The Evaluation of Living Renal Transplant Donors: Clinical Practice Guidelines[1]

Developed by the Ad Hoc Clinical Practice Guidelines Subcommittee of the Patient Care and Education Committee of the American Society of Transplant Physicians, Bertram L. Kasiske,[2] Mark Ravenscraft, Eleanor L. Ramos, Robert S. Gaston, Margaret J. Bia, and Gabriel M. Danovitch

These guidelines are designed to help physicians and patients in the evaluation of potential living kidney donors. Although the guidelines are meant to be comprehensive, they cannot cover every possible clinical situation. Indeed, each potential living donor is unique and it is not possible to define an evaluation process that can anticipate every possible contingency. Thus, these guidelines are not intended to be enforced too rigidly, nor should they replace good clinical judgment. Their limitations need to be clearly recognized.

The guidelines were developed by the Ad Hoc Clinical Practice Guidelines Subcommittee of the Patient Care and Education Committee of the American Society of Transplant Physicians (ASTP). Work began in September 1994, and was completed in December 1995. The areas covered were arbitrarily divided into sections. Each member of the ad hoc committee was assigned to be a reviewer for one or more sections. Sources of information included literature located using MEDLINE, bibliographies in pertinent publications, personal experiences, and opinions of colleagues. Draft versions of the guidelines were reviewed and discussed by the committee. A consensus draft version was reviewed by the full Patient Care and Education Committee and the Board of Directors of the ASTP. Individuals who were not members of the committee, but who had published research reports and reviews of specific topics covered by the guidelines, were also asked to review sections pertinent to their areas of expertise. Revisions were made as suggested by these individuals, who are listed in the acknowledgements. Because transplantation is a rapidly changing field, some areas of these guidelines may soon become outdated. We cannot predict what new developments may affect the way in which patients are evaluated for transplantation, nor can we know when such information is likely to become available. However, we feel that these guidelines should be reviewed and updated in 3 yr.

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This document is divided into sections: (*1*) an overview algorithm with annotations; (*2*) a detailed algorithm; (*3*) annotations for specific steps in the detailed algorithm; and (*4*) references cited in the annotations. The algorithm is designed to be followed in sequence, as suggested by the arrows. Hexagons contain specific questions to be answered, rectangles contain suggested actions, and rounded rectangles enclose directions for moving between sections. None of the actions suggested in the algorithm should be taken without careful review of the corresponding annotations. The numbers of the specific annotations correspond to the numbers in the algorithm enclosures.

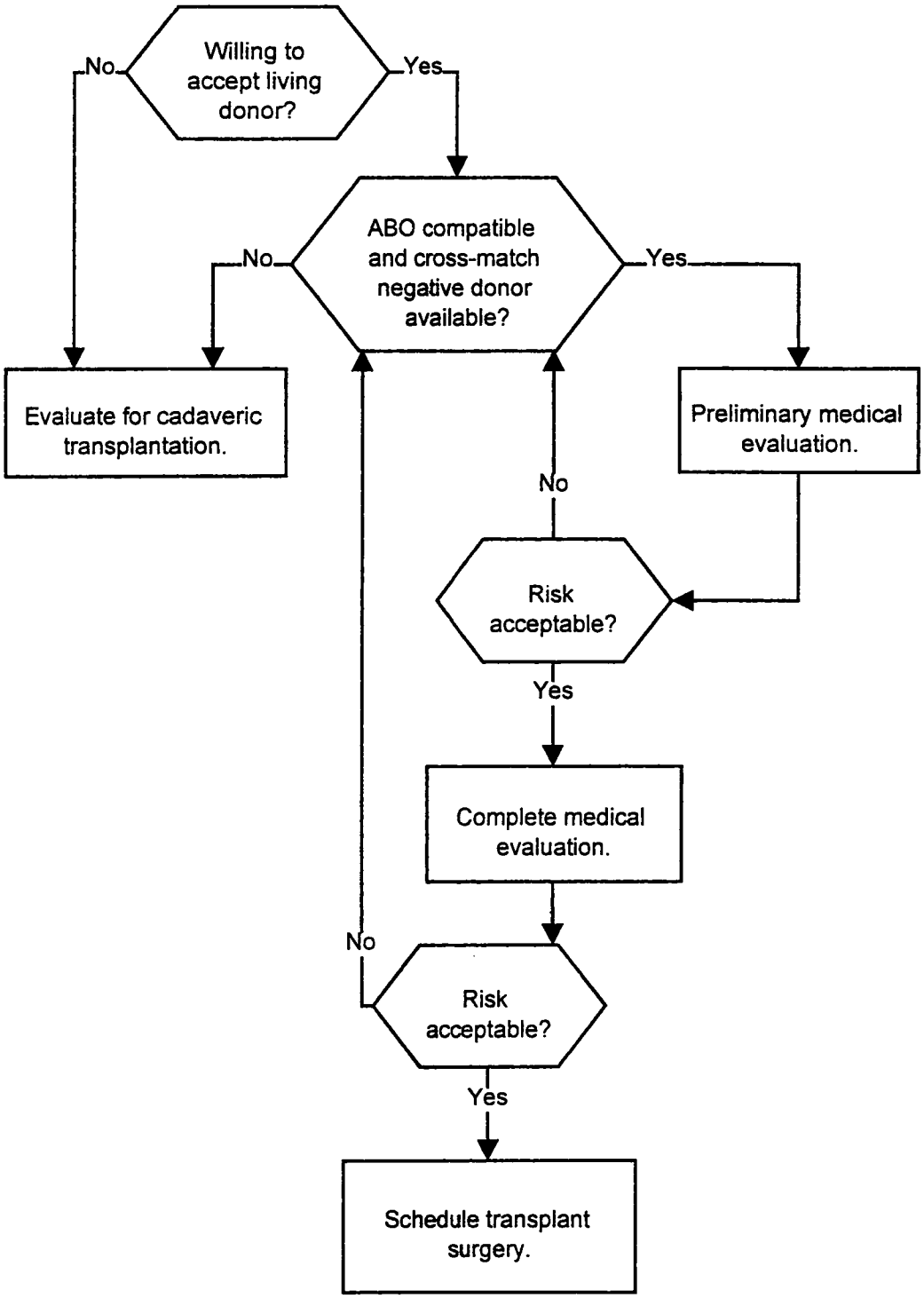
OVERVIEW ANNOTATIONS

This is an overview of the more detailed algorithm that follows. The detailed algorithm is designed to present, in a comprehensive manner, the major issues involved in the evaluation of potential living donors. Above all, this evaluation should ensure that the potential donor is both willing and able to donate a kidney. The sequence of the evaluation was chosen to maximize the probability that expensive and invasive tests would only be performed after other measures failed to exclude a potential donor. However, the exact order of the evaluation will need to be adapted to the specific situation unique to each individual patient and transplant center.

Blood typing, which is relatively inexpensive, is often the first test obtained in the evaluation of a living donor. If the donor has a blood type that is incompatible with that of the recipient, there is no need for further evaluation. Indeed, the ABO blood group barrier has only rarely been crossed in renal transplantation (1–3). Many centers also perform a cross-match as part of the initial evaluation to obviate the need for further work-up if an individual has a positive cross-match. If the potential donor and recipient are blood group compatible and cross-match negative, a preliminary medical evaluation can then be carried out. If the donor is not excluded on the basis of this preliminary assessment, a more extensive evaluation is then performed. In the end, a renal angiogram is obtained and a final cross-match is carried out just before transplant surgery.

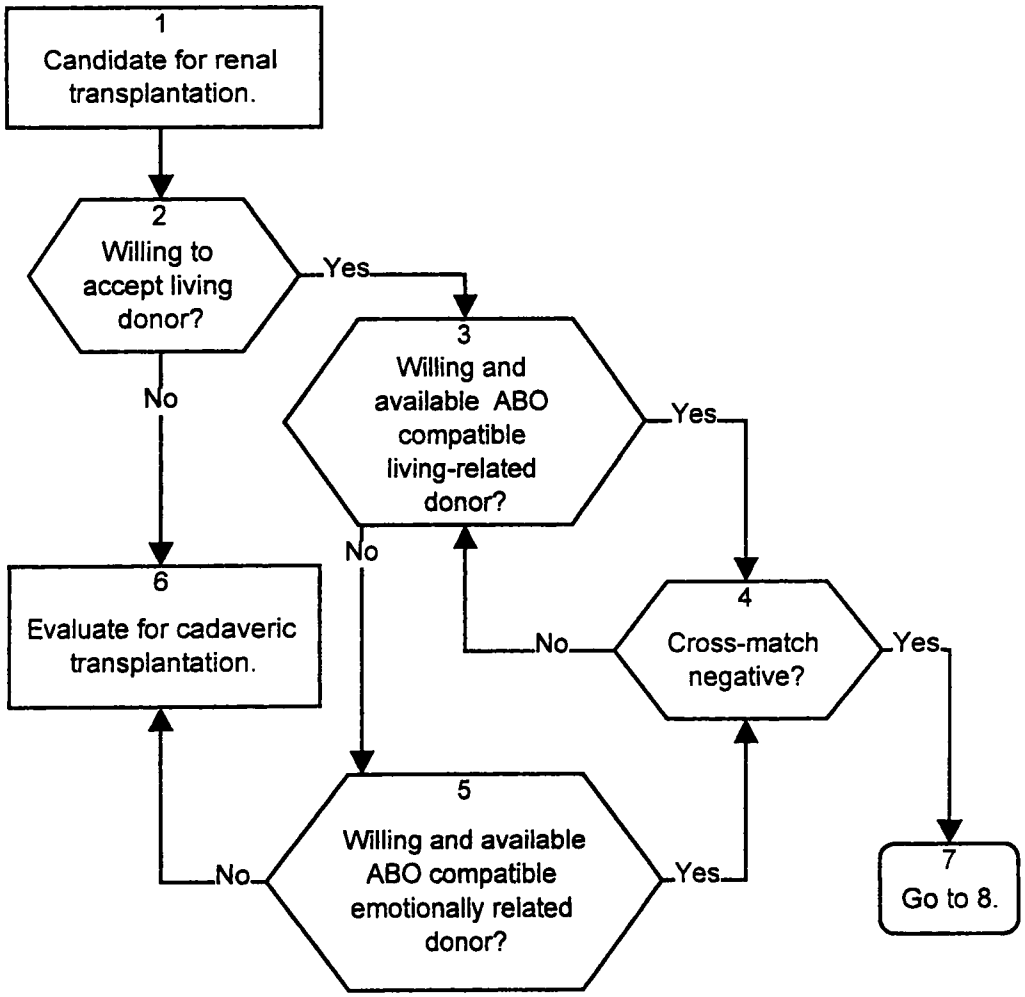
Ensuring the safety and well-being of the potential

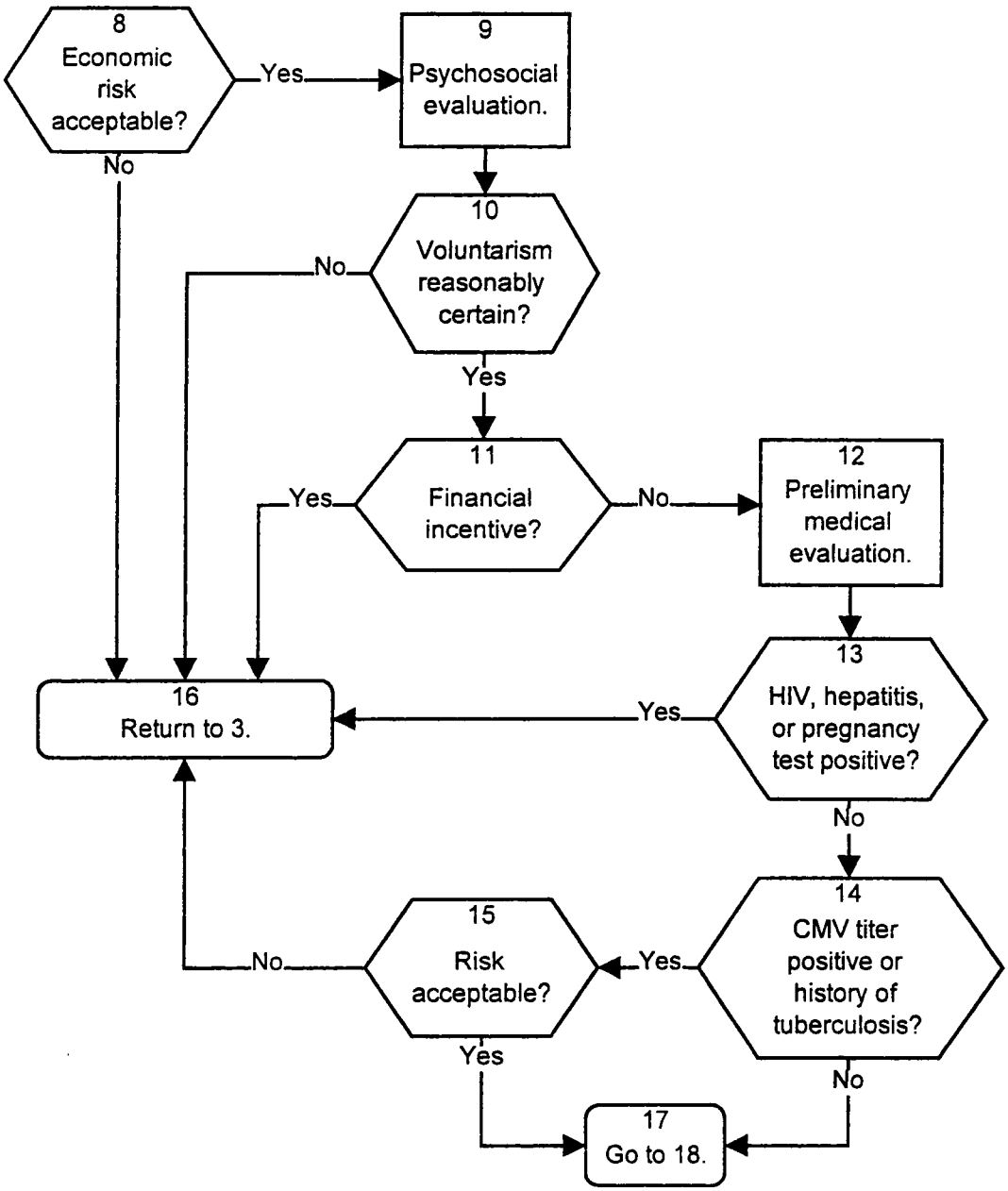
Overview.

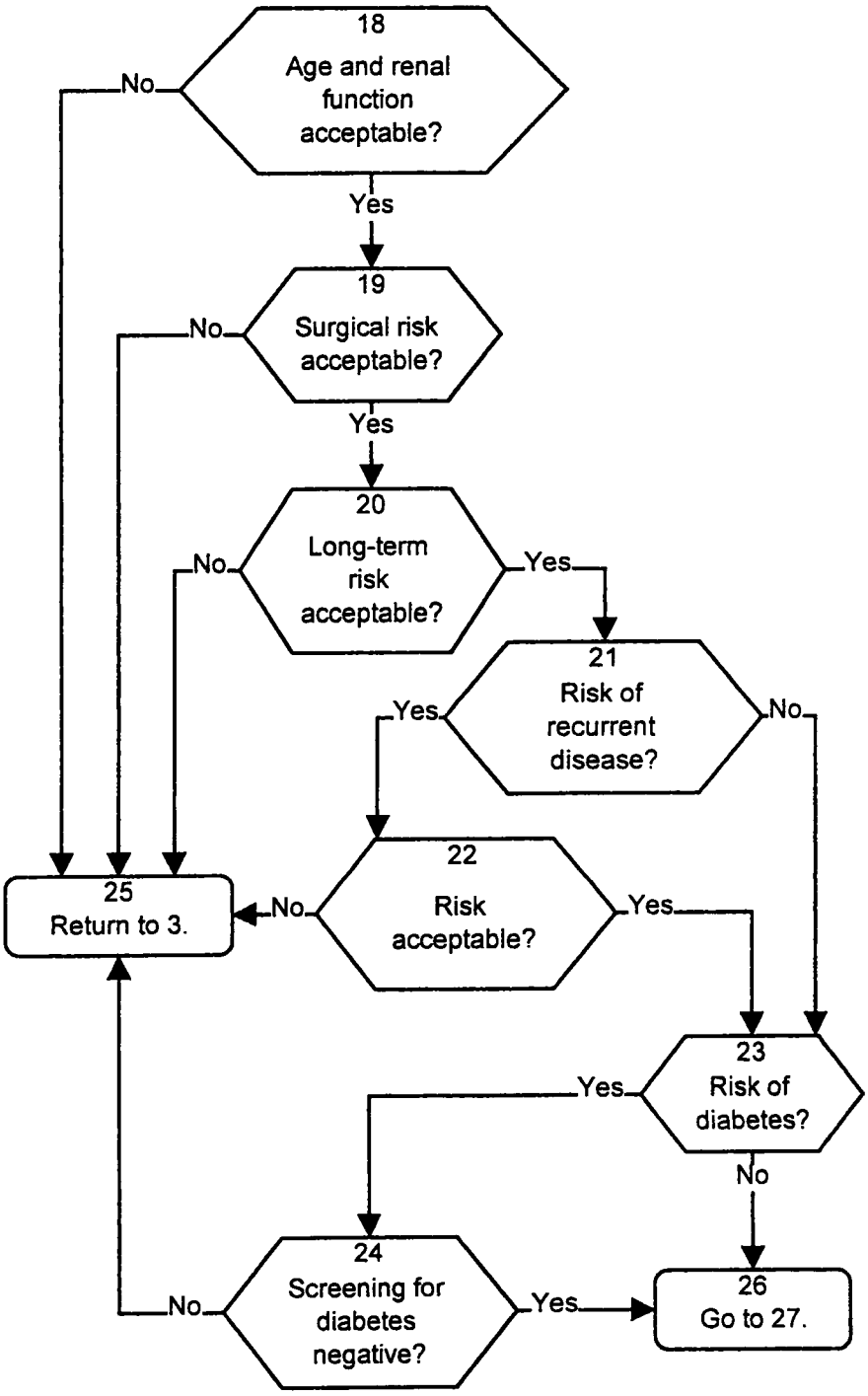

Willing to accept living donor?
No
Yes
ABO compatible and cross-match negative donor available?
No
Yes
Evaluate for cadaveric transplantation.
Preliminary medical evaluation.
No
Risk acceptable?
Yes
Complete medical evaluation.
No
Risk acceptable?
Yes
Schedule transplant surgery.

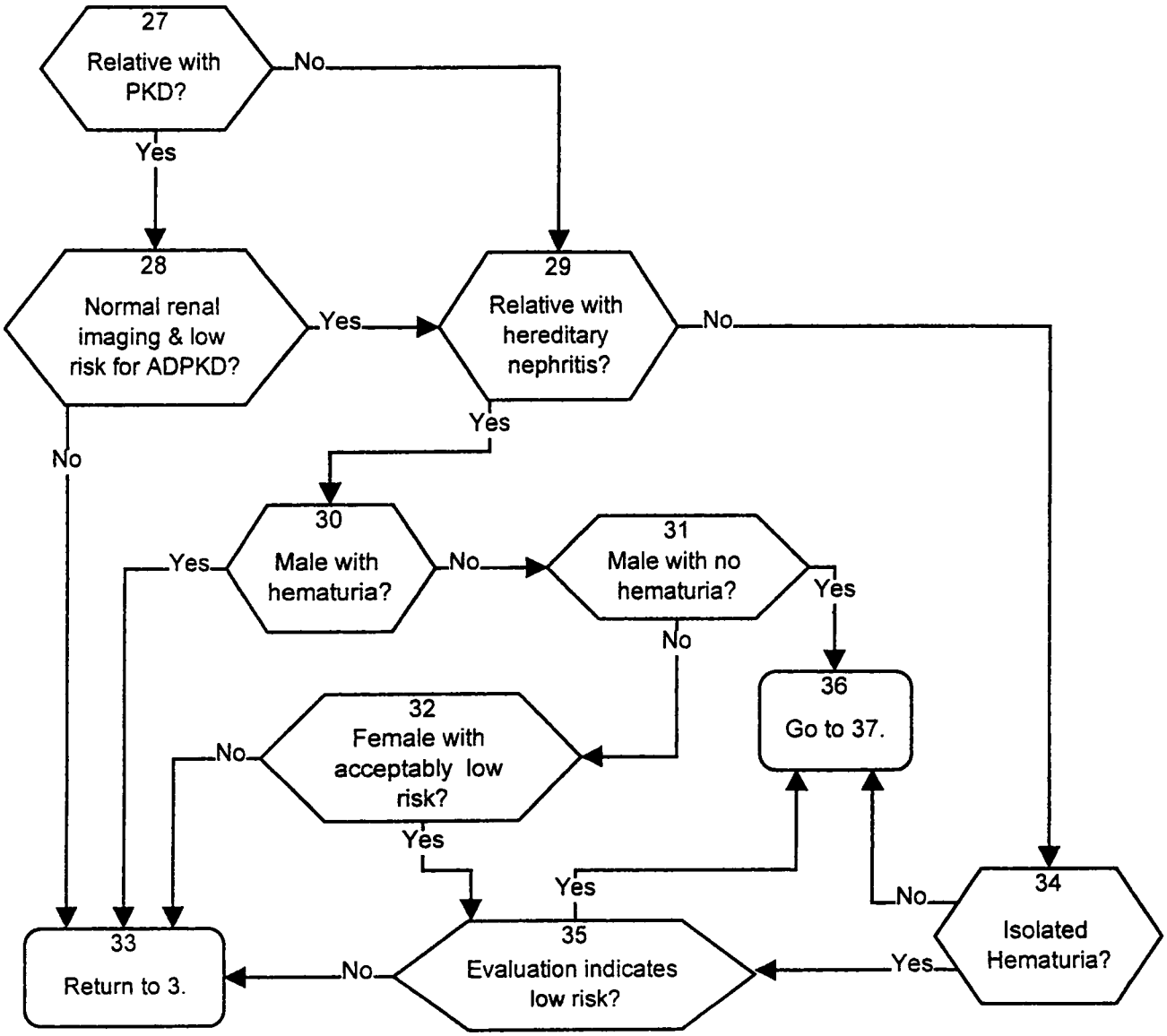
living donor is the most important goal of the living donor evaluation. This goal should not be compromised in any way by the desire to improve the welfare of the recipient, however strong and altruistic that desire may be. A living donor should only be used if the donor, and the physicians evaluating the donor, agree that the risks have been adequately defined and are acceptable.

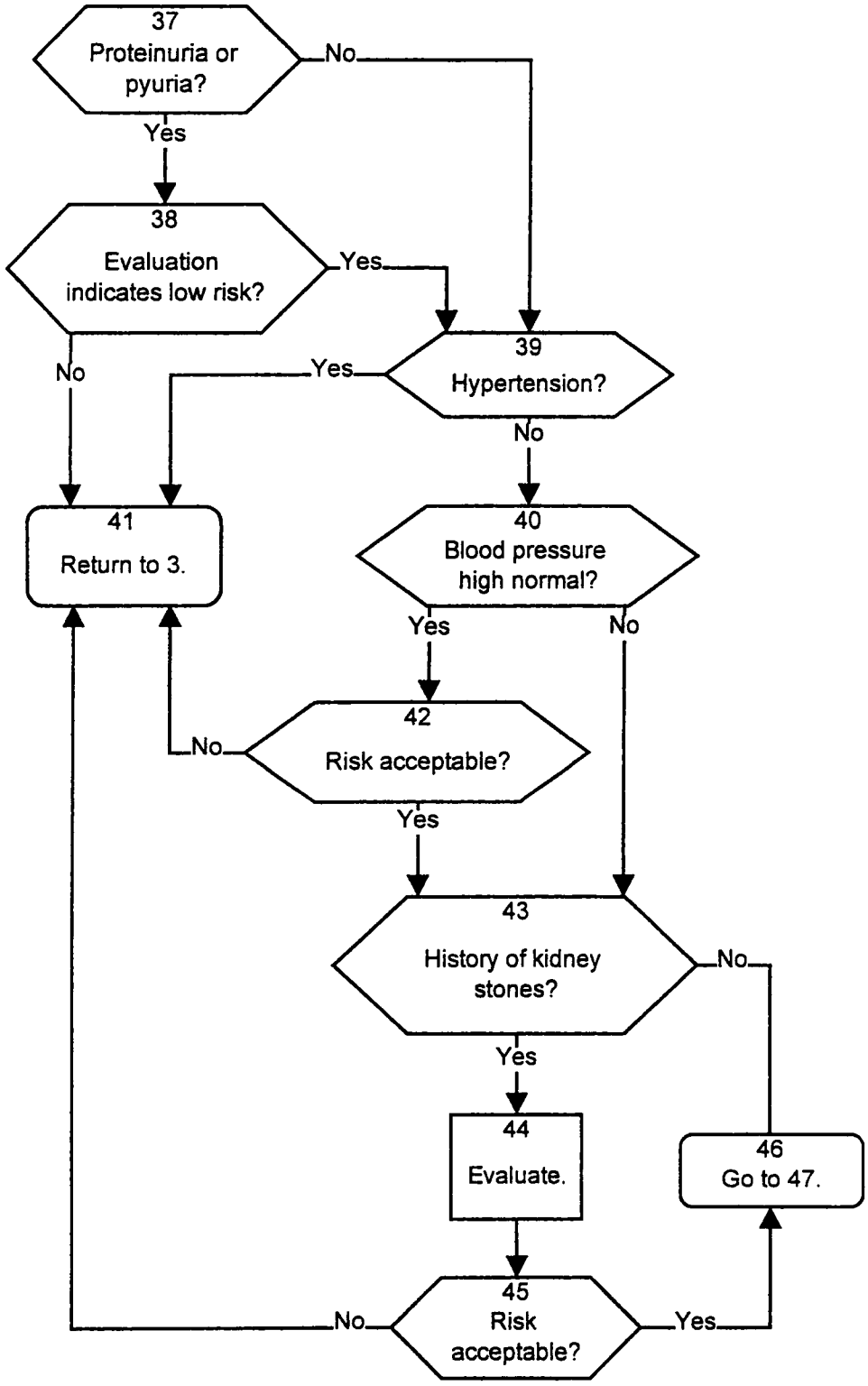
Detailed Algorithm.

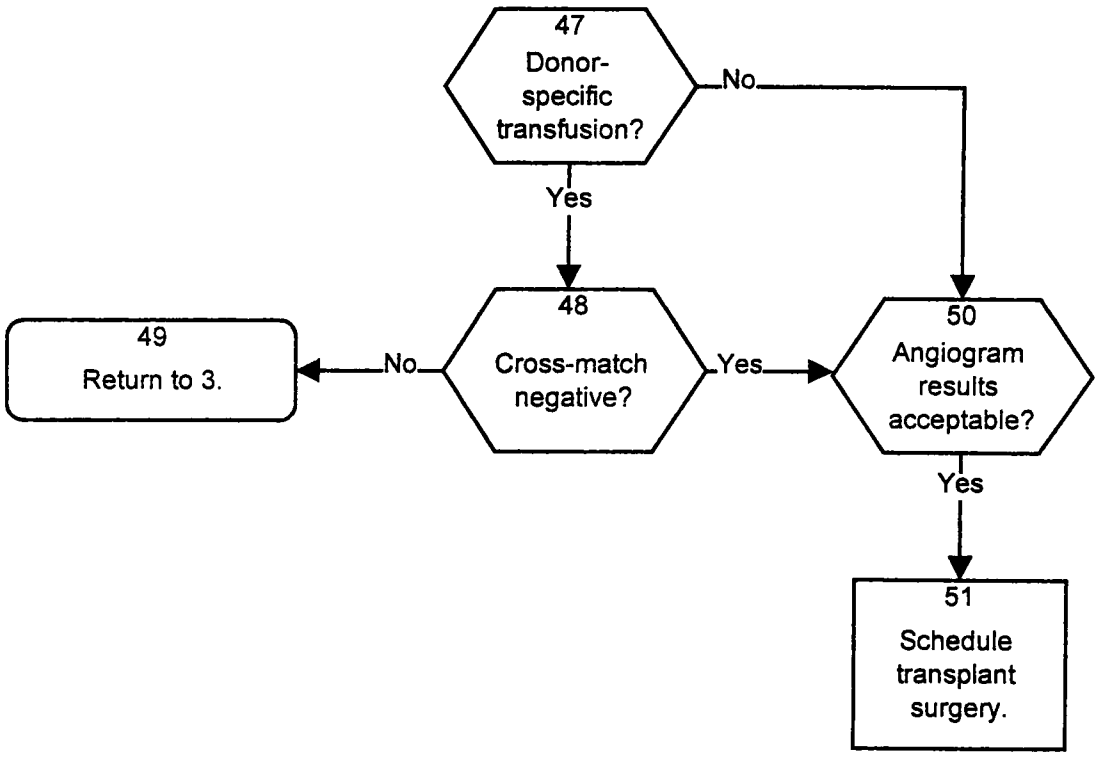



8
Economic risk acceptable?
Yes
9
Psychosocial evaluation.
No
10
Voluntarism reasonably certain?
No
Yes
11
Financial incentive?
Yes
No
12
Preliminary medical evaluation.
13
HIV, hepatitis, or pregnancy test positive?
Yes
16
Return to 3.
No
14
CMV titer positive or history of tuberculosis?
Yes
15
Risk acceptable?
No
Yes
No
17
Go to 18.


18
Age and renal function acceptable?
No
Yes
19
Surgical risk acceptable?
No
Yes
20
Long-term risk acceptable?
No
Yes
21
Risk of recurrent disease?
Yes
No
22
Risk acceptable?
No
Yes
25
Return to 3.
23
Risk of diabetes?
Yes
No
24
Screening for diabetes negative?
No
Yes
26
Go to 27.


27
Relative with PKD?
No
Yes
28
Normal renal imaging & low risk for ADPKD?
Yes
29
Relative with hereditary nephritis?
No
Yes
No
30
Male with hematuria?
Yes
No
31
Male with no hematuria?
Yes
No
36
Go to 37.
32
Female with acceptably low risk?
No
Yes
Yes
No
34
Isolated Hematuria?
35
Evaluation indicates low risk?
Yes
No
33
Return to 3.


37
Proteinuria or pyuria?
No
Yes
38
Evaluation indicates low risk?
Yes
No
39
Hypertension?
Yes
No
41
Return to 3.
40
Blood pressure high normal?
Yes
No
42
Risk acceptable?
No
Yes
43
History of kidney stones?
No
Yes
44
Evaluate.
46
Go to 47.
45
Risk acceptable?
No
Yes



DETAILED ALGORITHM ANNOTATIONS

1. See the ASTP Guidelines for the Evaluation of Renal Transplant Candidates (4)

2. Ethical Considerations for the Use Living Donors

Although the first successful renal transplant was from a living donor, the use of living donors has always raised ethical questions (5). Is it justifiable to risk major surgery (nephrectomy) in a healthy person to benefit someone with disease? The overall physical and psychological well-being of the donor is of paramount importance and must be assessed without regard to the needs of the recipient. However, the ethics of live donor transplantation demand close examination of risks and benefits for both donor and recipient. Voluntarism and informed consent must be ensured.

For the recipient of a living donation, the benefits can be expected to outweigh the risks. Living donation obviates the need to wait for a cadaveric kidney, and the evaluation of live donors can typically be performed in 1 to 2 months. In contrast, the median waiting time for a cadaveric kidney in the United States now approaches 2 yr, and the wait may be longer in some locales (6). With a live donor, the transplant can be timed to optimize outcomes for both donor and recipient. Indeed, a live donor greatly facilitates "preemptive" transplantation, or transplantation before dialysis initiation. Other benefits of living compared with cadaveric donor transplantation include: (1) reduced incidence of delayed graft function (and its attendant complications); (2) reduced risk of rejection and, therefore, fewer treatment-related side effects; (3) improved short- and long-term patient survival; and (4) improved short- and long-term allograft survival for both black and white recipients (7–9). Living donor transplantation thus reduces the recipient's risk of transplantation. In addition, other potential recipients also benefit by the reduced demand and increased supply of cadaveric kidneys.

Donors should be carefully informed of the inconveniences and short-term risks of diagnostic procedures, the pain and discomfort of nephrectomy, and the potential socioeconomic (Section 8) and psychologic (Section 9) risks. Death as a result of donor nephrectomy is exceedingly rare, major perioperative complications are unusual, and long-term risk appears to be small (Sections 19 and 20). Indeed, overall risk can be diminished by careful selection (10,11), and appears to be acceptable for many (12–17). Although the benefits for the donor are largely psychological, the donor does undergo a comprehensive medical evaluation that may detect previously unsuspected disease. However, the greatest benefit is from a sense of increased self-esteem, which may persist even after the allograft has failed (18–22). Up to 12 yr after nephrectomy, 97% of donors reaffirmed their decision to donate (18).

In the absence of medical contraindications, most centers consider the risk to the donor to be acceptably

low, and outweighed by benefits to both recipient and donor (10,11,18,20). However, because the benefits of donation are largely psychological, the decision must be carefully weighed by the potential donor. The transplant team needs to evaluate the risk to the donor, and provide accurate, information to both donor and recipient. If evidence points to excessive medical risk, it is appropriate to exclude a potential donor from further consideration. In the absence of such evidence, the person best qualified to weigh risks and benefits is the potential donor (19,23–25). The consent to donate must be well-informed, voluntary, and free of coercion (18,26). Consent can only be given by an individual who is competent and of legal age.

Live donor transplantation for a recipient who is at high risk for death or graft failure requires special consideration. For example, a high risk for recurrent glomerulonephritis in the allograft may be grounds for advising against the use of a living donor. Similarly, if the recipient's life expectancy is shortened by diabetes, cardiovascular disease, advanced age, or other conditions, it might be considered unwise to subject a donor to the risks of evaluation and surgery. Conversely, others might view that the timeliness, reduced risk of complications, and improved chances of success associated with living donor transplantation might be of particular benefit for a high-risk recipient (27–29). In each of these special circumstances, the likelihood of success in terms of both longevity and quality of life must be assessed by the transplant team and the family on an individual basis.

3. Willing and Available Living-Related Donor?

There is general consensus that the best donor is usually a member of the recipient's immediate family (24,26,30,31). If a transplant candidate is fortunate to have more than one potential living-related donor, selection should be based on both medical and nonmedical factors. When there is more than one potential donor, human leukocyte antigen (HLA) tissue typing may be especially helpful. Even with improved immunosuppression, substantial advantages are imparted to the recipient of an HLA-identical transplant, and the best graft survivals are achieved with HLA-identical sibling donors. Nevertheless, exceptions will arise in which the relative with the closest match is not necessarily the best donor. Non-medical considerations include the geographic location of donors, occupational risk for losing a kidney because of trauma, career demands, age, parental responsibilities, and family dynamics. The final decision regarding donor selection must be made by well-informed families in conjunction with the transplant team.

A careful and thorough family history should be taken to avoid commencing a work-up on obviously inappropriate donors (*e.g.*, because of a history of diabetes, hypertension, or renal disease). Generally speaking, all potential donors should be checked for ABO compatibility and all ABO-compatible donors should undergo tissue typing and cross-matching. Before this is done however, it is important to clarify Medicare coverage and the patient's insurance status because not all policies provide coverage for live transplantation, particularly for the patients who have not yet started dialysis. Some policies permit work-up of a single donor and some will only cover the medical expenses of the potential donor who actually donates (see Annotation 8, below).

It has traditionally been recommended that the best HLA-matched potential donor be evaluated first, and that relatives should be considered before emotionally related donors. However, because the results of all live transplants are excellent, good matching need not be the only determinant of donor choice. For instance, if a young recipient has the option between a 1-haplotype-matched transplant from a parent, or a 2-haplotype-matched transplant from a sibling, some physicians would use the parent as a donor because it is possible that the recipient may require another transplant later in life. Alternatively, others would use the 2-haplotype-matched sibling in the hope of minimizing immunosuppression requirements. These issues need to be discussed fully with the recipient and family, and the final educated decision left in their hands.

4. ABO Compatible?

Breaching the barrier of major ABO incompatibility without immunologic manipulation of the recipient to eliminate anti-donor isoantibodies almost invariably leads to hyperacute rejection and graft loss. The number of successful transplants using plasmapheresis or other maneuvers to cross the ABO barrier have been small (1–3), and these approaches should be considered experimental. Except in circumstances of extraordinary recipient need or an appropriately designed clinical trial, ABO-incompatible transplants are contraindicated (32).

5. Available Emotionally Related Donor?

There is a consensus that the best donor is usually a member of the recipient's immediate family (24,26,30,31,33,34). In the absence of a relative, most centers would now accept an emotionally related donor, such as a spouse, a relative of a spouse, an adoptive parent, an adopted son or daughter, or a close friend (35). With improved immunosuppression, successful outcomes (1 yr graft survival >90%) are now common using emotionally related donors, regardless of HLA compatibility (8,31,33,36,37). However, most physicians agree that there should be evidence of a strong, enduring, emotional commitment on the part of the donor (30,35,38). Current law in the United States bars commercial exchange of live donor organs (39). Likewise, major transplant organizations have taken a strong stand against such transactions (40).

8. Economic Risk Acceptable?

Medicare covers the cost of organ acquisition, including the cost of removing organs from living donors (41). Medicare-reimbursable organ-acquisition costs also include tissue typing and expenses incurred by donors (41). Thus the donor should incur little or no cost for medical evaluation and care directly related to donation. However, despite Medicare coverage, there is some financial risk for the potential donor (42).

The economic risk of donating a kidney should be discussed with the potential donor. There are few data documenting the potential monetary risks of kidney donation, and these risks undoubtedly vary from center to center and patient to patient. In a survey of donors from nine transplant centers geographically distributed throughout the United States, 76.7% of 536 respondents reported they encountered no financial hardship from donating, whereas 20% reported that the hardship was moderate and 3.2% said that it was severe (18). The expenses incurred by donors varied substantially. Although the median was only $62.50, 8.0% reported incurring at least $1000 in personal expenses. The respondents reported that economic support for expenses not covered by Medicare or third-party payers came from: sick leave (38.5% of respondents), vacation time (15.7%), borrowed money (7.2%), personal savings (12.5%), the recipient (7.9%), other family members (19.8%), or other sources (16.8%) (18). There were 3.8% who reported a change in the type of employment, and 7.2% who reported a change in work hours after recovery from surgery (18).

Donors should be told if they will not be compensated for lost time and income. Donors should also be told of the time that will be required for the evaluation process, hospitalization, and recovery, and that they may have to miss several days of work (Section 19). They should be told if they will need to pay expenses resulting from their travel to and from the transplant center. A survey of insurance companies indicated that kidney donation should not increase the cost of insurance (43). Similarly, in a survey of donors, 98.3% reported no precipitous increases in insurance premiums (18). However, a few donors reported difficulty in maintaining or obtaining health (4.2%), life (4.2%), or disability (2.3%) insurance. Insurability after donation was also found to be dependent on race (18). The remote possibility that the evaluation may uncover findings that could jeopardize the donor's insurability should also be discussed.

9 and 10. Psychosocial Evaluation

For an effective psychosocial evaluation, the transplant team should have access to appropriate resources, including a social worker, a psychologist, and/or a psychiatrist. Ideally, these individuals should have prior experience in dealing with transplant donors and their families, and should therefore have an in-depth understanding of the issues involved. In general, every potential donor should be evaluated by one of these individuals.

The psychological evaluation should first attempt to uncover clinical psychiatric disorders that would preclude donation. Generally, major affective disorders, personality disorders, a history of chemical dependency, or significant mental retardation become evident in the course of a routine psychosocial evaluation. A psychiatric disorder that may require the use of potentially nephrotoxic medications such as lithium carbonate should generally preclude transplantation. The potential consequences of donation need to be carefully weighed in individuals with unipolar or bipolar affective disorders. In most centers, individuals with a history of alcohol or drug abuse are considered to be acceptable donors if a period of abstinence, usually more than 6 months, is well documented (35). Mental retardation that impairs an individual's ability to understand the potential risks should generally preclude donation. The psychosocial evaluation should also ensure that: (*1*) donors are informed of potential psychosocial risks and benefits of donating a kidney; (2) potential psychosocial pressures influencing the donor's decision are uncovered and an assessment of the voluntary nature of the donor's willingness to donate is made; and (3) provisions are made for psychologic support for the donor after transplantation.

Donors should be informed that there are psychologic risks associated with kidney donation. A small minority of patients may, at some time, become depressed as a result of kidney donation. Minor feelings of depression are common in the immediate postoperative period. Indeed, in one study, 31% of 130 living-related donors reported feeling depressed in the post-surgical period (44). Depression in the living-related donor is also more likely to occur after graft failure (21,45). Usually, depression and other psychologic problems after donation are minor. Indeed, in a large multicenter survey, only 1 out of 536 donors reported emotional problems that were of sufficient magnitude to require the attention of a mental health professional (18). Nevertheless, there have been rare cases reported in which donors committed suicide after the kidney they had donated failed (46). Donation can, at least theoretically, have adverse effects on a marriage. In a survey of 371 donors who were married at the time of donation, 27 (7.1%) were divorced or separated at the time of follow-up, and 12 (44.4%) of these donors reported failed marriages within 1 yr of donation (18). Although none of the divorced or separated donors indicated that donation was the sole reason for the failed marriage, 33.3% stated that it was one of many reasons. Notably, a failed marriage was more likely to occur among individuals who reported that they were pressured to donate by other family members (18).

Most donors appear to enjoy the psychological benefits of donation. In a recent study of living donors, scores on six of ten psychological questions were

better among 494 donors than in the general population in Norway (47). In particular, donors were more likely to affirm that "life was worth living" and that they were more likely to be "cheerful" rather than "depressed." Similarly, in a long-term follow-up study of living-related donors, the Rosenberg Self-Esteem score was higher among donors after transplantation than before (48). In a survey of living donors, 97% of 536 unequivocally reaffirmed their decision to donate (18). In that same survey, 41.9% reported that their relationship with the donor had improved, 56.6% that it had been and continued to be good, whereas only 1.5% indicated a reduction in the quality of the relationship with the donor (18). In another survey, feelings toward the transplanted relative were much closer (compared with a little closer, same, or a little more distant) in 23% of donors (45).

A second major purpose of the psychologic evaluation is to uncover psychosocial pressures within the family that could influence the decision to donate, and could even be harmful to the potential donor. In one survey, 14.2% of 536 donors indicated that they felt at least some pressure from family members to influence their decision to donate (18). Individuals were more likely to receive pressure *to donate* from family members if the recipient was a parent, whereas there was more likely to be pressure *not to donate* if the recipient was a sibling (18). The psychosocial evaluation should also attempt to uncover reasons a potential donor may not want to donate, especially reasons the potential donor may be reluctant to divulge. Such reasons may include a fear of adverse consequences of donation, or even a fear that someone else in the family may need the kidney in the future. Potential donors must be told that a decision not to donate can be communicated to the recipient and other family members in a way that will preserve confidentiality, *i.e.*, it will be reported that the donor is "not medically suitable." The transplant team will shield the potential donor from specific inquiries by citing the need for medical confidentiality in all cases.

Finally, the psychosocial evaluation should lay the groundwork for post-transplant follow-up. After transplantation, the attention of family and caregivers usually shifts to the recipient, and the psychologic needs of the donor can easily become forgotten. Provision should be made for the donor to receive psychological support in the immediate post-transplant period and beyond. The fact that donors may have psychological problems if and when the graft fails should be kept in mind, and the donor should be given means for obtaining the necessary psychological support when needed.

11. Financial Incentive

Caregivers must make every effort to ensure that a donor is under no potentially coercive financial constraints. Special attention should be paid when the potential donor is not a relative, particularly when the relationship itself is potentially coercive, as might occur, for example, when the donor is an employee of the recipient.

12. Preliminary Medical Evaluation

Contraindications to donation discovered during the course of a preliminary medical evaluation may save time, money, and potentially adverse (physical and psychologic) effects of a more extensive evaluation. To avoid a conflict of interest and to preserve the donor's autonomy, the donor evaluation should, whenever possible, be carried out by individuals who are not the same as those responsible for evaluating and caring for the recipient (49). The preliminary medical evaluation should include a history and physical examination. In the medical history, particular attention should be given to hypertension, nephrolithiasis, proteinuria, hematuria, edema, or renal parenchymal infection. Evidence of established hypertension or renal disease may preclude the use of a donor and obviate further evaluation. Similarly, a history of multiple cardiovascular risk factors, diabetes mellitus, malignancy, or systemic disease that could have renal involvement may make further evaluation unnecessary.

A routine physical examination may also uncover conditions that would preclude donation. Height and weight should be used as part of the physical examination to assess obesity and its associated surgical risk. Blood pressure should be obtained on more than one occasion, especially if borderline values are noted. Other physical findings that would indicate an increased risk of general anesthesia and surgery, and may thereby lead to the exclusion of a potential donor, should be sought. Particular attention should be given to possible evidence of chronic pulmonary and/or cardiovascular disease. The preliminary medical evaluation should also attempt to uncover evidence of chronic renal disease that could compromise both the donor and recipient. Evidence for chronic infection and malignancies should also be sought.

With regard to malignancies, there are few data to suggest an interval of time beyond which it is safe for an individual with a history of a malignancy (currently in remission) to donate. Certainly, the donor should be free of active malignant disease and should not be receiving therapy for a malignancy. The Cincinnati Transplant Tumor Registry has documented a number of instances in which malignant tumors have been transmitted by the donor kidney (50). In 19 of these cases, the donors were living relatives who received therapy for cancer within 5 yr of donation, were found to have cancer at the time of donation, or developed cancer within 18 months after the procedure (50). The most common malignancies to be transmitted by these living donors were cancers of the kidney (7 of 19) and colon (3 of 19). Potential living donors for recipients whose original renal disease was bilateral renal cell carcinoma are at special risk of transmitting familial renal cell carcinoma (51).

13. Screening for Human Immunodeficiency Virus, Viral Hepatitis, and Pregnancy

The preliminary medical evaluation should include screening for human immunodeficiency virus (HIV), viral hepatitis, and pregnancy. Both the HIV and hepatitis viruses can be transmitted through the transplanted kidney (52–54). Evidence for HIV or hepatitis should preclude the use of that donor. Women should not be evaluated further while they are pregnant. How long after delivery women should wait before donating a kidney is unclear.

14 and 15. Cytomegalovirus and Tuberculosis

The preliminary medical evaluation should include immunoglobulin G (IgG) and IgM antibody titers for cytomegalovirus (CMV), because transplantation of a kidney from a patient who is CMV-positive is associated with a higher risk of CMV disease in the recipient (55–57). The donor CMV status will generally have no bearing on the individual's suitability to donate. However, if the donor is CMV-positive, the use of prophylactic measures in the recipient may be warranted. The preliminary medical evaluation should screen for tuberculosis, and include a chest x-ray and a skin test if there is no prior history of tuberculosis. There is some risk that tuberculosis may be transmitted with the donor kidney (58,59). Active tuberculosis is a contraindication to organ donation.

18. Donor Age and Renal Function

The early experience in living-related donor transplantation revealed that patient survival was inferior in recipients of kidneys from donors over the age of 51 yr (60). More recently, the survival of recipients of grafts from older donors has been reported to be comparable with that of recipients from donors less than 55 to 60 yr of age (61,62). Indeed, most studies now suggest that short-term (1 yr) (63–67) and long-term (5 yr) (64,66,67) graft survival rates are similar for kidneys from younger compared with older living donors. However, some researchers have still reported poorer long-term graft survival in donors over 60 yr of age (63,68). It has generally been reported that the function of older grafts, *e.g.*, grafts from donors over 55 to 65 yr of age, is reduced compared with the function kidneys from younger donors, but is, nevertheless, stable (64). However, some studies dispute this (66,69). Poorer graft function from older living donors should not be surprising, because nephrosclerosis was increased in baseline kidney biopsies from older donors (median age, 57 yr) (70).

In general, older living donors and their recipients should be made aware of the possibility that allograft function, and possibly even graft survival, may be compromised to some extent by the age of the donor. However, this should not necessarily preclude the use of an older living donor on an individual basis. Indeed, it is difficult to define an upper age limit for living donors. In a recent survey of United Network for Organ Sharing (UNOS)-approved centers, 27% used no defined age exclusion, 6% used 55 yr, 13% used 60 yr, 70% used 70 yr, 3% used 75 to 80 yr, and 13% had no policy (35).

In theory, size mismatches, whereby some kidneys may be too small and/or have too few nephrons for the size and metabolic demands of the recipient, could lead to graft failure (71). However, there currently appears to be inadequate data to justify the exclusion of living donors because they are smaller than their recipient (72).

Although it has recently been suggested that our standards may be too high (73), it is generally accepted that the donor's renal function should be normal, after correction for age and gender. Indeed, 58.8% of UNOS centers stated they excluded donors with a creatinine clearance rate <80 mL/min per 1.73^2, 21.2% with a creatinine clearance rate <60 mL/min per 1.73^2, and 2.5% with a clearance rate <40 mL/min per 1.73^2, whereas 10.6% did not exclude donors based on renal function *per se* (35). Unfortunately, inadequate urine collection, diet, and other factors may result in a low creatinine clearance rate in individuals with normal kidney function. An alternative method for measuring GFR should be considered before excluding a patient because of a low creatinine clearance rate. Dietary protein intake should also be considered, as low protein intake (0.3 gm/kg per day) has been demonstrated to reduce inulin clearance by about 9 mL/min compared with individuals on a moderate protein intake 1.0 gm/kg per day) (74). Because many factors influence the measurement of renal function, we are reluctant to specify a precise level of renal function below which a potential donor is not acceptable.

19. Surgical Risk

The risk of donating a kidney includes both the short-term perioperative risk, including pain and discomfort, and the long-term risk of having only one kidney. Exactly what information potential donors are told about the risks involved in renal donation appears to vary substantially from center to center (35). Information on perioperative risk comes from three sources: published data on the risk of any major surgery, published data on the specific risk of donor nephrectomy, and the personal experiences of the transplant team.

The American Society of Anesthesiologists (ASA) physical status index is the most commonly used index for assessing the risk of major surgery (75). Patients are assigned one of five classes: I, healthy; II, mild disease without functional limitations; III, severe disease with definite functional limitations; IV, severe disease that is a constant threat to life; and V, expected to die within 24 h. Patients being considered for donation will generally fall into Class I, and occasionally into Class II. Studies have shown that perioperative death rates are roughly proportional to ASA

class (76–78). The overall risk of death is less than 0.5% for patients in Class II (77,78).

Goldman *et al.*, have developed an index for assessing cardiovascular risk of major surgery (79). Points are assigned based on age, history of myocardial infarction, physical findings of heart failure, arrhythmias, routine laboratory tests (including potassium, bicarbonate, urea nitrogen and creatinine), and the type of surgery. Although some researchers have found that this index predicts major cardiac complications from surgery (80,81), others have not (82–84). A number of easily detectable risk factors, such as malnutrition (85,86), poorly controlled blood pressure (87), and diabetes (88), are associated with a greater surgical risk and preclude organ donation.

Estimates of the morbidity and mortality specifically associated with kidney donation can be made from surveys and from single-center studies. However, the true risk of donation may vary substantially from center to center. In a recent survey conducted by the ASTP, UNOS-approved centers were asked how many patients had died from kidney donation, and the number of patients in whom donation contributed to "potentially life-threatening or permanently debilitating complications" (35). Among the 75% of centers that responded to the survey, mortality was estimated to be 0.03%, whereas major morbidity was 0.23%. Mortality was also estimated to be 0.03% in a recent ad hoc survey of the American Society of Transplant Surgeons (16). On the basis of these data, the short-term surgical risk of kidney donation appears to be relatively small. However, data from surveys may be biased by under-reporting.

A number of individual transplant centers have reported data on the morbidity and mortality of live kidney donation. Through a MEDLINE search and a review of bibliographies from pertinent publications, a number of studies that reported data on the risk of kidney donation were located. We extracted data from all studies, except those that described the same patients in more than one report, in which case we extracted data from the most recent report. There were 27 reports (89–115); 13 published between 1970 and 1979 (90,95,98,100,101,103–105,108,109,111,112, 114), 12 published between 1980 and 1989 (91–94,96,97,99,106,107,110,113,115), and two published since 1990 (89,102). In these studies, there were 135 ± 127 (range, 22 to 628; total 3639) patients who had undergone donor nephrectomy. The mean (of mean) ages of the donors was 39 ± 5 yr (range of means, 31 to 51 yr; $N = 18$ centers). In 12 (57%) of the 21 studies reporting the maximum donor age, the oldest donor was over 60 yr old; in one report the oldest donor was 80 yr old (90).

Among all of the reports, there were only two deaths (0.05% of the total) directly attributable to surgery (90,112). One patient was 76 yr old at the time of surgery and died of halothane hepatitis (90), whereas another patient died of a pulmonary embolus (112). Another report attributed the death resulting from a motor vehicle accident to depression and alcohol abuse that possibly resulted from having donated a kidney that failed 3 yr earlier (109). Yet another publication cited two donor deaths learned from personal communications, without providing details or documentation (101). The 0.05% (2 of 3639) incidence of documented perioperative deaths reported in single-center studies is similar to the 0.03% mortality reported in surveys (16,35). To help potential transplant donors assess the meaning of this statistic, it may be useful to note that the chances of dying in a motor vehicle accident in the United States in 1993 was 0.02% (116). Thus, the risk of dying as a result of donor surgery is of a similar order of magnitude as the risk of dying as a result of a motor vehicle accident in 1 yr in the United States.

The morbidity of donor nephrectomy varies according to the definition of major and minor complications used by reporting centers. Among 13 centers that reported the rate of "major" perioperative complications, the rate was 4.4 ± 3.5% (mean ± SD; range, 0.0 to 13.0%) (90,91,93,94,96,100–103,106,107,111, 113). The reported rate for all perioperative complications was 31.8 ± 16.0% (12.2–63.0%) in 18 studies (89,93–98,100,103,104,106–108,110,112–115). Several studies described specific complications without defining an overall complication rate. Therefore, we also tabulated the rates of specific perioperative events. The following are the means, standard deviations, and maximums for all studies (the minimum was 0.0% for each study), listed in order of frequency: splenectomy, 0.2 ± 0.5% (2.3%); deep vein thrombosis, 0.2 ± 0.6% (3.0%); intra-abdominal abscess, 0.2 ± 0.7% (3.3%); wound hematoma, 0.3 ± 0.7% (3.0%); wound herniation, 0.3 ± 0.7% (3.0%); pulmonary embolus, 0.4 ± 0.8% (3.0%); intra-abdominal hematoma, 0.5 ± 1.2% (5.9%); pleural effusion, 0.9 ± 1.8% (5.6%); urinary retention, 1.0 ± 2.2% (9.3%); ileus, 1.0 ± 2.1% (10.0%); pneumonia, 1.6 ± 1.8% (6.7%); pneumothorax, 3.1 ± 4.1% (12.8%); wound infection, 4.3 ± 5.5% (26.7%); urinary tract infection, 5.3 ± 6.3% (25.0%); pulmonary atelectasis, 7.4 ± 10.8% (34.7%); pneumonia or atelectasis, 9.3 ± 10.8% (35.4%), other unspecified 5.3 ± 6.8% (27.8%). In this tabulation, we considered the absence of a complication in a particular report to indicate that the complication had not occurred. However, the fact that some events may not have been considered a complication in all centers may mean that the combined rates for some categories may be lower than the true rates.

Among the 14 centers that reported lengths of hospital stay, there was substantial center-to-center variability. The mean (of means) was 10.3 ± 3.6 days. The shortest mean stay was reported to be 6.4 ± 1.0 days (range, 4 to 9 days; $N = 115$ donors) (110), whereas the longest mean stay was 18.0 days (range, 6 to 33 days; $N = 62$ donors) (105).

20. Long-Term Risk

Several lines of evidence suggest that there is little long-term medical risk associated with renal donation. Because renal ablation in rats (the so-called "remnant kidney" model) can produce glomerular sclerosis with resultant proteinuria, hypertension, and renal insufficiency, investigators in several transplant centers have evaluated renal function in their donors 10 to 20 yr after nephrectomy. In these studies comprising data from 25 transplant centers, renal function has been consistently observed to remain stable with time, except for an age-related decrease in filtration rate (117). A small increase in proteinuria or microalbuminuria has been observed in 6 to 30% of donors (12,13,15,16,118–123) and an increase in hypertension has been reported in some (13,120,121, 124–126) but not all studies (12,15,16,53,118,123). When siblings have been used as control subjects in these studies, no increase in hypertension has been observed (16,118), suggesting a familial explanation for some of these findings. In the most recent study in which 78 donors were evaluated 21 to 29 yr after donation, hypertension and proteinuria were observed as a similar frequency in donors and their siblings and no donor with renal insufficiency was identified (16).

Similar findings have been noted in studies evaluating children and adults after unilateral nephrectomy for other reasons, such as trauma (17) or tumor (127). In these studies with 45 to 50 yr of follow-up, no adverse effect of nephrectomy on the development of hypertension or renal insufficiency was noted, although a small frequency of proteinuria of unknown clinical significance has been observed in some of these subjects. A recent meta-analysis confirmed the long-term safety of renal donation (128). In this meta-analysis, results of 48 reports of reduced renal mass involving 3124 patients and 1703 control subjects were combined. Organ donors comprised 61% of the subject population. Although unilateral nephrectomy caused a fall in GFR, there was no progressive decrement in this parameter over time. Similarly, a 50% reduction in renal mass was associated with an increased prevalence of proteinuria, but neither the prevalence nor degree of proteinuria was progressive over time in renal donors. Although a 50% reduction in renal mass tended to be associated with a small increment in systolic blood pressure, this increase did not lead to an increased prevalence of hypertension. Although longer follow-up is needed to confirm these data, current results suggest that the long-term risk of renal donation is low.

Despite the sizable amount of data attesting to the safety of renal donation, there have been a number of published case reports describing ESRD in renal donors (15,93,129,130). In a survey conducted by the ASTP, there were 15 donors who developed renal insufficiency after donation, 11 of whom had ESRD (35). None of the donors had evidence of renal disease before donation. Follow-up investigation of these donors indicated that most developed *de novo* renal disease. In six donors who presented with nephrotic syndrome or ESRD 10 to 20 yr after donation, no biopsy was performed to confirm the histology. The occurrence of renal disease or ESRD in these cases must be taken in the context of the number of cases expected during the period of observation (35).

In summary, data from single-center studies evaluating renal donors suggest that there is little long-term risk associated with renal donation, a conclusion corroborated by a meta-analysis of these studies (128). Furthermore, the occurrence of renal disease in isolated donors appears to be well within, or lower than, the risk expected in the general population. Although longer-term follow-up of renal donors is still needed, results to date indicate that renal donation is safe.

21 and 22. Risk of Recurrent Disease

There are three major questions pertinent to recurrent disease and living donation: (*1*) Should a kidney from a live donor be used if the recipient has an increased risk of losing that kidney because of the likelihood of recurrent disease? (*2*) Is there a greater chance that the recipient will lose the allograft from disease recurrence if a relative rather than an unrelated donor is used? (*3*) Will the same disease that caused renal failure in the recipient someday cause renal failure in the donor, and will the chance of this happening be increased by donation?

Almost all diseases affecting the native kidney can recur in the kidney transplant, with the exception of Alport's syndrome, polycystic kidney disease, and chronic interstitial nephritis. However, two diseases—focal segmental glomerulosclerosis (FSGS) and primary oxalosis—frequently recur in the graft (131,132). Although the exact etiology is unknown, there is growing evidence that circulating factor(s) in the recipient play a role in the recurrence of FSGS (132–134). In patients who have lost a first graft to recurrent FSGS, the risk of recurrence in the second graft may approach 60 to 80% (132,135–137). Therefore, live-donor transplantation should be used with caution in these patients.

In the case of primary oxalosis, there is a risk of oxalate deposition in the graft in the absence of simultaneous liver transplantation. Liver transplantation may provide a source of the deficient enzyme that leads to the accumulation of oxalate. In oxalosis, the possibility of better HLA-matching from a living-related donor may offset the risk of graft dysfunction if immunologic rejection is avoided. It has been suggested that any factor contributing to the inability to maintain copious urine output immediately after transplantation, *e.g.*, acute rejection, may lead to allograft failure (138). Therefore, for patients with primary oxalosis and a potential living donor, either simultaneous liver and kidney transplantation from a

live donor, or preemptive cadaveric liver transplantation followed by live donor kidney transplantation should be considered. For all patients with primary oxalosis, especially those considering kidney transplantation alone, physicians should consider preemptive transplantation before ESRD develops to minimize effect of release of accumulated tissue oxalate stores on transplant function (139). If the patient is reaching, or has reached, ESRD, physicians should consider: (*1*) aggressive preoperative or perioperative dialysis to decrease oxalate stores (138); (*2*) oral orthophosphate and pyridoxine administration (140); and (*3*) maintenance of a high volume of dilute urine immediately after transplantation.

An association between an increased risk of recurrence in recipients of living-related kidneys and specific kidney disease has been noted for IgA nephropathy and membranous glomerulonephritis (131). The reasons for this are not known, but may be related to genetic predisposition. In the case of IgA nephropathy, although recurrence may be seen in up to 80% of recipients of living-related transplants (141), the risk of graft loss is less than 10% within the first year after transplantation. Therefore, living-related transplantation need not be avoided. With regard to membranous glomerulonephritis, it has been reported by some that recipients of well-matched, living-related kidneys have a risk for recurrence as high as 50 to 60%, often within the first 3 to 4 months after transplantation (142–144). However, because only a few cases have been reported, it is difficult to precisely determine the risk of recurrent membranous nephropathy, and living-related transplantation should not be avoided. Nevertheless, recipients must be informed of the possible risk of recurrence.

Hereditary renal diseases other than Alport's syndrome and autosomal dominant polycystic kidney disease (ADPKD) may affect the living-related donor. These include: IgA nephropathy, hemolytic uremic syndrome (HUS), systemic lupus erythematosus (SLE), and cystinosis. Living-related donors for recipients with IgA nephropathy, particularly HLA-identical siblings (sharing HLA-B35), may have clinically silent IgA mesangial deposits. Indeed, in one center performing routine biopsies of living donor kidneys before revascularization, nine of 70 donors (13%) were noted to have mesangial IgA deposits on immunofluorescence and mesangial electron-dense deposits on electron microscopy (145). Although there appears to be no reported long-term detrimental consequences of donation to the donor in this situation (146,147), few long-term follow up studies have been reported. It would appear, however, that transmitted IgA deposits disappear as early as 12 days (148) to 1 month (149) after transplantation in the recipient. In the case of HUS, the possible familial inheritance of an endothelial prostacyclin synthesis abnormality, which may be important in the pathogenesis of HUS (150), should be discussed with the donor and recipient. With regard to SLE, it is reported that some family members of patients with SLE may be at increased risk of developing the disease themselves, particularly male relatives of men with the disease (151). Although the risk is small, it may be prudent to obtain serologic tests for SLE in asymptomatic prospective living-related donors.

23 and 24. Diabetes

The rationale for detecting diabetes in the potential donor is to avoid exposing that donor to risks that might result from donating a kidney in the setting of diabetes. Most agree that diabetes increases the risk of general anesthesia and surgery, so that excluding overt diabetes in a potential donor is important in minimizing the risk of donation. However, it is not as clear how much risk there is for an individual who donates a kidney and then subsequently develops diabetes. Specifically, does having one kidney increase the incidence or rate of progression of diabetic nephropathy if diabetes is diagnosed after donation? The answer to this question determines how important it is to assess the risk of developing diabetes in a potential donor.

Experiments carried out in rat models of Type I diabetes suggest that unilateral nephrectomy may accelerate the development of diabetic nephropathy (152,153). However, the applicability of these experiments to humans with diabetes is unknown. Indeed, there are reasons to doubt whether the results of these experiments in rats can be directly applied to humans. For example, the renal injury in these experiments was an accelerated form of the injury that rats normally develop with aging, and did not resemble the diabetic nephropathy that develops in humans. There are no data in humans addressing whether having one kidney instead of two accelerates the development or rate of progression of diabetic nephropathy. Therefore, we can only speculate what risk there might be for a potential donor who is not overtly diabetic, but who is found through testing to be at increased risk of developing diabetes in the future. This risk may also vary with the age of the potential donor. A 55-yr-old donor who develops diabetes 10 yr after donation is probably at less risk of developing diabetic nephropathy than a 20-yr-old who develops diabetes 10 yr after donation.

The theoretical risk of accelerating diabetic nephropathy by organ donation in a patient who is not yet diabetic must also be considered in light of the real risk of false-positive screening-test results. Until more information is available, physicians evaluating potential donors will need to weigh these issues and decide what screening tests are appropriate for each individual. In any case, the risk of diabetes and its possible consequences should be discussed with all potential donors. Indeed, it is reasonable that the wishes of the potential donor be taken into account in ordering screening tests for diabetes.

Although the genetic transmission of diabetes is poorly defined, a positive family history does identify

individuals who are at increased risk for developing diabetes (154,155). In families with members who have diabetic nephropathy, siblings of individuals with insulin-dependent diabetes mellitus (IDDM) and offspring of parents who have hypertension are at greater risk for diabetes and microvascular complications (154–157). Native Americans, African Americans, and Hispanics are groups at increased risk for diabetes and progressive complications. The American Diabetes Association recommends screening anyone with hypertension, hyperlipidemia, age greater than 40 yr, and nonpregnant women with history of gestational diabetes or a baby weighing greater than 9 pounds at birth (158). Attention is directed primarily toward identifying the undiagnosed non-insulin-dependent diabetes mellitus (NIDDM) patient. Screening is not recommended for IDDM in the under-20-yr age group because the disease has low prevalence and presents with a relatively rapid onset of classic symptoms. Risk factors alone are not sufficiently predictive in a given non-diabetic individual, and in absence of clinical diabetes, positive risk factors are not an absolute contraindication to donation.

There are several biochemical and hormonal response assays to screen for IDDM, but in clinical practice, the fasting plasma glucose and oral glucose tolerance test (GTT) remain the standards. Indeed, the National Diabetes Data Group and World Health Organization have adopted the fasting blood glucose and the 75 gram Oral GTT as recommended screening tests for diabetes (159). The hemoglobin A_1C level is useful in demonstrating long-standing hyperglycemia, but is not particularly helpful in screening for diabetes mellitus. Immunologic and genetic markers associated with diabetes have been identified (160–167), but they are not reliable enough to identify individuals at risk for IDDM, or to differentiate IDDM from NIDDM.

Oral GTT screening produces false-positive results in 4 to 10% of the healthy non-diabetic population, depending on the diagnostic criteria used (168). Less than 3% with impaired glucose tolerance, or "borderline diabetes," progress to overt IDDM each year. In many cases, abnormal GTT return to normal or remain "borderline" (168–170). Cases of borderline diabetes, or glucose intolerance, are often considered "high normals" to avoid undue patient anxiety, difficulties in obtaining employment or insurance, inappropriate dietary restriction, and inappropriate medication. In difficult cases, screening tests with increased sensitivity or specificity may be useful to evaluate fully the potential for glucose intolerance (171).

It is important to be certain that potential donors do not have conditions that can produce a positive GTT or abnormal fasting hyperglycemia. These include malnutrition, cirrhosis, hepatitis, portal-caval venous shunt, hormonal excess (hyperthyroidism, glucocorticoid excess, progestin and estrogen excess, and oral contraceptives), and hormonal deficit (hypoparathyroidism with hypocalcemia). Medications that can also produce hyperglycemia include diuretics, antipsychotics, antidepressants, lithium carbonate, phenytoin, β-blockers, and analgesics. Reactive hypoglycemia (defined by a glucose level less than 50 mg/dL during a GTT) may be detected during an oral GTT, and is generally a normal physiologic response.

Fasting plasma glucose and GTT are also used to screen for Type II diabetes, or NIDDM. Risk factors for NIDDM include age, obesity, history of gestational diabetes, and positive family history. There are no HLA markers associated with NIDDM and, unlike IDDM, HLA Class I expression is normal. The onset of NIDDM is often difficult to ascertain because NIDDM is frequently asymptomatic and may be present for more than 10 yr before diagnosis. In screening studies, approximately 50% of NIDDM patients diagnosed by GTT were unaware of their diabetic condition at the time of screening (172). In the past, it was thought that glucose intolerance could be a result of the physiology of normal aging (173,174), but this is no longer believed to be the case (175).

Glucose intolerance occurs in 2 to 3% of all pregnancies, usually at 24 to 30 wk of gestation. Potential donors and physicians should be aware that 30 to 50% of patients with transient, gestational diabetes will develop diabetes mellitus within 10 yr (176).

27 and 28. Polycystic Kidney Disease (PKD)

Autosomal recessive PKD (ARPKD) is not a diagnosis commonly made during donor evaluation, because this condition typically presents during infancy and is much less frequent than autosomal dominant PKD (ADPKD). Although there are forms of PKD that present later during childhood and adolescence (177), ARPKD should be evident by the time the patient is old enough to donate. The gene for ARPKD is located on chromosome 6, and direct assay for the gene is not yet available to aid in diagnosis (178).

ADPKD occurs in 1 in 400 to 1000 live births. About one half of cases will be diagnosed during lifetime, indicating a significant proportion of clinically silent disease (179). To screen effectively for clinically silent disease, it is necessary to understand the genetics and natural history of ADPKD. The ADPKD1 gene is located on chromosome 16, and an abnormality in this gene is present in a large proportion (86 to 96%) of ADPKD cases (180). An abnormal gene on chromosome 4 (ADPKD2) accounts for some of the remaining ADPKD cases (181). Although a ADPKD3 gene has been described, its chromosomal location has not yet been identified. Because cysts develop slowly in ADPKD, clinical diagnosis of patients under the age of 18 may be difficult, however, these individuals would not yet be old enough to donate. The age at which cysts are first detected may be partly determined by the genetic defect present; in ADPKD2, cysts are detected later than in ADPKD1 (182). For diagnosis, a total of three to five renal cysts bilaterally distributed is re-

quired, but these criteria may not identify young patients in whom cysts are not yet present, or may be too inclusive in older patients who have a greater incidence of acquired simple cysts. Therefore the criteria can be refined for age as follows (183):

1. In patients less than 30 yr of age, two cysts establish ADPKD. The cysts may be either unilateral or bilateral. (If the diagnosis was made only in patients with bilateral cysts, 11% of ADPKD cases would not be diagnosed.)
2. Between 30 and 59 yr of age, at least two cysts must be present in each kidney.
3. Over the age of 60, four cysts must be present in each kidney.

In patients with ADPKD1, the specificity of ultrasound diagnosis using these criteria is 85% at ages less than 10, increasing to near 100% by age 30 (184). Because of the possibility of a false-negative ultrasound below age 30, a negative renal ultrasound does not rule out ADPKD. Computed tomographic scanning may lower the age at which ADPKD can be ruled out, to 20 to 25 yr of age. In ADPKD2, the mean age at which cysts appear is somewhat later than in ADPKD1, and the progression to chronic renal insufficiency is also less rapid than in those with the ADPKD1 marker. Therefore, in a 30-yr-old patient who does not have the ADPKD1 marker, a negative ultrasound may not rule out later overt expression of ADPKD. Finally, diagnosis despite negative radiologic screening is possible by using DNA gene probe analysis. Flanking DNA markers linked to the ADPKD1 gene can pick up the disease in greater than 99% of cases (185) and assaying directly for the ADPKD1 gene is now possible (186). The donor evaluation is one indication for ADPKD1 screening of young individuals. Genetic markers for other ADPKD cases not resulting from the ADPKD1 defect are not yet as clearly defined, and non-PKD1 disease is not identifiable using genetic analysis.

In conclusion, ultrasound is usually sufficient to diagnose ADPKD in patients over the age of 30. In patients under the age of 30, computed tomographic scanning may permit exclusion of disease down to age 25. In patients under the age of 25, testing for the ADPKD1 and ADPKD2 genes could be considered to rule out ADPKD if gene testing is available, if the cost is not prohibitive, and if at least two other family members are available for testing.

29 and 32. Hereditary Nephritis

In families with documented inheritance of hereditary nephritis (or Alport's syndrome), living donors should be counseled with regard to possible development of the disease. In most kindreds, inheritance is x-linked (187,188). Asymptomatic males do not carry the abnormality, and heterozygous females may develop hematuria but rarely progress to renal insufficiency. Autosomal recessive inheritance occurs rarely; in this case, women are affected as severely as men, and passage from father to son may occur (unlike the x-linked disease) (189,190). Although positive family history is the norm, up to 15% of Alport's cases may have a negative family history, indicating a new mutation in the lineage (191). Clinical disease expression (hematuria, progressive renal failure, and sensorineural hearing loss), is similar irrespective of the pattern of inheritance, but variable in time of appearance and severity (190,192).

Screening of donors consists of examination for hematuria, renal function, auditory testing, and eye abnormalities such as anterior lenticonus, cataracts, and retinal lesions. Hematuria begins by the age of 5 in boys. As time passes, hypertension and renal insufficiency follow, often leading to ESRD by the age of 15 to 35. Renal biopsy is diagnostic, but early in the course of the disease may only show thinning of the basement membrane similar to thin basement membrane disease (193). Typical splitting of the glomerular basement membrane occurs in 30% of men by the age of 10, and in greater than 90% by the age of 30 (193). In the future, monoclonal antibodies detecting variations in the presence collagen chain determinants in affected basement membranes (194,195) or gene analysis (190,196,197) may identify hereditary nephritis patients or carriers, distinguish genetic variants, and differentiate patients with thin basement membrane disease (198) (which may present similarly to early hereditary nephritis).

In summary, *male relatives without hematuria* can be suitable donors for patients with hereditary nephritis. *Female relatives without hematuria* may be considered suitable donors, however, a women who might be a carrier should consider the possibility that she may have a child with the disease who might require transplantation. Molecular genetic testing, if available and affordable, can determine whether a woman is a carrier. *Female relatives with hematuria* and other evidence of renal involvement should not donate. Less clear is the case of a female heterozygote carrier who has asymptomatic hematuria. Such a person could agree to accept the risk (which is not currently quantifiable), if the need to donate is perceived to be great.

Finally, potential donors and recipients should be aware that a recipient with Alport's syndrome who receives a kidney from someone without Alport's syndrome may develop anti-glomerular basement membrane (anti-GBM) disease (199,200). Anti-GBM disease may result in graft failure (199,200).

34 and 35. Isolated Microhematuria

The evaluation of microscopic hematuria in a potential donor should be similar to that used in the general population. Routine screening with standard reagent strips commonly produces false positives, but false negatives are infrequent (201,202). Therefore, a negative result is quite reliable, whereas a positive result

should be confirmed by examining the urine sediment. Reagent strips may occasionally register the presence of blood in the urine when only one to two red blood cells per high-power field are present. The source of isolated microscopic hematuria may be either urologic or renal. Neoplastic diseases often cause hematuria. Hematuria combined with additional signs such as proteinuria, cellular casts, renal insufficiency, or hypertension is suggestive of glomerular disease, although the absence of these signs does not rule out glomerular disease. Glomerular diseases that most commonly cause hematuria include IgA nephropathy, thin basement membrane disease, or hereditary nephritis (203). Fever, heavy exercise, trauma, and urinary tract infection may also cause transient hematuria. Hematuria should not be blamed on anticoagulation, because an identifiable source is usually present (204).

Epidemiologic screening studies demonstrate isolated microscopic hematuria in up to 35% of young men (205), and up to 13% of postmenopausal women (206). Often no etiology is found in younger individuals. The literature supports noninvasive monitoring and follow-up of young individuals with isolated microscopic hematuria, given the low risk for malignancy if ultrasound or intravenous pyelogram is normal. Renal biopsy and cystoscopy are usually not necessary.

The situation is somewhat different in the older individual (over the age of 40 to 50 yr) with hematuria, because there is a greater chance of malignancy (207,208). Individuals over 40 to 50 yr of age require periodic follow-up with urinary cytology, and possibly repeat cystoscopy and radiography examinations. Approximately 1% of older patients with initially negative evaluations will be found to have a malignancy within 3 to 4 yr (207). Therefore, in considering donors with asymptomatic isolated microscopic hematuria, age should be taken into account.

Biopsy may be considered if no etiology for isolated microscopic hematuria is demonstrated by history, examination, laboratory findings, radiography, or cystoscopy. Regarding biopsy results, there are no large-scale reports of biopsy in living donors with hematuria. In an Egyptian study of 37 living donors with isolated microscopic hematuria, progressive renal disease was found on biopsy in a high proportion: hereditary nephritis in 25, nephrolithiasis in five, bilharzial cystitis in two, isolated glomerular deposition of C_3 in three, and glomerular deposits of IgA and IgM in one each (209). Potential donors with asymptomatic hematuria presented in 12% of families undergoing donor evaluation. It is not clear if these results apply to individuals in the United States. A recent survey of transplant centers in the United States indicated that 37% were willing to consider accepting patients with isolated microscopic hematuria for living donation if urologic evaluation and biopsy were normal (35).

37 and 38. Proteinuria and Pyuria

Proteinuria is probably most reliably detected in a 24-h urine collection. In general, urine total protein excretion rates greater than 150 to 200 mg/24 h or albumin excretion rates greater than 30 mg/24 h in the absence of infection is considered to be abnormal (210), and should be at least a relative contraindication to kidney donation. However, a small amount of postural proteinuria, *i.e.*, protein excretion that occurs only in the upright position, is usually benign (211). For this reason, some transplant centers would not automatically exclude a potential donor with postural proteinuria (35).

Pyuria, *e.g.*, more than one white blood cell per high-power field in a properly collected specimen (210), may be an indication of renal parenchymal disease due to chronic infection or other tubulointerstitial disorders. The cause of pyuria should be established before a potential donor is considered for transplantation. Only when it can be shown that the pyuria is the result of a reversible cause, *e.g.*, an uncomplicated urinary tract infection, should the evaluation proceed. A history of recurrent urinary tract infections may be an indication for urologic evaluation, including an intravenous pyelogram and cystoscopy, to exclude an underlying renal or urologic abnormality that would be a contraindication to kidney donation.

39 and 42. Hypertension

Hypertension, *i.e.*, systolic blood pressure persistently greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg (212), is at least a relative contraindication to kidney donation. By itself, a positive family history of hypertension is not a reason to exclude a potential donor. It is unclear whether individuals with elevated blood pressure in the office, but normal blood pressure at home, *i.e.*, "white-coat hypertension," are at increased risk for kidney donation (213). Also unclear is the role of 24-h ambulatory blood pressure monitoring in screening for hypertension in borderline cases. Frequent ambulatory cuff inflations apparently do not elicit the same reactive increase in pressure seen in the office (214). However, in the donor evaluation, the role of 24-hour ambulatory blood pressure monitoring *versus* multiple office or home measurements is unclear. Twenty-four-hour measurements that constitute normal are also incompletely defined, but current recommendations suggest a daytime average of 135 to 145/90 mm Hg or a 24-h average of 139/87 mm Hg as the upper limits of normal (215). Daytime average blood pressure below 135/80 mm Hg denotes normotension with a high degree of correlation to normal left-ventricular muscle mass. Echocardiographic evidence of left-ventricular hypertrophy, when the average blood pressure is between 135/80 mm Hg and 145/90 mm Hg, may indicate hypertension or a need for treatment (216). The average number of blood pressure readings above 140/90 mm Hg during waking hours and above

120/80 mm Hg during sleep (known as the blood pressure load) has been assessed in comparison to measures of cardiac hypertrophy. In mild to moderate hypertension, a 40% or greater blood pressure load correlates with end-organ (cardiac) hypertensive change (217).

Hypertension is one of the most common reasons for rejecting a potential donor before angiographic evaluation (218). This no doubt reflects the high prevalence of hypertension in the United States. Several studies have documented the natural history of hypertension in patients who underwent unilateral nephrectomy. Many reported that there is little or no increased risk of developing hypertension compared with the general population or age-matched control subjects (12,16, 17,118). However, others reported that the incidence of subsequent hypertension is increased, particularly in patients with risk factors before donation, or patients who had borderline hypertension (13,121, 124,125). Although few in number, there are reports of borderline or mildly hypertensive donors who had no evidence of progressive hypertension or renal complications after donation (13,125). In a recent meta-analysis of 48 studies examining the long-term effects of reduced renal mass, unilateral nephrectomy for organ donation or other reasons tended to be associated with a small increment in systolic blood pressure (128). However, this increment did not lead to an increased prevalence of hypertension (128).

Thus, although the evidence is not conclusive, the balance of data indicate that donating a kidney can worsen existing hypertension. Therefore, it is best to avoid potential donors who have hypertension. Less clear is the case of the individual with borderline hypertension, or the individual with occasional and mild increases in blood pressure. In any case, the possibility of an increased risk for hypertension in at least some living donors requires that the long-term follow-up of donors include blood pressure monitoring and treatment.

43 and 45. Nephrolithiasis

Nephrolithiasis is at least a relative contraindication to living donor nephrectomy because of the future risk that recurrent stones, obstructions, and infections will injure the remaining kidney. Nephrolithiasis not only places the donor at risk; inadvertent transplantation of a kidney with stones places the recipient at risk (219–221). Population studies indicate that patients who have passed one stone have an increased chance of passing additional stones (222). For calcium stones, 15% will pass a second stone within 1 yr, 35 to 50% within 5 yr, and 50 to 60% by 10 yr (223,224). When asymptomatic stones are present, symptoms develop in approximately 50% within 5 yr (225). In patients with primary gout, approximately 20% develop kidney stones, and the risk correlates with the degree of increased serum uric acid and hyperuricosuria (226). Patients who have combined stones formed of uric acid and calcium oxalate have a very high rate of recurrence (222). Struvite stones, particularly infection stones, are quite difficult to manage, and often form staghorn calculi and damage the kidney by obstruction or infection (222). The siblings of patients with cystinuria, an autosomal recessive inherited disorder of amino acid transport involving both intestinal epithelium and renal tubular cells, are at risk for the same condition. In addition, heterozygotes have an increased risk of forming calcium oxalate stones (222).

A history of stone formation need not be an absolute contraindication if the donor has passed only one stone, has stone disease that has been inactive for over 10 yr, and if nephrolithiasis is not currently present on radiographic studies. To be certain that there is no risk for active stone disease in the future, the donor with inactive stone disease should be carefully screened for risk factors and metabolic abnormalities. Should such a donor be accepted, lifelong medical follow up should include periodic stone risk assessment and medical treatment (including a general recommendation to avoid dehydration) to minimize any risks that are subsequently discovered.

Renal and ureteral calcifications are diagnosed by radiographic assessment before donation. The differential diagnosis of intrarenal calcifications includes calcified papillae, neoplasms, cholesteatomas, granulomas, and arterial calcification. Routine intravenous pyelography or plain films of the abdomen taken at the time of angiography will identify intracalyceal or ureteral stones. Ultrasound is recommended by some as a primary screen. For donor evaluation, because an intravenous pyelogram is performed routinely, ultrasound is used primarily to differentiate a nonradiopaque stone from a soft tissue mass. Although some transplant programs routinely screen donors for stones with a 24-h urine collection (10), most screen only those with definite risk factors and positive history (or significant family history). In patients with metabolic stone-forming abnormalities (gout, chronic aciduria, *etc.*) or a positive history of stones, a 24-h urine sample can be obtained to screen for individuals at high risk for recurrent stones, *e.g.*, low urinary volume, hypercalciuria, hypocitraturia, hyperuricosuria, and hyperoxaluria. Such patients should probably be excluded from donation. There is not a great deal of information in the literature to identify the frequency of donor non-acceptance because of nephrolithiasis. In one report of 159 donor candidates, 35 (22%) were rejected, and another 33 (21%) were accepted but failed to undergo nephrectomy. Nephrolithiasis accounted for the nonacceptance of one patient (218).

47 and 48. Donor-Specific Transfusion

For centers that perform donor-specific transfusions, this procedure should be carried out before angiography. Some recipients of donor-specific transfusions develop cytotoxic antibodies that preclude

transplantation with that donor. Thus, the angiogram should be performed only after a cross-match demonstrates that the transfusions have not led to sensitization.

Further discussion of the use of donor-specific transfusions can be found in the guidelines of the ASTP for the evaluation of renal transplant candidates (4).

50. Renal Angiogram

In an otherwise suitable potential donor, arteriography is used to define the renal vasculature and to look for other potential anatomic abnormalities that have escaped detection during the donor evaluation. The most important goal is to ensure that the donor's remaining kidney is anatomically normal. The overall risk of complications from angiography is less than 10% (227). Most of these complications were minor, *e.g.*, enlarging hematoma, prolonged bleeding, headaches, and nausea (227). However, the risk of more serious complications, including thrombosis, peripheral embolization, aortic and renal arterial damage, particularly in potential kidney donors, is reported to be approximately 2% (228). Although iodinated contrast media has nephrotoxic potential, contrast-induced renal failure is rarely encountered in individuals with normally functioning kidneys (229).

Angiography can be performed safely on an outpatient setting (230,231). The standard procedure is catheter angiography with selective renal arteriography, but some advocate abdominal aortography alone (228,232). Although evaluation of the renal vessels can also be performed using intravenous digital subtraction angiography (DSA) (233–236), intra-arterial DSA (102,237) and magnetic resonance angiography (238,239), all techniques (with the exception of standard catheter arteriography and intra-arterial DSA) are unable to detect multiple and/or accessory renal arteries reliably. The advantage of intra-arterial DSA in the ability to use smaller angiographic catheters and smaller volume contrast load (230). The main disadvantage of intra-arterial DSA is decreased spatial resolution compared with renal arteriography (240). The recently reported use of spiral computerized tomography in place of angiography in the evaluation of donors appears to be promising but needs further study before general acceptance (241–243).

On the basis of a normal angiogram, the left kidney is often selected for donation because of its longer renal vein (218). In women of childbearing age, the right kidney is preferred because the left kidney is protected from the hydronephrosis of pregnancy (218). Furthermore, kidneys with multiple renal arteries, early arterial bifurcations, or short renal arteries are generally avoided (218).

The use of kidneys with multiple renal arteries is associated with an increased risk of developing a urinary fistula (because of compromise of ureteral vascular supply) (244,245) and acute tubular necrosis (245). However, patient and graft survival rates were not significantly different with grafts having multiple compared with single renal arteries when surgery was performed by experienced surgeons (245,246). Surgical techniques, including extracorporeal end-to-side and common-channel anastomosis (247) or creation of an artificial patch (246), have minimized complications.

Rarely, fibromuscular dysplasia may be present in the donor renal artery. The detection of fibromuscular dysplasia has potential implications for both donor and recipient. For the recipient, resection or trimming of the involved segment (248) with or without creation of a Teflon patch (246) can lead to successful engraftment. However, fibromuscular dysplasia can recur in the allograft (248,249). In one radiographically confirmed case, recurrent fibromuscular dysplasia presented with severe hypertension after transplantation, which was successfully treated with percutaneous transluminal balloon angioplasty (248). Both donor and recipient should be informed that fibromuscular dysplasia may cause complications for the recipient after transplantation.

With regard to ensuring the safety of the donor, whether or not to accept a donor with unilateral fibromuscular dysplasia is a difficult question. The natural history of fibromuscular dysplasia of the renal artery is not well defined. Most data on the natural history is based on small series of patients who had fibromuscular dysplasia detected because of hypertension and/or decreased renal function severe enough to lead to renal angiography (250–252). In one retrospective report of patients who had serial renal angiograms, progression occurred in one third of cases (251). However, fibromuscular dysplasia detected as an incidental finding in an otherwise asymptomatic potential donor is probably less likely to progress. Likewise, the chance that the contralateral, normal kidney will someday develop renal artery disease is probably greater than normal, but nevertheless quite small. It is also possible that removing a kidney with renal artery disease may actually decrease the chances that the donor will someday develop hypertension. Deciding whether or not to exclude a donor with unilateral renal artery fibromuscular dysplasia from donation is difficult because the probabilities of the above events occurring are unknown. The question should be thoroughly discussed with the potential donor before any informed decision is made.

Some anatomic abnormalities found on angiography need not necessarily preclude transplantation. Renal artery aneurysms have occasionally been noted during donor arteriography, and resection with or without creation of an artificial patch has been reported to lead to successful engraftment (246,253). Small kidneys (9.7 to 11.0 cm) compared with normal contralateral (12.0 to 15.5 cm kidneys) have been successfully transplanted without undue risk to donors and recipients (254). Furthermore, there is evidence that hypoplastic kidneys may have an improve-

ment in GFR, RPF, and increase in parenchymal mass after transplantation (255). The latter occurred in the recipient of an HLA-identical kidney who did not receive cyclosporine. Transplantation of a small kidney with lower pole-scarring, presumably the result of reflux nephropathy (256), or kidneys with complete or partial duplicated urinary collecting system (257), benign cysts (257), ectopic kidneys associated with or without a short ureter (258) or hydronephrosis (259), and minimal stasis of the urinary system on intravenous pyelogram (253) have been reported to be associated with satisfactory graft function.

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