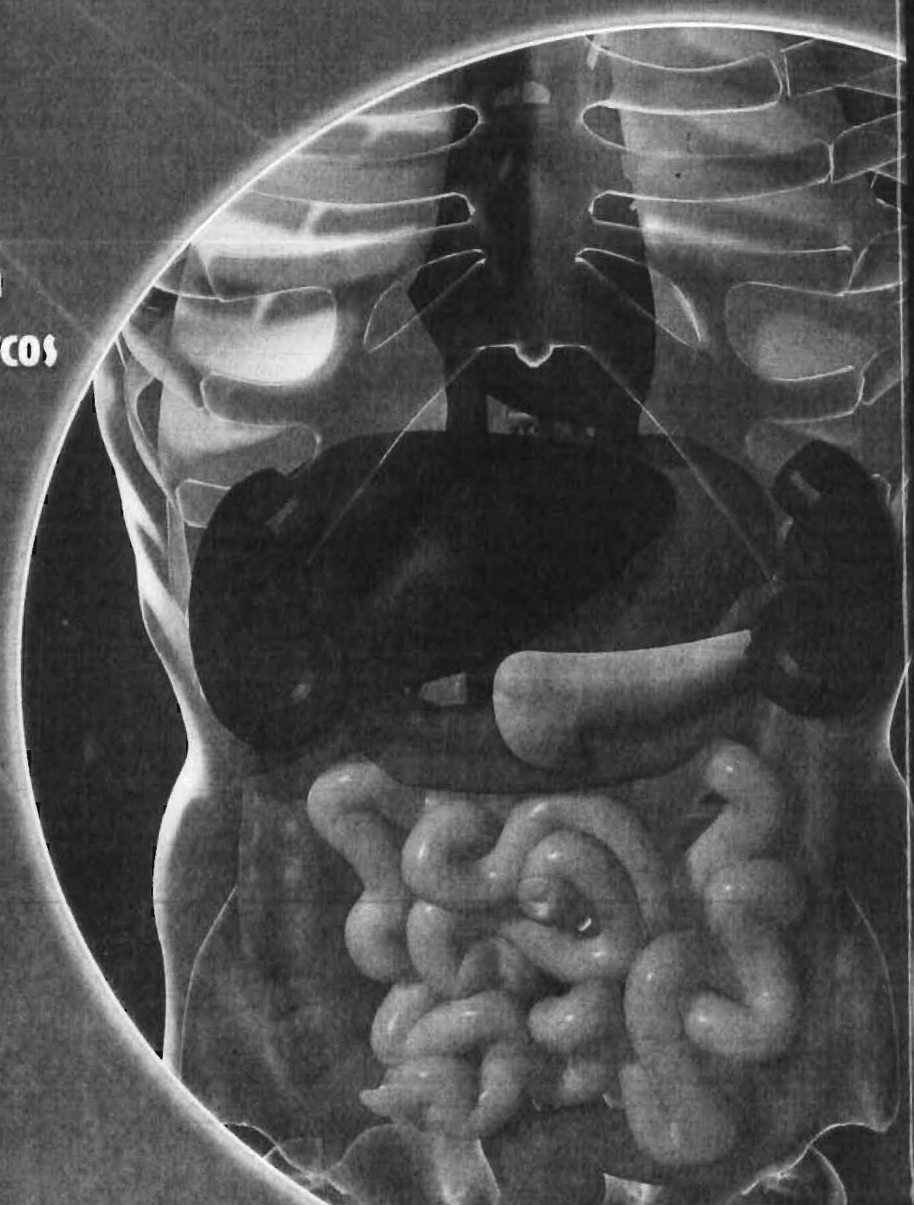




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1 Live-Donor Organ Transplantation: Then and Now

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INTRODUCTION

The concept of live-volunteer organ donation has been controversial ever since the first such operation was performed in 1953 in Paris by the team of Jean Hamburger. In the much-publicized inaugural case, a mother's kidney was transplanted to the extraperitoneal pelvic location of her non immunosuppressed son. The allograft functioned for three weeks before being rejected (1). The recipient operation, which had been developed by Rene Kuss (2), was essentially the same procedure as that employed for the historical identical twin cases of Murray and Merrill (3) and up to the present day. The donor operation also has changed only in its details.

During the ensuing 20 years (1953–1973), the conceptual framework of clinical renal transplantation that exists today was put in place in a succession of steps. The first of these steps (4) was largely dependent on kidney donation by live volunteers. In fact, it is unlikely that the modern era of kidney and other kinds of organ transplantation could have evolved as it did between 1953 and 1970 without the observations and advances made possible by the use of these early live donors. The reason was that organs from deceased donors during most of this time could be obtained only after cessation of heart beat and respiration. The clinical results using the ischemically compromised grafts were so poor and the clinical observations were so widely variable that deceased-donor organ transplantation had come to an impasse, both as treatment and as an instrument of discovery.

The practice of live donation was no secret and aroused surprisingly little negative reaction from the public. However, live donation was, from the beginning, an intractably divisive issue within the medical profession because it potentially placed healthy persons in harm's way and; therefore, appeared to violate the deep-rooted physician's tradition of *primum non nocere* (first, do no harm). Before support for live kidney donation could be solicited from religious leaders, government agencies, and ultimately the public, it was essential to develop agreement within the medical profession about the probity of this practice.

A kidney transplant-specific consensus was reached by the early 1970s in a series of ethical-medical conferences and publications (5,6) in which one of the authors of this chapter, Thomas E. Starzl (TES), was a foremost supporter of live donation. The seminal issue that had to be addressed was the doctor-patient relationship in which the physician assumes a specific kind of responsibility for the welfare of another human individual. Before the advent of transplantation, the doctor-patient agreement had been entered into without regard for its social or other ramifications. Because the "contract" between doctor and patient was so simple and clean, it had shielded the ill from evolving philosophical, religious, and legal caprices. Historically, the sole beneficiary of the "medical care umbrella" was the patient. What conceivable benefit was there for the healthy and well-motivated live donor?

A defensible way out was found at ethics conferences and in law courts with the argument that the fullness of the donor's emotional life and holistic welfare was very often dependent on that of the recipient. This argument was particularly persuasive under circumstances of intrafamilial organ transplantation. The long-term benefits to the donor could then be viewed as parallel, or even equivalent, to those of the recipient. Acceptance of this concept was a great relief to renal transplant surgeons whose early contributions to the new field had been so heavily

dependent on live donors. The work up and care of these donors had been provided exclusively by the recipient team (7), which also assumed a long-term responsibility for their follow-up.

By the time consensus was reached, two important events had improved the prospects for kidney transplantation. The first was acceptance in the late 1960s of the concept of brain death. This resulted in the immediate availability of better kidneys and other organs from dead but heart-beating donors. Second, the federally mandated end-stage renal disease (ESRD) amendment to the U.S. Social Security act of 1972, and similar legislation in several European countries, provided fiscal support for organ procurement from heart-beating deceased donors.

The American ESRD legislation caused an additional sea change. It also bolstered live kidney donation by underwriting for the first time the cost of work-up and operative care of the volunteer patients. A predictable effect of the federal financial incentive was peripheralization of the work up and other aspects of donor care. For example, kidney recipients and their donors frequently were referred from outlying hospitals as a pair, usually with a donor renal angiogram in hand. Now, the question arose whether the resulting division of responsibility for donor welfare could erode protection of these volunteers from coercion or even undermine safety standards of work up. At first, such concerns were minimal in Europe because live kidney donation was employed uncommonly, if at all, in most programs.

In the United States, where live donation had become widespread, it became difficult in some cases to identify who was looking after the donors' welfare. In the programs directed by one of the authors (TES) at the Universities of Colorado (until 1980) and Pittsburgh (1980-1992), live-donor kidney transplantation remained continuously available, but with the understanding that faculty and staff with ethical qualms could opt out of the performance of the donor operations. The consequence of this policy in Denver and Pittsburgh was the concentration of surgical experience by a subset of the total team. However, all members of the team were expected to participate in the event of complications. As before, the commitment to the donor as it related to complications from nephrectomy was construed to be for a lifetime.

The team leader of the Colorado and Pittsburgh programs (TES) discontinued participation in these operations in 1972 after a vascular accident during the work up of a donor in a referring hospital resulted in a foot amputation. Anxiety generated by this case was compounded by donor deaths at other centers, most of which were never formally reported. In fact, donor deaths occurring during work up (e.g., due to angiography complications), or from late complications of donor nephrectomy (e.g., intestinal obstruction) have never been included in donor mortality compilations. For the record, there have been no known deaths related to donor nephrectomy in either the Colorado or Pittsburgh experience; but because of incomplete late follow-up in some cases, a clean slate cannot be claimed with certainty.

THE HELSINKI DEBATE: LIVE ORGAN DONATION CIRCA 1986

The shifting ground of live kidney donation was evident in a formal debate at the 11th Congress of the International Transplantation Society, convened in Helsinki, Finland, in the waning days of August 1986. The program committee assigned Felix Rapaport the task of defending the procedure, with one of the authors (TES) as the designated opponent. Rapaport began by describing how scientific and medical advances had resulted in changed guidelines for live donation. The inference was that both the ethical issues and practical policies of live donation were moving targets, and that positions taken in 1986 would very likely be viewed as obsolete 20 years hence.

Like a document in a time capsule, the debate was preserved in the pages of the journal, *Transplantation Proceedings* (8,9). Now that the 20 years have passed, Rapaport's prophecies have come to pass. His primary justification for live kidney donation in 1986 was an eminently practical one: i.e., the rapidly growing unmet need for transplantable kidneys. Rapaport associated the shortfall with the improved survival and better quality of life with the advent of cyclosporine, and predicted that further refinements in immunosuppression would only increase the demand. He emphasized the safety of renal donation (citing estimates of one death per 2000 cases). Looking forward, he predicted that future strategies to induce tolerance would be fully applicable only under the circumstances of live donation: i.e., sufficient time for pretransplant recipient immune modulation.

The centerpiece argument by TES against live donation was concerned with the physical and emotional health risk to the donor under the increasingly commercial circumstances of the

emerging field. The risk already had been demonstrated by extensive experience: e.g., there had been 20 known deaths of kidney donors. A secondary concern was the difficulty of ruling out the psychological or economic coercion of donors. Finally, the possibility was raised that the convenience of performing prescheduled transplant operations could dampen enthusiasm, or even be a negative incentive, for deceased donor organ procurement. All of these issues continue to concern us today.

What was remarkable about the pro and con positions of 1986, however, was not the divergence but rather the commonality of the two points of view. There was concurrence that living donors provide better grafts, better biologic matches, and a higher quality of recipient life than can be achieved with deceased donors. Moreover, TES was even more specific than Rapaport in suggesting how live-donor blood products in advance of the kidney transplantation could be used to facilitate tolerance. The nonconfrontational nature of the debate was reflected in the final statements of the two presenters.

From the con perspective, it was stated that

... No one would ever operate on a living donor without being convinced in his deepest conscience that he or she was doing the right thing. What we do when we agree to engage in public discussions like this is to expose the deepest crevices of our consciences for criticism and sometimes ridicule. Thus, I want to conclude by honoring Felix Rapaport for coming here as he has done today to give his views about a decision that must be between the surgeon and the living donor, and between them alone (7).

In his pro summary, Rapaport recapitulated his conviction that even with 100% retrieval of all deceased donor kidneys potentially available in 1986 in the United States, there would be a shortage of grafts, with many deaths of recipients who otherwise could have returned to a useful place in society. He concluded:

This consideration raises the very real question as to whether the continuing resistance to living-donor kidney transplantation is ethically or medically justifiable today. The time may well have come for us to determine ... whether ... to advance the policy of preserving life, or to stand paralyzed by its taboos (8).

If there was an ethical divide between the 1986 Helsinki debaters, it was because the focus on one side (TES) was almost entirely on a perceived erosion of donor safety. On the other side, Rapaport's defense of live donation went well beyond the original "mutual donor-recipient benefit" argument, about which consensus had been achieved a decade earlier. Rapaport's position was that live kidney donation would be necessary to prevent pivotal societal problems, including the breakdown of the national ESRD program, which already was heavily weighted by transplant candidates on long-term dialysis who were vainly waiting for grafts. Moreover, the fiscal viability of many transplant centers depended on live donor organs. In Rapaport's view, the failure to exploit live donation would result in closure of these programs and thereby inhibit the homogeneous diffusion of renal transplantation into the national health care system. From the perspective of "group ethics," the death of one volunteer per 2000 donations was a statistical nonevent relative to the life years saved.

It is noteworthy that neither of the Helsinki debaters ever published again on the subject of live donation and that both scrupulously avoided public expressions of opinion. It was not merely a matter of mutual respect. There was really no right or wrong answer. In the 1990s, and for reasons he never explained, Rapaport opted out of personal participation in live donor cases at his own institution.

LIVE ORGAN DONATION 2006

History's judgment on the ethics of live donor organ transplantation probably will not be finalized for many more years. The ultimate verdict is apt to be harsh if genuinely effective alternative methods of treating organ failure such as, artificial organs, xenotransplantation, or stem cell-based strategies are developed. For the time being, however, live organ donation is an ethical *fait accompli*, including at the Universities of Colorado and Pittsburgh, for precisely the reason given by Rapaport. Because of the decreasing availability of deceased donor kidneys, live kidney donation has increased in Pittsburgh over the last 15 years to about the same extent

as that nationally. Moreover, the trail blazed by live donation of the kidney has expanded in selected centers throughout the world to all of the other transplantable organs except the heart.

Living donation of organs other than the kidney was mentioned only once in the 1986 Helsinki debate, and then with the unchallenged expression of hope that

... more complex donor operations such as partial pancreas removal or removal of portions of the liver for transplantation will not be extensively carried out in living volunteers since here the risk to the donor will be even greater (9).

The increased risk is best exemplified by the worldwide experience with live-donor liver transplantation (LDLT).

Support for LDLT in the United States and Europe was built on the socio-ethical base constructed by regulatory and oversight committees at the University of Chicago, where discussions were initiated at the urging of the surgeon, Christopher Broelsch (10). The first cases of the Chicago LDLT series were reported to the American Surgical Association in 1990 with a generally benign discussion from the floor (11). From the beginning, however, it was estimated that the mortality with these procedures would be approximately one in every 200–250 cases. Based on the world's known experience of nearly 6000 LDLTs, the prophecy has proved to be accurate, or possibly even an underestimate because some deaths have not been reported and very few have been described in detail (12). Nevertheless, it is clear that the mortality rate to date has been 10 or 15 times greater than that of kidney donation. Most of these losses attracted minimal public attention. However, some set off a frenzy of media attention and subsequent recriminations directed at specific institutions and individuals.

Recognizing that these incidents had brought LDLT to the brink of peer- and/or societal-imposed abandonment, liver transplant surgeons and hepatologists have taken determined steps to assure complete reporting of such cases to an audited registry of donor as well as recipient outcomes. It is hoped that analyses of these data will provide answers about risks and also clarify important unresolved issues (e.g., what are the relative merits of the right- and left-liver lobe operations?). Moreover, at meetings of registry participants such as the summit conference convened in Vancouver, Canada, on September 15th–16th, 2006, measures to increase donor safety could be discussed in a collegial and nonjudgmental manner. The procedure with the highest mortality has been removal of the right lobe.

In contrast to the multicenter case collection, right lobe donation has been safe and effective in single-center or single-surgeon series. For example, between 1998 and date, one of the authors, Amadeo Marcos (AM), performed 307 live donor liver operations at three successive university centers (Commonwealth University of Virginia, University of Rochester, and the University of Pittsburgh). In 289 (94%) of the cases, the right lobe was used. The incidence of early or late donor death, hepatic failure, or aborted operation was zero. This experience is described in Chapter 16. Here, we are concerned, first, with the influence on donor safety of recipient case selection; and second, with the ethical ramifications of the donor and recipient screening policies.

The donors in the single-surgeon series described in Chapter 16 were surrounded from the beginning with a highly protective ring against coercion, emotional damage, and technical or management errors. Unlike the diffusion of donor responsibility that took place 30 years ago in kidney transplantation, all liver donors in our program must be worked up and cared for at our transplant center. As the personal experience and that acquired in other LDLT centers was compiled, layers of security were added: for example, a pretransplant liver-needle biopsy has been an obligatory condition for donation. In addition, a constant element throughout the acquisition of this experience was the exclusion from LDLT candidacy of recipients whose chronic end-stage hepatic failure was unstable and of patients who had fulminant hepatic failure.

We believe that this restrictive policy is a key factor in avoidance of live donor mishaps. The urgency of donor work up for a recipient who is unstable may lead to errors of commission or omission. Urgent circumstances also can result in the performance of a futile donor operation, as has been exemplified by the experience reported by Broelsch et al., (13) from Essen, Germany. In the German experience, four recipients died intraoperatively after the donor operation had reached the stage of liver division into right and left lobes including transaction of the hilar

ducts ("*hepar divisum*"). Although the right lobes could be left in place after biliary reconstruction (two duct-to-duct, two hepaticojejunostomy), three of the four donors had significant early complications from the right lobe, and one of the three had a bout of septic cholangitis at 43 months that was relieved by dilatation of an anastomotic stricture.

Because unstable recipient disease can convert a meticulously-planned donor operation into a shamble, our opinion is that volunteer liver donation is an operation that should be used electively to treat patients who are not terminally ill. It could be argued that this policy is based on a medical-ethical syllogism. Even though their life may be miserable, most patients with stable end-stage liver disease have a survival prognosis of many months or even years. Therefore, it can be argued that the preferential target population for an organ allograft should theoretically be the one in which early deaths are most likely. This is, in fact, the basis for the UNOS deceased donor liver allocation system with which we are in unequivocal agreement.

However, LDLT requires a very different set of decisions across the full spectrum of health care stakeholders because it involves a double relationship for the doctor: with the donor as well as that with the recipient. Elective LDLT to a nonurgent recipient ostensibly is at odds with the "sickest first" philosophy behind the UNOS deceased donor liver allocation policy, but it is consistent with two higher priorities. First, it improves the safety of donor care as described above. Second, it meets the standard of long-term holistic health and welfare benefit for the donor with which live donor kidney transplantation was justified in the 1960s (see earlier). It is well known that grave illness is the single most negative recipient survival factor with liver transplantation. There is no way to assess the despair caused by a futile LDLT, or for that matter, by a failed live organ donation of any kind. Avoidance of this disillusioning outcome begins with recipient case selection.

As discussed earlier, Rapaport considered the benefits of a successful live organ donation in a larger context than that of the welfare of a specific donor and of a specific recipient. He envisioned the looming nightmare of a half-million patients waiting on dialysis. Because chronic artificial-liver support technology does not exist, waiting lists of liver transplant candidates inevitably will be kept small in the foreseeable future by "deaths while waiting." However, from Rapaport's "group ethics" viewpoint, the domino benefits of LDLT could relieve the overall liver graft shortage, prevent slippage of liver transplant candidates from elective into the grave disease categories, and assure a higher rate of return of recipients to a genuinely functional role in society.

A WILD CARD: PRETRANSPLANT IMMUNE MODULATION

Until recently, much of the progress in organ transplantation has depended on the development of increasingly potent immunosuppressants. Following the discovery in 1992 of donor leukocyte microchimerism in long surviving kidney, liver, and other kinds of human organ recipients (14,15), the leukocyte-chimerism-associated mechanisms were elucidated that directly linked organ and bone marrow cell engraftment, and eventually clarified the meaning of acquired transplantation tolerance (16,17). The resulting paradigm shift mandated revisions of many cherished dogmas, revealing how immunosuppression could be better timed and dosed, and suggested ways to effectively prepare recipients for organ transplantation by exposing them to donor leukocytes prior to arrival of the organ graft.

The foregoing insight was not fully developed until almost two decades after the 1986 Congress of the Transplantation Society. However, both participants in the Helsinki debate recognized that there would be sufficient time for the pretransplant recipient immunomodulation only under the circumstances of live donor transplantation. Consequently, both men emphasized that the incentive for live donor organ transplantation would be ratcheted up once the principles of effective immunosuppression-aided tolerance induction were delineated and exploited. The objective of efficient tolerance induction was ultimately accomplished in 2005 in patients undergoing LDLT with a protocol that can be generalized for transplantation of all kinds of organs. Immunosuppression is begun three weeks before organ transplantation, followed by an infusion of precursor and stem cell-enriched donor leukocytes. The organ transplantation subsequently is carried out in a patient who already is well on the way to a donor-specific tolerant state.

Preliminary results of the first five cases of LDLT were presented by one of us (AM) at an international conference in Pittsburgh, Pennsylvania, on March 11, 2006. The follow-ups are still too short to know whether this precise protocol is a definitive end to the search for the Holy Grail of organ tolerance or is only another step toward this objective. However, it is already clear that a high degree of at least partial tolerance can be reliably produced. This has opened a horizon for the more efficient use of the most precious resource of all, namely the allograft taken from a live volunteer donor. To avoid tragedies involving live donors, no matter of what organ, it will be necessary to heed those technical, management, and ethical lessons about live donation that have been learned in the past from bitter experience. A gold rush is gratifying only if the gold is not sullied.

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