

SCINTILLATION CAMERA IN THE EVALUATION OF RENAL TRANSPLANTS

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In recent years there has been a marked increase in both the frequency and success of renal homotransplantation. Rejection, vascular thrombosis, ureteral obstruction, acute tubular necrosis and extravasation are among the pathologic lesions that may threaten the transplanted kidney. Convenient and reliable techniques which can accurately and rapidly differentiate between these conditions are urgently needed to evaluate transplant function in the postoperative recipient.

With the advent of the gamma scintillation camera (1), radioisotope techniques have become available which permit serial function studies in the renal transplant patient. These techniques are atraumatic, free of side effects and reproducible; moreover, they can be repeated as needed with little risk to the patient.

The radioisotope compounds employed for these scintillation camera studies are ^{99m}Tc -sodium pertechnetate (^{99m}Tc -pertechnetate) and ^{131}I -sodium iodohippurate (^{131}I -Hippuran). The ^{99m}Tc -pertechnetate has been used successfully in dynamic vascular studies of the brain (2,3), heart (4,5), major vessels (6,7) and in studies of renal vascular perfusion (8). Hippuran accurately measures the concentrative and excretory function of the kidney (9,10) and can be used to delineate kidney morphology. The rate of Hippuran disappearance from the blood (Hippuran $T_{1/2}$) also gives reliable information about renal blood flow (11,12) which is of major importance in the functional evaluation of the renal transplant since changes in effective renal blood flow are among the earliest manifestations of the rejection reaction (12-14).

MATERIALS AND METHODS

The case material for this study was 23 patients from the Renal Service, Wadsworth Hospital, Veterans Administration Center, Los Angeles, who were referred to the Radioisotope Service during the past 1½ years for post-transplantation evaluation. The instrumentation employed was the Pho/Gamma Scintillation Camera (Nuclear-Chicago Corp.) with a 3-in. multichannel collimator. A 4,000-hole collimator

was used for technetium with its lower gamma radiation of 141 keV, and a 1,000-hole collimator was used for ^{131}I -Hippuran.

Patients were studied in the supine position. The scintillation camera crystal was positioned so that both renal transplant and the urinary bladder were included in the field of view. Ten to 15 mCi of ^{99m}Tc -pertechnetate was injected intravenously by rapid bolus injection, and serial 4-sec exposure scintiphotos were obtained for a total period of 32 sec. Without moving the patient, 300 μCi of Hippuran was then injected and serial 2-min-exposure scintiphotos were obtained. No attempt was made to split the crystal electronically to obtain differential counts from the kidney and bladder areas. During the Hippuran study, serial precordial counts were obtained at 2-min intervals for a total of 30 min with a collimated scintillation detector centered over the manubrium at the level of the second rib. Precordial radioactivity was subsequently plotted on semilog paper as a function of time, and the disappearance half-time was calculated from the 10-20-min segment of the slope.

The ^{99m}Tc -pertechnetate studies were visually analyzed for abnormalities of transplant vascular perfusion. Hippuran studies were used to evaluate transplant function and morphology as well as the excretory progression of the tracer from the renal cortex to the renal pelvis and ultimately to urinary bladder.

RESULTS AND SELECTED CASES

Table 1 summarizes the results obtained with these techniques in 10 selected patients with functioning transplants (18 total studies). At the time these studies were done, creatinine determinations were normal, 24-hr urinary outputs were normal and the patients were ambulatory. Several patients had already been discharged and were studied as out-

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patients. In all cases, vascular perfusion of the transplant was well outlined within 20 sec with pertechnetate. Hippuran was concentrated within 2 min by the normally functioning renal transplant. Bladder radioactivity was usually noted within 8 min (occasionally within 10–12 min). Hippuran disappearance half-time ranged from 26 to 44 min.

SELECTED CASE REPORTS

Case 1: normal study. AP, a 33-year-old white male, received a cadaver kidney on April 9, 1968.

He received irradiation, azathioprine and prednisone. At the time of his initial scintillation camera study (April 23, 1968) his creatinine was 5.0 mg% and his urinary output was approximately 1,500 ml/day.

Figure 1A shows a normal technetium perfusion study at 16 sec. The transplant is well demonstrated (A), and the right and left common iliac arteries are clearly seen (B and C). Hippuran concentration and excretion is normal at 2 min (Fig. 1B), and at 6 min urinary bladder activity is noted (Fig. 1C). The Hippuran disappearance half-time was 27 min

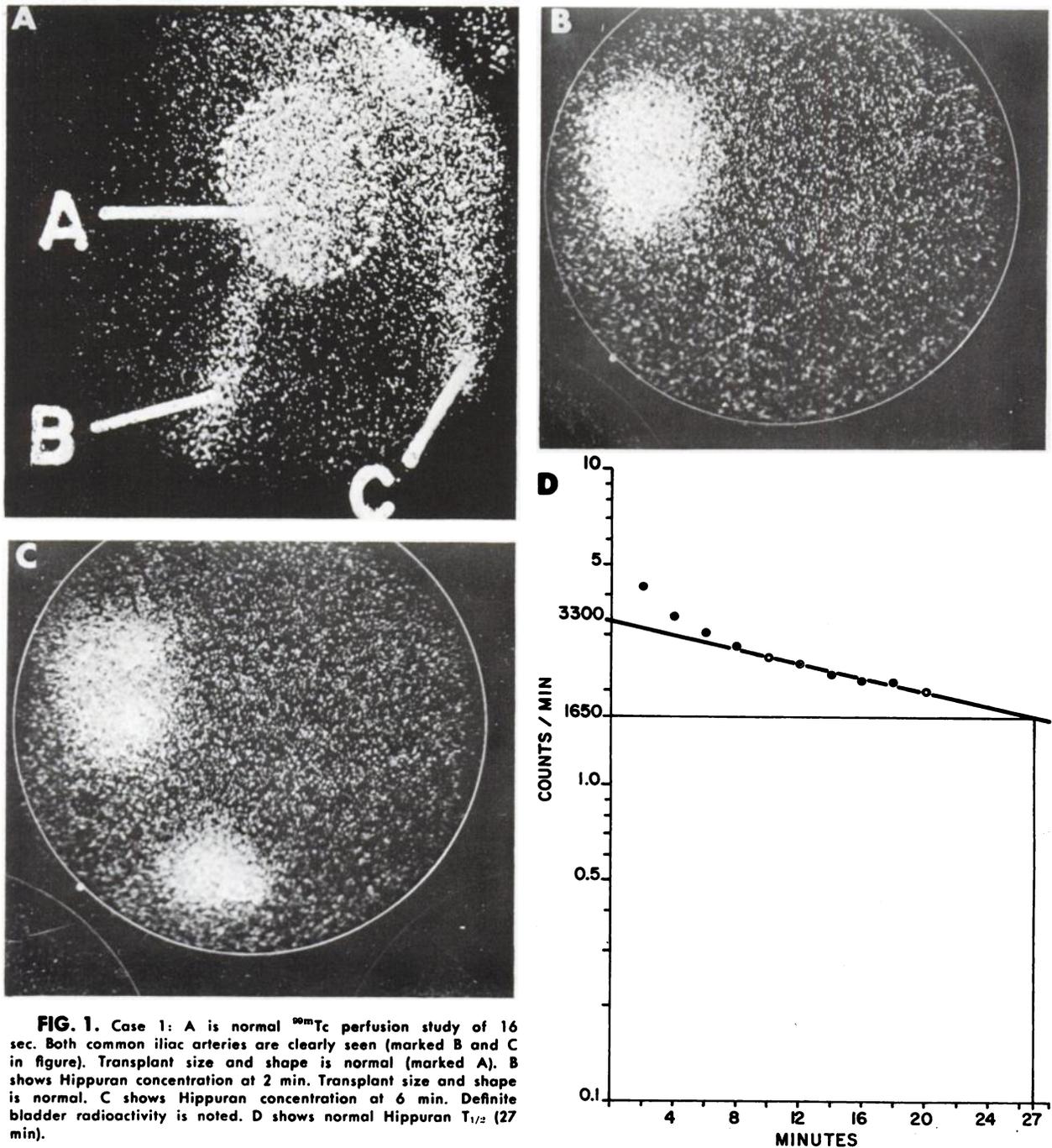


FIG. 1. Case 1: A is normal ^{99m}Tc perfusion study of 16 sec. Both common iliac arteries are clearly seen (marked B and C in figure). Transplant size and shape is normal (marked A). B shows Hippuran concentration at 2 min. Transplant size and shape is normal. C shows Hippuran concentration at 6 min. Definite bladder radioactivity is noted. D shows normal Hippuran T_{1/2} (27 min).

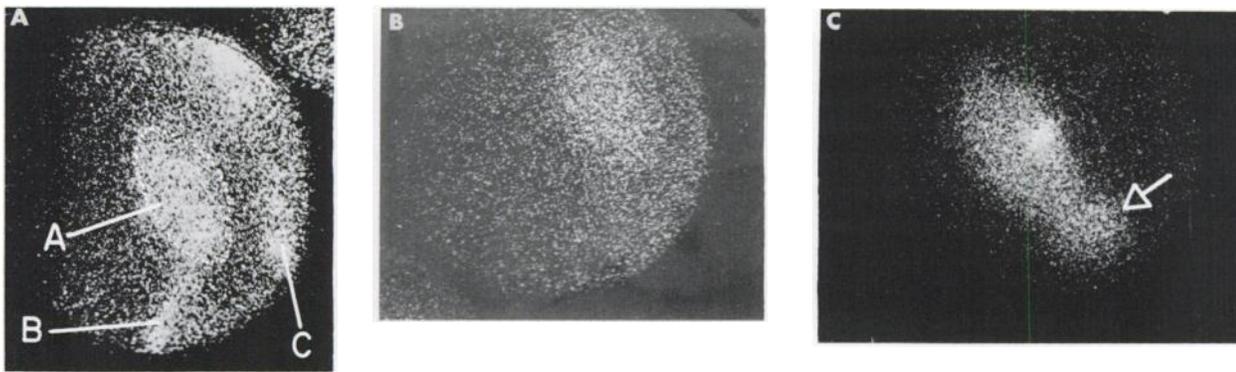


FIG. 2. Case 2: A is normal ^{99m}Tc vascular perfusion study at 12 sec. Transplant (marked A) and both common iliac arteries (marked B and C) are clearly delineated. B shows abnormal Hip-

puran concentration at 24 min. No radioactivity is present in renal pelvis or urinary bladder. C is normal Hippuran study at 10 min. Radioisotope concentrates in renal pelvis and urinary bladder (arrow).

(Fig. 1D). A repeat study on May 8, 1968 was normal, and on June 17, 1968 the patient was discharged with a creatinine of 1.3 mg% and a BUN of 27 mg%.

Case 2: acute tubular necrosis (ATN). JH, a 30-year-old Negro male, received a cadaver transplant on Feb. 28, 1969. The first scintillation camera study was done on March 3, 1969, and is shown in Fig. 2. The creatinine was 9 mg%, and the urinary output was 500 cc/24 hr. The ^{99m}Tc perfusion of the transplant was observed within 12 sec (Fig. 2A). However, concentration of Hippuran at 24 min (Fig. 2B) was poor, and no radioisotope was seen in the area of the renal pelvis or the urinary bladder. The findings were consistent with abnormally delayed parenchymal clearing of the radioisotope. The Hippuran disappearance half-time was 110 min. A repeat study was done on March 13, 1969. Clinically the patient was also improving, with a creatinine of less than 2 mg% and a urinary output of greater than 1,500 ml/24 hr. Again normal vascular perfusion of the transplant occurred at 12 sec. The Hippuran study (Fig. 2C) now demonstrated good concentration of Hippuran in the kidney at 10 min with noticeable concentration in the regions of the renal pelvis and urinary bladder. The Hippuran disappearance half-time was 36 min.

Case 3: rejection. Figure 3A is the ^{99m}Tc perfusion study in a 44-year-old white male 4 days post-transplantation, revealing very slight and irregular concentration of radioisotope at 20 sec. The Hippuran study (Fig. 3B) demonstrates minimal concentration at 20 min with no radioisotope concentration in the renal pelvis or urinary bladder areas. These findings are consistent with ischemia, with prolonged Hippuran transit time and with poor parenchymal clearing of Hippuran which is characteristic of ATN. The poor ^{99m}Tc perfusion study, however, suggested rejection. Two subsequent ^{99m}Tc perfusion studies

TABLE 1. SCINTILLATION CAMERA RADIOISOTOPE STUDIES IN FUNCTIONING RENAL TRANSPLANTS*

Patient	^{99m} Tc-perchnetate Vascular phase (arterial perfusion)	¹³¹ I-Hippuran				T _{1/2}
		Secretory phase (parenchymal concentration)	Excretory phase (renal pelvis concentration)	Bladder phase		
AP	16 sec	2 min	6 min	10 min	28 min	
	20	2	4	6	26	
FM	20	2	4	4	26	
	16	2	4	8	—	
	12	2	4	6	29	
	20	2	4	6	28	
EA	16	2	4	6	44	
EF	16	2	4	6	40	
AA	16	2	6	10	32	
	16	2	6	8	37	
RM	20	2	4	4	35	
	12	2	4	6	31	
	12	2	4	10	27	
RN	16	2	6	8	30	
PS	12	2	4	4	—	
VA	16	2	4	4	26	
JH	12	2	6	8	36	
	12	2	6	8	28	
Range	12-20	2	4-6	4-10	26-44	
Average	15.8	2	4.7	6.8	31.4	

* Cadaver kidneys (6) and live donors (4).

demonstrated even poorer concentration of the radioisotope. There was no Hippuran concentration in the region of the transplant. The patient ultimately developed an overwhelming bronchopneumonia and expired. Postmortem examination confirmed a severe rejection reaction.

Case 4: acute tubular necrosis with subsequent rejection. WA, a 30-year-old white male, received a cadaver kidney on Jan. 12, 1969. His urine out-

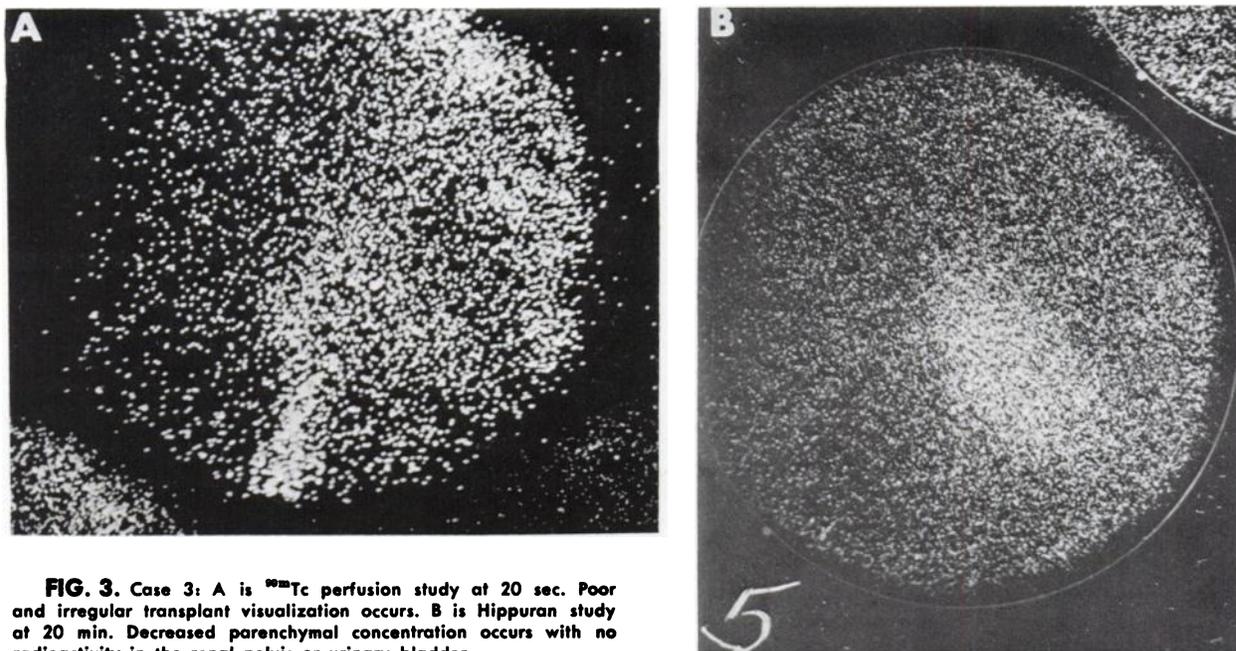


FIG. 3. Case 3: A is ^{99m}Tc perfusion study at 20 sec. Poor and irregular transplant visualization occurs. B is Hippuran study at 20 min. Decreased parenchymal concentration occurs with no radioactivity in the renal pelvis or urinary bladder.

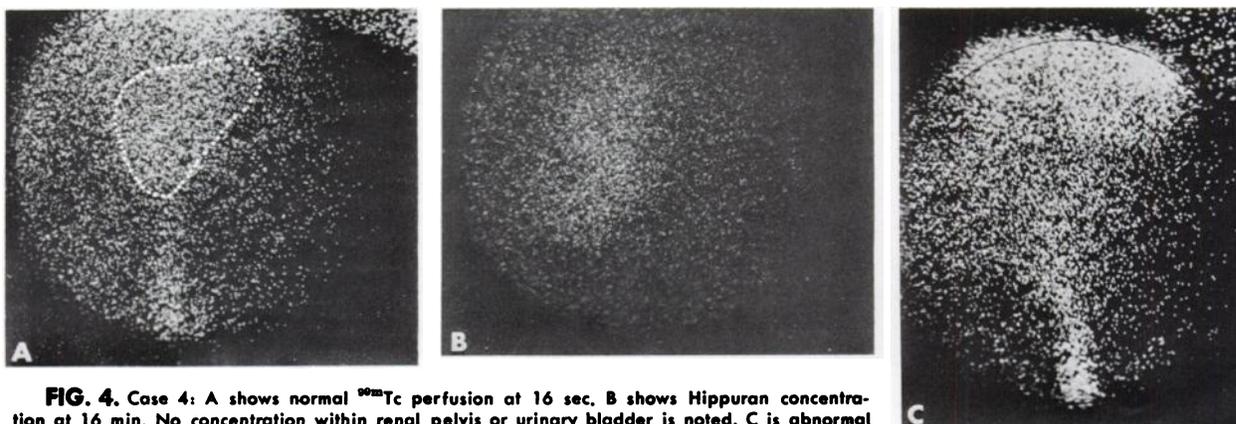


FIG. 4. Case 4: A shows normal ^{99m}Tc perfusion at 16 sec. B shows Hippuran concentration at 16 min. No concentration within renal pelvis or urinary bladder is noted. C is abnormal ^{99m}Tc perfusion study, revealing poor and irregular perfusion of the transplant. Kidney was removed 17 days later because of ATN and rejection.

put was less than 200 ml/24 hr, and his creatinine was approximately 10 mg%. Frequent hemodialysis was required.

The study shown in Fig. 4 was done 5 days post-operatively and reveals good arterial perfusion (Fig. 4A) but poor concentration of Hippuran, and no radioactivity present in the renal pelvis or urinary bladder (Fig. 4B). The Hippuran disappearance half-time was 80 min.

Despite azathioprine and prednisone and trials of mannitol and ethacrinic acid, the creatinine remained high and the urinary output low (less than 200 ml/day). A repeat study with ^{99m}Tc and Hippuran on Jan. 21, 1969, was unchanged, but the Hippuran disappearance half-time had risen to 92 min.

On Feb. 6, 1969, although the Hippuran studies were unchanged, there was poor and irregular ^{99m}Tc perfusion of the transplant (Fig. 4C). The Hippuran disappearance half-time had risen to 115 min. Rejection, in addition to acute necrosis, was suspected. Exploration of the kidney revealed no gross abnormalities. Open biopsy revealed "minimal rejection." External irradiation was administered but was without effect since the patient remained oliguric. On Feb. 23, 1969 the transplant was removed. The final diagnosis was rejection.

Although it is difficult to diagnose rejection in the presence of ATN because ATN is associated with elevated Hippuran disappearance half-time values, the increasing Hippuran disappearance half-time and

the sudden abnormality in ^{99m}Tc perfusion lent strong support to the diagnosis of rejection occurring in a cadaver kidney with ATN.

Case 5: localized ischemia secondary to arterial injury. JS, a 30-year-old Negro male, received a cadaver kidney on Feb. 20, 1969. At the time of surgery an accessory artery to the upper pole of the kidney was injured and sacrificed. A postoperative ^{99m}Tc perfusion study demonstrated an area of decreased perfusion involving the upper pole (Fig. 5A). The Hippuran clearance was abnormally delayed (Fig. 5B), and 2 hr later radioactivity remained in the upper pole region (Fig. 5C).

Case 6: incomplete ureteral obstruction. DH, a 30-year-old white male, received a cadaver kidney on Oct. 17, 1968. No immediate postoperative problems occurred. He received irradiation, azathioprine and prednisone. On Oct. 21, 1968, a ^{99m}Tc perfusion study was normal. Hippuran appeared in the bladder by 8 min (Fig. 6A). During the next 10 days the patient's creatinine rose from 6 to 10 $\mu\text{g}\%$ and the transplant site became tender. On Oct. 31, 1968, the ^{99m}Tc perfusion study was again normal (Fig. 6B) but the Hippuran did not appear in the urinary bladder until 20 min after injection (Fig. 6C).

Since partial ureteral obstruction was considered to be a possibility, exploration was done on Nov. 1, 1968. Swelling of the ureter with a marked decrease in lumen size was found.

Case 7: thrombosis of transplant renal artery. HS, a 39-year-old white male, received a cadaver kidney in June 1968 and was admitted to Wadsworth Hospital on Jan. 3, 1969, with an interstitial pneumonia. He responded at first to antibiotics and oxygen but later developed an irregular febrile course. Creatinine rose to 10 mg%, and urinary output decreased markedly. A retrograde pyelogram was unsuccessful. A ^{99m}Tc perfusion study revealed absence of transplant perfusion (Fig. 7A) consistent with a vascular thrombosis. The patient died suddenly several days later after an episode of severe respiratory distress. Postmortem examination revealed multiple pulmonary emboli, interstitial pneumonia and thrombosis of the transplant renal artery (Fig. 7B).

DISCUSSION

Since increasing numbers of patients with terminal renal disease are successfully undergoing kidney homotransplantation, it has become imperative that simple, atraumatic and reproducible procedures be devised to accurately assess transplant function. These methods must be free of significant morbidity. They must also be able to detect pathologic changes accurately and earlier than conventional methods, especially with regard to transplant rejection. The

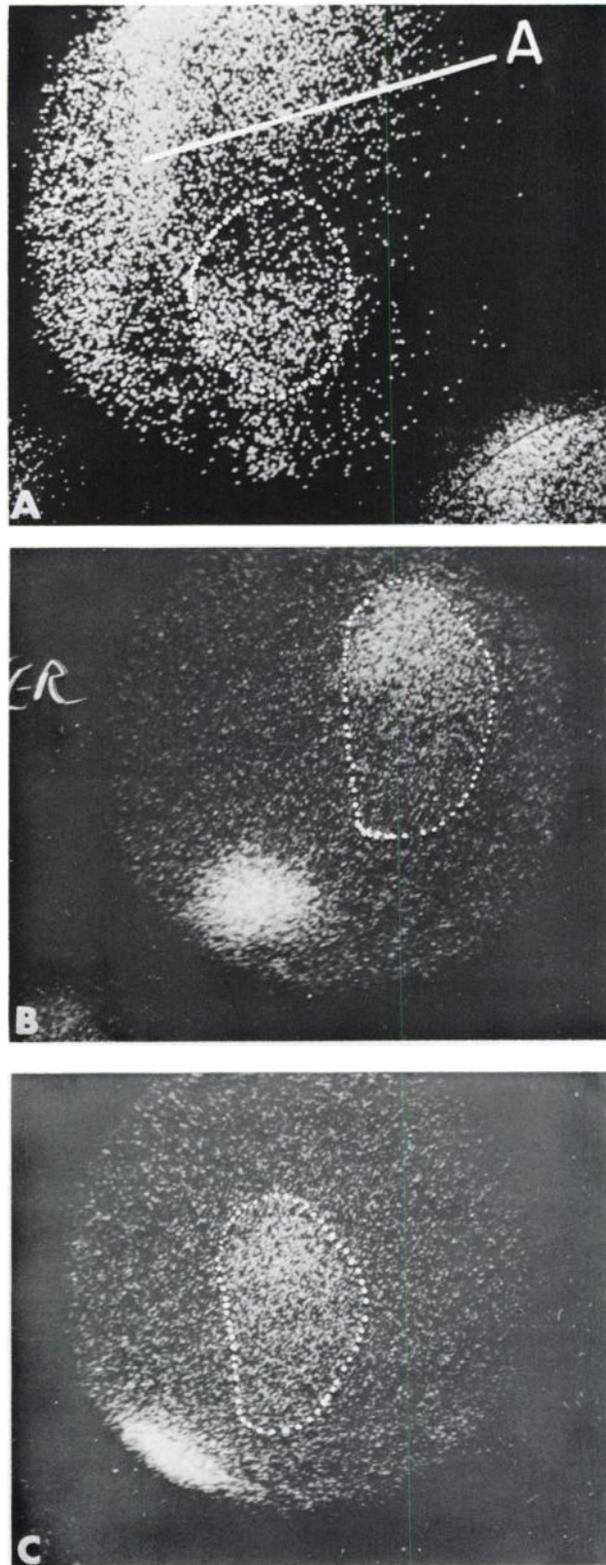


FIG. 5. Case 5: A is ^{99m}Tc perfusion study demonstrating defect in upper pole region. Note aorta (marked A) and its bifurcation to form both common iliac arteries. B is Hippuran study at 24 min. There is distinct retention of radioactivity in region of upper pole. Urinary bladder radioactivity is well seen. C, which is hippuran study at 2 hr reveals persistent retention of radioactivity in upper pole.

application of dynamic radioisotope techniques, which have become available with the advent of the scintillation camera, would appear to satisfy most of these requirements.

TRANSPLANT VASCULARITY

Technetium-99m-pertechnetate has proved to be an ideal agent for the evaluation of the vascular integrity of the transplant. It is readily obtained from a ^{99}Mo generator. Technetium-99m has a half-life of 6 hr and emits only gamma radiation of 141 keV, which is easily and efficiently detected by the sodium iodide crystal of the scintillation camera. A 10-mCi dose yields a total-body radiation dose of only 100 mrad; consequently large doses of this radionuclide compound can be used to obtain better resolution. Technetium-99m-pertechnetate is rapidly excreted by the GI tract after diffusion into extravascular fluid spaces.

Although this radionuclide has been extremely useful in delineating cerebral vascular structures (2,3), locating the site of vascular obstruction (6,7) and assessing renal vascular perfusion (8), it has only recently been utilized to evaluate the vascular integrity of renal homotransplants (15,16).

Since the major physiologic effect of transplant rejection is a diminution in renal blood flow (12-14), $^{99\text{m}}\text{Tc}$ -pertechnetate has also been useful in detecting rejection reactions. Failure to adequately visualize the transplant with $^{99\text{m}}\text{Tc}$ -pertechnetate has been a consistent finding (Cases 3 and 4). An exceptionally helpful feature in the diagnosis of rejection is a change from normal to abnormal $^{99\text{m}}\text{Tc}$ -pertechnetate perfusion associated with early symptoms and signs of rejection. In renal artery occlusion, the transplant is not visualized (Case 7) in contrast to rejection in which the transplant has a "moth-eaten," irregular and obviously abnormal appear-

ance. However, we have also encountered cases of rejection in which the renal perfusion studies have appeared relatively normal.

TRANSPLANT FUNCTION AND MORPHOLOGY

Since the introduction of Hippuran by Nordyke, Tubis and Blahd in 1960 (17), this agent has proven to be of considerable value in the diagnosis of bilateral and unilateral renal disorders. It can be used to evaluate renal concentrative and excretory function (9,10) and has been successfully employed in dynamic renal function studies in association with the scintillation camera (8,18-20).

Following administration, Hippuran can be visually monitored by the scintillation camera as it passes through the kidney parenchyma into the renal pelvis and ultimately into the urinary bladder. Such studies permit more complete evaluation of the morphological and functional state of the kidneys than the conventional Hippuran renogram technique (18). Although conventional renograms have been performed in post-transplantation patients with a modicum of success (21-24), dynamic visualization of the flow of radiohippuran through the transplanted kidney with the scintillation camera would appear to be a more reliable and more informative procedure (8,16,23,25). Furthermore, artifactual changes in the renogram curve due to the close proximity of the transplant to the urinary bladder present a major technical problem as a result of the subsequent accumulation of radioactivity within the bladder. To circumvent this problem the scintillation camera crystal may be electronically divided so that half of the crystal views the kidney transplant while the other half views the bladder (22,23). Our experience has shown, however, that there is significant crossover of radioactivity from the bladder area which inter-

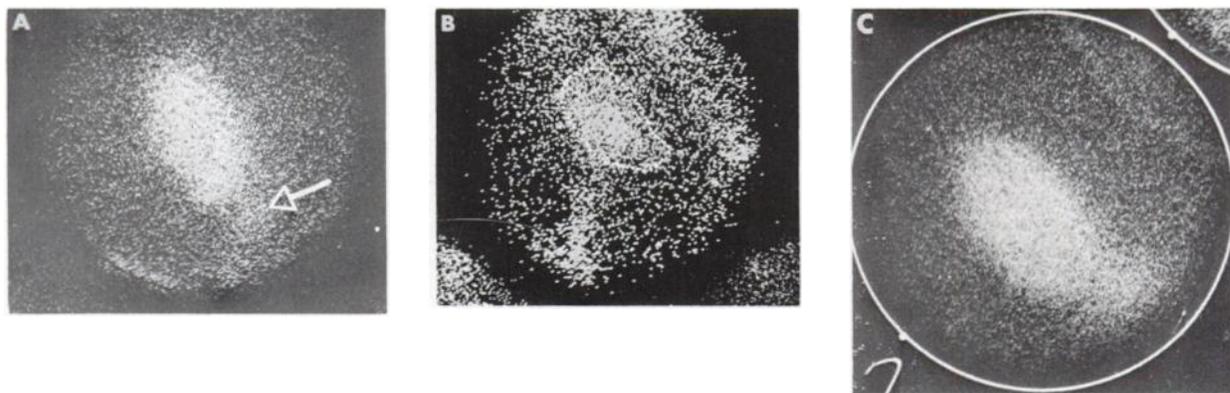


FIG. 6. Case 6: A shows Hippuran concentration at 6 min. Bladder radioactivity is well seen (arrow). B is normal $^{99\text{m}}\text{Tc}$ perfusion study 10 days later. C shows Hippuran concentration at 20 min. Bladder radioactivity is finally noted.

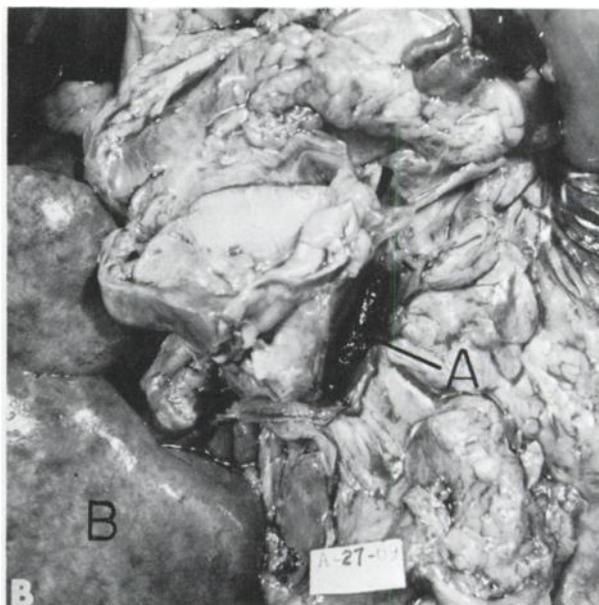


FIG. 7. Case 7: A is ^{99m}Tc perfusion study at 20 sec. Transplant is not visualized, and defect in region of left common iliac artery is present. B is autopsy specimen demonstrating thrombosis of transplant artery (marked A). Kidney transplant is noted in lower left corner (marked B).

feres with the precise interpretations of the data which are recorded by scintillation camera.

Normal values have been established for the appearance time of Hippuran in the kidney parenchyma and urinary bladder (Table 1). The importance of this aspect of transplant evaluation is well illustrated by Case 6.

Acute tubular necrosis. In contrast to living homo-transplants which function immediately, cadaver kidney transplantation is frequently associated with acute tubular necrosis (ATN) which is a result of ischemia sustained by the cadaver kidney prior to transplantation. Any pathologic process producing severe renal ischemia such as crush injuries, transfusion reactions and severe burns may produce ATN. In these cases, the common etiologic factor is hypotension associated with decreased renal flow and consequent renal ischemia. Histologically, the primary lesion is disruption of the basement membrane and tubulorhexis. Such changes lead to poor or absent tubular cell function and oliguria or anuria. Since characteristic findings have been observed with the scintillation camera in renal ischemia (26), it can be inferred that similar findings would be observed with ATN.

In scintillation camera studies performed on patients with ATN and patients with renal ischemia, initial concentration of Hippuran is poor, and only minimal accumulation occurs throughout the period of study. No radioactivity appears in the renal pelvis or urinary bladder. The poor parenchymal concen-

tration of Hippuran and the marked delay in parenchymal clearing is apparently secondary to a combination of factors: proximal tubular cell damage and basement membrane destruction; and delayed transit time with increased absorption of solute. The scintillation camera findings are reversed and a normal study may be obtained when the cadaver kidney begins to function, which is usually within 5–15 days (27).

Hippuran blood disappearance half-time. Hippuran may be used for the measurement of renal blood flow (28–31). Correlation with direct measurements of renal blood flow performed by the para-amino Hippurate (PAH) method has been excellent (28,30,31), but multiple arterial or venous blood sampling is required. External precordial monitoring of the disappearance of Hippuran radioactivity as proposed by Bianchi and Toni (32) provides a simple method for assessing renal blood flow. The usefulness and accuracy of this technique has been documented by Blaufox *et al* (31) and Razzak *et al* (11). Since renal blood flow determinations based on the slope of the blood radioactivity disappearance curve between 10 and 20 min can be correlated with values obtained by conventional PAH clearance methods (28,30,33), this time period has been used to calculate the Hippuran blood disappearance half-time in renal transplant patients.

The Hippuran blood disappearance half-time determination has proved to be of prognostic value in the evaluation of transplant function since the essen-

TABLE 2. SCINTILLATION CAMERA RADIOISOTOPE STUDIES IN PATHOLOGIC LESIONS ASSOCIATED WITH RENAL TRANSPLANTATION

Pathologic lesion	^{99m} Tc-pertechnetate Vascular phase (arterial perfusion)	¹²⁵ I-Hippuran			
		Secretory phase (parenchymal concentration)	Excretory phase (renal pelvis concentration)	Bladder phase	T _{1/2}
Renal artery occlusion	Absent	Absent	Absent	Absent	Increased
Renal cortical necrosis	Abnormal or absent	Absent	Absent	Absent	Increased
Acute tubular necrosis*	Normal	Decreased	Absent	Absent	Increased
Rejection					
Hyperacute	Absent	Absent	Absent	Absent	Increased
Acute	Normal or abnormal	Normal or decreased	Normal or decreased	Present	Increased
Chronic	Abnormal	Decreased or absent	Decreased or absent	Decreased or absent	Increased
Acute tubular necrosis with rejection	Abnormal	Decreased	Absent	Absent	Increasing
Ureteral obstruction					
Partial	Normal	Normal	Normal	Delayed	Normal
Complete	Normal	Normal	Increased	Absent	Normal or increased
Extravasation	Normal	Normal	Normal	Decreased or absent	Normal

* Cadaver kidney or live donor.

tial pathological process in the rejection reaction is a progressive destruction of the small intertubular blood vessels by infiltrating host immature plasma cells and lymphocytes (33-37) which results in a decrease in renal blood flow. Although some authors are of the opinion that the histopathologic picture differs depending upon whether or not host modification with immunosuppressants is attempted, all agree that the first abnormalities noted in either case are vascular in nature. This primary vascular lesion also occurs well before, and is most probably responsible for, the ensuing deterioration of renal tubular cell function.

The value of the Hippuran disappearance half-time as a sensitive indicator of the rejection phenomenon (12-14) has been substantiated by our studies. In normal subjects the Hippuran disappearance half-time does not exceed 25 min (11,29,30). In the present series, however, the Hippuran disappearance half-time of well functioning transplants varied from 26 to 40 min. In no instances have the values been less than 25 min (Table 1). The explanation for this discrepancy is not clear, unless it is related to a physiological reduction in renal function associated with the absence of one kidney or to a slight reduction in renal blood flow resulting from implantation of the transplant in the pelvis (13).

The primary value of the Hippuran disappearance half-time is its ability to detect rejection early, before other parameters of kidney function become abnormal. Often a single value is not as helpful as serial studies since initially elevated values may be observed in some patients with ATN despite decreasing creatinine and urinary output. Such serial values are readily obtained because the procedure can be performed daily if necessary. Serial measurements of hippuran disappearance half-time may be useful sometimes in differentiating ATN from rejection in cadaver kidneys (Case 4).

SUMMARY

Table 2 summarizes the findings of the scintillation camera radioisotope studies in various pathologic states which affect transplanted kidneys. Accuracy and reproducibility of these techniques have been excellent. These studies have correlated well with the patient's clinical course and are often more sensitive than conventional methods of transplant evaluation. As more experience is acquired, it is our impression that the scintillation camera will continue to assume a vital role in the evaluation of the kidney transplant.

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