$^{99m}Tc$-DMSA RENAL SCINTIGRAPHY IN THE DIAGNOSIS AND FOLLOW-UP OF ACUTE PYELONEPHRISIS IN CHILDREN

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99mTc-DMSA renal scintigraphy in the diagnosis and follow-up of acute pyelonephritis in children

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The aim of the present thesis was to define and evaluate a strategy for identification of children who are at risk of developing progressive renal lesions after acute pyelonephritis. Tc-DMSA renal scintigraphy is widely accepted as the most sensitive method for detecting parenchymal lesions and diagnosing acute pyelonephritis. Qualitative and quantitative evaluation standards were elaborated to improve the interpretation of DMSA scintigraphy. The normal DMSA distribution pattern, the average background uptake, and scintigraphic kidney length according to age were assessed in 95 presumably healthy kidneys. Furthermore, typical DMSA distribution patterns in acute pyelonephritis were assessed on 65 kidneys in 38 children, and typical DMSA distribution patterns of 152 kidneys with VUR in 101 children with and without previous pyelonephritis.

Measurement of scintigraphic kidney length, width and volume was validated in piglets and on a kidney phantom. The scintigraphic kidney length was found to be an accurate measure of renal size, whereas kidney width and volume were less reliable, at least on small kidneys. Criteria of kidney swelling in acute pyelonephritis were defined, and found to be beneficial for identifying reinfections in the absence of clinical symptoms.

In 34 children with acute pyelonephritis quantitative and qualitative DMSA scintigraphic findings were correlated to clinical symptoms and laboratory data, in the acute stage and at follow up. We found that quantitative DMSA scintigraphy in the acute stage of pyelonephritis and again after one year will identify children who are at risk of developing progressive renal lesions. Qualitative assessment of DMSA distribution pattern is not reliable enough in this respect.

Key words
DMSA-scintigraphy, pyelonephritis, kidney length, kidney radioactive uptake, progressive renal damage

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Signature Lena Wallin Date 1997-04-14
This thesis is based on the following articles, which will be referred to in the text by their Roman numerals.

I  $^{99m}$Tc-DMSA renal scintigraphy during kidney maturation. 


III  The significance of vesicoureteric reflux on kidney development assessed by dimercaptosuccinate renal scintigraphy. 

IV  Kidney size estimation by DMSA scintigraphy in piglets. 
Lena Wallin, Johan Thörne, John Palmer and Marika Bajc. Submitted for publication.

V  Kidney swelling - findings on DMSA scintigraphy. 

VI  Follow up of acute pyelonephritis in children by DMSA scintigraphy. 
Quantitative and qualitative assessment. 
Lena Wallin, Ingemar Helin and Marika Bajc. Submitted for publication.

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ABBREVIATIONS

CRP complement-reactive protein
DTPA dimethylentriaminpentaacetic acid
DMSA dimercaptosuccinic acid
E Coli Escherichia Coli
ESR erythrocyte sedimentation rate
$^{203}$Hg 203-mercurium
$^{197}$Hg 197-mercurium
$^{113}$I 113-iodine
IL-6 interleukin-6
IVU intravenous urography
KU/AD kidney radioactive uptake in percent of administered dose
MBq megabecquerel
MAG3 mercaptoacetyltriglycine
MUCG micturating urethrocystography
ROI region of interest
$^{99m}$Tc 99m-technetium
US ultrasonography
UTI urinary tract infection
VUR vesicoureteric reflux
1 INTRODUCTION

1.1 Renal imaging agents

Various substances have been used for the imaging of renal parenchyma and renal excretory pathways. Substances excreted by the urine are used for dynamic imaging. They also give a rough estimation of the parenchymal morphology. Other substances, accumulating in the parenchyma, are used for static imaging. They give a more detailed image of the parenchymal function.

The earliest application of radionuclides in evaluation of renal function was started with the work of Taplin (1956). He used $^{131}$I-hippuran that is excreted almost completely by the urine and has been widely used for dynamic studies and renal clearance measurement (Blaufox et al 1967). Subsequently $^{131}$I-hippuran was replaced by $^{99m}$Tc compounds which have better properties for imaging with gamma camera techniques. The most widely used agents for evaluation of renal function and morphology are $^{99m}$Tc-DTPA and $^{99m}$Tc-MAG3 (Taylor 1991). Because the renal extraction of MAG3 is twice that of DTPA, MAG3 has to a great extent replaced DTPA for the evaluation of renal excretory pathways and differential renal function.

For static imaging of renal parenchyma mercurial diuretics were first utilised (McAfee & Wagner 1960). They were marked with $^{203}$Hg that was later replaced by $^{197}$Hg (Sodee 1964). The mercurials delivered a high radiation dose, a circumstance that urged the development of $^{99m}$Tc compounds for substitution. One of the first $^{99m}$Tc compounds introduced for imaging of renal parenchymal was $^{99m}$Tc-gluconate (Charamasa & Budikova 1969). Thereafter $^{99m}$Tc-penicillamine substances were developed (Halpern et al 1972, Taylor et al 1977). Those compounds did not become widely used. A new substance, dimercaptosuccinic acid (DMSA), was introduced in 1974 by Lin et al. It showed excellent imaging properties and has become the predominantly used compound for evaluation of renal parenchyma.

1.2 Static renal scintigraphy with DMSA

1.2.1 Biokinetic behaviour of DMSA

Dimercaptosuccinic acid accumulates in epithelial cells of the proximal tubules (Lin et al 1974). It is extracted from the blood in peritubular capillaries (Müller-Suur & Gutsche 1995). The image shows the functioning renal cortex. Uptake defects represent areas where the mechanism for uptake in tubular epithelial cells is blocked by impaired blood flow and/or impaired tubular uptake from blood. The biokinetic behaviour of DMSA was studied by Enlander et al (1974) by cumulative urine excretion of DMSA. They found that 4 - 8 % of the injected dose was excreted after one hour and 26 - 30 % after 14 hours. The renal extraction was estimated to 4 - 5 % per renal passage with about 50% accumulated in the kidneys after one hour. A more recent study of the biokinetic behaviour of DMSA in children was presented by Evans et al (1996). They found
a slightly lower maximal renal uptake, 42 ± 5 % of the administered dose, which occurs after 6 - 7 hours. Liver uptake was 5 ± 2 % and the uptake in the spleen 2 ± 1 %.

1.2.2 Time for imaging

Arnold et al (1975) found that the DMSA scintigram visualises the parenchyma without interference from pelvocalyceal system. Therefore he recommended DMSA imaging for the detection of parenchymal lesions such as infarcts and pyelonephritic scars. Subsequently, DMSA scintigraphy was evaluated in a variety of renal diseases (Handmaker et al 1975). They showed that imaging performed two hours after the injection provided an excellent evaluation of functional renal anatomy. DMSA uptake reaches its maximum within 7 hours (Gordon et al 1987, Evans et al 1996). Because the half life time for $^{99m}$Tc is 6 hours scintigraphy should be performed within 6 hours after administration. In most centres scintigraphy is generally performed 2 - 4 hours after DMSA administration.

1.2.3 Sensitivity for renal lesions

Studies in animals show that static renal scintigraphy with DMSA is the most sensitive imaging method to identify parenchymal lesions (Rushton et al 1988, Parkhouse et al 1989, Risdon et al 1994). Typically the sensitivity is 80 - 90 % at a specificity above 90% with planar imaging. Using tomographic technique some authors have reported higher sensitivity compared to planar images (Giblin et al 1993, Majd et al 1996). This result was not reached by Mouratidis et al (1993).

1.2.4 Quantification

Quantitative evaluation of absolute renal DMSA uptake has been reported but no method has yet been generally accepted (Gordon et al 1987, Groshar et al 1991, 1994, Evans et al 1996). In most studies with DMSA scintigraphy evaluation is based on qualitative data, describing parenchymal distribution/uptake defects. Occasionally quantitative data of separate renal function are presented (Stokland 1996).

1.3 Kidney size measurements

Measurement of renal size in adults was practised as early as in the 1950s on intravenous urography (IVU) (Billing 1954, Moëll 1956). In children normal renal growth is accepted as an indication of a healthy kidney. Kidney size has been related to age, height, weight and body surface area (Hodson et al 1962, Simon 1964, Currarino 1965, Gatewood et al 1965). Geometric formulas have been used to increase the exactness of evaluation (Friedenberg et al 1965, Guy & Mounic 1971, Hegedüs 1972). For estimation of kidney size the relation between kidney length and vertebral height was found to be the most adequate guide (Eklöf &
Ringertz 1976). Ultrasonography (US) offered a new possibility for renal size measurement. Comparing sonographic kidney length with urographic kidney length it was observed that the urographic length exceeded the sonographic by 16% (Haugstvedt & Lundberg 1980). This discrepancy was not confirmed when compensation for the magnification factor was practised (Hederström & Forsberg 1985a). A difficulty with measurement of renal size with US is that the method is operator dependent. Inter- and intra-operator variability of typically 7-13% and 1-7%, respectively have been reported (Hederström & Forsberg 1985b, Schlesinger et al 1991, Sargent & Wilson 1992 Emamian et al 1995).

Normal values for kidney length on DMSA scintigraphy were presented by Sisayan et al (1994). They related kidney length to age, height and weight. They found that kidney length had non-linear relationships with the age and weight of the patients but correlated linearly with the height. Comparing scintigraphic and sonographic length they found that the scintigraphic length exceeded the sonographic by on average 10 mm.

1.4 Urinary tract infection (UTI)

1.4.1 Prevalence and importance of UTI

Urinary tract infection occurs in 1 - 4% of all children (Winberg et al 1975, Dickinson 1979). Reduction of renal parenchyma is found in 5 - 10% either at the first infection or later (Winberg et al 1975). Establishing the diagnosis of UTI is difficult in children, particularly so in infants. Therefore UTI in children is often unrecognised and untreated (Jadresic et al 1993). According to Clarke et al (1995) more than 90% of children over 5 years with renal lesions on DMSA scintigraphy have a history of symptomatic recurrent UTI. Decreased renal function is probably more common in UTI than previously believed (Pead and Maskell 1994). Progressive renal scarring (chronic pyelonephritis), may lead to hypertension, maternal and fetal complications during pregnancy and in some patients renal insufficiency (Torres et al 1980, Jacobsson et al 1989). About 23% of end-stage renal disease is thought to be related to UTI and vesicoureteric reflux (VUR) (Chantler et al 1980, NAPRTCS 1993). Therefore optimal management of UTI in children is important.

1.4.2 The diagnosis of acute pyelonephritis

The diagnosis of acute pyelonephritis is traditionally based on clinical signs and symptoms of fever, abdominal or flank pain or tenderness, associated with pyuria and positive urine culture. However, infants, and neonates in particular, frequently present with non-specific clinical findings such as irritability, poor feeding, failure to thrive, vomiting and diarrhoea (Bergström et al 1972). Since the symptoms, especially in infants, are often vague it is difficult to establish whether the infection involves the kidneys or is confined to the bladder. Different examinations, such as ureteral catheterisation, bladder washout, have been used to determine the site of the infection (Sheldon & Gonzales 1984).
reasons, including unreliability, invasiveness and nonavailability, these have not gained widespread acceptance for the evaluation of children with UTI. When the infection involves the kidneys most children, except neonates, present with fever (Winberg et al 1974). Other inflammatory parameters i.e. CRP, ESR, and IL-6 in urine and serum, are in general elevated in pyelonephritis and are widely used for the diagnosis (Majd et al 1991, Benador et al 1994, Melis et al 1992). Renal DMSA scintigraphy is highly sensitive and specific for the diagnosis of pyelonephritis and has emerged as the method of choice. It is significantly more sensitive in the detection of acute pyelonephritis than IVU and US (Conway & Cohn 1994, Rushton 1997).

1.4.3 Pathogenesis of pyelonephritis

The pathogenesis of pyelonephritis is not yet fully understood. It has been attributed to the interaction of bacterial virulence and host defence factors. In the presence of VUR infected urine allows ingress of bacteria into the renal parenchyma and precipitates infection. In the absence of VUR, ascending infection is related to the ability of uropathogenic bacteria to adhere to the uroepithelium (Roberts et al 1985, Bahrani et al 1994). Experimental studies have shown that P-fimbriated E Coli are more prone to ascend from the bladder to the kidneys than non-fimbriated E Coli (Roberts et al 1985). Furthermore, only one type of P-fimbriae, i.e. mannose-sensitive, has shown to be closely related to renal scarring (Harber et al 1986). In a majority of patients with acute pyelonephritis P-fimbriated E Coli are found in urine cultures. However, this finding does not identify children who develop parenchymal lesions as demonstrated by DMSA scintigraphy (Majd et al 1991).

In the development of renal lesions the interest has been focused on the patients’ immunological response to infection (Haraoka et al 1993, Jacobsson et al 1994). An increased level of the cytokine IL-6 in serum is related to renal involvement in UTI according to Hedges et al (1992). Bacteria producing hemolysin and cytotoxic necrotising factor seem to induce higher concentrations of IL-6 in serum (Jacobsson et al 1994). The spread of IL-6 to serum in patients with acute pyelonephritis may contribute to the fever and the elevation of CRP.

1.5 Vesicoureteric reflux

1.5.1 Pathogenesis of VUR

Retrograde flow of urine to the ureter is normally prevented by the valvular action of the ureterovesical junction. Inadequate fixation of the longitudinal muscle of the ureter to the trigonal musculature of the bladder leads to VUR. Moreover, it has been assumed that infection with inflammatory swelling around the intramural portion of the ureter may be a precipitating factor for reflux (Whitaker 1976). It is also believed that VUR can be caused by reversed ureteric peristalsis or urethral-bladder dysfunction (Jørgensen 1986).
1.5.2 Significance of VUR in renal scarring and controversies

Several systems are used to grade the severity of VUR. They are based on whether the reflux reaches the ureter, the renal pelvis and calyces, or whether dilatation occurs (White 1989). However, the presence or degree of VUR does not seem to influence the long term renal function according to Berg (1992).

Different theories have been developed to explain renal scarring associated with VUR. Some authors believe that high renal pressure alone in association with VUR may cause scarring (Jørgensen & Stödkilde-Jørgensen 1985). Others have shown that changed morphology and dysplasia develop already in the prenatal period (Anderson & Rickwood 1991, Najmaldin et al 1990). However, VUR without dilatation of the ureter and pelvis, seen during the first years of life, usually diminishes or disappears (Edwards et al 1977). Such VUR is more likely a sign of urinary tract immaturity than of anatomical abnormality. On the other hand, some authors argue that infected urine in VUR is the precipitating factor that causes renal scarring (Smellie et al 1981b, Hannerz et al 1987, White 1989).

It remains controversial whether VUR or infection is the most important factor behind renal scarring. Many authors have advocated that VUR is the main cause (Hodson and Edwards 1960, Hinman and Hutch 1962, Hannerz et al 1987, Smellie et al 1975, White 1989). Others have presented materials where all children with progressive renal damage had experienced breakthrough infections in the presence of VUR (Smellie et al 1981b, Verber & Meller 1989). By using DMSA scintigraphy it was found that that renal lesions occur even in the absence of VUR. The authors concluded that presence of VUR is not a prerequisite for renal scarring (Winberg et al 1982, Jakobsson et al 1992, Majd & Rushton et al 1992, Benador et al 1994, Ditchfield et al 1994, Stokland et al 1996). VUR in the absence of infection causes renal lesions in only about half of the kidneys as visualised by DMSA scintigraphy (Kass et al 1992). Presumably, VUR is only one of several risk factors for progressive renal scarring. Parenchymal lesion after pyelonephritis and repeated UTI are other factors associated with progressive scarring (Merrick et al 1995a,b).

1.6 Imaging in febrile UTI

Intravenous urography was introduced in the 1920s. The features of post-pyelonephritic scarring found on IVU have been described by Hodson (1959). IVU has become a traditional method for the examination of children with UTI. However, IVU has a low sensitivity for diagnosing acute pyelonephritis (Little et al 1965, Silver et al 1976, Traisman et al 1986, Sty et al 1987). Renal US was subsequently introduced for the diagnosis of pyelonephritis (Dinkel et al 1986, June et al 1985). Unfortunately, US sensitivity was not satisfactory for recognising parenchymal lesions (Björgvinsson et al 1991, Rickwood et al 1992, Tasker et al 1993, Stokland et al 1994). The introduction of DMSA scintigraphy in the 1980s gave a new possibility to visualise renal parenchymal function. The method was found to have a high sensitivity for detecting parenchymal lesions.

2 AIMS OF THE STUDY
The overall aim of the present thesis was to define and evaluate a strategy for identification of children who are at risk of developing progressive renal lesions after acute pyelonephritis. For that purpose we chose
- to study the normal DMSA distribution pattern in the kidneys according to age
- to establish reference values for scintigraphic kidney length according to age
- to delineate DMSA distribution patterns in acute pyelonephritis
- to delineate different DMSA distribution patterns in kidneys with VUR in children with and without a history of pyelonephritis
- to establish the accuracy of scintigraphic kidney size determination
- to establish criteria of kidney swelling
- to correlate DMSA distribution pattern and kidney activity uptake to clinical symptoms and microbiological data at follow-up after acute pyelonephritis

3 MATERIAL AND METHODS
3.1 Material
The patients, 283 children aged 10 days - 13 years, had been referred to our department with suspected or known renal disease. For the specific purpose of this study all 282 scintigrams (238 children) in our data base were re-evaluated.

3.1.1 Kidneys with normal distribution pattern (I)
For evaluation of the normal distribution pattern 85 children, aged 10 days - 13 years, were included. In 9 of the children suspicion of renal disease was subsequently dismissed and both kidneys were considered healthy. Seventy-six of the children had unilateral renal disease or malformation and a presumably healthy contra-lateral kidney. All included kidneys had normal findings on US and IVU. In 19 children (27 kidneys) scintigraphic kidney length was compared to sonographic length and in 10 children (17 kidneys) to urographic length.
3.1.2 Children with acute pyelonephritis (II, V, VI)

For the retrospective study of pyelonephritic patterns (II) 38 children, aged 15 days - 7 years, with clinical diagnosis of acute pyelonephritis were included. In 18 of the children a repeat scintigraphy after 5 - 8 months was obtained. All children had undergone renal US before scintigraphy. Micturating urethrocystography (MUCG) was performed on 34 children, and 8 children had undergone IVU.

In the prospective study of pyelonephritis (VI) 34 consecutive children, aged 14 days - 24 months, were included. All had clinical and microbiological signs of first time acute pyelonephritis. On all children US was performed in the acute stage, scintigraphy within a week from onset of symptoms, and MUCG within 8 weeks.

The study of scintigraphic signs of kidney swelling (V) comprised 38 children with clinical diagnosis of pyelonephritis, aged 15 days - 7 years (median 6 months). All children who were imaged two or three times by identical techniques were included. None of the children had hydronephrosis or other renal anomalies. The initial renal scintigraphy was performed on 24 children within a month after onset of symptoms, and on 14 children in a later phase. All underwent follow-up scintigraphies within 2 years.

3.1.3 Children with VUR (III)

For the study of distribution patterns in VUR 101 children (152 kidneys) with VUR in one or both kidneys were included. Children with acute pyelonephritis, and kidneys with VUR associated with additional abnormalities, were excluded from the study. Patients whose kidneys or ureters had been operated on were also excluded.

3.1.4 Piglets (IV)

For the validation of size measurements we used ten healthy piglets, weighing 4 - 18 kg.

3.1.5 Kidney phantom (IV)

A kidney phantom was made from Plexiglas. It had an oval-shaped cavity with length 120 mm and width 60 mm. A central mass was inserted (like the yolk in an egg) simulating the marrow and pelvis. The remaining space (the egg white), representing the cortex, was 1 - 2 cm wide and had a volume of 155 ml.

The kidney phantom, surrounded by plastic bags filled with water to simulate viscera in the abdomen, was placed in a Plexiglas container simulating the abdominal walls and the spine.
3.2 Methods

The children were examined at the Department of Pediatrics. They were referred to us on the basis of clinical symptoms, biochemical and microbiological findings and urine specimens indicating acute pyelonephritis. Urine specimens were analysed according to growth and type of bacteria at the Department of Clinical Microbiology. MUCG, US, and IVU were performed at the Department of Roentgenology. VUR was graded on a scale of 1-5 (Lebowitz et al 1985).

Renal scintigraphy was performed 3 hours after intravenous injection of $^{99m}$Tc-DMSA. Acquisition was performed in the posterior view with the child lying supine using a large-field-of-view ($27\times50$ cm$^2$) gamma camera equipped with a low-energy, parallel-hole collimator, interfaced to a computer. Data were collected in a 256x256 matrix, with zoom factor 2.5.

In the retrospective studies (I-III) acquisition was performed in one static image during 10 minutes (ca 300 kcounts), using a general-purpose collimator. The dose was 0.5 MBq $^{99m}$Tc-DMSA per kg body weight (minimum 10 MBq).

In the study of kidney swelling (V) and the prospective study (VI) acquisition was performed in dynamic mode with 10 one-minute images (15 for children under 7.5 kg) using a high-resolution, parallel-hole collimator. The dose was 2 MBq $^{99m}$Tc-DMSA per kg body weight, (minimum dose 15 MBq). The activity in the syringe was measured before and after injection. Images were checked for possible movements. Alignment of individual images was performed when necessary. The dynamic study images were then added to yield one static image on which evaluation was performed.

3.2.1 Qualitative evaluation

In the qualitative evaluation distribution pattern was analysed. For the purpose of making the evaluation more objective images were prepared and presented in a standardised manner with both smoothed and unprocessed versions of the image (Fig 1). Irregularities in kidney activity uptake were delineated by iso-count level contours of 20, 40, 60 and 80% of maximum pixel count in the entire image after smoothing $9\times9$ twice.

Criteria for kidney swelling:
1) isocontour level contours of 20 % - 60 % wider apart than ordinary in the whole kidney (Fig 1)
2) localised widening between isocontour level contours of 20 % - 60 % (can occur together with 1) above)
3) kidney length $\geq$110 % of expected according to age
4) ratio between kidney width and length > 0.55
5) average kidney uptake divided by average background activity $\leq$ 10.0
6) kidney length increase since a previous investigation 1.5 mm more than expected according to age

Swollen kidney was defined when three or more of the above criteria were fulfilled.
3.2.2 Quantitative evaluation

Quantitative evaluation includes the measurement of kidney length and width, separate renal function, background activity, and kidney uptake in percent of administered dose (KU/AD).

3.2.2.1 Kidney size measurements

Kidney length was measured as the longest distance from pole to pole on the 20 % iso-contour (I-VI). Kidney width was measured on the 20 % iso-contour on hilus level at right angle to renal length axis (Fig. 1) (IV - VI).

3.2.2.2 Separate renal function and background activity (I, VI)

For the measurement of separate renal function regions of interest (ROIs) were defined over each kidney by the 20 % iso-contour. Separate renal function was expressed as fraction of the total renal function. Accordingly, the number of counts in each kidney was divided by the sum of counts in both kidneys without background subtraction (I-VI). For background estimation a T-shaped region above and between the upper kidney poles was used (I, V, VI).
3.2.2.3 Kidney radioactive uptake (V, VI)

For calculation of KU/AD the administered dose was corrected for physical decay and camera sensitivity. The total number of counts in the kidneys was calculated in percent of administered dose and corrected for background activity. To calculate KU/AD in each kidney the separate renal function was used. No correction for tissue attenuation was applied.

3.2.2.4 In "vivo" versus in vitro measurements on piglets

The piglets were sacrificed 3 hours after injecting 2 M bq $^{99m}$Tc-DMSA per kg body weight. Renal scintigraphy was then immediately performed with the pig in the prone position. Planar 10 minute images were acquired simultaneously from the posterior and the anterior view with a large-field-of-view (27x50 cm$^2$) two headed gamma camera equipped with low-energy, high-resolution, parallel-hole collimators, and a computer. Data were collected and managed as for children. Tomography was performed immediately after planar imaging with a two headed large-field-of-view (38x51 cm$^2$) gamma camera with 90 degrees between the heads equipped with low energy high resolution collimators. Data were collected in 128x128 matrix with a zoom factor of 2.19. Rotation time was 30 minutes with rotation in 45 angular steps (90 azimuths) yielding 180 degrees of acquisition. Kidney volume was estimated from the 30 % isocount level of maximum voxel count in a set of transversal slices. Scintigraphic data obtained in the body of the piglet are denoted "in vivo".

After scintigraphy of the piglets the kidneys were removed. Kidney length was measured from pole to pole and width at the hilus by callipers. Kidney volume was measured by submerging it in water in a measuring glass (mean of two measurements). Planar scintigraphy of the excised kidneys was performed with the kidneys lying horizontally with each gamma camera head at a distance of 10 cms from the kidneys.

3.2.2.5 Kidney phantom

The phantom was filled with 25, 50 or 100 MBq pertechnetate dispersed in 160 ml water. Planar and tomographic images were acquired. Acquisition and calculations were made as for piglets.

3.2.3 Statistical methods

Comparisons between different measurements and estimations are presented as regression diagrams and equations. Statistical significances were calculated by Student's paired t-test. Values are expressed by their means ± 1 standard deviation. For calculating statistical significances of comparisons between patient groups we used chi-square test for two-by-two contingency tables with Yates' correction for continuity.
4 RESULTS

4.1 Qualitative evaluation

4.1.1 Normal distribution pattern (I)
In infants the distribution of DMSA in the kidney is homogenous (see Fig. 1). Lower activity in the medial part of the kidney is seen after 2 years of age. This characteristic is more prominent in older children.

4.1.2 Distribution patterns in acute pyelonephritis (II)
Four different distribution patterns in acute pyelonephritis were in order of prevalence: (i) pole defect(s), usually wedge-shaped (Fig. 1), (ii) scattered multiple defects, (iii) swollen kidney without areas of diminished uptake, and (iv) lateral wedge shaped defect. Distribution changes were, in the absence of VUR, found in 69 % of the kidneys.

4.1.3 Changes of distribution patterns at follow-up after pyelonephritis (II, VI)
Six months after acute pyelonephritis complete normalisation or improvement of the distribution pattern was found in 66 - 81 % of kidneys. Unchanged distribution pattern was found in 7 - 12 %. On the other hand, more pronounced changes were found in 11 - 22 %.
At the 1 year control no further improvement of the distribution pattern was seen in the kidneys which showed improved or unchanged pattern at 6 months. On the contrary in 34 % of the kidneys new parenchymal changes appeared. These distribution changes, not visible on the 6 month control, were always on the same locations as changes in the acute stage (Fig 2).

4.1.4 Distribution patterns in VUR (III)
Three main types of pathological DMSA patterns were found in VUR: (i) dysplasia, i.e. a small kidney with generally decreased uptake (23 %), (ii) medial defect (25 %) and (iii) pole defects (17 %). Normal distribution pattern was found in 31 % and atypical patterns in 4 %.
Normal pattern was significantly more frequent in kidneys with reflux grade 1-2. Dysplasia was significantly more frequent in kidneys with reflux grade 4-5.

4.2 Quantitative evaluation

4.2.1 Kidney size measurements
Average kidney length is 56 mm at birth (I). The kidney length increases with 12 mm during the first year and with 4 mm per year thereafter to puberty (Fig 3).
In the younger children scintigraphic length was in most cases larger than the sonographic length (I). In the older children similar values were obtained with both techniques. Urographic values were in general higher.
In children with VUR (III), and no history of pyelonephritis 42 % of kidneys
were smaller than expected, according to age. In children with VUR and a history of pyelonephritis 52% of kidneys were smaller than expected. In the acute stage of pyelonephritis (VI) mean kidney length was 101 ± 9% of expected, according to age. After 6 months the length had decreased slightly, but significantly, to 99 ± 7% (p = 0.002).

Figure 2 DMSA scintigraphies (dorsal view) on a 16 months old girl. Left panels show unprocessed images. Right panels show smoothed images with iso-count level contours of 20, 40, 60, and 80% of maximum pixel count. In the acute stage (upper panels) there is a large uptake defect in the upper pole of the right kidney. After 6 months (middle panels) this defect has disappeared. Decreased uptake has appeared in both poles of the left kidney. After another 6 months (lower panels) the uptake has improved in the left kidney. In the right kidney a new uptake defect has appeared in the upper pole.
Figure 3  Kidney length in relation to age of 94 healthy kidneys in 85 children, aged 10 days to 13 years. The dotted lines show ± 2 standard deviations of the regression lines. (Regression lines are not shown.)

One year after pyelonephritis the length was 100 ± 7 %. Also this slight increase, compared to the 6-month observation, was significant (p = 0.004). A different behaviour of kidney length was observed in six children with verified reinfection on the second DMSA scintigraphy (V). At that time criteria for swollen kidney were fulfilled in these children. On the initial scintigraphy the kidney length was 94 ± 5 % of expected according to age. The length had increased to 99 ± 6 % on the second scintigraphy (p = 0.01). On the third scintigraphy the length had decreased to 94 ± 5 % (p < 0.001) (Fig 4).

4.2.2 Background activity (I, V, VI)
In healthy children the background activity is low. It is fairly low even in the youngest infants, e.g. 14 % at birth, decreasing to 6 % during the first year of life, with no further change thereafter (I).
In the acute stage of pyelonephritis the background activity was on average higher than at follow-up i.e. 14 ± 4 % and 10 ± 2 %, respectively (p< 0.001) (V, VI).

4.2.3 Kidney size measurements in "vivo" versus in vitro (IV)
Scintigraphic kidney length in vivo overestimated anatomical kidney length by 2.6 ± 2.0 mm (3.9 ± 2.4 %) (Fig 5). Overestimation of scintigraphic width in vivo, 2.4 ± 1.9 mm, was similar to that of length which means that the difference in percent was larger (7.8 ± 3.9 %).
Figure 4 Kidney length in percent of expected according to age on the initial, second, and third scintigraphy in 6 children (11 kidneys) with signs of swollen kidney on the second scintigraphy (filled circles), and in 11 children (19 kidneys) with no signs of swelling on any scintigraphy.

The tomographic in vivo volume determination showed differences from submersion data which tended to decrease with increasing kidney size (Fig. 6). The average difference was 4.4 ± 5.0 ml (23 ± 13 %). Change of cut-off level for renal delineation did not alter the overestimation of volume in vivo.

4.2.4 Kidney phantom (IV)
At a cut-off level of 20 % of maximum pixel count, the scintigraphic phantom length overestimated the phantom callipers length by 6 mm (5 %). The corresponding figure for width was 5 mm (8 %). At a 35 % cut-off level the scintigraphic length and width underestimated the phantom length and width by 2 mm (2 %) and 3 mm (5 %), respectively. At a cut-off level of 30 % of maximum voxel count the tomographic phantom volume overestimated the phantom volume by 17 ml (11 %). With a cut-off level of 35 % of maximum voxel count the tomographic volume underestimated the phantom volume by 15 ml (10 %).

4.2.5 Kidney radioactive uptake (V, VI)
The kidney uptake (KU/AD) was lowest in the acute stage of pyelonephritis i.e. 9.6 ± 2.5 At follow-up KU/AD had increased to 12.1 ± 2.2 (p < 0.001) at 6 months without further significant increase.
**Figure 5** Relation between scintigraphic kidney length in situ of 10 piglets and calliper length of excised kidneys.

**Figure 6** Relation between tomographic kidney volume in situ of 10 piglets and submersion volume of excised kidneys.
Kidney radioactive uptake in percent of administered dose

<table>
<thead>
<tr>
<th>20%</th>
<th>18%</th>
<th>16%</th>
<th>14%</th>
<th>12%</th>
<th>10%</th>
<th>8%</th>
<th>6%</th>
<th>4%</th>
</tr>
</thead>
</table>

Figure 7 Kidney radioactive uptake in percent of administered dose (KU/AD) on the initial, second, and third scintigraphy in 6 children (11 kidneys) with swollen kidney on the second scintigraphy (filled circles), and in 11 children (19 kidneys) not fulfilling the criteria of swollen kidney on any occasion (open circles).

A different behaviour of KU/AD was observed in six children with verified reinfection on the second DMSA scintigraphy (V). They had on the initial scintigraphy a KU/AD of 11.7 ± 2.0. On the second scintigraphy KU/AD had decreased slightly, but significantly to 10.4 ± 2.5 (p = 0.005). On the third scintigraphy KU/AD had increased to 13.8 ± 1.5 (p < 0.001) (Fig 7).

4.2.6 Distribution pattern versus KU/AD (VI)

Distribution pattern and KU/AD did not correlate closely. Normalised distribution pattern or less pronounced uptake defect was found in 35 % of kidneys with decreased KU/AD. On the other hand it was found that in 30 % of kidneys with increased KU/AD the distribution pattern showed more pronounced uptake defects. A closer relation was found between KU/AD and infection.

4.3 Microbiology (VI)

All children with urine cultures growing < $10^4$ bacteria/ml at follow-up had increased KU/AD compared to the preceding scintigraphy. Conversely, 83 % of children with urine cultures growing ≥ $10^4$ bacteria/ml at follow-up had decreased KU/AD compared to the preceding scintigraphy. P-fimbriated strains of E Coli were infecting agents in 53 % of children in the acute stage. At follow-up E Coli was infecting agent in 24 % of children with urine cultures growing ≥ $10^4$
Table 1 Infecting agent in the acute stage and in urine cultures at 6 months and 1 year controls

<table>
<thead>
<tr>
<th>Infecting agent</th>
<th>Number of children</th>
<th>Acute stage</th>
<th>Culture $\geq 10^4$ bact/ml and decreased KU/AD at control</th>
<th>Culture $\geq 10^4$ bact/ml and increased KU/AD at control</th>
</tr>
</thead>
<tbody>
<tr>
<td>E Coli, P-pos.</td>
<td>18</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>E Coli, P-neg.</td>
<td>12</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Enterobacter</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Klebsiella</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Proteus</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

P-pos. signifies P-fimbriated strains of E Coli, and P-neg. non-fimbriated strains.

bacteria/ml (Table 1). One of 4 children with progressively decreased KU/AD had growth of P-fimbriated of E Coli in urine at each control, whereas two had growth of non-fimbriated E Coli and one had growth of Proteus at each control.

5 DISCUSSION

5.1 Material

5.1.1 Kidneys with normal distribution pattern (I)

To be able to identify pathological features on DMSA scintigraphy it is essential to know the normal distribution pattern, according to age. A reference material is especially important in infancy because of the kidney maturation process (Aperia et al 1981, Strauss et al 1981). The difficulties in obtaining reference material in children are well known. It is in general not ethically justifiable to perform studies on children without suspected or known disease. The "normal" material for our study (I) is based on two groups of children. The first group comprised children with subsequently dismissed suspicion of renal disease, in whom kidneys were normal as demonstrated by US, MUCG and IVU. The second group were children with unilateral renal disease in whom those kidneys were excluded only because they had duplex ureter/pelvis, hydronephrosis or VUR. It need to be pointed out that the excluded kidneys did not have seriously reduced uptake and
therefore would presumably not have lead to compensatory hypertrophy of the studied kidneys. For the purpose of this study it is reasonable to assume that the studied kidneys were also normal as regards function and size. In other studies of normal renal properties patients have been selected on similar grounds. (Gordon et al 1987, Sisayan et al 1993, Groshar et al 1994, Evans et al 1997)

5.1.2 Children with acute pyelonephritis (II, VI)

The study of the pyelonephritic distribution patterns was retrospective (II). We have reason to believe that they are representative because clinical, laboratory and roentgenologic data, in this material, do not differ significantly from those in the prospective study of pyelonephritis (VI). The main difference between the retrospective and prospective studies is the timing for follow-up scintigraphy. During the period of the prospective study special attention was paid to strictly defined times for performing the clinically indicated scintigraphies. Furthermore, our results from both studies are in agreement with other studies according to the distribution of parenchymal changes and the prevalence of VUR (Melis et al 1992, Majd & Rushton 1992, Benador et al 1994, Stokland et al 1996).

In study VI only children with first time pyelonephritis under 2 years of age were included. The reason was to avoid children with previous undiagnosed infections that may compromise the interpretation of scintigrams.

5.1.3 Children with swollen kidneys (V)

In the study of swollen kidneys the scintigraphies were performed at varying times. Children who developed infections during the study were identified by DMSA scintigraphy. We therefore believe that the results of this study can contribute to the understanding of scintigraphic findings in acute pyelonephritis and influence the management of children with UTI. We recognise that the study design has limited the possibility of drawing further conclusions.

5.2 Methods

5.2.1 Development of methods (V, VI)

During the progress of this study the scintigraphic method for clinical routine was gradually refined.

5.2.1.1 Change of collimator and radioactive dose

To increase image quality a high-resolution collimator, and a higher dose of DMSA (2 Mbq/kg body weight, minimum 15 Mbq) were introduced. The dose is similar to that recommended by the European Association of Nuclear Medicine. The change was introduced between studies III and V. The effect of the change on image interpretation was evaluated on repeated scintigraphies in children referred for examination both before and after the change. With high-resolution collimator small pattern inhomogeneities became slightly more distinct, without significant influence on the distribution pattern. The collimator change may,
however, have increased the sensitivity for detecting small pyelonephritic lesions. In the retrospect study of acute pyelonephritis (II), before the change we found pyelonephritic lesions in 80% of the kidneys. In the prospective pyelonephritic study (VI) after the change, the frequency of pyelonephritic lesions was slightly higher i.e. 90% of the kidneys. However, both frequencies are in the same range as that of others who found a sensitivity of 80 - 90% for detecting renal pyelonephritic lesions in experimental studies (Rushton et al 1988, Parkhouse et al 1989, Majd & Rushton 1992, Risdon et al 1994).

5.2.1.2 Movement artefacts

Immobilisation of the child by a vacuum pillow was introduced between studies III and V. By changing acquisition from static to dynamic mode with 10 one-minute images we were able to register movements. The vacuum pillow minimises, but does not completely prevent, movements of the child. In the dynamic study images can be corrected for movements, when necessary, by shifting one or more of the images. Thus re-acquisition can to a great extent be avoided. The possible effect of movement corrections on image quality was evaluated by comparing length measurements and distribution patterns on corrected and uncorrected summation images. Movements of 2 mm or less were found in 26/30 patients. These movements did not influence length measurements or the uptake pattern. Movements of 3 - 4 mm were found in 4 children. These movements caused less distinct uptake defects on uncorrected images (unpublished data).

The improvements gained by the vacuum pillow and the dynamic acquisition were modest. We conclude that the principal findings in studies I-III are valid also after the modification of the method.

5.2.2 Kidney delineation and choice of background (I-VI)

To get a standardised and objective kidney outline, the margins were defined by the iso-contour of 20% of maximum pixel count, estimated in the entire image. This approach yields a cut-off level that is the same for both kidneys. A problem can arise when renal function is severely reduced, i.e. when background is high (near 20%).

As the background activity in general is low, correction for background was used only for calculating KU/AD but not for separate renal function. Comparing different background regions it was found that the choice of background is unimportant at near normal renal function. If the renal function is poor the choice of background could be critical when measuring separate renal function (Gordon et al 1987).

5.2.3 Kidney size measurements (IV)

For validation of kidney size measurements (IV) we chose piglets with kidney size of relevance for pediatric practice. The kidney phantom was of adult kidney
size to represent the upper part of the size range. Because imaging was performed with equipment that was also used for clinical studies, the piglets had to be sacrificed before imaging. We have therefore not taken into account the possible effect of respiratory movements.

The tomographic kidney volume overestimated the anatomical volume consistently. The overestimation of the volume was greatest for the smallest kidneys. Thus kidney volume is not a reliable measure of kidney size in pediatric praxis.

Kidney length was the most accurate measure of kidney size.

The cut-off level of 20 % of maximum pixel count was chosen to define kidney margins, in the planar image, because on that level the border between kidney and background is particularly sharp. For lower cut-off levels the delineation of the kidneys may be less distinct, particularly in the diseased kidney. We found that with a cut-off level of 20 % the scintigraphic kidney length overestimates the anatomical kidney length by 4 % on average. This overestimation is a systematic error that, to some extent, can compensate for the inclination of the kidneys to the image plane. This inclination averages 25-30 degrees according to Farrant & Meire (1978). Considering the shape of the kidney such an inclination would render an underestimation of the kidney length of approximately 6 %. The positions of the kidneys do not generally vary between examinations, as shown on consecutive scintigraphies. Therefore, such systematic errors are less important on subsequent examinations, when the child is its own control. Our measurements of renal length on the scintigraphic image is standardised and essentially operator independent, with inter- and intra-observer variability below 2 % (unpublished data). On the contrary, US inter- and intra-operator variability are high, on average 7-13 % and 1-7 %, respectively, as reported by Hederström & Forsberg (1985), Schlesinger et al (1991), and Sargent & Wilson (1992). On repeated examinations this variability cause difficulties of knowing whether changes in renal size are due to observer variability, kidney growth, or diminished renal size.

5.3 Results

5.3.1 Distribution patterns (I-III, V-VI)

In the normal kidney the DMSA distribution is described as homogeneous throughout the cortex. In the medial part of the kidney lowered and heterogeneous uptake, corresponding to pelvis and areas overlying the pyramids is reported as normal in all ages (Piepsz et al 1991, Majd & Rushton 1992, Eggli & Tulchinsky 1993). We have developed the pattern recognition further by describing the change of the distribution with age (I). During the first two years of life the DMSA distribution is fairly homogeneous in the entire kidney that often has a rounded form. This pattern very probably reflects the lobular architecture of the immature kidney (Chantler 1976). From about two years of age the uptake in the medial part of the kidney is slightly lowered and heterogeneous. The older the child the more evident is this heterogeneity. We believe that during the maturation
process the kidney changes form and becomes more elongated with the pelvis gradually growing wider. Unawareness of this different distribution pattern in the youngest children may lead to underdiagnosis of pyelonephritis, and may have contributed to the lower incidence of pyelonephritic changes at lower ages (Benador et al 1994, Stokland et al 1996).

Acute pyelonephritis is usually manifested at scintigraphy as single or multiple areas of varying degrees of diminished cortical uptake of DMSA. We found that the majority of lesions occur typically in both poles (II, V, VI). The second most common pattern is scattered multiple areas of diminished uptake. Similar results are reported by others (Monsour et al 1987, Majd & Rushton 1992, Eggli & Tulchinsky 1993). The third most common pattern in our material was enlarged kidney without distinct uptake defects. Such a pattern was described as a less common finding by Majd & Rushton (1992). Some authors believe that this pattern represents the most severe form of pyelonephritis (e.g. Eggli & Tulchinsky 1993). An enlarged kidney with generally decreased uptake fulfil our criteria of swollen kidney. Swelling of the kidney is often present simultaneously with cortical uptake defects, and then often escapes attention on scintigraphy evaluation. However, swelling of the whole kidney, without distinct uptake defects, appear more frequently than generally appreciated. Such a DMSA distribution may be interpreted as normal and result in inaccurate treatment. The recognition of the swollen kidney is particularly important when clinical symptoms are not specific.

Normalisation/improvement of the distribution pattern at six months after acute pyelonephritis was found in 66 - 81 % of the kidneys. This rate of improvement is similar to data reported by Rosenberg et al (1992). However, it is difficult to find comparable studies in the literature because of the different times for follow-up scintigraphy. At the 1 year control no further improvement of the distribution pattern was seen in kidneys which showed improved or unchanged pattern at the 6 month control. This is in agreement with Eggli & Tulchinsky (1993). In other studies with follow-up at 1-2 years the rate of normalisation of pathological acute scintigrams varies between 44 and 64 % (Jakobsson et al 1994, Stokland et al 1996). The reason for this variation may depend on the selection of patients that varies according to age and previous infections. Those factors can greatly influence the distribution pattern. Moreover, subjective variations in interpretation may contribute (Piepsz et al 1993, Patel et al 1993).

More pronounced distribution changes at one year control compared to 6 months was found in 34 % of the kidneys. A similar finding was observed by Stokland et al (1996). They found an abnormal DMSA scintigram at follow-up after a normal initial scintigram in 24 % of the kidneys.

An important finding is new distribution changes, not visible at 6 months, appearing at the one year control. Interestingly, they were always on the same locations as changes in the acute stage. Similar results have been reported by Jakobsson et al (1994). A possible explanation is a silent or a breakthrough infection between the occasions for imaging. Another possibility is silent or breakthrough infection with swollen kidney pattern at the first control. A pattern
of such nature may obscure small uptake defects which are otherwise typical signs of pyelonephritis.

In study VI we found a higher incidence of bilateral changes (93 %) than in study II (58 %). The main reason for this is probably a learning effect, particularly for recognition of the swollen pattern. The change to high-resolution collimator may have contributed. The incidence of bilateral changes in our material is similar to that reported by Clarke et al (1995). They found bilateral changes in 78 % of boys under the age of 1 year and in 73 % of girls aged 5 years and over. On the contrary others have reported bilateral changes in less than 25 % of children (Majd & Rushton 1992, Benador et al 1994, Stokland et al 1996).

In study III we were able to delineate three main pathological patterns occurring in VUR, pole defects, medial defect and dysplasia. The types and frequencies of pathological patterns in the group with VUR without known infection did not differ from those in the group with VUR and pyelonephritis. Under-diagnosed pyelonephritis may have contributed to this result. On the other hand, the pathogenesis of renal scarring is complex and the mechanisms are not yet fully understood (Risdon 1997). The pattern with pole defects is in agreement with experimental studies on animals, where reflux was shown to cause damages with pole predominance (Jørgensen & Stödkilde-Jørgensen 1985, Ransley & Risdon 1975). The pattern with medial defect partly reflects dilated pelvis and calyces. Dysplasia, most frequently found in kidneys with higher degrees of reflux, may, to a great extent, represent maldevelopment as a result of prenatal reflux, as argued by Najmaldin et al (1990), Andersson & Rickwood (1991), and Risdon (1993).

5.3.2 Kidney length (I-III, V-VI)

Normal renal size and renal growth is in children a recognised indication of a healthy kidney. There is a close relation between kidney size and age as found by IVU and US (Hodson et al 1962, Eklöf & Ringertz 1976, Haugstvedt & Lundberg 1980). US has been proposed as the method of choice for measuring kidney size (Gordon 1990). Concerning IVU and US kidney length has shown to be the most convenient measure of renal size (Eklöf & Ringertz 1976, Emamian et al 1995). The possibility of using DMSA scintigraphy for estimation of kidney size was dismissed by Monsour et al (1987). However, others found it valuable (Sisayan et al 1993). We found that kidney length was not only the most convenient measure of renal size but also the most accurate (IV). Comparing scintigraphic to urographic kidney length (I) we found that the scintigraphic length is in general smaller than the urographic. Comparing scintigraphic and sonographic measurements no significant difference was found in the older children, while in infants, the scintigraphic kidney length was larger. On the other hand, some authors found that the scintigraphic kidney length exceeded the sonographic in all children (Sisayan et al 1993). Our results are partly in disagreement with studies showing no systematic difference between urographic and sonographic length (Hederström & Forsberg 1985). The renal growth in
healthy children was in our material 12 mm during the first year of life and 4 
mm/year thereafter to puberty. Similar results are reported by others using US 
and scintigraphy (Rosenbaum et al 1984, Sisayan et al 1993). We found that renal 
growth is impaired for some time after an episode of pyelonephritis but kidney 
length usually returns to the expected value a year later (V, VI). A similar 
observation was reported by Smellie et al (1981a). VUR is another cause of renal 
growth impairment. Anderson & Rickwood (1991) found smaller kidneys in the 
presence of higher grade of VUR. In our results reduced kidney size was also a 
frequent finding among kidneys with higher degrees of VUR (III). Moreover, we 
found a high incidence of kidney growth impairment associated even with low 
grade of VUR and in the absence of infection or other pathology.

5.3.3 Kidney radioactive uptake (V, VI)
An important finding was low KU/AD in the acute stage of pyelonephritis. At 
follow-up KU/AD had increased in all children without bacterial growth in urine. 
The magnitude of changes was small but statistically significant. Nevertheless, 
the KU/AD values in our results were for many patients within the "normal" 
range as estimated by Gordon et al (1985) and Evans et al (1996). However, in 
their work the "normal" range is rather wide. On the other hand we used each 
patient as her/his own control. Then even small changes become perceivable. 
Moreover, our results are not directly comparable to those of Gordon et al (1985) 
and Evans et al (1996). They used attenuation correction which we avoided 
because the estimation of kidney depth is operator dependent and may introduce 
an additional error.

5.3.4 Quantitative versus qualitative evaluation of DMSA scintigraphy (V, VI)
Uptake defects assessed by qualitative evaluation on DMSA scintigraphy are 
accepted for the diagnosis of pyelonephritis (Parkhouse et al 1989, Rushton et al 
1988, Risdon et al 1994). However, we showed that even kidneys without 
distinct uptake defects, but fulfilling the criteria for swollen kidney indicate 
pyelonephritis. Furthermore, quantification showed low KU/AD in all kidneys 
with acute pyelonephritic pattern.

When considering only qualitative assessment of the DMSA image we found that 
35 % of kidneys would have been judged as improved at follow-up, whereas 
quantitative measurement showed decreased KU/AD. On the other hand 71 % of 
kidneys, with qualitative signs of deterioration, showed increased KU/AD at 
follow-up. Moreover, 59 % of kidneys without changes of the distribution pattern 
showed increased KU/AD. Low KU/AD was found in children in the acute stage 
of pyelonephritis and in 83 % of those with bacterial growth of \( \geq 10^4 \) bacteria/ml 
in urine cultures at follow-up. Therefore KU/AD gives a relevant estimation of 
renal function.

The frequency of pathological changes on DMSA scintigraphy in infants were in 
our results higher compared to others (Benador et al 1994, Stokland et al 1996).
Unrecognised pattern of the swollen kidneys and small scattered uptake defects may contribute to this discrepancy.
Quantitative assessment makes it possible to detect decreasing renal function in the absence of distinct parenchymal lesions. That increases the sensitivity of DMSA scintigraphy and makes it an important means to identify children who need further follow-up.
An interesting observation is that recurrent infections caused changes always on the same locations, a finding also reported by Jakobsson et al. (1994). Therefore it is impossible with only qualitative assessment to distinguish whether changes are new or have occurred in the event of breakthrough or silent infection.

5.3.5 *Time for DMSA imaging in UTI (VI)*

It is important to establish the parenchymal state at the first infection to allow studies of the progression of renal damage and of functional loss thereafter. Moreover, DMSA scintigraphy in the acute stage helps to establish the correct diagnosis of pyelonephritis in the situation when clinical and laboratory findings are not clear.

Kidneys which showed improved or unchanged distribution pattern at 6 month follow-up did not show any further improvement at the 1-year control. Therefore it is reasonable to believe that these changes are permanent. This finding speaks in favour of a 6-month control for identifying children with permanent lesions as proposed by Eggli & Tulchinsky (1993). Some authors stressed the importance of identifying children with permanent lesions (Smellie 1995, Stokland et al 1996). In addition to that we argue that it is crucial to recognise children who are at risk of developing progressive renal damage. For this purpose the finding of new distribution changes at the one year control, not obvious at 6 months, is an important observation. In the kidneys with new changes decreased KU/AD was found in 70%. All but one of these children were free of typical clinical symptoms but had bacterial growth of $\geq 10^4$ bacteria/ml in urine cultures. With only a 6 month control we would miss those children.

During the year after the first UTI the children are vulnerable and recurrent infections are common (Winberg et al 1975). Therefore a 1-year follow-up after the first infection is more appropriate for recognising children who will benefit from further follow-up.
6 CONCLUSIONS

Qualitative and quantitative DMSA scintigraphy is a reliable method to identify children with renal involvement in UTI and bacteriuria.

Quantitative analysis is a necessary complement to qualitative assessment of DMSA distribution pattern.

Kidney length is an accurate scintigraphic measure of renal size.

KU/AD is a reliable index for measurement of renal function.

Renal growth is impeded for some time after pyelonephritis.

Moderate bacteriuria of $10^4$ bacteria/ml of urine is associated with renal functional deterioration.

In the strategy of identifying children at risk for developing progressive renal lesions it is necessary to perform DMSA scintigraphy in the acute stage and at follow-up - preferably after one year.
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FÖRBÄTTRAD BEDÖMNING AV NJURSKADOR HOS BARN MED URINVÄGSINFEKTIONER

Populärvetenskaplig sammanfattning

Urinvägsinfektioner är vanliga och förekommer hos 1 - 4 % av alla barn. Urinvägsinfektion kan ge upphov till njurinflammation och ibland kvarstående njurskada (ärr) efter läkning. Det finns risk för fortskridande njurskada om det finns kvarstående njurskada efter en urinvägsinfektion, om barnet får upprepade urinvägsinfektioner eller om det finns reflux (tillbakaflöde) av urin från urinblåsan till njurarna. Fortskridande njurskador kan leda till högt blodtryck, komplikationer hos fostret och modern vid graviditet och ibland till njursvikt. För att inte behöva utföra onödiga undersökningar på många barn är det därför viktigt att kunna identifiera de barn, som riskerar att få fortskridande njurskador. Dessa barn måste undersökas och behandlas på ett sådant sätt att vidare njurskador om möjligt förhindras.

Avsikten med detta arbete var att förbättra diagnostiken av njurskador vid njurscintigrafi med DMSA så att vi bland barn med njurinflammation kan identifiera dem, som riskerar att få fortskridande njurskador.


Vi standardiserade utförande och utvärdering av njurscintigrafi och började mäta njurstorlek. För att systematisera tolkningen av bilderna utvärderade vi på nytt, med den standardiserade metoden, 282 tidigare utförda njurscintigrafi på 238 barn.


Vi kartlade därefter de typiska skademönstren vid njurinflammation hos barn, som undersöks i samband med njurinflammation och efter tillfrisknandet.

Vi kartlade även olika skademönster på njurar med reflux från urinblåsan hos barn med respektive utan tidigare njurinflammation.

För att undersöka hur njurstorleken mätt på scintigrafiska bilder stämmer med den verkliga storleken scintigraferade och mätte vi njurarna på 10 smågrisar. Vi konstruerade och scintigraferade en njurmodell i plexiglas. Vi fann att
scintigrafisk njurlängd stämmer väl med den verkliga njurlängden medan mätning av bredd och volym är mindre tillförlitliga, åtminstone på små njurar.

Med hjälp av njurarnas scintigrafiska mönster och mätt kunde vi upptäcka nya urinvägsinfektioner med njurinflammation hos några barn trots att de saknade typiska symptom. Infektionerna kunde bekräftas med urinodlingar, och barnen fick antibiotikbehandling.

Därefter följde vi barn med akut njurinflammation. De scintigraferades i samband med insjuknandet, efter 6 månader och igen efter 1 år. Vi började då kvantifiera DMSA, dvs vi mätte mängden DMSA i njurarna vid de olika undersökningstillfällena. Mängden DMSA i njurarna är ett mått på deras funktion.

Vi fann att njurtillväxten hämmas en tid efter njurinflammation men återhämtar sig, om nya infektioner inte tillstöter. Njurfunktionen är försämrad vid insjuknandet i njurinflammation men också hos de flesta barn, som vid uppföljning har bakterier i urinen, även om de inte har symptom på urinvägsinfektion eller njurinflammation. Barn, som hade bakterier i urinen, med eller utan symptom, både 6 månader och 1 år efter insjuknandet fick fortsatt försämrad njurfunktion. Enbart granskning av njurarnas skademonster räckte inte för att identifiera dessa barn.

The aim of the present thesis was to define and evaluate a strategy for identification of children who are at risk of developing progressive renal lesions after acute pyelonephritis.

Tc-DMSA renal scintigraphy is widely accepted as the most sensitive method for detecting parenchymal lesions and diagnosing acute pyelonephritis. Qualitative and quantitative evaluation standards were elaborated to improve the interpretation of DMSA scintigraphy. The normal DMSA distribution pattern, the average background uptake, and scintigraphic kidney length according to age were assessed in 95 presumably healthy kidneys. Furthermore, typical DMSA distribution patterns in acute pyelonephritis were assessed on 65 kidneys in 38 children, and typical DMSA distribution patterns of 152 kidneys with vesicoureteric reflux in 101 children with and without previous pyelonephritis.

Measurement of scintigraphic kidney length, width and volume was validated in piglets and on a kidney phantom. The scintigraphic kidney length was found to be an accurate measure of renal size, whereas kidney width and volume were less reliable, at least on small kidneys.

Criteria of kidney swelling in acute pyelonephritis were defined, and found to be beneficial for identifying reinfections in the absence of clinical symptoms.

In 34 children with acute pyelonephritis quantitative and qualitative DMSA scintigraphic findings were correlated to clinical symptoms and laboratory data, in the acute stage and at follow up. We found that a quantitative DMSA scintigraphy in the acute stage of pyelonephritis and again after one year will identify children who are at risk of developing progressive renal lesions. Qualitative assessment of DMSA distribution pattern is not reliable enough in this respect.