Dynamic Renal Transplant Imaging with Tc-99m DTPA (Sn) Supplemented by a Transplant Perfusion Index in the Management of Renal Transplants

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We have performed 955 studies on 152 patients with 167 renal transplants. Images were recorded following bolus injection of 12–15 mCi Tc-99m DTPA (Sn). The data were stored on a computer and analyzed by generation of region-of-interest curves from (a) the iliac artery distal to the transplant, (b) the kidney, and (c) a background area. A perfusion index was adopted:

$$\frac{\textit{arterial counts per cell, integrated to peak}}{\textit{concurrent renal counts per cell}} \times 100.$$

In 276 studies the patient clearly had acute tubular necrosis (ATN), rejection, or a normal kidney on retrospective analysis. The normal perfusion index has a value below 150, and it increases with falling perfusion, such as is seen in rejection and in renal-artery stenosis. The use of this index in addition to sequential images and changes in the region-of-interest curves usually allows separation of rejection from ATN and, particularly, rejection from normals. When serial studies are performed, the separation of rejecting from nonrejecting transplants is excellent, although renal-artery stenosis may cause similar changes in perfusion.

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In the postoperative management of renal transplants there is need for a method of diagnosing vascular insufficiency, acute tubular necrosis (ATN), rejection, and problems of the urinary outflow tract. All of these may occur separately or in combination, and all may present as impairment of renal function with few specific features. An effective method should be safe, simple, and rapid, and should also be repeatable at intervals of 48–72 hr during the critical period of 2–3 wk following surgery. To date the most satisfactory methods have been those using radionuclides, which may be divided into two logical groups. First, there are those using I-121 Hippuran with a probe (*1*), gamma camera (*2*), and/or blood samples (*3*) to obtain basic numerical measurements. Second, there are methods using the gamma camera and Tc-99m-labeled agents to obtain images (*4*). We felt a need for a technique combining quantitation with images, and capable of dealing with the needs of a transplant unit performing over 100 transplants a year. The introduction of Tc-99m-DTPA (Sn), a chelate cleared by glomerular filtration (*5*), together with the animal work of Kirchner et al. (*6*) has led us to evolve a method that forms the subject of this report.

MATERIALS AND METHODS

Patients. Between January 1974 and September 1976 we performed 955 studies on 152 patients with 167 transplants. Of these, 779 were performed with computer quantitation, 169 were not quantitated, and in seven studies the transplant was not visualized. We now try to study every patient having a transplant within 24 hr of the operation, then on alternate days until discharge from hospital, and then whenever it is clinically indicated.

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Imaging. The patient lies supine on a couch or in his bed, with the head of the gamma camera positioned over the transplant, so that the bladder and iliac artery are in the field of view. A 12- to 15-mCi bolus of Tc-99m-DTPA (Sn) is injected into a peripheral vein, shunt or fistula, using the Oldendorf technique (*7*). The first image ("vascular phase") is recorded for 30 sec, starting at the time of tourniquet release. The next image (2 min) is recorded for 300,000 counts on a standard-field camera, or for 400,000 counts on a wide-field camera. The time required for this image is noted, and subsequent images are recorded for the same duration at 5, 10, 20, 25, and 30 min after injection. At 30 min an image of the catheter bag or bladder is recorded, unless it is already in the field of view. This is done even if there is no activity in the bag or bladder. If there is any possibility of obstruction of the ureter or extravasation of urine, a postmicturition image is recorded. If obstruction is still considered possible, delayed images are recorded at 60 and 90 min, with the same duration as the 2-min image, except for inclusion of a suitable factor to compensate for decay of the Tc-99m.

Quantitation. Concurrently with the imaging, the study is recorded using a dedicated minicomputer at a frame rate of 1/sec for 30 sec followed by 1/min for the next 29 min, using a 64 × 64 matrix. [Some studies have been recorded at one frame per second for 40 sec, followed by one every 20 sec to allow later reconstruction of the data at 1 frame per 20 sec for the total study, followed by deconvolution analysis (*8*).] At the end of the study the data are played back from the disc. Irregular regions of interest (ROIs) are defined over the iliac artery just distal to the transplant (usually best seen between 6 and 20 sec after injection), the transplant (with care not to include any portion of the kidney that overlies the iliac artery) and a background area lateral to the kidney.

Normalized time-activity curves are generated from these ROIs. They are displayed using frame number rather than time for the abscissa, which has the effect of expanding the initial (vascular) portion of the curves.

The curves are then processed using a FOCAL computer program that corrects the renal and arterial curves for changes in the background count rate. It then calculates the areas under the normalized arterial and renal curves up to the time of the peak of the arterial curve caused by the first passage of the bolus, the peak being selected by the operator (Fig. 1). The computer prints out the ratio of these areas as an index, given by

$$\text{Perfusion index} = \frac{\text{Area under arterial curve to peak}}{\text{Area under renal curve}} \times 100.$$

Where the two areas are identical, the index has a value of 100. As relative blood flow through the kidney falls, the area under the vascular phase of the renal curve becomes smaller (*6*), increasing the index. Conversely, as renal blood flow improves, the index falls.

The computer program also calculates the standard deviation of the index (based on the statistical uncertainty of the number of counts in the area under each curve) and displays the renal curve, corrected for background. The whole computer analysis takes about 5 min, and can be performed by a technologist.

The permanent record from the study consists of the images, the printout with the perfusion index, and photographic records of the ROIs, the time-activity curves, and the background-corrected renal curve.

Clinical criteria. The clinical status of the transplant was defined retrospectively. The transplant was classified as "normal" on the basis of good urine production with a normal serum creatinine level and with no features of rejection at the time of the study or within the next four days. ATN was considered to be present when there was oliguria after transplantation, provided that there was no evidence of any

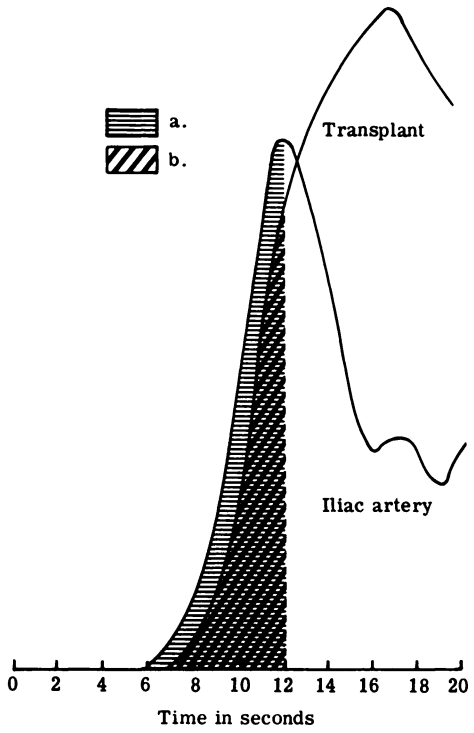


FIG. 1. Areas used for perfusion index, which is given by a (a/b) × 100.

TABLE 1

	Normal	ATN	Rejection	Renal-artery stenosis	Total
Studies	44	62	166	4	276
Patients	29	38	64	3	113
Transplants	29	41	70	3	143

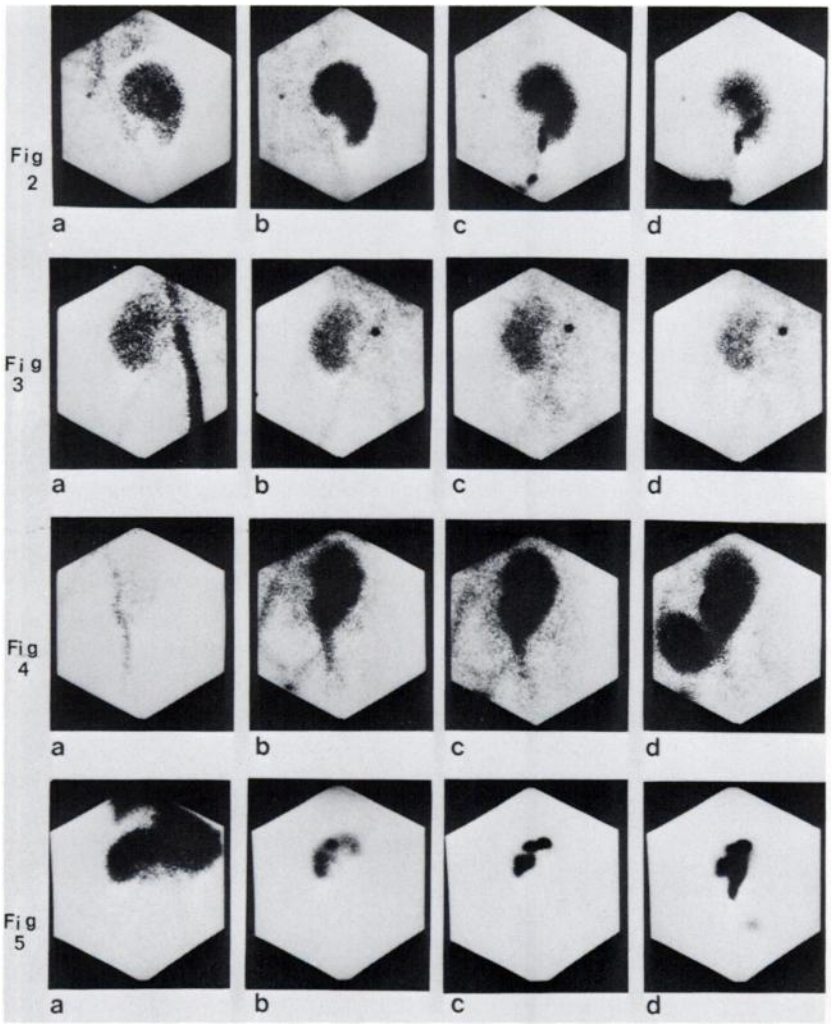
other disease and, in particular, that there was no evidence of rejection occurring within the next four days. Rejection was diagnosed on a combination of at least two features, including: a tender kidney, pyrexia, rise in blood pressure, rise in serum urea or creatinine, fall in serum bicarbonate, fall in urinary sodium excretion, findings on biopsy, or functional improvement associated with antirejection therapy. Renal-artery stenosis was demonstrated arteriographically. Table 1 shows the numbers in each group. Inevitably, many studies could not be allocated to any group, either because the clinical state was unclear (even in retrospect) or because it was in transition (for instance recovering from ATN or after treatment of rejection).

RESULTS

Normal. In the normal, well-functioning transplant (Fig. 2), the transplant is well seen on the 30-sec, vascular image. There is good selective accumulation of chelate, seen on the 2-min image; with transit into the collecting system by 5 min; and good renal clearance, as shown by the decrease in renal parenchymal activity between the 2-min and 30-min images.

Background activity remains low relative to the kidney, and a considerable amount of activity is present in the bladder at 30 min.

ROI curves show that the renal curve is almost superimposed on the arterial curve in the vascular phase, and the perfusion index in these normal transplants has always been below 150. In the later portion of the curve there is a clearly defined func-



FIGS. 2–5. In all studies (a) is the the 0–30 sec image, (b) the 2-min image, and (c) and (d) are images at 5 and 30 min. Fig. 2: Normal kidney. Fig. 3: Kidney anuric from ATN. Dense activity in left iliac vessels is due to injection into leg shunt. Fig. 4: Severe rejection. Fig. 5: Acute obstruction.

tional peak, reached at about 4 min, with a clearly defined slope thereafter (Fig. 6a).

Acute tubular necrosis. In ATN the transplant is usually well perfused (Fig. 3a), and this is reflected in the curves (Fig. 6b) and in the perfusion index (Fig. 7). Where there is initial impairment of perfusion, serial studies show no rise in the perfusion index, and recovery is indicated by return of the perfusion index to normal. In the later images in anuric ATN, the transplant is well seen at 2 min, then progressively less so. At first sight the kidney appears to be functioning, but the lack of radioactivity in the bladder points the difference. This is reflected in the curves by the progressive fall in the renal curve, with no functional peak (Fig. 6b). With recovery from ATN, the renal curve gradually develops a normal pattern (*9*).

Rejection. In the rejecting transplant there is impairment of perfusion, often visible in the vascular image (Fig. 4a) and seen as a relative flattening of the renal curve in the vascular phase (Fig. 6c). This impairment of perfusion, however, is readily demonstrated by the rise in perfusion index that accompanies the rejection. Figure 7 shows the values of the perfusion index in all cases of rejection. Note that there is some overlap with the normal range. Figure 8 shows the change in absolute value of the index in 75 rejection episodes where serial data were available. Figure 9 shows the change in the perfusion index, expressed as a percentage of the previous value, and expressed relative to the day rejection is recognizable clinically.

It will be seen that rejection is accompanied by a rise in the perfusion index and successful therapy by a fall in the index, whereas failure of therapy brings a continuing rise, or a persistence at a high level. These changes in perfusion index occur even in the presence of ATN.

In addition, changes are often visible in the images of the rejecting transplant, which are best seen by comparison of serial studies. The selective accumulation of chelate by the kidney often falls, and there may be delayed transit into the collecting system, which may be the only feature visible on the images. There is often prolonged intrarenal retention of chelate, seen in a comparison of the 2-min and 30-

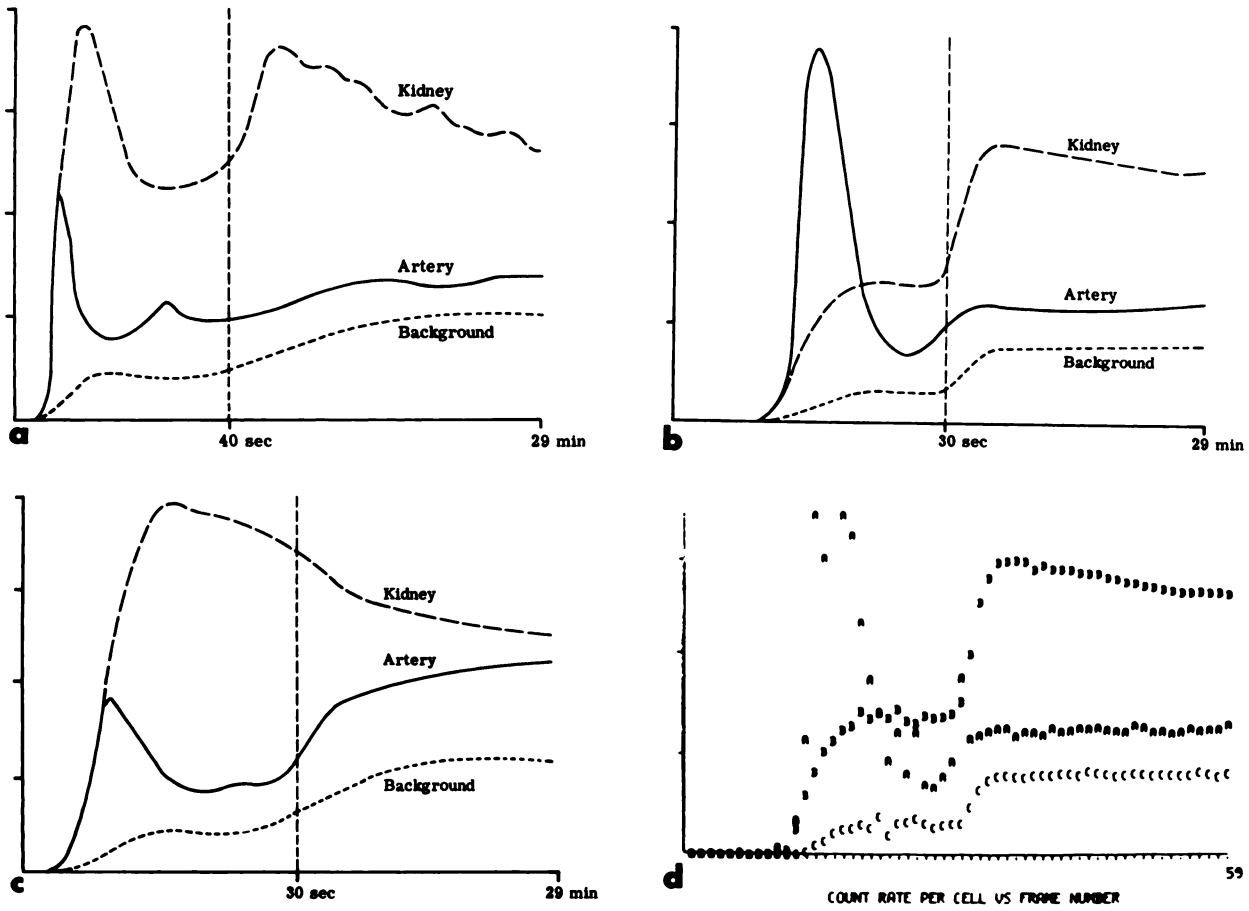


FIG. 6. Tracings of curves from computer. Note change of time scale. (a) Normal (recorded at 1 frame/sec for 40 seconds, then 1 frame/20 sec for 2 min). (b) Severe rejection. (c) Anuric ATN. (d) Same data as (b), photographed directly from computer screen.

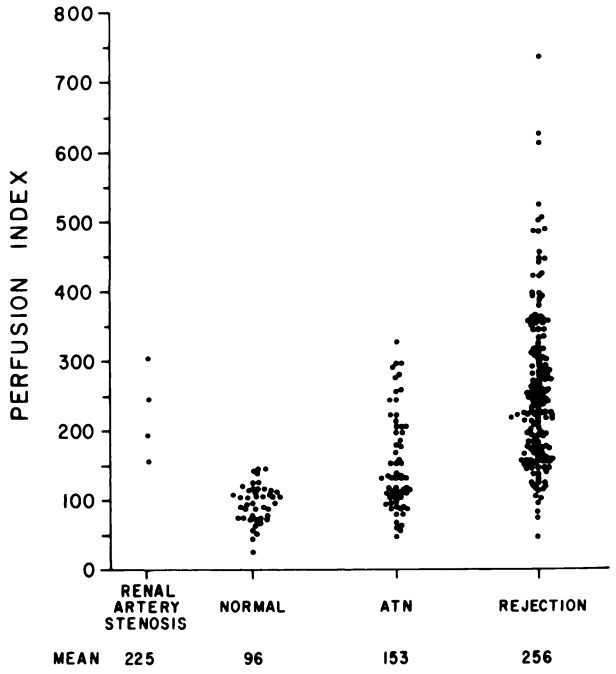


FIG. 7. Values of perfusion index in patients with known conditions.

min images. The collecting system is often prominent in those patients whose kidney is functioning, and this may suggest a diagnosis of obstruction, unless other features of rejection are looked for (see below).

Renal-artery stenosis. These patients would be expected to have impaired perfusion, and in them the perfusion index was always raised above 150.

Obstruction. We have seen one patient with simple obstruction, responding to surgery (Fig. 5). Here the kidney was well perfused (perfusion index 33) with good uptake of the chelate followed by rapid transit into the collecting system. We have also seen, however, many patients with acute rejection who showed varying degrees of stasis in the collecting system, resolving on antirejection therapy. In two cases surgery was performed on the basis of deteriorating renal function together with IVP appearances of obstruction. In neither case did function improve as the result of surgery, and in both the perfusion index was raised. In one case there was progressive deterioration of function and perfusion in spite of antirejection therapy, and the kidney failed to function. On retrospective review it was felt that this was a case of hyperacute rejection. In the other case, function improved only after antirejection therapy instituted partially on the basis of the impaired perfusion shown by the radionuclide study.

DISCUSSION

At an early stage in the history of transplantation, attention was focused on changes in blood flow through the transplant, and it was soon shown that there are marked changes from the normal pattern in association with rejection (*10*), and that these changes might occur before changes in urine output (*11*).

Since the effective renal plasma flow is related to renal blood flow, several groups have used measurement of the effective plasma flow as an indicator of renal blood flow, and have shown that changes occur in association with rejection in patients who are passing urine (*12*). However, in order to separate ATN from rejection, most groups have found it necessary to use additional techniques, such as the calculation of a "Hippuran Excretion Index" (*13*), which depends, however, on the formation of urine by the transplant.

An advantage of most of the methods that use [^{131}I] Hippuran is that they allow quantitation, and thus serial studies may be compared. However, the relatively long life of the compound makes it difficult to perform repeated studies at frequent intervals.

On the other hand, while methods using Tc-99m-labeled compounds can be repeated frequently, they have not, thus far, lent themselves to quantitation. Some workers (*13*) have combined studies with Tc-99m and I-131 agents, but if the studies are performed simultaneously, a high-energy collimator is needed, which degrades both the quality of the Tc-99m images and the counts available for quantitation. If the studies are performed serially, the combined study becomes long, and a high-energy collimator

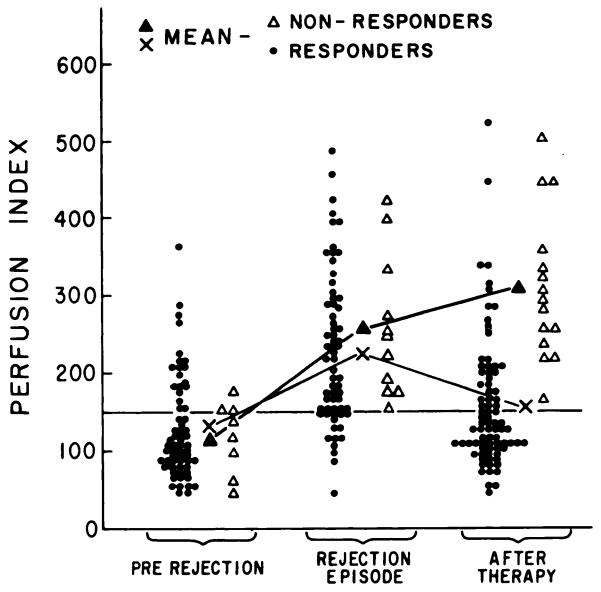


FIG. 8. Absolute change in perfusion index associated with rejection.

may still be necessary to eliminate degradation in the Tc-99m images if there is residual [^{131}I] Hippuran from previous studies.

We feel that our method, by separating changes in perfusion from changes in renal function, allows clearer analysis of the status of renal transplants, particularly in the later postoperative period. The perfusion index normally follows a sequence that would be predicted from animal experimentation (*14*), with variable impairment of perfusion in the immediate postoperative period, resolving over the next few days. During, and often before, rejection there is impairment of renal perfusion, which is reversed by successful treatment of the rejection.

Detailed attention to the technique of bolus injection, together with the use of a 140-keV, medium-resolution collimator, produces good statistics for the perfusion index, so that, typically, the index has a standard error of 5%. This allows the detection of relatively small changes in the index, so that the changes associated with rejection are readily detected. The use of an area distal to the kidney for the iliac artery ROI has the effect of exaggerating the small changes in renal blood flow at the expense of a linear scale, but in practice this is no problem.

Our experience suggests that it is necessary to exercise caution in the diagnosis of obstruction. A dilated ureter is a common finding after transplantation, and the swelling of the ureter and pelvis that occurs in acute rejection (*15*) may cause an appearance of obstruction and may be so diagnosed as the cause of the patient's anuria or oliguria unless the perfusion stage of the study is examined.

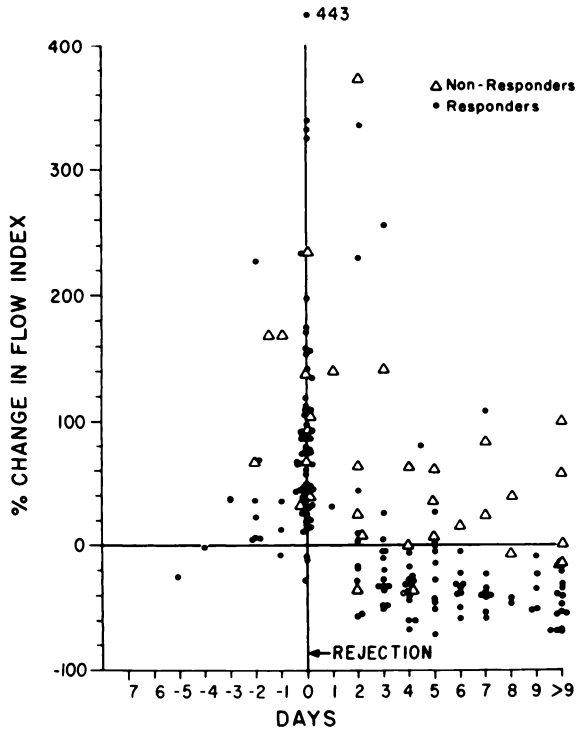


FIG. 9. Relative change in perfusion index associated with rejection.

For a method of investigating renal transplants to be suitable for routine use it must be safe, with no morbidity or mortality; rapid, as the patients are frequently ill; sensitive; and capable of being repeated on at least alternate days (anuric patients are dialysed on alternate days). The result must be available on the same day to be clinically useful. The method must also be able to resolve the various pathophysiologic processes (often multiple) that may affect a renal transplant.

We have found that our method meets all these criteria. It is safe, with no morbidity or mortality. It is well tolerated even by ill patients, who can be studied on their beds or in the transplant unit using a mobile gamma camera. It gives good images and can be repeated daily if necessary because of the short-life and high photon flux provided by Tc-99m, which gives good external counts for a given radiation dose to the patient. It is simple and rapid to analyze, as described above, the whole procedure lasting less than 45 min, including interpretation of the study.

In summary, we feel that we have developed a technique that helps to improve the management of the renal-transplant recipient, improving the accuracy of diagnosis, and allowing earlier, more reliable treatment.

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