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Kidney International, Vol. 28, Suppl. 17 (1985), pp. S-31–S-33

Protecting the patient's interest

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The ethical questions surrounding transplantation have become a cottage industry for some of the research "think tanks," where issues are considered in the rarified atmosphere of a retreat setting. Interestingly, written accounts of sick patients' rights after such deliberations are usually fuzzy.

As a result, potential violations of patient rights exist, and the scientific and administrative matrix in which we function could inadvertently permit or even promote patient abuse.

The landmark documents

In 1965, a symposium on medical ethics was convened in London at the Ciba Foundation [1]. It was clear that transplantation procedures, which had been a curiosity only two or three years earlier, were going to be used widely. Twenty-five participants were invited, including seven from the United States: Willard E. Goodwin, David W. Louisell, Joseph E. Murray, Keith Reemtsma, George E. Schreiner, Thomas E. Starzl, and C. E. Wasmuth.

The medical atrocities of World War II were still fresh in the collective mind, and three of the European participants (David Daube, Regius Professor of Law, Oxford; Herbert de Wardener, Nephrologist at Charing Cross Hospital; and Michael Woodruff, Professor of Surgery, Edinburgh) had experienced abject violation of their human rights during years spent in concentration camps.

Two documents that were part of the postwar reaction to the European and Asian atrocities were reproduced in the appendix of the Ciba proceedings. One was the Nuremberg Code and the other was its successor, the Helsinki Declaration. In plain language, the Helsinki Declaration divided human experimentation into two categories: advanced therapy that could be of direct and immediate benefit to the person who requests it or investigation that might benefit humankind, but which may not directly benefit the person undergoing the experimentation.

The nature of surgery almost always limits its investigation to the therapeutic category. With one possible exception, I have not carried out invasive procedures, including biopsies, except in the direct best interest of the surgical patient, and I have been reluctant to have others perform time-consuming, exhausting, or potentially dangerous studies on my patients, no matter how interesting the results might be.

Received for publication December 28, 1984

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The donor-recipient axis

The living-related donor

The possible exception mentioned above stems from a potential conflict of interest between the donor and recipient. In the early 1960's, the most convenient and perhaps only organ donors for many patients were family members. An organ that saved the life of another person was removed from a healthy and well-motived human being, a process well within the framework of conventional Judeo-Christian ethics. The act was compared to leaping into a lake to save someone who is drowning. But, concerns about the conditions under which these donations take place haunt us to this day.

The legal (and probably the moral) basis for living donations dates back to a 1954 Massachusetts court ruling that permitted an identical twin transplantation. The legal opinion reflected the probability that identical twins were so close, emotionally, as well as in every other way, that the loss of a kidney by the donor would be less devastating in the holistic sense than would be the loss of an identical twin sibling. Similar reasoning in subsequent court cases has been upheld and extended to other renal donations, including parents to offspring and other consanguineous combinations.

This lofty concept notwithstanding, many examples of donor abuse within families can be found. If a prospective donor is deficient in some way, usually intellectually, the family power structure may focus on him or her, the perceived deficiency serves as the basis of one's expendability. I have seen refusal of donation lead to ostracism within a family, or alternatively, donation could be a reluctant sacrifice offered to someone for whom there was little or no affection.

The question of coercion is a particularly important one with volunteer donors who may not possess their full civil rights. In an early Boston experience, and on a number of occasions since, minor identical twin donors (as young as 6 years of age) have been used. Of course, such donors must answer to their parents and thus are captive. The same captive concept applies to volunteer convict donors, who might be induced by emoluments, other favors, or, conceivably, threats to step forward. Although I was one of the first to use the expediency of living donation and have never had a donor die, the concept remains a troubling one to me, and I have not operated on a living donor since 1972.

Nothing is foolproof in medicine, and the hope that kidney donation would be without mortality was a vain one. Some 15 or 16 healthy volunteers have died after donor nephrectomy. Technical surgical accidents, pulmonary embolism, and anes-

thesia-related hepatic failure have been the most common causes. It may be that survivors with a single kidney face an increased hazard in the long run, as several recent, controversial reports have suggested. Questions abound that make the concerned physician uneasy.

The cadaveric donor

Obtaining organs from people who are dead is the alternative. At the London meeting in 1965, the concept of "brain death" was expressed for the first time. Kidneys were being removed from "beating heart" cadavers in Louvain, Belgium, and isolated examples of this practice in other European countries were reported. At first, this idea appalled me because I envisioned that the care of a trauma victim could be jeopardized by virtue of his or her candidacy to become an organ donor.

These fears were unfounded. The chances of a seriously injured patient being properly cared for were actually greatly increased by defining death by brain function rather than by the conventional criteria of cessation of heart beat and respiration. Under the circumstances that existed before, when someone with a serious central nervous system injury was brought into the emergency room, the physician was often obliged to make an on-the-spot decision about the patient's capability of survival. A negative decision precluded resuscitation, since it was almost impossible to discontinue ventilatory support later without being accused of murder. With the wide acceptance of brain death in the Western World, all such patients have a fair trial at resuscitation. Then, in an orderly way, it can be determined whether they are merely enduring heart-lung preparations, or if they have some prospect of having meaningful brain function restored. The quality of care and the discriminate application of such care to terribly damaged people has been one of the great fringe benefits of transplantation.

The potential abuse of resources

Regional franchises

Until a decade ago, only aggressive or wealthy patients with end-stage renal disease could stay alive. Chronic dialysis and transplantation were both too expensive for most others. Families became bankrupt in desperate efforts to keep one of their members alive.

The terrible quandary ended with the passage of the so-called HR-1 Bill of 1972. Since that time, competition has developed for the Federal End-Stage Renal Disease (ESRD) budget, which by 1982 had swollen to a $2 billion per year. An economic aristocracy was created for physicians and/or surgeons who controlled "regional concessions" for dialysis, vascular access surgery, and transplantation. The struggles that have ensued for various franchises within the ESRD Program, including cadaveric organ procurement agencies, sometimes have been mammoth.

Captive patient populations

In large cities or regions where a transplantation monopoly has been established, the resultant captive population of patients often has been well served. However, a center with poor results may be difficult to dislodge from its monolithic position, in which case most transplantation candidates would have no options to seek other avenues of care. Furthermore, a dehumanizing element can be introduced unconsciously with a captive practice. For instance, recipients on a cadaveric waiting list may feel that they cannot be demanding, express hostility, or deviate in any way from model behavior for fear of jeopardizing their candidacy. Personally, I believe that when a situation like this develops, the only alternative is to set up a competing transplantation team, since there are few things more degrading to patients than to be treated as a custodial case.

A potentially stultifying effect of the ESRDP

A large cash flow can contribute to the fixation of therapeutic practices at an unsatisfactory level since any major change is apt to affect the way that business is transacted to require inconvenient retraining and the acquisition of new knowledge. It has not been difficult to identify reactionary nephrologists and surgeons alike who became wealthy from the flow of Federal money, and whose riches then made them a powerful lobbying force against policy changes, in spite of their general lack of insight into the process of scientific inquiry and their miniscule record of discovery and contribution. Their refuge has been blind adherence to, and even insistence upon, historically important but dangerous, morbid, and ineffective immunosuppressive techniques, or a persistent dependence upon living, related transplantation with its generally less formidable immune barrier.

Randomized trialomania

I have heard it seriously proposed that *bona fide* candidates for liver or heart transplantation be randomized into those receiving therapy vs. controls. Few would object to describing such suggestions as randomized trialomania; however, trialomania can present with more subtle symptoms.

Premature randomization

An insistence upon carrying on randomized trials before learning the optimal use of new therapeutic tools may discredit promising developments. When the powerful new immunosuppressive agent, cyclosporine, was first used clinically, multiple, unanticipated management problems were encountered. More than 50 pilot cases were necessary before effective management schemes could be evolved, and these required combination therapy with steroids. There was no justification during this time for a randomized trial, yet, nearly continuous pressure to conduct such a trial came from several sources.

Randomization after the fact

Before the foregoing extensive pilot trials had been completed, it was obvious that cyclosporine-steroid therapy was superior to conventional double drug immunosuppression with azathioprine and prednisone, and that randomization against the latter double drug treatment would create an inequity. For a randomized clinical trial to be carried out ethically, it is necessary that the physician be convinced that he or she is dealing with the null hypothesis of no treatment differences.

For many transplant surgeons using cyclosporine-steroid therapy, a null hypothesis no longer existed. In spite of this, the institutional review board insisted upon a randomized trial in

primary cadaveric kidney recipients and it was conducted in 1981. The primary graft survival at the end of one year was 90% in the cyclosporine-steroid group, and 50% in the control group. The results were predictable, both from the preceding pilot trial and what had been learned about the potency and relative safety of cyclosporine from animal work.

A randomized trial is not an instrument of discovery, but rather a means of validation. Schneider [2] has pointed out that the significance tests applied to randomized trials ordinarily are concerned primarily with preventing erroneous rejection of a null hypothesis; thus, they will reveal treatment differences at an error level of 5% only for very large deviations or with very large samples. Because of these limitations, Schneider remarked acidulously that "significance tests are more adapted to preventing progress than to achieving it."

A revealing question that physicians might ask before assigning patients to a randomization study would be whether they would allow therapy to be decided by lot for themselves or their family members if they suffered from the same disease.

Summary

Notwithstanding recent developments, protection of patients' rights and the identification of potential areas of patient abuse will continue to be a complex problem.

Acknowledgments

This work was supported by research grants from the Veterans Administration and by the National Institutes of Health Grant AM-29961.

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