9. Howman-Giles R, Uren R, Roy LP, Filmer RB. Volume expanded diuretic renal scan in urinary tract obstruction. *J Nucl Med* 1987;28:824–828.
10. Sukhai RN, Kooy PM, Wolff ED, Scholtmeijer RJ. Predictive value of ^{99m}Tc-DTPA renography studies under conditions of maximal diuresis for the functional outcome of reconstructive surgery in children with obstructive uropathy. *Br J Urol* 1986;58:596–600.
11. Gilday DL. Paediatric nuclear medicine—technical considerations. First Asia and Oceania Congress of Nuclear Medicine, 1976 (Appendix 1).
12. Notley RG. The structural basis for normal and abnormal ureteric motility. *Ann Roy Coll Surg* 1971;49:250–267.
13. Gosling JA, Dixon JS. Functional obstruction of the ureter and renal pelvis. A histological and electron microscopic study. *Br J Urol* 1978;50:145–152.
14. Stewart CL, Jose PA. Transitional nephrology. *Urol Clin North Am* 1985;12:143–149.
15. Homsy YL, Williot P, Danais S. Transitional neonatal hydronephrosis: fact or fantasy? *J Urol* 1986;136:339–341.
16. Koff SA, McDowell GC, Byard M. Diuretic radionuclide assessment of obstruction in the infant: guidelines for successful interpretation. *J Urol* 1988;140:1167–1168.
17. Uson AC, Cox LA, Lattimer JK. Hydronephrosis in infants and children I. Some clinical and pathological aspects. *JAMA* 1968;205:323–326.
18. Johnston JH, Evans JP, Glassberg KI, Shapiro SR. Pelvic hydronephrosis in children: a review of 219 personal cases. *J Urol* 1977;117:97–101.
19. Ahmed S, Savage JP. Surgery of pelviureteric obstruction in the first year of life. *Aust NZ J Surg* 1985;55:253–261.

EDITORIAL

Tracking the Natural History of Infantile Hydronephrosis with Diuretic Renography

Congenital anomalies of the genitourinary system have a prevalence estimated at 4–7/1000 (*1*). These malformations, which account for a substantial number of children with renal failure, can be reliably identified with ultrasound between 16 and 18 wk of gestational age (*2*). Specific anatomic diagnoses can be defined sonographically and include ureteropelvic junction (UPJ) obstruction, duplex systems with polar hydronephrosis and ureterovesical junction obstructions with megaureter (*3*). However, "obstruction is not a single disease process, and its outcome cannot be predicted purely by anatomic appearance" (*4*). Hence many of the genitourinary anomalies initially defined sonographically are susceptible to later investigation by nuclear imaging techniques.

The sensitivity of ultrasonographic diagnosis is such that a wide spectrum of degrees of hydronephrosis (HN), including cases of minimal severity, are encountered. Management of these complex disorders presents a major, unresolved clinical problem in terms of natural history, and the unsettled question of the indications for surgery (*4*). Consequently there is a pressing clinical need for a reliable test to assess the necessity or appropriateness of surgical intervention in affected children.

A consideration of the functional significance of HN is fundamental to an understanding of the relevant diagnostic armamentarium. In the past, HN has always been considered to be pathologic. However, the condition does not necessarily worsen, and many patients have no reduction in renal parenchymal function. Up to 40% of patients after pyeloplasty for UPJ obstruction show no measurable postoperative improvement (*5*).

This clinical evidence for nonprogression of HN is consistent with experimental studies where surgically created ureteric obstruction is not followed universally by dilation of the kidney (*6*). Some have gone as far as to say that HN should be viewed as a beneficial compensatory mechanism.

It has been proposed (*4*) that the potential for development of HN depends on four salient factors:

1. Urinary output and flow rates during diuresis.
2. Anatomy and tightness of the obstruction.
3. Glomerular and tubular function.
4. Changes in compliance of the renal pelvis.

It should be noted that nuclear medicine techniques directly measure only Parameter 3. Parameters 1 and 2 are assessed partly and indirectly, and Parameter 4 is not estimated.

SIGNIFICANCE OF URETEROPELVIC JUNCTION (UPJ) OBSTRUCTION

This anomaly is the most common cause of prenatally diagnosed HN (*7*). Its etiology can be broken down into factors which may be extrinsic (vessels, bands, adventitial tissues), or intrinsic (an adynamic segment or true narrowing). Current evidence suggests that these two patterns are associated with different types of flow patterns across the UPJ and hence determine progression or equilibrium of the underlying pathology (*8*).

The classification of UPJ obstruction as intrinsic versus extrinsic may also be relevant to interpretation of the diuretic renogram. The test may be most reliable in the presence of moderate intrinsic obstruction, with or without additional extrinsic obstruction. In this situation, the pressure-exit flow curves will be flat so that normal flow rates are possible only when intrapelvic pressure is above normal (as is produced by the diuretic challenge). Here the slow emptying rate can be easily detected.

In mild intrinsic obstruction, the dilated pelvis may have reached a new equilibrium so it can respond to an increased flow rate by emptying normally: hence, the potential for false-negative test results. With extrinsic obstruction, the diagnosis can only be made when the kidney is overdistended.

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For reprints contact: Lorcan A. O'Tuama, MD, Division of Nuclear Medicine, Children's Hospital, Harvard Medical School, Boston, MA.

A further problem complicating the assessment of treatment response and other aspects of the natural history of UPJ obstruction arises from the limitations of the surgical observation. It is important to bear in mind a *functional* definition of "obstruction": it cannot be defined on the basis of a clinical test, nor on a surgical observation. Obstruction may be best defined as "any restriction to urinary outflow that, left untreated, will cause progressive renal deterioration" (*4*), or, we would add, prevent normal growth and development of an immature kidney.

DIAGNOSTIC EVALUATION OF UPJ OBSTRUCTION

Over the last two decades, two diagnostic tests have appeared that have major usefulness in assessing obstruction in the hydronephrotic kidney.

The Pressure Flow Study (Whittaker Test)

The pressure-flow test was introduced (*9*) to assess the severity of upper urinary tract outflow obstruction. A basic hypothesis underlying this test is that obstruction produces a constant resistance to outflow, necessitating elevated pressures to transport urine at high rates. The requisite pressure gradient is measured between the upper urinary tract and the bladder with a catheter in place. Perfusion at a high rate is used to stimulate the system, simulating diuresis, and the resultant pressure is recorded. Pressure > 20 cm H_2O with a flow of 10 cc/min is consistent with obstruction.

While the pressure-flow method has been a major advance in the assessment of UPJ obstruction, usefulness of the test is reduced by major limitations. First, not all obstructions are constant. Second, a "gray zone" of pressure recording (from 15 to 20 cm H_2O) is indeterminate for the presence of obstruction. Third, response of the renal pelvis to a distended, not a physiologic, situation is measured. Fourth, normative values have not been established for the young child.

Recently, a modification of the pressure-infusion method has been introduced (*10*), using a constant pressure system that compares concomitant flow rates. Lower flow at the same pressure suggests more "obstruction." The clinical applicability of this approach remains to be determined.

Diuretic Renography

This safe noninvasive technique for assessing UPJ obstruction was introduced in the late 1970's (*11*) and its clinical application has been detailed (*12–14*). The method depends on an underlying theory of delayed tracer mixing with the dilated compartment formed by a hydronephrotic pelvis.

The essence of the procedure involves the use of an effective radiopharmaceutical to monitor the rate of transit through the parenchyma including the collecting system. With incomplete drainage of tracer from the pelvicalyceal system, the patient is challenged so as to promote tracer excretion, by administration of an osmotic diuretic, typically furosemide (Lasix) 0.3–1 mg/kg, intravenously. The basic protocol for the performance of the diuretic renogram is well known to nuclear medicine practitioners and detailed in standard texts (*15*).

In this setting, the report of Choong et al. in the present issue of the *Journal* involves a retrospective review of 18 patients with suspected UPJ obstruction. Their interesting communication illustrates several aspects of the diagnostic usefulness of diuretic renography (DR), as well as raising some issues that pertain to the limitations of the technique.

They have been specifically concerned that inadequate hydration may be a factor hindering optimal employment of the DR technique, as have others (*14,16,17*). Consequently, they used as a provocative stimulus for the patients both volume expansion (10 ml/kg of 0.9% sodium chloride solution administered intravenously over 30 min preceding the scan), as well as furosemide (1 mg/kg). They classified the results of their studies as reflecting a status of the collecting system that was obstructed, nonobstructed or indeterminate.

Dr. Choong and coworkers conclude that intravenous hydration optimizes diagnostic accuracy in the diuretic study. In our practice, we have not used volume expansion as part of our evaluation and hence cannot offer comparative data. Our impression, however, is that their prevalence of indeterminate scans, 6/28 (21.4%), is not dissimilar to our experience, using the diuretic challenge during the patient's usual level of hydration. As these authors note, with commendable prudence, the diagnostic accuracy of the "volume-expanded" DR cannot be established conclusively from the present study, given the retrospective nature of the analysis.

Choong et al. usefully remind us of the limitations diagnostically, and prognostically, of a single scan not showing an obstructive pattern. Of a total of 20 indeterminate or nonobstructive appearing cases in their series, five were subsequently considered to have developed obstruction on progress scans. However, the basis for their results raises interesting questions about interpretation of the DR.

In arriving at their classification of renal excretion, the authors relied substantially on a quantification of tracer drainage, using estimates of the half-times for furosemide washout. The assessment of the half-time is described as having been done by "using a monoexponential curve fitted to the maximum slope".

This method may be open to some objection as being unduly subjective. In our experience, the washout curve frequently is multiphasic, with a succession of slopes. In such cases, the selection of the maximum slope may be dependent on a subjective interpretation of where the curve breaks, and is open to some interobserver variation. As an approach to dealing with this difficulty, we always record the percent residual of the pre-furosemide activity level of the time-activity curve and use that as an additional parameter for inferring possible outlet obstruction.

The use of furosemide washout time *as a sole criterion* can be misleading, in our view, for the diagnosis of obstruction. Many patients present a complex, multislope curve when the time-activity curve is displayed to reflect furosemide response. No consensus has been determined as to the proper approach for analysis of these mathematically complex functions. Linear, logarithmic and linear-logarithmic transformations of the data all have been advocated, and estimates of the washout are reached from the extrapolated data. Therefore, depending on the method used, the reported washout time may be dramatically different.

The difficulties presented in attempting to analyze a complex, multiple slope type of furosemide washout curve are illustrated by the data presented for Choong et al.'s Patient 16 (presented in their Fig. 1B). Here the initial study at 2 mo is classified as normal because a half-time of 15 min is obtained. This estimate is obtained from a fit to the first exponential component. The fractional retention of the tracer present before furosemide administration can be approximated from the radioactivity rates indicated on the graph ordinate. A ratio of the initial to the finally observed values is of the order of 5400/8922, 65.2%. In our laboratory, such a value would always be regarded as abnormal, irrespective of the furosemide half-time, as estimated from the initial slope.

A further problem complicating the assessment of treatment response and other aspects of the natural history of UPJ obstruction lies in the absence of a "gold standard" of obstruction. As already mentioned, the obstruction is most accurately interpreted as an abnormality of *function*, and therefore requires a functional definition.

In the study of Choong et al., the "final diagnosis" was based on surgical findings (with histopathologic correlation, when available). We would not find these criteria to be conclusive, however, since the observation of a UPJ obstruction at surgery, in our experience, is not based upon any standard of appearance, caliber, or configuration. Most, if not all, UPJs examined at the time of surgery for "obstruction" are probe-patent, often to a large caliber. To state that surgical observation confirms the existence of "obstruction" simply begs the basic question. Fundamentally, too little is known concerning the pathophysiology of congenital kidney obstruction to permit a clearcut statement assessing the presence of significant obstruction. Furthermore, the maintenance of equilibrium alone may not be beneficial in the infant kidney that would otherwise grow and develop with great rapidity during the first year of life. The effects of congenital obstruction upon renal growth and development remain to be elucidated.

Stimulated by the findings of Choong et al., it is timely to review several issues pertaining to the conduct of the DR in the child presenting with possibly obstructive HN.

OPTIMIZATION OF DR FOR ASSESSMENT OF UPJ OBSTRUCTION

Need for Detailed Individualized Study Design

DR is preeminently *not* the kind of test which should be delegated exclusively to the technologist. It is essential that the nuclear physician frequently checks the real-time image, and "quarterbacks" all details of the acquisition. While it is essential to have a general protocol for the conduct of DR, equal importance should be attached to modification of the basic plan according to the needs of the individual patient: a "tailored" examination is essential.

In illustration of this general statement, a particular mistake is to give the diuretic invariably, at 20 min, or other fixed time, after the tracer injection. The collecting system must be filled with tracer, extending right up to the point of questioned obstruction before the diuretic challenge. Otherwise, unlabeled urine fills up with radiopharmaceutical after the diuretic challenge, and hence obstruction may be misdiagnosed.

Need for Standardization of DR to Allow Interinstitutional Comparison of Results

As discussed above, we believe it possible to offer a somewhat different interpretation of furosemide washout data in the study of Choong et al. by using a different analysis parameter. This difference of view points up the need for a standardization of approach so that studies from different centers can be directly compared, permitting valid assessment of data from multicenter trials.

In the Division of Nuclear Medicine at Children's Hospital, we have practiced, and taught to our residents, over 15 yr, a standardized approach to the interpretation of the DR. For example, on the "parenchymal phase" (60–120 sec) image, the percentage uptake of tracer is estimated visually, and quantitatively, and recorded on a standardized scoring sheet. In a similar manner, other parameters, such as cortical transit time, image appearance in the final/or immediate pre-furosemide image, and analysis of the diuretic washout are systematically noted. The final impression is based on a consideration of all these parameters, and not on a single factor, such as the lasix washout time.

Many of these attempts at producing a measure of standardization into the DR appear again in a more recent proposal by a consortium of the Society for Fetal Urology and the Pediatric Nuclear Medicine Club of the Society of Nuclear Medicine (*18*). There seems no doubt that careful attention to detail, and standardization both of how the DR is acquired and interpreted, can only improve the quality of the information obtained, and facilitate exchange of knowledge both among nuclear medicine practitioners, and among our "consumer" clinician-colleagues.

Need for a Keener Sense Among Nuclear Medicine Diagnosticians of the Limitations of the DR

Our sense is that there is insufficient awareness of clinical circumstances which may substantially limit the di-

agnostic conclusions which may be reached from a DR. The study must always be interpreted in light of all other evidence of renal function. Fundamentally, renal function must be sufficient to extract tracer at a concentration permitting visualization of the pelvicalyceal compartment. Glomerular and tubular function must be adequate to ensure a diuretic response. Coexisting reflux of tracer into the pelvis is a notorious mimic of obstruction, and cannot always be detected from history. For this reason, we catheterize patients routinely, unlike Choong et al., who reserved this measure for patients reporting reflux. Catheterization also avoids confusion by the "pseudo-obstruction" to tracer transit sometimes produced by an overdistended bladder.

Consideration of the Issue of Functional Immaturity of the Kidneys in the Interpretation of the DR in the Very Young Child

Functional immaturity of the kidney in the very young child may present as a relatively sluggish rate of cortical transit and pelvic distribution of tracer. This situation presents a practical problem in interpretation of the clinical study, since clear normative values in these younger children have not been established.

In the child with unilateral HN, it has been suggested that an evaluation can be made by using the function of the contralateral kidney to establish the level of maturity that has been reached by the patient. If the apparently uninvolved kidney is functionally mature, then one can evaluate the UPJ at question by the criteria for a mature kidney.

Employment of a Standard Radiopharmaceutical for DR

Technetium-99m-mercuroacetyltriglycylglycine (Mag3; Mallinckrodt, St Louis, MO) has emerged as the radiopharmaceutical of choice for DR. MAG3 is comparable in its dosimetry to ^{99m}Tc-DTPA (*19*) and offers considerably higher initial renal clearance (*20*). In our hands, the percentage uptake assessed on the parametric phase image at 2 min with MAG3 tends to be 8–10 times greater than we had previously found with DTPA in a similar patient population. As would be anticipated from such favorable pharmacodynamics, MAG3 allows satisfactory quantification of renal function (*21*).

We have tried to present in bare outline the emerging concepts about the pathogenesis of congenital hydronephrosis and UPJ obstruction. There appears to be increasing recognition that HN must be regarded as a *functional* abnormality, played out against a variable setting of morphologic phenomena. Because of its capability to provide a unique set of functional data, diuretic renography, when performed with punctillious care, plays— and will continue to play— a major part in the evaluation of the child with congenital hydronephrosis.

However, for the optimal deployment of this useful technique, nuclear medicine physicians must have a realistic awareness of the clinical situations where the method can be employed most effectively (criteria that are clearly normal or clearly consistent with high-grade UPJ obstruction), and of situations where there is a lower level of diagnostic certainty (multislope furosemide washout curves, question of obstruction raised in a setting of reduced renal function, etc.). Especially in the clinical setting presented by equivocal situations, it would seem not only legitimate but ethical for us to lobby with our clinical colleagues for a greater number of *serial* DR studies so that the interaction of the disease process with renal maturation can be gauged. The attention to this aspect by Choong et al., who obtained serial DR in 13 out of 16 nonsurgically correlated kidneys, is a major strength of their study. In our view, this emphasis on serial examination should become the rule, rather than the exception, in the nuclear medicine evaluation of the child with HN.

Furthermore, the nuclear medicine physician arguably needs to have a greater appreciation of current research aimed at an understanding of the pathophysiology and thereby optimal diagnosis and management of congenital HN. The collaborative interinstitutional study mentioned is one of several that are underway to compare outcomes of observational and surgical management approaches. The critical, yet elusive requirement for any present or future studies approaching these questions is the development of an adequate method for assessment of outcomes.

The functional parameters measured in DR, although reflective of vital components, are not a global assessment of renal function. Particularly in a unilateral UPJ obstruction, little can be said *directly* about concentrating ability, acid/base and electrolyte handling. The long-term latency of complications from some kidney obstructions further complicates making an assessment of the relative clinical outcomes of different grades of HN. The absence of differences in the short term, using insensitive or irrelevant endpoints, does not establish the comparability of treatments, and therefore the validity of the diagnostic methods used.

CONCLUSION

Diuretic renography will continue to provide a unique and essential role in the evaluation of the child with congenital hydronephrosis, raising the question of UPJ obstruction. We reiterate four points which appear essential for the most effective utilization of the method:

1. Meticulous technique, with continuous monitoring, and attention to details including routine catheterization.
2. Systematic, multiparametric analysis of the study, as opposed to reliance on a single parameter, such as the half-time of furosemide response.
3. Serial studies, to increase reliability of assessment of UPJ function. (The achievement of Choong and co-workers in this

regard should be applauded and emulated).

4. Vigorous pursuit of attempts to standardize the technique of DR among different laboratories, allowing more effective comparison of data by various investigators.

When performed to these specifications, DR can be used not only to help with the diagnostic problems of the individual patient, but also as a vital tool in the task of arriving at a true understanding of the natural history of congenital HN, and of its effects on functional maturation of the developing kidney. This accomplishment should in turn allow the long-awaited achievement of establishing a rational policy for the management of the child with congenital HN.

Lorcan A. O'Tuama
S. Ted Treves
Craig A. Peters
Children's Hospital and Harvard Medical School
Boston, Massachusetts

REFERENCES

1. Boois E, Feingold J, Benmaiz H, Briard ML. Congenital urinary tract malformations: epidemiologic and genetic manifestations. *Clin Genet* 1975;8:37–47.
2. Bellinger MF, Comstock CH, Grosso D, Zaino R. Fetal posterior urethral valves and renal dysplasia at 15 weeks gestational age. *J Urol* 1983;129:1238–1239.
3. Mandell J, Blyth BR, Peters CA, Retik AB, Estroff JA, Benaceraf BR. Structural genitourinary defects detected in utero. *Radiology* 1991;178:193–196.
4. Koff SA. Pathophysiology of ureteropelvic junction obstruction. Clinical and experimental observations in pediatric urinary tract obstruction. *Urol Clin North Am* 1990;17:263–272.
5. Hendren WH, Radhakrishman J, Middleton AW Jr. Pediatric pyeloplasty. *J Pediatr Surg* 1980;15:133–144.
6. Claesson G, Josephson S, Robertson B. Experimental partial ureteric obstruction in newborn rats. VII. Are the long term effects on renal morphology avoided by release of the obstruction? *J Urol* 1986;136:1330–1334.
7. Brown T, Mandell J, Lebowitz RL. Neonatal hydronephrosis in the era of sonography. *AJR* 1987;148:959–963.
8. Koff SA, Hayden LJ, Cirulli C, Shore R. Pathophysiology of ureteropelvic junction obstruction: experimental and clinical observations. *J Urol* 1986;136:336–338.
9. Whittaker RH. Methods of assessing obstruction in dilated ureters. *Br J Urol* 1973;45:15.
10. Woodbury PW, Mitchell ME, Scheidler DM, Adams MC, Rink RC, McNulty A. Constant pressure perfusion: a method to determine obstruction in the upper urinary tract. *J Urol* 1989;142:632–635.
11. O'Reilly PH, Testa HJ, Lawson RS, et al. Diuresis renography in equivocal urinary tract obstruction. *Br J Urol* 1978;50:76–80.
12. Thrall JH, Koff SA, Keyes JW Jr. Diuretic radionuclide renography and scintigraphy in the differential diagnosis of hydroureteronephrosis. *Semin Nucl Med* 1981;11:89–104.
13. Maizels M, Firlit CF, Conway JJ, King LR. Trouble-shooting the diuretic renogram. *Urology* 1986;28:355–363.
14. Kass EJ, Fink-Bennett D. Contemporary techniques for the radioisotopic evaluation of the dilated urinary tract. *Urol Clin North Am* 1990;17:273–289.
15. Treves ST, Lebowitz RL, Kuruc A, Heyman S, Rosen P. Kidneys. In: Treves ST, ed. *Pediatric nuclear medicine.* New York: Springer-Verlag; 1985:66–72.
16. Sukhai RN, Kooy PM, Wolff ED, Scholtmeijer RJ. Predictive value of ^{99m}Tc-DTPA renography studies under conditions of maximal diuresis for the functional outcome of reconstructive surgery in children with obstructive uropathy. *Br J Urol* 1986;58:596–600.
17. Howman-Giles R, Uren R, Roy LP, Filmer RB. Volume expanded diuretic renal scan in urinary tract obstruction. *J Nucl Med* 1987; 28:824–828.
18. Conway JJ. "Well-tempered" diuresis renography: its historical development, physiological and technical pitfalls, and standardized technique protocol. *Semin Nucl Med* 1992;22:74–84.
19. Stabin M, Taylor A, Eshima D, Wooter W. Radiation dosimetry for technetium-99m-DTPA, and iodine-131-OIH based on human biodistribution studies. *J Nucl Med* 1992; 33:33–40.
20. Taylor A Jr, Eshima D. Effect of altered physiologic states on clearance and biodistribution of technetium-99m MAG3, iodine-131 OIH, and iodine-125 iothalamate. *J Nucl Med* 1988;29:669–675.
21. Russell CD, Thorstad BL, Yester MV, Stutzman M, Dubovsky EV. Quantitation of renal function with technetium-99m MAG3. *J Nucl Med* 1988;29:1931–1933.