Radionuclide Evaluation of Renal Transplants

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Chronic renal failure caused by hypertension or by parenchymal kidney disease is a very common global health problem. Patients with chronic renal failure have two therapeutic options, dialysis and transplantation, of which transplantation has become a preferred modality. This review article is an update of a more comprehensive previous review (*Semin Nucl Med,* 181-198, 1988) and concentrates on the changes that have taken place in this field in recent years. These changes comprise new criteria for the selection of transplant candidates, newer techniques for the diagnosis of medical and surgical complications after transplantation, the use of new tracers (Tc-99m MAG₃), and new antirejection regimens.
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RENAL TRANSPLANTATION has become the preferred treatment for end-stage renal disease because survival is longer than with dialysis.[1] Recently reported patient survival rates for cadaver grafts were 94% for recipients of a first or second graft and 92% for patients with multiple grafts.[2] The 1-year survival rate for a transplanted cadaver kidney was 80%, 74%, and 66% for first, second, and multiple transplants, respectively. Results were even better for living-related donor grafts, with graft survival rates of 95% for human lymphocyte antigen (HLA): identical grafts and about 90% for 1-haplotype–matched grafts. The projected graft half-lives were 26 years for HLA-identical grafts and 12 to 14 years for single haplotype-mismatched grafts.

Transplantation technology has progressed greatly since the first successful kidney graft performed 40 years ago between monozygotic twins.[3] Advances have occurred in methodology for identifying tissue antigens and antibodies.[4,5] New drugs are available for immunosuppression. Newer immunosuppressive agents currently in clinical trials include FK-506, Rapamycin, RS-61443, and 15-deoxysperqualin.[6] Monoclonal antibodies are also used to modify the immune response. OK-T3 is available for routine use and other monoclonal antibodies are undergoing trials. These agents can be used in rescue protocols to treat otherwise unresponsive rejection, and may ultimately lead to the development of steroid-free maintenance immunotherapy.

Many factors effect the long term results, including the quality of the transplanted kidney and the socioeconomic status, age, race, and general health of the recipient.[7] Chronic allograft nephropathy (chronic rejection [CR]) limits graft survival, but it is poorly understood and is not responsive to currently available therapy. Hypertension and complicating infections such as cytomegalovirus also limit graft survival.

COMPLICATIONS OF RENAL TRANSPLANTATION

Acute tubular necrosis (ATN), acute rejection (AR), and CR are the complications most commonly seen in referrals to Nuclear Medicine. ATN is seen in the immediate posttransplant period in a high percentage of cadaver grafts, but only infrequently in transplants from living related donors. Acute rejection typically occurs at least 4 or 5 days after transplantation. It is most common in the first year, but can occur at any time, particularly with lapses in immunotherapy. CR typically occurs after a period of 1 year, but episodes of AR can lead to residual impairment of function that is indistinguishable from CR on radionuclide studies. A number of less common complications can also be identified on radionuclide studies. These complications tend to occur at characteristic time intervals after transplantation, as indicated in Table 1.[8,9]

The immunologic complications are related to the quality of HLA matching between donor and recipient.[4,5] Best results are obtained in HLA-identical siblings and in cadaver grafts with HLA A, B, DR matches. When such close matching is not obtained, AR is common. It is graded histologically from grade 1 (interstitial

Table 1. Complications After Transplantation Pertinent to Nuclear Medicine

Complication	Most Frequent Time of Occurrence	Comments
Surgical		
Wound infection	Within first few weeks	Surgical and medical treatment
Abscess	Few days/weeks	Drainage
Hematoma	Within hours to days	Drainage
Lymphocele	Second to fourth month	Drainage, sclerosing agents
Urine leak	Within hours to days	Surgical repair
Obstruction		
Intrinsic pressure	Days, months, years	Clots, scars, calculi surgical repair
Extrinsic pressure	Days, months, years	Lymphocele, hematoma, drainage
Renal artery stenosis	Any time	Medical therapy, PTA or surgery
Medical		
Ischemic damage (ATN)	Present at time of kidney transplantation	Cadaveric Tx-common Resolves without therapy
Immunologic hyperacute	Within minutes to hours	Preformed antibodies, irreversible—rare
Acute	Rapid development after several days, most common during first three months	Predominantly cell mediated, reversible with therapy
Chronic	Usually after a few months or years, slowly developing	Humoral, irreversible
Other		
Cyclosporin	While on medication (high plasma levels)	Improvement after withdrawal
Recurrent disease	Any time	Biopsy

mononuclear infiltration), through grade 2 (focal severe tubulitis, mild to moderate intimal arteritis), to grade 3 (severe intimal arteritis with fibrinoid change, necrosis of medial smooth muscle cells, focal infarction, interstitial hemorrhage).[10] Swelling, pain, and fever are observed clinically. AR develops rapidly and is usually treated successfully.

CR is a slow, irreversible process leading to a gradual loss of graft function.[11] It is graded histologically from grade 1 (interstitial fibrosis and tubular atrophy), through grade 2 (similar but more extensive change), to grade 3 (severe fibrosis with loss of tubules).[10] The mechanism is not well understood, and the presently available antirejection drugs are not very effective.

Hyperacute rejection is seldom seen. Graft failure occurs immediately on transplantation. Within 1 hour, polymorph accumulation is seen in glomerular and peritubular capillaries.[10] Capillary thrombosis then occurs. It is presumably caused by preexisting antibodies that escape detection in pretransplantation screening.

A variety of surgical complications can occur. Vascular complications such as arterial or venous thrombosis, stenosis, arterial-venous fistulae, and pseudoaneurysms can occur either in the immediate postoperative period or later, and are all detectable by radionuclide studies.[12] Obstruction may be either intrinsic (clots, stones, ureteral stenosis) or extrinsic (lymphoceles, hematoma, abscesses) and are similarly detectable.[13] Urine leaks typically occur soon after transplantation and are also seen on radionuclide studies.

Impaired graft function often is caused by multiple contributing causes. AR frequently occurs before ATN has fully resolved. Cyclosporin toxicity may be a contributing factor, and it is difficult to identify. The original disease that necessitated transplantation may recur. Function may also be affected by drugs such as antibiotics, angiotensin converting enzyme inhibitors,[14] or radiographic-contrast agents.[15]

Although this chapter deals with radionuclide methods, alternative diagnostic procedures should be kept in mind. Sonography is excellent for detection of perigraft fluid collections and urinary tract obstruction, but to date has not proven reliable for identifying rejection.[16] For identification of stones and stenoses, intravenous urography may be performed with nonionic contrast agents.[15] For vascular complications, arteriograms may be performed with dilute contrast and digital subtraction.[12] CT and magnetic resonance imaging (MRI) can give very useful results in the differential diagnosis of surgical complications, but they currently play a limited role because of their cost.

GENERAL CONSIDERATIONS

Radionuclide diagnostic tests are valuable in renal transplantation because they provide a noninvasive means to evaluate transplant function quickly and quantitatively, while simultaneously screening for a variety of surgical complications. The differential diagnosis frequently requires correlation with the patient's clinical course, current therapy, prior scintigraphic findings, and the results of other diagnostic tests. For example, the scintigraphic findings are quite similar for ATN and AR, so that these two entities are best differentiated by progressive changes on serial studies. A baseline study 1 or 2 days after transplantation is particularly valuable.[9,17]

Only scintigraphic studies are capable of separating function of the graft from residual function of the native kidneys or any remaining prior failed graft. At low levels of graft function, one should not lose sight of the fact that not all of the measured renal function may be attributed to the graft.

Radionuclide measurements of renal function are conveniently divided into three categories corresponding to the classical three phases of the renogram described by Taplin.[18] The first phase corresponds to transit of a bolus of the tracer through the renal blood vessels after bolus intravenous administration and lasts perhaps for 5 seconds. The second phase corresponds to transit of excreted activity through the nephron to the pelvicalyceal system and lasts around 3 minutes. The third phase corresponds to the drainage of the pelvicalyceal system and is typically evaluated by monitoring renal activity for 20 min or longer. Taplin originally called the three phases vascular, tubular, and excretion phases. Later, with the introduction of new concepts, Taplin renamed these the tracer appearance, blood flow, and drainage phases.[18] The time from injection to peak activity was regarded by Taplin as a concept distinct from the three phases, being a measure of renal transit time. We suggest a further revision of the terminology again to coincide with current concepts. We suggest that the three phases be called vascular, tubular, and drainage phases (cautioning the reader that the tubular phase is the phase of the tubular transit, which, depending on the agent, may have nothing to do with

tubular function). Thus, we propose reverting in part to Taplin's original terminology.

VASCULAR PHASE: EVALUATION OF BLOOD FLOW

Data Acquisition

A large field of view camera with low-energy all-purpose collimator is placed over the anterior abdomen in such a way that the abdominal aorta, the graft, and both iliac arteries are included in the field of view. After bolus intravenous injection of Tc-99m pentetate (DTPA) (5 to 15 mCi or 185 to 555 MBq) or Tc-99m MAG$_3$ (3 to 10 mCi or 111 to 370 MBq), the images are acquired in 0.5- to 5-second frames (64 × 64 matrix) for 1 minute. The images are usually displayed as 2- to 5-second frames. Functional images can also be displayed, as described below under analysis. Time-activity curves are generated from regions of interest that include the whole kidney. Visual inspection of 2- to 5-second images establishes arterial patency, and excludes occlusion of the renal artery or its branches. Arteriovenous fistulae and pseudoaneurysms can be detected, but are rare complications. Nonrenal vascular abnormalities are occasionally seen as incidental findings. If a pancreatic graft is present, it too can be evaluated (Fig 1).

There are several methods for quantitative evaluation of the vascular phase.[19-28] The oldest and most widely used are Kirchner's kidney-to-aorta ratio and Hilson's perfusion index.[19,20] These relate renal blood flow to blood flow in the aorta or iliac artery. They can be used with any Tc–99m-labeled agents because only that part of the curve before the peak is used (Fig 2), but the count rate with I–131-labeled agents or with affordable doses of I–123-labeled agents are inadequate. Variations on these indexes can be presented as functional images. The use of functional images avoids the need for drawing regions of interest (ROIs), so that the subjective part of the analysis is performed by the viewer of the image rather than by whomever selected the ROIs.[29] The consultant is not then at the mercy of his technologist or resident. Vascular transit time can be measured by various computer programs and was found to separate ATN from AR both by Rutland[21] and by Chaiwatanarat et al.[28] The above quantities are indexes of
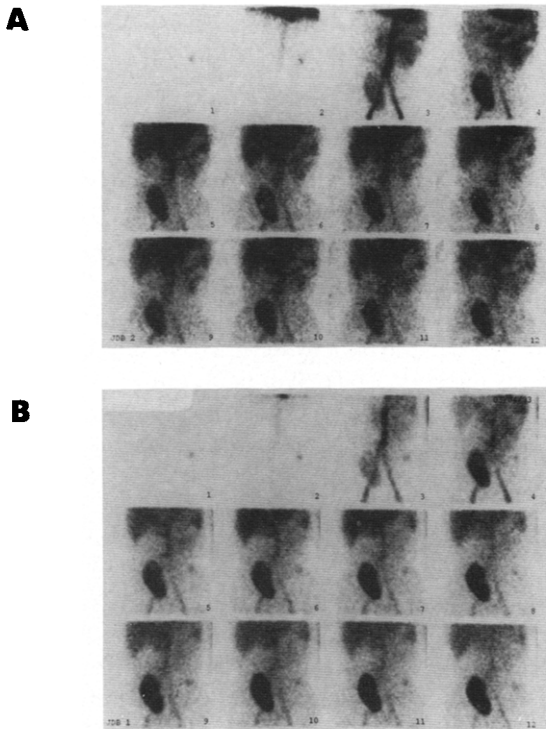
A

B

Fig 1. Perfusion study performed with Tc-99m DTPA (A) and Tc-99m MAG₃ (B) in a patient with normally functioning graft. On Tc-99m DTPA study the perfusion peak over the graft is reached before 10 seconds, after which the activity decreases. Because the tracer has relatively low extraction, the background value stays high. On Tc-99m MAG₃ study because of high tracer extraction, the activity in the graft steadily increases and the background decreases.

vascular transit phase at a higher frame rate than the rest of the study.

Data Analysis

The images are displayed at a frame rate of 1 to 3 minutes for visual inspection. Time-activity curves are generated from a whole-kidney ROI with background subtraction. A bladder time-activity curve is usually generated. Time-activity curves are sometimes generated from subregions of the kidney such as the cortex. If deconvolution analysis is used, then an input curve representative of blood activity is required, which is usually obtained from a ROI
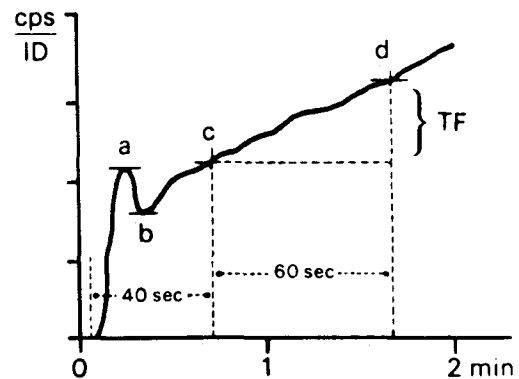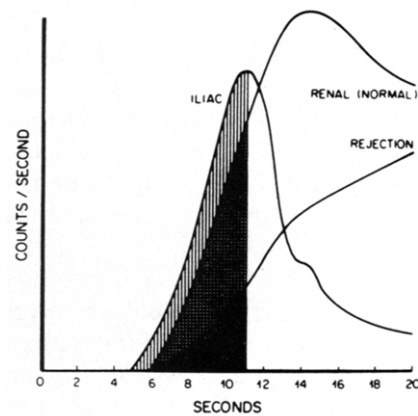

Fig 2. (top) Perfusion time-activity curves derived from graft and iliac artery ROIs using Tc-99m DTPA showing normal and rejection pattern. Hilson's perfusion index (PI) is calculated from the ratio of areas under the arterial and renal curves. (bottom) Perfusion curve from graft ROI performed with Tc-99m MAG₃ using analysis recommended by Bubeck. Transplant perfusion index (TP = a^2/b) is helpful to monitor ATN resolution, whereas transplant function index [TF = (d − c)] reflects changes during rejection.

blood flow rather than direct physiologic measurements. Peters et al[24] described a means of measuring true blood flow as a percentage of cardiac output. This method was validated in animal experiments and has been applied both to adults and to children.

TUBULAR PHASE: EVALUATION OF GLOMERULAR FILTRATION AND TUBULAR SECRETION

Data Acquisition

Data are acquired in 20- to 60-second frames for the duration of both tubular and drainage phases, a total of 20 to 30 minutes after injection. A 64 × 64 matrix size or higher is used. When I-131 orthoiodohippurate (OIH) is used, a high-energy collimator is required and the count rate is too poor to justify acquiring the
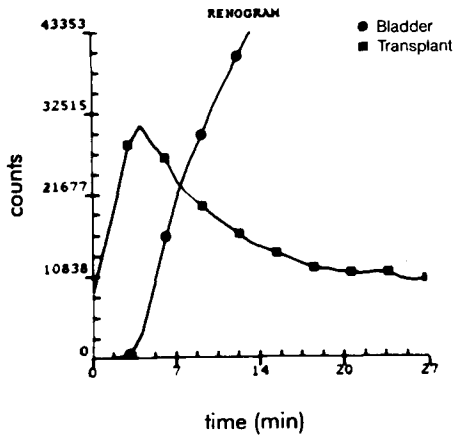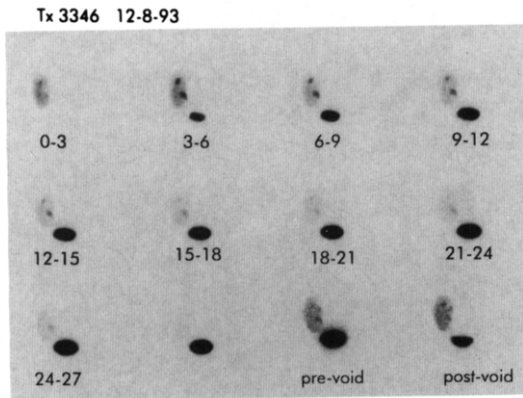
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Fig 3. Normally functioning cadaveric grafts 17 days after transplantation. (top) Dynamic series obtained with 3.5 mCi (130 MBq) of Tc-99m MAG₃ and displayed in 3-minute frames for 27 minutes. Prevoid and postvoid images are acquired for 60 seconds in a static mode. (bottom) Time-activity curve generated from the whole kidney and bladder ROIs. Quantitation: ERPF: 408 mL/min, activity excreted at 35 minutes 58%; EI: 0.85; T_{max}: 4 minutes; 20/3 minutes 0.50.

over the aorta. Various indexes of renal clearance of radiopharmaceutical can be calculated from the height, slope, or area under the renal time-activity curve during the tubular phase. Tubular transit time can be calculated by deconvolution analysis using a parenchymal ROI.[30,31] It can be approximated by whole-kidney transit time, or simply by the peak time. Various functional images may be displayed, either as an end in themselves or to assist in drawing parenchymal ROIs.[29]

## DRAINAGE PHASE: EVALUATION OF URINE FLOW

Data Acquisition

Data acquisition for the drainage phase, which normally extends to 20 or 30 minutes after injection, is normally the same as for the tubular phase. A slower frame rate would be adequate, but the small gain in the disk space and processing time is not normally worth the trouble.

Data Analysis

The images are normally displayed in the same format and in continuity with those from the tubular phase. Retained activity, whether in the pelvis or the renal parenchyma, is readily identified from the images. The distinction between cortical and pelvic retention is important, with parenchymal retention being the hallmark of ATN or AR and pelvic retention being the hallmark of obstruction. This distinction between parenchymal and pelvic retention is probably best made from raw images, although functional images, parenchymal transit time, and the like can be useful adjuncts.[32] Curves or

Fig 4. AR: 45-year-old woman received an allograft on August 24, 1992 from a living unrelated donor. On August 25, 1992, ERPF was 363 mL/min, activity excreted at 35 min: 67%, EI: 0.90, T_{max}: 3 minutes, 20/3 minutes: 0.32. The study presented here was performed on September 14, 1992 with 3.2 mCi (118 MBq) of Tc-99m MAG₃. It shows enlarged graft with prominent cortical retention and decreased excretion. ERPF: 107 mL/min, excreted activity at 35 minutes: 15%, EI: 0.49, T_{max}: 27 minutes, 20/3 minutes: 2.55.
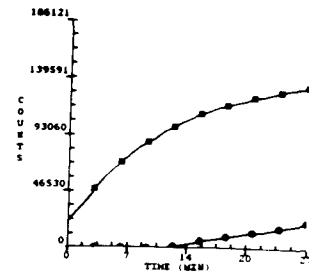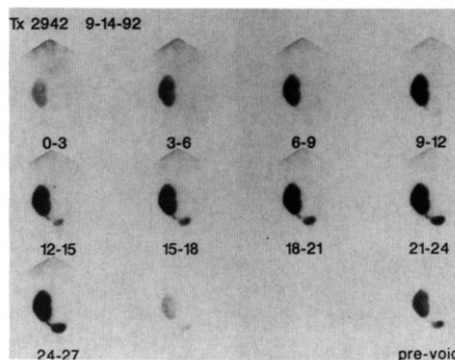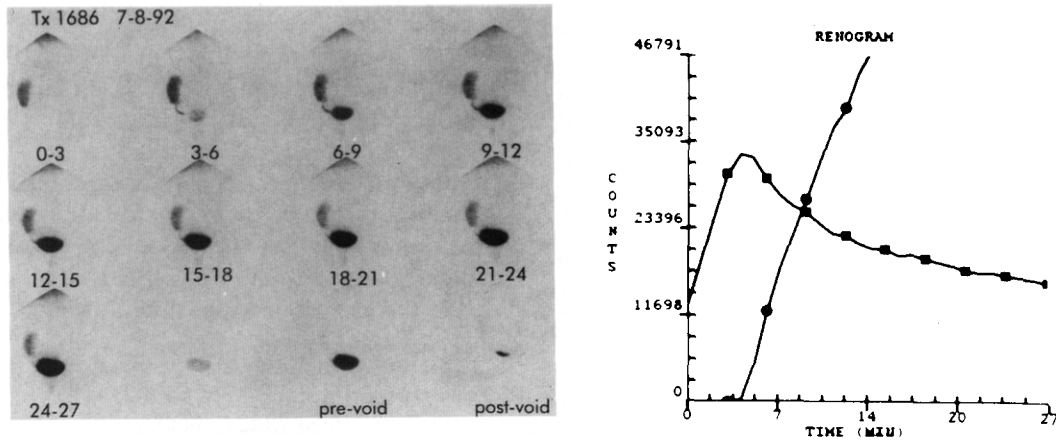
Fig 5. CR: 43-year-old woman received a cadaveric allograft on June 8, 1987. Its function was immediate and excellent. ERPF: 387 mL/min, T_{max}: 4 minutes. Over the next few years, the plasma creatinine has slowly increased to the level of 2.1 n·g/dL. The study presented here was performed on July 8, 1992 with 3.5 mCi (130 MBq) of Tc-99m MAG$_3$. The dynamic series shows normal tracer kinetics time. ERPF: 85 mL/min, excretion at 35 minutes: 20%, EI: 0.80, T_{max}: 5 minutes, 20/3 minutes, 0.6. ● bladder ■ transplant

parameters derived from a whole-kidney ROI are of no use in making this important distinction. Several quantitative indexes can be derived from the drainage phase, of which washout half-time is perhaps the most common. This can refer either to the true time to half the peak activity, or alternatively it can refer to a half-time derived by least squares fit to the postpeak counts. If parenchymal or pelvic retention is severe, there may be no peak, the curve rising continuously throughout the study. In such cases, no washout half-time can be measured. The excretory index (EI) is a valuable measure of retained activity, but it is not widely used because it requires collecting and counting samples of both blood and urine.[17] A simpler measure of retained activity is the ratio of background subtracted renal counts at 20 min to those at 3 min. A similar index is Oei's MAG$_3$ uptake capacity (MUC$_{10}$).[33]

PLASMA CLEARANCE METHODS

The classic physiologic measurements for renal function have been the glomerular filtration rate measured by inulin clearance and the effective renal plasma flow (ERPF) measured by para-aminohippurate (PAH) clearance. Estimates of these quantities can be obtained from a single blood sample obtained after an imaging dose of Tc-99m DTPA, I-131 OIH, or Tc-99m MAG$_3$. The methods have been described in detail elsewhere.[8,17,34-38] These measurements are simple to perform for any nuclear medicine department that operates an in vitro laboratory and they are more reliable than corresponding estimates obtained from the gamma camera. They have been a routine part of the

clinical radionuclide study of renal transplants at the University of Alabama at Birmingham for more than 20 years.

ALTERNATIVE IMAGING PROCEDURES

Although the radiopharmaceuticals most commonly used for monitoring renal grafts are analogs of traditional renal clearance agents, other approaches have been used. We describe them briefly in this section, although the remainder of this review refers only to the traditional approaches.

AR can be shown by imaging with Tc-99m-sulfur colloid.[39-45] The mechanism of uptake, as shown by autoradiography, is the trapping of labeled particles in fibrin thrombi.
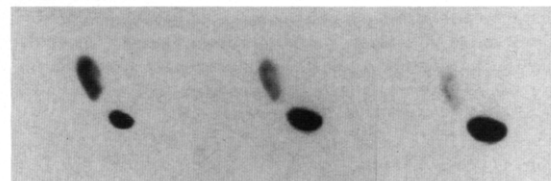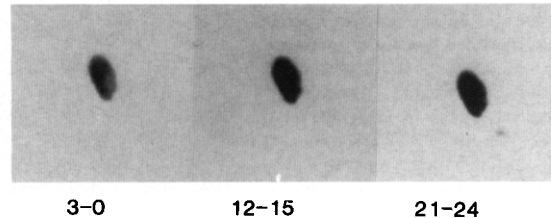

Fig 6. Selected frames of the baseline study (top) performed with 1 mCi (37 MBq) of Tc-99m-MAG$_3$ and repeated 1 hour later after ACE inhibition with 10 mCi (370 MBq) (bottom) show prominent increase of parenchymal transit time of the tracer resulting in prominent cortical retention—a hallmark of hemodynamically significant RAS. (Reprinted with permission.)
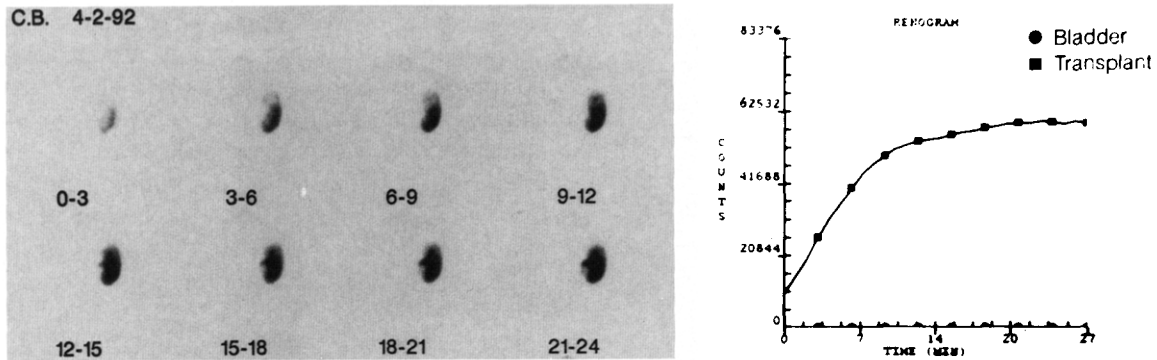
Fig 7. Obstruction (high-grade): 57-year-old man received a second cadaveric graft on March 16, 1992. His posttransplant course was that of slowly resolving ATN. Present study was performed on April 2, 1992 with 3.6 mCi (133 MBq) of Tc-99m MAG₃. Dynamic series shows low and slow uptake of the tracer. Large cold area in the first frame representing pelvis and calyces fills rapidly with activity, but ureter and bladder activity are absent. ERPF: 173 mL/min, Tmax: 26 minutes 20/3 minutes: 1.45. Biopsy on April 3, 1992 was normal. One week after the relief of obstruction (blood clot), the scintigram was normal, ERPF increased to 324 mL/min and T_{max} decreased to 5 minutes.

These thrombi occur in AR but not in ATN, so that the two entities can be clearly distinguished. False-positive findings have been reported with infections and with high-dose steroids.

Other agents have been used or are under investigation. Gallium-67 citrate[46] and radioiodinated fibrinogen are of only historical importance.[47-49] Radiolabeled white blood cells[50,51] and platelets not only[52-54] localize in rejecting grafts, but also in some other pathologic conditions. Various techniques have been used for cell labeling, including the use of labeled monoclonal antibodies.[55]

INTERPRETATION

In the normal transplant, peak activity is reached by 5 minutes and the activity has decreased to half the peak activity in another 5 or 6 minutes. With Tc-99m MAG₃ or I-131 or I-123 OIH, most of the tracer will be in the bladder by 30 minutes with little background activity[36-38,56-65] (Fig 3).

ATN is initially present in most cadaveric grafts and resolves spontaneously. The speed of recovery depends on the degree of ischemic insult. With tubular agents (I-131 OIH and Tc-99m MAG₃) the most conspicuous finding is delayed transit with delayed T-max, delayed T-1/2, high 20 to 3-minute ratio, and low EI.[66] These are the quantitative counterparts of parenchymal retention that can be seen on sequential images.[66] In severe cases, no activity is excreted into the bladder, a finding seen less commonly with AR. Blood flow and ERPF are decreased, but these findings tend to be less marked than the parenchymal retention. Paren-

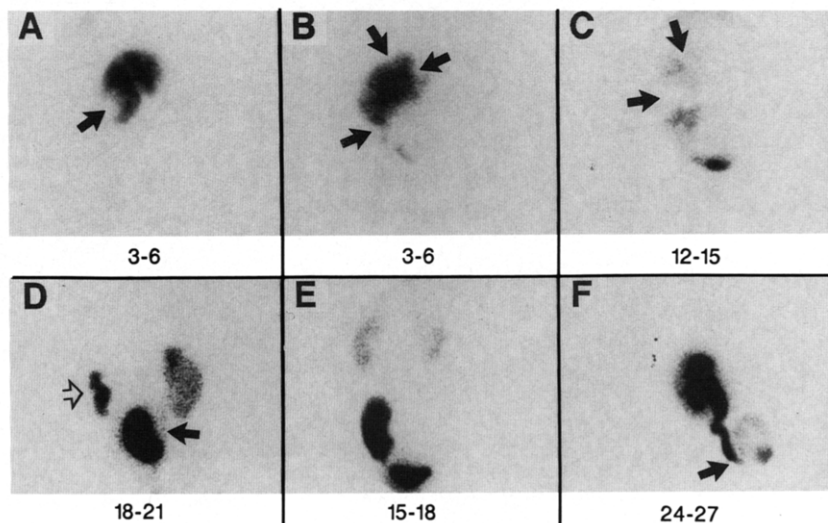Fig 8. Examples of findings reported in renal transplantation: abscess (A), metastatic disease (B), infarction (C), chronically rejecting graft in the right pelvis, new graft with ATN in the left pelvis and displacement of the bladder by hematoma (D) graft with mild AR; high-bladder activity is a sum of the urine activity drained from native kidneys and transplanted kidney (E) obstruction at the uretero-pelvic junction (F).
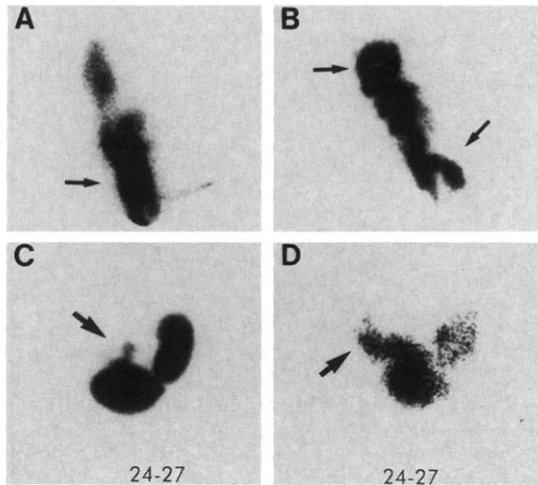
Fig 9. Selected images (24 to 27 min frames) from different studies showing: (A) Urine leak into the scrotum. (B) Urine leak from the region of uretero-bladder junction around the graft. (C) Small reflux into the duct of a transplanted pancreas (Tc-99m MAG₃). (D) More prominent reflux into the pancreatic duct (I-131 OIH). (C) and (D) should not be confused with urine leaks.

chymal retention is believed to be caused by decreased urine flow so that secreted activity is not flushed from the tubules. Severely impaired uptake or nonvisualization of the kidney is a poor prognostic sign, and suggests catastrophic problems, such as vascular obstruction, cortical necrosis, or hyperacute rejection. ATN is present at the time of transplantation and improves over the next few weeks. At our institution, the diagnosis of ATN is made by documenting the above findings on a baseline study performed 1 or 2 days after transplantation.[33,34,66-70] Without the baseline study, separation of ATN from AR is considerably more difficult.

For AR, the scan findings are similar to those of ATN, but the two can be separated by their time course (Fig 4). If present, ATN is seen on the baseline study and gets better during the next 2 weeks. AR rarely develops in the first few days, so it is characterized by a decrease in function on serial studies. When function starts to deteriorate, then a diagnosis of AR is made. The temporal changes are easily identified from a table showing ERPF and either 20 to 3-minute ratio or EI versus postoperative date.[66] This approach requires a routine postoperative baseline study, plus frequently repeated measurements in any patient whose progress is unsatisfactory. Occasionally, patients with ATN do not

recover function in 2 weeks, without any clear cut peak in function with subsequent deterioration to indicate the onset of AR. These are usually regarded as having AR even though an unidentifiable few may simply represent delayed recovery from ATN. Other approaches to the separation of AR from ATN have been blood-flow indexes, such as Hilson's index, which show more pronounced abnormality with rejection than with ATN, or the use of Tc-99m sulfur colloid scans, which show graft uptake in AR but not ATN.[20,23,39-45,71]

In contrast to AR and ATN, the graft with stable CR has thinned cortex with mild hydronephrosis, and it shows low uptake and normal parenchymal transit with absent or minimal cortical retention[30,69,70] (Fig 5). The cortical thinning is sometimes recognizable from the camera images. When CR is far advanced, parenchymal retention is again seen. All parameters tend to be grossly abnormal in a nonspecific pattern for an end-stage kidney.

The diagnosis of cyclosporin toxicity is difficult. The diagnosis is usually made by exclusion with the help of plasma cyclosporin levels. Patients on cyclosporin maintenance with no acute problems tend to have depressed ERPF without parenchymal retention, thus resembling CR.[72-74] Acute cyclosporin toxicity probably most often resembles mild AR on the radionuclide study, with abnormal measures of cortical retention in addition to depressed ERPF.[66] The changes are caused by reversible
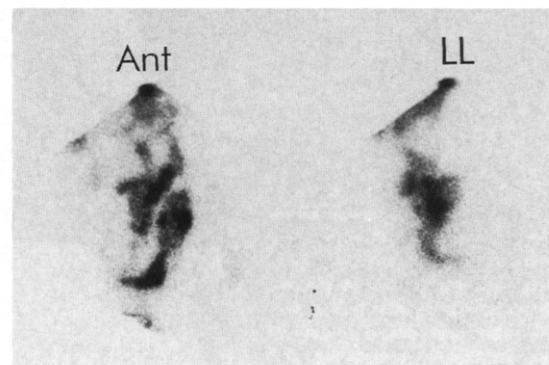

Fig 10. Four-hour delayed images (anterior and left lateral) from a study shown in Fig 9C shows large amount of activity in the gastrointestinal tract. This is a normal finding on studies performed with Tc-99m MAG₃ and should not to be confused with urine leaks.

vasoconstriction of the afferent arteriole,[75] sometimes accompanied by the development of nodular hyaline deposits.[10,76-78] Toxicity is more likely to occur when renal function is impaired, because toxic plasma levels are then harder to avoid. For this reason, cyclosporin administration is usually delayed in cadaver transplant recipients until ATN has resolved. Resolution of cyclosporin toxicity with dose adjustment is usually rapid, permitting retrospective diagnosis of cyclosporine toxicity.

Renovascular hypertension (Fig 6) sometimes occurs in renal transplants, usually as a result of graft artery stenosis, but occasionally from stenosis of a more proximal artery such as the iliac. The radionuclide studies typically resemble those in CR, unless the study is performed with angiotensin-converting enzyme (ACE) inhibitors.[73,79,80] ACE inhibition renography in patients with hemodynamically significant renal artery stenosis shows the same characteristic findings as with two kidney patients,

namely parenchymal retention of tubular agents and decreased uptake of Tc-99m DTPA or Tc-99m DMSA.[81,82]

Obstruction is identified, as with two kidney patients, by dilatation and retained activity in the collecting system (Fig 7). As with two kidney patients, the significance of these findings can be better assessed by diuretic renography. The same techniques and criteria are used. Lymphoceles are a common complication so the images should be inspected for organ displacement and for avascular photopenic regions[83] (Fig 8).

Significant urine leaks are usually readily identified[84] (Fig 9). The high-count rates, high urinary concentration, and low-background Tc-99m MAG_3 normally permit identification of leaks within 30 minutes. With I-131 OIH delayed images (after 2 to 4 hours) are sometimes helpful. With Tc-99m MAG_3, delayed images can be misleading because of hepatobiliary excretion with consequent gut activity (Fig 10).

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