

Tc-99m DTPA DYNAMIC RENAL SCINTIGRAPHY IN THE EVALUATION OF RENAL TRANSPLANTS: THE IMPORTANCE OF PERFUSION INDEX IN THE DIAGNOSIS OF RENAL ALLOGRAFT REJECTION

Pages with reference to book, From 139 To 148

Qaisar Hussain Siraj, Asma Inam-ur-Rehman, Amin Waqar, Syed Azhar Ahmed (Nuclear Medical Centre, Armed Forces Institute of Pathology, Rawalpindi.)

Mukhtar Hamid Shah, Rauf Iftilthar Ahmed, Mohammad Sadiq, Rehan Burney (D.N.S.R.P. (P.A.E.C), Combined Military Hospital, Rawalpindi.)

Abstract

Sixty patients with transplanted kidneys underwent dynamic renal scintigraphy using Technetium-99m DTPA. The Perfusion Index, in particular was found to be valuable in differentiating between the two major renal transplant complications of acute tubular necrosis and acute rejection. In addition, other complications like outflow obstruction, pararenal fluid collections, leakage, etc., were readily diagnosed with a high degree of accuracy (JPMA 38: 139,1988).

INTRODUCTION

Since the time of the first successful clinical renal transplant in Chicago¹, tremendous progress has been made in the technique. However, major potential complications jeopardise the function of the transplanted kidney as well as the life of the recipient. Since therapy differs for the various underlying conditions, an early definitive diagnosis and, if possible, prognosis must be provided to ensure the health of the transplant patient. Serum creatinine, blood urea nitrogen, and creatinine clearance are helpful, but lack specificity. The radionuclide studies are useful in the evaluation of renal transplants and can provide diagnostic criteria for prerenal, renal, and post-renal causes of acute post-transplant renal failure, as well as for prognosis². Prerenal conditions such as renal artery stenosis, renal conditions such as acute rejection (AR) or acute tubular necrosis (ATN), and postrenal conditions such as obstruction or leakage, which are the most common causes of acute post-transplant renal failure can be differentiated. As a result of the current increase in renal transplant surgery for end term renal failure in Pakistan, a sizeable number of patients are now being referred to the clinical nuclear medicine services for the radionuclide evaluation of the transplants. We present here, our experience of radionuclide studies in the evaluation of renal transplants at the Nuclear Medical Centre, Armed Forces Institute of Pathology, Rawalpindi.

MATERIALS AND METHODS

Patients receiving renal transplants locally as well as a few who had received transplants abroad and later came to us for assessment were evaluated. From April 1986 to May 1987, 98 radionuclide renal transplant studies were performed on sixty patients. Four of these patients had received transplants from cadavers and the rest from live related donors. There were nine females and fifty one males aged 17 to 54 years (mean age = 34.7 ± 9.5 yr). Graft survival in these patients ranged from one day to six years. The study was carried out using a modern large field of view gamma camera fitted with a low energy general purpose parallel hole collimator and linked to a dedicated On-line computer (Nova 4C). The patient was positioned under the camera so as to include the aortic bifurcation, the renal transplant,

and the bladder. Tc-99m DTPA was injected in a bolus dose of 6 mCi. The study was recorded on the computer, using a frame rate of 1 frame per second for the first 30 sec followed by 30 sec frames for the next 30 minutes. A 64x64 matrix was used, using word mode. In some patients images at 1-2 hr or later after injection were also recorded. Regions of interest over the iliac artery (distal to the transplant), the transplant (excluding any portions overlying the artery), and a background area were defined from the computer derived data, for analysis (Figure 1).

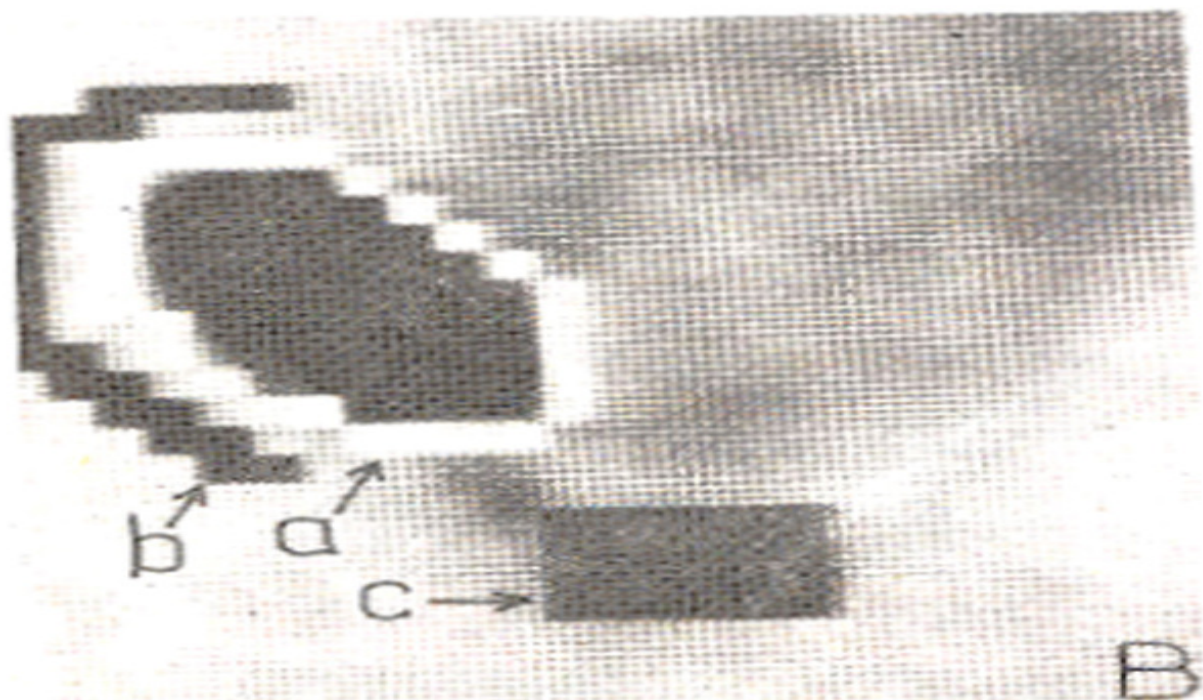
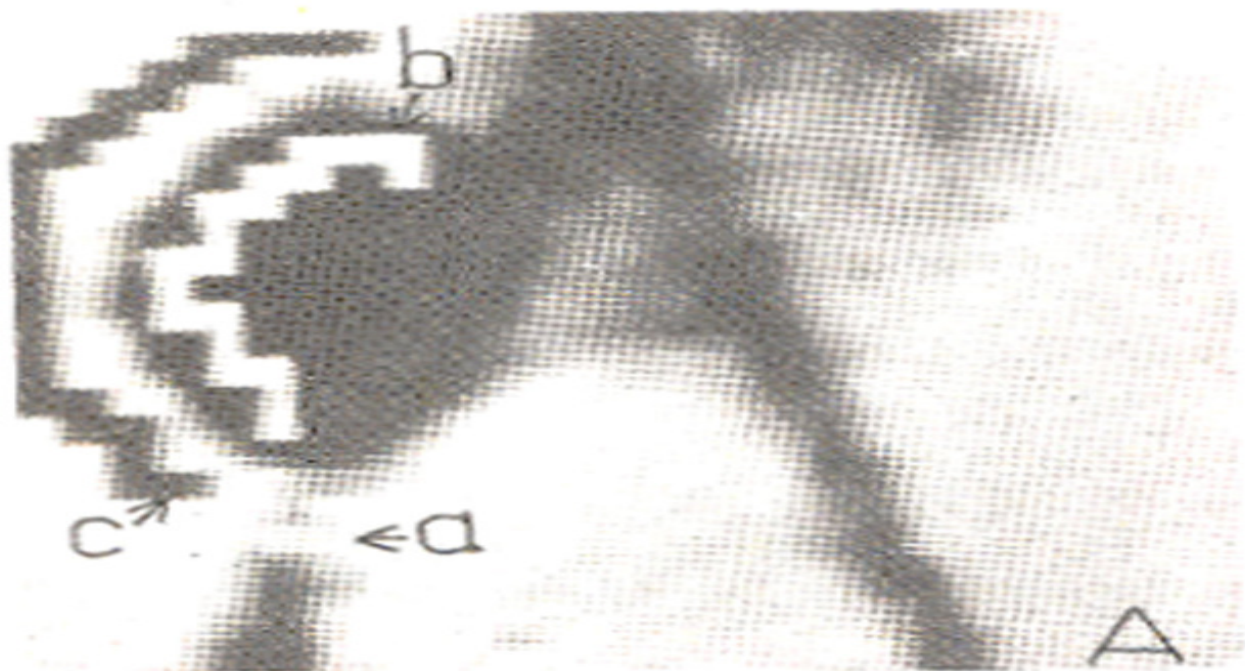


Figure 1. Regions of interest (ROI) for quantitative analysis.

**A. Perfusion Index ROIs drawn on iliac artery (a), renal cortex (b), and background (c).
B. Renogram ROIs drawn on kidney (a), Background (b), and bladder (c). Im.**

Activity-time curves for these regions were generated after subtraction of the background activity. Visual interpretation of the analogue images were correlated with the computer generated data and physiologic parameters like renal perfusion, selective renal uptake of the radio-pharmaceutical, transit time through the kidney, and clearance time of the radioactivity from the kidney, were evaluated.

Clearance was evaluated from the ratio of renal radioactivity to adjacent background radioactivity in the 1 mii image, because at this time the radioactivity cleared by the kidney is unlikely to have passed beyond the renal parenchyma into the collecting system. Perfusion index (PI), an index of relative renal blood flow, was obtained from the ratio of the areas under the arterial and renal curves during the first pass of radioactivity, by using the method described by Hilson³ (Figure 2).

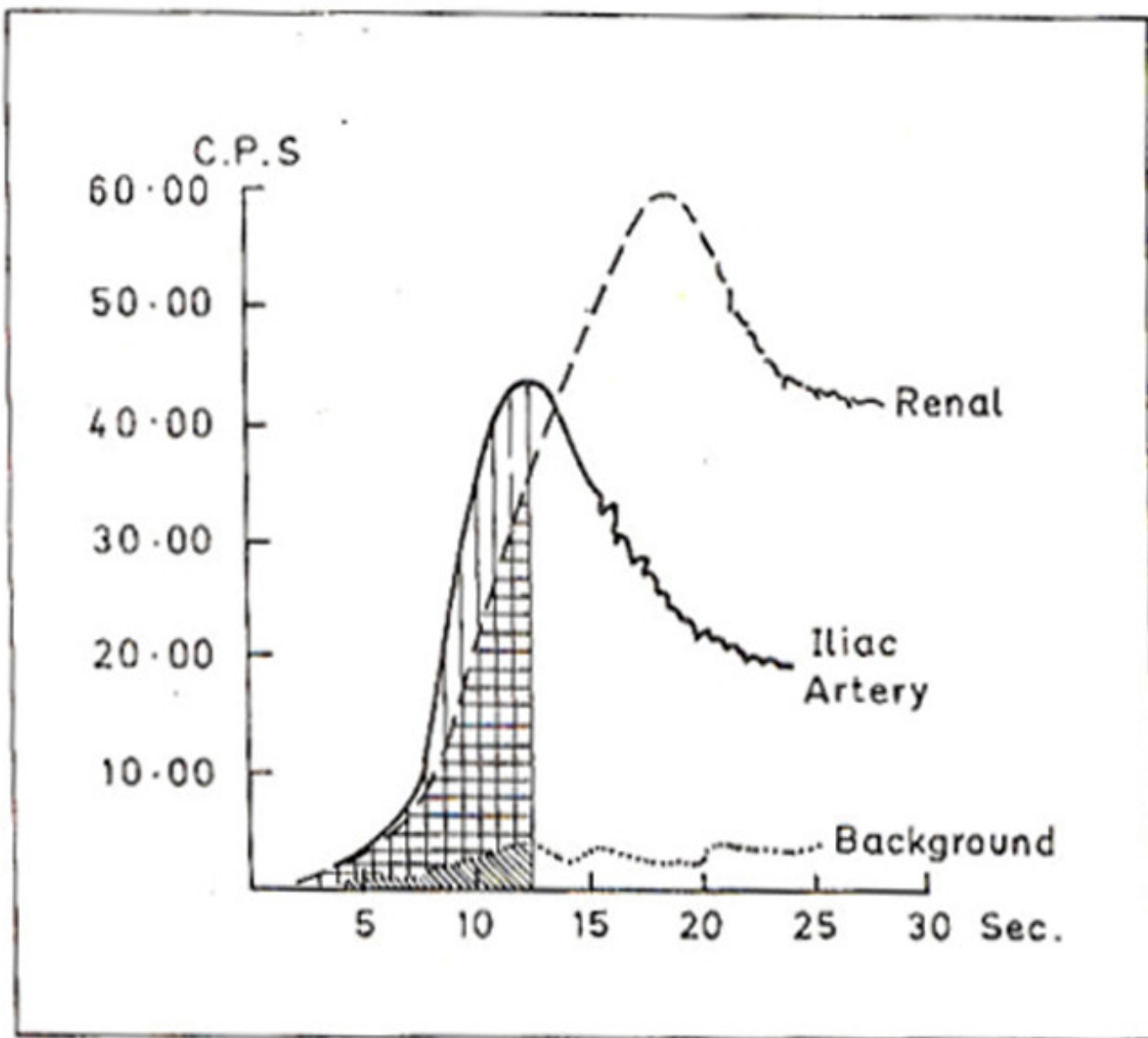


Figure 2.

$$\text{Perfusion Index} = \frac{\text{Area under the arterial curve}}{\text{Area under the renal curve}} \times 100$$

Each patient underwent a standard comprehensive diagnostic workup, including: history and physical examination, serial haematologic analysis, renal and liver function tests, urinalysis and urine cultures, as well as renal ultrasonography etc. Final diagnosis of the renal allograft status was based on clinical grounds aided by laboratory data and serial scintigraphic studies.

RESULTS

On the basis of all the available data including the radionuclide studies, the patients were divided into 5 groups. Those with normally functioning transplants (group 1), with acute tubular necrosis (group 2), with rejection (group 3), with urinary tract infections (group 4), and those with outflow problems (group 5). Figure 3 shows the range of PI values in various groups. The PI values (mean and s.e.m) for groups 1-5 were 1383 ± 26 , 184 ± 49 , 341 ± 103 , 141 ± 27 and 149 ± 17 respectively. There was no statistical difference in perfusion indices in patients with stable graft function and those suffering from acute tubular necrosis, ureteral obstruction or nephropathy. There was however, a significant increase ($P < 0.001$) in PI in patients with acute rejection.

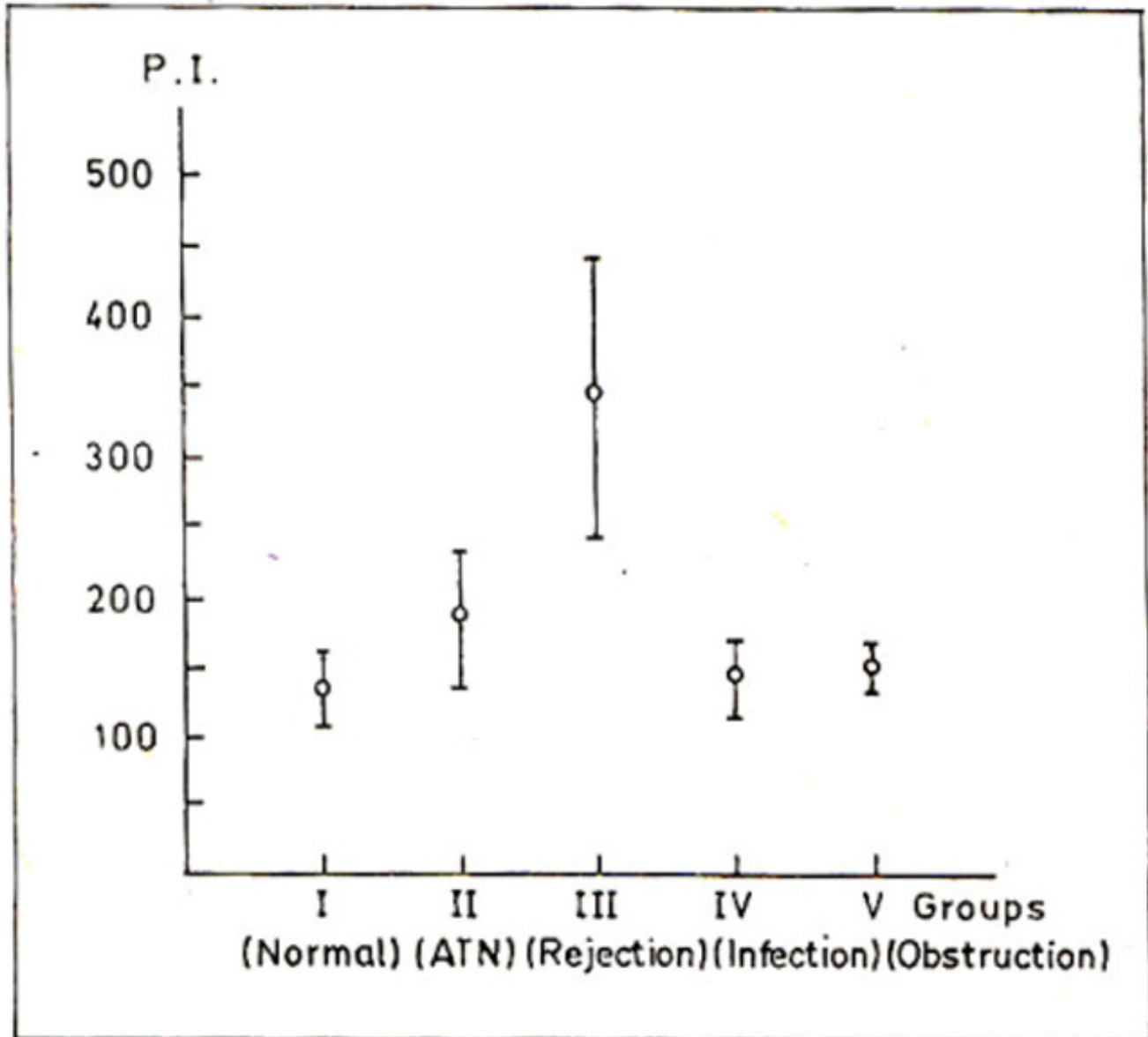
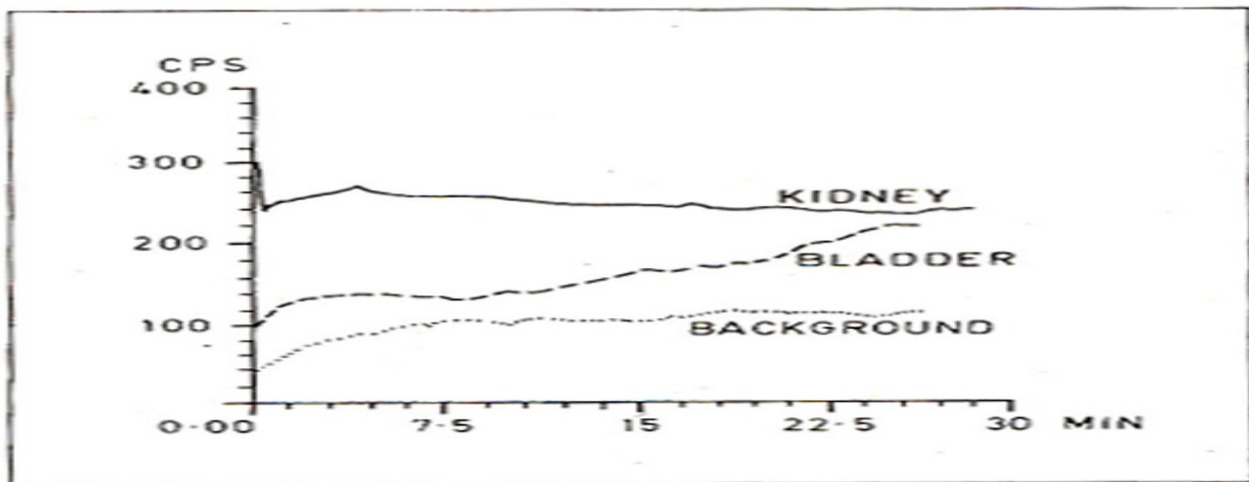
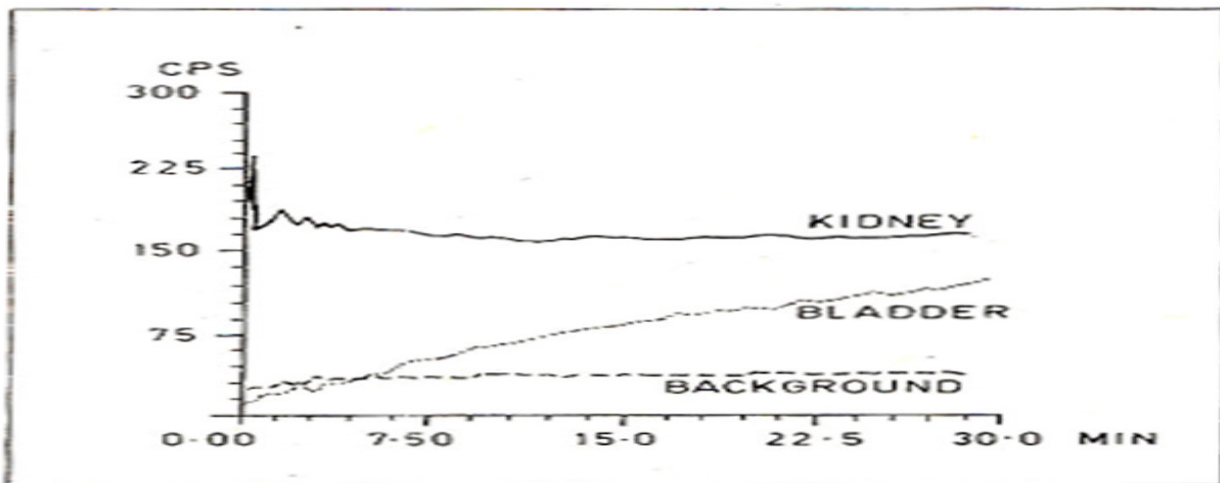
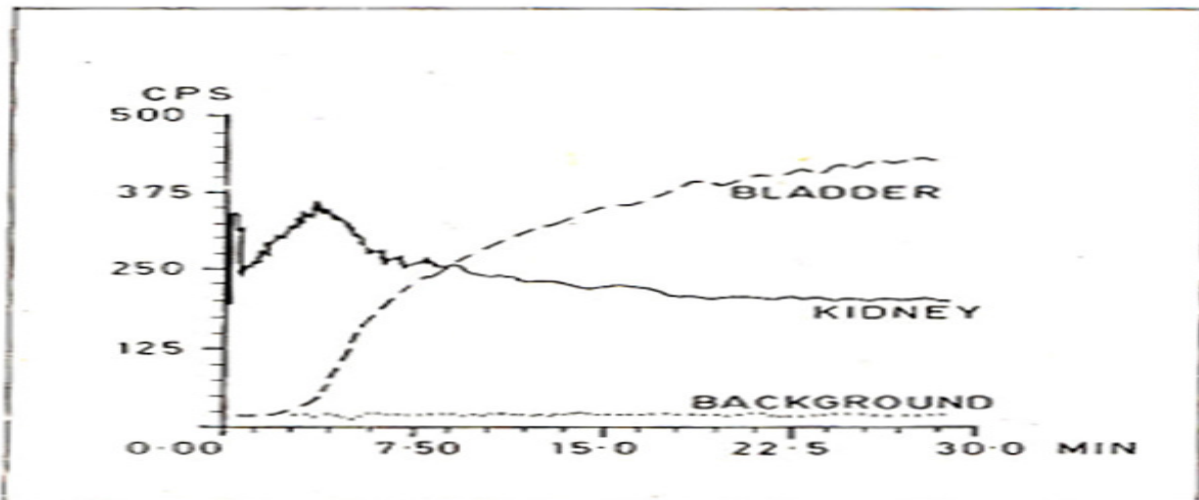


Figure 3. Perfusion indices (mean and s.e.m) derived from analysis of renograms of transplant recipients in different groups of patients.

Figure 3 shows the difference in perfusion in a kidney with AR as compared to a normally functioning transplant. All of the patients in Group 1 showed a renogram curve peaking at 3 to 6 min with steep slopes (Figure 4a),



(c)
Figure 4. (a) Renogram of a normally functioning renal transplant. (b) Renogram of a case of ATN. (c) Renogram of a case of rejection.

good selective accumulation of the radioactivity in the transplanted kidney at 2 min, and rapid clearance of the background activity (Figure 5).

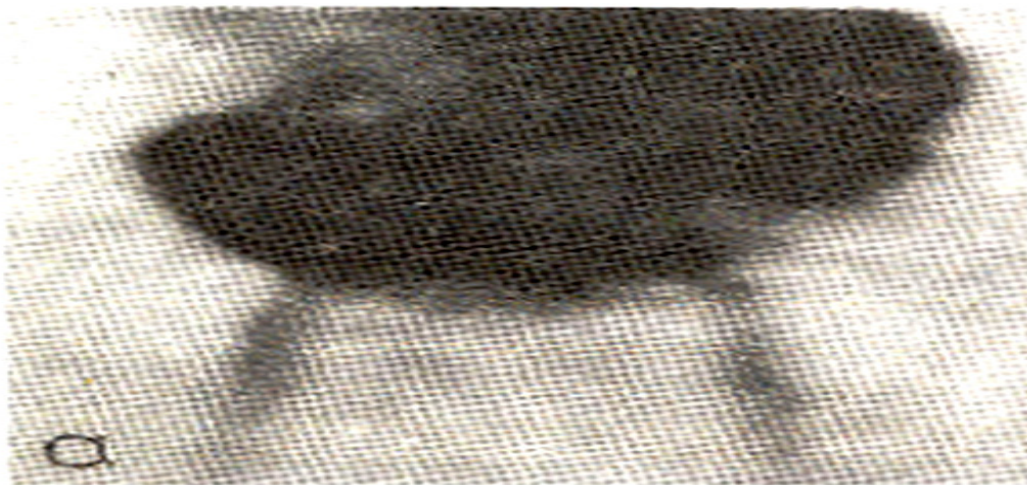


Figure 5. Sequential scintigraphs of a normal transplant showing (a) perfusion at 0–30 sec, (b) selective uptake at 2 min, and (c) excretion at 5 min.

In 8 patients with elevated BUN/Creatinine levels, scintigraphic assessment showed normally functioning transplants. Rapid return of BUN levels to normal were subsequently seen in 6 patients while in 2 patients error in BUN results was correctly predicted. ATN was diagnosed on the basis of the scintigraphic findings and was confirmed clinically by exclusion i.e. all other possible complications

were ruled out; and by the subsequent clinical and scintigraphic course of progressive improvement in the renal function. Thirty one scintigraphic studies demonstrated 19 episodes of ATN in 18 patients. The mean time since transplant in this group was 16 ± 16 days. The renal scintigraphs of the patients with ATN showed mildly reduced to good perfusion, poor clearance of background activity, varying degrees of delayed and diminished selective uptake of the radiotracer, and late appearance or non-appearance of activity into the collecting system (Figure 6).

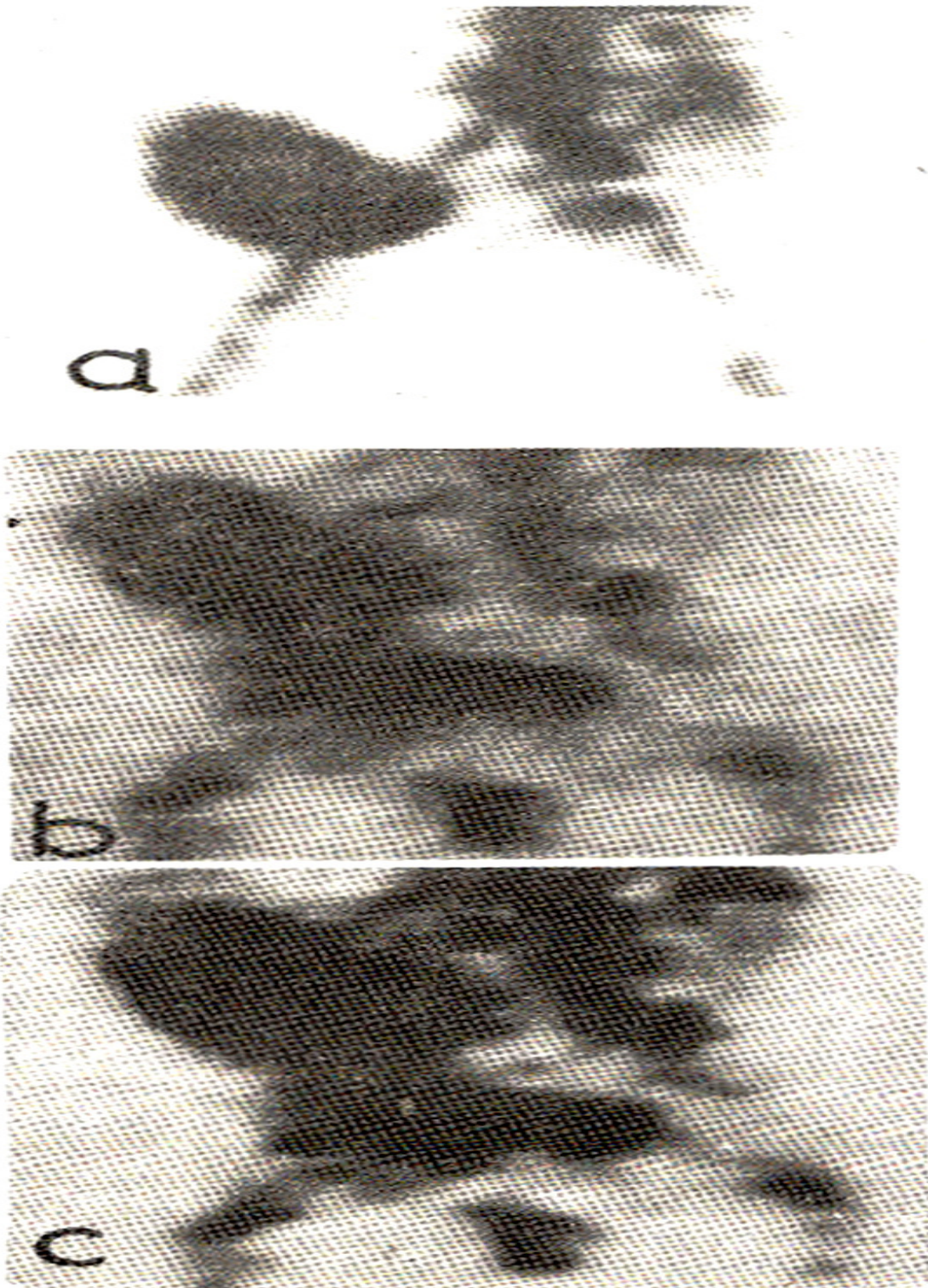


Figure 6. Sequential scintigraphs of a transplant with ATN showing (a) perfusion at 30 sec, (b) selective uptake at 2 min, and (c) excretion at 20 min.

The renogram curves ranged from those with delayed and blunted peaks with poor slopes to almost flat curves (Figure 4b). The severity of the scan and renographic appearances were seen to be in proportion to the clinical degree of the ATN status. Often a fairly good renal image at 2 to 5 min. was seen representing the blood pool rather than selective uptake, followed by fading of the renal image with

rising background levels. Acute rejection was diagnosed scintigraphically on the basis of reduced perfusion with a rise in the perfusion index, when a baseline PI was available, or by a high perfusion index, together with commensurate reduction in both perfusion and clearance. The diagnosis was confirmed by the clinical picture, ultrasound appearances when available, subsequent response to therapy, as well as serial scintigraphic studies. Fifteen scintigraphic studies documented 8 episodes of rejection in 7 patients. The renal scintigraphs obtained in patients in rejection showed moderately reduced to poor perfusion, with commensurately reduced clearance and selective uptake. Often renal concentration of the tracer was sufficient to permit visualization of the renal calyces and pelvis, and varying amounts of tracer depending upon the degree of rejection appeared in the urinary bladder. (Figure 7).

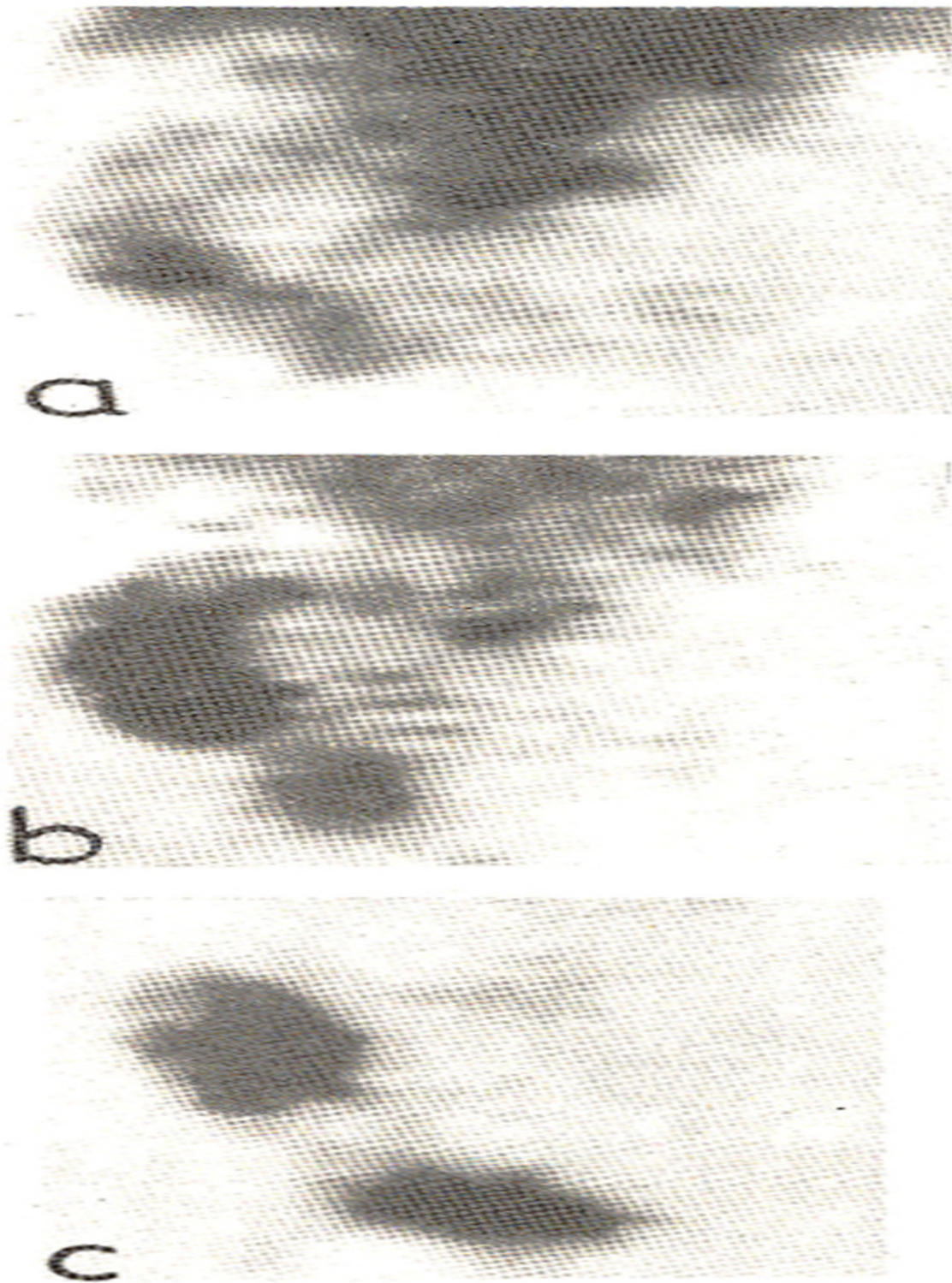


Figure 7. Sequential scintigraphs of a transplant with rejection showing (a) perfusion at 30 sec, (b) selective uptake at 2 min, and (c) excretion at 20 min.

The renogram curves ranged from low amplitude curves with diminished slopes to almost flat curves. However, wherever a peak could be defined, no delay in time to peak was noticeable. The renogram curves of the patients with moderate to severe rejection showed sharper peaks and steeper slopes as compared to the renogram curves of the patients with ATN, for the same degree of diminution in renal

function. The mean time since transplant in this group of patients was 60 ± 55 days indicating its generally late occurrence. Figure 4 (c) shows a representative renogram of a patient with acute rejection. Obstruction was documented on scintigraphy in 6 cases. Four showed mild to moderate degrees of obstruction with delayed renogram peaks, slow drainage of the tracer from the transplant, and ureteric dilatation. One patient manifested severe obstruction 10 wk. after the transplant operation, with a rising renogram curve. The obstruction was relieved by a resection of the stenotic distal, ureter and reimplantation. After the second operation he developed ATN which was diagnosed on scintigraphy 5 days postoperatively. Another patient showed partial obstruction to outflow of tracer from the transplant with a large photodeficient area inferior to the transplant on the 7th postoperative day. Ultrasound studies showed a large fluid collection causing the obstruction. Significant urinary tract infection (UTI) was diagnosed in 6 cases on the basis of urinalysis. One patient was in AR, while a second had ATN. On recovery from ATN, UTI still persisted. The renogram curves in the uncomplicated cases were generally normal, although sluggish outflow was seen in two cases. Perfusion and selective uptake were normal. One patient showed complete renal artery occlusion. No perfusion or selective uptake was seen in the transplant. A subsequent injection of Tc-99m stannous colloid also showed absence of perfusion with no tracer uptake in the transplant (Figure 8).



Figure 8. Tc-99m stannous colloid scan of a case of vascular occlusion.

This confirmed the diagnosis of renal artery occlusion and excluded the possibility of severe rejection. Four patients in this series showed persistently poor perfusion and uptake in a portion of the transplanted kidney representing confirmed operative trauma to a branch of the renal artery (Figure 9).

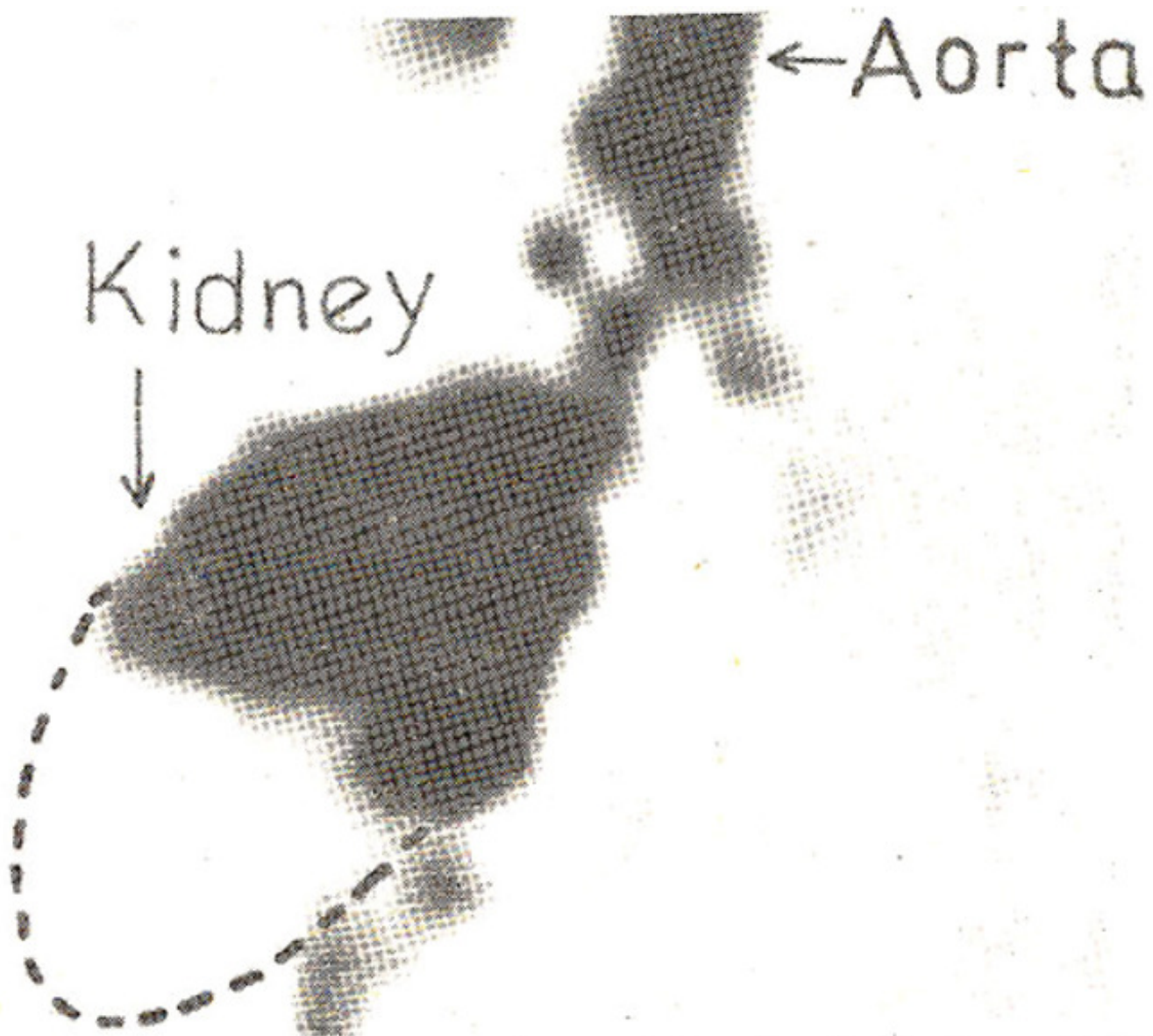


Figure 9. Absent perfusion and function in the lower half of renal transplant.

One such patient with a poorly perfused upper segment subsequently developed watery discharge from the operation wound on the 11th postoperative day. The scintigraphic study showed extravasation of activity from the renal pelvicalyces and accumulation of activity lateral to in the same study in which the urinary fistula was diagnosed.

DISCUSSION

Although the majority of transplanted kidneys are passing urine on return from the operating theatre, a proportion are anuric. In addition, anuria or severe oliguria may develop in the early or late postoperative period. The diagnostic role of radionuclide methods in the evaluation of renal transplant complications is well established⁴⁻⁶. The various radionuclide techniques which have been applied to the assessment of renal transplant problems include I-131 Hippuran renography^{7,8}, Tc-99m sulphur

colloid studies⁹, In-111 labeled leukocytes¹⁰ or platelets¹¹, Gallium citrate¹², radioiodinated fibrinogen¹², and Tc-99m DTPA studies^{3,13-15}. The Tc-99m DTPA studies have the apparent advantages of decreased study time, shorter biological half life, and improved anatomical detail of the collecting system, perirenal area and vasculature¹⁶. Additional parameters obtained from the DTPA study provide valuable diagnostic criteria in differentiating between the two common post transplant complication of ATN and rejection^{15,17,18}. The improved anatomical detail provides better assessment of the excretory dynamics in assessing post renal obstruction and leakage, and clearer visualization of extrarenal collection^{19,20}. The majority of the transplanted kidneys show an element of ATN. This may manifest itself as severe oliguria from the time of return from the operating theatre, or its onset may be delayed. The duration of oliguria from ATN has been reported from 2-31 days but longer periods of ATM are compatible with good graft function²¹. The findings of Tc-99m DTPA studies are diagnostic³. Generally ATN is characterized by relatively normal blood flow whereas rejection is characterized by poor blood flow; and this difference in blood flow can be demonstrated by the proper bolus injection of a technetium labelled radiopharmaceutical. In our series the kidneys with ATN were seen to be moderately well perfused with the maximum PI in each ATM episode between 117-275 in 17 out of 19 cases, with little or no subsequent selective parenchymal accumulation of tracer and poor clearance.

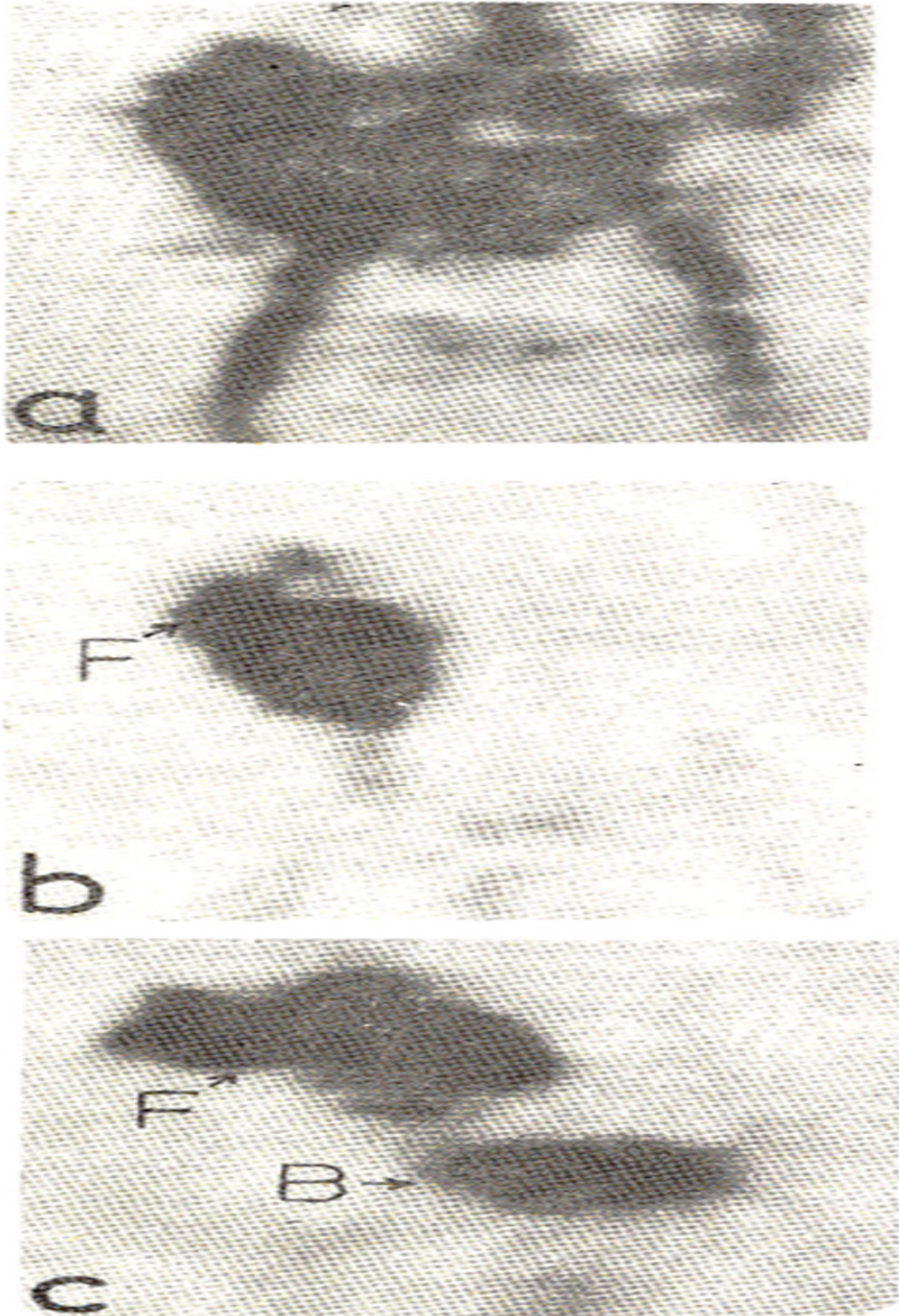


Figure 10. Sequential scintigraphs of a transplant with a urinary fistula showing (a) perfusion at 0–30 sec, (b) selective uptake at 2 min, and (c) excretion at 20 min. Note the activity in the fistula (F) and bladder (B).

The mechanism of relatively preserved renal perfusion in the face of decreased clearance in patients with ATM is unknown. Ischaemic damage to renal tubular cells may cause some cells to slough into the tubular lumen and secondarily cause obstruction²²; this process seems to be the major cause of

oliguria²³. Ischaemic damage also increases the permeability of the tubular basement membrane, allowing molecules that are filtered to diffuse back into the vascular compartment²². Serial imaging in patients with ATM was seen to demonstrate continuing perfusion with improvement in P1 and gradual return of function. Indeed long term follow-up of patients in ATM by Kjellstrand et al. demonstrated that they did not differ prognostically from patients who experienced immediate renal function²⁴. Acute rejection crises continue to pose a serious threat to patients receiving renal allografts, and are among the most difficult problems for those concerned with the management of such patients. Correct diagnosis of the transplant status is essential for initiation of the appropriate treatment, as undertreatment may result in the loss of the graft and overtreatment may endanger the life of the patient due to complications of immunosuppression. The diagnosis of acute rejection may, however, be hampered by a paucity of definitive clinical signs or symptoms, as well as by a lack of definitive biochemical or radiological diagnostic modalities capable of detecting early acute rejection and differentiating it from the many other conditions that can adversely affect renal function²⁵. Classic signs and symptoms of acute rejection; including decreased renal function, graft tenderness, fever, oliguria, and/or hypertension are frequently absent in most cases, and frequently occur in the course of graft ureteral obstruction, pyelonephritis, or drug induced renal dysfunction²⁶. Serum creatinine, blood urea nitrogen, and creatinine clearance are helpful, but lack specificity. The differentiation of acute tubular necrosis from rejection has been difficult and often uncertain even with the combination of clinical and laboratory information. It is generally agreed that damage to the microcirculation of the kidney occurs early in the course of acute rejection^{27,28}. These studies have shown that obstruction and disruption of peritubular capillaries and venules occur in association with infiltration of the allograft by lymphoblasts, and are one of the earliest manifestations of acute rejection. Further progression of AR produces fibrinoid necrosis of the walls of arterioles and small arteries. The deposition of fibrin and platelets on the damaged intima leads in turn to further obstruction of the cortical microcirculation and renal ischaemia and necrosis. The observation that microcirculatory changes precede functional derangement during AR is the basis for the usefulness of radionuclide renal studies in the evaluation of graft dysfunction after renal transplantation^{3,13}. The identification of a decreased blood flow provides a valid point that can be easily measured in any nuclear medicine laboratory. The Tc—99m DTPA study shows a rise in perfusion index, corresponding to the fall in renal blood flow which has been shown to occur as one of the earliest changes in rejection²⁹. Further refinement of this technique has established that selective analysis of cortical perfusion will enhance the accuracy of Tc—99m DTPA studies for the early detection of AR and in differentiating AR from non-immunological causes of renal allograft dysfunction. Anaise et al. have reported an accuracy of 94% in diagnosing AR using the cortex PI¹⁵. In our series the maximum P1 recorded during each rejection episode ranged between 234 to over 500, with lower values recorded in the very early stages and in the recovery phase. The decrease in renal function associated with rejection was evident on scintigraphy by reduced parenchymal accumulation and excretion of tracer. However, for the same degree of reduced blood flow, rejection was seen to generally exhibit a much better parenchymal accumulation than in ATN. This was reflected also in the renogram curve which for the same degree of renal dysfunction displayed better curve patterns with the significant earlier time to peak in cases of rejection as compared to cases of ATN. In patients with renal transplants, one of the most difficult periods clinically is between 4 days and 3 weeks when ATN and rejection may both occur³⁰. Serial radionuclide studies over several days to weeks proved to be particularly helpful in distinguishing ATN from rejection. ATN usually improves with time after the ischaemic insult and thus continuing perfusion with improvement in P1 was always seen, despite relatively poor parenchymal accumulation. In rejection the diminution of perfusion was persistent over a longer time period and often progressive. A positive response to therapy was heralded by a falling PI. In summary, our data support the hypothesis that decreased clearance with relatively preserved

perfusion in Tc—99m DTPA studies is sufficiently specific to be useful in differentiating ATN from the other causes of decreased renal clearance¹⁷. Acute renal failure attributable to postrenal conditions such as obstruction of the ureters or urinary extravasation can be readily diagnosed by scintillation camera studies. Obstruction is heralded by a delayed radionuclide uptake and peak count rate, with progressive accumulation of the radiopharmaceutical in the excretory system. The administration of furosemide (lasix) may alter the accumulation pattern of the radiopharmaceutical, and hence be useful for differentiating confusing conditions. Lower tract obstruction from haematoma, lymphocele, distal ureter necrosis, or occlusion of the ureteroneocystomy can be identified by the prolonged retention and excessive pelvic accumulation of the tracer. It is worth noting that obstruction of a transplanted kidney frequently presents with only subtle scan changes, i.e., a slight delay in excretion or a slight excess of pelvic activity. This is probably due to the fact that the obstructions we seek to detect are acute, often present for only hours and at most days. The more dramatic hallmarks such as massive pelvicalyceal distension, loss of cortex, or megaloureter do not have time to develop³¹ (Figure 11).



Figure 11. An excess of renal pelvic activity as a result of partial obstruction.

We conclude that the simple and non-invasive Tc-99m DTPA dynamic renal scintigraphy is an accurate, reliable, repeatable, and the single most important investigation for the assessment of the renal transplant status. Visual assessment of the scintigraphs aided by quantitative parameters like the perfusion index and the quantitative analysis of the renogram curves provide a wealth of data enabling us to accurately assess and differentiate between the major transplant complications.

REFERENCES

1. Lawler, R.H., West, J.W., McNulty, P.H., Clancy, E.J. and Murphy, R.P. Homotransplantation of the kidney in the human; a preliminary report. JAMA., 1950; 144 : 844.
2. Schlegel, J.U. and Lang, E.K. Computed radionuclide urogram for assessing acute renal failure. AJR., 1980; 134:1029.
3. Hilson, A. 1. W., Maisey, M.N., Brown, C.B. et al. Dynamic renal transplant imaging with Tc-99m DTPA (Sn) supplemented by a transplant perfusion index in the management of renal transplants. J. Nucl. Med., 1978; 19 : 994.
4. Rosenthal, L., Mangel, R., Lisbona, R. and Lacourciere, Y. Diagnostic applications of radio-pertechnetate and radiohippurate imaging in post-renal transplant complications. Radiology, 1974;111: 347.
5. Dubovsky, E.V., Logic, J.R., Dietelm, A.G., Balch, C.M. and Tauxe, W.N. Comprehensive evaluation of renal function in the transplanted kidney. J.Nucl. Med., 1975; 16: 1115.
6. Weiss, E.R., Bland, W.H., Winston, MA., Harten bower, D.L., Koppel, M. and Thomas, P.B. Scintillation camera in the evaluation of renal transplants. J. Nucl. Med., 1970; 11: 69.
7. Collins, J.J. Jr., Pizak, L. F. Jr., Tamvakopoulos, S.K. and Wilson, E.R. Serial renograms after kidney transplantation in man. Surg. Forum, 1963;14 :217.
8. Blaufox, M.D. and MenU, J.P. Evaluation of renal transplant function by iodohippurate sodium 1 -131JAMA.,1967;202 :575.
9. Frick, MY., Loken, M.K., Goldberg, M.E. and Simmons, RI. Use of 99m Tc-Sulfur colloid in evaluation of renal transplant complications. J. Nucl. Med., 1976; 17 :181.
10. Frick, MY., Henke, C.E., Forstorm, L.A., Simmons, R. A., McCullough, J. and Loken, M.K. Use of 111 In-labelled leukocytes in evaluation of renal transplant rejection. Clin. Nucl.Med., 1979;4 : 24.
11. Smith, N., Chandler, S., Hawker, R. J., Hawker, L. M. and Barnes, A.D. Indium-labelled autologous platelet as diagnostic aid after renal transplantation. Lancet , 1979; 2 : 1241.
12. George, E.A., Codd, J.E., Newton, W.T., Henry, RE. and Donati, R.M. Comparative evaluation of renal transplant rejection with radioiodinated fibrinogen 99mTc-sulfur colloid and 67 Gacitrate. J. Nucl. Med., 1976; 17:175.
13. Preston, D.F. and Luke, R.G. Radionuclide evaluation of renal transplants. JJ4ucL Mcci, 1979; 20 : 1095.
14. Kiepf, R.F., Kirchner, P.T. and Gerber, R.F. Clinical application of kidney to aortic blood flow index. J. Nucl. Med., 1976; 17: 537.
15. Anaise, D., Oster, Z.H., Atkins, H.L., et al. Cortex perfusion index: a sensitive detector of acute rejection crises in transplanted kidneys. J. Nucl. Med., 1986; 27: 1697.
16. Staab, E.V., Jones, T.M., Partain, C.L., et al A comparison of 99mTc-DTPA and 1-131 OIH in the evaluation of renal transplant function. (Abstr). 3. Nucl., Med., 1976; 17 : 537.
17. Shanahan, W.S. M., Kllngensmith, W.C. and Well, R. 99m-Tc DTPA renal studies for acute tubular necrosis; specificity of dissociation between perfusion and clearance. AJR., 1981; 136 : 249.
18. Singh, A. and Cohen, W.N. Renal allograft rejection; sonography and scintigraphy. MR., 1980;135: 73.
19. Bingham, J.B., Hilson, A.J.W. and MaAey, M.N. The appearances of renal transplant lymphocoeles during dynamic renal scintigraphy. Br. J. Radiol., 1978;51 : 342.
20. Spigos, D. G., Tan ,W., Pavel, D.G., Mozes, M., Jonasson, O. and Capek, V. Diagnosis of urine extravasation after renal transplantation. MR., 1977; 129 : 409.
21. Oliver, DO, In Kidney transplantation; principles and practice. Edited by Morris, P. J. New York, Grune and Straton, 1979, p. 58.
22. Donahue, J.F., Venkatachalam, M.A., Bernard B. B. and Levinsky, N.G. Tubular leakage and obstruction after renal ischaemia; structural- functional correlations. Kidney Int., 1978; 13 : 208.

23. Arendshorst, W., Finn, W.F. and Gottschalk, C.W. Micropuncture study of acute renal failure following temporary renal ischaemia in the rat. *Kidney Int.*, 1976; 10 (Suppl. 6): 5100.
24. Kjellstrand, C.M., Casali, R.E., Simmons, R.L., Shideman, J.R., Buselmeier, T.J and Najarian, J.S. Etiology and prognosis in acute post-transplant renal failure. *AJM.*, 1976; 61 : 190.
25. Winchester, J.F., Gelfand, M.C., Foegh, M.L., Heifrich, G.B. and Schreiner, G.E. Early indicators of renal allograft rejection. *Kidney Int.*, 1983; Suppl. 14: S-34.
26. Williams, G.M. in *kidney transplantation; principles and practice*. Edited by Morris, P.J. New York, Grune and Stratton, 1984, p. 335.
27. Tourville, D.R., Kim, D.U., Viscu, R., et al. Anticipation of renal transplant failure by postanastomosis biopsy and immunofluorescence. *Transplant. Proc.*, 1977; 9 : 91.
28. Porter, K.A. Morphological aspects of renal homograft rejection. *Br. Med. Bull.*, 1965; 21:171.
29. Hollenberg, N.K., Retik, A.S., Rosen, S.M., Murray, J.R., and Merrill, J.P. The role of vasoconstriction in the ischaemia of renal allograft rejection. *Transplantation*, 1968; 6 : 59.
30. Stazl, T.E. In *Experience in renal transplantation*. Philadelphia, Saunders, 1964, p. 142.
31. Strauss, H.W., Kirchener, P.T. and Wagner, H.N. Jr. *Diseases of the kidney*. Edited by Early, L. E. and Gottschalk, C.W. Boston, Little Brown, 1979, p. 160.