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# Pediatric Applications of Renal Nuclear Medicine

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This review should be regarded as an opinion based on personal experience, clinical and experimental studies, and many discussions with colleagues. It covers the main radionuclide procedures for nephro-urological diseases in children. Glomerular filtration rate can be accurately determined using simplified 2- or 1-blood sample plasma clearance methods. Minor controversies related to the technical aspects of these methods concern principally some correction factors, the quality control, and the normal values in children. However, the main problem is the reluctance of the clinician to apply these methods, despite the accuracy and precision that are higher than with the traditional chemical methods. Interesting indications are early detection of renal impairment, hyperfiltration status, and monitoring of nephrotoxic drugs. Cortical scintigraphy is accepted as a highly sensitive technique for the detection of regional lesions. It accurately reflects the histological changes, and the interobserver reproducibility in reporting is high. Potential technical pitfalls should be recognized, such as the normal variants and the difficulty in differentiating acute lesions from permanent ones or acquired lesions from congenital ones. Although dimercaptosuccinic acid scintigraphy seems to play a minor role in the traditional approach to urinary tract infection, recent studies suggest that this examination might influence the treatment of the acute phase, the indication for chemoprophylaxis and micturating cystography, and the duration of follow-up. New technical developments have been applied recently to the renogram: tracers more appropriate to the young child, early injection of furosemide, late postmicturition and gravity-assisted images and, finally, more objective parameters of renal drainage. Pitfalls mainly are related to the interpretation of drainage on images and curves. Dilated uropathies represent the main indication of the renogram, but the impact of this technique on the management of the child is, in a great number of cases, still a matter of intense controversy. Direct and indirect radionuclide cystography are interesting alternatives to the radiograph technique and should be integrated into the process of diagnosis and follow-up of vesicoureteral reflux.

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Pediatrics is a specialized field of application of nuclear medicine and many centers are still reluctant to perform radionuclide tests in children. The practical aspects of conducting the examination undoubtedly constitute the main difficulty: preparation and information of patient and parents, the capacity to handle the natural anxiety related to the procedure, the creation of a friendly environment (waiting room and gamma camera room), adequate immobilization of the patient, adaptation of the acquisition to the size of the patient (zoom and pinhole views), and the administration of intravenous injections and blood sampling with minimal dis-

comfort for the child. In addition, special attention should be given in this young age group to the problems of radiation protection and the variation in function of age of the biological distribution, uptake, and retention of radiopharmaceuticals. Similarly, numerous difficulties and pitfalls in the interpretation of images and functional parameters are evident during maturation. Finally, although many indications for nuclear medicine procedures are common to children and adults, there is a wide panel of specific pediatric indications of which the nuclear medicine physician should be aware.

Nephro-urology is probably the best illustration of this specificity. Although generally not more than 5% of the workload of a nuclear medicine department is devoted to this subspecialty, more than 60% of the pediatric examinations are aimed at exploring the urinary tract.

There are 2 main reasons for this difference. First, urinary tract infection is frequent in childhood, and approximately 80% of first infections occur before a child reaches 2 years of

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age. Association with structural abnormalities such as underlying vesico-ureteric reflux is not rare, and complications such as severe recurrent infections, scarring, loss of renal function and, in the long term, hypertension constitute a constant preoccupation for the pediatrician. Second, prenatal screening has led to the detection of a large number of uronephrological abnormalities. It is therefore understandable that the clinician is tempted to prevent further deterioration of the kidney. Nuclear medicine offers the possibility of evaluating, from the very early weeks, the function of the urinary tract, and the effect of any medical or surgical treatment.

What is the benefit of all these examinations? We are now at a point where many uncertainties related to the procedures have been clarified. Most of the uronephrological techniques are now better understood and are almost standardized. Some pitfalls of interpretation are known, the levels of sensitivity and specificity have been largely evaluated, robustness in reporting on a test has been checked on many occasions and experimental studies have validated these procedures.

However, there still is a long way to go, and we need much more rigorous work to evaluate the real utility of these examinations. Although we can identify the acute lesion of pyelonephritis, we still need to prove that the acute dimercaptosuccinic acid scintigraphy (Tc-99m DMSA) can modify the strategy of treatment and follow-up. A renal scar can be shown much easier than with the classical intravenous urography, but we still do not know what the consequence will be for the patient having 1, 2, or multiple scars. Are we forced to continue conducting the very unpleasant direct cystography in a 2-year-old child simply because of acute pyelonephritis, or, will a normal DMSA scan allow us to spare patients many unnecessary tests? Having the possibility of regularly evaluating the renal function of a hydronephrotic kidney by using renography already has completely changed the strategy of the surgeon and, although many uncertainties related to the criteria of surgery still remain, it is already very clear that only a minority of these children will now undergo surgery compared with the systematic surgical approach one generation earlier.

The details of the radionuclide procedures used in pediatric uronephrology are presently described in detail in various American and European guidelines and will be cited within. However, guidelines generally are a compromise between different opinions, based or not on solid evidence. This review should be regarded as an opinion based on personal experience, clinical, and experimental studies and numerous debates with clinicians involved in this particular field of medicine. Several technical aspects related to these procedures will be examined, but it was our feeling that, at the present time, more attention should be paid to the potential impact these techniques may have in the strategy of pediatric uronephrology.

## Glomerular Filtration Rate (GFR)

### Physiology

GFR generally is accepted as the most representative parameter of renal function. It is relatively constant under standard

conditions and, as opposed to tubular secretion, is independent of the urine flow. Because GFR may be reduced before the onset of symptoms of renal failure, its assessment enables earlier diagnosis and therapeutic interventions in patients at risk. Moreover, the level of GFR is a strong predictor of the time of onset of kidney failure as well as the risk of complications of chronic kidney disease.<sup>1</sup>

### Chemical and Radionuclide Methods

Inulin clearance with constant infusion and an indwelling catheter is the "gold standard" but is used only for research. Serum creatinine is a simple chemical parameter for a first-step gross evaluation of renal function. However, it is a poor guide to GFR because it is highly dependent on muscle mass and it is insensitive to changes in renal function until glomerular filtration is reduced substantially. It is, for instance, obvious, from the nonlinear relation between plasma concentration and clearance, that as much as half of the renal function can be lost before any significant increase of plasma creatinine occurs. On the contrary, the sensitivity of plasma creatinine for GFR changes is great once GFR decreases to less than 15 mL/min.

Schwartz's nomogram, particularly popular among pediatric nephrologists, has been established to predict creatinine clearance from plasma creatinine concentration, taking the age, gender, and body weight into account.<sup>2</sup> The accuracy of this nomogram is controversial, although it is often considered by some as sufficient for clinical use. The error in predicting the true clearance can be considerable and, like the plasma creatinine, the nomogram is unable to detect early changes in renal function. True GFR measurements are needed to identify early decline in kidney function. The algorithm is not reliable in children with insulin-dependent diabetes mellitus,<sup>3</sup> in liver disease,<sup>4,5</sup> and after liver transplantation.<sup>6</sup> Its use is inaccurate for the estimation of GFR in healthy potential kidney donors,<sup>7</sup> whereas, for those who GFR values are less than 30 mL/min/1.73 m<sup>2</sup>, the overestimation can reach 67%.<sup>8</sup> Creatinine clearance necessitates a precise urine collection which, in routine situations, represents the main source of imprecision, particularly in young children.

Plasma sample radionuclide clearances allow the detection of early renal impairment and an accurate estimation of hyperfiltration. Precise monitoring of GFR changes can be obtained, for instance, during nephrotoxic chemotherapy, for the entire range of GFR levels down to  $\pm 15$  mL/min/1.73 m<sup>2</sup>.

However, it is obvious that radionuclide estimation of overall GFR has not gained wide acceptance among pediatric nephrologists. Several factors have contributed to this lack of interest: a strong confidence in the daily used chemical techniques, even if biased by major errors; the price of the radiopharmaceutical and the radiation dose (even if negligible because of the small doses used for determining the plasma concentration); and the nonstandardization for many years of the radionuclide technique, which has led to inaccurate reports and loss of confidence in the results. One can only hope that the consensus conferences,<sup>9</sup> and the recently published

guidelines<sup>10</sup> may help to restore confidence in one of the most accurate quantitative techniques in nuclear medicine. Finally, the attitudes related to this technique are essentially variable from country to country and from department to department. In some countries, such as Italy, the pediatricians only rarely use the plasma samples technique, whereas in others, such as Denmark, Sweden, or the United Kingdom, these techniques represent the best approach for accurate and simple measurement of overall renal function.

## Tracers

The measurement of GFR can be obtained by means of radioactive tracers exclusively eliminated by the glomerulus. Chromium-51 ethylenediamine tetraacetic acid (51Cr-EDTA) is probably the best tracer for that purpose, because of the tight binding of Chromium-51 to EDTA and the low protein binding of the compound. However, it is not universally available. A valuable alternative is the use of technetium-99m diethylenetriaminepentaacetic acid (<sup>99m</sup>Tc-DTPA), providing that the purity is guaranteed. The use of <sup>99m</sup>Tc-DTPA requires systematic quality controls.<sup>11-13</sup> The various algorithms designed for the calculation of GFR have been applied using indifferently both tracers.

## Algorithms for Clearance Determination

The most accurate method for evaluating GFR by means of radionuclides is based on the plasma disappearance curve after a single bolus injection of a glomerular tracer. It has been shown that a biexponential fitting on the plasma curve is an acceptable representation of the true clearance.<sup>14</sup> However, this method, which is presently considered as a "gold standard," is used infrequently in children because of the difficulties related with multiple blood sampling. Two accurate simplified methods have been proposed for clinical routine in children.

### The Slope-Intercept Method

This method is based on the determination of only the late exponential by means of at least 2 blood samples at 2 and 4 h after the intravenous injection of the tracer. The intercept with the y-axis determines the initial distribution volume of the tracer, and the product of distribution volume and slope allows the calculation of the clearance.<sup>9,10</sup> This simplified method has been validated in both adults and children.<sup>15-17</sup> However, some details of the procedure are still a matter of debate, as detailed in the following subsections.

**Number of Blood Samples to Be Taken.** Two blood samples, taken at 2 and 4 h, allow an accurate estimate of the slope. It has been suggested that the slope could be more accurately determined using 4 samples between 2 and 4 h<sup>18</sup> because an error in one of the samples could then be easily detected. However, it has been shown<sup>19</sup> that as many as 13 blood samples are required to increase significantly the accuracy of the slope.

**Correction Factor for Having Neglected the Early Exponential.** By neglecting the early rapid exponential, one intro-

duces a systematic overestimation of the clearance, which can be corrected using 2 different published algorithms adapted to children, the Chantler's method<sup>17</sup> and the Bröchner-Mortensen's correction.<sup>16</sup>

In theory, Bröchner-Mortensen's quadratic correction takes better account of the higher contribution of the early exponential for high clearance values. In the practice, in the range of clearance values higher than 140 mL/min/1.73 m<sup>2</sup>, the error introduced by this correction is not to be neglected. Indeed, this quadratic equation has been established on the basis of clearance values not greater than 130 mL/min/1.73 m<sup>2</sup> and it is easy to show mathematically that, using this correction factor, one cannot obtain clearance values higher than 150 mL/min/1.73 m<sup>2</sup>. In other words, the Bröchner-Mortensen's correction underestimates GFR values greater than 100 mL/min/1.73/m<sup>2</sup> and introduces a considerable compression of the clearance values higher than 140 mL/min/1.73 m<sup>2</sup>. Monitoring of hyperfiltration, a well-known feature of nonequilibrated juvenile diabetes, will therefore be seriously hampered by using this correction factor.

The Chantler's correction is a simple proportional correction, applied to all levels of renal clearance, thus neglecting the increasing weight of the first exponential for high clearance values. Another drawback, underlined by the British Nuclear Medicine Society (BNMS) guidelines,<sup>18</sup> is the fact that this correction factor has been determined on a mixed population of adults and children older than 5 years of age. However, the errors introduced by using this correction factor might be less important than the compression of high clearance values using BM formula.

**Quality Control.** One can check the distribution volume obtained. It is generally considered that the distribution volume, obtained by interpolation of the slope on the y axis, represents the extracellular volume, which is expected to be, in human beings with normal or subnormal renal function, around 20 to 30% of body weight. In clinical practice however, this distribution volume, which is a simple mathematical interpolation and not a direct measurement, tends to vary in a much greater proportion. However, distribution volumes below 15% or above 50% should raise the suspicion of a significant error on any of the measurements mentioned hereby. In case of significant peripheral edema, any method exclusively based on plasma samples is invalid.

### The Single Blood Sample Method

This method is an entirely empirical one, aimed to find the best possible correlation between a reference method and a plasma concentration at a given time. According to the complex relation existing between the slope-intercept method and the so-called "distribution volume" method, one can only determine an adequate sampling time for a given range of clearance values.<sup>20</sup>

Several algorithms have been described.<sup>21,22</sup> One of them<sup>22</sup> is based on a single blood sample taken at 2 h and offers 2 significant advantages: the algorithm has been established on a basic set of children and tested successfully on a second set. Moreover, the algorithm has proven to be applicable what-

ever the age of the patient, the coefficient of correlation between the single blood sample and the 2 blood sample methods being close to 1.0 for all ages. Recently, it has been shown<sup>23</sup> that the algorithm remains valid for adolescents and young adults. The only major limitation is the level of clearance: the method is not valid below 30 mL/min/1.73 m<sup>2</sup>. In case of known or suspected renal insufficiency (clearly abnormal plasma creatinine) one should use the slope-intercept method.

The main advantage of the technique is the unique blood sample needed. A 27 Butterfly needle for intravenous injection and a 25 Butterfly needle for blood sampling replace favorably the more aggressive Venflon needle, particularly in infants. According to the BNMS guidelines,<sup>18</sup> the drawback of the single blood sample technique is the absence of quality control, since the slope of the late exponential cannot be determined anymore. It is however possible to get the same level of quality control as for the slope-intercept method, by creating artificially three different slopes, using arbitrary 20%, 25%, and 30% distribution volumes and calculating on that basis 3 different GFR values; a significant difference between the single sample clearance and the three calculated GFR indicates the presence of error.<sup>24</sup>

## Normal GFR Values

Estimated normal values, corrected for body surface, have been published.<sup>25</sup> The clearance level, uncorrected for body surface, increases progressively from birth to adulthood. The clearance, corrected for body surface area, increases from birth to approximately 2 years of age and then remains constant into adulthood. One major inaccuracy related to that publication has to be raised. Normal values were derived from young patients generally referred to the department of nuclear medicine because of acute pyelonephritis. The patients included in the study all had a normal left to right DMSA uptake ratio and no regional abnormalities on the DMSA images and were, on that basis, considered normal. The authors, at the time of the publication, were not aware of the fact that acute renal infection could result in severe hyperfiltration, in a kidney with or without DMSA defects.<sup>26,27</sup> New data, excluding acutely ill patients, have recently been analyzed. The same pattern of GFR, corrected for body surface, reaching an adult level around 2 years of age, was observed (Piepsz and coworkers, unpublished data). Although the range of normality in children after 2 years of age remains unchanged (80 and 140 mL/min/1.73 m<sup>2</sup>, respectively for percentiles 5 and 95), the mean normal value is significantly lower (104.4 mL/min/1.73 m<sup>2</sup> instead of the previously reported 113.9 mL/min/1.73 m<sup>2</sup>).

## Accuracy and Reproducibility of Simplified Methods

The wide range of normal values, in children older than 2 years of age, represents the physiological fluctuations of GFR from patient to patient rather than methodological flaws. Indeed it should be underlined that in younger children, and particularly in infants, the range is much smaller. The GFR,

not corrected for body surface area, in infants younger than 1 month of age, is close to 10 mL/min, with a small SD of 4 mL/min, suggesting that the methodological error is small, whatever the age.

The day to day reproducibility is a matter of controversy. It has been suggested by the BNMS guidelines<sup>18</sup> that at least a 20% change is required before a measured difference can be regarded as significant. This number mainly is based on a retrospective study of patients with chronic renal disease followed for a long period of time.<sup>28</sup> Such a cut-off level should fundamentally question the utility of this type of clearance. However, better reproducibility has been observed by others<sup>29,30</sup> and the conclusions of these guidelines should probably be less affirmative, until a prospective well-designed study clarifies the subject. Anyway, a similar level of day-to-day reproducibility is observed for the reference biexponential method and for the simplified methods, while the use of the slope alone for estimating GFR results in a lower reproducibility.<sup>31,32</sup> The reproducibility is even better for the single blood sample method than for the slope-intercept method.<sup>33</sup>

## Clinical Indications

Determining GFR by means of radioactive tracers can be useful in the following situations (1) evaluation and follow-up of renal function in chronic glomerular diseases, such as hemolytic-uremic syndrome and diabetes mellitus; (2) evaluation and follow-up of renal side effects of nephrotoxic drugs, such as ciclosporin or antibiotics; (3) estimation of absolute single-kidney GFR, by combining overall GFR with the split function obtained by means of the renogram (please see the section, "The Renogram"), in conditions such as unilateral or bilateral hydronephrosis, urinary tract infections with or without associated vesico-ureteral reflux, small kidney, single kidney, duplex kidney, urethral valves, pre- and postoperative follow-up; and (4) it can be considered every time renal impairment is suspected, even when plasma creatinine is in the normal range.

## Conclusions

The determination of overall renal function by means of plasma sample radionuclide technique has multiple advantages in pediatric practice: (1) it offers an accurate measurement of renal function for clearance values above 15 to 20 mL/min/1.73 m<sup>2</sup>; (2) it represent a noninvasive approach (one intravenous injection and one or two blood samples), friendly to the child, delivering a rather negligible amount of radiation; and (3) it provides an information significantly more accurate than the nonradioactive traditional measurements.

## Cortical Scintigraphy

### Tracers

There is presently a wide consensus on the preferential use of DMSA labeled with Technetium-99 m for cortical scintigraphy.<sup>34</sup> The tracer is taken up by the proximal tubular cells, directly from the peritubular vessels, and is therefore located

in the outer layer of the kidney with minimal activity in the medulla and the calyces. In 2 specific conditions however, the excretion of the tracer can significantly interfere with the interpretation of the images. In pronounced hydronephrosis with marked delayed transit, the excreted renal activity may accumulate in the calyces and pelvis, altering artificially the intrarenal tracer distribution. In Fanconi syndromes, the DMSA escapes the tubular cell and is found mainly in the urine, resulting in low renal activity.

Alternative tracers for renal imaging are those with a high excretion rate used for renography, such as Tc-99m MAG3 and I-123 Hippuran. They offer the advantage of combining cortical imaging with information about renal transit. They are however less accurate for the detection of cortical defects. Tc-99 m glucoheptonate is partly bound to the renal tubules and can be used for cortical imaging. However, the cortical uptake is significantly less than with DMSA. Moreover, as much as 40% to 65% of the tracer is excreted, and this may interfere with the activity retained within the cortex and complicate the interpretation of the images.

### Acquisition Procedure

Much effort has been devoted recently to the production of consensus and guidelines in this field.<sup>34-36</sup> Having an immobile child during the whole acquisition is mandatory for the quality of the image. However, drug sedation generally can be avoided. Images should be acquired 2 to 3 h after tracer injection. The collimator should be turned side up and the patient should lie on the camera in supine position. A high-resolution collimator is required. The matrix should be at least  $128 \times 128$ . At least 300,000 counts or 5-min counting per image are necessary. Pinhole views (2- to 3-mm aperture) may be useful, particularly in infants, but this technology is not used universally. There is still a need for a systematic approach to the normal and abnormal pinhole images. Posterior and posterior oblique views are recommended. However, it has been shown that the posterior view offers the most information concerning cortical integrity and should receive the highest priority. Obliques views may sometimes contribute to a change in the final report, although unusual.<sup>37</sup> The anterior view should be performed in horseshoe kidney and in ectopic pelvic kidney.

### Reporting and Image Quality

Reporting is preferably performed directly on the computer screen. A gray scale should be used rather than color images. The intensity of the image should be adapted to allow differentiation of the outer part of the kidney (cortex) and the less-active inner part (medulla, calyces, vascular structures). In a crying child, the kidneys are moving with the diaphragm, even if the child remains immobile. It is important to check for kidney movement before the child leaving the department: blurred or double outlines generally reflect the presence of movement.

### Interpretation of Images

The interpretation of the images generally is easy, although one should be aware of the existence of several normal vari-

ants, including spleen impression, variability in the shape of the renal contours, number and size of the columns of Bertin, persisting fetal lobulation, and poles appearing as hypoactive. For those clinicians not accustomed to the DMSA, the main pitfall in interpretation is probably a relative hypoactivity of a pole, contrasting with an underlying huge parenchymal mass and thus giving a false impression of a polar lesion. Lesions are described as single or multiple, small or large, with or without volume loss. The renal contours limiting the lesion can be indistinct but still regular, or on the contrary irregular, corresponding to a loss of parenchymal mass. The kidney can be small or swollen. When observed during the acute phase of pyelonephritis, hypoactive areas without deformity of the contours are likely to become normal during a late control image, whereas deformed contours often correspond to renal sequelae. However, it is not recommended to conclude the presence of renal sequelae on an "acute" DMSA. Permanent lesions can only be reported on the basis of late control studies at least 6 months after the acute infection. One should be aware of the fact that a persistent lesion is not necessarily a sequel of the most recent acute pyelonephritis but may be related to a previous one, or may even be congenital (dysplasia). There is at the present time no consensus about the usefulness of single-proton emission computed tomography (SPECT) for DMSA scintigraphy in children, although it may help in individual cases. When performing SPECT, attention must be paid to the risk of false-positive images<sup>38,39</sup> and to the necessity of heavy sedation in young children. It has been shown that SPECT images decrease the reproducibility in reporting on DMSA scintigraphy.<sup>40</sup>

### Sensitivity and Specificity

There is much evidence that DMSA scintigraphy is more sensitive than intravenous urography, ultrasound and even color Doppler in the detection of both acute lesions and late sequelae.<sup>41,42</sup> On the contrary, scintigraphic abnormalities are not specific: in case of acute urinary tract infection, regional defects can be attributable to acute infection but also to any other underlying disease, such as renal abscess, hydronephrosis, cysts, or duplex kidney with abnormal upper or lower moiety. It is therefore mandatory to combine scintigraphy with a technique, which allows one to differentiate between these situations: ultrasound has a low sensitivity for acute pyelonephritis but is useful in excluding any expansive lesion or huge dilation of calyces and pelvis.

### Validation

Animal models combining vesicorenal reflux and infection have shown the relation between the extension of the anatomical lesion (acute lesion or scarring) and the presence of a scintigraphic abnormality.<sup>43</sup> DMSA scintigraphy is normal in the absence of an anatomical lesion and only microscopic lesions, unlikely to give rise to scars, are missed on DMSA images.

## Reproducibility in Reporting

Poor as well as good interobserver reproducibility has been observed. A recent large study involving a great number of nuclear medicine physicians revealed a high concordance on normality or abnormality.<sup>44</sup> A similar level of interobserver reproducibility was reached, whether the lesion was acute or limited to a late scar.<sup>45</sup> This does not eliminate that in a significant number of cases, great discordance might be noted between different observers. Factors such as quality of images, lack of awareness of the normal patterns, and low renal function, may contribute to a poor reproducibility.

## Relative Function

The determination of left and right relative DMSA uptake is an accurate and robust quantitative measurement and should be systematically added to the scintigraphic images. Because of the high signal-to-noise ratio, background correction is probably not mandatory in cases with good renal function. A background can be introduced, however, by drawing for instance a small region of interest (ROI) above each kidney and another under each kidney, avoiding the bladder activity. In case of renal failure, this correction method is inaccurate. Correction for attenuation is not mandatory for relative function, except in the case of ectopic kidney anteriorly displaced. However, in case of pelvic kidney, the relative function remains inaccurate even after attenuation correction, because of the additional attenuation resulting from the pelvic bone. It has been shown that interobserver reproducibility of relative function measurement generally is good.<sup>46</sup> The normal lowest value for relative uptake usually is around 45%.

## Absolute Function

Determination of absolute function of each kidney separately by means of DMSA is used in different departments around the world. The renal counts at a given time are expressed as a percentage of the injected dose. The results were shown to be only fairly correlated with reference techniques, even when using SPECT.<sup>47,48</sup> Factors that may influence both the accuracy and the day-to-day reproducibility are the exact estimation of kidney depth, the timing of measurement,<sup>49</sup> and the quality of the preparation injected.

## Is DMSA Scintigraphy Useful in Clinical Practice?

The area of highest controversy is probably the place of cortical scintigraphy in the strategy of investigations in urinary tract infection (UTI). In children, 3% to 5% of girls and 1% to 2% of boys have had a symptomatic UTI,<sup>50</sup> and most of the first infections occur in children younger than 2 years of age.

The traditional attitude is to define "complicated" urinary tract infection on the basis of clinical and biological criteria, to treat this entity in a more aggressive way than in the case of simple cystitis, to prescribe a prophylactic treatment to protect the kidney from further deterioration, to perform systematically a micturating cystography to diagnose the grade of vesico-ureteric reflux, and to treat dysfunctional bladders. Having this approach in mind, DMSA scintigraphy has no

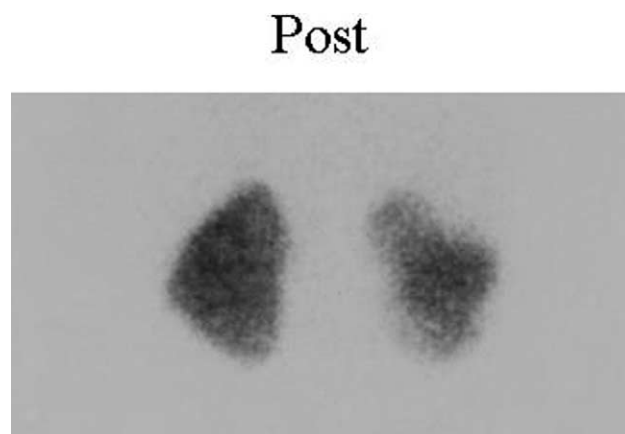
place either for the diagnosis of acute pyelonephritis or for adapting later on the strategy of management. It has been suggested<sup>51</sup> that even ultrasound is unnecessary, since underlying hydronephrosis is already detected during fetal life. This general attitude, based on clinical data, makes sense and is adopted by many centers around the world. However, attitudes based on high-risk groups are emerging that might change our traditional practice in a near future.

## Diagnosis of UTI

There is no doubt that the diagnosis of UTI relies on a urine culture obtained from a properly collected urine sample.<sup>52</sup> Theoretically, there is no place for imaging in that perspective. However, it has been shown in a prospective work performed in 2 different hospitals<sup>53</sup> that as many as 10% of children with strong clinical suspicion of acute pyelonephritis may present with repeated negative or equivocal cultures despite a positive DMSA scintigraphy (Fig. 1). One could argue about the fact that DMSA lesions might in those cases have preceded the infection. However, this is not the case because many of these lesions disappeared at late control. One can easily understand that in that subgroup of patients, the diagnosis of complicated infection would have been missed entirely in the absence of scintigraphy.

## Diagnosis of Acute Pyelonephritis

It is now an old tradition to diagnose upper UTI on the basis of clinical and biological symptoms, such as fever, septic signs, loin pain, high C-reactive protein, and an elevated number of white blood cells in peripheral blood. The validation of these criteria can be debated. It is based on bladder washout and ureteral catheterization studies performed on a limited number of patients before 1950. The results are open to criticism.<sup>54</sup> Patients with a full clinical picture of complicated UTI may or may not present with abnormalities on DMSA scintigraphy performed within the first week of infec-



**Figure 1** A 4-month-old boy with high fever, and repeated urine cultures that were negative. The DMSA scintigraphy shows important hypoactivity of the right upper pole, with deformity of renal outlines. The child was treated for acute pyelonephritis on the basis of the scintigraphy. A control scintigraphy 6 months later was entirely normal, confirming retrospectively the diagnosis of acute pyelonephritis.

**Table 1** Frequency of Abnormal "Acute" DMSA in the Case of Clinical Pyelonephritis: Selection of Large Series of Cases

Authors	Year	Percent Abnormal DMSA
Majd et al <sup>55</sup>	1991	66%
Rosenberg et al <sup>56</sup>	1992	52%
Melis et al <sup>57</sup>	1992	62%
Jakobsson et al <sup>58</sup>	1992	78%
Benador et al <sup>59</sup>	1994	67%
Levtchenko et al <sup>60</sup>	2000	68%
Hoberman et al <sup>61</sup>	1999	61%
Benador et al <sup>62</sup>	2001	65%

tion.<sup>55-62</sup> When analyzing the largest series of acute pyelonephritis (Table 1), it appears that approximately 65% of cases will present cortical abnormalities corresponding to the expected histological lesion. One of 3 patients considered as having acute pyelonephritis has no DMSA lesion. The risk for developing scars for a kidney with an acute DMSA lesion can reach 30%.<sup>60,62</sup> It is negligible in case of normal DMSA.

### Treatment of Acute Pyelonephritis

Several surveys and questionnaires are available concerning the way the clinicians are treating their patients. Some of them,<sup>63,64</sup> covering an entire region or even a country, have come to the conclusion that admission to the hospital and intense intravenous treatment is dependent mainly on the subspecialty of the clinician (general practitioner, general pediatrician, pediatrician working in hospital, or pediatric nephrologist) rather than on some objective clinical criteria. A recent personal small survey (unpublished) on 20 departments of pediatric nephrology in Europe (7 countries) has shown that most of the departments recommend intravenous treatment. The proposed duration of intravenous treatment was 1 to 3 days (34%), 5 to 7 days (33%), and 7 to 10 days (27%). A French consensus<sup>65</sup> recommends 7 to 10 days of aggressive intravenous treatment in young or very ill children. Hoberman and coworkers<sup>61</sup> propose an oral treatment with third-generation cephalosporins and consider intravenous treatment as unnecessary.

Which attitude should be applied? Hansson and Jodal<sup>66</sup> consider that "local traditions and beliefs guide the choice of treatment strategy. Controlled studies are lacking." Indeed, there are presently not more than 3 published prospective randomized studies<sup>60-62</sup> comparing, in acute pyelonephritis, 2 types of treatment. One of them is issued from our group<sup>60</sup> and showed that, in case of delay in treatment (more than 7 days after appearance of the first symptoms), more scars were noted at late control in the group having received 3 days of adequate intravenous treatment compared with the group treated intravenously for 7 days.

On the basis of this study, the following procedure has been defined in our department: children admitted for acute pyelonephritis are treated intravenously for 7 days. DMSA scintigraphy is performed systematically within 2 days of admission and intravenous treatment is stopped after 24-hour apyrexia if the scan is normal. This is an example on

how the type of treatment can be modulated on the basis of the acute DMSA. A similar approach has been proposed elsewhere.<sup>67</sup>

### Performing Micturating Cystography (MCUG)

A worldwide classic approach is to perform MCUG in any first UTI, to detect a vesico-renal reflux, and to modify the management of the patient. However, attitudes vary from center to center, the systematic indication of MCUG being, for instance, restricted to young children or to patients presenting with recurrent infections. The rationale for a systematic approach of reflux in case of infection is the close relationship described between reflux and scarring. A recent meta-analysis comparing DMSA patterns to the results of MCUG suggests that this relationship is not proven, with reflux often being associated with a normal kidney, whereas many scarred kidneys are observed in the absence of any reflux.<sup>68</sup> This apparent contradiction is probably attributable to 2 main errors in the design of many studies. First, the results of DMSA scintigraphy often are compared with MCUG without taking into account the timing of DMSA scintigraphy. There is no doubt that during the acute phase of infection, DMSA lesions can be seen with or without reflux, without evident correlation between the 2 parameters.<sup>55</sup> Second, a simple correlation between reflux and scarring does not take into account the fact that low-grade reflux (I and II), which is the most common type in case of UTI, is associated with a low risk of scarring.

The International Reflux Study,<sup>69</sup> in which 287 children were allocated on the basis of UTI and high-grade reflux (mostly grade IV) has revealed at entry as much as 80% of unilateral or bilateral scarring, which is much higher than what is observed in any population selected only on the basis of complicated UTI. A recent study<sup>70</sup> clearly showed that the more important the grade of reflux, the higher the number and the intensity of scars. On the basis of that association, it was interesting to see whether the presence of renal scarring on the DMSA scan could be an indicator for the decision to perform a MCUG in children with UTI. In this retrospective study on 303 children younger than 2 years, only 7 patients were found with normal DMSA images and high-grade reflux (grade III). In these patients, no scarring was noted during follow-up. It might be that DMSA scintigraphy could replace MCUG as a first-line investigation, this last examination being then performed only in case of abnormal DMSA. This strategy would spare a great number of unnecessary, unpleasant and invasive procedures. It has to be confirmed in a long term prospective study.

### Indication for Chemoprophylaxis

Since Smellie's pioneer work,<sup>71</sup> continuous chemoprophylaxis is widely given, sometimes for many years, to children with UTI and reflux. Recently, a meta-analysis has put this systematic approach in question.<sup>72</sup> Present attitudes toward prophylaxis are far from homogeneous, the indications depending on factors such as age, presence of reflux, grade of reflux, recurrence of infections, and dysfunctional bladder. A controlled study of patients with reflux grade III-IV has been proposed<sup>73</sup> The population at risk for scarring and further

kidney deterioration being the one with DMSA lesions during acute pyelonephritis, one could hypothesize that DMSA pattern, rather than MCUG, may serve as an indicator for chemoprophylaxis, which raises the need for a prospective randomized study with and without prophylaxis, patients being stratified according to both the DMSA and the MCUG results.

### Duration of Follow-up

It has been the merit of some clinicians to have followed prospectively large cohorts of patients with UTI, to detect any complication, such as recurrent infections, progressive scarring, or late complications of hypertension or renal failure.<sup>74-76</sup> The advantages of such prospective follow-up should be put in balance with the major drawback of keeping under medical control lots of children who are unlikely to develop complications. Vernon and coworkers have shown, on a large population of northern United Kingdom,<sup>77</sup> that children older than 4 years of age presenting an acute pyelonephritis without DMSA lesions will not develop any late scarring, whatever the grade of reflux or the recurrence of infections. Because children younger than 3 years of age are not more susceptible than older ones for the development of scars,<sup>78-80</sup> a similar prospective study should be extended to this young age group. Again, the DMSA scintigraphy, already performed during the acute phase of infection, could serve as a criterion for the decision or not of a careful long-term follow-up.

### Late DMSA and Scarring

Is it important to diagnose scars? From a recent review of the literature,<sup>81</sup> it is obvious that children and adults with pyelonephritic renal scarring are at risk of serious long-term complications, such as renal insufficiency, hypertension, and pregnancy-related complications. The interpretation of these studies is not straightforward. Most of these studies are retrospective and comprise rather small numbers of patients. Long-term studies<sup>71,82</sup> describe the evolution of young patients diagnosed at a time when medical care was different from the present one. The results may not represent the risks of the pediatric population of today. Moreover, it is probable that the risk at late age could be largely predicted on the basis of the characteristics at entry: number and size of the renal lesions, level of overall and single kidney GFR, initial blood pressure. In a recent Italian multicentric study, for instance, it has been shown that end-stage renal disease by age 20 years was 56% when the inclusion criteria were limited to children with a creatinine clearance below 75 mL/min/1.73 m<sup>2</sup>.<sup>83</sup> Having this in mind, an accurate approach of morphology and function of the kidney, at least at entry, is mandatory.

### Research

Although a huge literature covers the different aspects of urinary tract infection, the controversy is still immense in fields such as treatment of acute pyelonephritis, indication for chemoprophylaxis, role of vesico-ureteral reflux, scarring, and level of renal function. Local traditions and beliefs often replace strong evidence. End points should ideally be the complications at a later age, but the comparison between early and late DMSA scintigraphy has proven to be an ade-

quate surrogate end point.<sup>60-62</sup> There is a need for well-conducted prospective studies using these criteria.

## The Renogram

### Guidelines

During recent years great effort has been put into better standardization of the renogram in children. The "well-tempered diuretic renogram"<sup>84</sup> was a valuable effort to standardize the diuretic renogram. The consensus conference<sup>85</sup> was essentially centered on the determination of split function in children and adults. The EANM pediatric guidelines<sup>86</sup> covered all of the aspects of the renogram, including split function, transit determination and analysis of the diuretic curve.

Therefore, it is not the purpose of this review to redefine all the aspects of these guidelines but to emphasize somewhat more on some aspects of the renographic technique, such as new developments, or simply controversial points. Moreover, it also is our aim to explore the field of application of the technique, according to the experience of the author and to analyze how this technique has influenced the strategy of management in antenatally detected hydronephrosis.

### Interpretation of the Renogram

Since the 1970s, the physiological significance of the renogram is well recognized.<sup>87</sup> Flow, uptake, and excretion are overlapping within the so-called vascular, parenchymal, and excretion phases. The practical implication of this overlap is, however, not always well understood. The time to the maximum of the renogram ( $T_{max}$ ) is simply the equilibrium point between uptake and excretion and not the beginning of the excretion, which starts earlier. Describing grossly the renal transit on the basis of empirical parameters such as  $T_{max}$  or  $T_{max}/T_{20}$  is a reasonable approach, but one should be aware of the fact that the overall level of renal function may considerably affect these empirical parameters. Similarly, a simultaneous injection of tracer and furosemide often gives rise to a curve characterized by a short  $T_{max}$  followed by a flat third phase. Such a flat curve does not mean absence of excretion but an extraction from the blood equal to what has been excreted. The solutions to these limitations will be evoked in the paragraph on renal transit.

### Tracers

DTPA is the most widely used renal dynamic tracer. It is a small molecule that is exclusively filtered by the glomeruli with an extraction efficiency of 20%. MAG3 is almost exclusively excreted by secretion in the proximal tubules with an extraction fraction of approximately 50%.<sup>88</sup> The main reason to use this last tracer, or other tracers with high extraction rate such as Hippuran-I123 or Tc-99m EC, is the high target to background ratio resulting in good image quality, which is of particular importance in the infant who has an immature function. Prenatal screening of hydronephrosis is aimed at detecting as early as possible alterations of renal function to assure, from the beginning on, the adequate treatment and/or follow-up. One cannot expect to determine split function



with high accuracy by means of DTPA in the very first months of life. Improvement of initial low split function or deterioration of function can both occur within the first 6 months of life and may be overlooked on DTPA studies.

### Is it Acceptable to Use MAG3 Split Function to Estimate Split Glomerular Function?

It has been demonstrated in experimental models that both tubular and glomerular function are affected differently in some well-defined conditions. Acute experimental unilateral total ureteral obstruction gives rise to a glomerular function more depressed than the tubular function on the side of the obstruction.<sup>89</sup> This phenomenon is observed during the first few hours after obstruction, after which tubular and glomerular split function become comparable.<sup>90</sup> Acute ischemia provoked by complete ligation of the renal artery results in similar glomerulo-tubular imbalance.<sup>91</sup> In clinical practice, acute obstruction, such as observed in renal colics, gives rise to the same discrepancy between glomerular and tubular split function.<sup>92,93</sup> It also is well known that in renovascular hypertension, the administration of captopril may depress considerably the glomerular uptake function, without any effect on tubular uptake. However, there is a large body of literature confirming that in most nonacute situations in children and adults, such as nonrenovascular hypertension, renal insufficiency, hydronephrosis, megaureters, small kidney, duplex, both glomerular, and tubular function, are almost identical,<sup>93-97</sup> justifying the use of tubular tracers with high extraction for the estimation of glomerular split function.

### Parameters That May Affect the Determination of Split Function in Children Drawing Renal ROI

It is essential that renal ROI include the entire parenchyma. One should be able to modify the window, to enhance the contrast of the renal image. Moreover, because late accumulation of tracer can occur in the pelvis, one should verify that the renal ROI, which has been drawn on the first images of the acquisition, still contains the enlarged pelvis, as seen on the late images.

### Drawing Background ROI

Consensus and guidelines<sup>85,86</sup> suggest the perirenal background as the best compromise for the structures overlying the kidney area. The vascular component is underrepresented when using the popular subrenal area, whereas it is the tissular component that is underrepresented when using the liver and spleen area exclusively. It can be shown that, in a single kidney model, a background ROI located in the subrenal area of the absent kidney may give rise, in this absent kidney, to a split function as high as 25% of the total function<sup>98</sup>

In young infants, very dilated systems may complicate the drawing of the ROI, the danger being a perirenal ROI partially outside the patient. Adequate zoom should be intro-

duced at acquisition and, if necessary, one should avoid the external part of the background area.

### Algorithms for Split Function

The background corrected count between 1 and 2 min is well accepted as representing the split function (integral method).<sup>85</sup> Theoretically, the Rutland-Patlak plot<sup>99</sup> removes the vascular part of the background that has not been completely corrected by subtracting the perirenal activity. In the case of tubular tracers such as MAG3, the influence of this residual background activity on split function is negligible.<sup>100</sup> Moreover, new types of errors may result from basic assumptions inherent to the Rutland Patlak method: the tissular activity in the kidney ROI is assumed to be identical to the tissular activity around the kidney; the heart curve is assumed to represent the plasma curve; and the statistics on the Rutland-Patlak are less favorable than in the integral method. It has been shown that both the day to day reproducibility and the accuracy of split function are not improved by the additional use of Rutland-Patlak plot.<sup>100</sup> It is only in the case of low overall function or when a tracer with low extraction such as DTPA is used that the additional correction might become useful.<sup>101</sup> In the case of renal failure, any method aimed to determine split function is entirely invalid.

### Time Interval for the Calculation of Split Function

It is well accepted that renal uptake should be measured between 1 and 2–2.5 min after tracer injection. However, this constraint is dependent on the renal transit and the time necessary for a significant escape of tracer out of the kidney. Because the F0 furosemide test becomes more and more popular in children,<sup>102,103</sup> the escape out of the kidney, under influence of a high urinary flow, may occur more rapidly, sometimes before 2 min, in particular on the nondilated side. This factor should be taken into account when defining the time interval during which the split function should be determined, the risk being an underestimation of split function on the normal side.<sup>103</sup>

### Absolute Single Kidney Function

Several algorithms based on renal and heart counts have been proposed for calculating the absolute function of each kidney separately and the sum of both kidney functions representing the overall function.<sup>104-107</sup> The most simple one, and therefore the most popular one, is the calculation of the ratio between the renal counts between 1 and 2 min and the injected dose, an abacus that transforms this ratio into a clearance value.<sup>108-111</sup> However, many factors contribute to the inaccuracy of all these methods, namely the errors of estimating the true renal and plasma activity, ie, the heart curve is not a plasma curve,<sup>112</sup> the attenuation resulting from kidney depth can only be approximated, the nonrenal activity over the kidney ROI plays a more important role than for determination of split function. Whichever tracer is used, neglecting the additional vascular background will give rise to important inaccuracy.<sup>113</sup> These techniques are even less precise than creatinine-based formulae.<sup>114,115</sup> Plasma sample clearances are definitely more accurately and, therefore, it is not

surprising that until now no guidelines have been produced related to gamma camera clearances.<sup>9</sup> In our opinion, the combination of a plasma sample method for overall renal function, associated with a split function obtained from the renogram, constitutes the most accurate approach for single kidney function. For older children with conserved overall function, Tc-99m DTPA can be used for both purposes. In infants or in case of decreased overall function, the combined use of Tc-99m MAG3 for split function and Cr-51 EDTA is preferred. In both options, and in accordance with the glomerulotubular balance described previously, the results can be reasonably expressed as single kidney GFR, in mL/min.

## Renal Transit

Much has been written on this subject. We refer the reader to a recent overview of the literature.<sup>116</sup> In pediatric practice, the choice of the methodology should be adapted to the final objectives expected. The estimation of renal transit on the basic renogram is aimed at differentiating those kidneys able to eliminate adequately the amount of tracer that has been extracted from the blood pool from those with more or less delayed excretion, which will necessitate a furosemide provocation test. It is clear that for this purpose, simple methodology is sufficient. A normal, slightly delayed, or considerably delayed  $T_{\max}$  is an empirical semiquantitative parameter allowing decisions about a furosemide test. A transit delay is nevertheless not excluded despite a normal  $T_{\max}$ : a simple inspection of the images and the curves may reveal the insufficient renal drainage at the end of the basic renogram. The determination of "true renal transit" by means of any of the deconvolution techniques offers no obvious advantage in differentiating normal from abnormal transit or in separating simple stasis in a dilated system from a true impairment of flow. On the contrary, several constraints related to the use of deconvolution are violated in the case of dilated systems and, in the case of delayed transit, considerable underestimation of true renal transit is not excluded because the retention function has not been fully determined at the end of the renogram.<sup>116,117</sup>

Much effort has been put into the determination of cortical transit, allowing to avoid the problem of stasis into a dilated pelvis. Parametric images displaying a pixel-by-pixel time dimension have been proposed, such as a  $T_{\max}$ , mean time or mean transit time image<sup>118-120</sup> or factor analysis.<sup>121</sup> None of these techniques has proven to be superior to the others. Deconvolution on a predefined "cortical area" assumes that one knows in advance the exact limit between cortex and collecting system. Moreover, the additional difficulty in children with hydronephrosis is that the dilated system often overlaps considerably the cortical area, masking therefore a normal cortical transit.<sup>122</sup> Finally, according to Britton, the cortical transit should theoretically be able to separate those kidneys with simple dilated uropathy from those with a more severe type of nephropathy as a consequence of a "true obstruction."<sup>123</sup> However, there is no single article demonstrating that kidneys with impaired cortical transit are at higher risk for functional deterioration if left untreated.

## Furosemide Test

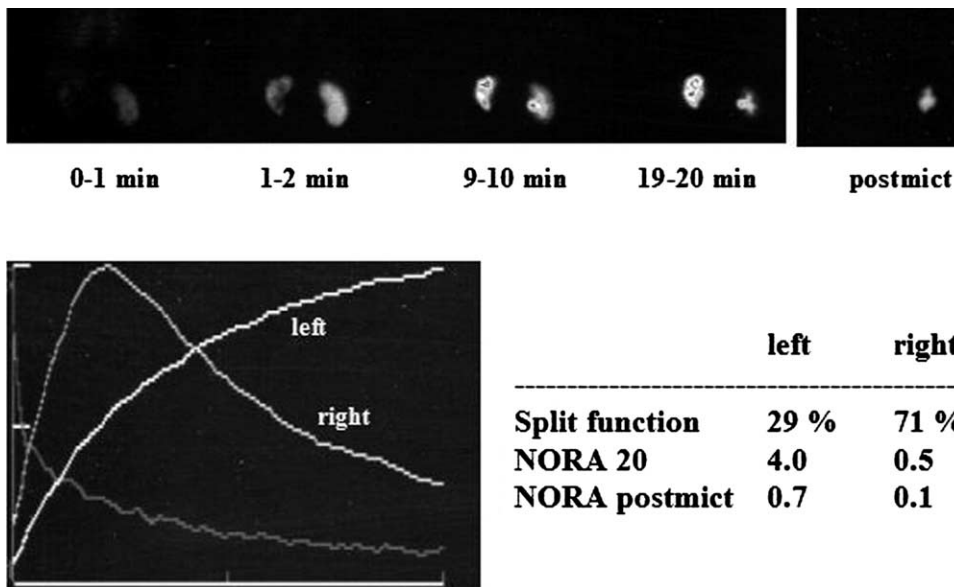
It was the hope, when the furosemide test was introduced<sup>124</sup> that it would be able to separate those kidneys with simple dilation and impaired transit because of the reservoir effect of the dilated cavity, from a more severe flow impairment related to obstruction. This is probably true in many adult cases with acquired hydronephrosis as a consequence of cancer or ureteral stones. In these cases, an impairment of renal transit or a poor response to furosemide undoubtedly reflects an obstructive phenomenon. Since the advent of fetal ultrasonography in the late 1970s, and the introduction of the systematic antenatal screening of hydronephrosis, the clinician is faced with an important population of asymptomatic infants with dilation of the collecting system. In these patients, the interpretation of the furosemide test is not necessarily straightforward. Although the different steps of the acquisition, processing and pitfalls have now been well circumscribed in guidelines and reviews,<sup>86,125,126</sup> several points are still controversial or simply ignored, as discussed in the following subsections.

### Hydration, Bladder Catheter, and Postvoiding Views

The European attitude is to maintain the test as a noninvasive procedure. For that reason, adequate oral hydration is preferred to intravenous hydration administered before and during the acquisition. Although bladder back-pressure is known as a factor that may give rise to a poor response to furosemide, placing a bladder catheter to avoid the accumulation of urine is not recommended in most of the cases. It can be replaced, in case of significant retention of tracer at the end of the test, by a late postvoiding image (Fig. 2) obtained after micturition and after gravity has facilitated drainage.<sup>122</sup> The time at which this late image should be performed should be standardized: it is easy to understand that performing the late image at 24 h would always give rise to an interpretation of "complete renal emptying." The time at which a late image should be performed depends on the clinical indication and the approximate level of transit time. In the case of hydronephrosis, in which we expect a prolonged transit time, the ideal time for the late image should be approximately 50-60 min after tracer injection.<sup>127</sup> After the end of the furosemide acquisition, small children are maintained in a vertical position in the arms of the accompanying adult or caregiver, and spontaneous voiding always occurs within the half an hour preceding the late image. Older children are simply encouraged to void and to walk during this period. A classical pitfall is to interpret this late image isolated from the furosemide acquisition. It would then systematically give a false impression of poor renal emptying on the hydronephrotic side. It is of great importance to scale this late image using the same maximum for all 3 acquisitions: basic renogram, furosemide test, and the late postmicturition image.

### Parameters Describing the Furosemide Curve, Including the Late Postvoiding Image

The  $T_{1/2}$  of the furosemide curve has been recommended as a parameter of choice to estimate the response to the diuretic, although the committee responsible for the "well-tempered

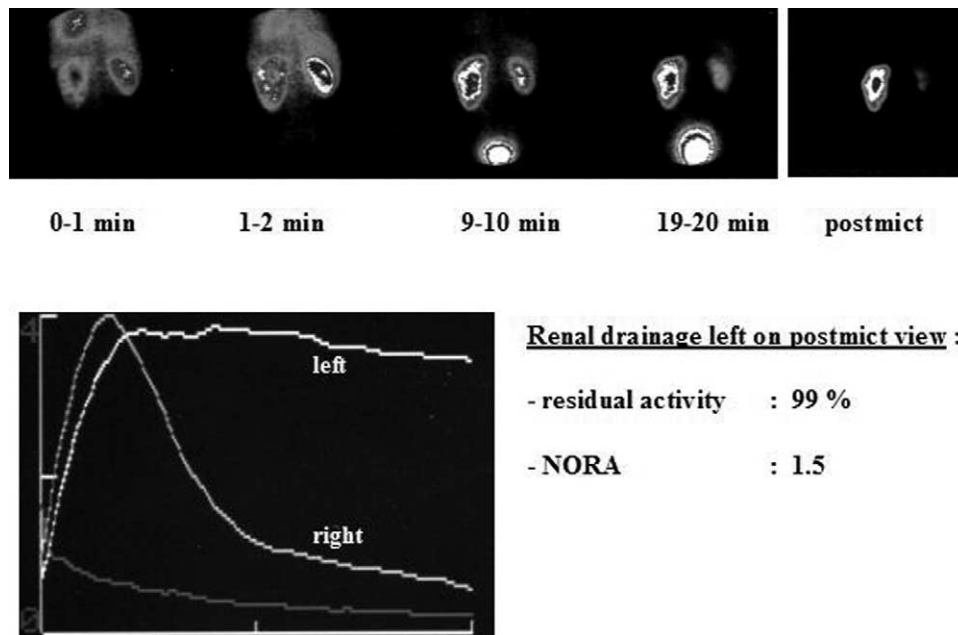


**Figure 2** A 14-year-old girl who underwent, 8 years before this renogram, a left pyeloplasty because of pelvi-ureteric junction stenosis. The MAG3 renogram shows an impaired transit on the left side (images, curves and high NORA value at 20 min). A late gravity- assisted and postmicturition image reveals a good renal emptying, without additional furosemide injection.

diuretic renogram” is aware of the fact that the value of T1/2 depends on the way this parameter is measured on the curve.<sup>84</sup> An additional pitfall is the fact that the initial height of the curve on which the T1/2 is based is dependent on the amount of tracer that has left the kidney before any diuretic has been administered. Paradoxically, the more that has left the kidney before the furosemide injection, the less steep the diuretic renogram will be (Fig. 3). The same paradox is encountered when expressing the residual postvoiding activity

in percentage of the activity present in the kidney when starting the diuretic renogram or at the end of the diuretic acquisition.<sup>128</sup> Finally, it is remarkable that all these criteria used to define the renal emptying during a F + 20 renogram have simply been transposed to the F0 renogram, without further validation.

It is therefore understandable that new parameters have been introduced, allowing a better expression of the amount having left the kidney or still present in the kidney. Output



**Figure 3** An 8-year-old boy with left hydronephrosis. Renogram performed under simultaneous injection of MAG3 and furosemide (F0 test). On the left side, the time to the maximum (T<sub>max</sub>) is reached at 4 min, but the curve remains flat afterward. This is a pattern often observed in F0 renograms. Images, including the postmicturition view, suggest an absence of renal emptying. The residual activity on the PM image is 99% of the activity seen on the last image of the renogram, thus confirming the poor emptying. However, such flat renogram, in opposition with a continuous ascending curve, means that a great part of the tracer which entered into the kidney has left the kidney. This is reflected by the moderately increased NORA value corresponding to a partial but significant renal drainage.

efficiency<sup>129,130</sup> is probably the most robust parameter for that purpose and describes at each moment of the acquisition (end of basic renogram, end of furosemide curve, postmicturition image) the amount of tracer that has left the kidney in percentage of what has really been taken by the kidney. Some drawbacks are inherent to the technique, mainly related to a properly adjustment of the integral of the heart curve on the early part of the corrected renogram.<sup>131</sup> As noted previously, the heart curve is only an approximate estimation of the true plasma curve, whereas the adjustment remains dependent on the quality of background correction. A practical simplification of this parameter is the use of "NORA" (normalized residual activity), which is a simple ratio between the activity at a given time of the acquisition (end of basic renogram, end of furosemide curve, postmicturition image) and the 1- to 2-min renogram activity.<sup>132</sup> This parameter reflects the amount that remains in the kidney. Both parameters (and particularly output efficiency) have the great advantage to be less dependent on the level of overall function than the traditional parameters. When both are applied to a general population of children having undergone the renographic procedure, they are fairly correlated.<sup>133</sup>

They can be applied whatever the moment of furosemide injection and allow the quantitative comparison of 2 successive tests performed in the same child, one using early furosemide injection (F0) and the other the F + 20. The final result, expressed either as the amount which has left the kidney (OE) or the amount still present in the kidney (NORA), will be approximately the same on the late postmicturition image using either F0 or F + 20.<sup>134</sup>

Normal values have been suggested on the basis of what was observed in normal contralateral kidneys.<sup>133</sup> Dilated but obviously nonobstructed kidneys (postoperative dilation, for instance) will be often characterized by much more altered drainage parameters, in the range observed in kidneys highly suspected of PUJ obstruction.

### **F + 20, F0, or F-15?**

Early furosemide injection was introduced initially to transform an equivocal F + 20 curve into either a normal curve or an obstructive pattern. In pediatric practice, however, as mentioned previously, the final drainage will be, in most cases, similar at a given time, whatever the moment of furosemide injection. The choice of timing for furosemide administration should be dictated by other reasons. The advantage of F + 20 is the possibility of estimating renal drainage on the basic renogram, in conditions similar to the normal urinary drainage during the daily life. One has then the choice to give or not to give the diuretic depending on the shape of the basic renogram. However, one can expect almost certainly, in case of a dilated collecting system, to observe poor drainage on the basic renogram. Therefore, in case the indication of the test is clear, it might be interesting to administer both the diuretic and the tracer simultaneously. For those who are in favor of using fine butterfly needles instead of placing a Venflon in small children, this technique permits the avoidance of 2 successive venipunctures. Moreover, it shortens the time of acquisition on the gamma camera. A theoretical drawback is

the striking change of urinary flow during the course of the renogram, since the maximal effect of the diuretic will occur only during the second part of the renogram. For those who feel uneasy with a procedure implying a dramatic urodynamic change during the acquisition, the injection of the diuretic 15 min before the tracer (F-15) will circumvent this drawback but offers no additional advantage compared with F0.

### **Interpretation of Drainage**

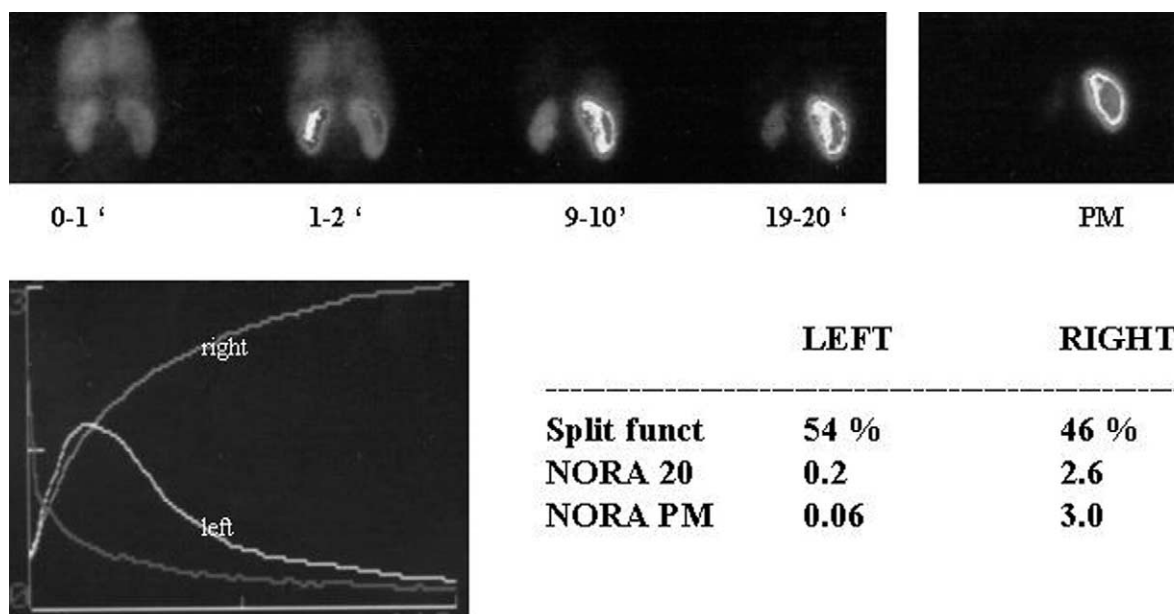
The interpretation of drainage is probably the main pitfall related to the technique. It is well accepted in the nuclear medicine world and also by the referring clinicians that an impaired transit during the basic renogram has no strong significance as far as obstruction is concerned. Any dilation of the collecting system such as observed in various situations, such as major reflux, extrarenal pelvis, and postoperative situations, may result in a "reservoir" effect. The furosemide test is aimed to separate a "lazy" collecting system from real impairment of urinary flow. Unfortunately, the "reservoir" effect may occur even during the furosemide acquisition and the late postmicturition images. Indeed, despite the increased urinary flow provoked by the administration of the diuretic, it might take a long time before the tracer, which has to occupy the whole dilated cavity, will be able to leave the kidney in significant amounts. The consequence of this volume effect is that one can probably reasonably exclude an obstructive phenomenon in case of a good response. Absence of significant drainage can only be described and quantified and should not be interpreted as representing true obstruction (Fig. 4). It has been suggested that this nonresponse to furosemide attributable to a large volume of the collecting system is characteristic of the young infant, because of immaturity and low renal function in that age group.<sup>135</sup> This is not the experience of our group. Poor responses to furosemide were not more frequent during the first 6 months of life and often did not improve at a later age in the absence of any surgical treatment.<sup>136</sup>

### **Parenchymal Images**

The morphological information contained in the early dynamic images should not be neglected. Images can be summated between 1 and 2 min and, using an appropriate gray scaling, may reveal the presence of a small kidney, regional areas of dysplasia or scarring such as in duplex kidneys or dilated reflux.

### **Vesicorenal Reflux or Movement Artifact?**

Beside the determination of the main quantitative parameters, one should be particularly careful in detecting transitory vesicorenal reflux during the renographic acquisition. It is not rare that a reflux episode can be detected in infants during the renogram, either because of a full bladder, or as a consequence of a spontaneous micturition. Such detection may spare a young child the aggressive direct cystography that often is planned in antenatally detected hydronephrosis. A sudden increase of activity in the late phase of the renogram is indicative of reflux. However, images should be carefully checked to exclude any movement artifact that could give rise



**Figure 4** An 11-year-old girl. Pelvi-ureteric junction stenosis discovered 2 years before this renogram, because of intermittent loin pain. No surgery was performed, and the child is now asymptomatic. On the MAG3 renogram performed under furosemide (F0 test), the split function is almost symmetrical, but the drainage is poor, even on the postmicturition view (NORA PM: 3.0). A poor response on furosemide cannot be considered as a criterion of further function deterioration.

to the same curve pattern (Fig. 5). Periodic variation in ureteral contraction also may cause the curve to increase.

## The Renogram in Pediatric Practice

### Pelviureteric Junction Stenosis (PUJ)

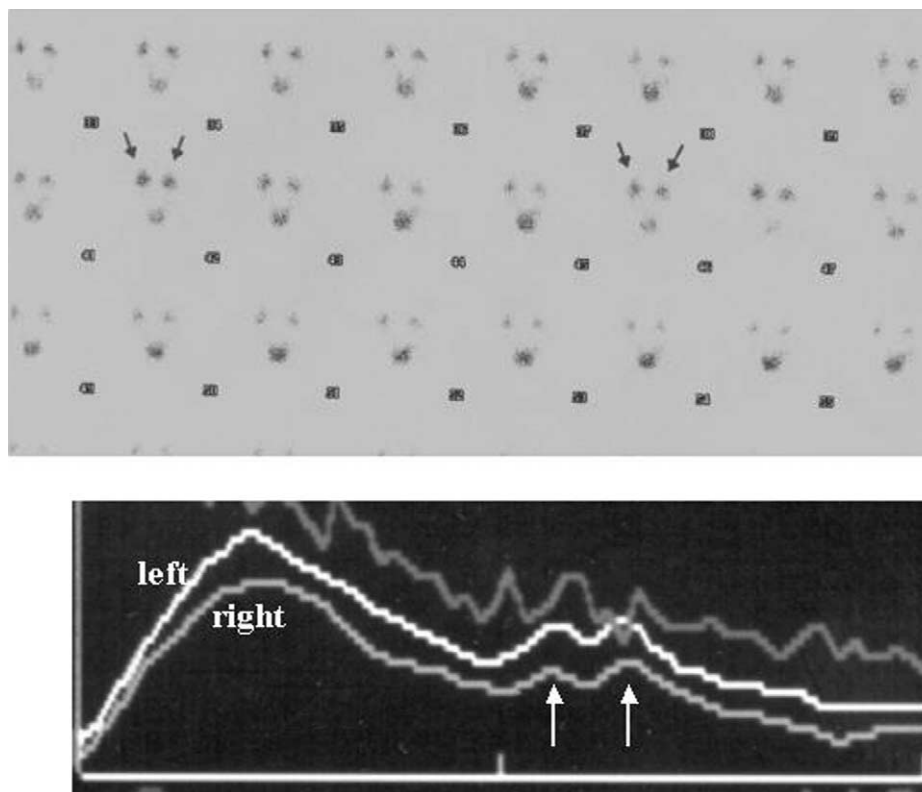
PUJ is undoubtedly the main indication in the postnatal period, although not a first-line examination. Dilation of the fetal collecting system is observed in approximately 0.25% of pregnancies<sup>137</sup> and the priority is to detect the presence of underlying urethral valves, representing a clinical emergency, or pathologies such as vesico-renal reflux, uretero-hydronephrosis or duplex kidney. Once these pathologies are excluded, isolated pelvic dilation will conceivably be the result of PUJ. These neonates with PUJ are in good health and present no symptoms. The natural history of this condition, as well as its optimal management, is still a matter of debate. Strategies of management are aimed to preserve renal function and to prevent the occurrence of severe infections.

**Is Surgery an Emergency?** A traditional statement found in the introductions of a great number of urologic articles over the past 50 years or more is that "it is important to diagnose obstruction since obstruction left untreated will lead to loss of renal function." This is undoubtedly true in case of total or subtotal obstruction, such as in urethral valves, in which obstruction should be relieved immediately. The antenatally detected PUJ is on the contrary a partial obstruction and does not represent a surgical emergency. In most of the cases, this situation, even untreated, will not lead to loss of function.

Numerous experimental studies have been produced to simulate the clinical model of antenatally detected PUJ. Chevalier

and Klahr<sup>138,139</sup> have demonstrated renal atrophy and apoptosis as a consequence of obstruction. However, it is clear that the models created are subtotal or total obstruction. The consequences of these types of obstruction do not represent what is observed in children with PUJ. Josephson, a pioneer in the experimental approach of this pathology, has shown long-term preservation of renal function and anatomy despite the created obstruction.<sup>140</sup> The Ulm and Miller's model that he used creates a partial obstruction but again might not necessarily mimic the degree of narrowing found in children. Stratifying the children with PUJ within 2 categories, those with and those without obstruction, is undoubtedly a too simplistic way to classify these patients. The degree of partial obstruction probably lies within a continuum, between slight and much more pronounced narrowing of the junction. Several factors, such as infection and position of the patient, can modify the degree of obstruction.

**Can Obstruction Be Defined at Entry?** The size of cavities, as measured by means of radiological techniques, not only depends on the degree of narrowing but also on factors such as compliance of the system and therefore cannot serve as a marker of obstruction. The pitfalls related to pelvic pressure measurements are well known. Differential function, as provided by the renogram, can be abnormally low as a consequence of obstruction, but additional factors such as associated renal dysplasia may explain an initial low function. Poor drainage under furosemide can be simply the result of the reservoir effect of a dilated cavity. Finally, inspection of the pelviureteral junction during the procedure of pyeloplasty will confirm, despite the narrowing of the junction, the still permeable lumen. The only definition of obstruction on



**Figure 5** A 6-month-old boy with bilateral grade V reflux. A 20-min MAG3 renogram was performed under furosemide stimulation (F0 test). One can identify easily, on both the images and curves (arrows), 2 clear episodes of vesico-renal reflux occurring during spontaneous voiding.

which there is an agreement, according to S. Koff, is “any restriction to urine flow, that left untreated, will cause progressive renal deterioration.”<sup>141</sup> This is unfortunately a retrospective diagnosis.

**Can Deterioration of Kidney Function and Anatomy Be Predicted?** There are no solid data demonstrating that the size of the renal cavity, the differential renal function, the level of pelvic pressure, or the response to furosemide constitute factors of risk for further deterioration. According to Koff,<sup>141</sup> hydronephrosis might constitute a kind of protection against the increased pressure as a consequence the narrowing. Noncompliant systems might constitute a factor of risk, since the elevated pressure will be directly transmitted to the kidney. The dosage of TGF-beta 1, as a marker of fibrosis and therefore of noncompliance, is worthwhile to be systematically evaluated.

**What Are the Risks of a Conservative Nonsurgical Attitude?** The experimental and clinical work of some pioneers<sup>140,142,143</sup> have encourage clinicians to have, in many circumstances, a conservative approach. Nevertheless, diverging opinions still exist and the controversy remains intense around the criteria for surgery and even the principle itself of no intervention in infants with PUJ.<sup>144</sup> Fear of loss of function, when the anomaly is known since fetal life, is put forward. Extensive compilations and critical review of the extremely heterogeneous literature have been published re-

cently.<sup>126,145,146</sup> The most striking point appearing from these reviews is the lack of rigorous approach and the total absence of randomized studies. Results are contradictory but these studies are not comparable.

**Is Expectancy Generally Justifiable?** As a matter of fact, overall results are encouraging. According to Josephson’s compilation,<sup>145,146</sup> 90% of 474 neonates allocated to watchful waiting were not operated. Only 10% were subjected to delayed pyeloplasty, mostly because of increase of pelvic size and/or decreasing differential renal function.

**How Often Did Symptoms Occur in Case of Expectancy?** Symptoms are not frequent. UTI is noted in approximately 5% and is generally of mild nature. Renal colic seems to occur extremely rarely.

**Does Huge Hydronephrosis Foretell Future Function Loss?** Josephson’s survey<sup>145</sup> showed that half of the expectancies had an initial gross hydronephrosis. Nevertheless, in 88% of them, the nonoperative treatment could be carried through. On the whole, reports of increasing pelvic size were rare. Thus so far, the presence of a gross hydronephrosis seems to have a limited prognostic value.

**What Is the Risk of Function Loss During Expectancy?** Again, according to Josephson’s compilation,<sup>145,146</sup> expectancy was successful in 90% of the cases. Crossover to delayed

pyeloplasty was decided in approximately 10% of cases, the reason being either pelvic size increase or deterioration of differential function. These events mostly occurred during the first 2 years of life.

For those kidneys with an initial differential renal function (DRF) less than 40%, expectancy led, according to Koff and coworkers<sup>143</sup> to improvement of function in approximately 70% of cases. In those cases with deterioration of function, late pyeloplasty, performed without delay, generally restored the initial DRF values. Early pyeloplasty, in case DRF was less than 40%, probably did not result in a higher percentage of cases with restoration of function. Similarly, suddenly unexpected complete loss of function has, in our personal experience, occurred only very rarely during conservative management. Complete loss of function, although very rare, also has occurred after uneventful pyeloplasty, according to our personal experience with experienced pediatric urologists.

**Does Early Surgery Result in Better Preservation of Split Function Than Late Surgery After the Deterioration of Function?** Patient series from the past are useless for such an analysis because they constitute a selected group of older and symptomatic cases. Clear answers can only come from well-designed prospective randomized studies.

**What Are the Long-Term Hazards of a Conservative Approach?** The experience on follow-up of conservatively treated patients is still limited in time and is not more than 10 to 15 years. In the past, however, when patients were addressed for PUJ discovered because of symptoms, DRF often was acceptable or almost normal, suggesting that the effect of symptoms on function was relatively modest. Long-term follow-up on these patients is needed to evaluate more precisely the frequency and consequences of clinical symptoms or the occurrence of complications such as severe tubular disease or stones.

**Alternatively, Is Early Surgery the Solution to Avoid Any Further Complication?** The occurrence of clinical complications is still possible in case of pyeloplasty. Severe and recurrent infections caused by multiresistant bacteriae may follow the surgical procedure. Variable surgical complications are possible in a minority of cases, from minor events such as leakage up to complete loss of renal function.

**In the Case of a Conservative Approach, How Often Should Examinations Be Performed?** Those in favor of a conservative approach insist about the necessity of close follow-up, particularly during the first 2 years.<sup>147</sup> Ultrasound is certainly the instrument of choice to rapidly detect any significant alteration of pelvic size. The information whether one can rely on repeated ultrasound to decide about performing a control renogram is still required. In other words, can one assume an unchanged or improved function on the basis of a stable or improved hydronephrosis?

### Other Clinical Indications

**Megaureter.** Like for PUJ stenosis, a conservative approach often is recommended, whether or not the megaureter is associated to hydronephrosis and/or vesicorenal reflux. The role of

the renographic study is to verify the quality of the underlying renal function and to assess the quality of renal and ureteral drainage, since the clinical question may be to differentiate a refluxing megaureter from an obstructive one because of vesico-ureteral stenosis. The furosemide test (F0 or F + 20) may give rise to the same uncertainty as for hydronephrosis. Good ureteral emptying on the late postmicturition image almost excludes the diagnosis of obstructive megaureter, while an important ureteral stasis can simply reflect the additional effect of a slow ureteral transit related to the enlarged reservoir and of a continuous input from the kidney.

**Duplex Kidney.** Although many duplex kidneys simply constitute normal variants, pathological duplex kidneys can give rise to clinical complications. Dysplastic moieties, ureterocolle, hydronephrosis, reflux, and obstruction may all lead to associated recurrent infections or pyonephrosis. Split function in case of normal duplex may be significantly out of the accepted 45% to 55% normal range. In case of pathological moiety, it has been shown that split function remains unchanged at follow-up during conservative management.<sup>148</sup> When deciding about a partial nephrectomy, the surgeon may be interested in evaluating the remaining function of the pathological moiety. In case of very low remaining function, the quantitative estimation is imprecise and one may probably better rely on the appearance or not of some renal activity on the late images to decide whether the function of this moiety is low or completely absent.

**Horseshoe Kidney.** It is not rare that the diagnosis of horseshoe kidney is made during the renographic procedure and has been missed on previous radiograph examinations. A diuretic challenge may be indicated in case of associated hydronephrosis due to vascular compression.

**Small and Dysplastic Kidneys.** Follow-up of split function is aimed to evaluate the long-term the outcome of both the normal and the abnormal kidney. It has been shown that in most of the cases split function remains unchanged for years, reflecting an equal maturation of the normal and the abnormal kidney.<sup>149</sup>

**Ectopic Kidney.** The precise determination of split function in case of pelvic kidney is hampered by the anterior displacement of this kidney not allowing an exact functional estimation. One simple way to correct, at least partially, for kidney depth using a single head gamma camera, is to perform at the end of the acquisition an anterior and posterior view and to determine, for each kidney separately, the number of counts in posterior alone and using the geometric mean. The ratio of both values is then used to correct the number of counts obtained during the renographic acquisition. One should be aware however that the attenuation due to the pelvic bone structure is still not corrected and gives rise to a significant underestimation of the function in the ectopic kidney.

**Place for Absolute Individual Kidney Function Determination.** In some clinical conditions, the split function is unable to assess the quality of the individual kidney function. This is

**Table 2** Advantages and Disadvantages of Direct and Indirect Cystography

	<b>Advantages</b>	<b>Disadvantages</b>
<b>MCUG</b>	<b>Morphology Grading Any age</b>	<b>High radiation burden Snaps shots, resulting in low sensitivity Invasive (bladder catheter)</b>
<b>Direct RN</b>	<b>High sensitivity Filling and voiding Any age Low radiation burden</b>	<b>Invasive (bladder catheter) No grading, no morphological data</b>
<b>Indirect RN</b>	<b>Noninvasive Low radiation burden Information about renal function</b>	<b>Partial bladder filling Low sensitivity Only in patients older than 3 years of age</b>

obvious, for instance, in case of single kidney or bilateral disease. In these cases, the combination of split function with an overall clearance by means of plasma samples (DTPA or EDTA) can be extremely helpful. As an example, it can clarify in some cases the ongoing controversy related to the supranormal function sometimes observed in antenatally detected hydronephrosis. As a matter of fact, it has been shown<sup>150</sup> that the abnormal high split function on the hydronephrotic kidney side may be simply the result of a low absolute function on the contralateral side, which was considered as structurally normal. Expressed in absolute function (ml/min), the function on the hydronephrotic side was in the normal range.

An unchanged split function generally is associated with a bilateral maturation of the individual absolute renal function.<sup>148,149,151</sup> A decreasing split function may still correspond to some functional maturation, although less pronounced than on the contralateral side.

The intensity of contralateral functional compensation can be precisely estimated and it is interesting to note that this compensation only occurs when the split function of the pathological kidney is less than 30%.<sup>152</sup> On a fundamental point of view, it is also interesting to note that in the case of asymmetrical function observed during the very first months of life, one would expect that the less-functioning kidney is using its functional reserve maximally and therefore not able to develop the same rate of maturation as on the contralateral side. In practice, and at least during the first two years of life, the maturation occurs symmetrically in both kidneys, resulting in an unchanged split function.<sup>149</sup>

## Radionuclide Cystography Techniques

Methods for both direct and indirect radionuclide (RN) cystography have been described elsewhere in detail.<sup>153,154</sup> Both techniques have advantages and disadvantages, compared with the classical radiological micturating cystourethrography (MCUG) and are summarized in Table 2.

The radiological technique is still widely used and remains the reference technique for most of the urologists. It allows

the detection of morphological abnormalities such as duplicated ureters, urethral valves, and ureterocoele. Moreover, the international grading system is now universally applied<sup>155</sup> and characterizes the intensity of reflux. However, reflux may be only intermittent and, for that reason, transient intense reflux may be completely missed. Placing a bladder catheter is an invasive procedure, in most of the cases poorly tolerated by the child and may give rise, despite all precautions, to severe iatrogenic pyelonephritis. The radiation burden is considerable.

Direct RN cystography is based on the same principle as MCUG and its invasiveness is identical. The bladder is progressively filled through a bladder catheter and both the filling phase and the voiding phase are entirely recorded. The sensitivity in detecting reflux is therefore higher than with MCUG. It can, like for MCUG, be applied to children of any age, since the active collaboration of the child is not necessary. The radiation burden is low. The technique has however not gained wide acceptance in the world. One reason for that is the poor resolution of the images, not providing any morphological information about the lower urinary tract. The second one is the fact that the urologist is familiar with the radiological grading system and the capacity to distinguish dilated from nondilated systems. The third one is probably the rather long occupation time of the gamma camera and the fact that many nuclear medicine physicians are not familiarized with the technique.

Indirect RN cystography comes as a complement to the renogram. At the end of the renogram, the tracer generally has left the kidneys and is filling the bladder. The child who wishes to void can then be asked to void in front of the gamma camera, thus allowing the visualization of active reflux. It is recommended to use a tracer with high extraction rate, such as Tc-99m MAG3. Unsatisfactory results are obtained with Tc-99m DTPA because of the increased residual renal activity. The technique, contrary to the 2 other ones, is not invasive and does not require a bladder catheter. The radiation burden is low and the technique offers the advantage of providing additional renal functional information obtained from the renogram. Unfortunately, the technique can only be applied to children older than 3 years of age, who are able to void on command, whereas most of the first UTIs occur before 2 years of age. Moreover, because of the incomplete bladder filling, the technique is much less sensitive than the direct techniques.<sup>156</sup> However, opinions diverge and some authors consider even the indirect technique as the most sensitive one. This generally is the case when the criteria for reflux are based on some debatable quantitative aspects, such as for instance a ureteral activity higher than three standard deviations of the ureteral background.<sup>157,158</sup>

## Which Technique for Which Strategy? Morphology of the Lower Urinary Tract

Precise information on urethral valves, ureterocoele, bladder diverticules, and duplicated ureters, which may influence the diagnosis and the further management, cannot be obtained by means of radionuclide cystography.



## Grading of Reflux

The urologist is familiar with the radiological MCUG International Grading System. It is clear, however, that direct RN cystography can tell the surgeon whether or not the reflux is reaching the kidney (corresponding at least to a radiological grade II reflux), if the reflux within the kidney is moderate or intense, intermittent or continuous, if it appears at low bladder filling or only at the end of the filling, or if the reflux is passive or active. Some degree of quantitation also is possible.

## Control of the Presence of Reflux

Once the reflux is diagnosed, any further control of the presence of reflux, either during conservative treatment or after a surgical procedure, should be obtained by means of RN direct cystography because of the higher sensitivity and the much lower radiation burden.

## Direct or Indirect RN Cystography?

This is still a matter of debate. If the information needed for further management is to know whether the reflux is still present and important, those in favor of the direct technique will consider the high sensitivity and the fact that it can be applied whatever the age. High-grade reflux can be observed on direct cystography, associated with severe cortical damage, whereas the indirect cystography is negative.<sup>156</sup> Those in favor of the indirect technique raise the point that both techniques can miss a similar number of significant reflux.<sup>159</sup> They consider that the intense bladder filling during direct cystography does not reflect the natural bladder filling in the daily life and may create artificial reflux, not necessarily linked to any significant clinical picture. Owing to the non-invasive character of the indirect cystography, it is reasonable to recommend this technique in children older than 3 years of age. In case of negative result, an additional direct cystography is mandatory to exclude with high confidence the presence of significant reflux. The cost-benefit of this double procedure should then be evaluated for each particular case.

## Is It Necessary to Check for Reflux in Each Case of Acute UTI?

Traditionally, the detection of reflux by means of cystography is recommended in any case of complicated urinary tract infection. For some authors, it is even the only imaging technique which makes sense in this context.<sup>51</sup> However, recent work tends to indicate that the presence or not of a renal lesion may represent the key for deciding about cystography studies.<sup>70</sup> This strategy would spare a great number of unnecessary invasive examinations.

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