J Am Soc Nephrol 15: 3270–3271, 2004

Renal Transplantation: A Half Century of Success and the Long Road Ahead

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In this issue of *JASN*, Doyle *et al.* give an historic overview of organ transplantation with emphasis on renal transplantation (1). In this overview the story is one of almost unparalleled success. As pointed out by Doyle *et al.* the major barriers to successful renal transplantation in the early yr of renal transplantation were perfecting the delicate technical requirements of kidney implantation, overcoming acute rejection and avoiding lethal infectious complications of immunosuppression (1). The review by Doyle *et al.* highlights the work of the clinical and basic researchers who through diligence, solid scientific investigation, and clinical intelligence allowed renal transplantation to become a routine procedure. Renal transplantation is one of the spectacular success stories in medicine during the 20th century. In fact, the advances in renal transplantation have advanced this modality to be the treatment of choice for end-stage renal disease (ESRD). In the seminal analysis by Wolfe *et al.,* a significant survival advantage of transplant over dialysis was demonstrated, an emphatic confirmation of this success (2). Renal allograft loss due to technical failure or early acute rejection, historically a major challenge, is currently exceedingly rare (3). Concomitantly the value of antiviral and fungal prophylaxis along with effective cytomegalovirus (CMV) treatment has lead to a marked decrease in death and morbidity due to infection (4).

However, when assessing outcomes in renal transplantation one must be very specific in regards to the outcome being addressed. If one utilizes acute rejection as our outcome, the last ten yr have seen remarkable improvements in this parameter, with acute rejection rates more than halving over the yr 1995–2000 (Figure 1) [with this trend continuing through 2004] (5). This decrease in acute rejection rates was achieved during a period of intense study and unprecedented introduction of new immunosuppressive agents. This improvement in acute rejection rates was in all likelihood reflective of the advent of these new therapies and the attendant increase in immunosuppressive regimens available to transplant professionals.

The paradigm for yr in renal transplantation has been that therapies that decrease acute rejection and early injury will naturally lead to improvements in long term allograft survival. Given the early results of renal transplantation and several retrospective analyses, this seemed a very reasonable expectation. In fact if we measure our outcomes as one yr graft survival we do see tremendous improvements over the last ten yr, with almost 90% of all allografts still functioning at one yr (6). As a natural consequence of this short term success along with the long term retrospective associations, early events (*e.g.* acute rejection in the first yr) have been utilized as surrogates for long term graft survival.

Unfortunately, the situation for long term graft survival is more complex than originally considered. While early events and markers, such as acute rejection and renal function are strongly associated with longer term graft survival, they fall short as reliable surrogate markers for long term graft survival (7). From the yr 1988–1995 projected data indicated significant improvement in long term graft survival, in fact it was projected that an almost doubling of graft half life took place during this era. This projected improvement was noted during an era of little new immunosuppressant development, only modest decreases in acute rejection, but improving one yr graft survival (8). The explanation of this improvement was postulated to be due to improvements in the learning curve of agents in use at the time. However, more recent data utilizing actual survival data indicate only modest improvement in longer term graft survival despite marked improvements in the short term during this period of time (9). While certain high risk groups such as re-transplants saw great improvement in longer term survival, this trend was not as impressive for the overall population. From 1988 through 1995 the average deceased donor allograft survival changed very little (approximately 8 yr). As opposed to the yr 1988–95, the yr of 1995–2000 saw an almost halving of acute rejection rates with continuing improvements in one yr graft survival, but again only very modest changes in long term graft survival could be found (9). What is one to make of this paradox? Current data seems to indicate that while it is necessary to prevent acute rejection and early injury, we cannot presume that this will necessarily extrapolate to longer graft survival (and ultimately longer patient survival).

As we near the yr 2005, the renal transplant community now must address the question of long term graft survival. We can no longer assume that prevention of early injury to the allograft ensures protection from late functional loss. The focus of future studies will have to address the processes that lead to late allograft loss.

The issues of calcineurin inhibitor injury and subsequent calcineurin inhibitor withdrawal under newer immunosuppres-

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1046-6673/1512-3270
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000146569.59482.8C

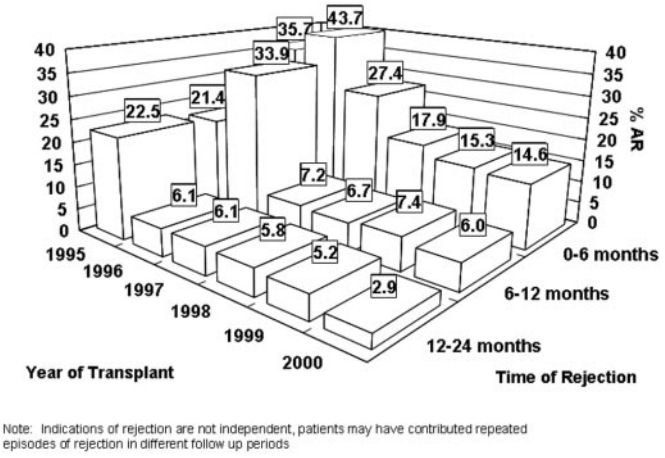

Figure 1. Incidence of early and late acute rejection episodes by era. Please note that indications of rejection are not independent; patients may have contributed repeated episodes of rejection in different follow-up periods.

sive agents such as sirolimus have garnered great attention (10). However, while calcineurin inhibitor nephrotoxicity is unquestionably a problem, it is still to be determined if withdrawing these agents will be the answer, as one has to remember that these are the agents that have revolutionized the field and brought us to the current standard. As we do not fully understand the immunology of late allograft loss it is premature to categorically and confidently assure that alternative strategies will confer equal immunologic protection. Regardless, given the toxicity of these agents a definitive answer to this question is a priority for future research.

Late immunologic injury is an important issue for study, because it is possible that agents effective against early immunologic events are not as effective for later immunologic injury, or that conversely minimization in the attempt to temper long term toxicity may lead to subtle immunologic injury. It is also possible that in these ds of immunosuppressive minimization recurrent disease might become a more important factor for graft loss. BK viral nephropathy has become an increasing problem and may under-score the delicate immunologic balance inherent in the art of transplant medicine. In addition, traditional factors in nephron loss such as hyperlipidemia, hypertension and diabetes need to be placed in proper perspective. While we must delineate the processes involved in late injury, we also cannot ignore the basic mechanisms of homeostasis and repair. It is also possible that the increasing complexity of our immunosuppressive regimens has made long term follow-up, adjustment to toxicity and efficacy failure increasingly problematic for physicians outside large transplant centers. Finally, the last decade has seen an increase in the transplantation of traditionally high-risk recipients along with a greater utilization of 'marginal" (or extended donor criteria) kidneys. The impact of this trend cannot be ignored when assessing long term outcomes.

So, after all this success we are still left with some very basic questions to answer. To address this issue in any type of practical manner we must first determine the reasons why grafts are lost and then define sensitive and specific immunologic and epidemiologic surrogate markers for late injury and functional loss. Clearly reliance on traditional early events (*e.g.* acute rejection) as surrogates for late functional loss needs to be reconsidered. In addition, selection of recipients and donor organs should be addressed in an objective and scientifically sound manner.

As pointed out by Doyle *et al.* the story of renal transplantation has been one of great success. The pioneers in our field who conquered early immunologic injury have allowed us to now turn our attention to the still to be defined late processes that lead to nephron loss.

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See related article, "Organ Transplantation: Halfway through the First Century," on pages 2965–2971.