) at all stretch ratios for concentrations of 2.5 _g/ml and 25 _g/ml.

Discussion:

These preliminary studies suggests that the bladder hypertrophy resulting from dysynergic outlet obstruction in the rat can be ameliorated with potassium channel openers and calcium channel blockers. The decreased hypertrophy in the treated group may arise from diminished stretch activated contraction, which is a potential promoter of hypertrophy. Diminished stretch activated contraction in Diltiazem exposed SCI rat bladders was also found. These agents may have a potential application in the treatment of the poorly compliant pediatric spina bifida bladder as well as in those infants with posterior urethral valves.

[1] Dean GE, Cargill RS, Macarak E, Snyder HM, Duckett JW, Levin R: Active and passive compliance of the fetal bovine bladder. J Urol 158, 1094-1099

Primary Bladder Neck Dysfunction in Children:
Results of Treatment with Alpha-adrenergic Antagonists

J.M. Donohoe, A.J. Combs, R. Misseri, M. Horowitz and K.I. Glassberg
SUNY Downstate, Brooklyn, NY

Introduction and objectives:
Primary bladder neck dysfunction (PBND) is characterized by abnormal average flow (Qavg) and maximum flow (Qmax) rates in the absence of anatomic obstruction, as well as abnormal funneling of the bladder neck on fluoroscopy. Lag time, defined as the time between the start of a voluntary detrusor contraction and the start of urinary stream, is prolonged in these patients. Alpha-adrenergic antagonists have proven effective in adults with this condition. We sought to determine the clinical efficacy of alpha-blockers in children with PBND by comparing their flow rates and their lag times both prior to and after initiation of treatment.

Materials and Methods:
We have identified a subset of twenty-seven pediatric patients with voiding dysfunction who have been diagnosed with primary bladder neck dysfunction (PBND) based on clinical presentation, videourodynamic studies and uroflowmetry. Eighteen of these children, 14 boys and 4 girls, underwent treatment with alpha-adrenergic antagonists. Dosage is based on age, stature and weight. Follow-up uroflow/electromyography (flow/EMG) was used to determine the Qavg, Qmax and lag time. Children with associated anatomical anomalies, known neurologic conditions and abnormal external sphincter activity were excluded from the study.

Results:
A total of 18 children, ages 8 to 23 years (mean 14.5) are currently being treated with alpha-adrenergic antagonists for PBND. Re-evaluation with flow/EMG was performed at a minimum of 4-weeks after starting medication. Mean follow-up is 14.7 months. Mean pre- and post- therapy Qavg were 5.4 ml/sec and 10.0 ml/sec ($P< 0.05$), respectively. Mean pre- and post- therapy Qmax were 10.5 ml/sec and 17.2 ml/sec ($P< 0.05$), respectively. Pre- and post-therapy lag times improved from 41.9 sec to 13.4 sec ($P= 0.14$) after initiation of therapy. All of the children have experienced varying degrees of symptomatic improvement. No adverse side effects were noted secondary to alpha-blocker therapy.

Conclusion:
We conclude that alpha blocker therapy is a safe and effective treatment for PBND in children.

When Can Persistent Hydroureteronephrosis in Posterior Urethral Valve Patients be Considered Residual Stretching?

J.M. Donohoe, R.P. Weinstein, A.J. Combs, D. Schulsinger, R. Misseri, M. Horowitz and K.I. Glassberg
SUNY Downstate, Brooklyn, NY

Objectives:
To determine the incidence of abnormal urodynamic findings in patients with persistent hydroureteronephrosis (HUN) and the effect on the dilatation once these parameters are treated. In addition, we wanted to determine under what circiumstances persistent HUN could be considered as residual stretching.

Materials and Methods:
Twenty posterior urethral valve patients with persistent HUN in 32 renal units (RU) were identified and divided into 3 groups based on the degree of HUN: mild, moderate and severe. Videourodynamic studies (VUDS) revealed varying degrees of hypocompliance in all 20 children and all were treated aggressively. The efficacy of this intervention was monitored with renal ultrasound and VUDS. HUN was regraded and categorized as either resolved, improved or unchanged.

Results:
Of the 32-RU with persistent HUN, 8 were graded as mild, 13 as moderate and 11 as severe. Following treatment, HUN resolved in 17-RU (10 boys), improved, often dramatically, to a lower grade in 9-RU (7 boys), and exhibited no grade change in 1-RU (1 boy). Three boys, representing 5-RU, who did not comply with the regimen were noted to have neither lessening of HUN nor improvement in urodynamic parameters. In regard to urodynamic parameters in all of our treated patients, all were markedly, if not completely improved. Of the 10-RU whose HUN did not completely resolve with treatment, primary bladder neck obstruction was present in 4 boys (5-RU) and thus, in part, was likely accountable for the persistent dilatation. The remaining 4-RU with persistent, albeit decreased, HUN and the 1-RU with unchanged HUN possess no distal ureteric obstruction or persistent identifiable urodynamic abnormality. These units thus can be labeled as residual stretching. Altogether HUN either resolved or decreased in 26 of 27-RU (96.3%) of medically compliant patients after treatment of the lower tract. In those who did not take their prescribed anticholinergic medication HUN did not lessen.

Conclusion:
We believe that HUN can be accepted as residual stretching only after the presence of abnormal urodynamic parameters have been investigated for and treated once detected. Hopefully attention to persistent HUN and aggressive management of abnormal urodynamic parameters will translate into improved long-term preservation of renal function.

Growth Factor-Mediated Phosphorylation of BAD Reduces Mechanical Strain-Induced Tubule Cell Death *in vitro*

S.C. Kiley[1], B.A. Thornhill[1], S.S. Tang[2], J.R. Ingelfinger[2], R.L. Chevalier[1]
[1]*University of Virginia School of Medicine,* [2]*Harvard Medical School*

Dephosphorylation of the pro-apoptotic protein BAD promotes interaction with BclXL on the outer mitochondrial membrane to induce cytochrome C release and initiate apoptosis. To investigate the mechanism of growth factor-mediated attenuation of tubule cell apoptosis in vivo [Kidney Int 54;38, 1998 & 57;882, 2000], we used a Flexercell Strain Unit with confluent cultures of immortalized rat proximal tubule cells (IRPTC) to simulate obstruction-induced stretch injury in vitro. TUNEL-positive (apoptotic) cells increased with increasing degree of axial strain applied to IRPTC cultures and addition of epidermal growth factor (EGF) or insulin-like growth factor-1 (IGF-1) during 4 hrs of 20% axial stretch decreased apoptosis by 54% and 55%, respectively ($p < 0.001$, $n = 3$ experiments). Neutralizing antibodies directed against either growth factor or its receptor blocked attenuation of apoptosis. BAD phosphorylation decreased 50% ($p < 0.001$, $n = 3$ experiments) with stretch injury and was restored to homeostatic levels by the addition of EGF or IGF-1. Western blots of IRPTC lysates indicated that BAD phosphorylation was mediated by EGF activation of the p44/p42 mitogen-activated protein kinase (MAPK) pathway or IGF-1 activation of the phoshatidyl inositol-3 kinase/Akt pathway. MAPKK inhibitor PD98059 pre-treatment blocked EGF/MAPK-mediated BAD phosphorylation, promoted release of cytochrome C and restored apoptosis to original levels. In vivo, BAD phosphorylation decreased by 50% in 3 obstructed rat kidneys relative to 3 intact kidneys ($p < 0.01$) and EGF restored BAD phosphorylation to homeostatic levels. This suggests the same mechanism operates in vivo and in vitro to reduce tubule cell apoptosis. Since neither EGF not IGF-1 induce 3H-thymidine uptake (growth) under the in vitro assay conditions, it is the convergence of signaling pathways at BAD phosphorylation that appears to be key to the growth factor-mediated reduction in stretch-induced apoptosis.

Dynamic Contrast Enhanced MR Imaging In Children: Comparison With Ultrasound And 99m TC-DTPA Scintigraphy In The Evaluation Of Unilateral Obstructive Uropathy

AJ Kirsch, M Perez, H Scherz, B Broecker, EA Smith, S Little, D Grattan-Smith
Emory University School of Medicine, Atlanta, GA

Introduction:
A combination of nuclear medicine techniques, ultrasound, and voiding cystourethrography (VCUG) are typically used to investigate hydronephrosis in children. In order to make appropriate clinical decisions regarding intervention, urologists need to be able to distinguish the dilated, poorly draining non-obstructed system from the system that is actually obstructed. One of the major problems is that there is no gold standard to assess obstruction. By combining anatomic and functional information in one study, MRI has the potential of providing clinically useful information regarding obstruction.

Methods:
Dynamic contrast enhanced MR imaging was performed in 41 children with unilateral hydronephrosis. Forty-four dynamic contrast enhanced MR studies were performed – two children had follow-up MR urography after six months and one had a follow-up study after pyeloplasty. They were 14 girls and 27 boys - with an age range of one month to fourteen years (mean 1.4 years). The information from the various imaging modalities was compared.

Results:
The MRI protocol was acceptable to all families and well tolerated by all patients. Diagnosis was incorrect in 4 cases when only ultrasound and renal scans were used. The final diagnoses by MR urography were 16 children with UPJ obstruction, 6 with primary UVJ obstruction, 4 with dilated but not obstructed systems, 7 with duplex systems, 5 with multicystic dysplastic kidneys, 3 with unilateral small, scarred kidney, and 1 child with an antenatal diagnosis of hydronephrosis who had normal study MR urography. The morphologic imaging with MR was superior to conventional imaging in all cases. There was 90% agreement in split renal function when nuclear and MRI scans were compared. Renal drainage curves were difficult to interpret due to variations in signal intensity related to gadolinium concentration. Sedation was performed safely without any complication.

Conclusion:
Dynamic contrast enhanced MR Imaging provides equivalent information about renal function and morphology in a single study without ionizing radiation. MRI has the potential to replace other imaging modalities in the investigation hydronephrosis in children.

Clinical Predictors of Abnormal Renal Biopsy in Congenital Ureteropelvic Junction Obstruction

Dawn L. McLellan, Seymour Rosen, Joseph G Borer, Stuart B Bauer, Bartley Cilento, Craig A Peters
Harvard Medical School, Boston, MA

Introduction and Objective:
Management of congenital ureteropelvic junction obstruction (UPJO) depends on an assessment of renal functional loss over time. Our objective was to define clinical parameters that may be determined pre-operatively to predict abnormal renal pathology that may predict impaired renal function.

Methods:
We prospectively evaluated 24 neonates (19 male, 5 female; right side 10, left 14) who underwent renal biopsy at the time of pyeloplasty for severe UPJO. Mean age at pyeloplasty was 14 mos. (range: 1.1-69 mos.). All underwent MAG3 diuretic renography in a standardized fashion and renal ultrasonography. The degree of hydronephrosis and caliectasis in all patients was evaluated by renal ultrasound and scored on a scale from 1 (mild)-5 (severe). A single pathologist graded the biopsies: (1) no abnormality; (2) occasional glomerulosclerosis; (3) limited glomerulosclerosis with mild interstitial fibrosis and tubular atrophy; and (4) over 20% glomerulosclerosis with extensive interstitial fibrosis and tubular atrophy (Ped Nephrol 14:820, 2000). Statistical analysis included linear regression, two-tailed t-test and chi square analysis.

Results:
Grade 1 biopsy score was seen in 4 patients, grade 2 in 11, and grade 3 in 9. Percent renal function, cortical transit time, and hydronephrosis score did not correlate with biopsy score ($r2 = 0.11$, 0.00 and 0.09 respectively). However, the combination of a hydronephrosis score of 5 and a wash out time ($t1/2 > 30$ minutes predicted a biopsy score of 3 with a sensitivity of 75% and specificity of 87.5% ($p = 0.0032$).

Conclusions:
Normal renal function was not predictive of an abnormal renal biopsy and may not be an adequate predictor of potential irreversible pathologic change. Patients with a hydronephrosis score of 5 and $t1/2 > 30$ minutes are at high risk of having grade 3 renal changes (glomerulosclerosis with interstitial fibrosis and tubular atrophy). Continued observational management in these patients may risk renal functional loss.

Preoperative Imaging Of Lower Pole Crossing Vessels and Relationship to Ureteropelvic Junction in Asymptomatic Newborns and Infants with Hydronephrosis

H-G. O. Mesrobian, B.A. Maxfield
Medical College of Wisconsin, Milwaukee, WI

A high incidence of crossing vessels has been reported to be present in children and adolescents with symptomatic ureteropelvic junction (UPJ) obstruction. Imaging of the renal vascular anatomy for the presence of an accessory lower pole vessel and its relationship to the UPJ in asymptomatic newborns and infants with prenatally detected hydronephrosis may be useful and portend progression and or symptomatic disease. For this purpose we describe in this pilot study, a three-dimensional imaging technique in newborns and infants with asymptomatic UPJ disease.

Four patients with UPJ disease underwent 3 D CT scanning in the prone position with simultaneous CT angiography. In the first run, 2.5cc/kg of contrast were injected at a rate of 2-3cc/sec and 3-mm axial images were obtained in abdominal and "renal" window/level/ kernels. After a five-minute delay, a second run (1 cc/kg at 2-3cc/sec) resulted in acquisition of 3-mm axial images as above to visualize the vessels and their relationship to the renal pelvis with now accumulated contrast. In addition, "curved" coronal 3-mm images to cover both kidneys, UPJ and vessels were obtained. The imaging results were then correlated with intraoperative findings.
The indications for pyeloplasty included decreasing renal function(1), increasing hydronephrosis(2) and gross hematuria following minimal blunt trauma (1).

Preoperative imaging correctly predicted the presence of an accessory crossing vessels at the UPJ in one patient, and their absence in an additional two. The fourth (and only adolescent) patient in whom imaging did not predict the presence of a crossing vessel, underwent a successful endopyelotomy and therefore intraoperative findings were not available.

This pilot study demonstrates that the presence or absence of lower pole crossing vessels and their relationship to the hydronephrotic UPJ can be demonstrated utilizing the imaging technique as described. Future studies will be aimed at correlating these findings with the likelihood of progression or emergence of symptoms in asymptomatic newborns and infants with prenatally detected UPJ disease.

The Favorable Outcome of Neonatal Uretero-Pelvic Junction Obstruction

J. Roberts and M. Rasoulpour
University of Connecticut, Hartford, CT

We retrospectively reviewed the outcome of neonates with prenatal hydronephrosis that were referred to the nephrology division of this children's hospital since its opening 5.8 years ago. Neonates with normal renal ultrasounds on 1st visit were excluded. Seventy-four patients met the inclusion criteria. There were 23 neonates with primary uretero-pelvic junction (UPJ) obstruction, 12 with primary vesico-ureteral reflux (VUR), 7 with primary mega-ureter, 4 with posterior urethral valves, 3 with extra-renal pelvis, and 2 with ectopic insertion of ureter. Nineteen patients with mild hydronephrosis who did not have voiding cystography were assigned as undetermined, although we suspect that most of them had UPJ obstruction. Four patients did not return for follow up. Five of the 23 patients with UPJ obstruction had bilateral disease, providing 28 renal units for this study. The magnitude of hydronephrosis on renal ultrasound was classified as mild, moderate, or severe. There were 12/28 kidneys with mild hydronephrosis at the entry, 12/28 with moderate, and 4/28 with severe. Furosemide-augmented renal scans were available on all patients with severe, and on 5/11 patients with moderate hydronephrosis. Of these patients, 2 had affected kidneys with perfusion of less than 40%, both of which had severe disease.

Outcome:

There was complete resolution of the hydronephrosis by ultrasound in 14/28 (50%) kidneys over a mean period of 18.4 (4-30) months, and improvement of hydronephrosis in 12/28 (43%) units over a mean period of 10.2 (2-42) months. One patient with severe hydronephrosis was referred to surgery, and the renal ultrasound of a patient with mild hydronephrosis became worse, however the patient's renogram remains normal. The following table illustrates the outcomes according to severity of hydronephrosis.

Conclusion:

Our data illustrates that UPJ obstruction carries an excellent outcome, however close clinical follow-up of these patients with imaging studies is required until hydronephrosis resolves.

	No. Resolved/Total (%)	No. Improved/Total (%)	Total (%)
Mild	5/12 (42)	6/12 (50)	11/12 (92)
Moderate	8/12 (67)	4/12 (33)	12/12 (100)
Severe	2/4 (50)	1/4 (25)	3/4 (75)

Macrophage Infiltration in Obstructive Nephropathy in Newborn Mice is Mediated by Selectins and Induces Tubular Apoptosis, Tubular Atrophy and Interstitial Fibrosis

Bärbel Lange-Sperandio, Barbara Thornhill, Alice Chang, Robert L. Chevalier
University of Virginia School of Medicine, Charlottesville, VA

Urinary tract obstruction during development leads to tubular apoptosis, tubular atrophy and causes interstitial fibrosis. Macrophages play a central role in this process. Selectins, a family of three adhesion molecules are involved in leukocyte recruitment during inflammation. We investigated obstructive nephropathy in triple selectin-deficient mice (EPL-/-), L-selectin deficient mice (L-/-) and wild type mice (WT). Newborn mice were subjected to complete unilateral ureteral obstruction (UUO) or sham operation within the first 48 hours of life, and were sacrificed 5 and 12 days later. Kidney sections were stained for macrophage infiltration (aF4/80), apoptosis (TUNEL), tubular atrophy (PAS), and interstitial fibrosis (Masson trichrome).

Macrophage infiltration in the obstructed kidney was decreased by 62% in EPL-/-, and by 51% in L-/-, when compared to WT at day 5 after UUO ($p<0.002$). Tubular apoptosis in the obstructed kidney decreased by 47% in EPL-/- and by 25% in L-/- compared to WT at day 5 after UUO ($p<0.04$). The reduction in tubular apoptosis was also found at day 12 after UUO showing a decrease by 45% in EPL-/- and 43% in L-/- ($p<0.001$). Tubular atrophy and interstitial fibrosis were significantly reduced in EPL-/- > L-/- compared to WT at day 12 after UUO. The number of apoptotic tubular cells was correlated with macrophage infiltration ($r=0.83$, $p<0.001$). To address the role of macrophages in apoptosis induction in vitro, TNF-a and INF-g activated murine macrophages (J774) were cocultured with murine tubular cells (PKSV-PR). Apoptosis was assessed by FACS after staining with Annexin V-FITC and propidium iodide. Activated J774 cells induced apoptosis in PKSV-PR cells either by direct cell-to-cell contact or by soluble factors when separated by a semipermeable membrane.

We conclude that following UUO, selectins mediate interstitial macrophage infiltration, which in turn induces tubular apoptosis, tubular atrophy and interstitial fibrosis. The work was supported by NIDDK 44756 and German Research Foundation (DFG La1257/1-1).

Mycophenolate Mofetil for the Treatment of Congenital Uropathy: Open Label Pilot Study

Howard Trachtman, Erica Christen, Katherine Freeman, Josephine Rini, Christopher Palestro, Robert Weiss, Eduardo Perelstein, Alex Constantinescu, Lynn Weiss, Lewis Reisman, Isabel Roberti, Carol Coppola, Denise Faherty

Background:

Congenital uropathy (CU) is caused by a wide variety of anatomic abnormalities including vesicoureteral reflux, Prune Belly syndrome, and dysplasia/hypoplasia. In the aggregate, CU accounts for nearly 40% of all cases of ESRD in pediatric patients. Progressive loss of kidney function occurs in patients with CU despite optimal surgical management, suggesting that non-structural factors are involved in the steady decline in GFR. There is infiltration of the CU kidney by immunoeffector cells that secrete various inflammatory and fibrogenic cytokines such as TGF-b. Administration of mycophenolate mofetil (MMF) to animals with the kidney ablation model of chronic renal failure reduces the number of macrophages and activated myofibroblasts in the interstitium, decreases proteinuria, and preserves GFR, without any beneficial effect on the hemodynamic determinants of kidney function.

Purpose:

This multicenter pilot study is designed to evaluate immunosuppressive therapy with MMF on the course of disease in pediatric patients with CU.

Participating centers:

Schneider Children's Hospital (Administrative Center, Howard Trachtman, Principal Investigator), New York Medical College, New York-Weill Hospital, Robert Wood Johnson Medical Center, St. Barnabus Medical Center (Livingston, NJ).

Funding:

This project is supported by a grant from Roche Pharmaceuticals Inc. (Project #CEL214).

Clinical protocol:

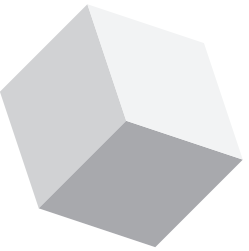
Patients with CU between the ages of 3-16 years will be eligible for inclusion in the study when the GFR declines below 50 ml/min/1.73m2. All diagnoses will be made based upon radiological studies and surgical reports and kidney biopsies will not be required. The study is divided into two phases: a 2-month Run-In followed by a 24-month Treatment Period. Patients will be evaluated monthly during the Run-In Period and for the first 3 months of the Treatment Period. Clinical assessments will be quarterly for the remainder of the Treatment Period. Patients will be examined and a CBC, serum biochemical testing, and urinary protein and albumin excretion will be measured at every visit. GFR will be measured by iothalamate clearance (plasma disappearance method) at 0, 12 and 24 months of treatment. Plasma and urinary levels of N-terminal propeptide of type III procollagen will be measured serially as an index of renal fibrosis. Urine cytometry to assess excretion of macrophages, T- and B-lymphocytes, and activated tubular epithelial cells will be done at entry and after 6, 12, 18, and 24 months of treatment. Trough levels of mycophenolic acid-glucuronide will be measured every 3 months during the Treatment Period.

Continued from Previous Page

Primary end points:
(1) GFR at the end of the Treatment Period;
(2) Frequency of ESRD.

Results:
The study was opened to patient enrollment in December 2001 and 2 children have been entered. The expected sample size is 12-15 children.

Anticipated result:
It is predicted that experimental treatment with MMF will result in a 50% smaller decrement in GFR over the course of the Treatment Period and will prevent the occurrence of ESRD. The results of this pilot study will provide preliminary data to guide the formulation of a full-scale double blind, placebo-controlled randomized clinical trial.



SPEAKER LIST

SPEAKERS

Carol E. Barnewolt, MD
Assistant Professor of Radiology
Harvard Medical School
Children's Hospital of Boston
300 Longwood Avenue
Boston, MA 02115
(617) 355-6312
(617) 264-7120
carol.barnewolt@tch.harvard.edu

Laurence S. Baskin, MD
Chief Pediatric Urology
Department of Urology
UCSF Children's Medical Center
400 Parnassus Ave., Rm. 610
San Francisco, CA 94143-0330
(415) 353-2200
(415) 353-2480
lbaskin@urol.ucsf.edu

Christopher R. Burrow, MD
Department of Medicine, Division of Nephrology
Mount Sinai School of Medicine
One Gustave L. Levy Place, Box 1243
New York, NY 10029-6574
(510) 494-4082
(510) 494-4014
chris.burrow@mssm.edu
cburrow@dna.com

Michael C. Carr, MD, PhD
Assistant Professor, University of Pennsylvania
School of Medicine
Department of Urology
Children's Hospital of Philadelphia
34th Street and Civic Center Boulevard
Philadelphia, PA 19104
(215) 590-2765
(215) 590-3985
mcarr@email.chop.edu

James C.M. Chan, MD
Professor and Chair, Pediatric Nephrology
Pediatric Nephrology
MCV Campus, Virginia Commonwealth University
1101 East Marshall Street
Richmond, VA 23298-0498
(804) 828-9608
(804) 828-6455
jchan@hsc.vcu.edu

Robert L. Chevalier, MD
Benjamin Armistead Shepherd Professor
Chair, Department of Pediatrics
University of Virginia
PO Box 800386
Charlottesville, VA 22908-0386
(434) 924-5093
(434) 982-3561
RLC2M@hscmail.mcc.virginia.edu

SPEAKERS

Linda Dairiki Shortliffe, MD
Department of Urology
Stanford University Medical Center
300 Pasteur Drive, MC 5118
Stanford, CA 94305-5118
linda.shortliffe@stanford.edu

H.K. Dhillon, FRCS
Perinatal Urologist
Great Ormond Street Hospital for Children
Great Ormond Street
London, WC1N 3JH
England
44 20 7405 9200, ext. 5499
44 20 7829 8841
mcgram1@gosh.nhs.uk

Jack Elder, MD
Div. of Pediatric Urology
Rainbow Babies/Childrens Hospital
11100 Euclid Ave.
Cleveland, OH 44106
jse@po.cwru.edu

Diane Felsen, PhD
Associate Research Professor, Pharmacology
Department of Urology
Weill Medical College of Cornell University
1300 York Avenue, Box 94, Room F940
New York, NY 10021
(212) 746-5796
(212) 746-3314
dfelsen@med.cornell.edu

Jorgen Frokiaer, MD, DMSc
Consultant, Associate Professor
University of AARHUS
AARHUS University Hospital - Skejby
Aarhus N, DK 8200
Denmark
45 8949 8401
45 8949 6012
jf@iekf.au.dk

Bernard Gasser, MD
Faculte de Medecine
Institut de Pathologie
4 rue Kirschleger
Strasbourg, France 67085
33 390243952
33 390244015
bernard.gasser@analyses-ulpou-strasbg.fr

Doris Herzlinger, PhD
Associate Professor
Department of Physiology
Weill Medical College of Cornell University
1300 York Avenue
New York, NY 10021
(212) 746-6377
(212) 746-8690
daherzli@med.cornell.edu

SPEAKERS

Mark P. Johnson, MD
Director of Obstetrical Services
Center for Fetal Diagnosis and Treatment
Childrens Hospital of Philadelphia and University
of Pennsylvania School of Medicine
34th Street and Civic Center Boulevard
Philadelphia, PA 19104
(215) 5900-2747
(215) 590-2447
johnsonma@email.chop.edu

Antoine Khoury, MD
Professor
Department of Surgery
The University of Toronto
555 University Avenue
Toronto, Ontario M5G 1X8
(416) 813-6580 or (416) 813-6460
(416) 813-6461
tony.khoury@sickkids.on.ca

Stephen A. Koff, MD
Chief, Section of Pediatric Urology/
Professor of Surgery
Division of Urology
Childrens Hospital and
The Ohio State University Medical Center
700 Childrens Drive, ED343,
Education Building
Columbus, OH 43205-2696
(614) 722-6625
(614) 722-6627
skoff@chi.osu.edu

Barry A. Kogan, MD
Professor, Urology and Pediatrics
Chief, Division of Urology
Albany Medical College
23 Hackett, MC 208
Albany, NY 12208
(578) 262-3296
(578) 262-6050
koganB@mail.amc.edu

Jordan Kreidberg, PhD
Div. of Nephrology
Children's Hospital
300 Longwood Ave.
Boston, MA 02115
jordan.kreidberg@tch.harvard.edu

Yeung Chung Kwong, MBBS, MD, FRCSE, FRCSG, FRACS, FACS, FHKAM (Surg), DCH
Professor & Chief, Division of Pedicatric Surgery
Department of Surgery
The Chinese University of Hong Kong
4/F, Prince of Weles Hospital
Hong Kong, China
(852) 2632 2953
(852) 2637 7974
ckyeung@cuhk.edu.hk

SPEAKERS

Helen Liapis, MD
Associate Professor of Pathology
and Immunology
Department of Pathology
Washington University School of Medicine
Campus Box 8118
660 South Euclid Avenue
St. Louis, MO 63110
(314) 362-0136
(314) 747-2040
liapis@path.wustl.edu

Douglas Matsell, MD
Associate Professor of Pediatrics
Child Health Research Institute
University of Western Ontario
2230-800 Commissioner's Road East
London, Ontario N6C 2V5
(519) 685-8379
(519) 685-8156
doug.matsell@lhsc.on.ca

Patrick H. McKenna, MD
Professor and Chairman
Division of Urology
Southern Illinois University School of Medicine
P.O. Box 19655, 301 N. 8th Street, Room 3A158
Springfield, IL 62794-9655
(217) 545-8860
(217) 545-7305
pmckenna@siumed.edu

Cathy Mendelsohn, PhD
Assistant Professor of Urology and Pathology
Department of Urology
Columbia University
630 West 168th Street, Room 1502
New York, NY 10032
(212) 305-1591
(212) 305-6851
clm20@columbia.edu

Hiep J. Nguyen, MD
Associate Professor of Urology and Pediatrics
Department of Urology
University of California, San Francisco
533 Parnassus Avenue, U575
San Francisco, CA 94143-0738
(415) 476-0326
(415) 476-8849
hnguyen@urol.ucsf.edu

Craig Peters, MD
Associate Professor of Surgery/
Assistant in Urology
Department of Urology
Harvard Medical School/Children's Hospital
300 Longwood Avenue
Boston, MA 02115
(617) 355-7796 or 4452
(617) 232-3467
craig.peters@tch.harvard.edu

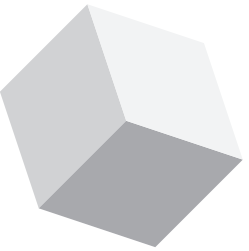
SPEAKERS

John C. Pope, IV, MD
Assistant Professor, Urologic Surgery
Assistant Professor, Pediatrics
Vanderbilt Children's Hospital
A-1302 Medical Center North
Nashville, TN 37215
(615) 936-1060
(615) 936-1061
john.pope@surgery.mc.vanderbilt.edu

Seymour Rosen, MD
Director of Surgical Pathology
Department of Pathology
Beth Israel Deaconess Medical Center; Harvard Medical School
330 Brookline Avenue
Boston, MA 02215
(617) 667-4344
srosen@caregroup.harvard.edu

Hiroyuki Sakurai, MD
Assistant Project Scientist
Division of Nephrology
University of California, San Diego
9500 Gilman Drive 0693
La Jolla, CA 92093-0693
(858) 822-3479
(858) 822-3483
hsakurai@ucsd.edu

George Steinhardt, MD
Professor of Surgery
Section of Urology
St. Louis University School of Medicine
3635 Vista Avenue
St. Louis, MO 63110
(314) 577-8790
(314) 268-5183
steinhmf@slu.edu



PARTICIPANT LIST

PARTICIPANTS

(as of 03/01/02)

Fatai O. Bamgbola, MD, FNMPC(Paed), Nig
Pediatric Nephrology Fellow
Pediatric Nephrology
Children's Hospital @ Montefiore/AECOM
3636 Waldo AV; APT # 2A
Bronx, NY 10463
(718) 548 4720
(718) 652 3136
FBAMGBOLA@AOL.COM

Josephine Briggs, MD
Director, DKUHD
DKUHD
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Building 31A, Room 9A17
Bethesda, MD 20892
(301) 496-3625
briggsj@hq.niddk.nih.gov

Francois Cachat, MD
Departement of Pediatrics
Division of Pediatric Nephrology
Lane Road, Bldg MR4
Charlottesville, VA 22906
(434) 924 2588
fc6b@virginia.edu

Michael S Forbes, Ph.D.
Lab. & Res. Specialist II
Pediatrics
Pediatric Nephrology
University of Virginia Health Sci. Ctr.
Box 801335
Charlottesville, Virginia 22908
(434) 924-2588
msf5c@virginia.edu

Gladys Hirschman, MD
Director, Pediatric Nephrology Program
DKUHD
National Institute of Diabetes
and Digestive and Kidney Diseases
National Institutes of Health
Democracy II, Room 630
Bethesda, MD 20892
(301) 594-7714

Weei-Yuarn Huang, M.D. Ph.D.
Clinical Fellow
Pathology
Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston, MA 02215 USA
(617)6675960
(617)2773658
whuang@caregroup.harvard.edu

PARTICIPANTS

Elizabeth Jackson, MD
Associate Professor
Department of Pediatric Nephrology
University of Kentucky
740 South Limestone Street
J455 Ky Clinic
Lexington, KY 40536-0284
(859) 257-1552
(859) 257-7799
ecjack1@uky.edu

Elaine S Kamil, MD
Clinical Director
Pediatric Division
Cedars Sinai Medical Cetner
8700 Beverly Blvd., Suite 1165
Los Angeles, CA 90048
(310) 423-4747
(310) 423-1676
elaine.kamil@cshs.org

Frederick Kaskel, MD, PhD
Professor of Pediatrics
Children's Hospital at Montefiore
Albert Einstein College of Medicine
111 East 210th Street
Bronx, NY 10487
(718) 655-1120
(718) 852-3136
fkaskel@aecom.yu.edu

Susan C Kiley, Ph.D.
Assistant Professor of Research
Pediatrics
Nephrology
University of Virginia
UVA Health System, PO Box 801334
Lane Road, Bldg. MR-4, Rm 2035A
Charlottesville, VA 22901
(434)982-0684
(434)982-4328
sck3k@virginia.edu

Barbel Lange-Sperandio, M.D.
Research Fellow
Pediatrics
Pediatric Nephrology
University of Virginia
MR-4, Lane Road
Charlottesville, VA 22908
(434) 924 2588
bls6n@virginia.edu

Monica Liebert, Ph.D.
Director
Office of Research
American Urological Association
1120 North Charles Street
Baltimore, MD 21201
(410) 223-6435
(410) 223-4369
MLiebert@auanet.org

PARTICIPANTS

Robert H. Mak, MD, PhD
Professor
Department of Pediatrics/Nephrology
Oregon Health and Science University
3181 SW Sam Jackson Park Road
Portland, OR 97201
(503) 494-7327
(503) 418-6718
makr@ohsu.edu

Dawn L. McLellan, MD
Fellow
Department of Urology
Children's Hospital of Boston
14 Orkney Road
Apt. 24
Brighton, MA 02135
(617) 355-8610
(617) 355-7760
dawnleemclellan@hotmail.com

Hrair Mesrobian, MD
Pediatric Nephrology
Medical College of Wisconsin
9000 West Wisconsin Avenue, Suite 403
Milwaukee, WI 53092
(414) 266-3792
(414) 266-1754
hmesrobi@mcw.edu

Christopher Mullins, PhD
Director, Cell Biology Program
DKUHD
National Institute of Diabetes
and Digestive and Kidney Diseases
National Institutes of Health
Democracy II, Room 639
6707 Democracy Boulevard
Bethesda, MD 20892
(301) 594-7717
mullinsc@extra.niddk.nih.gov

Caleb Nelson
Urology
University of Michigan
1500 E. Medical Center Drive
TC 2916, Box 0330
Ann Arbor, MI 48109
(734) 936-5760
cpnelson@umich.edu

Leroy Nyberg, MD, PhD
Director, Urology Program
6707 Democracy Boulevard
Democracy II Building
Bethesda, MD 20892
(301) 594-7717
(301) 480-3510
nybergl@ep.niddk.nih.gov

PARTICIPANTS

Patricio E. Ray, MD
Director, Research Center for Molecular Physiology
Center for Molecular Physiology
Children's Research Institute
111 Michigan Avenue, NW
Washington, DC 20010
(202) 884-2912
(202) 884-4477
pray@cncm.org

Majid Rasoulpour, MD
Director
Department of Pediatrics
Division of Nephrology
Connecticut Children's Medical Center
9 Wentworth Park
Farmington, CT 06032
(860) 545-9395
(860) 545-9914
mrasoul@ccmckids.org

Jonathan A. Roth, MD
Assistant Professor of Urology
Department of Urology
Division of Pediatric Urology
University of Virginia
Children's Medical Center
PO Box 800422
Charlottesville, VA 22908
(434) 924-9559
(434) 982-3652
jar9n@virginia.edu

Lena Simpson, RN
Clinical Nurse
Department of Pediatric Nephrology
University of Kentucky
740 South Limestone Street
J455 Ky Clinic
Lexington, KY 40536-0284
(859) 257-1552
(859) 257-7799
lfrile2@uky.edu

Barbara A Thornhill
Pediatrics
Nephrology
University of Virginia
300 Lane Road, MR-4, Room 2034
Charlottesville, VA 22903
(434) 924-2588
(434) 982-4328
bat6d@virginia.edu

Robert A Weiss, MD
Director, Pediatric Nephrology
Westchester Medical Center
Dept. Pediatrics
Munger Pavilion, New York Medical College
Valhalla, NY 10595
(914) 493-7583
(914) 594-3381
robert_weiss@nymc.edu

PARTICIPANTS

Pierre Williot, MD
Chief of Pediatric Urology
Montefiore Medical Center
3400 Bainbridge Avenue
Bronx, NY 10467
(718) 920-7479
(718) 547-2902
pwilliot@montefiore.org

Troels M. Jorgensen, MD
Professor
Urology Division
Department of Pediatric Urology
Aarhus University Hospital
Brendstrupgaardvej
Aarhusn, - 8200 Denmark
45 89495903
45 89496006
tmj@dadlnet.dk