Living-Donor Kidney Transplantation: A Review of the Current Practices for the Live Donor

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The first successful living-donor kidney transplant was performed 50 yr ago. Since then, in a relatively brief period of medical history, living kidney transplantation has become the preferred treatment for those with ESRD. Organ replacement from either a live or a deceased donor is preferable to dialysis therapy because transplantation provides a better quality of life and improved survival. The advantages of live *versus* deceased donor transplantation now are readily apparent as it affords earlier transplantation and the best long-term survival. Live kidney donation has also been fostered by the technical advance of laparoscopic nephrectomy and immunologic maneuvers that can overcome biologic obstacles such as HLA disparity and ABO or cross-match incompatibility. Congressional legislation has provided an important model to remove financial disincentives to being a live donor. Federal employees now are afforded paid leave and coverage for travel expenses. Candidates for renal transplantation are aware of these developments, and they have become less hesitant to ask family members, spouses, or friends to become live kidney donors. Living donation as practiced for the past 50 yr has been safe with minimal immediate and long-term risk for the donor. However, the future experience may not be the same as our society is becoming increasingly obese and developing associated health problems. In this environment, predicting medical futures is less precise than in the past. Even so, isolated abnormalities such as obesity and in some instances hypertension are no longer considered absolute contraindications to donation. These and other medical risks bring additional responsibility in such circumstances to track the unknown consequences of a live-donor nephrectomy.

J Am Soc Nephrol 16: 2098–2110, 2005. doi: 10.1681/ASN.2004100824

2004 marked the 50th anniversary of the first successful kidney transplant from a live donor to his identical twin. Since this historic medical event, kidney transplantation has progressed from an experimental procedure to the preferred treatment for ESRD. Living donation rates vary worldwide, but in Western countries, it has recently increased to be the predominant form of kidney transplantation (1–3). In the United States, the annual number of live kidney donors has surpassed the number of deceased donors since 2001, although the absolute number of transplants from deceased donors still outnumbers those from living donors (Figure 1) (4,5). However, in some locations, such as Asia and the Middle East, relatively few deceased-donor kidney transplants have been performed. For example in Iran, >95% of the transplant experience has been *via* live-donor transplantation, with 16,000 transplants done since 1984.

Living donation provides a better patient and allograft survival when compared with deceased-donor transplantation, especially when the live donor transplant is performed before the onset of dialysis (Figures 2 and 3) (6,7). This report presents a review of the current practices for the live kidney donor.

Published online ahead of print. Publication date available at www.jasn.org.

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Relationship of the Live Kidney Donor to the Recipient

More than 30% of the live kidney donors are now categorized as genetically unrelated to their recipient (living unrelated donor [LURD]; Figure 4). A transplant from a spouse or a friend is an example of LURD, but LURD transplants are also occurring from donors who are anonymous to their recipients (8). The ethical underpinning of this evolving practice is the excellent survival achieved by LURD transplantation (Figure 5) (9,10). The adjusted 5-yr allograft survival for an unrelated kidney transplant is no different from the survival achieved by the transplantation of a kidney from a parent or a child of the recipient or from a haploidentical sibling (5,10). Moreover, the outcome of a kidney transplant that is performed from a completely mismatched donor is no different from that from a haploidentical match (10,11). A better outcome is provided only by an HLA identical kidney (11). These observations have influenced decisions regarding the suitability of live donors who are spouses, friends of the recipients, or anonymous; there is little concern today about the degree of HLA match if the ABO blood type and T cell cross-match are compatible.

The gender of the living donor in the United States is more frequently female, constituting 60% of the live-donor population (12,13). This pattern is similar to what has been observed worldwide, with more male recipients undergoing live donor transplantation. Different ethnic groups, however, donate at the same rate as their population representation, although not

ISSN: 1046-6673/1607-2098

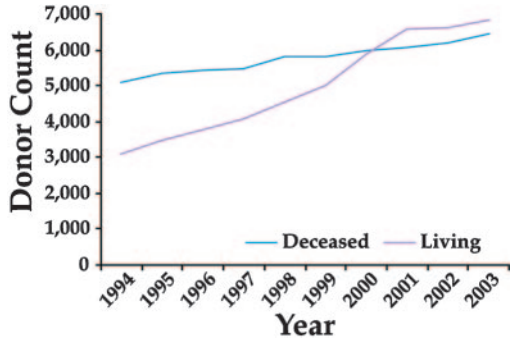

Figure 1. The number of living and deceased donors from 1994 to 2003. OPTN/SRTR Database, Annual Report, Draft 2004.

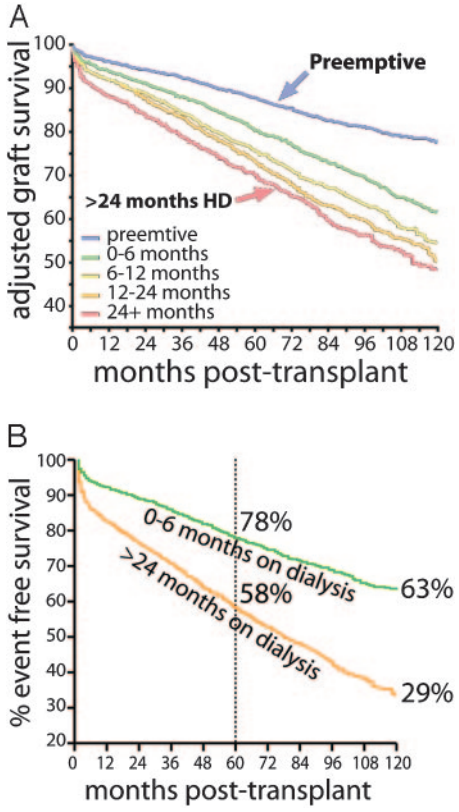

Figure 2. Graft survival as determined by dialysis time over 10 yr. Those who receive a preemptive transplant with living or deceased donor kidneys before starting dialysis have better long-term graft survival. When paired kidneys from a single donor are evaluated, allografts that go to a recipient who has been on dialysis for only 0 to 6 mo survive longer than those who have been on dialysis for >24 mo. Reprinted from reference 6, with permission.

necessarily to the same degree as the rate of ESRD in that population (Table 1) (12). Nonwhite prospective donors are more often turned down for donation because of the discovery of medical problems than prospective white donors (14).

Nondirected Donor

The success of LURD kidney transplantation has influenced transplant physicians to sanction the requests of individuals who wish to be anonymous donors, *i.e.*, "nondirected or altruistic donor." Thus, any person who is competent, willing to donate, free of coercion, and found to be medically and psychosocially suitable may be a live kidney donor (15,16). Three protocols of nondirected living donation have been developed to accommodate such donors: (*1*) a live-donor paired exchange, (*2*) a live-donor/deceased-donor exchange, and (*3*) altruistic donation.

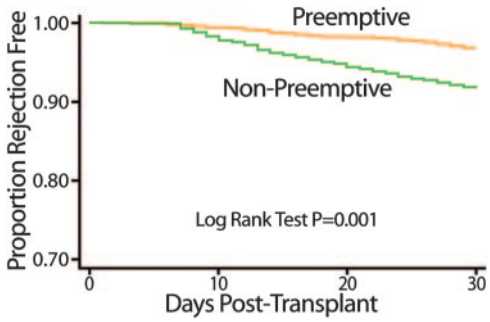

Figure 3. The proportion of recipients with biopsy-confirmed acute rejection according to the use of dialysis before transplantation. Acute rejection episodes are less during the first 30 d in those who receive a preemptive transplant. Reprinted from reference 7, with permission.

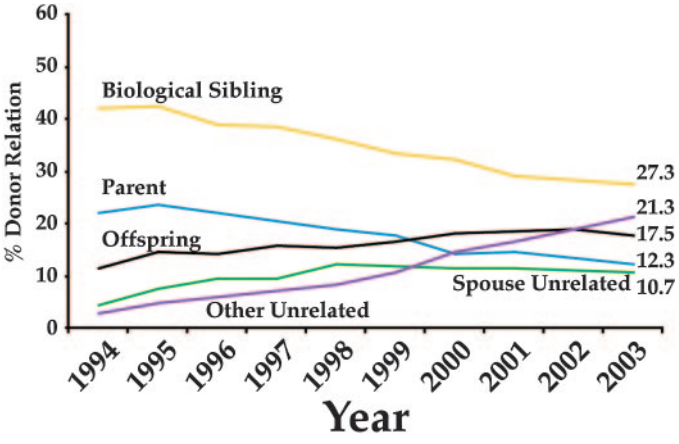

Figure 4. Donor relation to recipient by year, 1994 to 2003. There has been an increase in unrelated donation. OPTN/SRTR database Annual Report, Draft 2004.

Live-Donor Paired Exchange

This approach involves exchanging donors who are incompatible with their intended recipients so that, instead, each donates a kidney to a compatible recipient (17). The exchange derives the benefit of live donation but avoids the risk of incompatibility (18). Donors travel to the recipient centers and undergo nephrectomy simultaneously even when performed in different centers and at distant locations. Live-donor exchange procedures now have been performed worldwide (19,20).

Live-Donor/Deceased-Donor Exchange

United Network for Organ Sharing (UNOS) region 1 has devised a system to help recipients who have an incompatible

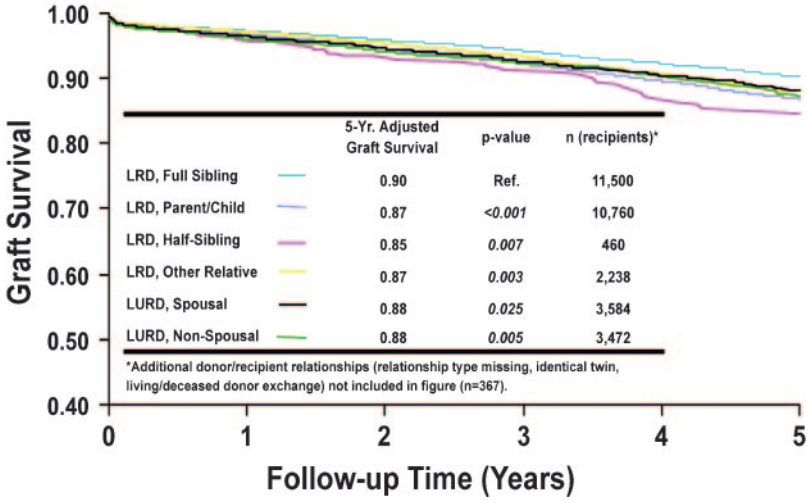

Figure 5. Five-year graft survival according to donor relationship to the recipient. OPTN/SRTR database, Annual Report as of August 1, 2003, Table 5.9b.

Table 1. Living donation by ethnicity, national data from OPTN/SRTR (12)[a]

Ethnicity	1999	2000	2001	US Population
White	69.4%	69.6%	69.6%	75.1%
Black	14.1%	12.6%	13.7%	12.3%
Hispanic	11.7%	12.2%	11.6%	12.5%
Asian	2.5%	2.9%	3.1%	3.6%

[a]OPTN/SRTR database, Annual Report as of August 1, 2003.

living donor and are also unable to undergo a live-donor paired exchange. After kidney transplantation from the living donor to the highest ranking appropriate individual on the center list, the incompatible recipient for whom the donor kidney was originally intended (the list exchange recipient) receives the right of first refusal for the next ABO identical or O-type (T cell cross-match negative) deceased-donor kidney available within the region.

The UNOS region 1 protocol is accomplished with the following provisions: The list exchange recipient is undergoing a first kidney transplant (simultaneous heart, liver, or pancreas transplant excluded), is on dialysis, is unsensitized (reactivity to a panel of HLA ≤10%, resides in New England, and is on the list of New England candidates (with an established care relationship with a UNOS region 1 center). The incompatible pairs each are reviewed by the Regional Renal Transplant Oversight Committee.

Selection of the List Recipient for the Live-Donor Kidney

In the region 1 protocol, the transplant center that evaluated and approved the donor notifies the OPO tissue typing laboratory to perform a match run of its listed recipients with the prospective donor. The recipient is identified using the standard allocation system for deceased donor kidneys. This system uses ABO blood type (identical) and time waiting as the principle determinants, although HLA matching (0 mismatch only), pediatric, and sensitization points are also awarded.

O List Effect

This exchange program has a clear utilitarian goal: To have more recipients undergo successful transplantation by expanding the pool of compatible live donors. However, affording the exchange recipient an allocation priority for an O blood type kidney has been criticized as a disadvantage for the O list of candidates who are awaiting a deceased-donor kidney (21,22). There is a temporary disadvantage for the longest waiting O candidates on the list at the time an exchange program is implemented. However, in region 1 experience, virtually all candidates who were bypassed on the day that the allocation priority was awarded to the exchange recipient have waited only several weeks to months longer than they would have without the exchange process.

Donor Exchanges and the National Organ Transplant Act of 1984

In the United States, living-donor exchanges must adhere to section 301 of the National Organ Transplant Act of 1984 (NOTA), which states, "It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation." Valuable consideration according to this act has traditionally been considered to be monetary transfer or a transfer of valuable property between the donor and the recipient (and, in some cases, an organ broker) in a sale transaction. Furthermore, the General Counsel to UNOS, Malcolm E. Ritsch, has provided the following position statement regarding donor exchanges and valuable consideration: "The donation of an organ is properly considered to be a legal gift, rather than a contractual undertaking. By definition, there is no consideration" at all in a gift transaction. Like all gifts, organ donations may be made for specific purposes. There is no valuable consideration under NOTA §301 in any of these living donation arrangements. In fact, there is no "consideration" present at all. The donor receives none, the recipient gives none and none is transferred to a broker (23).

Altruistic Living Nondirected Donation

A "screening" questionnaire administered to a prospective nondirected donor accomplishes at least three objectives: (*1*) It provides basic information regarding the donation process, including evaluation, operation, recovery time, potential donor costs, and long-term implications; (*2*), it elicits pertinent medical and social history from the potential nondirected donor that might influence candidacy (*e.g.*, obvious contraindications to donation); and (*3*), it initiates the discussion of the donor's motivation and capacity to comprehend the donor process (Table 2) (16). The motives of the nondirected donor should be established with care to avoid a prospective donor's intention of remedying a psychologic disorder *via* donation.

Many who inquire about nondirected donation (NDD) have only a limited understanding of these issues and, upon learning these basic realities, withdraw from the process (24). In the experience of the University of Minnesota, >60% of those who express an initial interest in NDD make no further contact with the transplant center after receipt of the educational information or after discussion about NDD with the center staff.

Table 2. Initial screening interview for nondirected donation[a]

Medical/personal history
How old are you?
Are you healthy and physically fit?
Do you have a history of cancer, heart disease, diabetes, kidney disease, or high blood pressure?
Do you take medications?
Have you undergone any previous operations?
Is there a history of kidney disease in your family?
Do you receive disability benefits for any reason? (This does not rule out a donor *a priori* who should not be discouraged to proceed. They should be asked to elaborate.)
Do you live alone; are you married?
Where do you live? (This will affect costs and convenience associated with donation.)
Knowledge about nondirected donation
How did you learn or hear about organ donation?
Do you understand that donating a kidney is not like donating blood?
Are you aware that the risks of donating a kidney include the possibility of dying?
Do you understand that there are risks to the recipient (*i.e.*, that the kidney may be rejected)?
Do you understand that you cannot be paid money for being a donor?
Are you aware that several months may be necessary to determine your suitability as a donor by required clinical and psychological testing?
Do you understand that you will not select your recipient and that he or she will be from the list of those who are already waiting?
Donor-related questions
Why do you wish to donate a kidney?
Have you told a member of your family that you wish to be a kidney donor?
Have you and your family considered the burdens associated with donation that could include out-of-pocket expenses for travel, doctor appointments, and time out of work?
Is there a specific time frame to have your donor surgery performed?
Would somebody be available to assist you at home during your recovery from surgery?

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Incompatible Live-Donor Transplantation

The hazard of hyperacute rejection has precluded transplantation of a kidney to a potential recipient who has an ABO blood type incompatibility or an HLA reactive antibody to the donor. Nevertheless, in concert with the expansion of LURD have come protocols that remove isoagglutinin and HLA antibodies by plasma exchange to overcome these biologic barriers (desensitization protocols) (25–28).

The key element of current desensitization protocols is the titer of the anti-ABO or anti-HLA antibody. Titers above certain thresholds (1:4) will not uniformly respond to treatment. Treatment has included the following components (Figure 6):

- One plasma volume pheresis every other day before transplantation until the anti-human globulin enhanced complement dependent cytotoxicity assay is negative;
- Intravenous IgG (gamimune or CMVIgG) replacement after each pheresis;
- Posttransplantation pheresis every other day (usually two to four treatments);
- Maintenance immunosuppression (tacrolimus, mycophenolate mofetil ± steroids) started before the first pheresis (27,29).

In addition to these elements, the two most experienced centers add rituxan, IL-2 blockers or ATG, and splenectomy for high-risk ABO incompatible recipients, posttransplantation anti-donor titer monitoring, and protocol allograft biopsies (Figures 7 and 8) (30).

With these approaches, 41 patients with donor-specific reactivity have undergone transplantation at the Mayo Clinic (20 with a positive cross-match and 21 with ABO incompatible grafts) (29,30). The acute rejection (humoral plus cellular) rate has been 43% for positive cross-match recipients; no hyperacute rejection has been seen in the ABO incompatible grafts. The 1-yr graft survival was 79% for positive cross-match transplants, 94% for ABO incompatible grafts, and 96% for conventional grafts. Fifty-five incompatible patients have undergone transplantation at Johns Hopkins. The acute rejection rate was 55% (31). The 3-yr patient and allograft survival was 86.3 and 86.3%, respectively. Comparable patient and graft survival from UNOS for unsensitized ABO compatible living-donor recipients was 94 and 87.6%, respectively. The opportunity for a potential recipient to undergo transplantation from an incompatible donor can be realized today by either donor exchange or

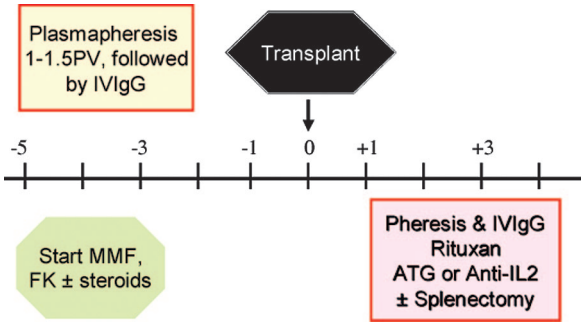

Figure 6. General protocol for desensitization of a positive cross-match. The major components are pretransplantation maintenance immunosuppression, pre- and posttransplantation pheresis, IgG replacement after pheresis, and posttransplantation induction with ATG or anti–IL-2 receptor antibody.

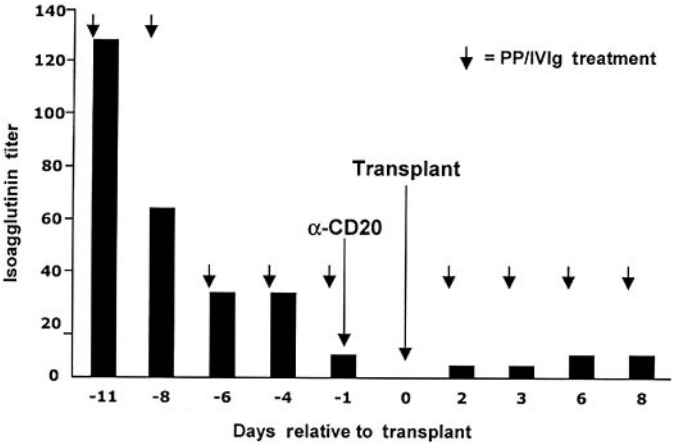

Figure 7. The desensitization protocol of the Mayo Clinic for ABO incompatible recipient/donor pairs and the usual isoagglutinin titer response. The recipient also starts on maintenance immunosuppression when starting pheresis. α-CD20, rituximab; PP/IVIg, plasmapheresis plus intravenous IgG infusion.

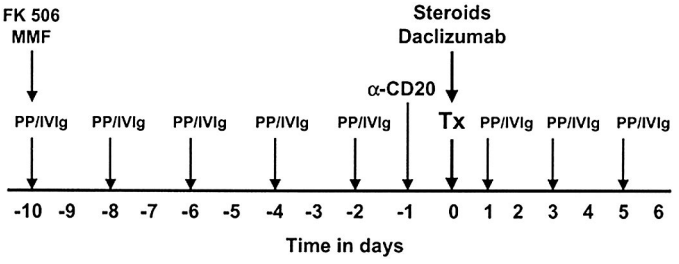

Figure 8. The desensitization protocol of the Johns Hopkins University for cross-match–positive recipient/donor pairs.

desensitization approaches. The advantage of the exchange procedure is the absence of recipient reactivity. The exchange procedure is also cost saving. Unless a national system of donor exchange is implemented, it is not likely that there will be a sufficient number of patients identified to undergo compatible paired donation (more than in an *ad hoc* situation as currently accomplished). Thus, the desensitization protocols otherwise serve the patient interests and should be a component of a comprehensive center plan of patient care.

Nephrectomy Procedures and Surgical Complications

Laparoscopic surgical techniques have been credited for the recent increase in living kidney donation's achieving shorter hospital stays (2 to 4 d compared with 3 to 7 d), less incisional discomfort, and an earlier return to work (12 to 21 d compared with 30 to 60 d) than after open procedures (32–37). Laparoscopic nephrectomy now accounts for >50% of the donor nephrectomy procedures in the United States (38). Large experiences from single centers have been reported from the Mayo Clinic, University of Maryland, and Johns Hopkins without the report of a death (33,35,36). Conversion to open nephrectomy occurs in approximately 2% of procedures.

The perioperative mortality reported for living kidney donors including both open and laparoscopic methods is 0.03%, although in a recent survey, all reported deaths were after laparoscopic nephrectomy (0.06%); none was reported after open procedures (38,39). In a survey of transplant centers by Matas *et al.* (39), re-operation was performed on 0.4% open, 1.0% hand-assisted laparoscopic, and 0.9% non–hand-assisted laparoscopic donor nephrectomies. Bleeding was a more common reason for re-operation after non–hand-assisted laparoscopic donation (35,36). A comparison of complications between procedures is shown in Table 3. The readmission rate was significantly increased for laparoscopic donors as a result of gastrointestinal complications (nausea, vomiting, constipation, or ileus). Although the mortality from living-donor nephrectomy is small, there is still a need for ongoing and accurate reporting of donor operative outcomes.

Medical Safety of Living Kidney Donation

The underlying premise of living kidney donation is that the removal of one kidney does not impair survival or long-term

Table 3. Comparison of open with laparoscopic living-donor nephrectomy[a]

	Open	HA LN	Non-HA LN
No. of procedures	5660	2239	2929
Reoperation	0.4%	1.0%	0.9%
Readmission	0.6%	1.6%	1.6%
Complications nonoperative	0.3%	1.0%	0.8%
DVT/PE	0.02%	0.09%	0.1%
Bleeding	0.1%	0.45%	0.2%
Rhabdomyolysis	0	0.09%	0.13%
Mortality	0	0.04%	0.07%

[a]Complications noted (%) after different types of donor nephrectomy. Open, open nephrectomy; HA LN, hand-assisted laparoscopic nephrectomy; non-HA LN, non–hand-assisted laparoscopic nephrectomy; DVT/PE, deep venous thrombosis/pulmonary embolus (39).

kidney function. Reports of relatively homogeneous northern European populations after nephrectomy by Narkun-Burgess (for trauma), Fehrman-Ekholm (for kidney donation), and Najarian (for kidney donation) suggested that live kidney donation is safe (Figures 9 and 10, Table 4) (38,40–42).

Nevertheless, Ellison *et al.* (43) identified 56 live kidney donors in the OPTN database who were subsequently listed for a kidney transplant. The rate of ESRD in donors was calculated to be 0.04%, comparable to the rate of ESRD in the general U.S. population (0.03%). The renal diagnosis in these patients was hypertension ($n = 24$), focal sclerosis ($n = 9$), chronic glomerulonephritis ($n = 7$), familial nephropathy ($n = 2$), diabetes ($n = 2$), and other ($n = 12$). In a report by Ramcharan and Matas (42), five (1%) of 464 located donors had developed ESRD and three others had abnormal renal function. The cause of renal disease was not determined.

A meta-analysis of reduced renal mass in humans was undertaken by Kasiske *et al.* (44). Multiple linear regression was used to combine studies and adjust for differences in the duration of follow-up, reason for reduced renal mass, type of control subjects, age, and gender. There were 48 studies with 3124 patients (renal mass reduction as a result of organ donation in 60.5%, cancer in 10.1%, infection in 8.1%, nephrolithiasis or obstructive uropathy in 6.8%, unilateral agenesis in 3.4%, trauma in 2.5%, other in 6.8%, and unknown in 1.6%) and 1703 control subjects. Renal mass reduction, gender, and age were associated with decreases in GFR. GRF was estimated on the basis of an isotopic determination in 13.7% and creatinine clearance in 45.8% or calculated using the Cockcroft-Gault equation in 40.4%. Unilateral nephrectomy caused on average a decrement of 17 ml/min in the GFR that tended to improve with each 10 yr of follow-up (average increase 1.4 ml/min per decade). A small, progressive increase in proteinuria was also noted (average 76 mg/decade) but was negligible after nephrectomy for trauma or kidney donation and most pronounced in those with renal agenesis or when there was more than a 50% reduction in renal mass. Nephrectomy did not affect the prevalence of hypertension but was associated with a small increase in the systolic BP that rose further with duration of follow-up. Living donation was assessed to be free of progressive renal dysfunction or increased incidence of proteinuria.

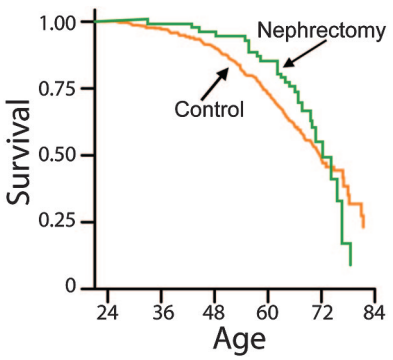

Figure 9. The survival of US servicemen who underwent unilateral nephrectomy during World War II in the field for trauma compared with servicemen in World War II who did not undergo nephrectomy. Reprinted from reference 40, with permission.

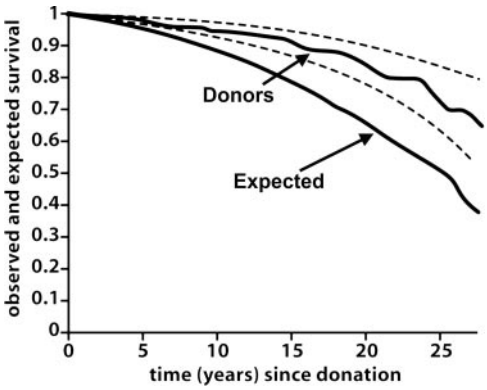

Figure 10. The observed compared with expected survival of living kidney donors in Sweden. The expected survival was calculated from the general Swedish population. Reprinted from reference 41, with permission.

Thus, the published evidence indicates that there is little long-term medical risk to a healthy donor after unilateral nephrectomy. However, the profile of the donor has changed to include those with isolated medical abnormalities such as hypertension, an increased body mass index (BMI), dyslipidemia, and stone disease. Recently, an international forum on the care of the live kidney donor was convened in Amsterdam, The Netherlands, to address these developments (45). Forum participants included >100 experts and leaders in transplantation, representing >40 countries from around the world, including the following continents: Africa, Asia, Australia, Europe, and North and South America. Forum participants agreed that before donation, the live kidney donor must receive a complete medical and psychosocial evaluation, receive appropriate informed consent, and be capable of understanding the information presented in that process to make a voluntary decision.

Medical Evaluation of the Live Donor

All donors should have certain standard tests performed to ensure donor safety (46). These include blood and urine screening tests, chest x-ray, electrocardiogram, an age- and family history–appropriate cardiac stress test, and radiographic assessment of the kidneys and vessels. An assessment of the anatomy may be accomplished by a renal arteriogram, computed tomography (CT) angiogram, or magnetic resonance angiogram, depending on local expertise. The CT angiogram has been shown to be reliably accurate (47).

An outline of the usual donor evaluation is shown in Table 5. Medical evaluation of the living donor has essentially been standardized (48,49) by two large conferences with broad representation from the transplant community (45). However, some testing issues (*e.g.*, type of urinary protein measurement, type of GFR determination) remain to be established (45).

Normal Renal Function and Live Kidney Donation

The threshold of normal renal function has seemed to decline with time. Inulin clearance studies in 1950 reported that the nor-

Table 4. Over 20 yr after donation[a]

	Preoperative (n = 78)	Postoperative (n = 57)	Siblings (n = 50)
Age (mean [range])	36.8	61 (40 to 83)	58 (29 to 83)
Serum creatinine (mg/dl [SD])	1.0 (0.1)	1.1 (0.01)	1.1 (0.03)
Creatinine clearance (ml/min [SD])	103 (4)	82 (2)	89 (3.3)
Urinary protein (mg/d)		n = 12, >150 mg/d	n = 10, >150 mg/d
BP (mean, mmHg)	118/76	134/80, 32% on antihypertensives	130/80, 44% on antihypertensives

[a]Living donor and nondonor sibling outcomes 20 yr or more after living donation (38).

mal GFR was 130 ml/min per 1.73 m^2 for young men and 120 ml/min per 1.73 m^2 for young women (50,51). An age-related decline in renal function of 10 ml/min per 1.73 m^2 was noted after age 40 such that the GFR at age 80 was half of that at age 40. More current studies have been performed using ^{125}I or cold iothalamate (50,52,53). Gonwa *et al.* (52) reported a GFR of 102 ± 15 ml/min per 1.73 m^2 for men and 114 ± 17 ml/min per 1.73 m^2 for women aged 21 to 30 yr. The GFR for men and women aged 51 to 60 was 84 ± 13 and 79 ± 15 ml/min per 1.73 m^2, respectively. Rule *et al.* (53) recently reported on the GFR of 365 potential renal donors. Those with a history of a primary renal or systemic disease were excluded as were those with a BP >140/90 mmHg, a fasting serum glucose >126 mg/dl, a protein excretion >150 mg/d, or abnormal urinary sediment. Normalized GFR results are shown in Table 6. In general, it seems prudent to require living donors to have a GFR at the average of the age-specific GFR. The majority of centers have chosen a GFR of 80 ml/min per 1.73 m^2 to be the lower limit for donation (45,48,49).

Donor Hypertension

The evaluation for hypertension should include BP measurements by experienced providers on three separate occasions; verification of elevated levels should be undertaken with ambulatory BP monitoring as approximately 10 to 20% may be found to have normal BP (49,54–56). If elevated BP are detected and the prospective donor is still under consideration, then a chest x-ray, electrocardiogram, echocardiogram, and ophthalmologic evaluation should be performed to look for secondary consequences of hypertension. In addition, a 24-h urine collection for albumin excretion or a spot urine for albumin:creatinine ratio should be performed along with a urinalysis and a formal GFR measurement.

If donors with hypertension donate, then they should be followed longitudinally by the transplant center to ensure optimal treatment. Such a program is ongoing at the Mayo Clinic. This program has accepted hypertensive donors with a clinic BP of >140/90 mmHg or ambulatory BP of >135/85 mmHg. Those who have hypertension and have been selected for donation have also been older than 50 yr; white; and demonstrated BP control with an angiotensin-converting enzyme inhibitor and hydrochlorothiazide, a normal GFR (by iothalamate clearance) for age, and no microalbuminuria (56). To date, 24 donors have been followed for >6 mo; BP is controlled and GFR is as expected for donation and age. Before the Joint National Committee redefinition of hypertension, many donors had BP approaching 160/95 without apparent morbidity (57,58). However, more detailed information about these donors and their long-term outcomes (over 30 yr) is needed before generally accepting hypertensive individuals as donors (38,56,57).

Donor Obesity

The importance of obesity for the living donor is the impact of obesity on renal function. Obesity without nephrectomy is associated with hypertension and proteinuria (59–64). Proteinuria is associated not only with the development of renal disease but also with cardiovascular disease (65,66). Obesity as a risk factor for renal insufficiency after unilateral nephrectomy was studied by Praga *et al.* (59) in 73 patients from Spain. People who underwent unilateral nephrectomy without known disease in the contralateral kidney were found to develop proteinuria and renal failure over 10 to 20 yr after nephrectomy when they had a BMI >30 kg/m^2 at the time of surgery (Figure 11). The average BMI in the obese group at nephrectomy was 31.6 kg/m^2 compared with 24.3 kg/m^2 in the nonobese group.

The impact of smoking and obesity on the development of proteinuria was evaluated by Tozawa *et al.* (60) in subjects from Okinawa Japan. These investigators screened 5403 men and women in 1997 and then reevaluated them again in 1999. At initial screening, the subjects had no proteinuria by dipstick examination and a serum creatinine of <1.2 mg/dl for men and 1.0 mg/dl for women. The subjects were reevaluated for proteinuria in 1999. Proteinuria was associated with the number of cigarettes smoked especially for men (relative risk [RR] 1.32), hypertension (RR 1.56), BMI at baseline >25 kg/m^2 (RR 1.45), and diabetes (RR 2.27; Figure 12). Thus, obesity and smoking could increase the risk for a donor to develop proteinuria and thus renal disease, cardiovascular disease, and cancer. Careful instruction about possible future health risks needs to be given to donors who are obese or smoke and should possibly be considered in the context of informed consent. Education on healthier life choices and weight reduction programs also should be included in the plan for donation.

The future of obesity also includes the risk for diabetes. Even without overt obesity, those with a family history of diabetes or other associated risk factors should be concerned about their future risk to develop the disease. As diabetes is a contraindication to live kidney donation, all prospective donors should be evaluated with a fasting blood sugar, and a 75-g 2-h oral glucose

Table 5. Donor evaluation

History: Look for/ask about
hypertension
diabetes
nonsteroidal anti-inflammatory inhibitors/ medications/herbs
family history
IVDA
infections
vascular
vocation/avocation
willingness to donate
Physical exam: Evaluate/look for
blood pressure
weight/height
arthritis
autoimmunity
cancer
prostate
breast
colorectal
lymph node
cardiovascular disease
Laboratory
urinalysis
electrolytes, liver panel
fasting blood glucose and lipid profile
CBC with platelets, coagulation screen
24-hour urine, creatinine clearance and progein excretion or GFR measurement (iothalamate clearance) and protein determination
antiviral screening: HCV, HBV, HIV, EBV, CMV, HSV
PPD (controversial in nonendemic area), RPR
electrocardiogram, chest x-ray
PAP, prostate examinaion
age/family history determined
ETT, echocardiogram
colonoscopy ultrasound
Mammogram/PSA
Anatomic evaluation per the local expertise
computed tomography angiogram
Magnetic resonance angiogram
arteriogram

[a]HCV, hepatitis C virus; HBV, hepatitis B virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HSV, herpes simplex virus; PPD, purified protein derivative; RPR, rapid plasmin reagent; ETT, exercise tolerance test; PSA, prostate-specific antigen.

tolerance test should be performed when they have a fasting glucose >100 and <126 mg/dl, a first-degree relative with diabetes, a history of gestational diabetes or delivery of infants over 9 pounds, a BP >149/90, fasting triglyceride levels ≥250 mg/dl, a BMI >30 kg/m^2 or an HDL ≤35 mg/dl, or are younger than 40 yr and have a second-degree relative with diabetes.

Table 6. Age-associated GFR in living-donor candidates (53)[a]

Age (yr)	Percentile			
	2.5	5	Mean	95
20	87	91	111	136
25	84	88	109	133
30	81	85	107	131
35	79	83	104	128
40	77	81	102	126
45	74	78	99	123
50	72	76	97	121
55	70	73	94	119
60	67	71	92	116
65	65	69	89	113
70	62	66	87	111
75	60	64	84	109

[a]nGFR expressed as ml/min per 1.73 m^2.

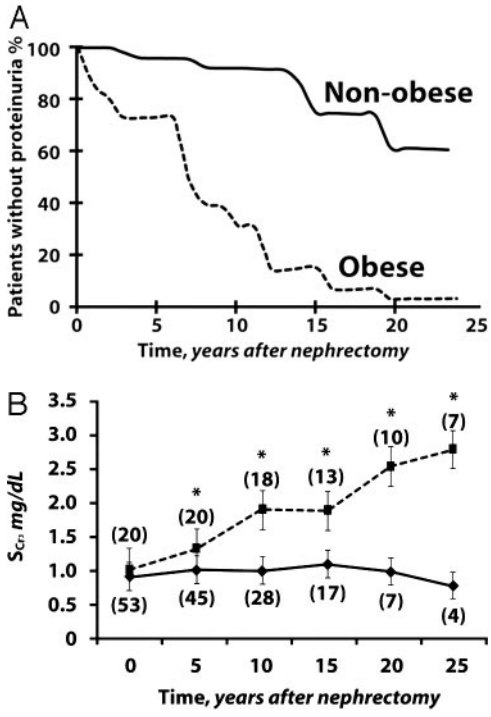

Figure 11. The development of proteinuria and renal insufficiency after unilateral nephrectomy according to body mass index at the time of surgery. The average follow-up time after nephrectomy was 19.6 yr for the obese compared with 11.3 yr for the nonobese subjects. Reprinted from reference 59, with permission.

Stone Disease

Nephrolithiasis has been considered an absolute contraindication to live kidney donation until recently (48,49). The problem is the ability to determine the rate of recurrence and the risk for complete urinary tract obstruction (67). It would seem prudent not to accept those with high rates of recurrence, such as

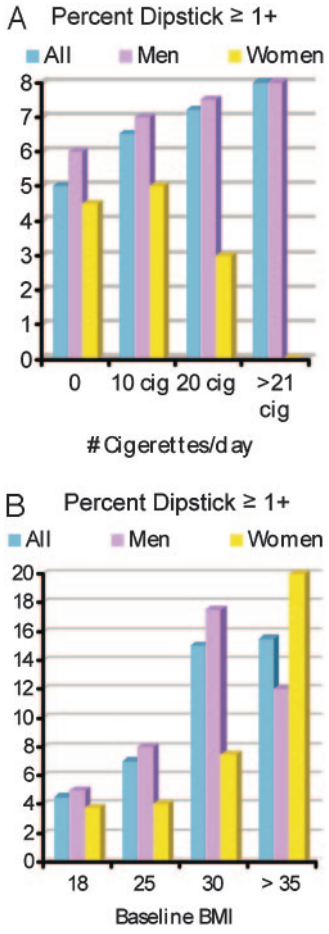

Figure 12. The relationship of cigarette smoking and obesity to development of proteinuria in a population study. Cig, cigarettes smoked per day; BMI, body mass index. Reprinted from reference 60, with permission.

those with cystine or struvite stones. In addition, those with systemic disorders that lead to high rates of recurrence, such as primary or enteric hyperoxaluria, distal renal tubular acidosis, sarcoidosis, inflammatory bowel disease, or other conditions that cause nephrocalcinosis *etc.*, should not donate. However, an asymptomatic potential donor with a current single stone may be suitable if the donor does not have a high risk for recurrence, the current stone is <1.5 cm in size, and it is potentially removable during transplant (Amsterdam forum). The evaluation of an asymptomatic donor with a single previous episode of nephrolithiasis should include a serum calcium, creatinine, albumin, parathyroid hormone, spot urine for cystine, a urinalysis and urine culture, a helical CT, the analysis of the previous stone if known, and a 24-h urine for oxalate and creatinine.

History of Malignancy and Infectious Disease

A history of the following malignancies usually excludes live kidney donation: Melanoma, testicular cancer, renal cell carcinoma, choriocarcinoma, hematologic malignancy, bronchial cancer, breast cancer, and monoclonal gammopathy (45). A history of malignancy may be acceptable for donation only when previous treatment of the malignancy does not decrease renal reserve or place the donor at increased risk for ESRD and previous treatment of malignancy does not increase the operative risk for nephrectomy. A history of malignancy may be acceptable when the specific cancer is curable and the potential transmission of the cancer can reasonably be excluded. Examples include colon cancer Dukes A >5 yr ago, nonmelanoma skin cancer, or carcinoma *in situ* of the cervix. Consent to receive a renal transplant must include a discussion with the donor and the recipient that transmission of malignant disease cannot be completely excluded.

It is inadvisable to accept as a living donor an individual with a history of active infection that would put the donor at risk for developing renal disease or requiring nephrotoxic treatments. Some of these infections include HIV, hepatitis C, hepatitis B, recurrent urinary tract infections, and malaria (45).

Coagulation Profile

A history of venous thromboembolism should be ascertained before an in-depth coagulation workup. Unless the history reveals a medical concern that would necessitate a comprehensive coagulation profile, these tests are expensive and not likely to yield consequential information (68,69). Oral contraceptives and hormone replacement therapy are commonly used and present an increased risk for postoperative venous thrombosis and thus should be withheld for at least 1 mo before an elective surgery (69,70).

Removing Financial Disincentives to Be a Live Kidney Donor

The US Congress has addressed the issue of living organ donation during the past few years with legislative resolutions to enhance the opportunity for transplantation. The Organ Donor Leave Act permits federal employees, in any calendar year, to take 7 d of paid leave to serve as a bone marrow donor and 30 d of paid leave to serve as an organ donor. Following suit, several states, hospitals, and businesses have extended the federal law.

The recently enacted Organ Donation and Recovery Improvement Act directs the Secretary of the Department of Health and Human Services to award grants to states, transplant centers, qualified organ procurement organizations, or other public or private entities for reimbursement of travel and subsistence expenses incurred by individuals in making a living organ donation. The pertinent sections of the bill are in Appendix 1.

Insurance Issues

Payment for a living-donor evaluation and transplant should be covered by the recipient's insurance. Medicare covers the donor costs for eligible recipients who undergo kidney transplantation. However, there has been a recent trend for private recipient insurance companies to deny coverage of the donor evaluation and demand that the donor's insurance be billed. Only when the claims are rejected has the recipient's insurance

considered payment. Recipient payers ascertain that the donor is receiving medical care and therefore the evaluation should be covered by the donor's insurance. However, it is the recipient, not the donor, who is benefiting from the surgery, and this practice places the donor at risk for exceeding the lifetime limits of his or her medical coverage.

Life insurance is occasionally denied to living donors because some companies have decided that nephrectomy may decrease donor survival. However, studies to date have shown donors to have equal or improved survival compared with the general population (41). Congress may need to consider legislation that would prohibit denial of life or medical insurance for living renal donors on the basis of donation.

Concerns for the Future

ESRD is increased in those who smoke, are obese, and have a family history of renal disease (64,71–73). Although smoking may be on the decline, it is still not obsolete, and the weight of the world's population is increasing (www.oas.samhsa.gov). In the United States alone, 60% of the population is overweight, with 30% classified as obese (74–77). Included in those who are gaining weight are adolescents (75,77). Adolescents spend hours on the computer or in front of the TV rather than exercising (78), and their caloric intake often outweighs their needs (79,80). Obesity and smoking, in addition to causing diabetes and renal disease, increases the risk for cancer (including renal cell cancer), microalbuminuria, and cardiovascular disease (81,82). Thus, the future renal donor may not be the same as the donor from the past, and the changes in our culture need to be taken into consideration when selecting the living donor.

Elements of a Living Donor Program

Promotion of donor safety is the golden rule of living-donor programs. To maintain donor safety, the prospective donor first must be educated about the process, procedure, and future risks of donation. The next step is a full physical evaluation to ensure that they are healthy and that there are no major risk factors that would lead to renal disease in the future. The donor then must be evaluated for psychologic and social barriers to donation. The prospective donor must be informed of any undue limitation to transplant success in the prospective recipient. All of these steps require the presence of a transplant coordinator, physician, social worker, psychologist or psychiatrist, and surgeon. Importantly, there should be a designated living-donor advocate during this process. The advocate should be experienced in the field of transplantation and be a social worker, coordinator, psychologist, psychiatrist, or physician. This advocate should advise the donor independent from recipient interests.

The final determination of donor suitability rests with the attending surgeon who performs the nephrectomy procedure. However, the donor advocate should have the authority to intervene if the physicians are unaware of a sufficient reason to stop the donation. The advocate may discover that the donor is being coerced and the donor may not have been comfortable to reveal this conflicted dynamic to the surgeon.

The intent of the donor may be influenced by the relationship of the prospective donor to the recipient. For instance, a parent or a spouse may conceivably accept more medical risk than a stranger or a colleague because he or she personally will benefit from the recipient's coming off dialysis. Nevertheless, donor autonomy cannot overcome medical judgment, and no center should be compelled to perform a transplant when the risks to either the donor or the recipient is determined to outweigh the benefit for either.

Conclusion

Living donors are heroes. Medical providers need to inform potential donors fully of the risks of the procedure and long-term health implications on the basis of published information and that assessed from their own medical evaluation. New approaches to incompatible donor recipient pairs are providing good short-term success and will continue to be developed. Legislation has been enacted by Congress to remove disincentives for the live donor. In this environment, living donation will continue to increase. Health care providers will need to monitor continually the safety of this growing process.

Appendix 1: HR3926, A Bill to Amend the Public Health Service Act to Promote Organ Donation, and for Other Purposes

Organ Donation and Recovery Improvement Act: (Sec. 2) Expresses the sense of Congress that the federal government should carry out programs to educate the public with respect to organ donation, including the need to provide for an adequate rate of donations. States that Congress (*1*) acknowledges the importance of discussing organ and tissue donation as a family, (*2*) recognizes the contribution made by each living individual who has donated an organ, and (*3*) acknowledges the advances in medical technology that have enabled organ transplantation through living organ donors to become a viable treatment option.

(Sec. 3) Amends the Public Health Service Act to authorize the Secretary of Health and Human Services to award grants to states, transplant centers, qualified organ procurement organizations, or other public or private entities for reimbursement of travel and subsistence expenses incurred by individuals toward making living organ donations. Authorizes FY 2004 through 2008 appropriations.

(Sec. 4) Directs the Secretary to (*1*) directly or through grants or contracts establish a public education program to increase awareness about organ donation and the need to provide for an adequate rate of donations and (*2*) support the development and dissemination of educational materials to inform health care professionals about organ, tissue, and eye donation issues, including those relating to patient, family, and cultural sensitivities.

Authorizes the Secretary to make (*1*) peer-reviewed grants or contracts to public and nonprofit private entities for studies and demonstration projects to increase organ donation and recovery rates, including living donation, and (*2*) grants to states for organ donor awareness, public education and outreach activities, and programs designed to increase the number of organ donors within the state, including living donors.

Authorizes additional FY 2004 through 2008 appropriations for such studies and grants.

Authorizes the secretary to award matching grants to qualified organ procurement organizations and hospitals to establish programs coordinating organ donation activities of eligible hospitals

and qualified organ procurement organizations. (Defines an eligible hospital as a hospital that performs significant trauma care or a hospital or consortium of hospitals that serves a population base of not fewer than 200,000 individuals.) Requires a grantee to (*1*) establish joint organ procurement organization and hospital-designated leadership responsibility and accountability, (*2*) develop agreed-on project performance goals, and (*3*) collaboratively design and implement a data collection process to provide ongoing project feedback. Authorizes FY 2004 through 2008 appropriations.

(Sec. 5) Directs the secretary, through the Director of the Agency for Healthcare Research and Quality, to (*1*) develop scientific evidence supporting increased donation and improved recovery, preservation, and transportation of donated organs and (*2*) support efforts to develop a uniform clinical vocabulary and technology and to enhance the skills of the organ procurement workforce. Authorizes FY 2004 through 2008 appropriations.

(Sec. 6) Directs the secretary, by December 31, 2005, and biennially thereafter, to report on organ donation and recovery activities.

(Sec. 7) Authorizes the secretary to establish and maintain mechanisms to evaluate the long-term effects associated with living organ donations by individuals who have served as living donors.

(Sec. 8) Directs the secretary, in consultation with appropriate entities, including advocacy groups for populations that are likely to be disproportionately affected by proposals to increase cadaveric donation, to report on the ethical implications of such proposals.

(Sec. 9) Eliminates certain grant authority with respect to qualified organ procurement organizations.

Acknowledgment

We thank William Applegate of government relations with the American Society of Transplantation for assistance in the review of legislative activity for living donation.

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