Quantitative ^{99m}Tc-DMSA Uptake in Experimental Pyelonephritis

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Quantitative ^{99m}Tc-dimercaptosuccinic acid (DMSA) renal uptake was studied in unilateral reflux-related pyelonephritis in pigs. The changes to absolute % dose uptake and differential uptake occurring with induction and after treatment of pyelonephritis were correlated with the DMSA images and renal pathology. **Methods:** Quantitative uptake in 53 young pigs was obtained from planar images acquired 6 h after injecting the dose. Baseline studies were made (Q1), and studies were made again after urinary infection was established (Q2), when 8 pigs had normal (no defect) renal images (group A), 23 had photon-deficient (reversible) focal defects (group B) and 22 had photon absent (irreversible) focal defects (group C). Q3 studies were made in 21 animals from groups B and C after 3-wk antimicrobial treatment. **Results:** At Q2 the affected kidney differential uptake was unchanged for group A and reduced for groups B and C (respective mean changes −1.7%, $P < 0.01$; and −5.5%, $P < 0.01$). The absolute % dose uptake was unchanged in pyelonephritic kidneys, but increased in the contralateral nondiseased kidneys in groups B and C (respective mean increases +1.4%, $P < 0.05$; and +5.4%, $P < 0.01$), while remaining unchanged for group A. In group C, global renal accumulation was actually increased above the Q1 values. After treatment (Q3) the reduced pyelonephritic kidney differential uptake persisted in groups B and C. In group C, however, the increased absolute % dose uptake by the contralateral kidney was less marked and not significantly different from Q1 values in this small group. **Conclusion:** Induction of unilateral pyelonephritis produced a small reduction in diseased kidney differential uptake that was greatest in the group with irreversible imaging defects. The method did not discriminate individuals with reversible and irreversible imaging defects. The decrease in pyelonephritic kidney differential uptake resulted from increased DMSA accumulation (absolute % dose uptake) by the nondiseased contralateral kidney, while that in pyelonephritic kidneys remained unchanged. After treatment, the reduced pyelonephritic kidney differential uptake persisted, but the elevated global DMSA accumulation seen for group C (with irreversible imaging defects) was not sustained and was variable.

Key Words: pyelonephritis; swine; radionuclide imaging; succimer; renal counterbalance

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In two previous publications we reported ^{99m}Tc-dimercaptosuccinic acid (DMSA) imaging appearances in acute pyelonephritis and developing renal scars using a pig model (*1,2*). The first correlated the scintigraphic appearances with the underlying pathology in untreated pyelonephritis (*1*). The second reported a parallel experiment investigating the effects of 3-wk antimicrobial treatment on the scintigraphic and pathological abnormalities (*2*).

The abnormal scintigraphic appearances in pyelonephritis were either focal areas of photon deficiency with an intact renal outline (termed B defects) or areas featuring complete photon absence (termed C defects). Most B defects were associated with "early" pathology (inflammatory changes without fibrosis) in untreated animals (*1*). After treatment, most B defects resolved scintigraphically, and any remaining pathological changes were minor (seen in 88%; 37/42) (*2*). In contrast, most photon-absent C defects had underlying "late" pathology (established scars with interstitial fibrosis), although one-third were associated with large early lesions (*1*). After treatment nearly all the C defects persisted (13/15), and underlying pathology always showed substantial macroscopically evident scars or craters (15/15) (*2*).

In addition to the qualitative analysis, quantitative ^{99m}Tc-DMSA uptake was evaluated in animals with unilateral disease to examine whether this contributed further to distinguishing reversible from irreversible renal damage. This study describes the changes in ^{99m}Tc-DMSA uptake occurring in parallel with the alterations in the renal image after the induction of pyelonephritis, as well as after 3-wk antimicrobial therapy.

MATERIALS AND METHODS

Experimental Design

This quantitative study of ^{99m}Tc-DMSA uptake was performed in conjunction with the qualitative studies previously reported (*1,2*). The protocol included kidneys with a variety of image abnormalities occurring during the evolution (2–28 d) of acute pyelonephritis and early scar formation. Fifty-three male pigs with surgically induced unilateral vesico-ureteral reflux (VUR) and urinary infection were studied. Sequential ^{99m}Tc-DMSA studies were undertaken. Once a required defect was established, 32 animals were killed to correlate the scintigraphic and pathological appearances described earlier (*1*). The remaining 21 pigs followed an extended protocol of 3-wk antimicrobial treatment, with final ^{99m}Tc-DMSA studies when the pigs were killed and the kidneys examined (*2*). Quantitative ^{99m}Tc-DMSA uptake was evaluated at three study points: (a) after inducing VUR, but before instituting a urinary infection, when the kidneys appeared normal (preinfection;

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Q1); (b) after the required imaging defects were established and immediately before either killing the pigs or initiating treatment (postinfection; Q2); and (c) in treated animals, after the 3-wk antimicrobial treatment period, immediately before killing (post-treatment; Q3).

At each study point (Q1, Q2 and Q3), three results were acquired: (a) the qualitative scintigraphic appearance of the renal image (graded A, B or C); (b) absolute % dose uptake (individual kidney uptake as percentage of the injected dose); and (c) the differential uptake ("refluxing" or pyelonephritic kidney uptake as percentage of the combined left- plus right-kidney uptake). The animals were grouped according to the grade of DMSA imaging abnormality after the infection period (the postinfection Q2 study point). The changes in ^{99m}Tc-DMSA absolute and differential uptake were examined with the induction of pyelonephritis and after treatment of the lesions causing the imaging abnormalities in those animals assigned to this protocol.

The experimental protocol and all procedures were conducted in accordance with British law (Animals [Scientific Procedures] Act 1986).

The Pig Model

The pig model with infected VUR and segmental pyelonephritis has been described in detail previously (*1–3*). Unilateral VUR was induced surgically, in pigs aged 7 to 8 wk, and, after a healing period, urinary infection was introduced using a culture of *Escherichia coli* or a fecal suspension. At intervals of no more than 1 wk, all animals underwent urinary tract ultrasound examination and urine microbiological examination.

Of the 21 pigs remaining after the extended treatment protocol, 19 had formal treatment starting immediately after the postinfection Q2 uptake study with a single dose of gentamicin (2mg/kg body weight). This was followed by nitrofurantoin (approximately 5 mg/kg body weight/day) given throughout the 3-wk treatment period. There were 2 additional pigs included that did not have formal treatment, but with imaging defects which were nevertheless resolved within the 3-wk period.

^{99m}Tc-DMSA Scintigraphy

The gamma camera (Searle 001-EB6413; Searle Ltd., Erlangen, Germany) was fitted with a multipurpose low-energy collimator and interfaced to an Elscint Apex 110 computer (Elscint Ltd., Haifa, Israel). The ^{99m}Tc-DMSA preparation contained 750 MBq in a 5-mL volume. For each study, a weighed dose (containing 3–4 MBq/kg body weight) was given by intravenous injection using a butterfly cannula. The animals were lightly anesthetized with an O_2/N_2O/halothane mixture for the injection and imaging procedures. At an accurately recorded interval about 6 h after the dose injection, renal images (magnified × 2) were acquired in the posterior (200s; 250,000–450,000 counts) and postero-oblique (150,000 counts) projections. This was done by positioning the animals prone, carefully avoiding any lateral rotation, below but in contact with the gamma camera face, which was made exactly horizontal (180° in both planes) for the posterior images.

Renal Image Appearances

The images were displayed on a black-and-white monitor with the full gray scale available. Normal or abnormal areas were characterized as follows. A: Normal, no photon deficient area on either the posterior or oblique views. B: A focal defect with an appearance, on either the posterior or the posterior-oblique view, of incomplete photon loss with an intact renal outline (i.e., there was diminished uptake, but functioning cortex extending to the renal margin could still be identified within the defect), B1: when photon deficiency was minimal or barely detectable; or B2: when photon deficiency was marked or severe. C: A focal defect in which there was complete photon loss apparent on both the posterior and oblique views (i.e., within the defect there was complete loss of uptake and absent functioning cortex, so that the normal renal outline was lost).

Individual kidneys were classified as either normal (A) or according to the worst defect displayed. Thus kidneys classed as B1 had only B1 defects but those classed B2 or C could include kidneys with additional defects of a lower grade.

Quantification of ^{99m}Tc-DMSA Uptake

From the posterior (200 s) image, individual kidney counts (IKC) were obtained after correcting for background and tissue depth. Background subtraction was determined from two superimposed regions of interest (ROIs) of different sizes placed over each renal image in turn. The mean renal depth for each kidney was assessed from ultrasound and a correction made for attenuation of activity by tissue.

Absolute % dose uptake was recorded as individual kidney activity (counts/unit time; IKC) relative to the activity in the injected dose and expressed as percent. The dose activity was calculated by equating the weight of the dose with the activity of a known weight of a standard (approximately 0.4 mL) drawn from the same preparation of ^{99m}Tc-DMSA. The activity of the residue in the dose syringe and butterfly was subtracted. Both dose weight and standard weight were determined from the difference in weights between the full and empty (preweighed) syringes. The activity of the standard and of the residue were recorded (for 10 s) twice each from two marked areas of the gamma camera face, the same as those used for recording activity in left and right kidneys. Corrections for decay were made.

Differential uptake was recorded from the "refluxing" kidney renal counts relative to the combined left- plus right-kidney counts and expressed as percent.

The accuracy of the tissue depth correction in influencing the uptake values obtained from the kidneys in place in the animal (in situ) was assessed in 32 pigs. These animals had an additional 24-h image acquired immediately before kill, and the absolute and differential uptake results were compared with the respective uptake measurements obtained from imaging the isolated (ex situ) postmortem kidneys.

Analysis

Absolute % dose uptake and "refluxing" kidney differential uptake values were log transformed to obtain group statistics (geometric mean, subsequently referred to simply as the mean, and 95% confidence intervals [CIs]). The changes in uptake parameters occurring with infection and with treatment were analyzed from the differences between paired uptake values in individual animals (Q2-Q1; Q3-Q1). The 95% CIs were calculated from the mean ± SE × ≈ 2; $t_{0.025\,df}$. Tests of significance were performed as appropriate, using one-way analysis of variance or the paired or two-sample *t* test for samples with unequal variances when necessary (i.e., for postinfection data). The method of Bland and Altman (*4*) was used to compare the uptake measures calculated from the kidneys in place in the body (in situ kidneys) with those calculated from the postmortem (ex situ) kidneys.

RESULTS

Correlation Between Imaging Appearances and Pathology

At the outset (Q1), all kidneys had normal (grade A) images. All contralateral "nonrefluxing" kidneys had normal images throughout the study periods and no pathology present at kill. At the postinfection (Q2) study point, the ages of the pyelonephritic lesions (as depicted by imaging defects) varied between 2 and 14 d for kidneys with B defects, and between 6 and 28 d for kidneys with C defects. The 8 kidneys with a normal image at Q2 were those in which no imaging abnormalities were detected during varying periods of persisting urinary infection despite established VUR.

Figure 1 shows the correlation between the "refluxing" kidney image and the underlying pathology at kill, either after infection only (Fig. 1A) or after infection and treatment (Fig. 1B).

In Situ Versus Ex Situ Uptake Values

In the 32 pigs studied to examine the accuracy of the tissue depth correction, the results showed that total (left-plus right-kidney) absolute % dose ^{99m}Tc-DMSA uptake was slightly underestimated from the kidneys in situ (the difference, in situ − ex situ, mean −2.1, SD 4.5; CI −3.73 to −0.47). The results for differential uptake showed that the small in situ underestimate of absolute % dose uptake was distributed equally between the two kidneys of a pair. There was good agreement between the in situ and ex situ estimates (the difference, in situ − ex situ, mean 0, SD 1.45; CI −0.52 to +0.25).

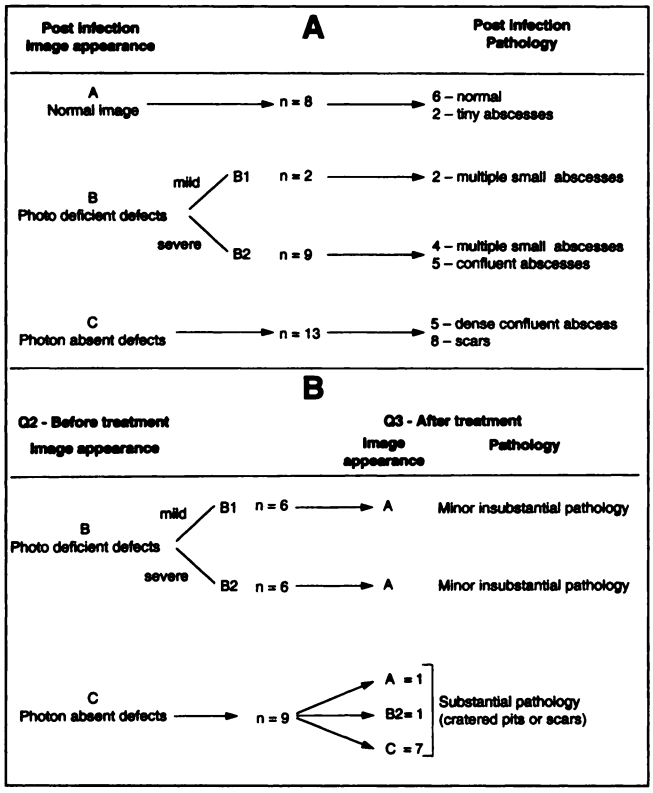

FIGURE 1. Correlation between renal image appearances and underlying pathology for individual kidneys (n). (A) At postinfection Q2 (untreated pyelonephritis). (B) At Q3 after 3-wk antimicrobial treatment (treated pyelonephritis). All kidneys had normal images at preinfection Q1.

Changes in Quantitative ^{99m}Tc-DMSA Uptake

At the outset (preinfection; Q1), when all kidneys in groups A, B and C had normal images, there were no statistical differences in uptake values between the groups. All groups had mean for differential uptake of 50%. The means for absolute % dose uptake by the "refluxing" kidney were between 20% and 22%. There was little variation in values within the groups.

For comparing groups B and C, Figure 2 shows the group means with 95% CIs for differential pyelonephritic kidney uptake and for absolute % dose uptake values at each of the study points (Q1 preinfection, Q2 postinfection or pretreatment and Q3 post-treatment).

Differential "Refluxing" Kidney Uptake. Between the preinfection Q1 and postinfection Q2 study points, the mean of the differences (Q2 − Q1) showed group A was unchanged, group B was slightly reduced (mean −1.71, $t_{22\ df}$, 2.90; $P < 0.01$) and group C was more markedly reduced (mean −5.5, $t_{21\ df}$, 5.51; $P < 0.01$) (Table 1). This difference between groups B and C was significant ($t_{34\ df}$, 2.03; $P = 0.002$). Treatment did not effect any further mean changes in differential uptake for groups B or C (Table 2; Fig. 2).

Absolute % Dose Uptake by the "Refluxing" Kidney. There was no significant change to absolute uptake % dose by the "refluxing" kidney in any group either after infection or after treatment. (Tables 1 and 2).

Absolute % Dose Uptake by the Contralateral Kidney. With infection there were significant changes to absolute % dose uptake by the nondiseased contralateral kidney in groups B and C. The means of the differences (Q2 − Q1) showed group A was unchanged, group B was slightly increased (mean +1.41, $t_{21\,df}$, 2.44; $0.05 > P > 0.01$) and group C was more markedly increased (mean +5.4, $t_{21\,df}$, 4.50; $P < 0.01$). The difference between groups B and C was significant ($t_{30\ df}$, 3.00; $P = 0.005$) (Table 1). For group B, treatment effected no further mean change. The small but significant mean increase observed with infection persisted (mean of the differences Q3 − Q1, +2.3%, $t_{10\ df}$, 2.55; $0.05 > P > 0.01$). For group C, there was considerable variability within the small population treated, making interpretation of the effects of treatment difficult (Table 2). Treatment effected a mean decrease (Q3 − Q2) of −3.6% (SD 6.3%), and the mean of the differences, Q3 − Q1 (+3.3%, SD 4.6%), showed that with infection followed by treatment there was a tendency for a mean increase from the outset (preinfection Q1), but this was not statistically significant.

Global (Left + Right Kidney) Absolute % Dose Uptake. The global accumulation of DMSA after infection (Q2) was significantly raised for group C (mean increase 5.2%, SD 8.2%; $P < 0.01$) but unaltered for groups A and B. Within group C individual global values for absolute % dose uptake

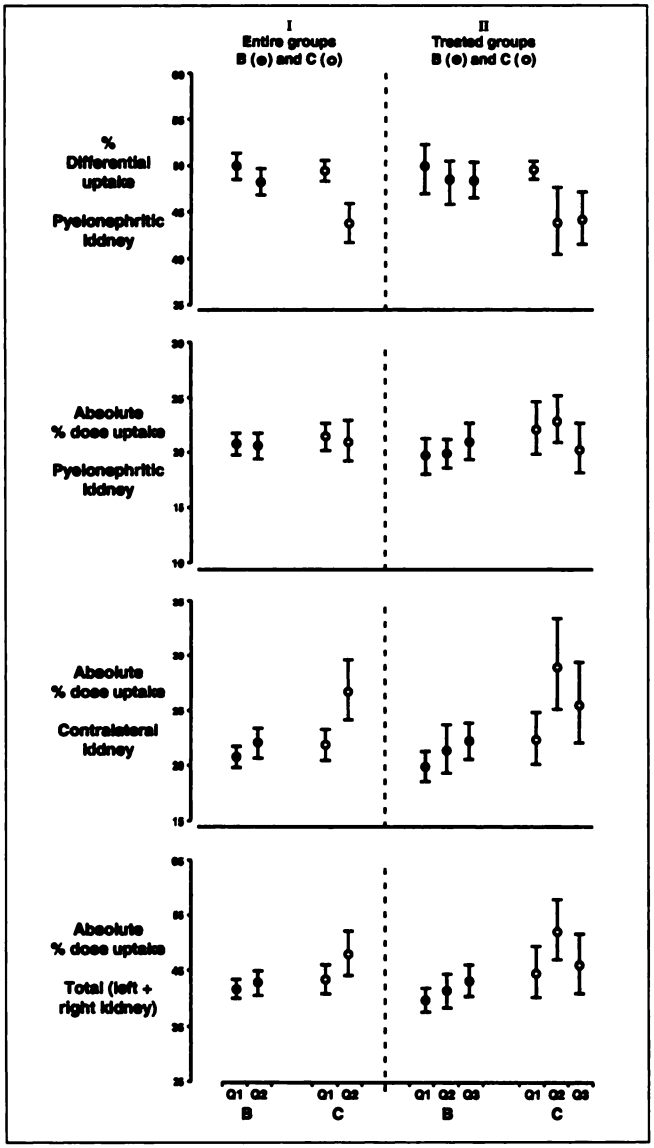

FIGURE 2. Quantitative ^{99m}Tc-DMSA uptake results. (I) Effects of induced pyelonephritis, entire groups B (n = 23, 22*) and C (n = 22). (II) Effects of treatment after induced pyelonephritis, subgroups B (n = 12, 11*) and C (n = 9). Means and 95% confidence intervals for pyelonephritic kidney differential uptake and absolute % dose uptake values at pre- (Q1) and post- (Q2) infection and after treatment (Q3). *Missing results in one animal at Q1 for absolute % dose uptake due to technical problems.

ranged between 36% and 79%, compared with maximum values of 43% and 52% recorded for groups A and B, respectively. For group C, treatment effected a mean decrease of −6.1% (SD 10%), and the ultimate (Q3) group mean was not different to that at the outset (Q1), but large variability within the group made interpretation difficult.

Differential "Refluxing" Kidney Uptake Versus Absolute % Dose Uptake

The relationship between changing differential uptake and changing absolute % dose uptake was examined by regression analysis.

The regression equation for the change (with infection) in absolute % dose uptake by the diseased "refluxing" kidney (y) on the change in differential uptake by that same "refluxing" kidney (x) was $y = 0.399 + 0.249x$ (adjusted r statistic = 0.08, $F_{1,50\ df} = 5.45$; $P = 0.02$). Thus for a 5% decrease in "refluxing" kidney differential uptake (when $x = -5$) the absolute % uptake by that same kidney remained virtually unchanged, decreasing by 0.85%. The regression equation for the change in the nondiseased contralateral kidney absolute % dose uptake (y) on the change in differential "refluxing kidney" uptake (x) was $y = 0.28 - 0.78x$ (adjusted r statistic = 0.41, $F_{1,50\ df} = 37.0$; $P < 0.0001$). Thus for a decrease of 5% in differential "refluxing kidney" uptake, contralateral kidney absolute % dose uptake increased by 4.2%.

Differential Uptake and Scintigraphic Appearances of Individual Kidneys

At the postinfection (Q2) study point, individual values for "refluxing" kidney differential uptake showed increasing variation with the severity of the imaging defects (Fig. 3). In groups A (n = 8) and B1 (n = 8), differential uptake was always within clinically acceptable ranges (43%–57% or 45%–55%) (*5,6*). A differential uptake below 45% was observed in only 2 of 15 in group B2 and 9 of 22 in group C. Values of 38% or less excluded all group B kidneys, but were seen in only 4 group C kidneys. The wide range of values (33.2%–50.2%) in group C reflected a variety in the extent of the imaging defects observed. Small C defects, albeit in three zones, barely reduced differential uptake so that it remained within the normal range.

DISCUSSION

This study shows that changes in quantitative ^{99m}Tc-DMSA renal uptake in unilateral pyelonephritis are more marked in animals developing the irreversible (type C) imaging defects than those with (type B) defects amenable to treatment. After the induction of pyelonephritis, the overall renal accumulation of ^{99m}Tc-DMSA was enhanced, rather than diminished as might have been expected.

The importance of the type B and C imaging defects in distinguishing reversible from irreversible pyelonephritis was established in our earlier work (*1,2*), which provided detailed analysis of the pathology underlying the imaging defects and made comparisons with previous similar studies. (*7–9*).

Before induction of pyelonephritis, initial values showed the expected normal renal uptake of ^{99m}Tc-DMSA that approaches 50% of the dose distributed equally between the paired kidneys (*5,10,11*). After the induction of unilateral pyelonephritis, there was a statistically significant difference in the mean differential uptake of ^{99m}Tc-DMSA between those pyelonephritic kidneys exhibiting B defects (mean 48%) and those with C defects (mean 44%). Nevertheless, the difference was insufficient to be of value in the clinical setting, where the normal range may extend between 43% and 57% (*5*), and there was considerable overlap in individual values between groups B and C.

TABLE 1
Changes in Uptake Values with Infection

Group	n	Differential uptake % (VUR/total L + R) Mean	Differential uptake % (VUR/total L + R) 95% CI	Absolute % dose uptake VUR Mean	Absolute % dose uptake VUR 95% CI	Absolute % dose uptake Contralateral Mean	Absolute % dose uptake Contralateral 95% CI
A (normal)	8	−0.2	−1.8 to +1.5	−1.5	−4.8 to +1.9	−1.5	−4.9 to +1.9
B (photon deficient)	22*; 23	−1.7†	−3.1 to −0.5	−0.1	−1.1 to +1.0	+1.4†	+0.2 to +2.6
C (photon absent)	22	−5.5†	−7.6 to −3.4	−0.3	−2.0 to +1.5	+5.4†	+2.9 to +7.9
B versus C *P* values		0.002		ns		0.0005	

*Group B one animal excluded from absolute uptake % dose results due to technical problems.
†Statistically significant changes ($P < 0.05$).
VUR = vesico-ureteral reflux; L = left; R = right; CI = confidence interval; ns = not significant.
Differences Q2 − Q1; Means and 95% CIs (Mean ± SE × ≈ 2; $t_{0.025\,df}$).

Despite the decrease in differential uptake with induced pyelonephritis, absolute % dose uptake remained unaltered in diseased kidneys irrespective of the severity or type of imaging defects. At the same time, absolute % dose uptake by the nondiseased contralateral kidneys increased and was significantly greater for group C than for group B. The increase in absolute % dose uptake by the contralateral kidney almost entirely accounted for the decrease in diseased kidney differential uptake. In other words, rather than a functional deficit in DMSA handling by the diseased kidney, there was apparent "hyper-uptake" by the contralateral kidney. A consequential increase in the global or total (left plus right) kidney accumulation of ^{99m}Tc-DMSA was most clearly observed in group C. That DMSA accumulation (absolute % dose uptake) remained unaltered in the pyelonephritic kidneys implies there was also a compensatory hyper-uptake in those areas unaffected by the pyelonephritic lesions.

In the 21 animals given antimicrobial treatment after developing imaging defects, the diseased kidney differential uptake remained diminished for group C. The results for absolute % dose uptake suggested a small readjustment in DMSA accumulation between the diseased and contralateral kidneys, although these overall mean changes were small and inconclusive.

The small but clearly apparent hyper-uptake by the contralateral kidney and the absence of diminished uptake by the diseased kidney have not been previously documented. There are, however, few reports on quantification of absolute % dose uptake, and we know of no other animal or clinical studies directly comparable with this study. Clinically, with unilateral disease in general, there is a decrease in absolute % dose uptake by the affected kidney with a compensatory increase by the contralateral kidney (*11*). The adaptive increase in absolute uptake that approaches but does not exceed the total uptake levels by paired normal kidneys is seen most clearly in solitary kidneys and in response to experimental unilateral nephrectomy (*11–13*).

In a clinical study of established reflux nephropathy, otherwise called chronic segmental pyelonephritis, Goldraich et al. (*14*) observed a reduced absolute % dose uptake in a proportion (52/86; 60%) of kidneys with renal scars, but 37% (32/86) had normal differential uptake. An increased or "hypertrophied" absolute % dose uptake was also noted in 3 scarred and 10 normal kidneys, but there was insufficient

TABLE 2
Changes in Uptake Values with Treatment

Group	n	Differences	Differential uptake % (VUR/total L + R) Mean	Differential uptake % (VUR/total L + R) 95% CI	Absolute % dose uptake VUR Mean	Absolute % dose uptake VUR 95% CI	Absolute % dose uptake Contralateral Mean	Absolute % dose uptake Contralateral 95% CI
B (photon deficient)	11*; 12	Q2 − Q1	−2.0	−4.4 to +0.4	−0.1	−1.7 to +1.6	+1.7	−0.3 to +3.8
		Q3 − Q1	−1.5	−3.8 to +0.8	+0.9	−0.8 to +2.7	+2.3†	+0.3 to +4.2
C (photon absent)	9	Q2 − Q1	−5.5†	−8.7 to −2.2	+0.7	−2.5 to +4.0	+6.8†	+3.9 to +9.7
		Q3 − Q1	−5.2†	−7.7 to −2.7	−1.8	−5.7 to +2.2	+3.3	−0.3 to +6.8

*Group B: one animal excluded from absolute % dose uptake results due to technical problems.
†Statistically significant ($P < 0.05$) changes from initial. There were no significant changes with treatment, i.e., comparing Q2 with Q3.
VUR = vesico-ureteral reflux; L = left; R = right; CI = confidence interval.
Q1 = Preinfection; Q2 = Postinfection; Q3 = After 3-wk antimicrobial treatment. Differences Q2 − Q1; Q3 − Q1; Means and 95% CIs (Mean ± SE × ≈ 2; $t_{0.025\,df}$).

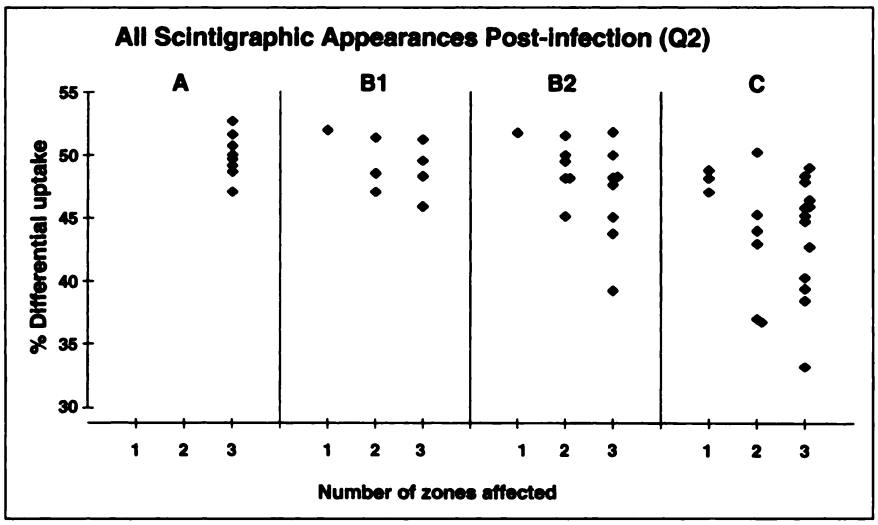

FIGURE 3. Differential uptake and scintigraphic appearances at postinfection (Q2). Individual values for affected or pyelonephritic kidneys. A = normal image, B1 = mild defects, B2 = severe photon-deficient defects and C = photon absent defects, present in 1, 2 or 3 renal zones (upper pole, midzone, lower pole).

detail to interpret this in terms of the findings of the present study.

Evidence for a hyperfunctional uptake of DMSA by the contralateral kidney in response to unilateral disease comes from a recent controlled study of children with severe grade unilateral VUR (*15*). In this study, quantitative SPECT of ^{99m}Tc-DMSA uptake showed the more typical mean compensatory increase in contralateral kidney % dose uptake proportional to the diminished uptake by the diseased kidney (*15*). Analysis of the % dose uptake per cubic centimeter of functional volume showed that low uptake by the diseased kidney was the result of lost functional volume, not diminished uptake, by the surviving nephrons. In contrast, the mean increase in uptake by the contralateral kidney was due to greater uptake, or hyperfunctional uptake, by existing nephrons and not functional volume enlargement. This hyperfunctional uptake was distinct from that demonstrated in this study, in that it was confined only to the contralateral kidney and was sufficient only to compensate for lost uptake by the diseased kidney.

It is possible that the difference between clinical findings and those of this animal study may reflect a greater sensitivity in the detection of small changes in quantified ^{99m}Tc-DMSA uptake, and it is pertinent that this experiment tested the effects of entirely unilateral pyelonephritis. Unlike studies in the clinic, the pig model allowed the interpretation of results without the confounding influence of other renal abnormalities such as dysplasia, pre-existent scars or damage to the contralateral kidney.

Although the mechanisms of the renal accumulation of ^{99m}Tc-DMSA are not fully established, the proximal tubules, where renal ^{99m}Tc-DMSA accumulation occurs, have the potential to acquire more than is delivered by standard clinical dosage (*16*). Previous work has shown that, after unilateral nephrectomy, the pig can achieve within 1 wk a rapid adaptive increase in ^{99m}Tc-DMSA uptake (*12*). The increases in ^{99m}Tc-DMSA absolute uptake % dose observed in the present study usually occurred within 3 wk, and are unlikely to be the result of compensatory growth. An extraordinary aspect of this study is the adaptive response to focal areas of lost renal uptake whereby DMSA accumulation by the remaining functional nephrons increased more than was necessary to achieve compensation.

The observed supernormal absolute uptake of ^{99m}Tc-DMSA by the nondiseased kidney, while the diseased kidney maintains a normal uptake despite obvious focal image defects, is difficult to explain, but suggests a circulatory blood-mediated hormonal or autocoid action elicited in a homeostatic response to the pyelonephritic insult. Experimental studies using the unilateral and single kidney Macaque models with induced pyelonephritis showed there was a rapid increase in renin activity and serum renin after infection (*17,18*). It is tempting to speculate that enhanced renal ^{99m}Tc-DMSA uptake may in part be mediated through renin-activated angiotensin II, with an increase in filtration fraction caused by selective vasoconstriction of the efferent arterioles and the maintenance of glomerulotubular balance by a proportional increase in proximal tubular transport and secretory activities. Whatever the reasons, the enhanced ^{99m}Tc-DMSA uptake observed in this experiment was small and could well reflect an initial reaction to the complex of inflammatory processes before a balanced renal homeostasis has been achieved.

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