The role of diuretic renography has become central in cases of upper tract dilatation, and in the first paper in this section the difficulties in interpreting results in asymptomatic congenital hydronephrosis are examined. These difficulties and controversies exist despite the presence of guidelines and consensus protocols, probably because renography procedures differ among centres. The authors found that there is a need for renography to be standardized for the optimum value to be obtained from the procedure.

There are three papers from Los Angeles which attempt to standardize the measurement of bladder compliance, from both the theoretical and clinical perspective, and which assess the detrusor pressure rise of a normal bladder when filled to capacity.
is reproducible among different centres when evaluating the hydronephrotic kidney.

Protocols from The Society for Fetal Urology [1], The Paediatric Committee of the European Association of Nuclear Medicine (EANM) [2] and the International Consensus Committee of the Ninth International Symposium on Radionuclides in Nephrourology [3] provide guidelines for standardized procedures. The former protocol, which was introduced a decade ago, recommends more invasive procedures, and the evaluation of drainage does not account for the influence of gravity, kidney function and pelvis size, important variables that are implemented in the recent EANM protocol. Despite these guidelines and consensus protocols, procedures differ among centres and cause difficulties when comparing studies. Furthermore, the existing controversy in interpreting the results also makes comparison difficult. The purpose of this report is therefore to discuss the acquisition and processing procedures, and the interpretation of the diuretic renogram in children with hydronephrosis, and to exemplify some of the potential pitfalls.

BACKGROUND AND DEFINITIONS

The principle of renography is based on the intravenous administration of a radiopharmaceutical accumulated and excreted by the kidneys, and which can be detected externally by a γ-camera. By defining two regions of interest (ROI) around the kidneys, a renogram can be constructed based on registration of radioactive decay within the defined areas. The renogram monitors the arrival of the radiopharmaceutical into and its escape from the kidney in a dynamic sequence, allowing estimation of two aspects of renal function; the DRF, which is the relative tracer uptake from the blood, and excretion.

$^{99m}$Tc-DTPA, $^{99m}$Tc-MAG3 and $^{99m}$Tc-ethylenediamine (EC) are renal radiopharmaceuticals suitable for that purpose. DTPA is the most widely used tracer, as it is a small molecule that is exclusively filtered by the glomeruli, with an extraction efficiency of 20% in the mature kidney [4]. DTPA readily crosses the capillary bed, resulting in a high extra vascular distribution of tracer and a high background activity [4]. MAG3 is almost exclusively excreted by secretion in the proximal tubules [5] with a higher extraction fraction than DTPA (about 50% in the mature kidney [4]) and MAG3 remains essentially within the intravascular space, resulting in a high target-to-background ratio, good image quality and more accurate numerical values, particularly when kidney function is low or immature. The renal extraction of EC is even higher (70% in the mature kidney [6]) and therefore particularly attractive in patients with renal failure or immature function, but is unavailable outside Turkey and a few other countries. The administered activities for renographic investigation in a child is recommended to be adjusted to body surface area, and is 15–70 MBq for MAG3 and 20–200 MBq for DTPA, corresponding to an effective dose of 0.026–0.0029 and 0.024–0.0027 mSv/MBq, respectively, depending on the age of the child and given a 1-h bladder voiding period [2,7]. The radiation burden is therefore low and the difference negligible between a DTPA and a MAG3 study.

FIG. 1. Images and diuretic renography curves (including a PMI) of an F0 MAG3 study at 18 months old in a child with left prenatally diagnosed hydronephrosis. Ultrasonography 3 weeks earlier showed a 23-mm dilatation of the left pelvis. The left kidney DRF is 56%. The images show micturition during the 0–20-min study and between the 20-min image and the PMI which was obtained 45 min after the MAG3 administration. (Images kindly provided by Prof Isky Gordon).

METHODS

We comprehensively assessed published papers on the subject of diuretic renography, assessing methods of interpretation and procedural factors.

RESULTS

Interpreting the renogram comprises images, curves derived from ROIs and numerical data from analysis of the curves. The curve can be divided into three phases [8] (Fig. 1). Initially there is a rapid rise in the curve in the first few seconds, reflecting the speed of injection and the vascular supply to the kidney; this phase is not generally analysed in infants. The second phase is where the radiopharmaceutical is being accumulated by the kidney but there is no excretion; this phase lasts for 2–3 min after injection. The increase in renal activity during this phase is representative of relative renal function. Therefore, the relative function must be calculated during the first 2 min of the renogram. Using any other period for calculating relative kidney function is inappropriate, as the function of the contralateral normal kidney will be underestimated, because there is significant escape of tracer from the kidney, and function of the hydronephrotic kidney is thereby overestimated. In the normal kidney the radiopharmaceutical starts to leave the kidney after 2–5 min, initiating the third phase of the renogram. Importantly, the peak of the renogram curve ($T_{max}$) does not represent the moment at which excretion from the kidney begins, but merely the equilibrium between uptake and excretion from the kidney. A flat third phase of the renogram represents equilibrium, with the same amount of radiopharmaceutical extracted from the blood by the kidney as is excreted. A continuously rising curve reflects the presence of renal stasis, which nevertheless can be observed in an unobstructed dilated system. The use of diuretic renography, which classically follows
the renogram, is based historically on the assumption that the radiopharmaceutical retained in an unobstructed dilated system will be washed out when urine output is high, whereas it will be retained in the system if obstructed.

**PROBLEMS AND PITFALLS OF INTERPRETATION IN HYDRONEPHROSIS**

Estimating and interpreting the DRF is independent of the degree of hydronephrosis, state of hydration, bladder status, gravity, the use of a diuretic and the level of renal function (unless it is very low) [3,10]. A poor signal-to-noise ratio because of renal insufficiency or the use of DTPA in small infants may result in an inaccurate estimate of DRF.

DRF is influenced by activity in the extrarenal interstitial tissue included in the renal ROI. Thus background activity must be subtracted and the accuracy of the estimate depends on the method of background subtraction, the most adequate, according to a recent consensus, being probably an area around the kidney [11]. If dilatation is severe in the young child, difficulties may arise in drawing a perirenal area still within the body of the child, and the perirenal background should be substituted by background ROI above and below the kidney [2].

Once the renal curves are corrected for extrarenal background activity the DRF can be calculated. Two well-accepted algorithms can be used for that purpose, i.e. the integral method and the Patlak-Rutland method [2,11]. Some recommend the use of both methods, as a similar result undoubtedly constitutes quality control.

If the diuretic is administered early (15 min before or together with the injection of the tracer) intrarenal transit may be accelerated, with the risk of underestimating DRF if there is excretion to the pelvis within the period for calculation [12]. Such an accelerated renal transit can easily be detected by considering both the images where tracer may be seen in the bladder very early and the peak of the renogram; if the peak occurs earlier than 2 min, the interval which can be used for calculating the DRF should be less than the time to the peak.

Interpreting the DRF is generally easy and this variable is therefore suitable for the follow-up. A DRF of 45–55% is considered to be within the normal range [2,11,13]. As DRF measures relative function, observed changes may reflect changes in the opposite kidney. It is therefore important to be aware of the clinical context, including the possibility of bilateral renal damage or contralateral compensatory functional increase. Estimating absolute renal function may provide a better answer to the question of whether the function on the abnormal side is decreasing or the opposite side is increasing its function. γ-Camera methods, expressing renal activity during the second minute of the renogram as a percentage of the injected dose, are used by some investigators for evaluating absolute unilateral function [14]. However, these methods, because they are imprecise, have not achieved a general consensus [11,15,16]. Overall blood sample clearance methods, using 99mTc-DTPA or 51Cr-EDTA combined with the DRF derived from the renogram, offer better accuracy [15].

There is no definition of a ‘significant’ reduction (or increase) in DRF. Only a few studies have evaluated the reproducibility of the MAG3 DRF in repeated studies, and the total variation on the estimate consists of both biological and methodological variation. The reliability of the DRF can be divided into the accuracy, which defines the difference between the measured value and the ‘true’ value, and the precision, which is determined by the variation between repeated analyses when renal function is expected to be unchanged [17]. The accuracy of MAG3 DRF has been tested against DMSA DRF in children during the follow-up of UTI [18]. There was no systematic bias between the methods and the SDs of the difference were <3%. In healthy adults with no known renal pathology the SDs of the difference between successive investigations was 2–3%. However, although a change in DRF of >3% may be statistically significant, the physiological variation may be higher, especially in the infant. A decrease in DRF of ≥5% [19], 10% [20–23] or >10% between repeated investigations is often used as an indication of deterioration. Often the renogram is taken in a state of renal immaturity and succeeding maturation results in a higher extraction of the tracer by the kidney [24], and so the variability between successive investigations in the infant might be more important than the absolute values.

The classical variables of the diuretic renogram are simply descriptive. After injecting frusemide at the end of the renogram (F+20) [3,25,26] a postdiuretic drainage curve is obtained which is traditionally classified according to the postdiuretic T½ time, i.e. the time is simply the rate of change of activity in the dilated renal pelvis and defined as the time for half of the accumulated radionuclide to leave the renal pelvis [27]. A T½ of >20 min is thought to indicate obstruction [26], assuming that one period, e.g. 20 min, can be used to diagnose obstruction. However, controversies exist on how to calculate T½ [1,28] and depending on the method used, there can be different interpretations of the diuretic renogram.

When the postdiuretic curve falls rapidly and T½ is short, impaired renal drainage can be excluded. However, the shape of the drainage curve [and thereby T½] is influenced by several variables, e.g. hydration, renal function, timing of the diuretic administration, effect of gravity and bladder fullness, and the volume of the pelvis, which if not accounted for may lead to an erroneous conclusion of ongoing obstruction.

Maintaining the child (of whatever age) vertical allows a normal gravitational effect on urinary drainage. The traditional acquisition of a diuretic renogram with the patient supine does not allow this effect on urinary drainage, which is reflected in findings of poor drainage in a third of normal kidneys contralateral to hydronephrotic kidneys on the diuretic renogram [30]. Therefore it was proposed to evaluate what is remaining in the pelvis after micturition and after gravity has facilitated drainage, instead of just assessing the curve [2].

The renogram curve and possibly the F+20 diuretic curves are influenced by renal function. Low DRF will affect the descending
part of the renogram curve and for the same intrarenal transit it is possible to have very different shapes of the curves, depending simply on the DRF [31]. Decreased overall function may cause insufficient or slow pelvic filling, particularly on thehydronephrotic side, and thus a poor response to a diuretic stimulus. Renal function should therefore be integrated in the evaluation of drainage from the hydronephrotic immature kidney, or in the kidney with impaired function. Described later are some recently introduced objective variables of drainage, e.g. the pelvic excretion efficiency (PEE), output efficiency (OE) and normalized residual activity (NORA), that consider renal function [30–32].

**HOW SHOULD DRAINAGE BE ESTIMATED?**

The child must be adequately hydrated before the study, to produce a sufficient diuretic response for interpreting the drainage curve [2,13]. If dehydrated, insufficient urine production will cause stasis of the tracer in the pelvis and the frusemide response may be decreased [25]. Whereas intravenous hydration is used by some [1,3], oral hydration is considered adequate in most patients by others [2,13].

**Timing of diuretic injection:** there are different protocols where frusemide is injected 15 min before (F–15), simultaneously with (F0) or 20 min after (F+20) the injection of radiopharmaceutical, and currently there is no evidence to suggest that one method best [2]. However, giving the MAG3 and the frusemide simultaneously (F0) requires only one injection, a major advantage in infants and children for those institutions using a single injection, a major advantage in infants and children who had two successive renograms taken, one F0 and one F+20, with no significant clinical event between them, that the residual activity on the PMI, expressed in terms of these two variables, was comparable. Similarly, the residual activity at the end of the 20 min F0 renogram was comparable to what was obtained at the end of the 15 min washout curve in F+20 [35]; this requires further confirmation.

The interpretation of drainage results should include the images, the curves and the numerical data derived from the curves.

**WHAT IF FRUSEMIDE IS INJECTED EARLY (F0 OR F–15)?**

The time at which the diuretic is injected influences the drainage curve. Traditionally, frusemide is injected at the end of the renogram (F+20) [3,25,26]. Those advocating this method consider it important to record beforehand the way the kidney can handle the tracer (and therefore the urine) with no additional frusemide. However, the maximum diuretic effect of frusemide is at 15 min after injection [3] and this may not necessarily be reached at the end of the frusemide challenge. Using simultaneous injection of tracer and diuretic (F0) the renogram obtained will not be recorded in the steady state, with urinary flow increasing considerably between the beginning and end of the acquisition. If frusemide is injected 15 min before the scan the kidney will be in a state of maximum diuresis, with a pelvis full of non-isotopic urine before the MAG3 arrives. The curve then represents tracer filling the fully dilated renal pelvis, when the kidney is at maximum and rather constant urine production. Indeed, pelvic volume may vary considerably, depending on when frusemide is given and on the compliance, and there is currently no way to incorporate the pelvic volume in the analysis of the diuretic challenge [34].

Nevertheless, can a renogram obtained in F+20 condition be compared to a F0 renogram in the same patient? Obviously not when trying to apply the traditional criteria of the F+20 washout curve (T½) to the renogram in F0. However, recently described variables, where calculations were based on the residual activity, might allow this kind of comparison [35]. The OE and PEE are analogous physiological, robust and well-validated variables [30,32,36,37] which, based on the cardiac curve and the renal activity at a given moment of the acquisition, allows an evaluation of the amount which left the kidney and expressed as a percentage of what came in. The NORA is a simplification of those variables and is the renal activity at a given moment divided by the renal activity at 2 min [31].

The OE, PEE and NORA are less influenced by overall renal function than, e.g. T½, but not independent of renal function, limiting the potential for establishing absolute thresholds [36,39]. However, the three variables allow an objective measurement of the renal drainage, provided there is adequate standardization of the procedure [30,31,39,40].

Simple qualitative estimates of drainage might be misleading, particularly when frusemide is given together with the tracer. In that case, it is not rare to see a short T½, followed by a flat curve, giving a false impression of poor drainage. It was shown in children who had two successive renograms taken, one F0 and one F+20, with no significant clinical event between them, that the residual activity on the PMI, expressed in terms of these two variables, was comparable. Similarly, the residual activity at the end of the 20 min F0 renogram was comparable to what was obtained at the end of the 15 min washout curve in F+20 [35]; this requires further confirmation.

**WHAT IF THERE IS INCOMPLETE DRAINAGE AT THE END OF DIURETIC RENOGRAPHY?**

Good drainage is easy to identify on the images, curves and data analysis, as all will show that there is either very little or no tracer left in the kidney at the end of the study. The problem in interpretation is when there is incomplete drainage at the end of diuretic renography.

The shape of the basic renogram gives useful information about drainage; an early peak (3–4 min) and a rapidly descending third phase excludes any delay in renal emptying. Renal stasis is characterized by a prolonged time to reach T½, and a flat or continuous ascending curve. Good drainage either on the postdiuretic images or a rapidly falling...
postdiuretic curve confirms simple stasis. However, in minority of unobstructed hydronephrotic kidneys there is a continuously rising or plateau-shaped diuretic curve, despite including a PMI. The volume of the pelvis will also affect the drainage curve, as a large pelvis will require more time to fill and drain than a smaller renal pelvis (Fig. 2). In general, the larger the pelvis the more dilution of radiopharmaceutical can be expected, and the more caution is needed in evaluating the drainage curve [41]. At the extreme, poor drainage might be apparent if the pelvis is large despite the absence of any obstruction [39,42]. The investigator should be aware of that pitfall and should not reach a diagnosis of obstruction on the simple basis of no or poor drainage on the renogram. Ultrasonography of the pelvis before and after the administration may be helpful.

PARENCHYMAL IMAGES
The final analysis should include careful scrutiny of the images. Dynamic images can be summed at 1–2 min and, using an appropriate scaling, may give useful information about regional function, although the quality of information is generally considered less accurate than that obtained using DMSA scintigraphy. Parametric images reflecting transit in each pixel of the renal area may reveal a regional abnormal kinetic behaviour, entirely different from the remaining part of the kidney, with lower uptake and much longer transit, typical for a pathological duplex kidney.

CONCLUSION
Renography is the cornerstone for guiding the clinical management of asymptomatic congenital unilateral hydronephrosis. Provided the investigation is standardized and potential pitfalls considered, it provides valuable and reproducible quantitative information on DRF and drainage.

CONFLICT OF INTEREST
None declared.

REFERENCES
9 Samal M, Nimmon CC, Britton KE, Bergmann H. Relative renal uptake and


14 Gates GF. Glomerular filtration rate. estimation from fractional renal accumulation of 99mTc-DTPA (stannous). *AJR Am J Roentgenol* 1982; 138: 565–70


34 Koff SA. Determinants of progression and equilibrium in hydrourephrosis. *Urology* 1983; 21: 496–500


41 Gordon I. Diuretic renography in infants with prenatal unilateral hydrourephrosis. an explanation for the controversy about poor drainage. *BJU Int* 2001; 87: 551–5


Correspondence: Anni Eskild-Jensen, Department of Clinical Physiology and Nuclear Medicine, Aarhus University Hospital – Skejby, DK-8200 Aarhus, Denmark. e-mail: eskild-jensen@dadlnet.dk

Abbreviations: DRF, differential renal function; EANM, European Association of Nuclear Medicine; ROI, region of interest; EC, ethylenedicycsteine; PEE, pelvic excretion efficiency; OE, output efficiency; NORA, normalized residual activity; PMI, postmicturition image.