Renal Graft Evaluation with Pertechnetate and I-131 Hippuran. A Comparative Clinical Study

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This retrospective study compared standard clinical and biochemical data from 50 graft recipients against 533 I-131 Hippuran sequential scintigrams and 515 [^{99m}Tc]pertechnetate serial scintigrams. All grafts included in this study are cadaver kidneys. The majority of the studies were made during the early posttransplantation period. Anuria or oliguria of at least 4 days duration was seen in 18 patients. The study spans 574 days of oliguria during which 136 dual-tracer studies were made. I-131 Hippuran renography of functioning grafts was carried out 397 times, and the Tc-99m sequential scintigraphy 379 times. In all, 47 episodes of acute rejection were registered clinically in functioning grafts, 36 of which were recognized during Hippuran renography and 38 with the pertechnetate study. False-positive errors were seen 12 times during renography. The study also demonstrated that furosemide will significantly and predictably influence renography and the pertechnetate study. This seems noteworthy since furosemide is extensively used in posttransplant management.

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Numerous workers have explored the value of radionuclide studies in the assessment of renal grafts (*1–5*). I-131 Hippuran renography seems to have found the widest acceptance. This is partly because the method permits graft evaluation during anuria, when biochemical data tend to be misleading. Repeat studies are well tolerated by the patient, so that renography is effectively used for sequential graft evaluation.

Technetium-labeled radiotracers have found wide acceptance in the evaluation of vascular patency in renal grafts (*6,7*). We felt that [^{99m}Tc]pertechnetate could be used to evaluate vascular bed patency if the time of examination were brief, minimizing the problems of interpretation inherent when vascular escape proceeds at an unknown rate. It was felt that a pronounced change in the perfusion of the graft, perhaps accentuated by a different rate of pertechnetate escape from the vascular bed, might result in typical and easily recognized changes of pertechnetate transit patterns during times of rejection.

The present study sought to evaluate the usefulness of pertechnetate for renal graft evaluation and to compare the results with those obtained with I-131 Hippuran renography.

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METHODS

We report on the retrospective evaluation of 515 serial

pertechnetate scintigrams and 533 I-131 Hippuran renograms obtained as routine control examinations of 50 graft recipients, all of whom had received a cadaver kidney. Forty were men and ten were women. The mean age of the recipients was 31.8 yr, the range 13–49 yr. The initial examination was always made within 24 hr after graft implantation, the first examination being used as a reference for the second study. Any subsequent study was then compared with the one immediately preceding. Examinations were made at short intervals during the initial period after transplantation, later at times of graft rejection, urologic complication, or improved graft function. Hippuran renography immediately preceded the pertechnetate flow study. We used a 12 in. gamma camera for the early studies, a 15 in. gamma camera in the later ones. Data were stored on magnetic tape and were analyzed by minicomputer. A general-purpose medium-energy parallel-hole collimator was used in the studies. The energy window was set at 25%, centered over the main photopeak.

Emission renography followed injection of 200 μCi I-131 Hippuran*, independent of body weight. For each scintigram counts were collected for 60 sec. Scintiphotos were made starting with the injection, and at 1,2,3,4,7,9,14, and 19 min. The examination was terminated after 20 min. Time-activity curves were generated over the transplant, and over a background (BG) area of equal size, placed medially and next to the renal graft (Fig. 1A). For uptake determinations, BG subtraction was not performed. The Hippuran uptake of the graft was expressed as a percentage of the sum of graft activity and the BG region of interest (ROI), using secretory rise and 3-min amplitude. To obtain the value for secretory rise, impulses were counted from the 36th to the 120th sec over kidney and BG ROI. The sum of counts from both ROIs was given the value 100%, so that the impulses measured over the graft were expressed as percentage of the total counts gathered. The value of the 3-min amplitude was calculated similarily, by taking the sum of the amplitudes of both time-activity curves at 3 min, and calculating the percentage value for the transplant. Graft assessment was based on three factors: (a) direction of the numerical parameters, (b) tracer appearance time in the bladder, and (c) intrarenal hippurate transport as indicated by the change in tissue activity. This was visually determined by comparing the activity at 3 min, or at bladder appearance time, with the tissue activity at 14 min.

Immediately following rapid i.v. injection of 7 mCi pertechnetate, the arm of the patient was raised. Scintigrams were made at 5-sec intervals for 40 sec. Data were collected on tape for a total of 1 min. ROIs were placed over the graft and over the iliac artery of the other side (Fig. 1B). The latter area was generally one-fourth of that of the kidney ROI, and was then prorated to correspond to the area used for the kidney. The ROIs

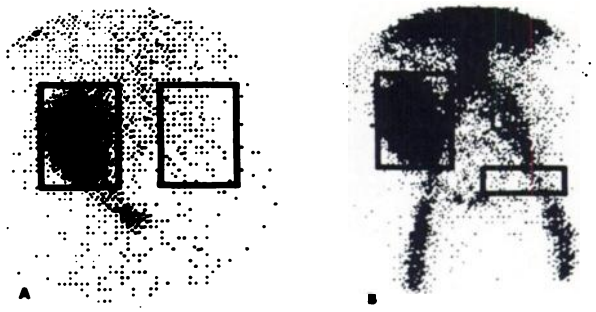

FIG. 1. (A) Representative image of graft following i.v. injection of 200 μCi I-131 Hippuran. Counts were gathered from 0–180 sec. Typical ROIs for graft and BG area are shown. (B) Representative image of graft and iliac vessels following injection of 7 mCi pertechnetate. Counts were gathered from 5th–15th sec. Typical ROIs for graft and BG area are included.

were kept identical from one examination to another. Time-activity curves were generated over the transplant and over the corresponding BG area. This was followed by BG subtraction. The net time-activity curve was used to compute a numerical value for each examination, by dividing the height of the peak of the net curve into the height of the distal curve segment. Grafts with abnormal perfusion patterns often have delayed peak times, compared with the peak times registered over the BG curve. The BG curve was therefore placed beneath the graft's flow curve. If peak appearance was delayed, we used the amplitude of the graft's flow curve as seen at the time of BG peak for the calculations. The value obtained by dividing height into the distal curve segment was arbitrarily called the V value, and is a relative value. The V value of the most recent examination was divided into the V value of the preceding examination to derive a Q value. Q values of 0.8–1.0 indicated a stable pertechnetate transit pattern. Falling Q values signaled a negative transit pattern development; rising Q values indicated a positively changed transit pattern. In evaluating the vascular patency of the graft the following factors were considered: (a) form of the flow curve and Q value, (b) sequential scintiscans, and (c) individual scintiscans.

The results of the radiotracer procedures were compared with the clinical and biochemical data for the examination day, as well as 3 days preceding and following it. The biochemical and clinical data used were: serum creatinin, serum urea, leukocyte count, platelet count, blood pressure, body temperature, fluid intake and urine excretion (ml), graft palpation, and sensations of discomfort or pain at the site of the graft. Furosemide administration was noted. Rejection was considered to occur when immunosuppressive therapy was initiated. The status of the graft at a given time was determined by two observers who reviewed all laboratory data and then classified graft development as stationary, improving, or impaired.

TABLE 1. RESULTS OF RAPID SERIAL PERTECHNETATE SCINTIGRAPHY AND I-131 HIPPURAN RENOGRAPHY OF 18 PATIENTS DEMONSTRATING A TOTAL OF 574 DAYS OF POST-TRANSPLANTATION ANURIA

No. of patients	Probable cause of anuria	Anuria total days	Anuria duration per pat. (days)	No. of exams	Frequency of study (days)	No. of detected acute rejections		Graft development	Did sequence of examinations predict outcome			
						Pertechnetate	I-131 Hippuran		Pertechnetate yes	Pertechnetate no	I-131 Hippuran yes	I-131 Hippuran no
1	Hyper acute rejection	55	55	14	3.9	2	1	Improved	1	0	1	0
11	ATN	250	23	68	3.7	7	5	Improved	10	1	10	1
1	Chronic rejection	83	83	14	5.9	3	3	Explanted	1	0	1	0
4	Acute rejection	163	41	31	5.2	0	0	Explanted	4	0	4	0
1	Vascular kinking	23	23	9	2.6	0	0	Improved	1	0	1	0

RESULTS

Eighteen patients demonstrated a period of oliguria or anuria lasting from 4 to 83 days (Table 1 and Figs. 2 and 3). This was seen 12 times during the immediate posttransplant period. Thus 24% of all graft recipients experienced a period of graft failure immediately after transplantation. In 11 of these 12 patients, anuria was considered to be due to so-called "acute tubular necrosis" (ATN), and in one due to vascular kinking.

Episodes of acute rejection, followed by anuria, were seen five times, and one patient had repeat examinations during anuria resulting from chronic rejection. In all, the study spans a total of 574 days of anuria, during which 136 dual-tracer procedures were carried out. On average, one repeat study was made every 4 days during anuria.

Repeat emission renograms demonstrated graft development correctly during anuria or severe oliguria in 17 out of 18 patients. Once, the sequence of examination failed to identify graft improvement, which became obvious when the kidney began urine production. Acute rejections were noted nine times, which were all verified in pertechnetate serial scintigraphy. One graft failed to demonstrate Hippuran uptake immediately after graft implantation, and angiography indicated vascular kinking. The organ was relocated to correct this, and improved results followed in both tracer procedures. Urine production began after 23 days. One episode of probable hyperacute rejection was noted. Hippuran

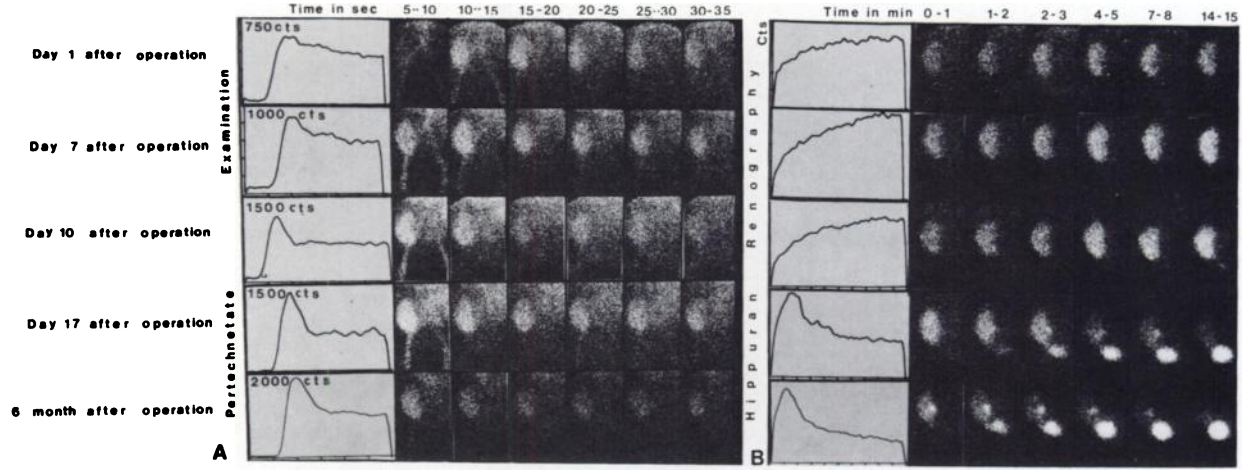

FIG. 2. (A) Rapid serial pertechnetate scintiphotos and time-activity curves generated over graft of patient with postoperative anuria of 10 days duration. Sequence of examinations demonstrates recovery of perfusion-curve pattern. (B) Emission renograms and scintiphotos demonstrate recovery of Hippuran transport after ATN.

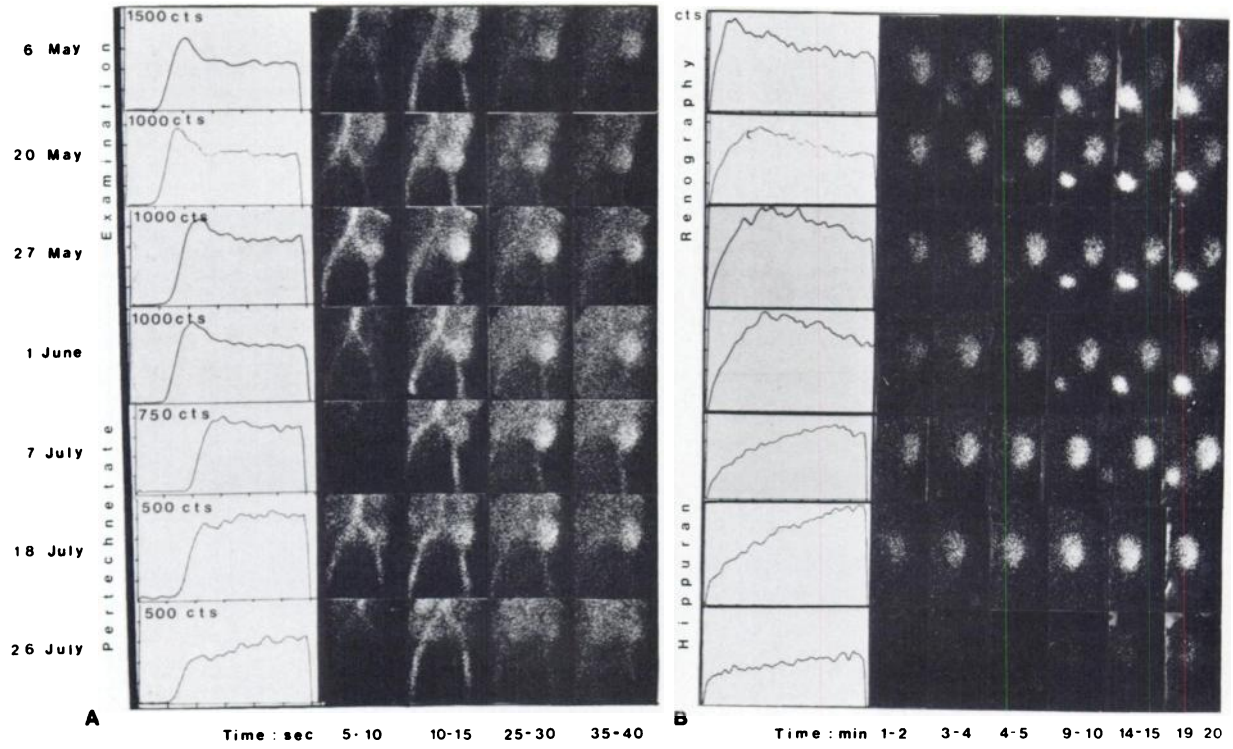

FIG. 3. (A) Sequence of perfusion scintigrams documents change in perfusion pattern during destruction of graft due to stenosis of renal artery. (B) Hippuran sequence scintiphotos and renogram curves also document destruction of graft.

uptake was reduced at the first examination and was absent 1 week later. After appropriate immunosuppressive therapy, the graft showed scintigraphic improvement, during the second week. After 55 days of anuria—complicated by at least one more scintigraphically identified rejection episode—urine production set in. The patient was discharged 84 days after transplantation, with functioning graft and serum creatinine at 2.4 mg%. Four grafts lost their ability to excrete Hippuran after an episode of acute rejection, and had to be explanted.

Serial pertechnetate scintigraphy correctly identified graft development in 17 of 18 oliguric patients, with graft improvement not recognized in one case. Signs of acute rejection were noted 12 times. All rejections identified with emission renography were verified with the pertechnetate study. Three rejection episodes, seen with pertechnetate scintigraphy, failed to be visualized by renography. During the episode of hyperacute rejection, the graft's pertechnetate transit pattern failed to show massive deterioration, so that it contrasted sharply with renography in this case.

TABLE 2. REJECTIONS OF 43 GRAFTS: COMPARISONS OF RAPID SERIAL TcO_4 SCINTIGRAPHY, I-131 HIPPURAN SEQUENTIAL SCINTIGRAPHY, AND CLINICAL FINDINGS

	Signs of rejection		Clinical signs suggesting rejection:					
Rejections	Pertechnetate	Hippuran	Creatinin	Urea	Urine vol.	Temperature	Leukocytes	BP
32	+	+	28	29	19	8	12	7
5	+	−	4	5	3	3	2	1
3	−	+	2	1	1	0	3	3
3	−	−	3	3	3	1	2	0
1	+	*	1	1	0	0	0	0
1	−	*	0	1	0	0	0	0
1	*	+	1	1	0	0	0	0
1	*	−	0	1	1	1	1	0

* Equivocal.

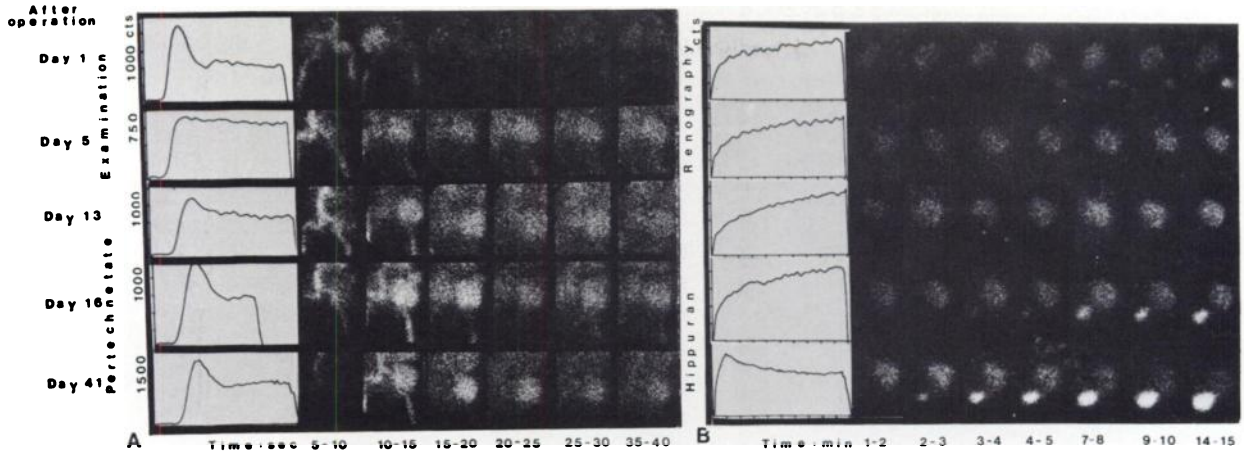

FIG. 4. (A) Serial pertechnetate scintigraphy and time-activity curves of patient incurring rejection episode on Day 5 after graft implantation. Improvement of perfusion pattern accompanies successful immunosuppressive therapy, clearly visible on Day 13. (B) Sequence of emission renograms. The rejection episode on Day 5 was accompanied by oliguria, so that tracer failed to appear in bladder during examination. Scintigram on Day 13 failed to indicate improvement.

Forty-seven episodes of acute rejection were registered clinically in functioning grafts (Table 2 and Fig. 4B). Hippuran renography identified the rejection episode 36 times (84%) failing to do so nine times (16%), and in two cases the study could not be evaluated. Three of the nine false-negative errors were associated with the injection of 500, 600, and 1920 mg of furosemide, given during the 24 hr preceding the scintigraphic study in order to deal with the rejection episode. Follow-up studies, days later, belatedly registered the graft deterioration in two patients. We cannot explain the remaining six errors. Furthermore 19 examinations gave scintigraphic results suggesting acute rejection, which was not supported by the clinical findings. One patient's furosemide therapy of 160 mg/day was withheld on the day of renography. The scintigraphic result was suggestive of acute rejection. Two patients had elevated temperatures (37.9°C and 38.5°C) and reduced urine excretion. Three times, biochemical data demonstrated slow graft deterioration, the time interval from the previous examination was long (8, 7, and 3 mo, respectively), and the scintigram mirrored the graft's decline. Vascular thrombosis suggesting massive rejection with graft destruction was seen once. The false-positive scintigraphic finding could not be explained in 12 examinations (Table 3).

Rapid serial scintigraphy with pertechnetate was done 379 times in functioning grafts, and it identified 38 of the 47 episodes of acute rejection (Fig. 4A and Table 3). Two studies could not be evaluated. Three of the seven false negatives occurred in conjunction with the furosemide therapy already mentioned. Thirteen false-positive errors were found, two during the fever episodes, three in association with the long interval to the previous examination, and one as a result of vascular thrombosis. Once ureteral obstruction resulted in a pertechnetate flow pattern indicative of rejection. Six times the false-positive results could not be explained.

While graft rejection could be identified with changes in the pertechnetate flow pattern, we also tried a more subtle evaluation. Of the 359 flow curves not influenced by rejection, 219 (61%) studies mirrored the graft's development, whereas 142 (39%) studies gave results that were not in complete agreement with the clinical data. Slight clinical improvement appeared as stability in the tracer studies, or as more improvement than had actually occurred. Clinical stability might appear in scintigraphy as a minor change in either direction. In 42 cases such divergence appeared to have a cause. Twenty-two of the 42 examinations were preceded by changed furosemide therapy of at least 150 mg per day. Six times a sudden

TABLE 3. FREQUENCY WITH WHICH CLINICAL OR SCINTIGRAPHIC DATA SUGGESTED EPISODES OF ACUTE REJECTION IN FUNCTIONING GRAFTS

	No. of exams	Frequency of clinical signs of acute rejection	Clinical sign of rejection verified scintigraphically	Not examined day of rejection	Clinical rejection (false-negative errors)	Clinically stable (false-positive errors)
Tc-99	379	47	38	2	7	6
I-131	397	47	36	2	9	12

TABLE 4. COMPARISON OF RESULTS OF INITIAL EXAMINATION AND SURVIVAL TIME OF 43 RENAL GRAFTS EXAMINED WITH 200 μCi I-131 HIPPURATE

	No. of patients	Grafts lost (Patient No.)	Survival time of destroyed graft (mo)	Cause of graft destruction
Good initial function	26	14	2.0	acute rejection
		48	18.0	chronic rejection
		15	4.0	acute rejection
		40	0.6	acute rejection
		17	0.5	acute rejection
Intermediate initial function	10	49	18.0	chronic rejection
		35	0.8	acute rejection
		16	3.0	acute rejection
Poor initial function	7	4	4.0	chronic rejection
		6	3.0	urologic complications
		3	1.0	graft rupture
		13	4.5	chronic rejection

increase in the diuretic dose resulted in misleadingly good curves, and 16 times sudden reduction of the medication led to flow curves suggesting slight graft deterioration. In 20 studies falling Q values were seen in the second or third postoperative examination. There was no curve deformation, nor were there clinical signs indicating graft deterioration.

The first examination had prognostic value. The results of emission renography indicated that 26 of 43 grafts had good initial function. Good function was considered to exist when the tracer appeared in the bladder during the 20 min of the examination. Five of these grafts were explanted. Ten grafts had an initial tubular function of intermediate quality, considered to exist when the graft showed good Hippuran accumulation but poor excretion. Three of these grafts were destroyed. Seven of the 43 grafts were found to have poor initial tubular function, defined to exist when I-131 Hippuran accumulation was greatly reduced or lacking. Four of these seven grafts were lost (Table 4).

A good perfusion pattern was registered in 22 of the 43 initial examinations with pertechnetate. Only three grafts had to be explanted. A good flow pattern required a sharp peak in the curve. Twelve patients had flow patterns of intermediate quality: the second segment of the curve was elevated, resulting in the lack of a clear peak in the curve. Lastly, nine patients demonstrated poor initial perfusion pattern, and four of these transplants had to be removed. A poor perfusion pattern was felt to exist when the graft failed to show up clearly with the tracer (Table 5). Seven patients were not included in this comparison, since data on the status of the graft at the time of the study could not be located.

The first examination's prognostic value was similar for both of the tracers. Roughly 15% of the grafts showing good results in the first examination, with either tracer, were lost. Approximately 50% of the transplants were destroyed when the initial examination brought results indicating poor postoperative function. A comparison of the two procedures shows that each method may nevertheless bring widely divergent results in individual examinations. Six of the 12 grafts lost had poor results in one of the initial examinations, and these grafts were lost by chronic rejection or postoperative complications. Grafts with good or intermediate patterns in one of the initial studies were lost during episodes of acute rejection.

DISCUSSION

Patients with anuria or oliguria have been examined separately in the study, since particular difficulty is encountered in the evaluation of grafts at such times. Biochemical tests tend to be misleading, making it risky to compare the chemistry with the scintigraphic findings. ATN was felt to be the cause of anuria in 11 of the 12 patients showing immediate posttransplant anuria, since the grafts were cadaver kidneys and since long-term improvement was seen. Our data demonstrate that the tracer procedures used are effective in monitoring grafts during extended periods of anuria or oliguria. We find it noteworthy that two grafts initially incapable of Hippuran uptake, but which recovered, were visualized with serial pertechnetate scintigraphy during the time of massive tubular dysfunction. Similar results have been reported elsewhere (*8*). Grafts not visualized by either method were destroyed.

The inability to differentiate acute rejection from acute tubular necrosis made it desirable to obtain initial scintigrams early after implantation. A comparison of the two tracer procedures shows that they were equally

TABLE 5. COMPARISON OF RESULTS OF INITIAL EXAMINATION AND SURVIVAL TIME OF 43 RENAL GRAFTS STUDIED WITH 7mCi PERTECHNETATE

	No. of patients	Grafts lost (Patient No.)	Time to graft destruction (mo)	Cause of graft destruction
Good perfusion pattern	22	35	0.8	acute rejection
		14	2.0	acute rejection
		6	3.0	urologic complications and GI bleeding
Intermediate perfusion pattern	12	17	0.5	acute rejection
		40	0.6	acute rejection
		3	1.0	graft rupture
		16	3.0	acute rejection
		13	4.5	chronic rejection
Poor perfusion pattern	9	4	4	chronic rejection
		15	4	acute rejection
		48	18	chronic rejection
		49	18	chronic rejection

effective in identifying rejection. Three instances of acute rejection were not identified by either procedure, the results being influenced by furosemide therapy.

Under furosemide, renal blood flow increases, and the increase is independent of innervation (*9*). It has been shown that furosemide changes the renal hemodynamics by reducing vascular resistance (*10*), through vascular dilation resulting from stimulation of the prostaglandin system (*11,12*). Indeed, the use of furosemide has been advocated to improve blood flow during the early post-transplant period (*13*). Note that large quantities of furosemide must be given if the results of our examination are to be influenced. Furthermore, we were able to identify the furosemide effect only when a *change* in medication occurred.

It was not our goal to measure renal blood flow with serial pertechnetate scintigraphy. Rather, we sought to identify changes in flow pattern. This required that the flow pattern should be stable while the vascular bed is unchanged. The curve evaluation is based on the comparison of peak height with the amplitude of the distal curve segment—i.e., after 1 min. This relationship seems to be stable from one examination to another, even if absolute values show considerable variation. Transplant vascularity and perfusion patterns have been evaluated previously with rapid pertechnetate scintigraphy. Indeed, Rosenthall described a method very similar to ours, but his limited number of examinations did not permit the sensitivity of the method to be assessed (*14*). Our results are in agreement with those of Rosenthall and suggest that pertechnetate is effective when used for graft evaluation. We cannot, however, concur with Murphy, who reported that this agent is of little value in the assessment of grafts, due to escape of the tracer into the extravascular compartment (*15*). We note that injection technique can influence the pertechnetate curve pattern. Slow injection results in peak delay and an elevated distal curve segment, which lowers the Q values. These possible errors are easily identified by observing the rise of the BG curve. A flattened rise identifies errors of injection.

Renal transplant evaluation is more common with Tc-99m chelates than with pertechnetate. The glomerular-filtered chelates appear to be prominent since their use results in excellent scintiscans. Evaluation is based solely on sequential scintigraphy (*6,16,17*), as well as on a combination of sequential scintigrams and generated time-activity curves (*7,18–21*). Excellent scan quality appears to accentuate structural assessment. The known pharmacokinetics have also helped chelates gain acceptance. While the technetium chelates are widely used in graft assessment, the use of pertechnetate is not unusual (*1,14,22–26*). Assessment has generally been based on sequential scintigraphy, following injection of 10–15 mCi of the tracer. We believe that the superior scan quality obtained with Tc-99m chelates suggests their use when evaluation is to be based primarily on scintiphotos. When time-activity curves are to be generated, both approaches appear useful, pertechnetate's advantage being in lower cost without apparent loss of kinetic information. The examination's brief duration makes pertechnetate transit primarily dependent upon renal perfusion. Rejection is initially a disorder of the interstitium and the vasculature of the graft (*27*). Thus while pertechnetate kinetics appear to be less clear than those of DTPA, the pertechnetate transit pattern changes are signal. Comparing Tc-99m DTPA with pertechnetate, we found similar time-activity curves early after transplantation. We generally did not extend the study beyond 1 min. In well-functioning grafts, the

distal curve segment is raised. Hilson et al., examining the Tc-99m DTPA, used an approach similar to ours in that they also registered the transit pattern over the graft immediately after tracer application (*21*). During the initial 40 sec of the examination, the curves generated appear to be similar to those seen with pertechnetate. We value Hippuran's functional images, but believe that altered perfusion patterns at rejection are identified at a considerable saving with pertechnetate.

Others have reported that the first scintigraphic examination with I-131 Hippuran has prognostic value (*28–30*). Kjellstrand, and also Rössler, using Hippuran renography, compared survival time of grafts showing little or no Hippuran uptake against transplants with good initial uptake. Both authors report considerable differences in graft survival in these groups. Whittaker et al. (30) evaluated initial function in terms of the onset or failure of urine production by the graft while the recipient was still in the operating room. These results were compared with long-term renal function as determined by creatinine clearance. Graft survival time was positively correlated with good initial function. Whittaker suggests that nonfunctioning grafts are endangered by excessive diagnostic procedures. While poor initial function appears to have prognostic implications, we found it notable that our patients with poor initial function in one of the two studies often lost their grafts in early chronic rejection. Furthermore, poor initial function, defined with function scintigrams, often resulted in clear differences for individual studies. Thus a poor initial perfusion pattern might be associated with an intermediate initial function by Hippuran renography. This became particularly striking when results of the first postoperative examination were compared for the grafts that were destroyed. Twelve grafts were lost, and five of these had initial examinations with diverging results in the two tracer studies. Our results indicate that both studies have prognostic value, and that they are complementary.

FOOTNOTES

* Since mid-1978 we have used I-123 Hippuran.

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SOUTHWESTERN CHAPTER SOCIETY OF NUCLEAR MEDICINE 25th ANNUAL MEETING

March 28-30, 1980 Shamrock Hilton Hotel Houston, Texas

ANNOUNCEMENT AND CALL FOR ABSTRACTS

The Scientific Program Committee of the Southwestern Chapter of the Society of Nuclear Medicine invites submitted abstracts of original work in Nuclear Medicine from members and nonmembers of the Society of Nuclear Medicine to be considered for the 25th Annual Meeting to be held March 28-30, 1980, at the Shamrock Hilton Hotel in Houston, Texas.

The program will include submitted scientific papers, invited speakers, and teaching sessions covering areas of current interest in Nuclear Medicine. The program will be approved for credit toward the AMA Physicians Recognition Award under Continuing Medical Education Category I through the Society of Nuclear Medicine.

Scientific exhibits also are solicited for this meeting. Use the abstract submission guidelines listed below. Descriptions of the exhibits, including size, shape, and necessary lighting and support requirements should be listed on a separate sheet. Exhibits will be judged on scientific content in the technologist and professional level categories and awards presented.

ABSTRACT GUIDELINES:

Submitted abstracts should contain a statement of the purpose, the methods and materials used, results, and conclusions. The title, authors, and institutional affiliations should be included at the top of the abstract page. The name of the author presenting the paper must be underlined. If needed, supporting data should be limited to no more than two separate pages of figures and tables and should be included with the abstract.

Accepted abstracts only will be published and should not exceed 300 words.

Original abstract and four copies should be sent to the Program Chairman:

Raleigh F. Johnson, Jr.
Nuclear Medicine Division
University of Texas Medical Branch
Galveston, TX 77550

For further information regarding the program, write or telephone (713) 765-2926.

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