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EDITORIAL

The Third Epoch: "Kidney Plus" Transplantation

The first epoch of kidney transplantation began over a century ago when successful, experimental kidney transplantations were performed on animals at the Vienna Medical School (1902). However, the initial success was subsequently beset by noteworthy failures in kidney transplantation including rabbit-to-human attempts (France, 1909), human-to-human allograft implantation without immunosuppression (1950), and partially successful human-to-human transplantations under the aegis of glucocorticoid steroid congeners (1950s) after the recognition of the etiopathogenic importance of the immune system to rejection. This first epoch of kidney transplantation ended on December 23, 1954. On that day, the team of Dr John Murray successfully transplanted the kidney of an identical twin to his brother.

Buoyed by Murray's "perfect match" surgery, the science of organ transplantation entered its second epochal stage. Continual improvements in tissue typing, organ preservation and procurement, and then, immunosuppression followed rapidly during the 1960s and complemented advances in surgical technique. Kidney transplantation exponentially became an increasingly prevalent phenomenon, and superior outcomes to those receiving chronic renal replacement therapy were apparent to those so involved and patients! In parallel with these burgeoning activities, the administrative components of transplantation evolved and our present-day regulatory organizations evolved from these critical efforts. In fact, the United Network for Organ Sharing celebrated its 25th anniversary in March 2009.

Noteworthy is that the agencies and societies dedicated to kidney transplantation have established clearcut outcome metrics for recipients and the not-to-be forgotten donors. The bar was set "high," and the high standards imposed are, in part, responsible for why the kidney has been transplanted successfully far in excess of any other organ, with the following laudable outcome data: (1) 1-year patient survival after deceased-donor transplantation is 94.1% (unadjusted), (2) 1-year patient survival after living-donor transplantation is 98%, (3) allograft survival after deceased-donor transplantation is 89.7% (unadjusted), and (4) allograft survival after living-donor transplantation is 95.1%. All of this is underscored by the compelling fact that kidney transplantation is no longer novel; it is "mainstream" as espoused on the United Network for Organ Sharing web site. Granted, nearly 100,000 persons have undergone successful kidney transplantation, and the annual number of transplants exceeds 18,000. Unfortunately, despite these positive data, currently, nearly 78,000 individuals await renal allografts.

With this as pretext, the third epoch of kidney transplantation is characterized by dual-organ transplantion involving the kidney as one half of the combination, namely, "kidney plus (another organ)" transplantation.

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Presently, it is not uncommon for patients to undergo evaluations for dual-organ transplantation: simultaneous pancreas-kidney, orthotopic liver-kidney, and heart-kidney transplantations. However, these combined procedures remain fraught with hazard, even when practiced at "centers of excellence." Previously, the excessive mortality associated with type 1 diabetes precluded many of the afflicted from kidney transplantation. However, improvements in the care of such individuals have substantially prolonged patients' lives and their probabilities of developing nephropathy and end-stage kidney failure. Thus, simultaneous pancreas-kidney transplantation is a function of medical progress and relevant to patients who could not achieve adequate glycemic and/or blood pressure control in the period preceding the onset of diabetic kidney disease. Comparable advances in the treatment of end-stage liver disease have taken place. Despite the increasing prevalence of progressive liver disorders, primarily those attributable to the hepatitis C virus, alcoholic liver disease, and now nonalcoholic steatohepatitis, many patients have the opportunity for longer-term survival via orthotopic liver transplantation. With desperate illness comes desperate measures, and many acute or chronic "liver" patients with high model for end-stage liver disease scores develop acute kidney injury within the rubric of type 1 or type 2 hepatorenal syndrome. Hepatorenal syndrome occurs in 10% of hospitalized patients with cirrhosis and ascites and has a frequency of 8% to 20% per year in decompensated cirrhosis.

In addition, it is not atypical for patients who have already undergone solitary-organ, nonkidney transplantation to "abruptly" appear with kidney disease—the consequence of prolonged and perhaps unduly excessive exposure to nephrotoxic agents, principally, calcineurin inhibitors that have been shown to promote tubulointerstitial fibrosis through a panoply of mechanisms, including those that involve the renal microvasculature and transforming growth factor-beta. Protocol biopsies have confirmed the onset of histologic damage within a relatively brief interval (less than 2 years), despite "low therapeutic" drug levels of calcineurin inhibitors in solitary renal allograft recipients. By contrast, recipients of hepatic and cardiac organs have often been treated to comparatively much higher calcineurin inhibitor levels, and it is unsurprising that CKD is present and essentially "expected" in long-term survivors. Furthermore, at the time when CKD is discovered, the cardiac transplant recipient will often manifest variable degrees of decompensation, thereby compounding the preexistent clinical burden with the cardiorenal syndrome.

Like the two epochs preceding it, the third epoch is characterized by a period of exploration, advancements in technology, and informed specification of those medical and surgical methods and techniques that will hopefully optimize patient results. Such recommendations characteristically stem from consensus opinions rendered by multilateral congresses comprised of the relevant, pursuant parties. Thus, there are "gray zones" for "kidney plus" transplantation, wherein "best practice" guidance from clinical trials is lacking for these patients. In this issue of *Advances in Chronic Kidney Disease*, the Guest Editor, Connie L. Davis, MD, has coordinated a series of articles dedicated toward improving our understanding of the issues that confront kidney transplantation physicians who are involved with post-heart, -liver, and -lung patients as well as dual-organ transplantation evaluations. The unique problems that differentiate these individuals from conventional kidney-only transplant recipients are enumerated. Moreover, valuable logical and practical advice regarding the approach to caring for these patients is rendered by the authors.

In particular, the optimal management of kidney failure of cardiac, liver, and lung failure in the pretransplant interval is reviewed. Here, optimizing renal replacement therapy when applicable is critical, and the timing of therapy is equally important as the technique. In addition, published recommendations relevant to patient selection for dual-organ transplantations are presented. In parallel, the issue of establishing a renal diagnosis by biopsy in azotemic patients presenting with heart or liver failure also resurfaces. Lastly, expert commentaries on individualized immunosuppressive therapy and the requirement for vigilance regarding transmissions of infectious

disorders from donors to recipients are provided.

Taken together, I echo the sentiments of Dr Murray, who stated that his lofty accomplishment belonged not to him alone but to the team that he guided. Yes, it will truly require a coordinated, focused, and dedicated effort among the multiple disciplines that interact on behalf of "kidney plus" transplant recipients, in order to not only aspire to but also to achieve the outcomes that these patients seek and deserve.

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Editor