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Use of Living Donors in Kidney Transplantation in Man

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A series is presented of 238 living renal donors who have been followed for periods of from eight months to eight years. Careful selection of donors is mandatory in order to avoid postoperative mortality or morbidity. Anatomic variations which may affect the donor or recipient operations are discussed. There were no deaths, and postoperative complications were usually minor. The most common were atelectasis or pneumonitis or both, pneumothorax, and urinary tract infection. No patients developed permanent renal insufficiency. Compensatory hypertrophy of the remaining kidney resulted in restoration of creatinine clearance and para-aminohippuric acid clearance to two thirds or more of preoperative values. The use of related living donors is justified by the low risk to the donor and the prolongation of life in the recipients.

Since the inception of the renal transplantation program at the University of Colorado Medical Center, heavy reliance has been placed upon the use of living donors. One justification for continuation of this practice has been the superior results that have been obtained in recipients of intrafamilial renal transplants as compared to recipients of kidneys obtained from nonrelated volunteers or cadavers.[1-3] The other justification must be the demonstration of an acceptable risk to healthy well-motivated donors who are exposed to the major operative procedure of nephrectomy. In 1964, our experience with the first 74 living donors was reported.[4] From then until June 30, 1969, this total grew to 238 volunteers. Observations on this large group of patients will constitute the basis for this report.

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Case Material

The 238 donors gave their kidneys to 225 recipients. There were 138 male and 100 female donors. The ages ranged from 18 to 57 years. The relationship between donors and recipients is shown in the following tabulation:

Number of recipients	225
Number of donors	238
Mothers	53
Fathers	30
Brothers	62
Sisters	37
Aunts	1
Uncles	5
Cousins	3
Nieces	2
Identical twins	3
Nonidentical twins	3
Wives	5
Husbands	1
Unrelated volunteers	33

Although nonrelated volunteers were employed early in our program, this practice was discontinued in November 1965, and no nonconsanguineous volunteers have been accepted since then.

Selection of Donors.—In discussing kidney donations with those who wish to volunteer, an objective account is given concerning the risk to themselves and the chances of salvaging the recipient patient. The donor is made to realize that there still is a significant chance of early transplant failure and that it is impossible to predict the long-term results of homotransplantation.

Pains are taken to be sure that the ABO blood groups in the donor and recipient are either identical or compatible.[4] Lymphocyte matching by the Terasaki technique[2] is also performed. However, because of the limited number of potential donors within a family group, good tissue matches are often not obtainable. Consequently, poor matches (C or D) are very often accepted.

After a candidate is determined to be a potential donor, he is carefully evaluated both psychologically and physically, and the investigations shown in the following tabulation are performed:

ABO blood group
Leukocyte antigen profile
Complete blood cell count
Serum electrolytes
Fasting and two-hour postprandial blood glucose
Lying and standing blood pressure (×3)
Electrocardiogram
Chest radiographs
Blood urea nitrogen (BUN) (×2)
Creatinine clearance (×2)
Urinalysis, including microscopic examination (×2)
Urine culture (×2)
Intravenous pyelogram
Aortogram

Only if all the other studies are satisfactory is aortography performed. The latter investigation is of the utmost importance in determining which kidney is to be used. If multiple renal

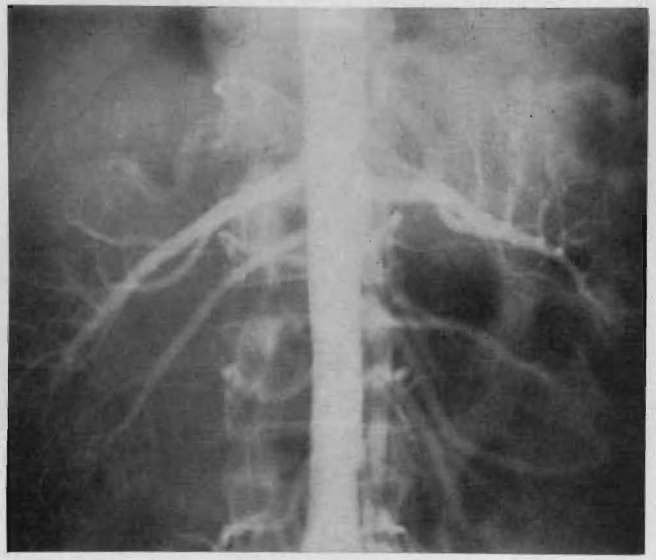


Fig 1.—Bilateral double renal arteries.

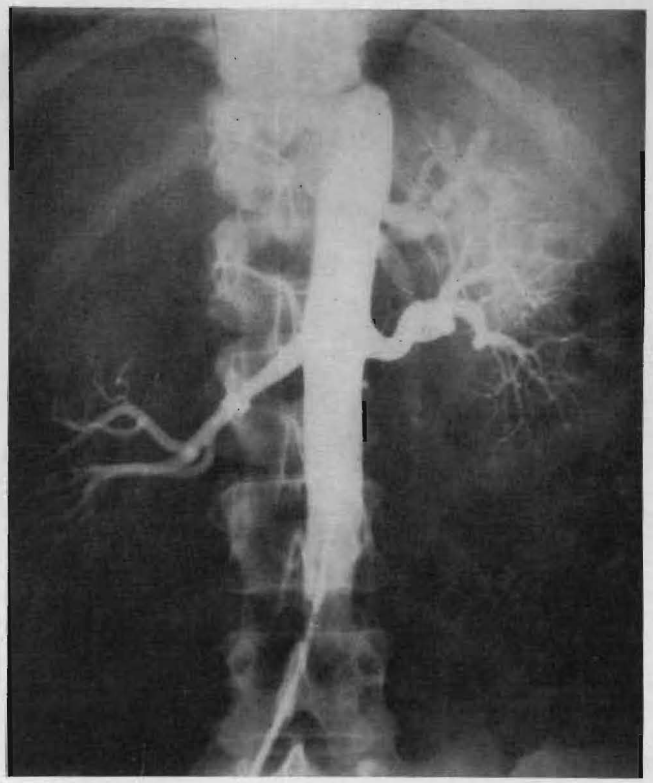
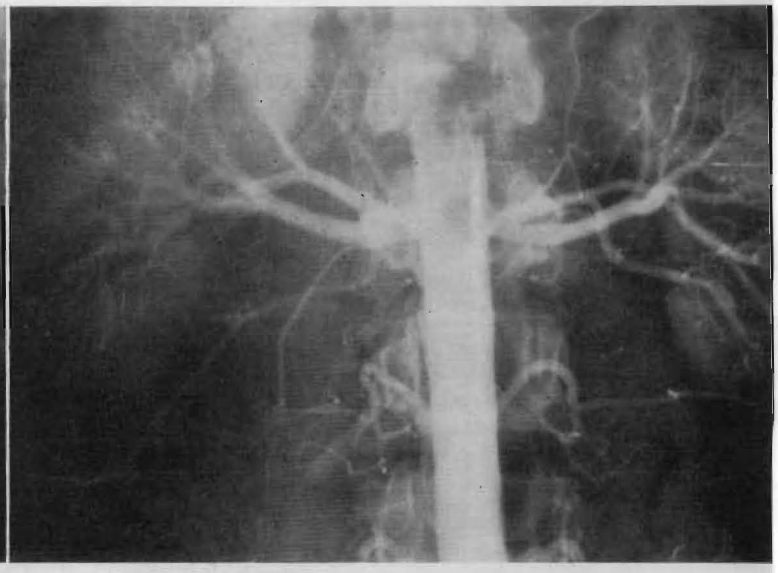


Fig 2.—Previously unsuspected fibromuscular hyperplasia of right renal artery in prospective woman donor; because of propensity of this disease to be bilateral, patient was not used as donor.

arteries are present on one side only, the kidney with the single artery is usually utilized. If bilateral double renal arteries are known to be present (Fig 1), the operation in the recipient can be modified so that both vessels can be anastomosed although there is a significantly increased risk of technical failure.[4] Occasionally, aortography will demonstrate an anomalous polar branch of the renal artery which can be preserved during donor nephrectomy.

On occasion, aortography has led to a decision against accepting renal donation. Previously unsuspected fibromuscular hyperplasia of one of the renal arteries (Fig 2) has been one contraindication because of the propensity of this disease to develop bilaterally. On the other hand, the mere presence of a unilateral abnormality does not preclude operation providing the less perfect organ is removed. Kid-

Fig 3.—**Left,** Studies on prospective donor; intravenous pyelogram showing left kidney which was 2.5 cm shorter and 2 cm narrower than that on right; both kidneys functioned well. **Right,** Discrepancy in size of two kidneys is again well seen; note early bifurcation of renal arteries; such arteries need to be divided close to their origins from aorta to ensure that only single arterial anastomosis will be performed in recipient.



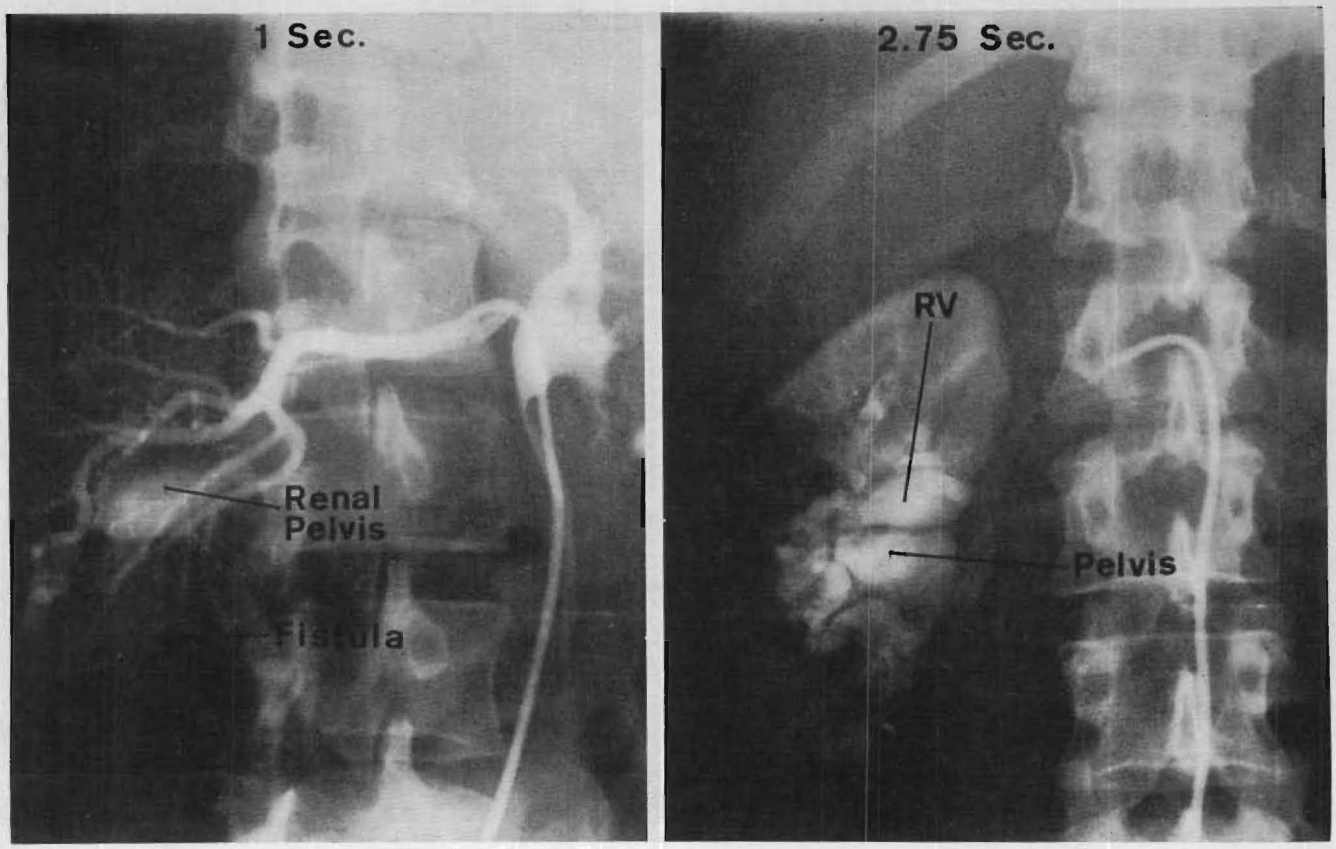


Fig 4.—Selective renal arteriogram in donor known to have renal arteriovenous fistula. **Left,** Fistula lies below and lateral to renal pelvis. **Right,** Renal vein is filled with contrast medium only 2.75 seconds after injection.

neys have been used in spite of their small size (Fig 3) although they contained an intrarenal arteriovenous fistula (Fig 4) and despite the presence of significant atherosclerosis.

The Operation.—As this has already been described in detail elsewhere,[4] only modifications in technique will be mentioned here. Systemic heparinization of the donor and total body hypothermia were used in some of the very early cases in order to protect the transplanted kidney. These practices have been abandoned. Instead, the excised kidney is perfused with a cold electrolyte solution immediately following its removal.[4]

In the past, exposure was obtained through a thoracoabdominal incision, with excision of the anterior portion of the eleventh rib. If possible, the pleural space was not opened. Better exposure of the important hilar structures and of the upper pole of the kidney can be obtained if the anterior portion of the tenth rib is excised and the underlying portion of pleura and diaphragm are deliberately opened. This approach has been used in at least half the donors. At the end of the operation, the diaphragm and pleura are repaired. Prior to closure of the pleura, a No. 20 French catheter is introduced into the pleural space and all air and fluid evacuated, after which the catheter is removed.

Results

Venous Anomalies.—Forty-four patients had anomalies of the venous drainage from the kidney, as shown in the following tabulation:

Lumbar vein(s) entering renal vein	22
Double renal veins	11
Triple renal veins	3
Quadruple renal veins	1
Retroaortic left renal vein	8
Anomalous left ureteral vein	3
Renal vein draining into left-sided inferior vena cava	1

Lumbar veins entering the back of the renal vein are potentially dangerous as these short vessels are difficult to recognize, and blind dissection of the back wall of the renal vein may tear these vessels, causing considerable bleeding. The presence of two or more renal veins does not present a problem as there are rich venous interconnections in the human kidney, and all but the largest veins can be safely ligated.[4] However, in three cases with two large renal veins of equal size, both were used for anastomosis in the recipient.

In eight cases, a retroaortic left renal vein was encountered, and in one other case the left renal vein drained into a left-sided inferior vena cava. These anomalies resulted in shorter lengths of renal veins being removed with the kidneys, but these did not cause any problems in the recipient operations.

Anomalies of the ureteral venous

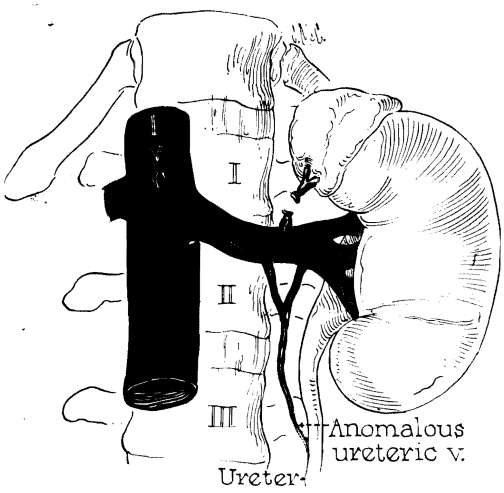


Fig 5.—Anomalous venous drainage of ureter; ligation of such anomalous vessels can lead to venous infarction of ureter.

drainage of the kind shown in Fig 5 may occasionally constitute a special hazard. In one such case, an accident was avoided when test occlusion of the anomalous vein caused cyanosis of the entire distal ureter; the vessel was therefore spared. In two other cases, venous infarction occurred, presumably as a consequence of ligating a similar anomalous vein. Both the ureters were lost in their entirety, and one of the recipient patients eventually died as a consequence of the resulting technical problem.

Arterial Anomalies.—In 37 patients, arterial anomalies were encountered, as shown in the following tabulation:

Double renal arteries	24
Triple renal arteries	3
Anomalous upper polar artery	13

In most cases, multiple arteries were diagnosed on preoperative aortography, but on three occasions these were only discovered during the donor operation.

In donors known to have multiple arteries bilaterally, the kidney with the largest vessels was operated upon, and a double or a triple arterial anastomosis was performed. In eight cases, the second artery was small and was ligated with a resultant small infarct in the kidney.

In 13 other cases, an anomalous upper polar artery arose from the renal artery at some distance from the kidney. In such cases, dissection was kept as far from the upper pole as possible to avoid injury to this vessel. If the vessel could not be preserved, a variable but always small infarct of the upper pole occurred.

Complications.—No deaths occurred, but there was one or more complications in 112 (47%) of the donors, as shown in the following tabulation:

Atelectasis or pneumonitis or both	33
Small pleural effusion	12
Pneumothorax	26
Urinary retention	7
Urinary tract infection	24
Hepatic dysfunction	4
Gastric distention or intestinal ileus or both	4
Wound infection	4
Transient nerve palsies	4
Hematoma of deltoid muscle	2
Deep-vein thrombosis and possible small pulmonary embolus	3
Prolonged incisional pain	3
Transient hypertension	10
Transient hematuria	3
Nephrocalcinosis	1
Acute glomerulonephritis	1
Suspected acute tubular necrosis	1

Most but not all of the complications were mild and easily remediable.

Postoperatively, fever was common in the first 24 to 48 hours. In many cases, this was caused by a minor degree of atelectasis or pneumonitis and cleared within hours or days, with a regimen of deep breathing and coughing. Nasotracheal suction was occasionally necessary, as was antibiotic therapy. One patient required bronchoscopy for the removal of tenacious secretions.

None of the pleural effusions required aspiration. Eighty-one percent of the pneumothoraces were minor and resolved without treatment. Five patients with a larger pneumothorax required needle aspiration or catheter drainage of the pleural space.

Urinary retention requiring catheterization was observed in 3% of the patients. Significant urinary tract infections were mild and asymptomatic and were usually detected on routine postoperative urine culture when 10,000 or more colonies per cubic millimeter of gram-negative organisms were encountered. These infections resolved rapidly with appropriate chemotherapy in all but one patient who had repeated urinary tract infections.

Disordered liver chemistries in four patients (2%) may have been related to anesthesia. They are unlikely to have been related to intraoperative blood transfusions which were rarely necessary. However, one donor did develop hepatitis two weeks after nephrectomy; she made a satisfactory recovery. A fifth patient was hospitalized elsewhere with questionable hepatitis about five months after operation, and recovery was prompt.

One patient had a transient brachial plexus palsy. He and three others also had temporary peroneal nerve palsies, probably caused by compression against the operating table by the neck of the fibula as the patient lay in the lateral position. With standard physical therapy, the palsies resolved completely within a few weeks. Extra padding to protect the head and neck of the fibula from pressure has eliminated this complication.

Wound infections were remarkably few in number. However, two of them caused protracted morbidity. One took several months to heal, and the second, which occurred as a complication of a wound hematoma, discharged silk sutures for two years before finally healing.

Two of the patients were a few weeks pregnant at the time of the operation, which was unknown to the doctors and the patients themselves. The pregnancies progressed satisfactorily, and both patients were delivered of normal infants. Three patients had late incisional pain, and one required a partial rib resection before her symptoms were relieved.

The donors have been followed from eight months to eight years. Only one has died. He was killed in an accident at work nearly two years postoperatively. He had had excellent renal function up until that time. Twenty-two months after operation, another donor was readmitted with proteinuria and hematuria and was considered to have acute glomerulonephritis. The disease promptly went into remission. Another donor developed nephrocalcinosis in the remaining kidney but continues to have excellent renal function.

Two donors developed urethritis many months or years after operation, but no evidence of renal disease was found in either of them. Both improved rapidly with treatment.

Postoperative Renal Function.—After eight months to eight years of follow-up, chronic renal insufficiency has not developed in any of the donors. In the immediate postoperative period, transient elevations of blood pressure were observed in 10 patients (4%) (preceding tabulation). Microscopic hematuria was occasionally observed in the first few days after operation, and frank hematuria was seen on three occasions (preceding tabulation). In one patient, the cause of this was suspected to be due to a small infarct in the remaining kidney, but a renal scan proved to be normal.

One donor had a fall in creatinine clearance to 30 ml/min and a rise in BUN to 55 mg% within one week after nephrectomy (preceding tabulation). The abnormalities receded in three weeks, and the donor was thought to have had a partial acute tubular necrosis in the remaining kidney.

In 29 of the first 75 donors studied between one and 18 days postoperatively, a mean increase in BUN and creatinine of 26% and 33%, respectively, occurred.[5] Clearance levels of endogenous creatinine and of para-aminohippurate were 70.5% and 70.2%, respectively, of the preoperative mean, indicating a rapid 40% increase in the function of the remaining kidney.[5]

Further studies performed on an average three years after nephrectomy[6] indicated that the clearances of creatinine and para-aminohippuric acid (PAH) were still only 71% and 66%, respectively, of corresponding preoperative values. These studies, together with those previously reported, indicated that the increase in glomerular filtration rate and estimated renal plasma flow were complete within seven days, and thereafter no further functional improvement occurred. Impairment of compensatory response with increasing age was also demonstrated.

Comment

As mentioned at the outset, the outlook after transplantation from a consanguineous donor is very significantly better than after transplantation of a nonrelated kidney. This has been our experience from the outset, and the conclusion is confirmed by reports from the Human Kidney Transplant Registry.[3] Our figures, as well as those of the Registry, also show that there is no advantage in using a kidney from a nonrelated volunteer donor versus a cadaveric donor. Consequently, the only living volunteers who have been considered in our program since 1965 have been family members. The benefits to the uremic patient of receiving a familial kidney must be balanced against the potential harm that may be inflicted upon the donor. It is upon this latter point that much of the data of the present communication is specifically focused.

Our own experience supports the general contention that donor nephrectomy is an exceptionally safe procedure. While the incidence of nonlife-threatening complications has been 47%, in most instances these complications were mild and easily remediable. In only three instances out of 238 cases, there was a late morbidity (1.3%). There have been no deaths related to the operation. Moreover, all but one of the 238 donors is still alive, the exceptional patient having died of trauma. There have been no examples of late renal failure in this donor series, although one of the patients developed evidence of acute glomerulonephritis, and another one has nephrocalcinosis. The follow-ups in these two patients have been 3½ and seven years.

It is of some interest to compare these results with those obtained in other transplantation centers. The groups at Peter Bent Brigham Hospital,[7] the Medical College of Virginia,[8] the University of California at Los Angeles,[9] and the Cleveland Clinic[10] have all used substantial numbers of living donors. A full documentation of their experience has not been published aside from the facts that major complications have been rare and that no deaths have occurred. So far as is known, mortality of donor nephrectomy throughout the world has been zero.

The most serious basis for hesitancy in performing this operation has come from the report of Liljequist.[11] He had 13 donors. Among this group, there were two examples of postoperative hepatitis and two more of low-grade postoperative renal failure. The unusually high incidence of hepatitis in these patients may have been a reflection of a hepatitis epidemic then going on in the Stockholm hemodialysis facility.[12] The renal failure in 15% of their cases has never been satisfactorily explained.

So far, the evidence from our observations has been that the health and life expectancy of the donor population has not been adversely affected. This is what would have been anticipated from the results of Kohler's[13] study of the life survival of patients after unilateral nephrectomy for renal disease. The situation in kidney donors is, of course, different in that a fraction of the preexisting renal function is sacrificed, whereas in ordinary urological nephrectomy, this is not the case.

In animals, unilateral nephrectomy is followed by prompt hypertrophy and hyperplasia of the remaining kidney.[14-17] Following removal of one kidney of the dog, urea clearance reaches 65% to 70% of preoperative values within 20 days.[18,19]

Thirty days after nephrectomy in the dog, renal blood flow achieves 75% to 85% of preoperative values.[19,20]

In man, unilateral removal of a normal kidney is followed by an increase in the volume and mass of the remaining kidney and is compatible with a normal life span in the absence of residual disease of the urinary tract and remaining kidney. Renal function in our donors in the immediate postoperative period has returned to approximately 70% of preoperative values of creatinine clearance and PAH clearance and has remained at this level with follow-ups of from two to four years.[6] Similar figures were reported in four donors studied from 11 to 19 months after operation by Donadio et al.[21]

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Discussion

MAURICE SLAPAK, MD, Boston: We were very interested in the presentation with regards to the compensatory hypertrophy which we first studied in this sort of situation three or four years ago with Dr. David Hume. We studied 43 cases from the first postoperative day with very frequent studies, employing cobalt-57 B12 clearances and endogenous creatinine and insulin clearance. Our results were a little different from those reported by Dr. Penn. In the first place, the recipients sometimes achieved over 90% compensatory hypertrophy. This seemed to vary very clearly with age, so that a young individual losing a kidney hypertrophied his remaining kidney fully and rapidly while an elderly individual underwent the same process more slowly and less fully.

In terms of the recipient, the amount of compensatory hypertrophy seemed to depend almost entirely on the number of rejections so that each rejection, as it were, wiped out a set of functioning glomeruli. Again we also showed that the live donors did very much better than the ones to whom the donor had been cadaveric.

A last question: In view of the fact that you handled 33 cases of pneumonitis, 26 pneumothoraces, and 12 small pleural effusions, don't you think you might wonder whether the donor nephrectomy could be done without entering the chest?

ISRAEL PENN, MD, Denver: In reply to Dr. Slapak's comments as regards the age of the donor, we have found that there is a very close correlation between the age of the donor and the rate of compensatory hypertrophy, and this does appear in our manuscript. The younger the patient, the more prompt the rate of compensatory hypertrophy.

In our early practice, we performed the operation through an extrapleural approach. We used to operate through the 11th rib bed and tried to avoid opening the pleura, but we found we had difficulty in getting complete exposure of the renal hilum. Also, we encountered problems in freeing up the upper pole of the kidney, particularly when trying to avoid injury to a previously unsuspected anomalous upper polar artery.

By operating through the tenth rib bed, we were able to obtain better lengths of renal artery and vein while avoiding problems with previously unsuspected vascular anomalies.